医療保障総合政策調査・研究基金事業

高額医薬品の適正使用の推進のための調査研究

報告書

令和 7 年 3 月

健康保険組合連合会

目次

はじめに

医学・医療の進歩と人口の高齢化に伴い、国民医療費が増加の一途を辿るなか、高額な医薬品の保険適用が相次いでいる。本会では、令和4年度より、医療保険制度の持続可能性を確保するとともに、医療の質や患者のQOLを向上させる観点から、高額医薬品の適正使用を推進するための調査研究を進めている。必要な基礎データの収集・分析を行う外部研究機関の臨床研究に資金協力を行い、そこから得られる知見や成果を共有し、政策活用することを主な目的としている。

実施に当たっては、業務委託先であるSATOMI臨床研究プロジェクト（SCP、國頭英夫代表理事・日本赤十字社医療センター化学療法部長）が、高額医薬品の適正使用のための臨床研究を外部研究機関へ再委託し、高額医薬品の使用実態や国内外の適正使用の取組事例のほか、経済性、患者メリット、副作用などQOLへの影響等について検討を行う。SCPは本会に対して、上記の検討事項に加え、臨床データ収集・分析の進捗状況、研究成果等について、定期的（年2回程度）に報告を行うこととしている。

令和6年度までの3年間の取り組みの成果として、〇高額医薬品の使用実態調査について9本の論文を専門誌に掲載（6年10月）、〇中医協の要請にもとづく「費用対効果評価と診療ガイドラインのあり方に関する検討会」の設置（7年1月。國頭氏が参加し、本事業の成果を活用）、〇骨太方針2024への関係事項の記載（6年6月）―などがあげられる。成果をさらに具現化していくためには継続的な取り組みが必要であり、本事業を令和7年度以降も延長して実施することがすでに決定している。

本報告書は令和4年度から6年度までの3年間の取り組みとその成果をとりまとめたものである。内容には医学研究の専門用語等が含まれるほか、実際に専門誌に掲載された論文（英語）等が含まれるが、現場の医師や国内外の研究者等にご覧いただくこともあると考えられることから、あえてそのまま掲載している。とりまとめにご尽力いただいた國頭代表理事に深謝申し上げるとともに、本報告書が今後の高額医薬品の適正使用に向けた取り組みや議論のための一助となることを切に願う。

健康保険組合連合会

1.背景と事業の目的

国民医療費は増加の一途をたどり、令和 4 年度の国民医療費は 46.7 兆円、前年度の 45 兆円余に比べ 1.66 兆円（3.7%）増加で、これには新型コロナ対策費は含まれていないのでそれも含めると年間 50 兆円程度もしくはそれ以上であり、昭和から平成に変わった頃の倍をはるかに超える。国民医療費の GDP に対する比率は 8.24%（前年度 8.13%）であった（https://www.mhlw.go.jp/toukei/saikin/hw/k-iryohi/22/dl/data.pdf）。

うち薬剤費は 11 兆円を突破したと推定されている。薬価ベースの医薬品市場統計データをみると、2011 年が 9 兆 4816 億円で 2021 年は 10 兆 5990 億円と、約 1 兆円増加している。従来はいわゆる生活習慣病に対する薬剤が多かったが、抗腫瘍剤が 2014 年以降に薬効別の 1 位となり、2011 年が 6252 億円で 2021 年は 1 兆 6553 億円とこの間に 3 倍弱の急増を示し、10 年間の薬剤費の上昇分はほぼ抗腫瘍剤で占める計算になる。

個々の薬剤を売り上げベースで見ても、2023 年度では免疫チェックポイント阻害剤（ICI）のキイトルーダ ・オプジーボ・イミフィンジがそれぞれ 1649 億円・1487 億円・1207 億円で第一・三・四位を占め、一部（EGFR 変異陽性）肺癌にのみ適応があるチロシンキナーゼ阻害剤（TKI）の分子標的薬タグリッソが 1071 億円で第六位にランクされている（データ元・IQVIA）。

なぜ医療費特に悪性腫瘍に対する医療費が急増しているかというと、医療の高度化（医学の進歩）と人口の高齢化が主因であり、この二つは誰の責任でもないし、誰にも止められない。前者のため、薬剤の開発コストは 9 年ごとに倍増し、2016 年時点で一つの新薬を市場に出すのに平均で 3000 億円がかかると言われている。また後者に関しては、2055 年には日本で最も人口が多い年齢層は 81～82 歳だと指摘されている。誰がその負担をするのだろうか。

一方で医薬品の費用対効果については、欧米諸国に遅れて日本でも評価制度が 2016 年から試行的に、また 2019 年から本格的に導入されているが、我が国では結局、費用対効果の評価は医薬品の公的保険での給付の適応判断には組み込まれず、わずかに薬価制度を補完する形による価格調整にだけ応用されるにとどまった。よって日本では評価の役割や議論が軽視されがちであると指摘されている。

負担が可視化されなければ無駄遣いに繋がるというのは、例えば新型コロナの「薬」ラゲブリオが、中医協でも「費用増加」すなわち効果は認められずコストが嵩んだだけだったという評価がなされたにも関わらず、患者負担が免除されたため 2023 年度は 1455 億円と国内の薬剤売上第二位で、世界中の 3 分の 2 を使っていたというような事実からも示唆される。

これらにより我が国の国民皆保険制度は破綻の危機にあるが、医療者の危機意識は乏しい。一つには、国民皆保険と高額療養費制度に守られて一定以上の医療費は自己負担分に

上限が設けられてので、それを超えた分は患者の負担が変わらないため医療者も「どのくらい使っているか」を意識せずに診療できるという理由がある。

従来、医療者は医療コストのことは考えなくても良い、もしくは考えるべきではないというような風潮があったが、我々が拠って立つべき保険医療制度もしくは国家財政そのものが危うくなってきたら、そんな悠長で呑気なことを言ってはいられない。本事業は、我が国の医療の持続可能性を担保するために、高額薬を中心とした現代の癌医療において実際にどのような診療が行われ、どのような問題があるのか、今後どうすべきなのかを検討するために開始された。

自体は切迫しているため、実態把握のための調査研究・観察研究とともに、実際に治療の適正化への方向性を盛り込んだ臨床試験（介入研究）についても開始し、またそうした臨床試験をいかに行うかの体制作りについても同時並行的に展開していく。

2.問題点のまとめ

医療費高騰と医療の商業化に伴う費用対効果の低下は世界共通の問題であり、特に高額薬剤が次々と登場するがん医療では欧米でも見直しの気運が進んでおり、カナダの Booth 博士らは”Common sense oncology”（常識的な腫瘍学）[1)]を取り戻そうという運動を進めている。一言で言えば、「効果があるもの（だけ）を大事にしよう」という、極めて当たり前（なので「常識的」）の主張である。この「当たり前」が「当たり前」になっていないことが現代医療の欠点だが、特に日本では問題点の指摘すらなされない。

日本では、高額の医薬品が次々と登場し、どうしても薬価にのみ注目が集まるが、本邦での新薬の薬価は、「製薬企業が値段を決める」米国に比べて低く、欧州諸国に比べてもさほど高くはない（円安のため、企業側にとっては「不当に安い」と判断されているくらい）。問題は、承認されたものが全て保険償還の対象になることで、例えば韓国では同じように「承認」されている薬剤も、高額のものや費用対効果が低いと判定されたものは保険医療での使用が不可能もしくは限定されているのに対し、日本では全て使える。

しかも高額療養費制度の存在により、自己負担は一定以上にはならないようになっているので、「どんなに高い薬を使っても患者の負担は同じ」という、費用対効果を考慮に入れるインセンティブが全くかからない仕組みになっており、現場のコスト意識は失われている。

例えば、大腸癌の化学療法に併用される血管新生阻害剤は何種類かあって、いずれも効果も副作用も同等であるにもかかわらず、ラムシルマブ[2)]はベバシズマブの数倍（バイオシミラーに比べると 10 倍以上）という法外な価格差が生じている。通常なら市場の原理でこういう「高いだけ」の品物は駆逐されるはずであるが、医薬品だけはそうはなっていない。

コスト意識が働かないと、本当にその治療が患者のベネフィットに繋がっているかどうかを無視して、無駄で無理な医療を行うことが「患者のため」で思考停止してしまって正当化される。日本で医療コストが上がっているのは（アメリカ[3)]と違い）価格ではなく使用量が多いためなのだが、そうした観点からの反省は少なく、データもほとんどない。政府の医療費抑制策はもっぱら（全体的な）価格抑制であり、効率が悪く本質に迫っていない。

一方で、医薬品開発の主導権は現在企業にあり、NIH 予算が日本と比べて桁外れに大きいアメリカでさえ、研究開発費の「出所」の半分以上は製薬企業などである[4)]。臨床研究も企業の主導で行われるので、当然のことながら「より多く使う」ことに主眼がおかれる。ちなみに標準治療開発のための臨床研究は一件数千万円～数億円程度であり、企業は問題なくその費用を負担するが、国（AMED）の研究費は最大で年間 1500 万円程度である。さらに、2018 年に制定された臨床研究法によって、臨床研究を行うための事務的ハー

ドルが著しく高くなり、当初の法律の趣旨と真逆の結果すなわち「その事務作業とコストを負担できるのは企業による研究だけ」となってしまっている[5)]。

以上まとめて、医療費高騰の問題点は、

・医療の商業化に伴う費用対効果の低下は世界共通の問題である
・日本は価格よりも使用量が問題だが、その認識は薄い
・日本では、費用対効果を考慮に入れるインセンティヴがかからない
・臨床研究・治療開発のレベルで、企業の論理が優先する仕組みになっている

などとまとめられる。これらに目を向け、手をつけていかねば我が国の医療は財政的に破綻するのは自明だが、「ほぼ手付かず」どころか「誰も目を向けていない」状態にあり、打開策は容易ではない。

3.調査研究体制

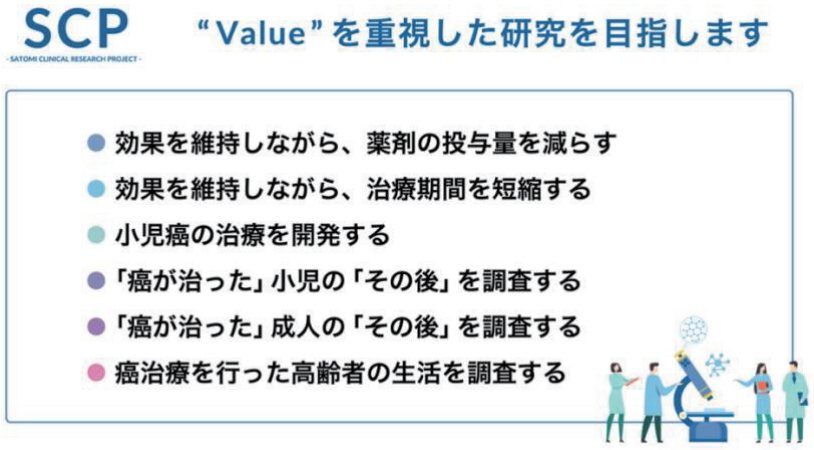
3-1.SATOMI 臨床研究プロジェクト（SCP）設立の経緯と趣旨

非営利型一般社団法人 SATOMI 臨床研究プロジェクト（SCP）は、2021 年に”value”（価値）の高い治療を開発する臨床研究支援を目的として設立された（https://s-cp.or.jp）。ここで”value”とは、
Value = Benefit / (Toxicity + Cost)
の式で表される。

従来、治療は効果（benefit）と副作用もしくは毒性（toxicity）の比で表されていた。これに基づき、「この治療は、効果は高いけど副作用が強いので慎重にせねばならない」とか「この薬は、大して効かないが副作用が少ないので使いやすい」などというような臨床判断がなされていた。Value は、これにコストの要素を加えることにより、「この薬は、大して効かないが副作用が少ないので使いやすい、のだがべらぼうに高い」場合はどう判断するか、を考える指標である。

アメリカでは米国臨床腫瘍学会 ASCO が、”ASCO Value Framework”[6]、また欧州では欧州臨床腫瘍学会 ESMO が”Magnitude of Clinical Benefit Scale”[7]という基準を作成し、この value 評価を行うようになってきているが、我が国では診療ガイドラインに載せる・載せないの基準は「統計学的有意差」が主体であって、コストは半ば意図的に無視されてきた。SCP は医療の持続可能性を念頭に設立された、おそらくは本邦で最初の団体である。欧米では、同様の趣旨の研究団体として、シカゴ大学の Mark Ratain 教授が代表を務める Optimal Cancer Care Alliance（https://optimalcancercare.org）がある。

SCP の目指す研究を下記の表に示す（HP から）。



なおこのうち、小児癌に関しては、稀少疾患であるランゲルハンス細胞組織球症の長期フォローアップ研究への研究支援を行なっている（https://s-cp.or.jp/from-the-field）が、

この報告書の内容と直接の関係はないため「4.本調査研究事業に関する SCP の活動内容」の項目からは割愛する。

SCP は、設立当初は、主に趣旨に賛同した個人からの寄付で運用されていた。代表理事は日本赤十字社医療センター化学療法部長の國頭英夫である。

3-2.調査研究内容とその実施体制

SCP はその予算規模からして、自前で臨床研究を立ち上げて遂行することはできない。よって、既存の研究団体と協力し、その研究を支援するもしくは研究を企画立案することで「目指す研究」を行っていく。協力団体としては、「目指す研究」の性質上、製薬企業の影響を受けない、公的研究費などで賄われるものに限定される。2022 年～2024 年の研究において、その主な協力者は次の二つである。

・日本臨床腫瘍研究グループ（JCOG）
代表者：大江裕一郎・国立がん研究センター中央病院副院長

・公益財団法人パブリックヘルスリサーチセンター先端生命医科学研究所がん臨床研究支援事業（CSPOR）
代表者：井原徹・学校法人白梅学園理事長

SCP は、JCOG および CSPOR に対して、上記の目的のための臨床研究等にかかる業務を委託する。JCOG および CSPOR において、

▽高額医薬品の使用実態調査
▽国内外の適正使用のための取り組み事例検討
▽適正使用のための取り組みの必要性（経済性、患者メリット、副作用など QOL への影響等）の検討

などを行うとともに、この目的に沿った観察研究・介入研究（臨床試験）を支援する。臨床データの収集、分析は JCOG および CSPOR が行う。

4.本調査研究事業に関する SCP の活動内容

SCP が関与する研究事業は多岐にわたり、この健康保険組合連合会事業の調査費のほか、上述のように個人からの寄付や、国立研究開発法人日本医療研究開発事業（AMED）からの研究費、さらには CSPOR の研究費などで運用されている。各々を切り分けることは困難であるため、以下多少なりとも健保連の調査研究事業と関連したものを「活動内容」として報告書を作成する。

4-1.JCOG 関連

JCOG：日本臨床腫瘍研究グループ（https://jcog.jp）は、国立がん研究センター研究開発費（旧がん研究助成金）班会議を中心とする共同研究グループで、国立がん研究センター中央病院臨床研究支援部門が研究を直接行う研究班の集合体である。16 の臓器別研究グループがあり、それぞれが可能な限り AMED 研究費も獲得して試験の運用を行なっている。また、各種の常設委員会および専門員会を設置し、円滑な試験遂行に努めている。

JCOG は法人格を持たない「グループ」であり、銀行口座なども持たないので、予算は国立がん研究センター中央病院もしくは AMED 研究費を獲得した施設から、各研究機関（病院）に配分される。

4-1-1.JCOG 医療経済小委員会設立

“Value”の高い治療を標準治療として確立し、患者の利益に繋げるためには、治療開発の段階すなわち臨床試験の企画立案および遂行の時点からコストを含めた検討が必須になる。このため、SCP 代表理事の國頭は 2022 年 3 月の JCOG 運営会議において「医療経済評価小委員会」の設立を提案し、承認された。以下その設立趣意書を転記する。

悪性腫瘍に対する薬物療法の進歩は著しく、進行癌でも 5 年～10 年以上の長期生存も得られるようになり、薬物単独での「治癒」の可能性も出てきています。手術や放射線治療の進歩と相俟って、これらを組み合わせた集学的治療によりさらに生存率の改善が期待されます。

ただし、これら新規の薬物療法は、分子標的治療にしても免疫チェックポイント阻害剤にしても、また新規の抗癌剤にしても、非常に高価です。2012 年にカナダの Ian Tannock 先生が ASCO の教育講演で、進行大腸癌の治療成績は生存期間が 2 倍になったがそのコストは 340 倍になった、と affordability および sustainability について警鐘を鳴らしています。それから 10 年、がん薬物療法のコストはさらに加速度的に上昇を続けています。

Tannock 先生たちは、OCCA（Optimal Cancer Care Alliance）という団体を設立し、癌治療の”value”=benefit/(cost+toxicity)を最適化する研究を模索していますが、翻って我が国では、国民

皆保険に守られて、癌治療コストの問題は表面化していません。日常臨床でも、せいぜいが「病院の収益に眼を配る」程度の注意しか払われていません。JCOG 研究でも、この”value”が問題になる（つまり、治療効果がコストに見合うのか、が議論になる）ことはほとんどありません。

しかしながら超高齢化社会となった日本で、コストを気にせず「治療の進歩」を追い求めるのには限界があります。実際、健康保険組合は高額医療の支払のためどんどん保険料を値上げし、それでも負担に耐えかねて解散するという事例が増えています。その分を引き受けるべき国家財政も、第二次大戦前を超えるレベルの負債を抱え、破綻の危機が囁かれています。日本が誇る国民皆保険制度は累卵の殆きにあり、すでに崩壊しているという指摘まであります。

私（國頭）は 2015 年の肺癌学会で初めてこの問題を取り上げ、2016 年の財政制度等審議会で高額薬について議論を提起しました。その結果、薬価は多少とも抑制されていますが相変わらず高く、かつ次々と「さらに高い」薬が出てきます。これは、医療の高度化すなわち医学の進歩を反映しているのですから、止めることはできません。

ならば、破局的結末を防ぐためには、我々医療者一人一人が、いかにして限りある医療資源を賢く使っていくか、を考えるしかありません。医療レベルを落とさずに、”value”を高めてコストを抑制し、affordability と sustainability を維持するためには、臨床研究に医療経済評価を組み込むことが必須と考えます。

上記の目的を達成するために、JCOG に医療経済評価委員会設立を提言いたします。二宮尊徳は「道徳なき経済は犯罪であり、経済なき道徳は寝言である」と言っています。我々もまた、寝言を呟くのではなく、覚醒して医療を語らなければなりません。

日本赤十字社医療センター化学療法科　國頭英夫

小委員会委員長には國頭が指名された。なお、「医療経済評価小委員会」はのちに「医療経済小委員会」に改称された。JCOG の規定に基づき、ポリシーが承認された時点で「医療経済小委員会」は「医療経済委員会」になる。

2025 年 1 月末現在、小委員会は委員長 1、副委員長 1、事務局 3、委員 21（JCOG 臓器別 16 グループのうち消化器内視鏡グループを除く 15 グループから）、外部委員 4 名と、オブザーバー約 150 名で構成されている。

小委員会では対面＋オンラインのハイブリッド形式により会合を開催し、講師を招いた特別講演（勉強会）のほか、後述する高額医療の調査研究、JCOG 臨床試験ポリシー策定などを行っている。

会合の日付と講師（敬称略）を列挙する。アカデミアのみならず、エコノミスト、製薬企業、看護師、メディア、規制当局など様々な方からそれぞれの立場でご講演いただいた。

第一回　2022.06.18 講師：西澤和彦（日本総研調査部）

第二回　2022.09.10 講師：五十嵐中（横浜市立大学薬学部）

第三回　2023.01.07 講師：上杉素直（日本経済新聞政策報道ユニット）
第四回　2023.03.25 講師：河本光博（財務省主税局調査課）
第五回　2023.06.24 講師：白沢博満（MSD 株式会社）
第六回　2023.09.30 講師：祖父江由紀子（東邦大学大森病院）
第七回　2024.01.20 講師：成瀬道紀（日本総研調査部）
第八回　2024.04.20 講師：白岩健（国立保健医療科学院）
第九回　2024.11.02 講師：森田智視（京都大学医学部医学統計生物情報学）

4-1-2.JCOG 観察研究

内科の高額薬の登場ほど派手ではないが、癌の手術治療も技術的に進歩し、低侵襲で患者の高齢化にも対応できるようになった。ただしこれはあくまで短期的な、すなわち「さしあたり重大な合併症なく、退院できる」ところまでのことである。また、一般的には 5 年生存を持ってその癌は「治った」と判断するのが通常であるが、本当にそれでいいのか、5 年以降はどうなっているのかの裏付けはなく、「5 年生存率」はあくまで慣習的な指標とされているにすぎない。

ところが長期的にそうした（「上手くいった」）患者がどうなっていくのか、長期の生命予後および機能的予後はどうであるのかを検討した研究は驚くほど少ない。直接的に医療費削減につながるわけではないが、患者が「生きていく」以上はそれ以降も医療資源を使うわけであるので、それに見合った日常生活活動度（Activities of daily living, ADL）や生活の質（Quality of life, QOL）を保っているのか、長期的な転帰も含めて把握していくことは非常に重要である。

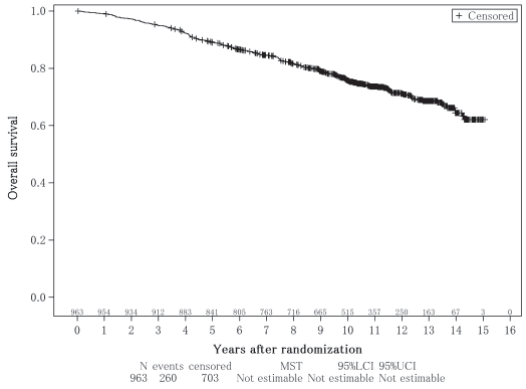
従来の臨床試験データを補完する意味でも、SCP は JCOG の研究組織や既存の臨床試験データを利用して、こうした問題を検討していった。3-1.に掲げる表の「『癌が治った』成人の『その後』を調査する」および「癌治療を行った高齢者の生活を調査する」に該当する。

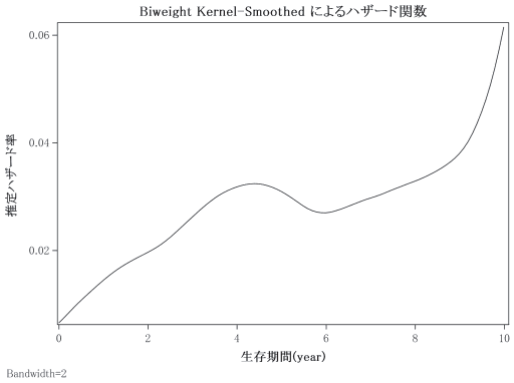
4-1-2-1.JCOG0707A 1 （早期肺癌切除後の長期的転帰に関する観察研究）

本研究は、JCOG0707「病理病期 I 期非小細胞肺癌完全切除例に対する術後化学療法の臨床第 III 相試験」[8)]の附随研究である。本研究では、リンパ節転移はないが一定以上の腫瘍径を有する肺癌（すなわち、進行癌とは言えないが、厳密な意味では早期癌の範疇にも入らないもの）に対する術後化学療法の比較を行ったが、従来の薬剤である UFT に比べ新規薬剤の TS 1 の優越性は示せなかった。両群の 5 年生存割合は 89%であった。

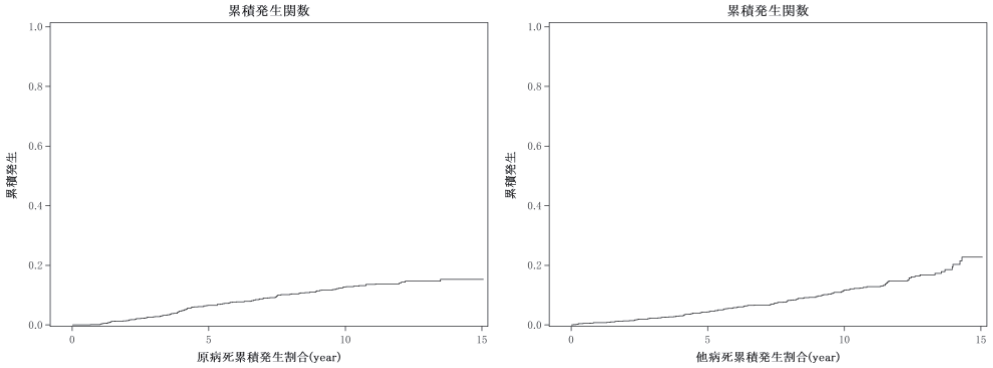
5 年生存をもって「癌が治った」と考えるのであれば、生存曲線は 5 年以降はプラトーに達するはずであるが、実際には 5 年以降も同じように下がり続け、8 年生存割合は

81.5%、10 年生存割合は 75.6%である。（下図左）また、死亡ハザードは、4〜6 年時点でいったんやや下がるが、それ以降は再上昇していく（下図右）。





この原因としては、遅発再発による原病死と、二次癌を含む他病死の双方が関与している可能性がある。術後 5 年以降のデータを解析してみると、原病死に関する推定累積発生関数は、従来想定されていた「5 年で頭打ち（プラトーに達する）」とは異なり、ほぼ一直線状に増加し、10 年を過ぎてやっと鈍化した（下図左）。一方、他病死に関する推定累積発生関数は、予想通り増加を続け、10 年以降に加速している（下図右）。



ハザード関数は 10 年を過ぎてはじめて他病死が上回り、こうした比較的早期の肺癌術後では、原病再発が予後に与える影響が予想以上に大きいことがわかった。

一方、二次癌発生については、肺癌と肺癌以外に分けると、肺の二次癌累積発生割合は、登録後 5/8/10 年で 6.1%/9.8%/10.9%で、多変量解析で非腺癌（HR 1.59, p=0.05）が関連因子となった。一方で肺以外の二次がん累積発生割合は、登録後 5/8/10 年で 7.9%/11.5%/13.9%で、多変量解析で喫煙歴あり（HR 2.23, p<0.01）のみが有意な関連因子となった。

従来は、喫煙者に対して「二次肺癌の発生のリスクを考え、検診を推奨する」という考え方が主流であったが、データからは必ずしもそうではなく、非喫煙者も二次肺癌の発生が十分あり、むしろ喫煙者は肺以外の二次癌の発生に注意を払う必要があると示唆された。

これらの知見は、「肺癌を手術して治った」患者の「その後」に対し、どう医療資源を分配していくかを考える上で貴重な示唆を与える。

4-1-2-2.JCOG1710A（高齢者肺癌手術例に対する ADL の転帰を評価する前向き観察研究）[9)]

本試験は、既知の評価項目では測定されていなかった術後の患者の生活機能の「質」を、高齢者機能評価ツールを用いて評価し、術後に ADL が高度に低下する患者の絶対数およびその要因を特定することを目的とする前向き観察研究である。本試験では 75 歳以上の非小細胞肺癌手術患者を対象として、老研式活動能力指標（老研式 IADL：下表）を術前後で評価し、術後 6 か月時点で老研式 IADL の非悪化割合（3 点以上悪化しなかった割合）を主な評価項目とした。

表　老研式活動能力指標

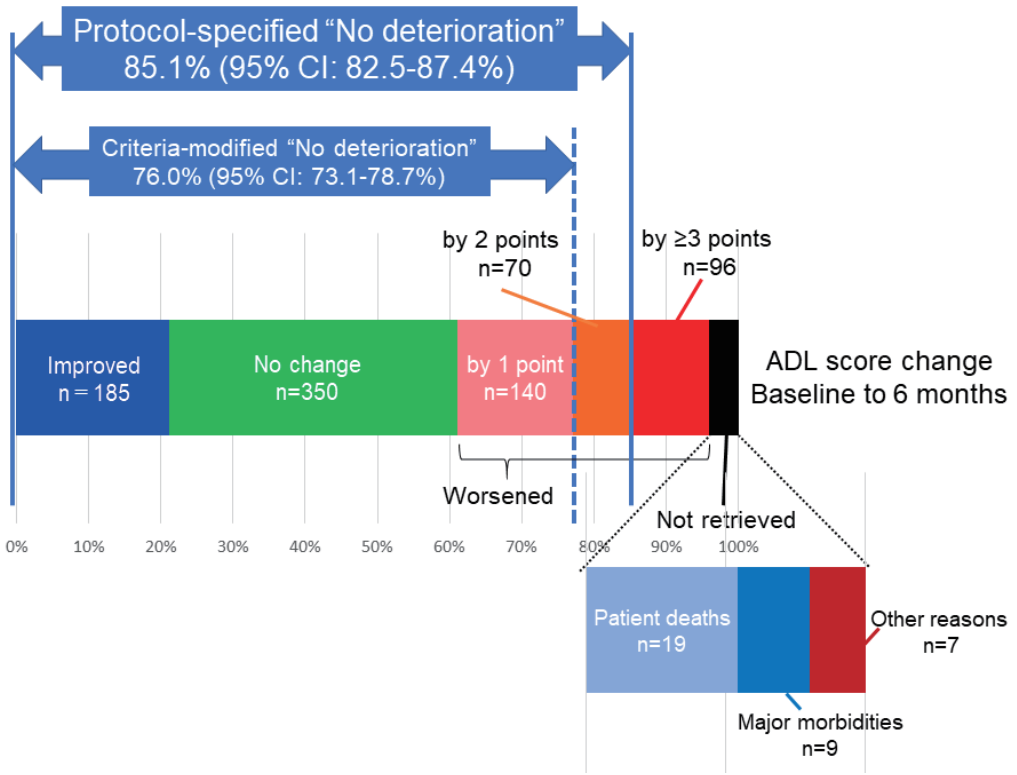
	質問	1	0	1 か 0 を記入
1	バスや電車を使って 1 人で外出できますか	はい	いいえ	
2	日用品の買い物ができますか	はい	いいえ	
3	自分で食事の用意ができますか	はい	いいえ	
4	請求書の支払いができますか	はい	いいえ	
5	銀行預金・郵便貯金の出し入れが自分でできますか	はい	いいえ	
6	年金などの書類がかけますか	はい	いいえ	
7	新聞を読んでいますか	はい	いいえ	
8	本や雑誌を読んでいますか	はい	いいえ	
9	健康についての記事や番組に関心がありますか	はい	いいえ	
10	友だちの家を訪ねることがありますか	はい	いいえ	
11	家族や友だちの相談にのることがありますか	はい	いいえ	
12	病人を見舞うことができますか	はい	いいえ	
13	若い人に自分から話しかけることがありますか	はい	いいえ	
		合計得点		点

我が国では高齢者肺癌手術例は実数、全手術例に占める割合ともに増加傾向にある。高齢者肺癌手術例に対する後方視的な検討は多数なされているが、いずれも術後の生存率／再発率や術後早期の合併症発生率／術後死亡率、およびそれらの予測因子を検討したものである。言わば「手術を乗り切れるか、命が助かるか」の検討であり、「助かった命でどのような生活が送れるか」の検討はされていない。高齢患者では、生命予後以上に「手術は無事終了したとしても、術後に元のような生活ができるのか」が関心事であることは日

常診療の経験から推測されるが、術後の ADL 低下を予測して情報を患者に還元する根拠となるデータは存在せず、本研究は極めてユニークなものである。

結果として、術後半年時点でこの老研式 IADL が 3 点以上悪化せず、「ADL が保たれた」とみなせた患者は 85.1%であった（下図）。

※3 点以上のスコア悪化（96 名）もしくは術後スコアの取得不能（35 名：何らかの ADL 低下の結果と考える）を除いた 85.1%が「ADL が保たれた」とみなせる患者

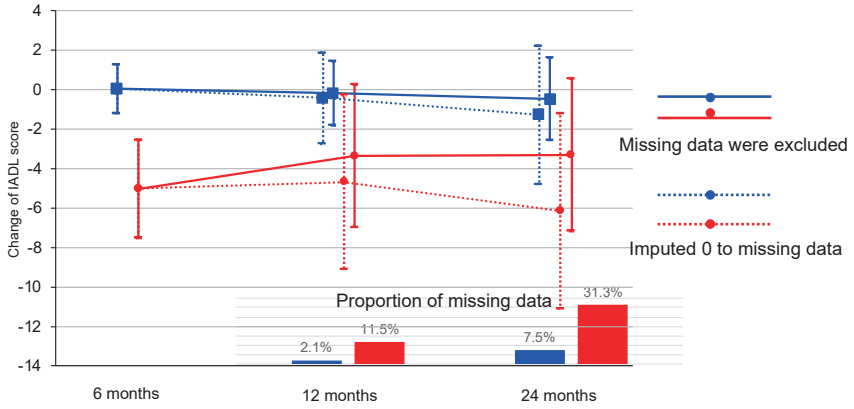


術前の PS 不良、G 8 スコア不良および区域切除（部分切除に比べ）などが ADL 低下の予測因子であった。ただし、2 年までのフォローでは、縮小手術である部分切除は腫瘍再発による ADL 低下の影響があり、区域切除に「追いつかれて」しまっている。

悪化の要素としては、上記の IADL 表のうちスコア 10～13 の社会的要素がもっとも大きく、高齢者の術後 ADL を保つためには「社会的に引きこもらないこと」が重要だと考えられた。

2 年時点の長期成績では、やはり腫瘍再発（およびデータ欠損を「ADL 低下」とカウントする研究規定）の影響があり ADL が保たれた割合は 73.6%と低下するが、6 ヶ月時点で ADL が保たれている症例ではその後の低下はなく、また 6 ヶ月時点で ADL が悪化した症例でも一部はその後の改善が見られる（右頁図）。

欠損値を除外した解析（実線）では、6 ヶ月時点で ADL 悪化のあった症例（青線）もなかった症例（赤線）も、それ以降はさらなる ADL 悪化はみられない。



なお、6 ヶ月時点の ADL 低下と QOL 悪化には相関関係はなかった。このことから、一般に QOL と ADL は同一のものと考えられているが、実際には異なる側面を見ていて、別個に評価すべきものであると示唆される。

本研究ではさらに、患者の介護度についても調査しているが、介護度の悪化（重症化）はほとんど見られず、少なくとも肺癌については、機能予後的な観点からも、本邦の外科医は正しい症例選択と適切な治療を行なっていると言える。ただし上記のごとく「社会的な活動を保つ」ことが重要な課題と考えられる。

4-1-3.JCOG 介入試験支援

臨床研究からコストの軽減を図り、もって Value = Benefit / (Toxicity + Cost)の向上を目指すには、直接的には介入試験で value の改善（コストの軽減、ベネフィットの維持）を示さねばならない。コストはまた Cost = Price ✕ Volume すなわち薬価と使用量の積として表される。アメリカでは薬価が高いことがコスト上昇の主因とされているが、日本の「高額薬」の値段は欧州諸国と同程度で、薬価引き下げによるコスト削減には限界がある。また、臨床試験では薬価を操作することはできない。

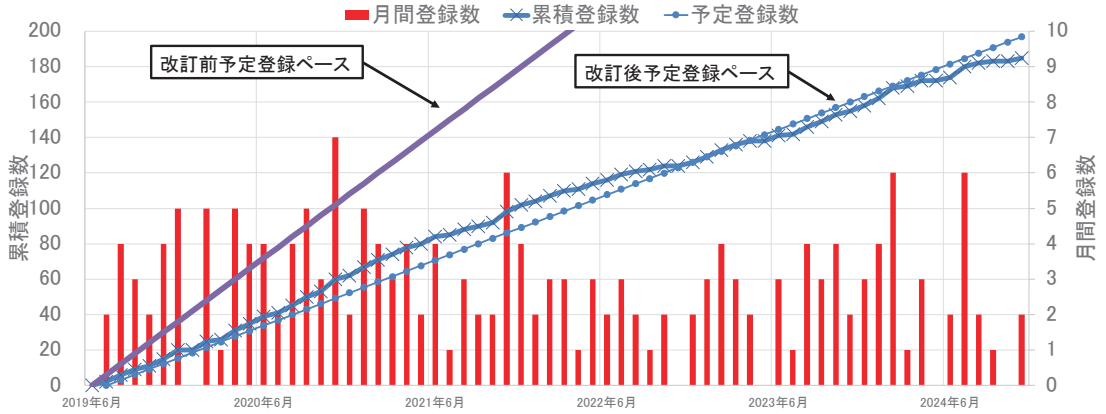
一方で、最近の免疫チェックポイント阻害剤（ICI）や分子標的薬剤（TKI など）は、至適な用量設定がされていないという批判がなされている。これは主に、一時代前の殺細胞性抗癌剤の用量設定（最大耐用量まで上げる）を踏襲していることに起因すると指摘されている。その結果、多くの薬剤は過量投与になっており、これを最適化することにより効果を損ねることなく毒性とコストの削減が期待できる。

このような optimization（最適化）研究、もしくは de-escalation（軽減化）研究と呼ばれるものには、投与量を減量する・投与間隔をあける・投与期間を短縮するなどいくつかの方法がある。SCP 発足当時に、JCOG ではこのうち「投与期間短縮」の比較試験がすでに開始されていて、SCP ではこれらの研究について支援を行った。

4-1-3-1.JCOG1701：SAVE study（非小細胞肺癌に対する PD-1 経路阻害剤の継続と休止に関するランダム化比較第 III 相試験）[10)]

本研究は、進行・再発非小細胞肺癌（NSCLC）患者を対象に、PD-1 経路阻害薬（ニボルマブ、ペムブロリズマブ、アテゾリズマブ）の継続と休止の有効性を比較するランダム化比較第 III 相試験である。52 週以上投与され進行が認められない患者を対象に、治療を休止する群と継続する群に割り付け、全生存期間（OS）を主要評価項目とし、副次評価項目として無増悪生存期間（PFS）、治療戦略有効期間（TFS）などを設定した。本試験では、有害事象の軽減や患者の通院負担および医療コスト削減を目的とし、休薬した患者も病気が悪化したときには再開する規準を設定することで安全性と効果の両立を図った。予定登録患者数は 172 人であり、登録期間は 5.5 年、追跡期間は 3 年で計画された。

2019 年 5 月に開始したが、登録が遅れたために、登録期間を延長するプロトコール改訂などを行った。最終的に 186 人が登録され、試験は 2024 年 11 月に登録を終了した。追跡期間は 3 年間を予定しており、結果は 2026 年頃に公表される見込みである。



ちなみに仮説が検証された時の経済学的意義の試算をする。

対象となる非小細胞肺癌症例は約 4 万人（年間の肺癌症例数 12 万人、死亡数 8 万人から推定）、うち 1 年時点で治療有効なのは 30%程度で 12,000 人この時点で治療を休止し、40%ではそのまま投与せずに終了、残り 60%は再発し 8 ヶ月程度の再投与をすると仮定（継続した場合と生存期間は同じ）。継続した場合に比べ投与量は 40%+60%*4/12＝60%減少する。免疫チェックポイント阻害剤は各種あるが、最も安価（2024 年時点）なペムブロリズマブ（キイトルーダ ）を使ったとして、一回 42 万円を 3 週に 1 回なので週 14 万円*52 週*60%で一人当たり 437 万円の節約、年間で約 520 億円の節約となる。

一方で、試験遂行による節約効果もあり、90 人の患者で上記の休止（再発したら再投与）を行うので、この研究を行うことにより 437 万円✕90 人で、約 3 億 9000 万円の節約となる。

※附随研究 JCOG1701A1（PD-1 経路阻害薬の休薬に関する血液検体による効果予測因子および予後因子に関する探索的研究）

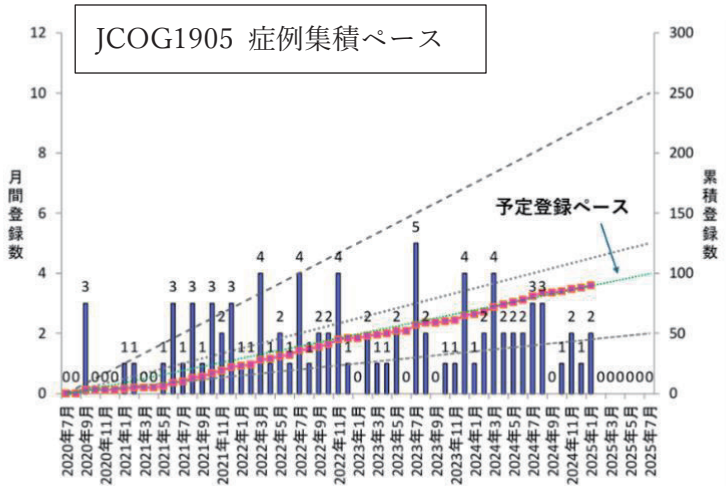
こちらは、JCOG1701 に附随する探索的研究である。本研究では、非小細胞肺癌の治療における PD-1 経路阻害薬の効果予測因子を血液試料や腫瘍組織を用いて調査する。具体的には、①血中循環腫瘍 DNA（ctDNA）、②免疫チェックポイント阻害薬の血中濃度、③これらに対する抗体の有無や量を調査し、腫瘍組織や正常 DNA と比較解析を行うことで、治療効果や再発リスクを予測可能なバイオマーカーを探索することを目的とする。特に、治療効果の目安となり継続の可否の判断に最も重要と考えられる ctDNA の解析については、Guardant Health Inc.との共同研究により実施され、解析費用の一部は SCP を通して本調査事業の研究費により負担された。本研究には合計で 83 人が登録されている。

4-1-3-2.JCOG1905：STOP study（進行性腎細胞癌に対する PD-1 経路阻害剤の継続と休止に関するランダム化比較第 III 相試験、https://jcog.jp/document/1905.pdf）

本研究は、進行性腎細胞癌患者を対象に、PD-1 経路阻害薬（ニボルマブ、ペムブロリズマブ、アベルマブ）の継続と休止の有効性を比較するランダム化比較第 III 相試験である。PD-1 経路阻害薬を 48 週以上投与され、病勢進行が認められない患者を、治療を継続する群と休止する群にランダムに割り付け、主要評価項目として全生存期間（OS）を設定した。副次評価項目には、無増悪生存期間（PFS）や治療戦略有効期間（TFS）などを含めた。本試験では、休止群が継続群と比較して非劣性であることを示し、休止群において有害事象の軽減や医療コスト削減といったベネフィットを得ながらも、十分な治療効果を維持できることを明らかにすることを目的とする。また、休止群に割り付けられた患者に対しては、病勢が進行した場合に治療を再開する規準を設定し、安全性を確保している。予定登録患者数は 100 人であり、登録期間は 5 年、追跡期間は 4 年である。

進捗状況

本研究は 2020 年 7 月に開始されたが、患者登録の進捗が遅れたため、予定登録患者数を 250 人から 100 人に変更するプロトコール改訂を実施した。2025 年 1 月末時点で 90 人が登録されており、2025 年 7 月 19 日までに患者登録を終了する予定である。その後、4 年間の追跡期間と 1 年間の解析期間を経て、2030 年に結果が公表される見込みである。



※附随研究 JCOG1905A1（PD-L 1 経路阻害剤の休薬に関する血液検体による効果予測因子および予後因子に関する探索的研究）

こちらは、JCOG1905 に附随する探索的研究であり、進行性腎細胞癌の治療における PD-1 経路阻害薬の効果予測因子を血液試料や腫瘍組織を用いて調査することを目的としている。具体的には、①末梢血中の CD8 陽性 T 細胞表面における PD-1 経路阻害薬の結合割合、②末梢血および腫瘍微小環境における免疫細胞の解析、③血中循環腫瘍 DNA（ctDNA）の解析を行い、治療効果や再発リスクの予測因子となるバイオマーカーの探索を目指す。解析費用の一部は SCP を通して本調査事業の研究費により負担された。本附随研究には、2025 年 1 月末までに 36 人が登録されている。

4-1-4.高額医療の調査研究

JCOG 医療経済小委員会では、まず高額薬使用の実態調査として、進行癌の初回治療に現場では実際にどういう治療レジメン（薬剤の作用機序別の分類ではなく、具体的な薬剤名まで挙げて）が使用されているかその頻度を調べ、検討することとした。

各レジメンの治療費用（薬価のみ）を計算し、グループ間・疾患間での比較のために月当たりの費用を算出する。効果（特に高額の分子標的薬剤や免疫チェックポイント阻害剤が出現する以前の標準だった「化学療法」との比較で）については文献的な報告を加える。もし同効でコストが違うものがあれば特に注目する。さらに、高齢者（75 歳以上）と非高齢者（75 歳未満）に分けて集計することとした。

調査期間は 2021 年 7 月～2022 年 6 月（一部でずれても可、だが、基本的に 1 年間）であり、JCOG16 グループのうち 9 グループ（肺がん内科・胃がん・乳がん・婦人科腫瘍・大腸がん・泌尿器科腫瘍・脳腫瘍・肝胆膵・頭頸部がん）が参加、治癒が望めない進行癌

で、網羅的ではなく各領域の代表的な（比較的頻度の多い）疾患に対しての初回治療内容を、Google フォームを使って各施設から集計してもらった。合計 17 疾患（同じ「肺癌」でも、小細胞癌と非小細胞癌、また EGFR 変異陽性とドラーバー遺伝子陰性などは全て別々の「疾患」とカウントする）についてデータが集計された。参加した施設はのべ 442 施設、患者数は 15,564 人でうち 29%が高齢者であった。

各グループ別に集計された 9 論文[11)-19)]の概略を、順次記載する。いずれも、各論文の要約（abstract）の日本語訳を最初に、続いて特徴的なもしくは重要と思われるデータを記載していく。

図中の略語
JCOG：日本臨床腫瘍研究グループ
OS：全生存期間
mOS：median OS,生存期間中央値
PFS：無増悪生存期間
HR：ハザード比
IO：免疫治療薬（ICI を含む）
ICI：免疫チェックポイント阻害剤（高分子の免疫治療抗体製剤）
TKI：チロシンキナーゼ阻害剤（低分子の分子標的薬剤）
VEGF：血管内皮増殖因子（血管新生阻害治療の標的）
EGFR：上皮性増殖因子（大腸癌・肺癌などの一部での治療標的）

1. 泌尿器科腫瘍 https://doi.org/10.1093/jjco/hyae045

進行前立腺癌と腎細胞癌患者の実地治療の趨勢およびそのコスト：日本での調査

背景

進行した（ステージ 4）前立腺癌および腎細胞癌の予後は不良である。いくつかの治療が開発されたが、非常にコストが高い。この研究では、ステージ 4 の前立腺癌および腎細胞癌未治療例に対して使われる薬物療法を調査し、その月あたりコストを計算した。

方法

2022 年 4 月から 2023 年 9 月の期間に、日本臨床腫瘍研究グループ参加施設で未治療の前立腺癌および腎細胞癌に対して初回治療に使われた薬剤を調査した。薬剤コストは 28 日あたりで算出された。

結果

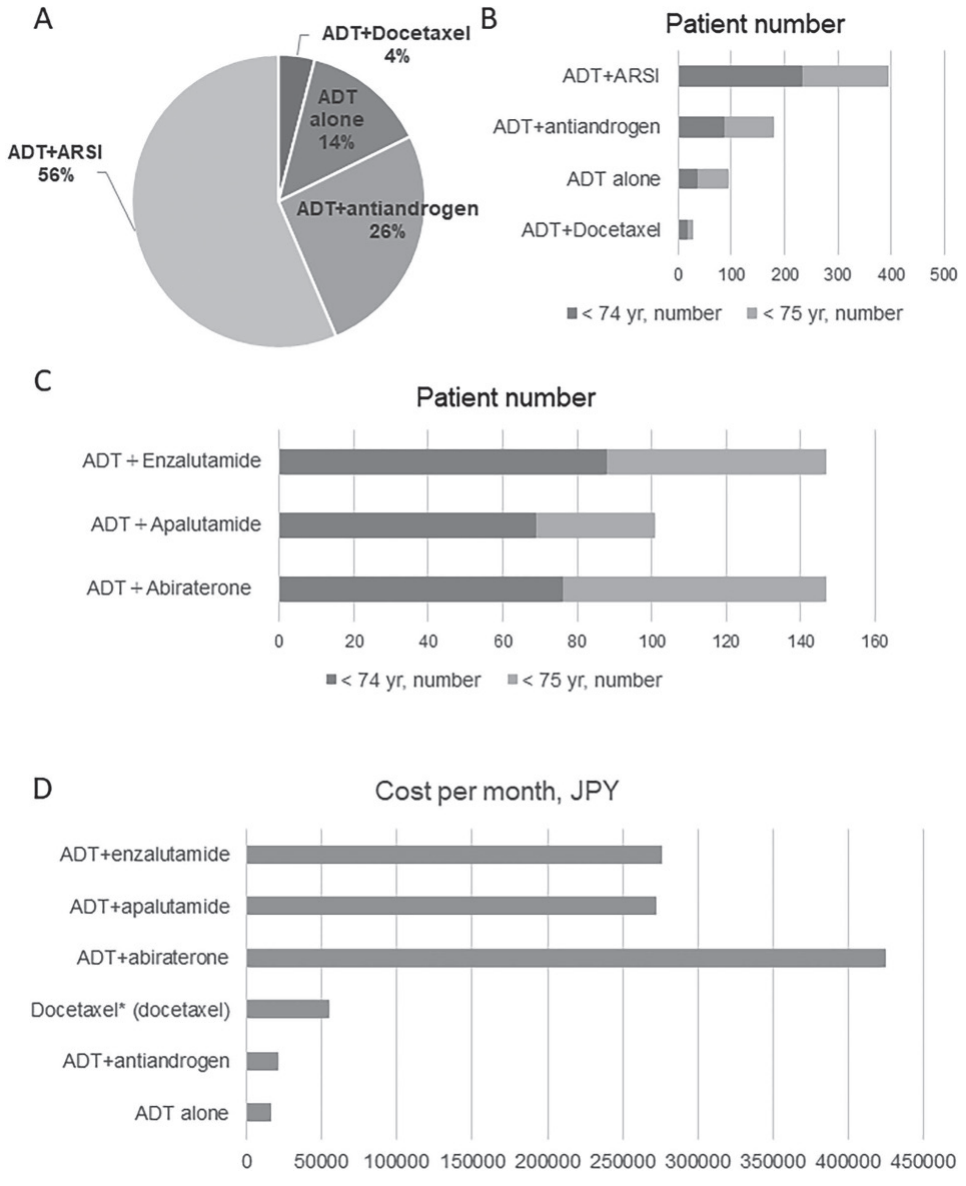
700 人のステージ 4 未治療前立腺癌症例の調査では、男性ホルモン抑制療法と男性ホルモン受容体シグナル阻害剤の併用療法がもっとも多く使われていた（56%）。この併用療法は従来の治療に比べ 10.6 倍から 30.8 倍のコストがかかった。137 人のステージ 4 未治療腎細胞癌症例の調査では、91%で免疫療法剤をベースにした治療が行われていた。全ての患者で月あたりの治療コストは 50 万円以上、また 80.4%の患者で月あたりの治療コストが 100 万円以上だった。免疫療法剤をベースにした併用治療では、チロシンキナーゼ阻害剤単独（國頭註：従来の治療法）に比べコストは 1.2 倍から 3.1 倍だった。

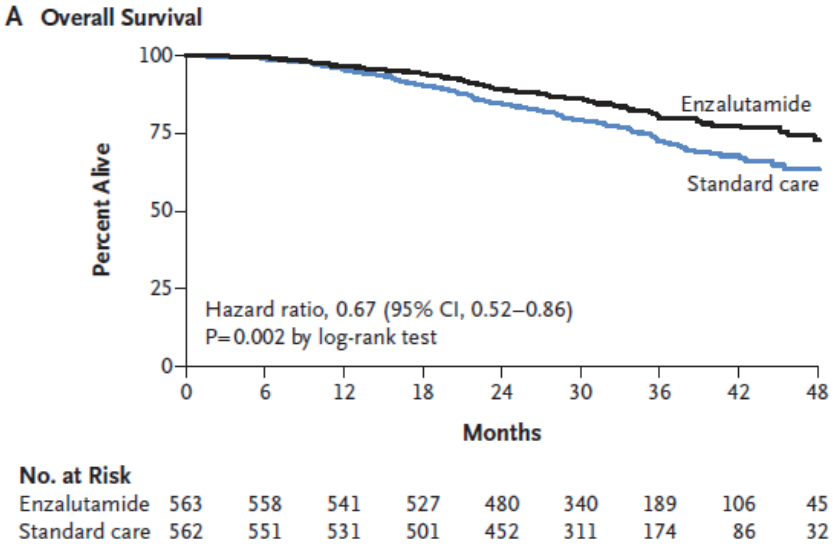
結語

我々の知る限り、これはステージ4の未治療前立腺癌および腎細胞癌に対し、年齢とコストで層別した最初の報告である。我々の結果は、日本の患者の大多数は最新の有効な治療法を受けていて、財政的な負荷は高いことを示している。

前立腺癌
A＆B：治療別の患者数（治療頻度）
C：ARSI の中での各薬剤別の治療頻度
D：薬価

ADT:アンドロジェン（男性ホルモン）抑制療法
ARSI：アンドロジェン（男性ホルモン）受容体シグナル阻害剤

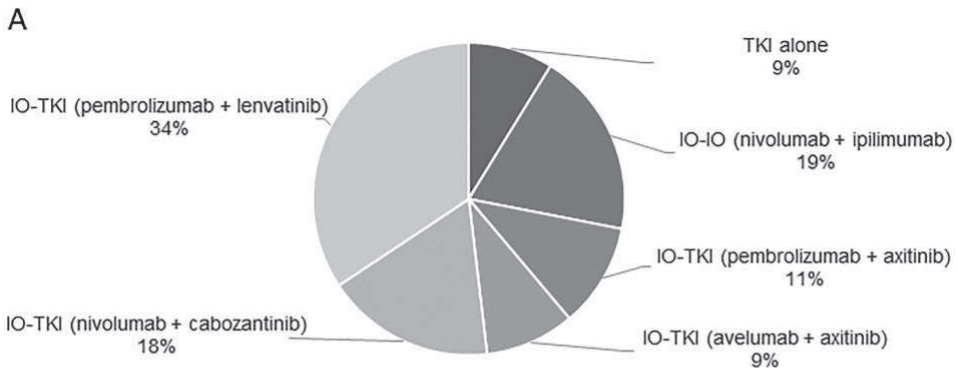


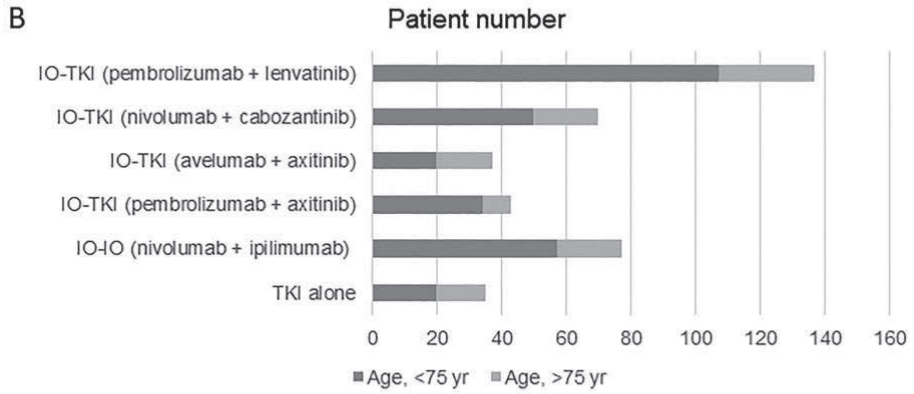


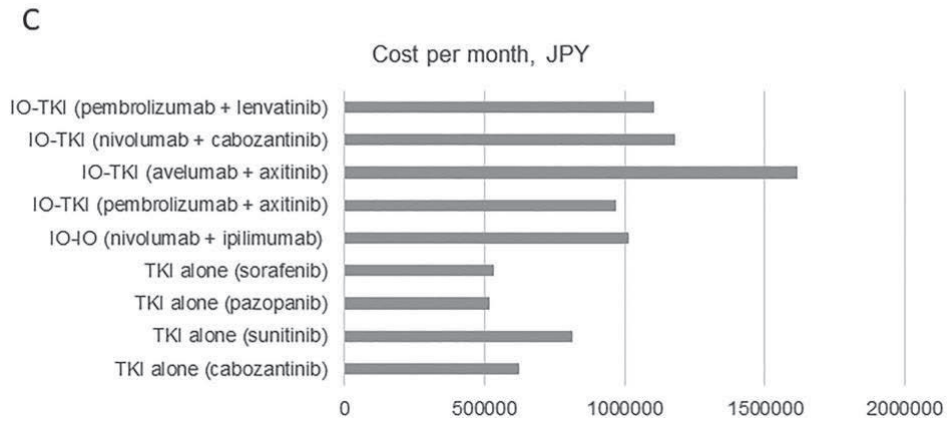
アンドロジェン（男性ホルモン）受容体シグナル阻害剤の治療効果

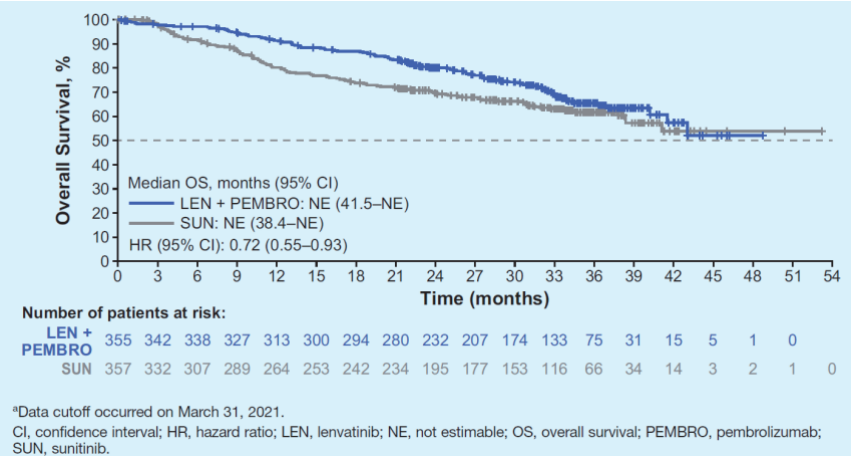
腎癌

A&B：治療患者数（薬剤使用頻度）
C：薬価









TLI+IO 併用療法（LEN+PEMBRO）と TKI 単独（SUN）との治療効果の差、全生存期間

2. 肝細胞癌 https://doi.org/10.1093/jjco/hyae048

2021-22 年における日本での進行肝細胞癌に対する初回全身治療のコスト負荷の現状

背景

進行肝細胞癌に対する最近の全身治療の進歩は患者の生存期間延長に寄与しているが、高い薬価は患者および社会への重い負担となっている。本研究は、日本における進行肝細胞癌患者に対する初回全身治療内容を調査し、治療によるコストを概算することを目的とする。

方法

この研究では、我々は 2021 年 7 月から 2022 年 6 月の間に進行肝細胞癌で初回全身治療を受けた患者のデータを集積した。それぞれの治療の月あたりのコストは通常の用法で体重 60kg の男性が受けたものと仮定して算出した。データは治療内容ごとに、非常に高いコスト（100 万円/月以上）、高いコスト（50 万円/月以上）、およびそのほか（50 万円/月未満）に分類した。

結果

24 施設から集められた 552 例の患者のデータが解析され、439 例（79.5%）がアテゾリズマブとベバシズマブ併用、98 例（17.8%）がレンバチニブ、15 例（2.7%）がソラフェニブでの初回治療を受けた。上記治療の初回治療の月あたりコストは次の通り；アテゾリズマブとベバシズマブ併用は 1,176,284 円、レンバチニブは 362,295 円、ソラフェニブは 571,644 円。合計で 82.2%が「高いコスト」の治療を受け、その多くは「非常に高いコスト」のアテゾリズマブとベバシズマブ併用を受けていた。

結語

進行肝細胞癌に対する全身治療の進歩は患者の生存期間延長に寄与したが、治療コストも増加し、患者と社会双方への負担となっている。

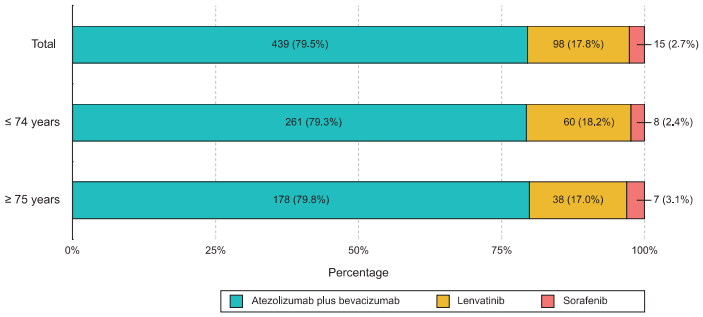
今後の趨勢：同効同種で効果も低いのにコストは上がる？

現在の治療内容（薬剤治療頻度）

Table 1. Results of pivotal studies for advanced HCC and cost in Japan

Regimen	Publication year	median OS (months)	median PFS (months)	Mean dose intensity (%)	Cost[a] (JPY)
Atezolizumab plus bevacizumab (11)	2020	19.2 (9)	6.9	95 (Atezolizumab) 93 (Bevacizumab)	1 176 284
Durvalumab plus tremelimumab (13)	2022	16.43	3.78	not reported	3 806 181 (first month) 1 329 232 (after the first month)
Durvalumab (13)	2022	16.56	3.65	not reported	1 329 232
Lenvatinib (10)	2018	13.6	7.4	88	362 295
Sorafenib (9)	2008	10.7	5.5[b]	84 (12)	571 644

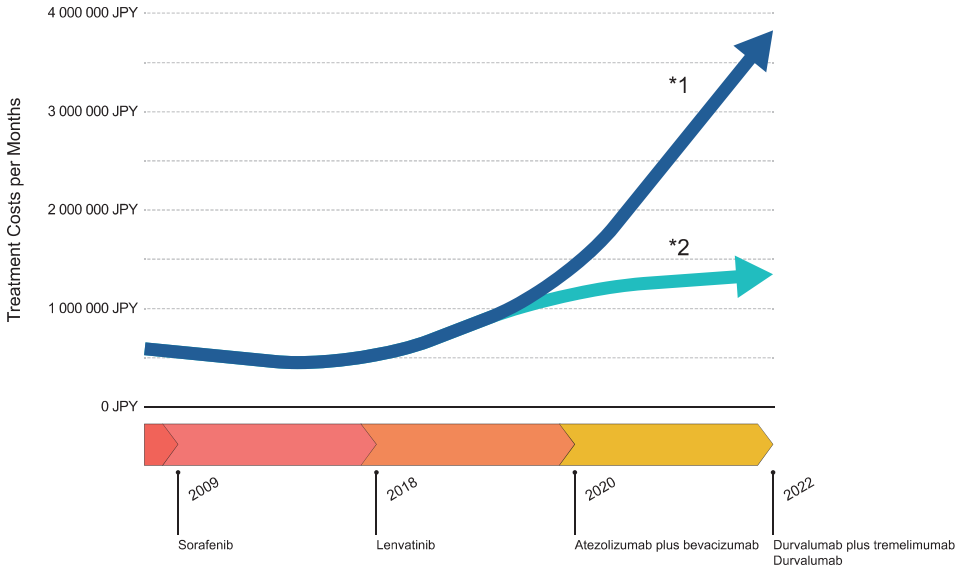
OS, overall survival; PFS, progression-free survival; JPY, Japanese yen. [a]The costs were calculated as the cost for body weight (60 kg) per month (30 days). [b]Time to radiologic progression.



コストの予想：

*1：新しい Durvalumab+Tremelimumab 療法が広く採用された場合

*2：現在の治療内容が主流であり続ける場合



3. 婦人科腫瘍 https://doi.org/10.1093/jjco/hyae089

婦人科悪性腫瘍に対する化学療法の高いコスト

背景

婦人科悪性腫瘍の予後は、最近の分子標的薬剤と免疫チェックポイント阻害剤の出現によって改善した。しかしながら、これらの薬剤は高価であり、医療コストの増大につながっている。

方法

日本臨床腫瘍研究グループ（JCOG）医療経済委員会は、参加施設に対してアンケートを行い、2021 年 7 月から 2022 年 6 月までの高額治療の使用頻度を調査した。

結果

進行卵巣癌と子宮頸癌に対する標準治療について 57 施設が調査対象となり、卵巣癌については 39 施設（68.4%）の 854 例、子宮頸癌については 37 施設（64.9%）の 163 例について回答があった。卵巣癌に関しては、854 例中 505 例（59.1%）の患者が、月あたりコスト 50 万円以上である PAPR 阻害剤を含む治療を、また 111 例（130%）が月あたりコスト 20 万円以上であるベバシズマブを含む治療を受けていた。これらのコストは、従来の治療のそれのそれぞれ約 20 倍および 10 倍に相当する。子宮頸癌では、79 例（48.4%）が月あたりコスト 20 万円以上であるベバシズマブを含む治療を受け、このコストは、従来の治療のそれの約 10 倍であった。

結語

この調査では、70%以上の卵巣癌患者が PAPR 阻害剤またはベバシズマブを含む治療を受け、約 50%の子宮頸癌患者がベバシズマブを含む治療を受けていた。これらの治療は、従来の治療の約 10 倍から 20 倍のコストがかかる。これらの知見は、将来の医療経済研究、特に費用対効果とその関連事項に有用な情報を与える。

卵巣癌治療での費用対効果

治療頻度、コストおよび（文献的）生存率

Niraparib/Olaparib が PARP 阻害剤（遺伝子修復酵素阻害剤）
TC は通常の化学療法
Bev は血管新生阻害抗体剤 bevacizumab

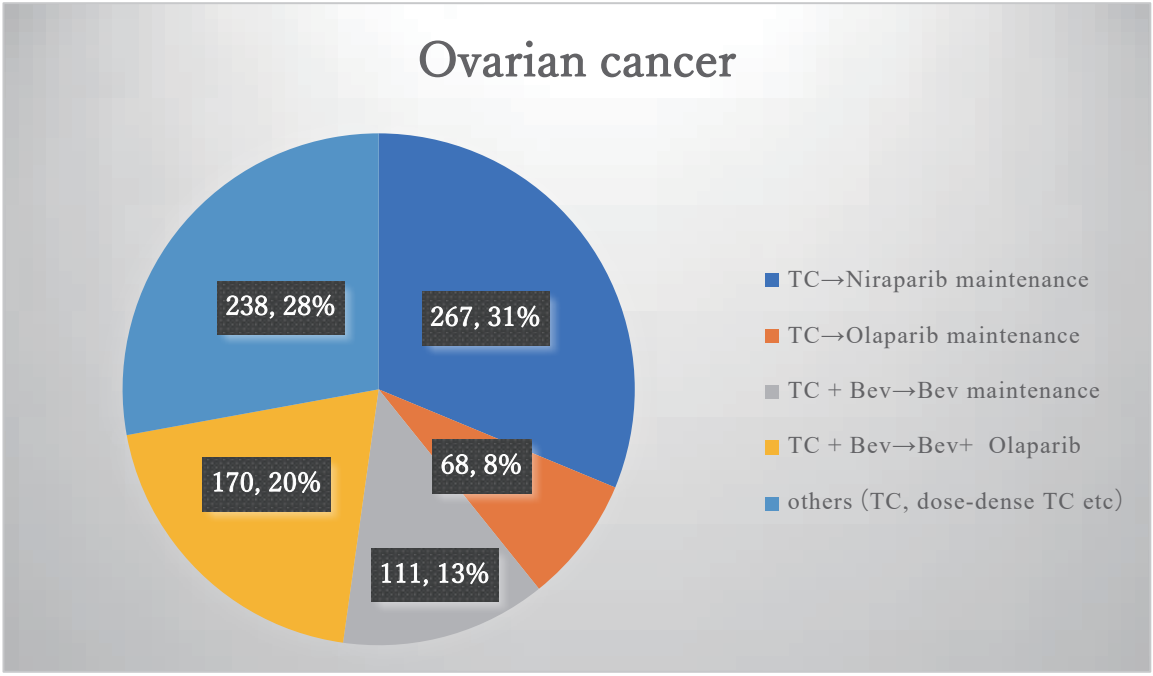
Treatment	Age, <75 yr	Age, >75 yr	Total	Cost per month, JPY
TC→Niraparib maintenance	231 (27%)	36 (4%)	267 (31%)	27,561→558,960
TC→Olaparib maintenance	64 (7.5%)	4 (0.5%)	68 (8%)	27,561→574,560
TC + Bev→Bev maintenance	89 (10.5%)	22 (2.5%)	111 (13%)	264,222→236,661
TC + Bev→Bev + Olaparib maintenance	158 (18.5%)	12 (1.5%)	170 (20%)	264,222→811,221
TC	n/s	n/s	n/s	27,561

2 年生存率：84%対 77%（プラセボ）

3 年生存率：84%対 80%（プラセボ）

生存中央値：39.7m%対 39.3m（プラセボ）

TC, paclitaxel + carboplatin; Bev, Bevacizumab; JPY, Japanese yen; n/s not surveyed



選択された治療内容の頻度

4. 肺癌 https://doi.org/10.1093/jjco/hyae094

日本における進行肺癌に対する高額治療（日本臨床腫瘍研究グループ肺癌内科グループ研究）

緒言

肺癌治療はこの 10 年で飛躍的進歩を遂げたが、高い薬価のため、薬物治療コストは爆発的に上昇した。現在までに、日本でどういう治療がどの程度使われ、合計のコストがどれほどか、についてのデータはない。

方法

日本臨床腫瘍研究グループの肺癌内科グループ研究に属する 60 施設に対して、2021 年 7 月から 2022 年 6 月までの間に、日常臨床で進行肺癌に対して行われた初回治療の情報を収集した。ドライバー遺伝子変異陰性の非小細胞肺癌、EGFR 変異陽性非小細胞肺癌、進展型小細胞肺癌の 3 つの腫瘍タイプについて調査された。

結果

免疫チェックポイント阻害剤もしくは免疫チェックポイント阻害剤と化学療法の併用による最近の治療のコストは、従来の化学療法に比べ 20 から 55 倍高かった。遺伝子変異陰性の非小細胞肺癌患者 3738 人中 2573 人（68.8%）において、月当たりのコストは 50 万円以上であった。2555 人（68.4%）が免疫チェックポイント阻害剤を受けていた。EGFR 変異陽性非小細胞肺癌患者 1486 人中 1290 人（86.8%）において、月当たりのコストは 50 万円以上であった。1207 人（81.2%）がオシメルチニブを投与されていた。進展型小細胞肺癌患者 1079 人のうち 607 人（56.3%）が月当たりのコスト 50 万円以上の免疫チェックポイント阻害剤治療を受けていた。高齢の非小細胞肺癌患者は、若年者に比べ高額治療を受ける割合がやや高かった。

結語

最近の治療コストは従来の化学療法の何倍もする。本研究では、進行肺癌では高額治療が広く使われ、中にははっきりしたエビデンスなしに使われるものもあった。医療者は自分たちの使う治療のコストにも注意を向けるべきである。

同効同種薬剤選択の実態

EGFR：上皮性増殖因子受容体（ここに変異があると、特異的阻害剤：TKI が有効）

EGFR遺伝子変異陽性非小細胞肺癌

レジメン	全体	74歳以下	75歳以上	PFS(m)	OS(m)	薬価
オシメルチニブ単剤	1207(77.1)	758(78.1)	449(84.2)	18.9	38.6	18540.2円/錠
ゲフィチニブ単剤	31	14	17	10.2	31.8	3288.3円/錠
エルロチニブ単剤	16	12	4	10.2	31.8	10109.2円/錠
アファチニブ単剤	81(5.2)	62	19			
ダコミチニブ単剤	1	1	0			
エルロチニブ＋ベバシズマブ	3	3	0			
エルロチニブ＋ラムシルマブ	83(5.3)	56	27			
ゲフィチニブ＋カルボプラチン＋ペメトレキセド	2	2	0			
治験	80	63	17			
その他	62					
計	1566	971+α	533+α			

オシメルチニブ単剤（80mg/錠）：1ヶ月で56.5万円，18.9ヶ月で1068.7万円/人，全員で128億円.

ゲフィチニブ単剤（250mg/錠）：1ヶ月で10万円，10.2ヶ月で102.3万円/人

8.7ヶ月のPFS延長に対して，966.5万円/人かかっている.

N Engl J Med. 2018 Jan 11;378(2):113-125.
N Engl J Med . 2020 Jan 2;382(1):41-50.

Erlotinib + Bevacizumab (447,335)	3 (0.2)	3 (0.3)	0 (0)
Erlotinib + Ramucirumab (1,264,050)	83 (5.6)	56 (6.2)	27 (5.2)

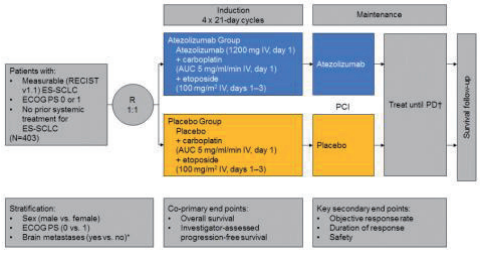
Erlotinib（TKI の一つ）は、血管新生阻害剤と併用されることがある
Bevacizumab/Ramucirumab とも同種同効だが、コストは後者がはるかに高い
しかし後者の方が好んで使われている（5.6% vs 0.2%）

ドライバー遺伝子変異/転座陰性進行・再発非小細胞肺癌

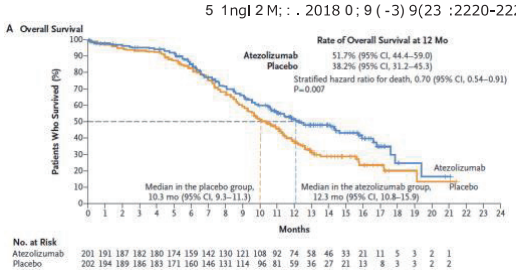
レジメン	全体	74歳以下	75歳以上	計	6週ICI薬価	PFS	OS	5yOS
ニボルマブ＋イピリムマブ	349(8.8)	176(7.1)	173(15.6)	718(18.1)	160.7万円	5.1	17.1/17.4	24/19
カルボプラチン＋ペメトレキセド＋ニボルマブ＋イピリムマブ	221(5.6)	189(7.6)	32(2.9)			6.4	15.8	NE
シスプラチン＋ペメトレキセド＋ニボルマブ＋イピリムマブ	25	24	1			6.4	15.8	NE
カルボプラチン＋パクリタキセル＋ニボルマブ＋イピリムマブ	123	102	21			6.4	15.8	NE
ペムブロリズマブ単剤	605(15.3)	297(11.9)	308(27.7)	1504(38.1)	85.8万円	7.7	26.3	31.9
カルボプラチン＋ペメトレキセド＋ペムブロリズマブ	497(12.6)	388(15.6)	109(9.8)			9.0	22.0	19.4
シスプラチン＋ペメトレキセド＋ペムブロリズマブ	81	79	2			9.0	22.0	19.4
カルボプラチン＋アブラキサン＋ペムブロリズマブ	167	116	51			8.0	17.2	18.4
カルボプラチン＋パクリタキセル＋ペムブロリズマブ	154	128	26			8.0	17.2	18.4
アテゾリズマブ単剤	24	15	9	333(8.4)	112.8万円	8.1	20.2	NE
カルボプラチン＋アブラキサン＋アテゾリズマブ	128	83	45			7.0	18.6	
カルボプラチン＋ペメトレキセド＋アテゾリズマブ	48	28	20			7.6	18.1	
シスプラチン＋ペメトレキセド＋アテゾリズマブ	6	4	2			7.6	18.1	
カルボプラチン＋パクリタキセル＋ベバシズマブ＋アテゾリズマブ	127	120	7			8.3	19.5	
カルボプラチン＋パクリタキセル＋ベバシズマブ	50	37	13	832(21.1)				
シスプラチン＋ゲムシタビン＋ネシツムマブ	18	18	0					
カルボプラチン＋ペメトレキセド	302(7.6)	212(8.5)	90(8.1)					
シスプラチン＋ペメトレキセド	43	43	0					
カルボプラチン＋アブラキサン	238(6.0)	144(5.8)	94(8.5)					
カルボプラチン＋パクリタキセル	181	127	54					
治験	214	160	54					
その他	351							
計	3952	2490＋α	1111＋α					

各種 IO と化学療法の組み合わせが乱立し、上表にあるように様々なレジメンが使用され、「多数派の患者で使われるもの」はない（最も頻度が高いペムブロリズマブ単剤でもせいぜい 15.3%）。薬価は大きく異なるが、高いもので治療効果が大きい（OS 良好）というわけでもない。

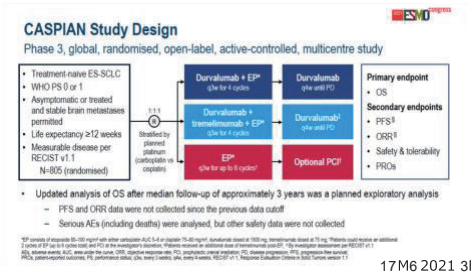
進展型小細胞肺癌



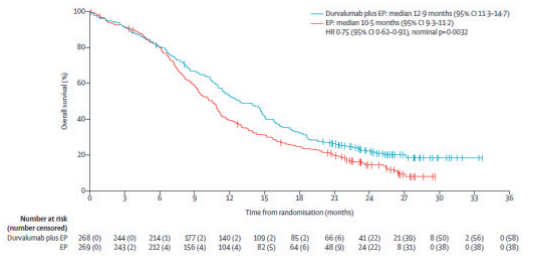
5 1ngl 2 M; : . 2018 0 ; 9 (-3) 9(23 :2220-2229.



5 1ngl 2 M; : . 2018 0 ; 9 (-3) 9(23 :2220-2229.



17M6 2021 3B. (1



38n9; t 6 n9ol. 2021 28n-22(1 :51-(5.

2 種類の ICI で治療効果は同じ

進展型小細胞肺癌

レジメン	全体	74歳以下	75歳以上	PFS(m)	OS(m)	ICI中央値	ICI薬価
カルボプラチン＋エトポシド＋アテゾリズマブ	222(18.4)	149(19.4)	73(17.2)	5.2	12.3	7	563, 917
カルボプラチン＋エトポシド＋デュルバルマブ	290(24.0)	185(24.1)	105(24.8)	5.1	12.9	7	1,240,617
シスプラチン＋エトポシド＋デュルバルマブ	95(7.9)	94(12.2)	1(0.4)	5.1	12.9	7	1,240,617
シスプラチン＋イリノテカン	8	7	1			0	
シスプラチン＋エトポシド	67	61	6			0	
カルボプラチン＋エトポシド	381(31.5)	190(24.7)	191(45.0)	4.3	10.3	0	
治験	50	40	10				
臨床試験	80	43	37				
その他	16						
計	1209	769+α	424＋α				

カルボプラチン＋エトポシド＋アテゾリズマブ：1回の投与で57.9万円，ICI7回の投与で400.6万円，全員で8億8944万円
カルボプラチン＋エトポシド＋デュルバルマブ:1回の投与で125.5万円，ICI7回の投与で874.3万円，全員で25億3558万円
シスプラチン＋エトポシド＋デュルバルマブ:1回の投与で125.8万円，ICI7回の投与で875.3万円，全員で8億3148万円
カルボプラチン＋エトポシド:1回の投与で1.3万円，4回投与で5.2万円，全員で1994万円
（70歳，身長：170cm，体重：60kg, BSA 1.7, Cr 0.8, Ccr 72.9にて計算）

PFSを約1ヶ月，OSを約2ヶ月延長するのに，アテゾリズマブで395.4万円，デュルバルマブで869.1万円かかっている.

治療効果は同じだが薬価が高い方の使用頻度が大きい

5. 乳癌 https://doi.org/10.1093/jjco/hyae109

日本の転移性乳癌診療ガイドラインで推奨されている初回治療のコスト増加の現状

背景

乳癌発生率と有病率の増加と、診断・治療技術の進歩により、癌が保険医療体制に与える財政負担が問題提起され、治療へのアクセス維持に懸念が生じている。

方法

この研究は日本臨床腫瘍研究グループ（JCOG）乳癌グループに属する 51 施設でウェブによるアンケートを用いて行われた。調査期間は 2021 年 7 月から 2022 年 6 月までである。転移性乳癌により初回治療を受けた患者を対象とした。初回治療として受けた各々の治療の割合を集計した。従来の治療との比較で、現時点での標準治療により増加したコストが計算された。

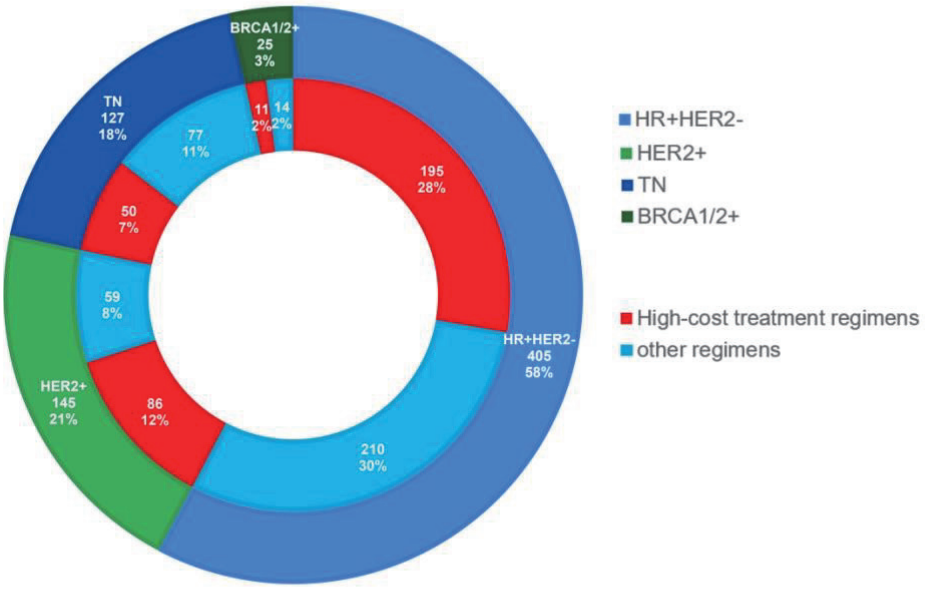
結果

合計 702 人の患者が調査された。うち 342 人（48.7%）が、推定での月あたりコスト 50 万円以上の高コスト治療を受けていた。そのうち 16 人（4.7%）は月あたりコスト 100 万円以上の超高コスト治療を受けていた。53 人の（15.5%）患者は高コスト治療を受け、かつ 75 歳以上であった。超高コスト治療を受けた高齢者が 1 人（0.3%）いた。現状使われる薬剤のうち、アベマシクリブによるコスト増加が最も顕著で、患者一人当たり 6,365,670 円かかった。二番目がパルボシクリブで 4,011,248 円、ついでアテゾリズマブで 3,209,033 円だった。

結論

これらの知見は、高コスト治療の経済的負担を評価するのに、薬価のみではなく総コストの増加を考慮する必要があると示している。

月コストも高いが治療効果が良くなるほど投与期間が延長し総コストも高くなる
HR,HER2,TN,BRCA1/2+：乳癌のサブタイプ
NSAI：ホルモン剤、CDKI：分子標的剤
上図：使用頻度、下表：コスト（月あたり＆トータルでのコスト）



Subtype	Comparator	Cost of comparator/ month	Novel treatment regimen	Cost of novel treatment regimen/month	Clinical benefit Median PFS	Incremental cost/month	Incremental cost administered for median PFS
HR+ HER2-	NSAI	6,531JPY	NSAI+CDKIs （palbociclib）	437,848JPY	9.3months gained	431,317JPY	4,011,248JPY
	NSAI	6,531JPY	NSAI+CDKIs （Abemaciclib）	481,581JPY	13.4months gained	475,050JPY	6,365,670JPY
HER2 +	Tmab+DTX	159,179JPY	Tmab+Pmab+DTX	486,093JPY	6.3months gained	326,914JPY	2,059,558JPY
TN	nab-PTX	361,485JPY	nab-PTX+ atezolizumab	1,180,586JPY	2.5months gained	819,101JPY	3,209,033JPY
	nab-PTX	361,485JPY	nab-PTX+ pembrolizumab	932,682JPY	4.1months gained	571,197JPY	2,341,908JPY
	PTX	25,635JPY	PTX+ pembrolizumab,	669,126JPY		643,491JPY	2,638,313JPY
	CBDCA+GEM	38,298JPY	CBDCA+ GEM+ pembrolizumab	681,792JPY		643,494JPY	2,638,325JPY
BRCA 1/2+	capecitabine	39,720JPY	olaparib	574,560JPY	2.8months gained	534,840JPY	1,497,552JPY
	eribulin mesylate	300,857JPY				273,703JPY	766,368JPY
	vinorelbine	24,042JPY				550,518JPY	1,541,450JPY

6. 胃癌 https://doi.org/10.1093/jjco/hyae104

日本臨床腫瘍研究グループ（JCOG）胃癌グループによる、HER2陰性の切除不能進行・再発胃癌に対する初回治療における高額薬使用の実態調査

緒言

様々な悪性腫瘍に対して、分子標的薬剤と免疫チェックポイント阻害剤が開発され、治療成績は向上した。しかしながら、これら薬剤は高価であり、日本での使用実態とコストに関する調査はほとんどない。この研究は、実臨床での進行・再発胃癌に対する初回化学療法の使用状況とそのコストを調査することを目的とする。

方法

調査は 2022 年 1 月から 2022 年 12 月の間に JCOG の 92 施設で初回治療が開始された HER2陰性の進行・再発胃癌患者を対象とした。治療内容のデータはグーグルフォームで集められた。月あたりコストが 50 万円を超す治療が「高額」と定義された。

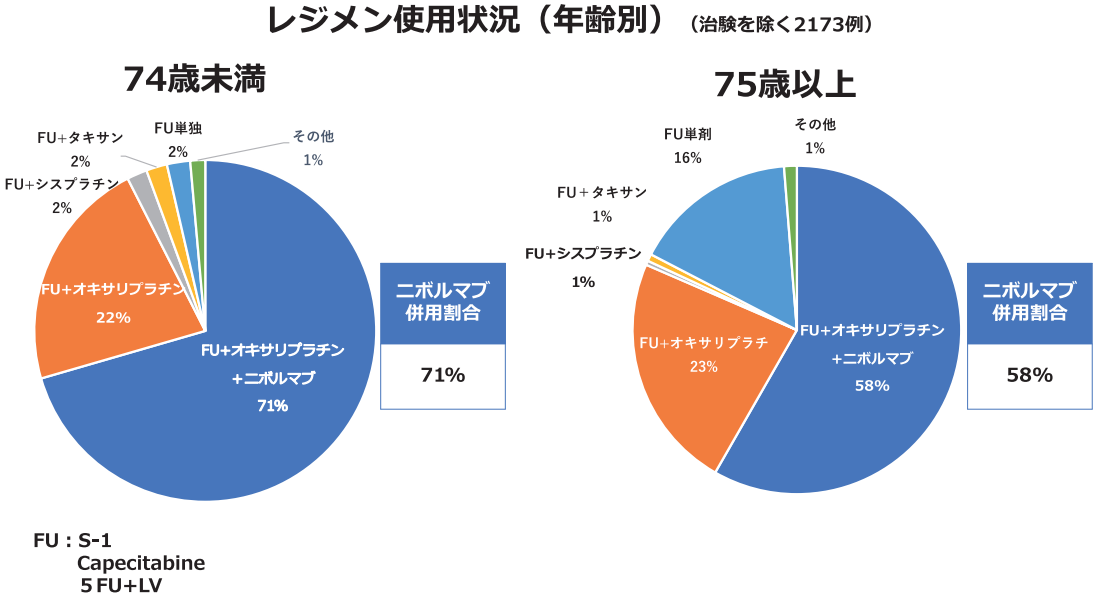
結果

化学療法内容に関するデータは 2023 年 3 月から 5 月の間に、全 92 施設から 2173 患者について集積された。日本胃癌学会治療ガイドライン第6版で推奨もしくは条件付き推奨された治療内容が行われた 2113 例について解析した。フッ化ピリミジン（S-1 またはカペシタビンまたは 5-FU/LV）、オキザリプラチン、ニボルマブ 3 剤投与が「高額」治療に該当した。月あたりコストは 767,648～771,046 円であった。ニボルマブを含む治療はフッ化ピリミジンとオキザリプラチンによる通常の化学療法に比べ 20 倍以上のコストがかかった。この高額治療は 2113 人中 1416 人（67%）に行われた。74 歳以下では 71%が、75 歳以上では 59%に行われた。

結論

HER2陰性進行・再発胃癌においては、従来の化学療法の 20 倍以上のコストの初回治療が 3 分の 2 に行われ、75 歳以上の患者でも半数以上に行われていた。この知見は将来における薬剤の費用対効果に関する医療経済研究に有用である。

治療選択
年齢によらず高額薬ニボルマブ（ICI）が過半数で選択されている

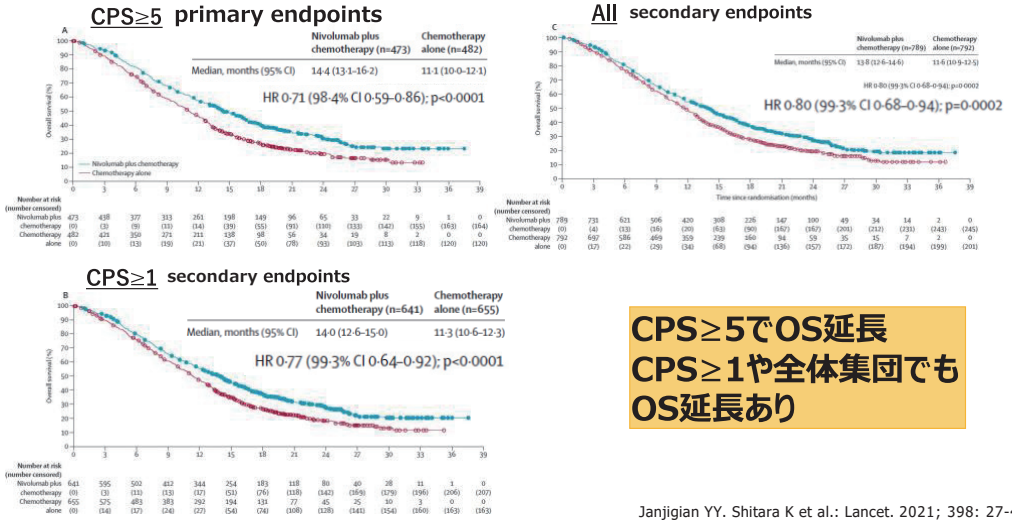


FU：S-1
Capecitabine
5FU+LV

ニボルマブの治療効果はマージナル

CPS：癌細胞表面に出ている、ニボルマブなど ICI の標的分子（これが高いと ICI は効果が高いとされている）

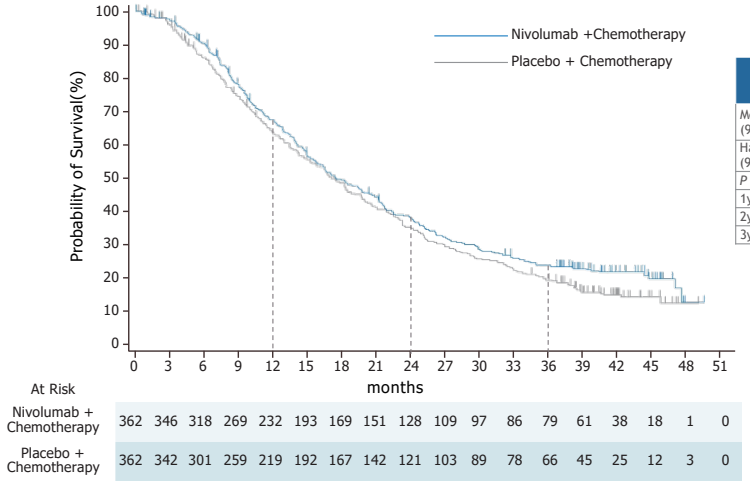
CheckMate 649 study　Overall survival



CPS≥5でOS延長
CPS≥1や全体集団でもOS延長あり

Janjigian YY. Shitara K et al.: Lancet. 2021; 398: 27-40.

ATTRACTION4試験　：36-month follow-up



At Risk																	
Nivolumab + Chemotherapy	362	346	318	269	232	193	169	151	128	109	97	86	79	61	38	18	1	0
Placebo + Chemotherapy	362	342	301	259	219	192	167	142	121	103	89	78	66	45	25	12	3	0

	Nivolumab + Chemotherapy N = 362	Placebo + Chemotherapy N = 362
Median OS, months (95% CI)	17.45 (15.67-20.83)	17.15 (15.18-19.65)
Hazard ratio (95% CI)	0.89 (0.75-1.05)	
P value[a]	0.1564	
1yr OS rate (%)	67.4	63.5
2yr OS rate (%)	37.9	35.1
3yr OS rate (%)	23.9	19.4

- 11.4% (9/79[b]) in NIVO+Chemo and 48.5% (32/66[b]) in Placebo+Chemo of 3-year survivors received subsequent immunotherapy

[a]Not a pre-planned statistical test. [b]Including 22 patients in NIVO+Chemo and10 patients in Placebo+Chemo who were continuing study treatment

L.-T. Chen. et al. JGCA 2023

7. 大腸癌 https://doi.org/10.1093/jjco/hyae110

実臨床における転移性大腸癌初回治療の治療コスト：日本臨床腫瘍研究グループ（JCOG）大腸癌グループの調査

緒言

転移性大腸癌の治療成績はここ数十年で目覚ましく向上したが、薬剤コストもまた相当に増加した。この研究は、日本において転移性大腸癌に対し初回化学治療としてどういうものが実臨床で使われ、そのコストはいかほどか、を調査することを目的とする。

方法

我々は 2021 年 7 月から 2022 年 6 月の間に JCOG 大腸癌グループの 37 施設で初回治療を受けた転移性大腸癌患者のデータを集積し、その治療コストを計算した。各治療の月あたりコストは標準的使用、すなわち体重 70kg で体表面積 1.8m^2 の男性患者を想定して見積もった。治療内容のデータはグーグルフォームで集められた。治療は「非常に高額」（月あたりコスト 100 万円以上）、「高額」（月あたり 50 万円～100 万円）、「そのほか」（月あたり 50 万円以下）に分類された。

結果

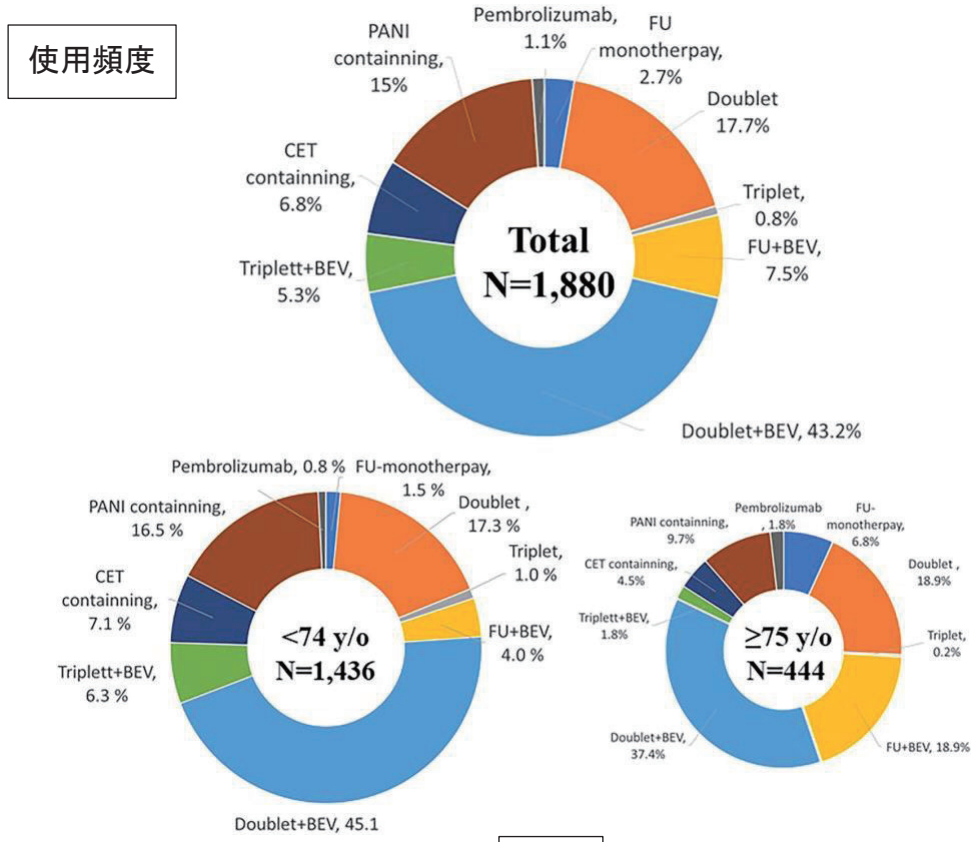
1880 症例が集積され、24%は 75 歳以上だった。78%に対して分子標的薬を含む治療が行われた。最も汎用されていたのは 2 剤併用化学療法（フッ化ピリミジン+オキザリプラチンもしくはイリノテカン）にベバシズマブを併用する治療で（43%）、その次が 2 剤併用化学療法にセツキシマブまたはパニツムマブを併用する治療（21%）だった。分子標的薬を含む治療（月あたり 85,406 円～843,602 円）は、殺細胞性薬剤のみの治療（月あたり 17,672 円～51,004 円）よりもはるかに高額だった。16%の患者（75 歳未満では 17%、75 歳以上では 11%）がパニツムマブやペムブロリズマブをふくむ「高額」治療を受けていた。

結論

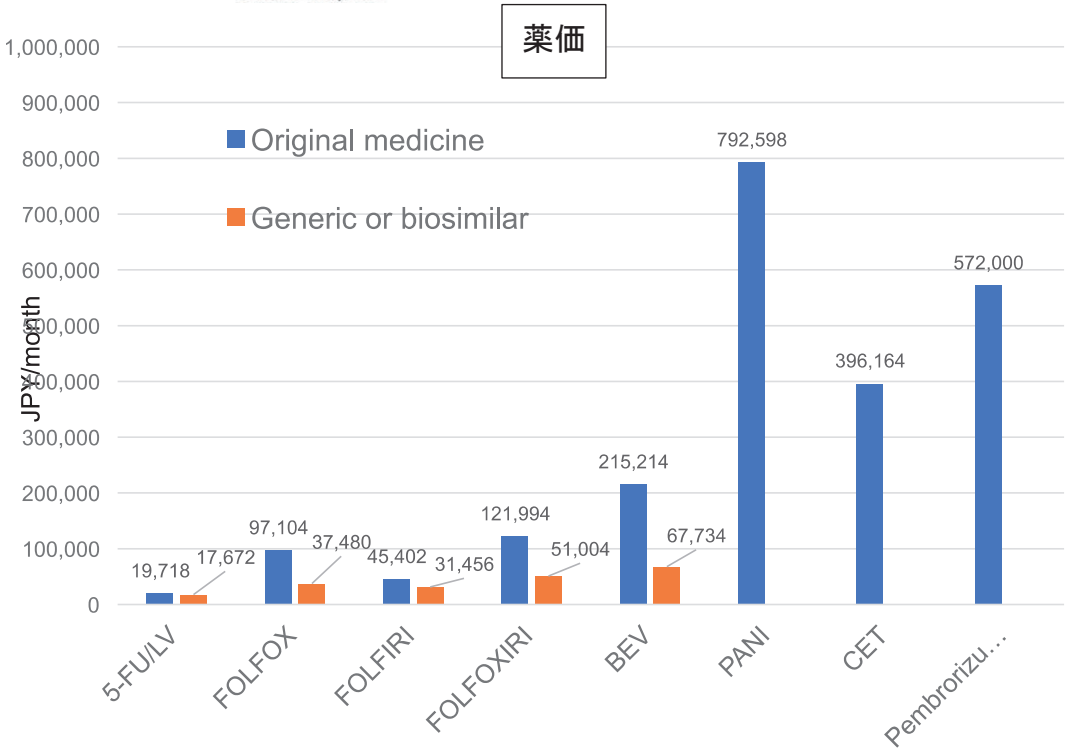
16%の患者が月あたり 50 万円を超えるコストの初回治療を受けており、コストを押し上げる原動力になったのは主に分子標的薬であった。

CET と PANI は同効同種だがコストは倍違う、ただし「高い」PANI の方が使用頻度高い

使用頻度



薬価



8.　頭頸部癌　https://doi.org/10.1093/jjco/hyae117

日本における再発もしくは転移性頭頸部扁平上皮癌初回化学療法の使用頻度とコスト

背景

過去 10 年間で、日本を含む世界において、新しい抗悪性腫瘍剤が再発もしくは転移性頭頸部扁平上皮癌の予後を改善した。しかしこのことはまた、医療保険支出を増加させ、患者と社会に重い負担をかけている。この研究ではどの化学療法が選択されるかの頻度とそのコストを調査した。

方法

2021 年 7 月から 2022 年 6 月までの間に 54 施設で初回化学療法を受けた再発もしくは転移性頭頸部扁平上皮癌と診断され、多く使われる 8 種類の治療のうちのいずれかで治療された患者のデータを集積した。鼻咽頭癌の患者は除外した。それぞれの治療がなされた患者数と、最初の月および年あたりのコストが集計された。

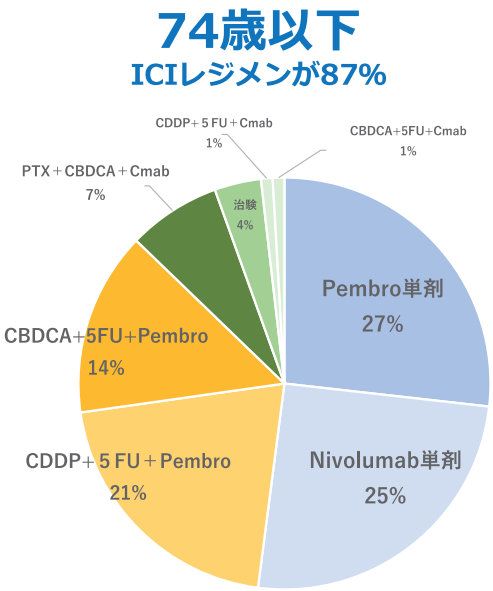
結果

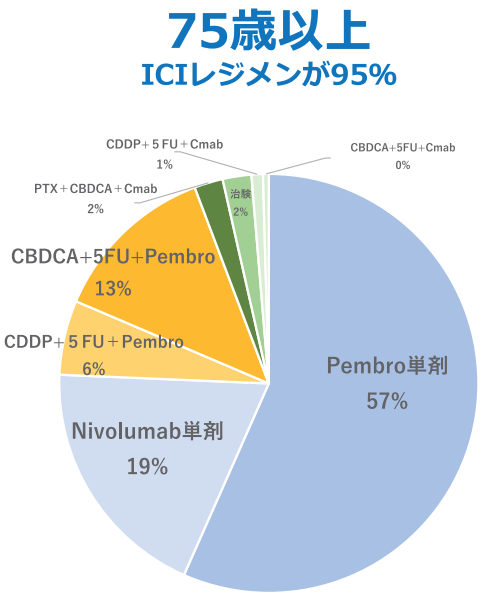
907 人（75 歳未満 674 人、75 歳以上 233 人）が集積された。330 人（36.4%）がペムブロリズマブ単剤、202 人（22.3%）がニボルマブ単剤治療を受けていた。90%以上の患者が免疫チェックポイント阻害剤単剤もしくは化学療法との併用で治療された。最初の 1 ヶ月の治療コストは 612,851 円から 849,241 円だった。2012 年までの標準的な化学療法のコストは月あたり約 20,000 円だった。この 10 年間で再発もしくは転移性頭頸部扁平上皮癌への化学療法のコストは月あたり 60 万円から 80 万円、以前に比べ 30 倍から 40 倍増加した。

結論

再発もしくは転移性頭頸部扁平上皮癌の初回化学療法のコストは月あたり 60 万円を超える。この 10 年で再発もしくは転移性頭頸部扁平上皮癌の予後は改善したが、化学療法のコストは急増し、患者と社会に重い負担を与えている。

使用化学療法内容





コスト

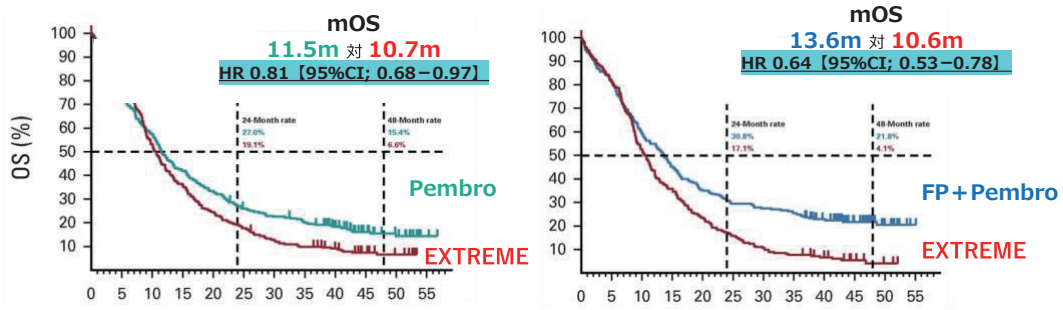
ICI使用レジメンは58万円/月以上

レジメン	1月の薬価（円）
Nivolumab単剤	**733,240**
CDDP+5FU+Pembro	**615,120**
CBDCA+5FU+Pembro	**596,000**
Pembro単剤	**580,493**
CDDP+5FU+Cmab	375,533
PTX+CBDCA+Cmab	347,280
CBDCA+5FU+Cmab	258,146

効果

CPS：癌細胞表面に出ている、Pembro など ICI の標的分子（これが高いと ICI は効果が高いとされている）

ITT



Pembro単剤 →・CPS≧1で生存期間延長（優越性）
→・CPSスコアに関わらず生存期間劣っていない（非劣性）
FP＋Pembro →・CPSスコアに関わらず生存期間が延長（優越性）

CPS スコアで Pembro が「効きやすい」と判定される人は単剤でも生存期間が延長する
化学療法と Pembro の併用では、CPS スコアで「効きにくい」と判定される人を含めても生存期間が延長する

9.　脳腫瘍　https://doi.org/10.1093/jjco/hyae116

日本臨床腫瘍研究グループ（JCOG）脳腫瘍グループ参加施設における悪性脳腫瘍の医療コスト

目的

この研究は、日本における実臨床での悪性脳腫瘍特に膠芽腫と中枢神経リンパ腫に対しどのような治療法が選択され、コストはいかほどかを検討することを目的とする。

方法

我々は日本臨床腫瘍研究グループ（JCOG）脳腫瘍グループに属する 47 施設で 2021 年 7 月から 2022 年 6 月までの間に治療された膠芽腫および中枢神経リンパ腫の新規診断症例の治療法選択について、ウェブによるアンケート調査を行なった。膠芽腫および中枢神経リンパ腫の新規診断症例の治療の総コストと月あたりコストを算出した。

結果

74 歳以下の膠芽腫に対し最も行われた（46.8%）治療は手術+術後テモゾラミド併用放射線治療だった。この治療の総コストは 750 万円だった。追加治療としてカルムスチン植込み（15.0%の症例）、腫瘍治療電場療法（14.1%の症例）、ベバシズマブ（14.5%の症例）が行われ、それぞれ 124 万円（初回治療）、144 万円/月、22 万円/月の追加コストを伴った。

中枢神経リンパ腫に関しては、手術（生検）+リツキシマブ・メトトレキセート・プロカルバジン・ビンクリスチン併用（R-MPV）療法が年齢にかかわらず最も汎用（42.5%）されていた。この治療は月あたりコストが 107 万円であった。中枢神経リンパ腫に対する, R-MPV をベースとする化学療法のうち 3 種類は、月あたりコスト 100 万円以上の超高コスト治療だった。

結論

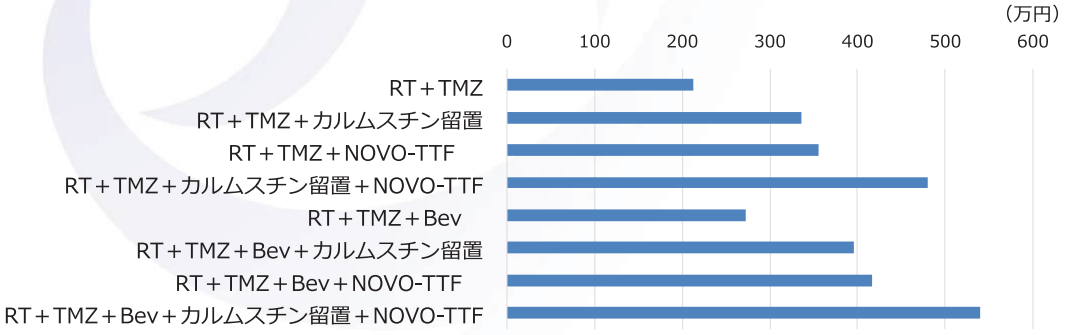
悪性脳腫瘍の治療は概ね高価であり、ベバシズマブのような費用対効果不良の治療も多く使われる。この研究の結果は、悪性脳腫瘍の費用対効果を検討する将来の医療経済研究の企画に役立つと考える。

膠芽腫:「新治療」はカルムスチン・NOVO-TTF・Bev の三種類しかない
この組み合わせで治療選択がされる(上図)
「治療法が乏しい」ので Bev のように無効な治療(下図)も使われてしまう

初発膠芽腫

NAGOYA UNIVERSITY HOSPITAL

費用

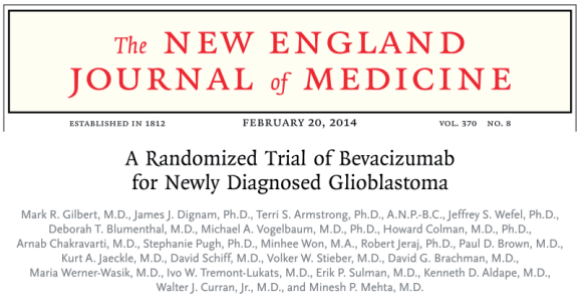


＊カルムスチン：124万円（8個留置時）
NOVO-TTF： 144万円
Bev： 60万円

初発膠芽腫

NAGOYA UNIVERSITY HOSPITAL

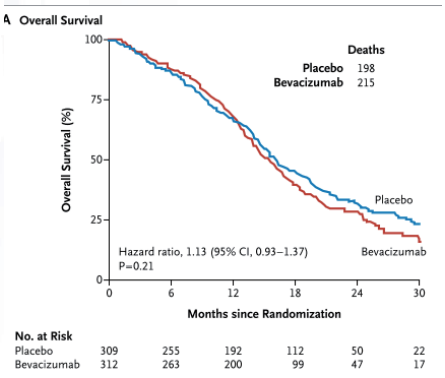
Bevacizumab
RTOG0825


The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 FEBRUARY 20, 2014 VOL. 370 NO. 8

A Randomized Trial of Bevacizumab for Newly Diagnosed Glioblastoma

Mark R. Gilbert, M.D., James J. Dignam, Ph.D., Terri S. Armstrong, Ph.D., A.N.P.-B.C., Jeffrey S. Wefel, Ph.D., Deborah T. Blumenthal, M.D., Michael A. Vogelbaum, M.D., Ph.D., Howard Colman, M.D., Ph.D., Arnab Chakravarti, M.D., Stephanie Pugh, Ph.D., Minhee Won, M.A., Robert Jeraj, Ph.D., Paul D. Brown, M.D., Kurt A. Jaeckle, M.D., David Schiff, M.D., Volker W. Stieber, M.D., David G. Brachman, M.D., Maria Werner-Wasik, M.D., Ivo W. Tremont-Lukats, M.D., Erik P. Sulman, M.D., Kenneth D. Aldape, M.D., Walter J. Curran, Jr., M.D., and Minesh P. Mehta, M.D.

N Engl J Med. 2014 Feb 20;370(8):699-708.

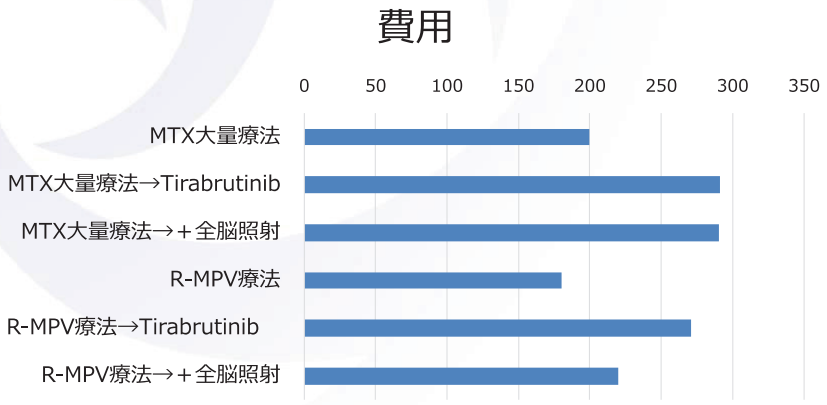


Median OS: Bev: 15.7 months
Placebo : 16.1 months

日本だけで、初発膠芽腫に対してBevの使用認可あり

リンパ腫：治療効果に差あり（高価だけど、治療効果も大きい）

初発中枢神経原発悪性リンパ腫



＊Tirabrutinib：　91万円（＊ただし、毎月毎に増加）

初発中枢神経原発悪性リンパ腫

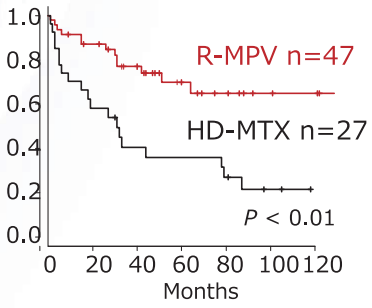
RESEARCH ARTICLE

Cancer Medicine WILEY

***CD79B* Y196 mutation is a potent predictive marker for favorable response to R-MPV in primary central nervous system lymphoma**

Junya Yamaguchi[1] | Fumiharu Ohka[1] | Chalise Lushun[2] | Kazuya Motomura[1] | Kosuke Aoki[1] | Kazuhito Takeuchi[1] | Yuichi Nagata[1] | Satoshi Ito[3] | Nobuhiko Mizutani[3] | Masasuke Ohno[4,5] | Noriyuki Suzaki[5] | Syuntaro Takasu[6] | Yukio Seki[6] | Takahisa Kano[7] | Kenichi Wakabayashi[8] | Hirofumi Oyama[8] | Shingo Kurahashi[9] | Kuniaki Tanahashi[1] | Masaki Hirano[1] | Hiroyuki Shimizu[1] | Yotaro Kitano[1] | Sachi Maeda[1] | Shintaro Yamazaki[1] | Toshihiko Wakabayashi[1,10] | Yutaka Kondo[11] | Atsushi Natsume[1] | Ryuta Saito[1]

Cancer Med. 2023 Mar;12(6):7116-7126.



	HD-MTX (n=27)	R-MPV (n=47)
奏効率 (CR)	48.1%	85.1%
5年無増悪生存率	20.9%	61.6%
5年生存率	36.0%	69.9%

これら 9 論文をまとめると [20]、17 疾患の多くで高額医療が行われ、月当たりのコストでは 50 万円以上になるものが中央値 59%（1QR：44%、 3 QR：87%）であった。全体の 17%が月 100 万円以上の高額医療を受けていた。10〜15 年前に「標準」であった”conventional chemotherapy”に比べ、コストは概ね 10〜50 倍程度に跳ね上がっていた。

高齢者は多少高額治療の割合が減っていたが、これは「高額だから」ではなく、毒性のため薬剤を差し控えるためと推測された。中には肺癌の Nivolumab+Ipilimumab、頭頸部の Pembrolizumab のように、高齢者に好んで使われる高額治療もあった。

また、乳癌の CDK4/6 阻害剤や前立腺癌の ARSI のように、 PFS が長く、「よく効く」ものは治療期間も長くなり、総コストが上がることが示された。

一方で Benefit は胃癌の Nivolumab のようにマージナルなものから、極端な場合卵巣癌や脳腫瘍の Bevacizumab のように「ない」ものまであった。ただし、これらはもともと他疾患で承認されていた薬剤の適応拡大がほとんどで、すでに薬価は決まっているためその腫瘍系で効果が少ないことは薬価には反映されない。

さらに、同種同効で値段の違うものもあるが、気にせずに使われている。この例は多く、肺癌の VEGF 阻害剤や ICI、前立腺癌の ARSI、腎癌の ICI、TKI、肝細胞癌の ICI、大腸癌の EGFR 抗体などがあった。これも適応拡大がほとんどで、すでに薬価は決まっているため結果的に歪な薬価設定になっている。

命に関わる疾患の治療でコストを「費用対効果」の観点から検討することには抵抗も多いが、この調査の結果からは、同種同効の薬剤では薬価の安いものを優先するなど、少なくとも全く患者の不利益にならずにコストを節約する方法も示唆される。さらに、TKI や ICI など最近の薬剤は、開発の段階で治療用量が過量投与に設定されていることが多いと指摘されており、治療効果を損ねないように用量を下げ、副作用とコストを下げる臨床研究を行うことも重要と思われる（実際の研究については下記 4-2.など参照）。

4-1-5.JCOG 臨床試験ポリシー

従来は、JCOG のように公的研究費で運営され、公的な性格が強い研究グループの臨床研究でも、治療成績の改善と新しい標準治療の確立を目指した試験を企画立案するにあたってはコストのことは度外視し、「いくら金をかけて、改善の度合いがわずかであっても」統計学的有意差を生み出すことができればそれは「成果」とみなされた。

しかしそれでは医療の（少なくとも現行の保険医療制度の元での医療の）持続可能性を顧みないことになり、公的研究グループとしての責務を果たしていないとの謗りを免れない。JCOG 医療経済小委員会では、JCOG で行われる臨床試験に医療経済評価を盛り込むことが必須と考え、グループのポリシーを策定中である。素案を下記に示すが、今年中に JCOG 運営委員会で承認されて発効する予定である。

本ポリシーは、「高い薬を研究に使うな」とブレーキをかけることが目的ではない。ただ大きなコストをかける治療法は、単に「統計学的に有意な差」を出すだけではなく、それに見合った高い効果をもたらさねばならない、という、いわばごく当たり前の認識を共有することを目的としている。また、実際に医療経済評価を行う時にはどのようにすべきかという指針も提示している。

（以下、ポリシー素案：運営委員会審査承認前なので、一部変更の可能性あり）

Japan Clinical Oncology Group

ポリシー No. XX
タイトル：医療経済
適用範囲：研究グループ、医療経済評価研究、プロトコール審査委員会

医療経済

Health Economics

1. 目的

本ポリシーの目的は、JCOG における医療経済評価研究を行う際の指針を示すことである。具体的には、JCOG 研究における、①すべての JCOG 試験で医療経済の側面に関する検討を行うこと、②JCOG における医療経済評価研究を行う際の指針、についての指針を明らかにすることである。

なお、専門領域によって医療経済評価に対する考え方や実態が異なるため、本ポリシーでは疾患特異的な内容には言及せず、専ら、医療経済評価研究に関する基本的な考え方を示すこととする。

2.本委員会設立の背景

悪性腫瘍に対する薬物療法の進歩は著しく、進行癌でも５年～10 年以上の長期生存も得られるようになり、薬物単独での「治癒」の可能性も出てきている。また、手術や放射線治療の進歩と相俟って、これらを組み合わせた集学的治療によりさらに生存率の改善も期待される。

しかしながら、これら新規の薬物療法は、既存の薬物療法に比べ非常に高価であることが多い。それに伴い、がん薬物療法のコストも加速度的に上昇を続けている。2004 年にはSchrag が、進行大腸癌の治療成績は生存期間が２倍になったがそのコストは 340 倍になった、と affordability および sustainability について警鐘を鳴らしている。カナダの Tannock らは、OCCA（Optimal Cancer Care Alliance）という団体を設立し、癌治療の”value”=benefit/(cost + toxicity)を最適化する研究を模索している。一方で我が国では、癌治療コストの問題は表面化していない。これは我が国では国民皆保険制度や高額療養費制度があるため、患者や医療者が薬剤費の高騰について意識することが少ないことも一因にはあると考えられる。したがって、日常診療では治療効果がコストに見合うのか、が議論になることはほとんどないのが現状である。

医療の高度化すなわち医学の進歩とそれに伴う治療費の高騰は止めることはできない。しかし昨今、超高齢化社会となり医療費の高騰が続く本邦において、このままコストを気にせず「医学の進歩」を追い求めるのには限界があると考えられる。したがって、いかにして限りある医療資源を賢く使っていくか、を考える必要がある。がん治療において、新規の治療を

日常診療に組み込む際には臨床研究のデータを判断材料にすることが多いが、臨床研究においてそのコストを評価基準にいれることは限られている。しかしながら、医療レベルを落とさずに、”value”を高めてコストを抑制し、affordability と sustainability を維持するためには、臨床研究に医療経済評価を組み込むことが必須と考える。

上記の目的を達成するために、がん臨床試験を扱う JCOG に医療経済委員会を設立し、がん臨床試験において医療経済の視点からも、治療の”value”を評価し、JCOG 試験の価値を高めていくものとする。

3. 委員会の役割

JCOG 試験における本委員会の役割は、以下に示すとおりである

- すべての JCOG 試験で医療経済の側面に関する検討を含めることを必須とする。具体的には、コンセプト審査に提出された JCOG 本体研究に対し、医療経済評価研究を推奨するかの審査を行う。
- JCOG 試験における医療経済評価研究の指針を示す。
- 医療経済評価研究を立案する際のコンサルテーションを提供する。

4. 用語説明

本ポリシーで用いられている用語に関する説明を以下に示す。

- **医療経済評価研究**：医療技術や治療法の費用（コスト）と効果（ベネフィット）を分析し、その医療技術の費用対効果を評価する研究を指す。
- **効用値**：QOL（生活の質, Quality of life）を一次元ととらえ、死亡した状態と等価である 0 から完全に健康な状態と等価である 1 までの間の値として数値化したものである。QALY（質調整生存年, Quality-Adjusted Life Year）を算出する際に使用される。
- **DPC（包括支払い制度）方式**：病院が DPC 対象病院である場合、診断群分類（DPC）に基づいて包括払いとなる。診断された病名（DPC コード）ごとに決められた基本点数（1 日あたりの定額入院費）、手術、麻酔、特殊な処置などの出来高算定（DPC に含まれない費用）と在院日数等を踏まえて、入院費用を算出する方式である。
- **外保連試案**：外科系学会社会保険委員会連合（外保連）に加盟する 114 の外科系学会により調査・検証された全術式のコスト・技術料データであり、術式ごとに「技術難易度」「必要スタッフ数」「所要時間」を精査して「人件費」を算出し、さらに「使用材料・機器・室料等のコスト」を配賦して「総費用」を算出している。

5. JCOG 試験におけるコンセプト審査

「2.2.医療経済評価研究の現状」で示したとおり、昨今癌治療に対するコストは上昇し続けており、特に新規の薬剤や治療にその傾向が強い。JCOG で実施される臨床試験は標準治療を変える目的で実施されており、試験の結果により新規治療がガイドライン等を通じて本邦の日常診療で普及される可能性が高くなる。もし、標準治療となった新規治療が高額であった場合、患者や国に与える経済的な影響も少なくないと考えられることから、臨床試験の立案段階で、その新規治療がもたらすリスク/ベネフィットに医療経済的な観点も踏まえて検討する必要がある。

そこで、JCOG 医療経済委員会は、コンセプト審査に提出された JCOG 本体研究に対し、医療経済評価研究を推奨するかの審査を行うこととする。**各研究グループは、コンセプトの提出にあたり「医療経済審査シート」（別紙）も提出する**こと。

5.1. 対象とするコンセプト

コンセプト審査に提出された JCOG 本体研究を対象とする。観察研究や附随研究、治験や国際共同試験は対象としない。また、手術手技を比較する試験であって、群間で使用する医療機器に差が見込まれない試験も対象外とする。

5.2.医療経済審査シートに記載する内容

医療経済審査シートには、標準治療・試験治療それぞれについて以下の情報を表形式で記載する。プロトコール治療に複数のモダリティを含む場合は、それぞれのモダリティについて記載すること。費用については詳細な額ではなく概算額でもよい（●万円、等）が、その算出の根拠となった情報（その時点の薬価等）についても医療経済審査シートには記載すること。

薬物治療

- **レジメン**：標準治療や試験治療にいくつかのレジメンを含む場合にはそれぞれについて記載する。
- **月額**：そのレジメンを使用した場合の月額を記載する。実際の患者負担金額ではなく、各種データベースに掲載される薬価を基に記載すること。レジメンにいくつかの投与法がある場合には代表的なもののみで良い。レジメンにいくつかの薬剤を含む場合（例：表 5.2.1.の「薬剤 C＋薬剤 D」）は、合計額を記載する。レジメンの実施期間が 1 か月未満である場合には、1 回の投与費用を代わりに記載する。

  ※　後発品（ジェネリック）がある場合にはその価格としてもよい。

※　標準体重については、試験共通の体重を設定せず、試験毎に設定する。

- **プロトコール治療として実施した場合の薬剤費**：設定した月額を基にプロトコール治療として上記の用量で実施した場合の薬剤費を記載する。プロトコール治療の期間が定められていない場合には、それぞれの群で期待される投与期間、ならびにその期間に対応する薬剤費を記載すること。
- **支持療法のコスト**：プロトコール治療として支持療法が含まれており、ほぼ全例で副作用が発生するものについては記載する。

表 5.2.1. 各群の薬物療法にかかるコスト

	レジメン	月額	プロトコール治療として実施した場合の薬剤費		支持療法のコスト
標準治療	薬剤 A	XXX 円	X か月 or X 年	XXX 円	XXX 円
試験治療	薬剤 B	YYY 円	Y か月 or Y 年	YYY 円	YYY 円
	薬剤 C＋薬剤 D	ZZZ 円	Z か月 or Z 年	ZZZ 円	ZZZ 円

※　詳細は最新の医療経済審査シートも確認すること

<u>放射線治療</u>

- **放射線治療**：照射法（通常照射/IMRT/SBRT/粒子線治療の別、および通常照射の場合の部位数）については代表的なものを記載する。大きく金額の異なる選択肢がある場合にはそれぞれについて記載するのが望ましい。
- **線量分割**：いくつかの線量分割の選択肢がある場合、代表的なもののみでよい。
- **プロトコール治療として実施した場合の費用**：上記の設定で放射線治療を実施した場合の費用を記載する。プロトコール治療として実施した期間内の総額（原則、加算も含む）を記載すること。
- **支持療法のコスト**：プロトコール治療として支持療法が含まれており、ほぼ全例で副作用が発生するものについては記載する。

表 5.2.2. 各群の放射線治療にかかるコスト

	放射線治療	照射部位	線量分割	プロトコール治療として実施した場合の費用	支持療法のコスト
標準	SBRT/IMRT 等		XX Gy/XX 回	XXX 円	XXX 円

治療					
試験治療	SBRT/IMRT等		YY Gy/YY回	YYY 円	YYY 円
	SBRT/IMRT等		ZZ Gy/ZZ回	ZZZ 円	ZZZ 円

※　詳細は最新の医療経済審査シートも確認すること

手術治療

- **医療機器**：いくつかの医療機器を含む場合にはそれぞれについて記載する。
- **入院費用**：その治療を行った場合に生じると想定される、一般的な入院費用を記載する。DPC 方式での算出や外保連試案データの活用等が考えられるが、算出方法は問わない。
- **附随する処置のコスト**：プロトコール治療として何らかの特別な処置や検査が含まれており、ほぼ全例で生じるものについては記載する。

表 5.2.3. 各群の手術治療にかかるコスト

	医療機器	入院費用	附随する処置のコスト
標準治療	胸腔鏡/腹腔鏡/ロボット等	XXX 円	XXX 円
試験治療	胸腔鏡/腹腔鏡/ロボット等	YYY 円	YYY 円

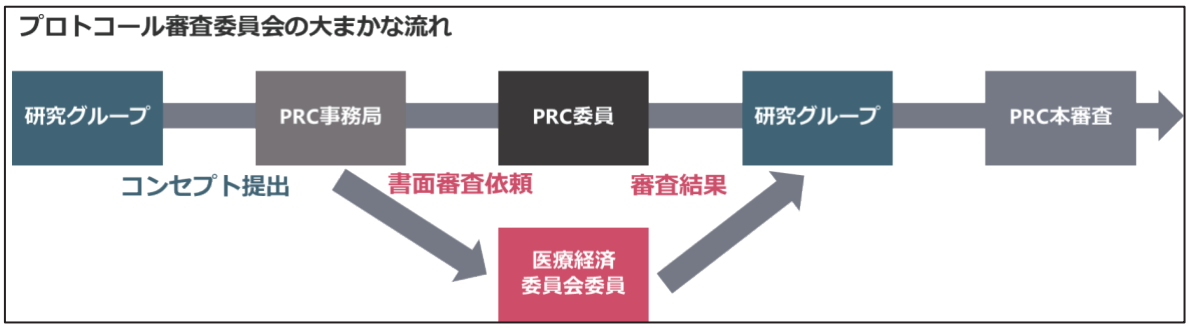
※　詳細は最新の医療経済審査シートも確認すること

5.3. コンセプト審査の手順

研究グループはコンセプト作成の際、別紙の「医療経済審査シート」を作成し、研究のコンセプトを JCOG-PRC 委員会に提出する際の資料の一部とする。JCOG 医療経済委員会事務局は PRC 事務局よりコンセプトならびに医療経済審査シートを受領する。

コンセプト・医療経済審査シートを受領した JCOG 医療経済委員会事務局は、医療経済委員会委員の中からレビュー担当を指名し、医療経済の観点からの審査を依頼する。審査の依頼を受けた医療経済委員会委員は、

原則 2 週間以内に審査コメントを付記した「医療経済審査シート」を JCOG 医療経済委員会事務局に返信する。返信を受領した JCOG 医療経済委員会事務局は、PRC 事務局に「医療経済審査シート」を速やかに提出する。



5.4 審査意見

コンセプトに対する審査意見は以下の内容を「医療経済審査シート」に記載する。試験治療のベネフィットや期待する上乗せ効果、検証する仮説※と、その治療に必要なコストを踏まえた審査意見とすること。

※ 治療効果の要約を標準治療に対する試験治療のハザード比で行う場合に信頼区間上限がハザード比 1 を下回ることを示す優越性(superiority)なのか、ハザード比 1 未満の値を下回ることを示す大幅な優越性(super superiority)なのか、等

審査意見

□ 審査意見なし
□ 医療経済評価研究を推奨する
　□ 効用値のデータが必要
　□ 効用値のデータは不要
□ 再検討を勧告する

審査コメント(推奨/勧告の場合は必須)

審査を担当する JCOG 医療経済小委員会委員は、「医療経済審査シート」の「評価委員の手引き」に沿って、審査意見、審査コメント(必要時)を付ける。

審査意見なし

- 試験治療が標準治療に比べて廉価の場合には、原則「審査意見なし」とする。

- 試験治療が標準治療より高価な場合でも、試験治療によってもたらされるベネフィットが、そのコストに見合うと判断される場合には、「審査意見なし」とする。
- 医療経済委員より規定の期間内に「医療経済審査シート」の提出がなかった場合、「審査意見なし」とする。

医療経済評価研究を推奨する

- 試験治療が標準治療に比べ著しく高価である場合、「医療経済評価研究を推奨する」とする。医療経済評価研究を推奨する場合には、その理由について審査コメントを付記する。
- 推奨する医療経済評価研究において、効用値のデータ収集の必要/不要をコメントする。収集する効用値は EQ-5D-5L を推奨する。
- 医療経済評価研究を実施するにあたり、QALY の検討は不要(生存年の評価のみで構わない)と考えられる場合は、「効用値のデータは不要」とする。
- 医療経済評価研究を実施するにあたり、QALY の検討が必要と考えられる場合は、「効用値のデータは必要」とする。
- 効用値を評価するにあたり、対象とする疾患に対し、既報等で妥当な効用値(QOL 値)が得られていると考えられる場合は、QOL 調査は不要とする。妥当な効用値(QOL 値)がない場合は、QOL 調査の実施を推奨し、その場合は原則 EQ-5D-5L を評価する。効用値を含めた QOL 調査の実施について必要時には、適宜当委員会や他の委員会に相談する。

再検討を勧告する

- 試験治療が標準治療に比べ著しく高価であり、かつ試験治療で得られるベネフィットに見合わないと判断される場合、「再検討を勧告する」とする。再検討を勧告する場合には、その理由について審査コメントを付記する。
- その試験の取り下げ勧告を意図するものではないが、コンセプト検討会で検討する上での付帯意見とする。

6. 医療経済評価研究

6.1. 医療経済評価研究の概論

医療経済評価は、治療の効率性を効果(有効性や安全性)の観点に加えて「費用」の経済的観点も踏まえて評価する目的で実施される。医療経済評価においては、試験治療の標準治療に対する「効果」と「費用」の大小 4 つの組み合わせが考えられ、それぞれに対応した意思決定が行われる(図 1)。

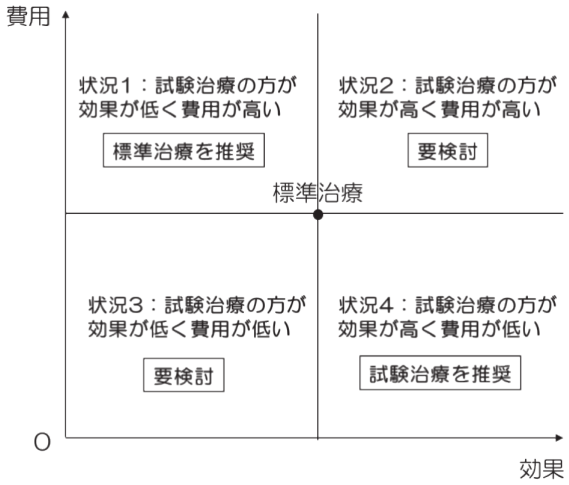


図 1：費用対効果平面

治療の「効率性」は、増分費用効果比（Incremental Cost Effectiveness Ratio: ICER）で評価されることが一般的である。たとえば、ICER は治療 A を治療 B に置き換えることにより、追加で 1 単位の効果を得るのにいくらかかるかの指標である。

$$\mathrm{ICER} = \frac{\text{費用}(\mathrm{B}) - \text{費用}(\mathrm{A})}{\text{効果}(\mathrm{B}) - \text{効果}(\mathrm{A})}$$

一般的な医療経済評価では「保険償還の決定、価格決定の参考」、「社会的な医療政策の決定」、「当該医療技術の利用判断」の目的に応じて「費用」と「効果」の指標が選択される。たとえば、費用に関しては「分析の立場」に応じて費用の範囲が定められている（下表 6.1.1.）。また、効果の指標に関しては、原則として質調整生存年（QALY: quality-adjusted life years）が推奨されている。

表 6.1.1. 費用対効果評価の目的と分析の立場の関係

目的	立場	費用の範囲
保険償還の決定、価格決定の参考	公的医療支払者の立場	公的医療保険制度における医療費のみ
社会的な医療政策の決定	公的医療・介護の立場	公的医療保険制度における医療費+公的介護費
	限定された社会の立場	公的医療の立場や公的医療・介護の立場に生産性損失を加えたもの
当該医療技術の利用判断	患者の立場	患者・家族が負担する医療費、OTC、介護費

医療経済評価においては「費用最小化分析」「費用効果分析」「費用効用分析」「費用便益分析」の 4 つの分析手法が挙げられる（下表 6.2.2.）。

表 6.2.2.医療経済評価の主な分析手法

分析手法	説明
費用最小化分析	効果指標（有効性および安全性）が対照技術と同一であることが明らかになっている（または期待されている）ことを前提とし、費用の大小により医療技術を比較する分析方法
費用効果分析	効果として、生存年数や 物理的な尺度（イベント 発生の有無など）を用い、費用と比較する分析方法
費用効用分析	効果として，効用値から 算出される QALY（質調整生存年）を用い、費用 と比較する分析方法
費用便益分析	効果をすべて金銭に換算し、医療技術の使用により発生した費用と比較する分析方法

「費用最小化分析」は、治療効果が同一であることが明確な場合に使用できる。「費用効果分析」は、治療効果を時間や生存割合などの具体的なアウトカムで評価し、各治療にかかるコストを比較するため、がん治療における直接的な効果を評価する手法として適している。「費用効用分析」は、健康状態の改善を QALY（質調整生存年）などの統一的な尺度で測定できるため、異なる疾患にまたがる比較が可能であり、政策立案者にとって有用である。「費用便益分析」は健康の価値を金額に置き換えることが困難である。

6.2.3. 医療経済評価研究における評価尺度

主に悪性腫瘍に対する標準治療の確立を目指す JCOG 試験において、医療経済評価の目的や分析の立場は必ずしも上記の目的には合致しない。さらに、QOL や費用の情報収集を行う際には、その労力や得られる結果の精度を踏まえて情報収集の範囲を検討する必要がある。本章では JCOG 試験で医療経済評価を行う際の費用と効果指標の収集項目の目安を示す。

A）評価する費用について

医療経済評価研究では以下の費用を収集できる。

① プロトコール治療の費用

JCOG 試験においては、レジメンのコース数を収集していることが多く、当該薬剤等の費用がわかれば算出は可能なため、原則評価する。

② 支持療法・後治療の費用

支持療法は薬剤の特性により併用する支持療法が大きく変わることが想定される場

合には収集を検討する。また、後治療についてはプロトコール治療終了後の後治療が群間で大きく変わることが想定される場合には収集を検討する。なお、JCOG 試験では一般的にプロトコール治療終了後の初回の後治療の内容を収集していることが多い。

③ 交通費や介護費、入院費などの費用

例えば試験治療により通院の頻度が減る、入院期間が短くなるなどにより群間であきらかなコストの差が見込まれる場合には収集を検討する。入院費レセプトからも収集可能だが、個人情報になるため、研究毎に適切な同意を取得すること。

B) アウトカムについて

① 予後

予後は、患者の将来的な健康状態や治療の成果を示す指標である。医療経済評価においては、全生存期間(OS: Overall Survival)や無増悪生存期間(PFS: Progression-Free Survival)など、特定の疾患に関連する予後指標が使用される。

② QOL(Quality of Life)

QOL は、患者の生活の質(Quality of Life)を評価するための指標である。QOL は身体的、心理的、社会的な側面を含む広範な概念で、患者の主観的な健康状態や生活の質を把握するためにアンケート調査などが用いられる。医療経済評価においては、QALY を算出する際の QOL として簡便な質問票として EQ-5D が使用される。ただし、非劣性試験などで特異的な QOL のメリットがある場合には、特異的な QOL も推奨される。

③ 質調整生存年(QALY: Quality-Adjusted Life Year)

QALY は生存年数と QOL の両方を統合した健康状態を数値化した指標である。具体的には、生存年数に QOL 値で重み付けしたものであり、1QALY は完全な健康状態で生存する価値である。

6.2.4. 医療経済評価の分析方法

JCOG 医療経済委員会としては、最低限「費用効果分析」を行うことを推奨する。ただし、試験治療によるメリットを QOL で測ることや、政策決定の観点から QALY による評価が適切である場合には「費用効用分析」を追加で行うことを推奨する。

6.2.5. 主たる判断規準に医療経済評価を組み込むか

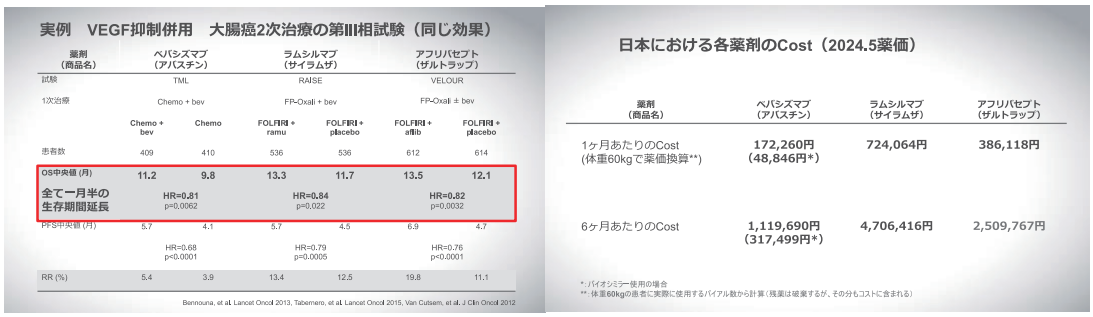
コンセプト審査で医療経済評価を推奨された場合でも、治療の効率性を判断するための明確な基準が存在しないため主たる判断規準に組み込むことは必須とはしない。仮に、研究者の判断で主たる判断規準に医療経済評価を組み込む場合にはプロトコールに事前記載することを推奨する。

なお、研究終了後の論文には、実施した医療経済評価の内容を含めることとするが、本体研究論文にするか、別論文にするかは規定しない。

4-1-6.診療ガイドラインへの反映

4-1-4.の高額治療調査からは、いくつかの治療および薬剤では、「効果同じ・副作用同じ・値段だけ違う」同種同効剤があり、現場ではこれを気にせずに使っていることがわかった。このような事例は以前から指摘されており、2012 年のニューヨークタイムズには、大腸癌の二次治療で化学療法に併用される血管新生阻害剤として、従来から bevacizumab（アバスチン）が承認されているが、新たに aflibercept（ザルトラップ）が承認された。しかしその効果（化学療法への上乗せ）は一月半の生存期間延長（下表左）で、bevacizumab と同等であり、ニューヨークのメモリアルスローンケタリングがんセンターは、アバスチンの倍の薬価がついたザルトラップを院内採用しなかった（https://www.nytimes.com/2012/10/15/opinion/a-hospital-says-no-to-an-11000-a-month-cancer-drug.html）。

その後、同じく血管新生阻害剤 ramucirumab（サイラムザ）も、全く同様の効果（一月半の延命）によって大腸癌の二次治療に日米ともに承認されているが、コストはさらに高かった（下表右）。これはサイラムザが先に胃癌で承認され、高い薬価がすでについていたことによる。アメリカでは以上の理由からサイラムザを大腸癌治療に使うことはコスパが悪として戒められているが、日本では気にせず使われている（初回治療ではないため今回の調査対象から外れる）。



実例　VEGF抑制併用　大腸癌2次治療の第III相試験（同じ効果）

薬剤（商品名）	ベバシズマブ（アバスチン）		ラムシルマブ（サイラムザ）		アフリバセプト（ザルトラップ）	
試験	TML		RAISE		VELOUR	
1次治療	Chemo + bev		FP-Oxali + bev		FP-Oxali ± bev	
	Chemo + bev	Chemo	FOLFIRI + ramu	FOLFIRI + placebo	FOLFIRI + aflib	FOLFIRI + placebo
患者数	409	410	536	536	612	614
OS中央値 (月)	11.2	9.8	13.3	11.7	13.5	12.1
全て一月半の生存期間延長	HR=0.81 p=0.0062		HR=0.84 p=0.022		HR=0.82 p=0.0032	
PFS中央値 (月)	5.7	4.1	5.7	4.5	6.9	4.7
	HR=0.68 p<0.0001		HR=0.79 p=0.0005		HR=0.76 p<0.0001	
RR (%)	5.4	3.9	13.4	12.5	19.8	11.1

Bennouna, et al. Lancet Oncol 2013, Tabernero, et al. Lancet Oncol 2015, Van Cutsem, et al. J Clin Oncol 2012

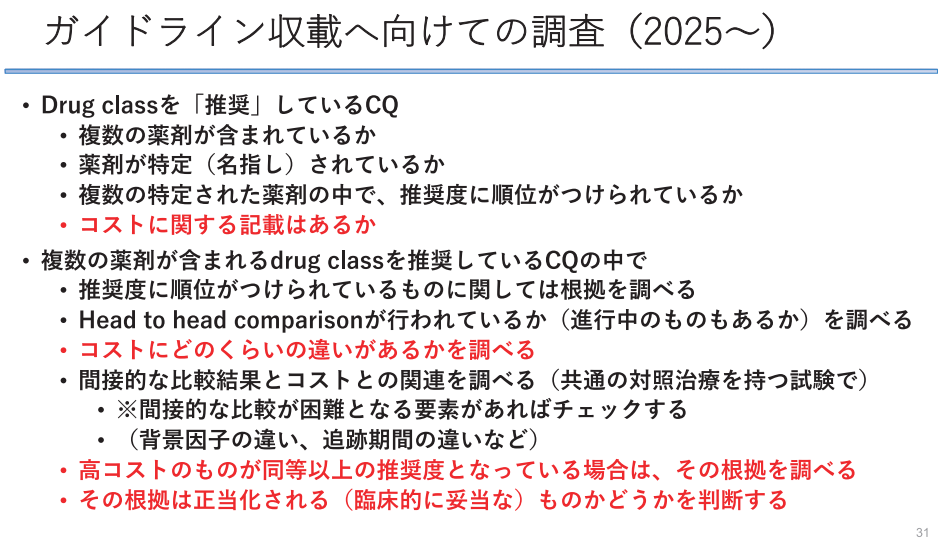
日本における各薬剤のCost（2024.5薬価）

薬剤（商品名）	ベバシズマブ（アバスチン）	ラムシルマブ（サイラムザ）	アフリバセプト（ザルトラップ）
1ヶ月あたりのCost (体重60kgで薬価換算**)	172,260円 (48,846円*)	724,064円	386,118円
6ヶ月あたりのCost	1,119,690円 (317,499円*)	4,706,416円	2,509,767円

*：バイオシミラー使用の場合
**：体重60kgの患者に実際に使用するバイアル数から計算（残薬は破棄するが、その分もコストに含まれる）

このような事例から、少なくとも治療効果を損ねずにコストを下げ、value を高めることは、新規の試験のデータを待たずとも可能であると思われる。各学会が出す診療ガイドラインは、日本医療機能評価機構が厚労省の委託事業として行っている作成マニュアル（https://minds.jcqhc.or.jp）において、医療経済についても記載することが求められているが、実際には癌の診療ガイドラインでは全くそのような部分は見当たらない。

JCOG 医療経済小委員会では、次なる調査として、2025 年から各癌腫の診療ガイドラインについて下表のような項目を精査し、まずは「効果・副作用が同等もしくは違うというエビデンスがないのであれば、シンプルに値段が安いものを上位で推奨する」ことを学会のガイドライン委員会に働きかけることを予定している。これにより「患者の利益を全く損ねずにコストを下げる」ことができるはずである。



この働きかけにあたっては、国立保健医療科学院などとの協力をすべく、すでに中医協の要請により保健医療科学院が開始している「費用対効果評価と診療ガイドラインのあり方に関する検討会」に JCOG 医療経済小委員会の國頭が参加している。

診療ガイドラインにコストのことを盛り込むことができれば（そういう項目を作ることができれば）、下記に示すような減量試験など治療最適化の研究の成果もそこに速やかに記載することができる。

4-2.CSPOR 介入研究

4-1-3.に記載したように、最近の ICI や分子標的薬剤（TKI など）は、至適な用量設定がされていないという疑問が持たれていて、FDA では治療の最適化のために project optimus（https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus）を立ち上げ、新薬の用量設定の適正化を図っている。

すでに市販され使用されている薬剤の、optimization（最適化）研究、もしくは de-escalation（軽減化）研究については、すでに JCOG の「投与期間短縮」の研究を紹介したが、CSPOR と SCP は投与量に関して過量である可能性が高い薬剤を取り上げ、用量減量すなわち「減薬」によるその治療の最適化と”value”の向上を目指す臨床試験を行っている。

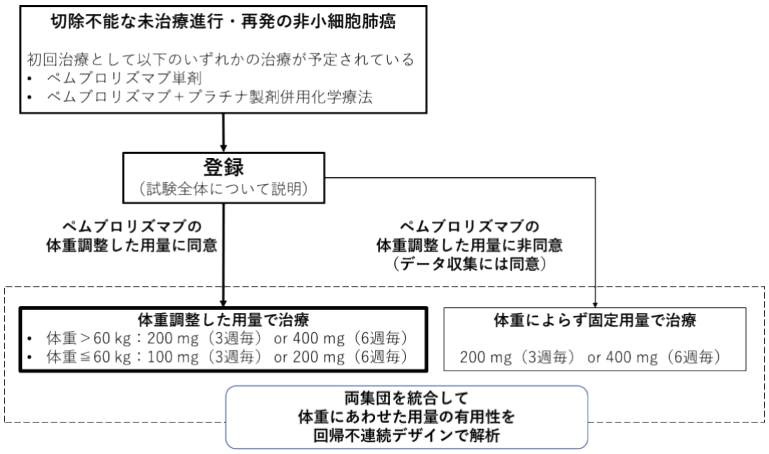
このような試験は製薬企業のサポートは絶対に得られないため、AMED など公的研究費の支援を申請しており、採択もされてはいるが、用途も制限されまたそもそも予算額が絶対的に不足しており、公益財団法人である CSPOR の「持ち出し」によって行われている。SCP は健保連からの調査研究費他で支援しているが、それでも足りない。研究者側の熱意と自己犠牲に頼る研究体制は長続きしないが、AMED 側はそのような大きな視野に欠けるようで、残念である。

4-2-1.CSPOR LC-08：PRICE study（未治療進行・再発非小細胞肺癌に対するペムブロリズマブの至適投与量に関する試験、https://jrct.niph.go.jp/latest-detail/jRCTs031230682）

本研究は、進行・再発非小細胞肺癌患者を対象に、PD-1 経路阻害薬ペムブロリズマブの至適投与量を検討する試験である。ペムブロリズマブの投与量は 3 週毎投与で当初体重あたり 2mg/kg と設定されたが、その後確たるエビデンスなしに（製薬企業曰く「利便性のため」）に一律 200mg とされた。この投与量に関しては、特に平均的な体格（体重 60kg 程度）の日本人には明らかに過量である。

本試験ではペムブロリズマブ+/-化学療法で初回治療を受ける非小細胞肺癌患者を体重で投与量を決定し、60kg 以下の患者は 100mg で、60kg 超の患者を 200mg で治療する（下図シェーマ参照）。解析は回帰不連続デザインで行い、無増悪生存期間（PFS）を主要評価項目とし、200mg 投与（体重 60kg 超）の群が体重での用量設定に近い 100mg 投与（体重 60kg 以下）の群に勝るかどうかを検討する。予定登録患者数は 450 人であり、登録期間は 2.5 年、追跡期間は 1.5 年で計画された。

今後国立がん研究センター研究所薬効試験部と協力して、ペムブロリズマブの薬物動態に関する附随研究を行っていく予定である。



2024 年 4 月に開始したが、臨床研究法上の特定臨床研究として審査・承認した東京医科大学の臨床研究審査委員会（CRB）が不備により認定を取り消されたため、国立がん研究センター中央病院の CRB に移管しており、そのこともあって登録が遅れ、2024 年末段階で 60 例の登録にとどまっている。各施設に積極的に呼びかけを行い、登録推進に努めている。予定では 2026 年 9 月で登録終了、2029 年春に結果公表となる。

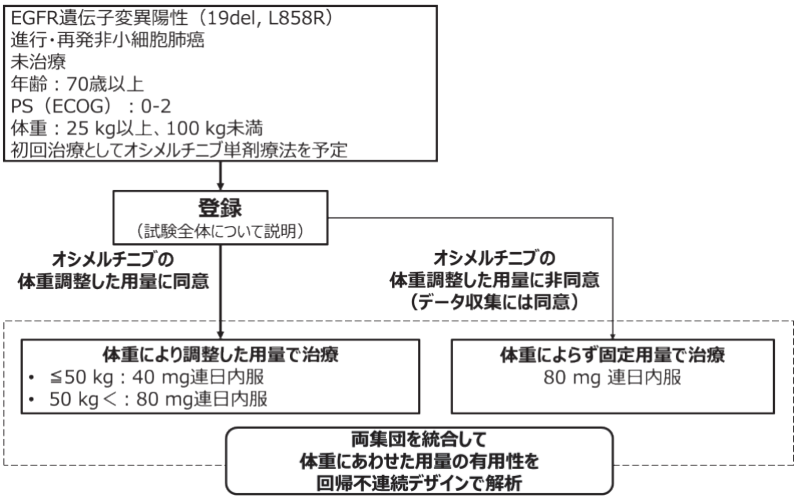
ちなみに仮説が検証された時の経済学的意義の試算をすると、ペムブロリズマブの 2023 年度売上は 1650 億円だが、非小細胞肺癌はその 1/3 として 550 億円と推定する。体重が標準以下の半数の患者では半分量への減量が可能となるので全体の 1/4 を節約されることになり、年間で約 140 億円の節約となる。

一方で、試験遂行による節約効果もあり、220 人の患者で減量予定だが、75%の患者が同意するとして、165 人で減量投与される。一回量が 21 万円のバイアル 2 つから 1 つになるので一回につき 21 万円節約される。ペムブロリズマブの平均投与期間は 10 ヶ月程度、3 週に 1 回投与だから 14 回程度の投与として一人当たり 294 万円の節約、全体で約 4 億 8500 万円が節約される。

4-2-2.CSPOR LC-09：MONEY study（未治療進行・再発非小細胞肺癌に対するオシメルチニブの至適投与量に関する多施設共同研究）[21)]

本研究は、70 歳以上の高齢で Epidermal Growth Factor Receptor activating mutation（EGFRm）を有する未治療進行・再発非小細胞肺癌患者を対象に、EGFR 阻害剤であるオシメルチニブの至適投与量を検討する試験である。オシメルチニブの投与量は 80mg/d とされているが、実際には用量設定のための臨床試験では 20〜240mg/d で奏効率に差はなく、かつその後の薬物動態研究でもその範囲内の投与量では drug exposure と奏効には相関はなく、ただ下痢や皮疹などの毒性とは相関があった。よって特に体格の小さい高齢者では過量である可能性が高い。

本試験ではオシメルチニブで初回治療を受ける 70 歳以上の EGFRm 非小細胞肺癌患者を体重で投与量を決定し、50kg 以下の患者は 40mg で、50kg 超の患者を 80mg で治療する（下図シェーマ参照）。解析は回帰不連続デザインで行い、無増悪生存期間（PFS）を主要評価項目とし、80mg 投与（体重 50kg 超）の群に比べて 40mg 投与（体重 50kg 以下）の群が非劣性を示せるかどうかを検討する。予定登録患者数は 550 人であり、登録期間は 2.5 年、追跡期間は 2 年で計画された。



2023 年 9 月に開始し 2024 年末段階で 190 例が登録されているにとどまっている。各施設に積極的に呼びかけを行い、登録推進に努めている。予定では 2026 年 3 月で登録終了、2029 年春に結果公表となる。

ちなみに仮説が検証された時の経済学的意義の試算をすると、オシメルチニブの 2023 年度売上は 1070 億円だが、うち 70 歳以上は 60%と推定されるので 640 億円。体重が標準以下の半数の患者では 80mg 錠剤（18540 円）から 40mg 錠剤（9670 円）への切り替えが可能となるので全体の 1/4 弱を節約でき、年間で約 150 億円の節約となる。

一方で、試験遂行による節約効果もあり、250 人の患者で減量の規定だが、80%の患者が同意するとして、200 人で減量投与される。一日量が 80mg 錠剤（18540 円）から 40mg 錠剤（9670 円）になるので 8870 円節約、投与期間は 20 ヶ月（600 日）程度とされているので一人当たり 532 万円の節約、全体で約 10 億 6000 万円の節約となる。

4-2-3.AMED 班会議と新規研究

上記 MONEY 研究は AMED 革新的がん医療実用化研究事業の令和 5 年度二次公募の領域 5（新たな標準治療を創るための研究）；領域 5-4-1（高額薬剤の投与期間等を検討する多施設共同臨床試験）に、JCOG1701 および JCOG1905 とともに採択されており、また PRICE 研究は同じく AMED 革新的がん医療実用化研究事業の令和 6 年度二次公募の Field 4（がんの標準治療の確立、ライフステージに応じたがん治療に関する研究）；Field4-1-2（高額薬剤の投与法等を検討する多施設共同臨床試験）に採択されている。ただこの 2 年で AMED に採択された「高額薬を使ったがん治療の適正化」に関する研究課題は以上 4 つのみであり、すなわち SCP 以外にはそうした研究に目を向ける動きがほとんどないことを表している。

これは、製薬企業スポンサーの研究では企業が大々的に広報宣伝を行い、また参加施設も積極的にリクルートするが、AMED 自体はそのような積極的な活動をしないこと、またそもそも AMED の研究予算は企業主催の研究に比べて 10 分の 1 にも満たない、などの事情が絡んでいると思われる。

AMED に採択された課題に関しては進捗状況の管理のため、「班会議」を開くのが一般的であり、SCP も 2024 年 1 月 8 日に MONEY 研究の、また 2025 年 1 月 16 日に MONEY 研究と PRICE 研究の「國頭班会議」（と言う名称になる）をオンラインで開催した。会議に当たっては、こうした治療適正化研究の啓蒙のため、研究参加施設の医師や研究補助員のみでなく、AMED や健保連、さらにはメディア（NHK など）・規制当局（財務省など）・そのほか（日本総研など）に広く声をかけ、オブザーバー参加をいただいた。2025 年の会議には、研究の幅を広げるため、がん研究センター研究所や（PRICE や MONEY 研究の対象疾患である）進行肺癌以外の医師にも広報し、出席者があった。

このような班会議の活動から、PRICE においては国立がん研究センター研究所薬効試験部の濱田哲暢先生と、ペムブロリズマブの薬効動態（血中濃度測定）解析の附随研究を企画した。また、比較的早期の肺癌の術後治療（再発予防目的）における治療の適正化研究について、呼吸器外科の専門医グループと新規研究の立案中である。

4-3.海外との協調

海外でも、効果を維持しながら薬剤費を下げ、sustainability と affordability の維持に努めようという動きはあり、2016 年に value in cancer care consortium（Vi3c）が設立された。この組織は 2021 年に optimal cancer care alliance（OCCA）と改称され、「患者さん一人ひとりが，がんを効果的に治療するために必要な最適量の薬剤を受け取れるようにする」ことを使命として活動を続けている（https://optimalcancercare.org）が、製薬企業とのコンフリクトがあり、活動資金も十分ではない。

しかしながらそれでも、慢性骨髄性白血病の治療薬や前立腺癌の治療薬で「効果を保ちながら投与量を減らす」研究に成功している。また高額薬の代表格である免疫チェックポイント阻害剤について、投与量を削減したり投与期間を短縮したりする研究の取りまとめを行っている（この中には、JCOG1701 や JCOG1905 など日本からの研究も含まれる）。

OCCA の初代理事長の Ian F. Tannock 博士からの招待もあり、SCP は 2022 年 5 月 21 日の OCCA 第一回オンライン会議に出席し、その内容は第一回の JCOG 医療経済小委員会で報告された。また 2023 年 9 月 11～12 日に行われた OCCA 第三回会議（オンライン：プログラムは下記）にも出席し、JCOG1701 研究、PRICE および MONEY 研究についてプレゼンテーションを行い、全体討論に参加した。

OPTIMAL CANCER CARE ALLIANCE
Optimal Dosage. Best Outcome.

CENTER FOR PERSONALIZED THERAPEUTICS

3rd Optimal Cancer Care Alliance Meeting

ADDRESSING THE IMPORTANCE OF OPTIMAL DOSING OF ANTICANCER AGENTS

September 11, 2023 (Day 1)

Time (EDT)	Abstract #	Presenter	Location	Topic
2.00 pm		Dr. Tannock	Toronto	Introduction (& chair)
2.05 pm		Dr. Kesselheim	Boston	*FDA and optimal dosing*
2.30 pm	Discussion			
2.45 pm	103	Dr. Savard	Ottawa	The Rethinking Clinical Trials (REaCT) program: optimising patient care through pragmatic, practice-changing, patient-centred research
3.05 pm	116	Dr. Ng	Ottawa	REaCT 5G: A randomized study comparing bone pain after 5 days of filgrastim or one day of pegfilgrastim for primary febrile neutropenia prophylaxis during neo-/adjuvant chemotherapy for early breast cancer
3.15 pm	117	Dr. El Kababji	Ottawa	Rescuing poorly accruing clinical trials with AI-generated synthetic data
3.25 pm	Discussion			
3.40 pm	104	Dr. Araujo	Brazil	Prescription pattern of abiraterone in Brazil - a survey of medical oncologists
3.50 pm	108	Dr. Bromley	UK	Comparison of standard dose and reduced dose treatment of metastatic prostate cancer with enzalutamide, apalutamide or darolutamide: a rapid review
4.00 pm	111	Dr. Turco	Belgium	EORTC 2238 "DeEscalate", a pragmatic trial to revisit Intermittent Androgen Deprivation Therapy in the era of new AR pathway inhibitors
4.10 pm	114	Dr. Stadler	Chicago	Extended relugolix intervals for prostate cancer
4.20 pm	Discussion			
4.35 pm	112	Dr. Lacombe	Belgium	The EMA Cancer Medicines Forum: a way forward for treatment optimisation
4.45 pm	113	Dr. Corrie	UK	Pilot of a UK process to fund dose optimisation research studies
4.55 pm	115	Dr. De Backer	Belgium	A new approach for clinical trials testing a less intensive treatment regimen
5.05 pm	124	Dr. Gandhi	Houston	Science-driven Clinical Dosing of Ibrutinib in Chronic Lymphocytic Leukemia
5.15 pm	Discussion			
5.30 pm	**Close**			

OPTIMAL CANCER CARE ALLIANCE
Optimal Dosage. Best Outcome.

CENTER FOR PERSONALIZED THERAPEUTICS

3rd Optimal Cancer Care Alliance Meeting

ADDRESSING THE IMPORTANCE OF OPTIMAL DOSING OF ANTICANCER AGENTS

September 12, 2023 (Day 2)

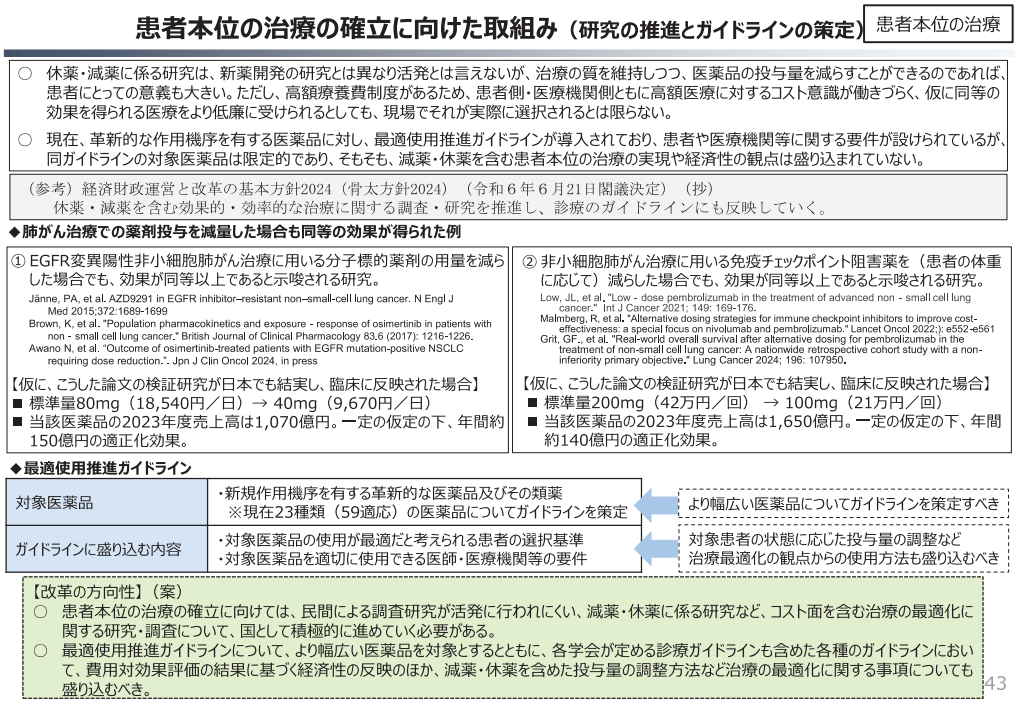
Time (EDT)	Abstract #	Author	Location	Topic
9.00 am		Dr. Ratain	Chicago	Introduction (& chair)
9.05 am		Dr. Bouche	Belgium	*Optimising the funding of optimisation trials – Thinking long-term*
9.30 am	Discussion			
9:45 am	123	Dr. Sonke	NL	Primary outcome of the Phase 3 Sonia trial
9.55 am	110	Dr. Tsukita	Japan	Multi-institutional study of osimertinib dose-optimization in non-small cell lung cancer patients with EGFR activating mutation aged 70 years or older (MONEY study)
10.05 am	Discussion			
10.20 am	105	Dr. Goto	Japan	Trial in Progress: Randomized phase III study comparing cessation or continuation of PD-1 Pathway Blockade for patients with advanced non-small-cell lung cancer (SAVE study)
10.30 am	109	Dr. Kunitoh	Japan	Pembrolizumab dose-optimization study with regression discontinuity design in patients with non-small cell lung cancer to avert excessive toxicity and cost (PRICE study)
10.40 am	102	Dr. Marimuthu	India	Real World Outcomes with Induction chemotherapy & Low dose Nivolumab for Stage III NSCLC ineligible for upfront Local therapy - A Retrospective study from a Tertiary Referral Centre in India
10.50 am	101	Dr. Georgy	India	Outcomes with Induction Low Dose Nivolumab plus Chemotherapy for Locally Advanced Inoperable Non-Metastatic HNSCC: Possible Minimum Dose Threshold for Efficacy?
11.00 am	Discussion			
11.15 am	118	Dr. Wisely	India	Low dose nivolumab with TKI in advanced HCC: Real world outcomes from India
11.25 am	120	Dr. John	India	Nivolumab usage patterns combined with TKI for mRCC: financial toxicity and clinical outcomes from self-paying patients in India. Is low dose an option when access is limited?
11.35 am	106	Dr. Peer	Bethesda	A Preliminary Pharmacokinetic Analysis of Standard vs Extended Interval Dosing of Pembrolizumab and Nivolumab in Patients with Advanced Solid Tumors
11.45 am	Discussion			
12.00 pm	119	Dr. Danson	UK	Optimising PD1 monoclonal antibody treatment in patients with advanced melanoma: Patient experience in the DANTE Trial
12.10 pm	107	Dr. Merrick	UK	Patient perspectives on OPTimising Immune Checkpoint inhibition (OPTIC) – a qualitative study
12.20 pm	121	Dr. Coschi	Canada	A survey of Canadian Healthcare providers' and patient representatives' understanding of Project Optimus
12.30 pm	Discussion			
12.45 pm	**Close**			

4-4.規制当局への働きかけ

現在では臨床研究の主体は製薬企業がスポンサーとなってなされるが圧倒的に多く、また上述のように我が国では臨床研究法によってアカデミア主体の臨床試験は非常にやりづらくなってきている。この結果、アカデミアに籍を置く研究者の発想も、患者の利益よりも「市場の利益」に偏ってしまっていると指摘されている。

すぐに理解できるように、製薬企業は自社の売り上げの減少をもたらすような高額薬剤の optimization（最適化）／de-escalation（軽減化）研究をサポートすることは決してない。よって、このような研究は公的なサポートが必須であるが、従来は財務省や厚生労働省も「医療費の削減」を言う割に実際に「手を出す」ことはあまりなかった。SCP は財務省主計局などへの働きかけを通して、AMED の公募に「高額薬剤の投与法等を検討する多施設共同臨床試験」のような研究課題を入れる活動を行なってきた。

最近になってようやく政府側も本腰を入れて取り組む姿勢を見せ始め、例えば 2024 年度の経済財政運営と改革の方針（「骨太の方針」、https://www5.cao.go.jp/keizai-shimon/kaigi/cabinet/honebuto/2024/2024_basicpolicies_ja.pdf、2024 年 6 月 21 日）では「休薬・減薬を含む効果的・効率的な治療に関する調査・研究を推進し、診療のガイドラインにも反映していく」と明記された。さらに 2024 年 11 月 13 日の財政制度等審議会財政制度分科会には、下記のように「患者本位の治療の確立に向けた取組み」として、下記のような最適化研究推進に関する提言が盛り込まれている。
（https://www.mof.go.jp/about_mof/councils/fiscal_system_council/sub-of_fiscal_system/proceedings/material/zaiseia20241113/01.pdf）



患者本位の治療の確立に向けた取組み（研究の推進とガイドラインの策定） 患者本位の治療

○ 休薬・減薬に係る研究は、新薬開発の研究とは異なり活発とは言えないが、治療の質を維持しつつ、医薬品の投与量を減らすことができるのであれば、患者にとっての意義も大きい。ただし、高額療養費制度があるため、患者側・医療機関側ともに高額医療に対するコスト意識が働きづらく、仮に同等の効果を得られる医療をより低廉に受けられるとしても、現場でそれが実際に選択されるとは限らない。

○ 現在、革新的な作用機序を有する医薬品に対し、最適使用推進ガイドラインが導入されており、患者や医療機関等に関する要件が設けられているが、同ガイドラインの対象医薬品は限定的であり、そもそも、減薬・休薬を含む患者本位の治療の実現や経済性の観点は盛り込まれていない。

（参考）経済財政運営と改革の基本方針2024（骨太方針2024）（令和６年６月21日閣議決定）（抄）
休薬・減薬を含む効果的・効率的な治療に関する調査・研究を推進し、診療のガイドラインにも反映していく。

◆肺がん治療での薬剤投与を減量した場合も同等の効果が得られた例

① EGFR変異陽性非小細胞肺がん治療に用いる分子標的薬剤の用量を減らした場合でも、効果が同等以上であると示唆される研究。

Jänne, PA, et al. AZD9291 in EGFR inhibitor–resistant non–small-cell lung cancer. N Engl J Med 2015;372:1689-1699
Brown, K, et al. "Population pharmacokinetics and exposure - response of osimertinib in patients with non - small cell lung cancer." British Journal of Clinical Pharmacology 83.6 (2017): 1216-1226.
Awano N, et al. "Outcome of osimertinib-treated patients with EGFR mutation-positive NSCLC requiring dose reduction.". Jpn J Clin Oncol 2024, in press

【仮に、こうした論文の検証研究が日本でも結実し、臨床に反映された場合】
■ 標準量80mg（18,540円／日）→ 40mg（9,670円／日）
■ 当該医薬品の2023年度売上高は1,070億円。一定の仮定の下、年間約150億円の適正化効果。

② 非小細胞肺がん治療に用いる免疫チェックポイント阻害薬を（患者の体重に応じて）減らした場合でも、効果が同等以上であると示唆される研究。

Low, JL, et al, "Low - dose pembrolizumab in the treatment of advanced non - small cell lung cancer." Int J Cancer 2021; 149: 169-176.
Malmberg, R, et al. "Alternative dosing strategies for immune checkpoint inhibitors to improve cost-effectiveness: a special focus on nivolumab and pembrolizumab." Lancet Oncol 2022;1: e552-e561
Grit, GF., et al. "Real-world overall survival after alternative dosing for pembrolizumab in the treatment of non-small cell lung cancer: A nationwide retrospective cohort study with a non-inferiority primary objective." Lung Cancer 2024; 196: 107950.

【仮に、こうした論文の検証研究が日本でも結実し、臨床に反映された場合】
■ 標準量200mg（42万円／回）→ 100mg（21万円／回）
■ 当該医薬品の2023年度売上高は1,650億円。一定の仮定の下、年間約140億円の適正化効果。

◆最適使用推進ガイドライン

対象医薬品	・新規作用機序を有する革新的な医薬品及びその類薬 ※現在23種類（59適応）の医薬品についてガイドラインを策定	より幅広い医薬品についてガイドラインを策定すべき
ガイドラインに盛り込む内容	・対象医薬品の使用が最適だと考えられる患者の選択基準 ・対象医薬品を適切に使用できる医師・医療機関等の要件	対象患者の状態に応じた投与量の調整など治療最適化の観点からの使用方法も盛り込むべき

【改革の方向性】（案）
○ 患者本位の治療の確立に向けては、民間による調査研究が活発に行われにくい、減薬・休薬に係る研究など、コスト面を含む治療の最適化に関する研究・調査について、国として積極的に進めていく必要がある。
○ 最適使用推進ガイドラインについて、より幅広い医薬品を対象とするとともに、各学会が定める診療ガイドラインも含めた各種のガイドラインにおいて、費用対効果評価の結果に基づく経済性の反映のほか、減薬・休薬を含めた投与量の調整方法など治療の最適化に関する事項についても盛り込むべき。

43

このように、「当局」も一定の認識を得始めているようではあるが、変革の時期には仕組みを変更してもそのまま放置するともとに戻ってしまうとも指摘され、常にフォローアップし進化・進捗させる継続的な取組が必要になる。今後とも当局への働きかけを続けるとともに、また研究者側にも「製薬企業の意向に反し、その利益にならないテーマでも研究はできて、業績をあげることも可能である」と知らしめ、協力を得ていくことが重要と思われる。

4-5.他団体・組織との協調

JCOG や CSPOR のように直接的に共同研究を行っている「パートナー」（もしくは委託機関）の他、下記の施設とは定期的にまた不定期に連絡を取りつつ、研究事業の展開のため協力を乞うている。

・国立がん研究センター研究所薬効試験部：薬物動態解析などの附随研究に関して
・国立保健医療科学院：診療ガイドラインに医療経済を組み込むことに関して
・公益財団法人日本医療機能評価機構（Minds ガイドラインライブラリ）：上記同じ
・（株）日本総合研究所調査部：医療経済に関する助言、討論
・日本経済新聞、朝日新聞、東京新聞、NHK：広報活動などについて（下記 4－6.参照）
・新潮社：新書刊行予定

この他にも、できるだけ多くの団体・組織に研究の趣旨を理解してもらい、協力を仰ぐ必要があると考えている。関連学会にも働きかけたいところではあるが、学会は製薬企業のサポートなくしては成立しないので、製薬企業の不利益になるような「最適化研究」に積極的に関与することは難しいようであり、せいぜい単発的な話題として「取り上げてもらう」、といったところが残念ながら現状である。

4-6.広報活動

医療費の急増・財政の逼迫・保険医療システムの危機については、医療者にも一般にも、「なんとなく」は知られているが、はっきりと認識されているとは言い難い。「なんのために、こういう（さしあたってのメリットがなさそうな）研究活動をやっているのか」について理解を得ることができなければ、こちらが社会と乖離してしまうことになりかねない。研究を進め、事態の打開を図るには、一般（すなわち患者と家族）にも、医療者にも広報活動を行なって、正しい情報を広める必要がある。

広報活動に関しては、健保連事業よりも先に SCP が設立された事情もあり、一部、健保連調査事業のスタート以前に行なったもの・開始されたものも含まれるが、下記メディアなどを通して高額薬治療の現状を紹介し、問題点を指摘した。各々の詳細は SCP の HP（https://s-cp.or.jp）に記載されている。

- M3.com 連載”Cost, value and value trials”（2021.9 月～2022.11 月）
  単行本化「誰も考えようとしなかった癌の医療経済」（2023.7 月、中外医学社）
- 医学界新聞インタビュー　第 3439 号（2021.10.4）
- SCP ホームページ（2021.10.25 開設：https://s-cp.or.jp）
- デジタル朝日「論座」2022.1.6 配信
- 朝日新聞「ひと」2022.1.15 朝刊
- NHK おはよう日本（2022.6.5 放送）
- 東京新聞 2022.6.23・6.30 朝刊
- 日本海新聞「潮流」2022.5 月～10 月（毎月連載）
- ニッポン放送「ドクターズボイス」（2023.3.23 放送）
- Youtube SATOMI チャンネル（2023.4 月開設：
  https://www.youtube.com/@satomi_ch
- 財務省広報誌「ファイナンス」2023.4 月号
- 東京新聞 2023.8.31・9.7 朝刊（垣添忠生・対がん協会会長との対談）
- 公益財団法人札幌がんセミナー機関誌「The way forward」2023 年 12 月号（同上・垣添先生との対談詳細）
- NHK ニュース 7（2024.6.8 放送）
- 朝日新聞 2024.9.7 朝刊「多事奏論」
- NHK ニュース北海道（2024.11.1 放送）
- NHK おはよう日本（2024.12.3 放送）
- 雑誌「医薬経済」2024.12.15 号
- NHK みみより！解説（2025.1.23 放送）

5.今後の展望と課題

5-1.短期的活動

ここ数年の活動としては、まず第一に、診療ガイドラインにコストのことも盛り込むよう、JCOG 医療経済（小）委員会の活動を通して各学会に働きかけることがある。ただし臨床研究団体である JCOG 単独での提言ではインパクトに欠けるので、国立保健医療科学院や、診療ガイドラインマニュアルに関する厚労省委託事業である EBM 普及推進事業（Minds；母体は公益財団法人日本医療機能評価機構）、また健保連などと協議検討し、共同で提出することが必要と思われる。

第二に、現在すでに進行している PRICE や MONEY といった治療最適化の研究を完遂し、結果公表に繋げる必要がある。現時点ではこれらの症例集積は必ずしも順調とは言えないが、研究者側や患者の啓蒙を通して、研究の推進を図っていく。実際、JCOG1701 や JCOG1905 も症例集積には非常に苦労していたが、特に JCOG1701 は最適化研究としては世界最大規模の臨床試験としてなんとか完遂に漕ぎ着けている。さらに、これらの試験の結果を正しく評価し、医学界の中のみならず、広く一般にその意義を訴えていかねばならない。このためメディアとの協調も必要になる。

第三に、単発の研究で終わってしまってそのまま立ち枯れでは「徒花」に終わるので、術後治療の最適化を含め、新規のアイデアを具体化し、またさらに新規の研究を企画立案していくことが重要である。そのためには OCCA など海外の研究者との協力が必須と思われる。

5-2.長期的活動

健保連による本事業が終了した後も、仮に今 SCP が行なっている・行おうとしている活動が全てうまくいったとして、3 年や 5 年で「日本の危機」が回避できるはずもない。SCP は主に癌領域の課題に取り組んでいるが、治療の最適化・コストの削減などは全ての分野で行わなければならない。そのためには現在の活動の成果を示しつつ、医学界全体に、また社会一般に問題の存在とその解決をアピールし、その一方で地道な研究活動を続けていく必要がある。

5.3.結語

医療費の高騰や保険医療制度の危機、財政の逼迫などは社会一般にも認識はされ、「無駄を省く」がその解決策として提唱されている。しかしながら、そういった「解決策」のほとんどは、「他人の無駄」を指摘するだけで、「あいつらが無駄をしている」と非難し

ているにすぎない。極端な場合は「あいつらが無駄をしているのだから、それをどうにかするのが先で、俺たちが身を削る謂れはない」と言うような、モラルハザードを疑うような論調も見聞きする。

SCP は、そんな態度は卑しいと考える。まずは自分たちのやっている「無駄」を削るべきで、実際、我々は癌医療の専門家なのだから、例えば生活習慣病の医療などよりも癌医療について「どこに無駄があるか、どこが削れるか」がわかるはずである。まずは自分たちの熟知している領域で研究を進め、それを提示して他の領域の方々にも協力を仰ぐ、というのが我々の方法だが、果たして破局的な結末を回避できるかどうか、「間に合うかどうか」はわからない。

ただ、間に合わないかもしれないから諦め、自分たちだけのことを考えればいい、と責任を放棄してしまっては、将来世代に対して顔向けができない。

6.文献（*のついているものは巻末に全文を掲載）

1) Booth CM, et al. Common sense oncology: outcome that matter. Lancet Oncol. 2023;24:833-835
2) Bach PB. Ramucirumab for Colon Cancer and the Problem of Rising Prices Independent of Benefits. Oncologist 2015;20:983-4.
3) Papanicolas I, et al. Health Care Spending in the United States and Other High-Income Countries. JAMA 2018;319:1024-1039.
4) Moses H 3rd, et al. The anatomy of medical research: US and international comparisons. JAMA 2015;313:174-89.
5) Kunitoh H, et al. A Survey of Researchers on Clinical Trials Act. Jpn Pharmacol Ther 2019; 47 Suppl 1: s59-66
6) Schnipper LE, et al: American Society of Clinical Oncology statement: A conceptual framework to assess the value of cancer treatment options. J Clin Oncol 2015; 33: 2563-2577
7) Cherny NI, et al: A standardised, generic, validated approach to stratify the magnitude of clinical benefit that can be antici- pated from anti-cancer therapies: The European Society for Medical Oncology Magnitude of Clinical Benefit Scale (ESMO-MCBS). Ann Oncol 2015; 26: 1547-1573
8) Kunitoh H, et al. A phase III study of adjuvant chemotherapy in patients with completely resected, node-negative non-small cell lung cancer (JCOG 0707). JTCVS Open 2020;4:90-102.
9) *Takei H, et al. Prospective, Multi-Institutional Observational Study of Deterioration in Activities of Daily Living in Elderly Patients After Lung Cancer Surgery. JTO Clin Res Rep 2023;4 :100550.
10) Nomura S, et al. A randomized phase III study comparing continuation and discontinuation of PD-1 pathway inhibitors for patients with advanced non-small-cell lung cancer (JCOG1701, SAVE study). Jpn J Clin Oncol 2020;50:821-825.
11) *Osawa T, et al. Real-world treatment trends for patients with advanced prostate cancer and renal cell carcinoma and their cost—a survey in Japan. Jpn J Clin Oncol. 2024;54:1062-1070.
12) *Imaoka H, et al. Current status of the cost burden of first-line systemic treatment for patients with advanced hepatocellular carcinoma in Japan, 2021–22. Jpn J Clin Oncol. 2024;54:1071-1077.
13) *Takahashi N, et al. High cost of chemotherapy for gynecologic malignancies. Jpn J Clin Oncol. 2024;54:1078-1083.

14) *Watanabe K, et al. High-cost treatments for advanced lung cancer in Japan (Lung Cancer Study Group of the Japan Clinical Oncology Group). Jpn J Clin Oncol. 2024;54:1084-1092.
15) *Iwatani T, et al. Status of incremental costs of first-line treatment recommended in Japanese clinical guidelines for metastatic breast cancer patients. Jpn J Clin Oncol. 2024;54:1093-1099.
16) *Nishina T, et al. A real-world survey on expensive drugs used as first-line chemotherapy in patients with HER2-negative unresectable advanced/recurrent gastric cancer in the stomach cancer study group of the Japan clinical oncology group. Jpn J Clin Oncol. 2024;54:1100-1106.
17) *Takashima A, et al. Real-world treatment costs of first-line treatment for metastatic colorectal cancer: a survey of the JCOG colorectal cancer study group. Jpn J Clin Oncol. 2024;54:1107-1114.
18) *Yokoyama K, et al. Frequency of use and cost in Japan of first-line palliative chemotherapies for recurrent or metastatic squamous cell carcinoma of the head and neck. Jpn J Clin Oncol. 2024;54:1115-1122.
19) *Motomura K, et al. Cost of medical care for malignant brain tumors at hospitals in the Japan Clinical Oncology Group brain-tumor study group. Jpn J Clin Oncol. 2024;54:1123-1131.
20) *Kunitoh H, et al. Confronting the problems we had hoped to avoid. Jpn J Clin Oncol. 2024;54:1059-1061.
21) *Tsukita Y, et al. Multi-institutional study of osimertinib dose-optimization in non-small cell lung cancer patients with EGFR activating mutation aged 70 years or older ('MONEY' trial). Jpn J Clin Oncol. 2024;54:730-734.

ORIGINAL ARTICLE

Prospective, Multi-Institutional Observational Study of Deterioration in Activities of Daily Living in Elderly Patients After Lung Cancer Surgery

Hidefumi Takei, MD,[a,b] Hideo Kunitoh, MD,[c,*] Masashi Wakabayashi, MSc,[d] Tomoko Kataoka, DDS,[d] Yuta Sekino, MD,[d] Tomonori Mizutani, MD,[e] Masahiro Tsuboi, MD,[f] Norihiko Ikeda, MD,[g] Hisao Asamura, MD,[h] Morihito Okada, MD,[i] Makoto Takahama, MD,[j] Yasuhisa Ohde, MD,[k] Jiro Okami, MD,[l] Satoshi Shiono, MD,[m,n] Keijyu Aokage, MD,[f] and Shun-ichi Watanabe, MD,[o] on Behalf of the Lung Cancer Surgical Study Group of the Japan Clinical Oncology Group, Japan

[a]*Department of Thoracic Surgery, Kyorin University, Tokyo, Japan*
[b]*Department of Thoracic Surgery, Showa University, Tokyo, Japan*
[c]*Department of Medical Oncology, Japanese Red Cross Medical Center, Tokyo, Japan*
[d]*Japan Clinical Oncology Group Data Center/Operations Office, National Cancer Center Hospital, Tokyo, Japan*
[e]*Department of Medical Oncology, Kyorin University, Tokyo, Japan*
[f]*Department of Thoracic Surgery, National Cancer Center Hospital East, Kashiwa, Japan*
[g]*Department of Surgery, Tokyo Medical University, Tokyo, Japan*
[h]*Division of Thoracic Surgery, Keio University, Tokyo, Japan*
[i]*Department of Surgical Oncology, Hiroshima University Hospital, Hiroshima, Japan*
[j]*Department of General Thoracic Surgery, Osaka City General Hospital, Osaka, Japan*
[k]*Department of Thoracic Surgery, Shizuoka Cancer Center, Shizuoka, Japan*
[l]*Department of General Thoracic Surgery, Osaka International Cancer Institute, Osaka, Japan*
[m]*Department of Thoracic Surgery, Yamagata Prefectural Central Hospital, Yamagata, Japan*
[n]*Department of Surgery II, Faculty of Medicine, Yamagata University Hospital, Yamagata, Japan*
[o]*Department of Thoracic Surgery, National Cancer Center Hospital, Tokyo, Japan*

Received 4 March 2023; revised 7 July 2023; accepted 7 July 2023
Available online - 17 July 2023

***Corresponding author.**

Disclosure: Dr. Kunitoh reports receiving personal fees from Taiho Pharmaceutical, Daiichi-Sankyo, Merck Sharp & Dohme, Johnson and Johnson, Yakult Honsha, and AstraZeneca; and has a consulting or advisory role in Daiichi-Sankyo outside the submitted work. Dr. Wakabayashi reports receiving personal fees from Nihon Mediphysics Co. Ltd. outside of the submitted work. Dr. Mizutani reports receiving personal fees AstraZeneca KK, Chugai Pharmaceutical Co. Ltd. outside of the submitted work. Dr. Tsuboi reports receving personal fees from Johnson & Johnson Japan, AstraZeneca KK, Eli Lilly Japan, Chugai Pharmaceutical Co. Ltd., Taiho Pharma, Medtronic Japan, Ono Pharmaceutical Co. Ltd., Merck Sharp & Dohme, Bristol-Myers Squibb KK, Teijin Pharma, and Novartis; has a consulting or advisory role in AstraZeneca, Chugai Pharmaceutical Co. Ltd., Merck Sharp & Dohme, and Novartis; and received grants from Boehringer Ingelheim Japan, Merck Sharp & Dohme, AstraZeneca KK, Ono Pharmaceutical Co. Ltd., Bristol-Myers Squibb KK, MiRXES, and BMG outside of the submitted work. Dr. Ikeda reports receiving personal fees from AstraZeneca, Chugai pharma, Pfizer, Taiho pharma, Merck Sharp & Dohme, Boehringer Ingelheim, Eli Lilly, Ono pharma, Teijin, Nihon Mediphysics, Bristol-Meyers, and Olympus; received personal fees from Medtronics and Johnson & Johnson; and received grants from AstraZeneca, Chugai pharma, Pfizer, Taiho Pharma, Merck Sharp & Dohme, Boehringer Ingelheim, Eli Lilly, Ono pharma, Teijin, Nihon Mediphysics, and Fuji film outside of the submitted work. Dr. Asamura reports receiving grants from Taiho pharma, Johnson & Johnson, Covidien, Eli Lilly, AstraZeneca, and Astellas outside of the submitted work. Dr. Okada reports receiving personal fees from Taiho Pharmaceutical, Johnson & Johnson, Covidien, Eli Lilly, Chugai Pharma, AstraZeneca, Ono Pharmaceutical, and CSL Behring; and received grants from Taiho Pharmaceutical, Nippon Kayaku, Chugai Pharma, Covidien, Johnson & Johnson, Daiichi-Sankyo, Yakult Honsha, Eli Lilly Japan, Nihon Mediphysics, Pfizer, Mochida Pharmaceutical Co. Ltd., Shionogi, Ono Pharmaceutical, and Kyowa Hakko Kirin outside of the submitted work. Dr. Shiono reports receiving personal fees from Novartis, AstraZeneca, Johnson & Johnson, Intuitive, Covidien, Chugai Pharmaceutical, Eli Lilly, and KM Biologics outside of the submitted work. Dr. Aokage reports receiving personal fees from Johnson & Johnson KK, Eli Lilly Japan KK, AstraZeneca KK, Chugai Pharmaceutical Co. Ltd., Teijin Pharma Ltd., Covidien Japan, Medical tribune KK, and CSL Behring KK; and has a consulting or advisory role in Taiho Pharmaceutical Co. Ltd., Olympus Corporation, and AstraZeneca KK outside of the submitted work. The remaining authors declare no conflict of interest.

This study was presented at the World Conference on Lung Cancer, a worldwide virtual event held on September 8-14, 2021.

Address for correspondence: Hideo Kunitoh, MD, Department of Medical Oncology, Japanese Red Cross Medical Center, 4-1-22 Hiro-o, Shibuya-ku, Tokyo 150-8935, Japan. E-mail: kunito_hideo@med.jrc.or.jp

Cite this article as: Takei H, Kunitoh H, Wakabayashi M, et al. Prospective, multi-institutional observational study of deterioration in activities of daily living in elderly patients after lung cancer surgery. *JTO Clin Res Rep*. 2023;4:100550.

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2023.100550

ABSTRACT

Introduction: To determine the rate of deteriorating activities of daily living (ADL) and to investigate predictive factors in elderly patients undergoing surgery for NSCLC.

Methods: Patients with NSCLC aged 75 years or older who underwent curative surgical resection were evaluated using the Tokyo Metropolitan Institute of Gerontology Index of Competence Instrumental ADL (TMIG-IADL) and the Japanese version of EuroQol 5-dimensions 5-level (EQ-5D-5L) quality-of-life scale administered at baseline and at 6 months postoperative. The primary end point was the rate of living patients without substantial deterioration of TMIG-IADL, defined as a decline greater than or equal to three points. Multivariable logistic regression was performed to determine risk factors for deteriorating ADL.

Results: Between May 2019 and May 2020, 876 of the 986 screened patients enrolled from 47 institutions were eligible and included in the analysis. TMIG-IADL and EQ-5D-5L scores were obtained from 96.0% and 92.6% of the patients, respectively. At 6 months postoperative, 745 patients (85.1%, 95% confidence interval: 82.5%–87.3%) reported no significant ADL deterioration, and 96 of 841 patients (11.4%) with postoperative score data reported significant deterioration. The social domain was the most frequently affected activity. In multivariable analysis, poor performance status, low G8 geriatric screening score, segmentectomy (versus wedge resection), and surgery lasting less than 3 hours were associated with deteriorating ADL. Worsening EQ-5D-5L scores by minimally important difference or more were observed in 22.1% of the patients. Changes in TMIG-IADL and EQ-5D-5L scores were poorly correlated.

Conclusions: Approximately 15% of elderly patients with NSCLC experienced significant ADL deterioration at 6 months postoperative.

Keywords: Non–small cell; surgery; Elderly patients; Activities of daily living; Quality of life

Introduction

Lung cancer is a leading cause of cancer-related deaths in Japan, with more than 75,000 deaths reported in 2020. With the aging of the general population, the incidence of lung cancer is expected to increase, with more elderly patients undergoing surgical resection. According to a survey by the Japanese Society of Thoracic Surgery,[1] 44,859 patients in Japan underwent surgery for primary lung cancer in 2018 and nearly 60% of these patients were aged 70 years or older. In fact, 6115 of the patients who underwent resection (14%) were 80 years or older, and both the number and proportion continue to increase.

Many studies have investigated the postoperative outcomes of elderly patients with lung cancer. A Japanese study, which included 367 patients aged 80 years and older who underwent surgical resection for clinical stage I lung cancer[2] reported that serious complications occurred in 8.4% of the patients and that the rates of postoperative mortality and 5-year survival were 1.4% and 55.7%, respectively. A recent prospective cohort study by the Japanese Association for Chest Surgery[3] evaluated 895 octogenarians using a comprehensive scoring system for surgical risk and reported a 30-day postoperative mortality rate of 1.0% and a 3-year survival rate of 86.7%. This study[3] also identified several predictive factors for surgical risk and survival. However, most of the previous studies on elderly patients with NSCLC only evaluated postoperative morbidity and mortality[4,5] and overall survival (OS), and not functional outcomes.

Postoperative activities of daily living (ADL) are critically important for both patients and their families. Although the importance of functional outcomes in elderly populations has been reported,[6–10] few studies have evaluated postoperative ADL and quality of life (QOL) despite the notable impact of surgical stress on frailty in elderly patients.[5,11,12]

Whereas the prognosis of patients with lung cancer undergoing surgery has markedly improved, with 5-year OS rates of 90% or more for node-negative NSCLC, comorbidities including second primary cancers account for a significant portion of deaths.[13–15] Treatment for these comorbidities can be compromised by frailty owing to postoperative deterioration of the patient's physical condition.[16]

In elderly patients with lung cancer, therefore, ADL and QOL after surgery are important not only for their care and comfort but also for their prognosis. Without the information on postoperative ADL and QOL, patients and families cannot make well-informed choices for treatment among available options including surgery, radiotherapy, chemotherapy, immunotherapy, and supportive care.[10,17]

We conducted an observational study to evaluate postoperative ADL and QOL in elderly patients aged 75 years and older with NSCLC. We aimed to elucidate the rate of ADL deterioration in elderly patients undergoing surgical treatment for NSCLC and to determine the predictive factors for ADL deterioration. We used the Japanese version of EuroQol 5-dimensions

5-level (EQ-5D-5L),[18,19] a globally validated QOL assessment tool, and the Tokyo Metropolitan Institute of Gerontology Index of Competence Instrumental ADL (TMIG-IADL),[20,21] a 13-item validated scale for geriatric ADL and is the only scale of its kind available in Japan.

Here we report the ADL and QOL of patients at 6 months postoperatively, which are the main objectives of the study.

Materials and Methods

Eligibility

Figure 1 summarizes the study flow. Patients aged 75 years or older with radiologically suspected clinical stage 0 to III NSCLC were enrolled. Patients with tumors that were determined as amenable to complete resection and were planned to undergo primary surgery were included. The other inclusion criteria were as follows: (1) radical surgery scheduled within 14 days after enrollment; (2) competency to undergo comprehensive geriatric assessments using TMIG-IALD, G8 geriatric screening, Charlson comorbidity index (CCI), and engaged in social situations before surgery; and (3) competency to communicate in written Japanese. Pathologic diagnosis before surgery was not mandatory. Patients with active invasive malignancy with a disease-free period of shorter than 5 years, those with induction treatment or previous chemotherapy, and those with a history of previous surgical lung resection were excluded.

All patients provided written informed consent form before study enrollment. The present study was conducted according to the tenets of the Declaration of Helsinki and approved by the institutional review boards of all participating institutes (Japanese Red Cross Medical Center institutional review board approval number: 2019-973, on April 26, 2019). The study was registered with the UMIN Clinical Trials Registry (UMIN000036796).

Study Design and Treatment

This was a prospective, multi-institutional observational study conducted by the Lung Cancer Surgical Study Group of Japan Clinical Oncology Group.

Baseline geriatric function assessment before surgery was performed using TMIG-IADL[20,21] (see Supplementary Table 1*A* for specific questionnaires and scores) and G8[22] (see Supplementary Table 1*B* for specific questionnaires and scores). Baseline information on the social situation, such as habitation, CCI score[23] (see Supplementary Table 1*C* for specific conditions and scores), polypharmacy status,[24] and Japanese version EQ-5D-5L scores[18,19,25] (see Supplementary Table 1*D* for specific questionnaires), were also obtained before surgery. Surgical procedures were not specified in the study protocol. Patients with a final pathologic diagnosis of NSCLC were observed for ADL outcomes. Patients undergoing non-curative surgery and those with neuroendocrine tumors, such as small cell carcinoma, large cell neuroendocrine carcinoma, or carcinoid tumor were excluded from follow-up and subsequent data acquisition.

The EQ-5D-5L questionnaire was administered at 6 months, with responses directly mailed to the research office by the patients, whereas the TMIG-IADL questionnaire was administered by attending physicians at 6, 12, and 24 months to evaluate the long-term surgical impact on ADL. The present study reports the data at postoperative 6 months, which include the primary end point described below.

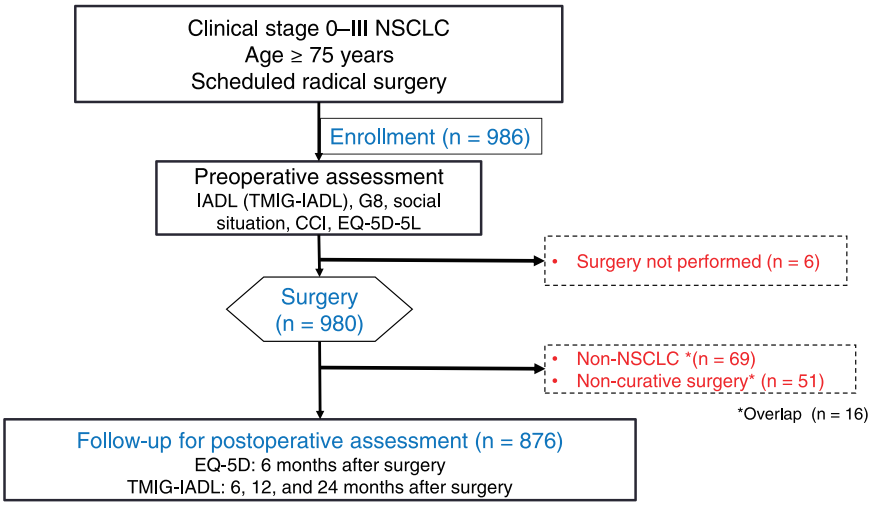


Figure 1. Study flow chart. CCI, Charlson comorbidity index; EQ-5D, EuroQol 5-dimensions; G8, geriatric screening tool; IADL, instrumental activities of daily living; TMIG-IADL, Tokyo Metropolitan Institute of Gerontology Index of Competence Instrumental Activities of Daily Living.

End Points

The primary end point was the rate of patients without ADL deterioration at 6 months after surgery. The TMIG-IADL[20,21] (Supplementary Table 1*A*) is a 13-item index of competence on three domains and includes five items in instrumental self-maintenance, four items in effectance (defined as effective interaction with one's environment) or intellectual activity, and four items in social role. A higher TMIG-IADL score indicates better capacity for activity. A previous Japanese study[26] revealed that the SD of TMIG-IADL score was 3.0 points in the elderly population; therefore, in the present study, the protocol-specified ADL deterioration was defined as a decline of at least three points in TMIG-IADL score or missing ADL data, because it was presumed that it is likely that most of the missing data actually indicate worsening of the patient's condition. This cutoff was on the basis of the distribution-based method to determine the minimally important difference (MID).[27] A sensitivity analysis with the threshold of "ADL deterioration" with a change in score of two points was also performed; this "criteria-modified" ADL deterioration was defined as TMIG-IADL score deterioration of at least two points or missing data.

Patients with missing postoperative TMIG-IADL data were classified as exhibiting ADL deterioration. The time point of 6 months was determined by consensus of the surgeons on the basis of the consideration that elderly patients were extremely unlikely to achieve functional recovery after 6 months after surgery.

The secondary end points were TMIG-IADL scores at 12 and 24 months, EQ-5D-5L score at 6 months, OS, relapse-free survival (RFS), and rates of serious postoperative complications, defined as greater than or equal to grade 3 within 30 days of surgery according to the Common Terminology Criteria for Adverse Events version 5.0-Japan Clinical Oncology Group criteria.

EQ-5D-5L QOL scores were calculated according to the method by Ikeda et al.[25] The MID was set at 0.061 for the EQ-5D-5L QOL scores, as reported by Shiroiwa et al.[28]

Statistical Analysis

The calculated sample size was 810 to obtain the half-width of a 95% confidence interval (CI) for the primary end point of within 3.5%. To account for ineligible patients, the planned sample size was set at 1000. A two-sided p value of less than 0.05 was considered statistically significant. The rate of patients without TMIG-IDAL deterioration and the CI were estimated on the basis of binomial distribution. To determine risk factors for ADL deterioration, univariable and multivariable logistic regression analyses were performed using various demographic and clinical variables (see Supplementary Table 1*E* for specific classifications of factors). These variables were used to estimate the rate of patients without ADL deterioration at 6 months. The OS and RFS are estimated using the Kaplan-Meier method.

Exploratory analyses were performed to determine the extent to which the three domains (instrumental self-maintenance, effectance, and social role) were affected in patients with ADL deterioration.

Deterioration of EQ-5D-5L scores by more than the MID and the CI were estimated on the basis of binomial distribution, and the correlation between the changes in EQ-5D-5L and TMIG-IADL scores was evaluated by Spearman's rank coefficient.

All statistical analyses were performed using SAS release 9.4 (SAS Institute, Cary, NC).

Results

Study Cohort

A total of 986 patients from 47 institutions were enrolled between May 20, 2019 and May 29, 2020. According to the final pathologic results, 876 patients had NSCLC, underwent complete resection, and were followed up to assess ADL and QOL (Fig. 1).

Table 1 details the study cohort characteristics. A total of 301 (34.4%) and 71 patients (8.1%) were aged 80 to 84 years and 85 years old and above, respectively. The remaining 504 patients (57.5%) were aged 75 to 79 years. Only three patients (0.3%) underwent pneumonectomy. Combined resection, such as pulmonary arterioplasty, bronchoplasty, and costal resection, was performed in 13 patients (1.5%).

The mean plus or minus SD of the baseline TMIG-IADL scores were 11.6 plus or minus 1.8. The SD was smaller than that previously reported in the general population, implying the study population, selected for surgical treatment, might be less heterogeneous in terms of ADL.

Survival and Postoperative Complications

During a median follow-up of 6.2 months, 14 of the 870 patients with available follow-up data died; the causes were primary lung cancer and other causes in 4 and 10 cases, respectively. Among 868 patients with data on relapse and follow-up, 44 patients died or experienced a relapse. The 6-month OS and RFS rates were 98.7% and 96.0%, respectively.

Grade 3 or higher postoperative complications occurred in 86 of the 876 patients (9.8%) who underwent complete resection. The most frequent complication was pulmonary leakage (3.1%) followed by lung infection (1.4%). Grade 4 postoperative complications occurred in 19 patients (2.2%). There were three deaths (0.3%) during the 30-day postoperative period.

Table 1. Baseline Characteristics and Surgical and Pathologic Factors of 876 Patients With NSCLC Who Underwent Complete Resection

Characteristics	Number of Patients (%)			
Sex				
Male	491 (56.1)			
Female	385 (43.9)			
Age (y)		Median: 79	Range: 75-92	Q1-Q3: 77-82
Clinical stage (UICC-TNM eighth classification)				
0	29 (3.3)			
IA1	131 (15.0)			
IA2	254 (29.0)			
IA3	158 (18.0)			
IB	134 (15.3)			
IIA	36 (4.1)			
IIB	96 (11.0)			
IIIA	35 (4.0)			
IIIB	3 (0.3)			
ECOG Performance status				
0	717 (81.8)			
1	152 (17.4)			
2	5 (0.6)			
3	1 (0.1)			
4	1 (0.1)			
Smoking history				
Never	363 (41.4)			
Ever	513 (58.6)			
Smoking years		Median: 43	Range: 0-66	Q1-Q3: 30-54
Number of daily cigarettes		Median: 20	Range: 0-80	Q1-Q3: 15-30
Emphysema				
No	623 (71.1)			
Yes	253 (28.9)			
Interstitial pneumonia				
No	788 (90.0)			
Yes	88 (10.0)			
Number of medications				
0	63 (7.2)			
1-3	255 (29.1)			
4-9	464 (53.0)			
$\geq$ 10	94 (10.7)			
Operation				
Wedge Resection	95 (10.8)			
Segmentectomy	133 (15.2)			
Lobectomy	639 (72.9)			
Bilobectomy	6 (0.7)			
Pneumonectomy	3 (0.3)			
Lymph node dissection				
ND0-1	371 (42.4)			
ND2a or more	505 (57.6)			
Combined resection				
No	863 (98.5)			
Yes	13 (1.5)			
Operation time (min)		Median: 157	Range: 33-524	Q1-Q3: 119-205
Histology				
Adenocarcinoma	678 (77.4)			
Squamous cell carcinoma	169 (19.3)			
Large cell carcinoma	1 (0.1)			
Adenosquamous carcinoma	16 (1.8)			
Others	12 (1.4)			

(continued)

Table 1. Continued

Characteristics	Number of Patients (%)				
Pathologic stage (UICC-TNM Eighth classification)					
0	31 (3.5)				
IA1	171 (19.5)				
IA2	207 (23.6)				
IA3	114 (13.0)				
IB	127 (14.5)				
IIA	45 (5.1)				
IIB	96 (11.0)				
IIIA	74 (8.4)				
IIIB	11 (1.3)				
Postoperative chemotherapy					
None	837 (95.5)				
Tegafur-uracil	30 (3.4)				
Platinum-based	8 (0.9)				
Missing	1 (0.1)				
Postoperative radiotherapy					
None	874 (99.8)				
Yes	1 (0.1)				
Missing	1 (0.1)				
G8 score at enrollment		Mean: 14.0	Median: 14	SD: 1.8	Range: 6.5–17	
CCI score		Mean: 0.9	Median: 0	SD: 1.2	Range: 0–8	
Baseline TMIG-IADL score		Mean: 11.6	Median: 12	SD: 1.8	Range: 2–13	Q1–Q3: 11–13

CCI, Charlson comorbidity index; ECOG, Eastern Cooperative Oncology Group; G8, geriatric screening tool; ND0, no node dissection; ND1, hilar node dissection; ND2, mediastinal node dissection; TMIG-IADL, Tokyo Metropolitan Institute of Gerontology Index of Competence Instrumental Activities of Daily Living; Q1, first quartile; Q3, third quartile; UICC, Union for International Cancer Control.

The TMIG-IADL Data

The TMIG-IADL questionnaire data were not available for 35 patients; the causes were death, incapacitating complications such as brain infarction, and other or unknown reasons in 19, nine, and seven patients, respectively (Fig. 2). Thus, the TMIG-IADL questionnaire data were successfully retrieved from 96.0% (841 of 876) of all patients and 98.1% (841 of 857) of all living patients.

At postoperative 6 months, the TMIG-IADL score changes ranged from −13 to +5; the scores worsened (by one point or more) in 306 (36.4%), stable in 350 (41.6%) and improved in 185 (22.0%), respectively, among the 841 patients for whom the scores were retrieved (Fig. 2). There was a statistically significant trend for worsening of the score ($p < 0.0001$ by Wilcoxon signed rank test), even after excluding dead or incapacitated patients for whom postoperative scores were not available. This trend was observed in almost every strata of sex, age, tumor stage, PS, smoking, operation method, or baseline G8, except for those who underwent wedge resection. A total of 95 patients underwent wedge resection, and their postoperative TMIG-IADL scores were missing/worsened in 31 (32.6%), stable in 41 (43.2%), and improved in 23 (24.2%), without significant overall change ($p = 0.18$ by Wilcoxon signed rank test)

Patients With and Without ADL Deterioration

In 745 of the 876 patients, the TMIG-IADL scores either improved (in 185 patients or 21.1%), did not change (in 350 patients or 40.0%), or worsened by less than or equal to two points (in 210 patients or 24.0%) at postoperative 6 months. TMIG-IADL score deterioration of greater than or equal to three points was observed in 96 patients (11.0%). The rate of patients without protocol-specified ADL deterioration (missing or worsened by ≥3 points) was 85.1% (95% CI: 82.5%–87.3%) (Fig. 2).

Because the SD of the study population was 1.8, we made a sensitivity analysis with the threshold of "ADL deterioration" changed to two scores. TMIG-IADL score deterioration of greater than or equal to two points was observed in 166 patients (19.7% of the 841 patients), and, including the missing data counted as deterioration, the criteria-modified overall rate of "patients without ADL deterioration" was 76.0% (95% CI: 73.1%–78.7%) (Fig. 2).

The rate of ADL deterioration was higher in patients with grade 3 or higher serious postoperative complications (n = 86) than in those without (n = 790). The rates

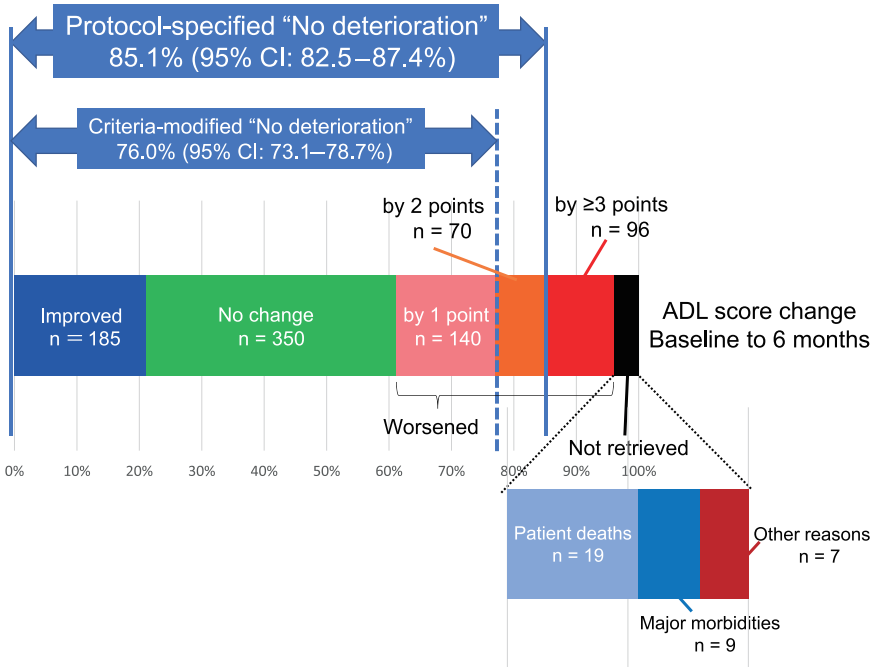


Figure 2. Changes of the TMIG-IADL (Tokyo Metropolitan Institute of Gerontology Index of Competence Instrumental Activities of Daily Living) scores from baseline to postoperative 6 months. Colored columns represent patients with TMIG-IADL scores improvement, no change, worsening by one point, worsening by two points, worsening by three points or more, or missing postoperatively. Those with missing data are then subclassified according to the reasons: patient deaths, major morbidities and others. The rate of patients without a score worsening by greater than or equal to three points or missing (protocol-specified "no deterioration") is the primary end point of the study, whereas criteria-modified "no deterioration" means TMIG-IADL score deterioration of greater than or equal to two points or missing data. ADL, activities of daily living; CI, confidence interval.

of patients without ADL deterioration were 61.6% and 87.6% in patients with and without serious postoperative complications, respectively, with an OR of 4.397 (95% CI: 2.711–7.129, $p < 0.0001$) to experience ADL deterioration. Of the 86 patients with grade 3 or higher serious postoperative complications, 21 (24.4%) and 16 (18.6%) reported stable and improved scores, respectively.

Subset Analysis of Factors Predicting ADL Nondeterioration

The univariable analysis was performed to identify factors associated with ADL nondeterioration at 6 months (Table 2). ADL deterioration was significantly more frequent among male patients, those aged 80 years or older, those with a performance status (PS) (by Eastern Cooperative Oncology Group) score of at least 1, and those with a smoking history of more than 20 years. Patients with emphysema, interstitial pneumonitis, low G8 scores, and high CCI scores were significantly more likely to experience ADL deterioration at 6 months. In addition, those treated with at least four regular medications were more likely to be associated with ADL deterioration at 6 months. There was no clear association of ADL deterioration with surgical procedures including the extent of lung resection; however, patients undergoing combined resection were significantly more likely to experience ADL deterioration.

Multivariable analysis indicated that only the following four clinical factors were associated with significant ADL deterioration, namely: (1) poor preoperative PS; (2) low G8 score; (3) segmentectomy (versus wedge resection); and (4) surgery lasting shorter than 3 hours (see Supplementary Table 1*F* for results of the multivariable analysis, which details the four significant factors).

Changes in Specific ADL Subscales

Among the 841 patients with available data on TMIG-IADL scores at 6 months, a score worsening of at least one point was present in the instrumental self-maintenance, effectance, and social role domains in 16.2%, 17.0%, and 36.4% of the patients, respectively (Table 3). The worsening seemed to be strongest in the social role domain. We considered that this finding might have reflected the coronavirus disease 2019 (COVID-19) pandemic, and performed additional analyses in patients categorized according to the time of enrollment.

Table 2. Univariable Analyses of Factors Associated With Nondeterioration of ADL by TMIG-IADL at 6 Months After Surgery

Factor	Classification	Number of Patients	Rate of No Deterioration (95% CI)	OR (95% CI)	*p* Value
Sex	Male	491	82.7 (79.1-85.9)	1 (reference)	
	Female	385	88.1 (84.4-91.1)	0.648 (0.440-0.954)	0.0280
Age (y)	≤79	504	87.7 (84.5-90.4)	1 (reference)	
	≥80	372	81.5 (77.1-85.3)	1.624 (1.118-2.357)	0.0108
Age (y)	≤84	805	86.0 (83.4-88.3)	1 (reference)	
	≥85	71	74.7 (62.9-84.2)	2.080 (1.176-3.679)	0.0119
Clinical stage	0	29	86.2 (68.3-96.1)	1 (reference)	
	IA1	131	91.6 (85.5-95.7)	0.573 (0.169-1.946)	0.3720
	IA2	254	87.4 (82.7-91.2)	0.901 (0.294 - 2.757)	0.8549
	IA3	158	87.3 (81.1-92.1)	0.906 (0.285-2.875)	0.8667
	IB	134	79.9 (72.1-86.3)	1.577 (0.506-4.915)	0.4321
	IIA	36	94.4 (81.3-99.3)	0.368 (0.062-2.169)	0.2693
	IIB	96	74.0 (64.0-82.4)	2.201 (0.697-6.948)	0.1787
	IIIA+B	38	73.7 (56.9-86.6)	2.232 (0.621-8.019)	0.2184
ECOG Performance status	0	717	87.6 (85.0-89.9)	1 (reference)	
	1	152	73.7 (65.9-80.5)	2.520 (1.650-3.850)	<0.0001
	2-4	7	71.4 (29.0-96.3)	2.823 (0.539-14.767)	0.2191
Smoking history	Never	363	88.7 (85.0-91.8)	1 (reference)	
	Ever	513	82.5 (78.9-85.7)	1.671 (1.124-2.485)	0.0112
Smoking years	0	364	88.7 (85.0-91.8)	1 (reference)	
	1-19	51	94.1 (83.8-98.8)	0.493 (0.147-1.653)	0.2518
	20-39	132	78.8 (70.8-85.4)	2.121 (1.250-3.599)	0.0053
	≥40	328	82.0 (77.4-86.0)	1.728 (1.124-2.656)	0.0127
Respiratory comorbidity	No	588	87.9 (85.0-90.5)	1 (reference)	
	Yes	288	79.2 (74.0-83.7)	1.916 (1.314-2.795)	0.0007
Emphysema	No	623	87.3 (84.5-89.8)	1 (reference)	
	Yes	253	79.5 (73.9-84.3)	1.781 (1.211-2.620)	0.0033
Interstitial pneumonia	No	788	86.3 (83.7-88.6)	1 (reference)	
	Yes	88	73.9 (63.4-82.7)	2.228 (1.328-3.736)	0.0024
Number of medications	0	63	92.1 (82.4-97.4)	1 (reference)	
	1-3	255	89.8 (85.4-93.2)	1.317 (0.458-3.578)	0.5893
	4-9	464	83.0 (79.2-86.3)	2.380 (0.925-6.124)	0.0721
	≥10	94	77.7 (67.9-85.6)	3.337 (1.186-9.388)	0.0224
Operation	Wedge Resection	95	88.4 (80.2-94.1)	1 (reference)	
	Segmentectomy	133	81.2 (73.5-87.5)	1.768 (0.823-3.796)	0.1441
	Lobectomy	639	85.5 (82.5-88.1)	1.301 (0.668-2.531)	0.4390
	Bilobectomy	6	83.3 (35.9-99.6)	1.527 (0.163-14.305)	0.7106
	Pneumonectomy	3	66.7 (9.4-99.2)	3.818 (0.319-46.657)	0.2899
Lymph node dissection	ND0-1	371	84.6 (80.6-88.2)	1 (reference)	
	≥ND2a	505	85.4 (82.0-88.3)	0.946 (0.650-1.376)	0.7708
Combined resection	No	863	85.4 (82.9-87.7)	1 (reference)	
	Yes	13	61.5 (31.6-86.1)	3.656 (1.177-11.353)	0.0250
Operation time	<180 min	548	83.8 (80.4-86.8)	1 (reference)	
	≥180 min	328	87.2 (83.1-90.6)	0.757 (0.510-1.125)	0.1685
G8 score at registration	≥15	380	90.5 (87.1-93.3)	1 (reference)	
	≤14	495	80.8 (77.1-84.2)	2.269 (1.506-3.149)	<0.0001
CCI score	0	447	88.8 (85.5-91.6)	1 (reference)	
	≥1	429	81.1 (77.1-84.7)	1.848 (1.263-2.704)	0.0016

ADL, activities of daily living; CCI, Charlson comorbidity index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; G8, geriatric screening tool; ND0, no node dissection; ND1, hilar node dissection; ND2, mediastinal node dissection; TMIG-IADL, Tokyo Metropolitan Institute of Gerontology Index of Competence Instrumental Activities of Daily Living.

Among the 230 patients enrolled before September 2019 (for whom the primary end point was evaluated before April 2020, when the first state of emergency for the COVID-19 pandemic was declared in Japan), a score worsening of greater than or equal to one point at 6 months was detected in the instrumental self-maintenance, effectance, and social role domains in 12.6%, 17.8%, and 30.9% of the patients, respectively.

Table 3. Worsening of Scores in Each Specific Item and Domain in the Tokyo Metropolitan Institute of Gerontology Index of Competence Instrumental Activities of Daily Living Among Patients Who Responded to Both the Preoperative and Postoperative Surveys (N = 841)

Item	Number of Patients Reporting Score Worsening	% (95% CI)
1. Can you use public transportation (bus or train) by yourself?	73	8.7 (6.9-10.8)
2. Are you able to shop for daily necessities?	42	5.0 (3.6-6.7)
3. Are you able to prepare meals by yourself?	66	7.9 (6.1-9.9)
4. Are you able to pay bills?	37	4.4 (3.1-6.0)
5. Can you handle your own banking?	43	5.1 (3.7-6.8)
Domain: Instrumental self-maintenance (items 1-5) by one point or more	136	16.2 (13.8-18.8)
Domain: Instrumental self-maintenance (items 1-5) by two points or more	60	7.1 (5.5-9.1)
6. Are you able to fill out forms for your pension?	58	6.9 (5.3-8.8)
7. Do you read newspapers?	44	5.2 (3.8-7.0)
8. Do you read books or magazines?	66	7.9 (6.1-9.9)
9. Are you interested in news stories or programs dealing with health?	31	3.7 (2.5-5.2)
Domain: Effectance (items 6-9) by one point or more	143	17.0 (14.5-19.7)
Domain: Effectance (items 6-9) by two points or more	37	4.4 (3.1-6.0)
10. Do you visit the homes of friends?	135	16.1 (13.6-18.7)
11. Are you sometimes called on for advice?	113	13.4 (11.2-15.9)
12. Are you able to visit sick friends?	142	16.9 (14.4-19.6)
13. Do you sometimes initiate conversations with young people?	87	10.3 (8.4-12.6)
Domain: Social role (items 10-13) by one point or more	306	36.4 (33.1-39.7)
Domain: Social role (items 10-13) by two points or more	120	14.3 (12.0-16.8)

CI, confidence interval.

Conversely, a score worsening of greater than or equal to one point at 6 months was detected in the instrumental self-maintenance, effectance, and social role domains in 17.5%, 16.7%, and 38.5% of the 611 patients enrolled after October 2019 (Supplementary Table 1*G*). The differences between pre and post–COVID-19 score changes were not statistically significant except for social role domain score ($p = 0.0426$ by chi-square test). Therefore, despite the presence of a certain degree of COVID-19 effect on ADL, this effect was unlikely to be great and the "social role" was the most affected domain in both periods.

Changes in QOL

The preoperative and postoperative EQ-5D-5L questionnaire data were available for 864 (98.6%) and 821 (93.7%) of the 876 patients, respectively. The score changes could be analyzed in 811 patients (92.6%) who were also included in the primary end point analysis. On the basis of an MID of 0.061 for the EQ-5D-5L score, QOL deterioration (by MID or more) was observed in 179 patients (22.1%), whereas 115 (14.2%) reported QOL worsening by less than MID, 280 (34.5%) reported no change, 85 (10.5%) reported QOL improvement by less than MID, and 152 (18.7%) reported improvement by MID or more. Preoperative poor PS (2–4 versus 0) and smoking history (ever versus never) were significantly correlated with predetermined (i.e., by MID or more) QOL deterioration at 6 months. QOL score changes were not significantly different between those with and without grade 3 or higher serious postoperative complications, although this comparison is biased because they were limited to patients "fit enough" to fill in postoperative QOL questionnaires.

The correlation analysis including these 811 patients indicated that the changes in TMIG-IADL and EQ-5D-5L scores were poorly correlated (Spearman's rank correlation coefficient = 0.2884), as illustrated in Figure 3. The kappa coefficient for the agreement between deterioration/nondeterioration of TMIG-IADL (by $\geq$3 points) and QOL (by MID of $\geq$0.061) scores was 0.2655, confirming poor correlation (see Supplementary Table 1*H* for specific data).

Of the 811 patients with both baseline and postoperative EQ-5D-5L scores, 125 (15.4%) and 154 (19.0%) revealed improvement in Pain/Discomfort item and Anxiety/Depression item, respectively. These patients were more likely to report improved TMIG-IADL or overall QOL scores (Supplementary Table 1*I*).

Discussion

In the present study, data on preoperative and postoperative ADL could be obtained from 98.1% of 876 elderly patients undergoing curative surgery for NSCLC

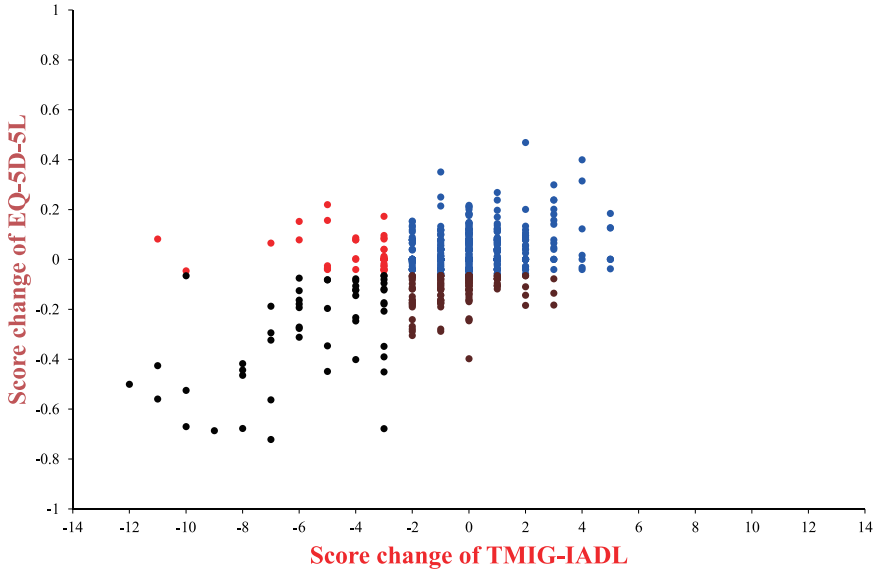


Figure 3. Correlation between changes in the TMIG-IADL score and the changes in the EQ-5D-5L score after surgery. Red and black dots represent those with substantial ADL deterioration (TMIG-IADL score worsened by ≥3 points), whereas brown and black dots represent those with substantial QOL deterioration (EQ-5D-5L score worsened by ≥0.061 points). TMIG-IADL and EQ-5D-5L scores were poorly correlated (Spearman's rank correlation coefficient = 0.2884). EQ-5D-5L, EuroQol 5-dimensions 5-level; QOL, quality of life; TMIG-IADL, Tokyo Metropolitan Institute of Gerontology Index of Competence Instrumental Activities of Daily Living.

who were alive at 6 months. In nine of the 16 alive patients with missing data, the cause of their exclusion was incapacitating complications, which were undoubtedly associated with ADL deterioration as we had anticipated when determining the primary end point of the study. Therefore, data on ADL were only "truly missing" from seven of the 876 patients (<1%). In addition, data on QOL could be obtained from greater than 90% of the patients. Therefore, in the current study, evaluating postoperative ADL and QOL outcomes was feasible despite the disruptive effect of the COVID-19 pandemic during the study period.

With the aging population in Japan, the number of elderly patients with lung cancer, including those undergoing surgical resection, is rapidly increasing.[1,3] Despite improvements in surgical safety and OS,[2,3] data on the impact of surgery on long-term ADL and QOL, which are critically important for patients and families, are limited.[8,10,11] Previous studies have focused on short-term morbidity and mortality of surgical procedures and OS.[2–4] However, aside from survival, the ADL and QOL of patients as cancer survivors should also be evaluated.

In the present study, we confirmed the favorable survival outcomes of surgery in elderly patients with NSCLC, on the basis of surgical mortality and 6-month OS rates of 0.3% and 98.7%, respectively. However, although there was considerable variability in postoperative ADL change, with some suffering from remarkable worsening and others reporting maintained or even improved activities, ADL scores significantly tended to worsen at postoperative 6 months. Protocol-specified ADL deterioration (defined as a decline of ≥3 points in TMIG-IADL score or missing ADL data) was not observed in only 85% of the patients, indicating that the remaining 15% of the patients experienced significant functional loss after surgery.

ADL maintenance or recovery was not determined solely by short-term postoperative complications. Although patients who experienced grade 3 or higher surgical complications were statistically significantly more likely to suffer from ADL deterioration, more than 60% achieved ADL recovery at 6 months, with some even reporting "improved" postoperative ADL or QOL. On the other hand, one out of every eight patients without grade 3 or higher postoperative complications experienced significant ADL deterioration. Therefore, operative complications are not a surrogate for long-term functional recovery, and ADL should be evaluated as a distinct end point.

Univariable analyses revealed that male sex, age of at least 80 years, poor PS, smoking history, emphysema, interstitial pneumonia, daily use of multiple medications, low baseline G8 score, high CCI score, and combined resection were associated with postoperative ADL deterioration at 6 months. In multivariable analysis, the following four predictive factors remained significantly associated with ADL deterioration at 6 months: (1) poor preoperative PS; (2) low baseline G8 score; (3) segmentectomy (versus wedge resection); and (4) surgery lasting shorter than 3 hours. The clinical relevance of the

observed association between shorter surgery duration and ADL deterioration remains unclear and could be a statistical anomaly. Or it might be owing to bias that clinically higher-risk patients underwent operation by more experienced surgeons. In any case, it could be concluded that having shorter surgical time would not lead to the maintenance of postoperative ADL. Information on these predictive factors would aid in patient counseling, treatment decision-making, and perioperative care for elderly patients.

Although there were no significant correlations between surgical procedures and ADL deterioration by univariable comparisons, the multivariable analysis did indicate that wedge resection was associated with less ADL deterioration, especially versus segmentectomy. In a recently published Cancer and Leukemia Group B trial,[29] "sublobar" resection was found to be noninferior to lobectomy in early-stage NSCLC, which is compatible with the study by Japan Clinical Oncology Group.[15] However, in this Cancer and Leukemia Group B trial, both wedge resection and segmentectomy were included in the "sublobar resection" group. Given the different effects on ADL, it might be inappropriate to put wedge resection and segmentectomy together as "less invasive" surgical procedures.

Of note, preoperative comprehensive geriatric assessments were significantly associated with short-term surgical complications during the first 30 days in the previous study by the Japanese Association for Chest Surgery.[3] In the present study, we used the simplified G8 assessment,[22] which was also associated with functional outcomes at a longer term of 6 months. On the other hand, age alone did not predict functional outcomes. These results reconfirm the importance of pretreatment assessment using geriatric scales.[3,30,31] The currently ongoing data collection and analyses aim to determine whether patients experience additional ADL deterioration during longer follow-up periods of 12 and 24 months after surgery and to identify predictive factors.

We also collected QOL data using the EQ-5D-5L questionnaire, given that QOL and ADL are not identical. In fact, in the current study, not only the postoperative data retrieval rates were different, but the changes in TMIG-IADL and EQ-5D-5L scores were poorly correlated. QOL deterioration by the MID or more was reported by 22.1% of the patients, which was higher than the rate of patients with ADL deterioration. These results could have reflected the different data collection methods but suggest that ADL and QOL should be separately evaluated despite their comparable importance. Future studies should elucidate whether ADL or QOL has a bigger impact on long-term outcomes in elderly patients undergoing surgery for lung cancer.

The present study has several strengths. This was a multi-institutional prospective study with large cohort size. Previous studies on postoperative patient-reported outcomes (PROs) reported only modest responses. For example, in a European study on the economic burden of patients with resected NSCLC,[32] the authors reported that 306 of the 526 (58%) invited patients completed the survey. In another study by Heiden et al., [33] which investigated the PROs after NSCLC resection in 334 patients, each of the PRO scores at 6 months could be collected from only half the patients or less. In our study, however, the PRO data retrieval rates were very high for both ADL and QOL, despite the disruptive effect of the COVID-19 pandemic on clinical trials.[34]

On the other hand, we also acknowledge the weaknesses and the limitations of the study. First, as is the case in most surgical observational studies, our patients are selected for curative operation and are undoubtedly "fitter" than the general elderly population. Most of them have a PS of 0, with few comorbidities, and the SD of baseline ADL was smaller. The generalizability of our results to more frail populations, thus, remains unclear. Second, although the cutoff value for the QOL has been set at 0.061 according to a previous report on MID,[28] no data are available regarding the changes in the TMIG-IADL score for clinically relevant ADL deterioration. We embraced the distribution-based method[27] and defined deterioration as a change of one SD in the TMIG-IADL score. Although used in previous studies evaluating the effect of brain radiotherapy cognitive functions,[35–37] this approach could be criticized as arbitrary.

Third, we did not have reference data to determine whether the rate of patients experiencing ADL deterioration of 15% was expected or not. Puts et al.[38] investigated the 6 months postoperative ADL in 112 elderly patients who underwent breast cancer surgery and reported that 21.9% suffered from functioning deterioration, with which no variable was associated. In a larger, the international, multicenter Geriatric Oncology Surgical Assessment and Functional rEcovery after Surgery (GOSAFE) study,[39] 945 elderly patients who underwent surgery for various cancers were analyzed for EQ-5D, with worsening and recovered scores at postoperative 3 and 6 months, respectively. No definitions of MID were given in either report. In a study with longer (5-year) follow-up, ADL change was investigated in 239 elderly patients with breast cancer, and Lemij et al.[40] reported that treatment was not associated with physical activities. Although it seemed that our results are not inconsistent with these previous reports, direct comparisons are difficult owing to differences in disease status and evaluation methods. In particular, we cannot precisely differentiate the effect of surgery-induced versus "normal" deterioration process of the aged patients, although it would be unlikely that many

"normal" elderly people suffer from a significant functional loss in 6 months. Comparisons with other modalities, such as radiotherapy, would be greatly informative for treatment selection. Fourth, information on the excluded patients, such as those who underwent noncurative surgery, is missing. In fact, some of the patients might have received effective target-based drugs with no ADL deterioration.

Future oncology trials should adopt a comprehensive approach and include ADL and QOL assessment irrespective of the treatment modalities chosen. There was a significant number of patients who reported improvement of postoperative ADL or QOL; 185 (21.1%) reported TMIG-IADL score improvement, and 152 (18.7%) reported that their QOL was improved by MID or more. This could be attributed to the physical and psychological burden of cancer and the subsequent curative operation leading to "disease-free" status.

In conclusion, our analyses of ADL and QOL in a large cohort of patients from a large number of institutions across Japan revealed that, even in this selected group with limited generalizability, a significant proportion of elderly patients who underwent curative surgical resection for NSCLC experienced ADL deterioration at 6 months after surgery, highlighting the need for further studies elucidating the predictive and contributory factors. The fact that ADL and QOL changes were not uniform, with some reporting improved postoperative ADL/QOL, makes it all the more necessary to have better tools in predicting who will feel better versus worse after surgery.

CRediT Authorship Contribution Statement

Hidefumi Takei: Conceptualization, Investigation, Methodology, Resources, Visualization, Writing - original draft, Writing - review & editing.

Hideo Kunitoh: Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Visualization, Writing - original draft, Writing - review & editing.

Masashi Wakabayashi: Data curation, Formal analysis, Methodology, Software, Validation, Visualization, Writing - review & editing.

Tomoko Kataoka: Data curation, Software, Validation, Writing - review & editing.

Yuta Sekino: Data curation, Software, Validation, Writing - review & editing.

Tomonori Mizutani: Conceptualization, Methodology, Visualization, Writing - review & editing.

Masahiro Tsuboi: Investigation, Resources, Writing - review & editing.

Norihiko Ikeda: Investigation, Resources, Writing - review & editing.

Hisao Asamura: Investigation, Resources, Writing - review & editing.

Morihito Okada: Investigation, Resources, Writing - review & editing.

Makoto Takahama: Investigation, Resources, Writing - review & editing.

Yasuhisa Ohde: Investigation, Resources, Writing - review & editing.

Jiro Okami: Investigation, Resources, Writing - review & editing.

Satoshi Shiono: Investigation, Resources, Writing - review & editing.

Keijyu Aokage: Investigation, Project administration, Resources, Writing - review & editing.

Shun-ichi Watanabe: Conceptualization, Funding acquisition, Project administration, Supervision, Writing - original draft, Writing - review & editing.

Acknowledgments

The study was supported in part by the National Cancer Center Research and Development Funds (29-A-3 and 2020-J-3) from the Ministry of Health, Labor, and Welfare of Japan, and by the Research Fund of National Federation of Health Insurance Societies. The funders had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Participating Institutions

National Hospital Organization Sendai Medical Center, Tohoku University Hospital, Yamagata Prefectural Central Hospital, Ibaraki Prefectural Central Hospital & Cancer Center, Tochigi Cancer Center, Gunma Prefectural Cancer Center, National Cancer Center Hospital East, Chiba Cancer Center, Chiba University Graduate School of Medicine, National Cancer Center Hospital, Kyorin University Faculty of Medicine, Tokyo Medical University Hospital, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Keio University Hospital, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Juntendo University Hospital, Nippon Medical School Hospital, St.Marianna University School of Medicine, Kanagawa Cancer Center, Yokohama Municipal Citizen's Hospital, Kitasato University School of Medicine, Niigata Cancer Center Hospital, Nishi-Niigata Chuo National Hospital, Niigata University Medical and Dental Hospital, Kanazawa University School of Medicine, Shizuoka Cancer Center, Aichi Cancer Center Hospital, Nagoya University School of Medicine, Kyoto University Hospital, Osaka University Graduates School of Medicine, Osaka Metropolitan University Hospital, Osaka International Cancer Institute, Osaka Habikino Medical Center, National Hospital Organization Kinki-Chuo Chest Medical Center, Osaka City General

Hospital, Kobe University Graduates School of Medicine, Hyogo Cancer Center, Kurashiki Central Hospital, Okayama University Hospital, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, Hiroshima University Hospital, National Hospital Organization Shikoku Cancer Center, National Kyushu Cancer Center, Nagasaki University Hospital, Kumamoto University Hospital, Kumamoto Chuo Hospital, Oita University Faculty of Medicine.

Japan Clinical Oncology Group Data Center and Operations Office

H. Fukuda (Data Center Director), T. Shibata (Statistics Section).

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2023.100550.

References

1. Committee for Scientific Affairs, The Japanese Association for Thoracic Surgery, Okada M, et al. Thoracic and cardiovascular surgeries in Japan during 2018: annual report by the Japanese Association for Thoracic Surgery. *Gen Thorac Cardiovasc Surg*. 2021;69:179–212.
2. Okami J, Higashiyama M, Asamura H, et al. Pulmonary resection in patients aged 80 years or over with clinical stage I non-small cell lung cancer: prognostic factors for overall survival and risk factors for postoperative complications. *J Thorac Oncol*. 2009;4:1247–1253.
3. Saji H, Ueno T, Nakamura H, et al. A proposal for a comprehensive risk scoring system for predicting postoperative complications in octogenarian patients with medically operable lung cancer: JACS1303. *Eur J Cardio Thorac Surg*. 2018;53:835–841.
4. Stokes WA, Bronsert MR, Meguid RA, et al. Post-treatment mortality after surgery and stereotactic body radiotherapy for early-stage non-small-cell lung cancer. *J Clin Oncol*. 2018;36:642–651.
5. Tan H, Saliba D, Kwan L, Moore AA, Litwin MS. Burden of geriatric events among older adults undergoing major cancer surgery. *J Clin Oncol*. 2016;34:1231–1238.
6. Brown LM, Gosdin MM, Cooke DT, Apesoa-Varano EC, Kratz AL. Health-related quality of life after lobectomy for lung cancer: conceptual framework and measurement. *Ann Thorac Surg*. 2020;110:1840–1846.
7. Hurria A, Dale W, Mooney M, et al. Designing therapeutic clinical trials for older and frail adults with cancer: U13 conference recommendations. *J Clin Oncol*. 2014;32:2587–2594.
8. Wildiers H, Mauer M, Pallis A, et al. End points and trial design in geriatric oncology research: a joint European Organisation for Research and Treatment of Cancer-alliance for clinical trials in oncology-International Society of Geriatric Oncology Position article. *J Clin Oncol*. 2013;31:3711–3718.
9. Le Saux O, Falandry C, Gan HK, You B, Freyer G, Péron J. Changes in the use of end points in clinical trials for elderly cancer patients over time. *Ann Oncol*. 2017;28:2606–2611.
10. Montroni I, Saur NM, Shahrokni A, Suwanabol PA, Chesney TR. Surgical considerations for older adults with cancer: a multidimensional, multiphase pathway to improve care. *J Clin Oncol*. 2021;39:2090–2101.
11. Siddique A, Simonsick EM, Gallicchio L. Functional decline among older cancer survivors in the Baltimore longitudinal study of aging. *J Am Geriatr Soc*. 2021;69:3124–3133.
12. Downing A, Morris EJ, Richards M, et al. Health-related quality of life after colorectal cancer in England: a patient-reported outcomes study of individuals 12 to 36 months after diagnosis. *J Clin Oncol*. 2015;33:616–624.
13. Chesney TR, Coburn N, Mahar AL, et al. All-cause and cancer-specific death of older adults following surgery for cancer. *JAMA Surg*. 2021;156:e211425.
14. Kunitoh H, Tsuboi M, Wakabayashi M, et al. A phase III study of adjuvant chemotherapy in patients with completely resected, node-negative non-small cell lung cancer (JCOG 0707). *JTCVS Open*. 2020;4:90–102.
15. Saji H, Okada M, Tsuboi M, et al. Segmentectomy versus lobectomy in small-sized peripheral non-small-cell lung cancer (JCOG0802/WJOG4607L): a multicentre, open-label, phase 3, randomised, controlled, non-inferiority trial. *Lancet*. 2022;399:1607–1617.
16. Liu MA, Keeney T, Papaila A, et al. Functional status and survival in older nursing home residents with advanced non-small-cell lung cancer: a SEER-Medicare analysis. *JCO Oncol Pract*. 2022;18:e886–e895.
17. DuMontier C, Loh KP, Bain PA, et al. Defining undertreatment and overtreatment in older adults with cancer: a scoping literature review. *J Clin Oncol*. 2020;38:2558–2569.
18. Brooks R with the EuroQol Group: EuroQol: the current state of play. *Health Policy*. 1996;37:53–72.
19. Tsuchiya A, Ikeda S, Ikegami N, et al. Estimating an EQ-5D population value set. The case of Japan. *Health Econ*. 2002;11:341–353.
20. Koyano W, Shibata H, Nakazato K, Haga H, Suyama Y. Measurement of competence: reliability and validity of the TMIG index of competence. *Arch Gerontol Geriatr*. 1991;13:103–116.
21. Taira N, Sawaki M, Uemura Y, et al. Health-related quality of life with trastuzumab monotherapy versus trastuzumab plus standard chemotherapy as adjuvant therapy in older patients with HER2-positive breast cancer. *J Clin Oncol*. 2021;39:2452–2462.
22. Kenis C, Decoster L, Van Puyvelde K, et al. Performance of two geriatric screening tools in older patients with cancer. *J Clin Oncol*. 2014;32:19–26.
23. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373–383.

24. Lichtman SM, Cohen HJ, Muss H, Tew WP, Korc-Grodzicki B. From assessment to implementation and beyond in cancer and aging research. *J Clin Oncol*. 2021;39:2217–2225.
25. Ikeda S, Shiroiwa T, Igarashi A, et al. Developing a Japanese version of the EQ-5D-5L value set. *J Natl Inst Public Health*. 2015;64:47–55.
26. Koyano W, Hashimoto M, Fukawa T, Shibata H, Gunji A. [Functional capacity of the elderly: measurement by the TMIG index of competence]. *Nihon Koshu Eisei Zasshi (Jpn J Public Health)*. 1993;40:468–474 [Article in Japanese].
27. Revicki D, Hays RD, Cella D, Sloan J. Recommended methods for determining responsiveness and minimally important differences for patient-reported outcomes. *J Clin Epidemiol*. 2008;61:102–109.
28. Shiroiwa T, Fukuda T, Ikeda S, et al. Japanese population norms for preference-based measures: EQ-5D-3L, EQ-5D-5L, and SF-6D. *Qual Life Res*. 2016;25:707–719.
29. Altorki N, Wang X, Kozono D, et al. Lobar or sublobar resection for peripheral stage IA non-small cell lung cancer. *N Engl J Med*. 2023;388:489–498.
30. Hamaker ME, Jonker JM, de Rooij SE, Vos AG, Smorenburg CH, van Munster BC. Frailty screening methods for predicting outcome of a comprehensive geriatric assessment in elderly patients with cancer: a systematic review. *Lancet Oncol*. 2012;13:e437–e444.
31. Corre R, Greillier L, Le Caër H, et al. Use of a comprehensive geriatric assessment for the management of elderly patients with advanced non-small-cell lung cancer: the phase III randomized ESOGIA-GFPC-GECP 08-02 study. *J Clin Oncol*. 2016;34:1476–1483.
32. Andreas S, Chouaid C, Danson S, et al. Economic burden of resected (stage IB-IIIA) non-small cell lung cancer in France, Germany and the United Kingdom: a retrospective observational study (LuCaBIS). *Lung Cancer*. 2018;124:298–309.
33. Heiden BT, Subramanian MP, Liu J, et al. Long-term patient-reported outcomes after non-small cell lung cancer resection. *J Thorac Cardiovasc Surg*. 2022;164:615–626.
34. Bakouny Z, Labaki C, Bhalla S, et al. Oncology clinical trial disruption during the COVID-19 pandemic: a COVID-19 and cancer outcomes study. *Ann Oncol*. 2022;33:836–844.
35. Rodriguez de Dios N, Counago F, Murcia-Mejia M, et al. Randomized phase III trial of prophylactic cranial irradiation with or without hippocampal avoidance for small-cell lung cancer (PREMER): a GICOR-GOECP-SEOR study. *J Clin Oncol*. 2021;39:3118–3127.
36. Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. *JAMA*. 2016;316:401–409.
37. Palmer JD, Klamer BG, Ballman KV, et al. Association of long-term outcomes with stereotactic radiosurgery vs whole-brain radiotherapy for resected brain metastasis a secondary analysis of the N107C/CEC.3 (Alliance for Clinical Trials in Oncology/Canadian Cancer Trials Group) randomized clinical trial. *JAMA Oncol*. 2022;8:1809–1815.
38. Puts MTE, Monette J, Girre V, et al. Changes in functional status in older newly-diagnosed cancer patients during cancer treatment: a six-month follow-up period. Results of a prospective pilot study. *J Geriat Oncol*. 2011;2:112–120.
39. Montroni I, Ugolini G, Saur NM, et al. Quality of life in older adults after major cancer surgery: the GOSAFE international study. *J Natl Cancer Inst*. 2022;114:969–978.
40. Lemij AA, Liefers G, Derks MGM, et al. Physical function and physical activity in older breast cancer survivors: 5-year follow-up from the Climb Every Mountain study. *Oncologist*. 2023;28:e317–e323.

JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2024, 1–10
https://doi.org/10.1093/jjco/hyae045
Original Article

OXFORD

Original Article

Real-world treatment trends for patients with advanced prostate cancer and renal cell carcinoma and their cost—a survey in Japan

Takahiro Osawa[1,*], Keita Sasaki[2], Ryunosuke Machida[2], Takashi Matsumoto[3], Yoshiyuki Matsui[4], Hiroshi Kitamura[5] and Hiroyuki Nishiyama[6]

[1]Department of Urology, Hokkaido University Hospital, Sapporo, Japan, [2]Japan Clinical Oncology Group Data Center/Operations Office, National Cancer Center Hospital, Tokyo, Japan, [3]Department of Urology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, [4]Department of Urology, National Cancer Center Hospital, Tokyo, Japan, [5]Department of Urology, Faculty of Medicine, University of Toyama, Toyama, Japan and [6]Department of Urology, Institute of Medicine, University of Tsukuba, Ibaraki, Japan

*For reprints and all correspondence: Takahiro Osawa, Department of Urology, Hokkaido University Hospital, N15 W7 Kita-ku, Sapporo 060-8638, Japan. E-mail: taka0573@gmail.com

Received 14 February 2024; Editorial Decision 25 March 2024; Accepted 28 March 2024

Abstract

Background: Advanced (Stage IV) prostate and renal cancer have poor prognosis, and several therapies have been developed, but many are very costly. This study investigated drug regimens used in patients with untreated Stage IV prostate cancer and renal cell carcinoma and calculated the monthly cost of each.

Methods: We surveyed first-line drugs administered to patients with untreated Stage IV prostate cancer and renal cancer at Japan Clinical Oncology Group affiliated centers from April 2022 to March 2023. Drug costs were calculated according to drug prices in September 2023. Individual drug costs were calculated or converted to 28-day costs.

Results: A total of 700 patients with untreated Stage IV prostate cancer were surveyed. Androgen deprivation therapy + androgen receptor signaling inhibitor was the most common regimen (56%). The cost of androgen deprivation therapy + androgen receptor signaling inhibitor was 10.6–30.8-fold compared with conventional treatments. A total of 137 patients with Stage IV renal cancer were surveyed. Among them, 91% of patients received immune-oncology drug-based regimen. All patients received treatments with a monthly cost of ≥500 000 Japanese yen, and 80.4% of patients received treatments with a monthly cost of ≥1 million Japanese yen, of combination treatments. The cost of immune-oncology drug-based regimen was 1.2–3.1-fold that of TKI alone.

Conclusion: To the best of our knowledge, this is the first report of a survey of first-line drug therapy in untreated Stage IV prostate cancer and renal cell carcinoma stratified by age and treatment costs. Our results show that most Japanese patients received state-of-the-art, effective treatments with high financial burden.

Key words: renal cell carcinoma, prostate cancer, immune-combination therapy, treatment cost

Introduction

Japan is facing an unprecedented super-aging society (1). Prostate cancer and renal cell carcinoma (RCC) are the most common urologic cancers among older adults. In Japan, the incidence of prostate cancer is ~15 per 10 000 population, and it was the leading cancer in men in 2019 (2). The average age of patients with prostate cancer is 71.3 years, and the 10-year cancer-specific survival proportion for Stages I–III and IV (14.6% of all patients) are ~90% (good prognosis) and 36.9% (poor prognosis), respectively. By contrast, the average age of patients with RCC is 65.5 years. Similar to prostate cancer, the 10-year cancer-specific survival proportion for Stages I and II and IV (16.2% of all patients) are ~80% (good prognosis) and 7.3% (poor prognosis), respectively (3). Both prostate cancer and RCC have extremely poor prognoses when diagnosed at Stage IV when metastasis has occurred.

The standard treatment for Stage IV prostate cancer was androgen deprivation therapy (ADT) (4). However, metastatic prostate cancer that initially responded to ADT became resistant to ADT and progressed to metastatic castration-resistant prostate cancer within 2–3 years (5). Subsequently, new therapies were developed, and docetaxel, abiraterone, enzalutamide and apalutamide, in combination with ADT, impaired disease progression and improved overall survival (OS) in randomized clinical trials (6–15). This is now the current standard of care.

The standard of care for Stage IV RCC has reached a turning point: inhibitors of the programmed cell death receptor pathway (immune-oncology drug: IO) in combination with a tyrosine kinase inhibitor (TKI) (IO–TKI combination) or in combination with other IO agents (IO–IO combination) were compared with the TKI sunitinib alone. IO–TKI and IO–IO combination therapy showed improved response rates, progression-free survival and OS compared with TKI sunitinib alone (16–26). Thus, with the development of new therapeutic approaches, improvement in prognosis has been achieved, but both TKIs and IOs are expensive treatments.

Although the development of new therapies has improved prognosis, the cost of new drug therapies for cancer treatment has skyrocketed in recent years, which has become a problem worldwide (27–29). For example, high drug costs threaten healthcare budgets and limit funding for other areas such as public investment. In countries that, unlike Japan, do not have universal health insurance, the high cost of prescription drugs can lead to high out-of-pocket costs for individual patients, making drugs unaffordable for those who need them. Recently, higher drug costs have been widely reported across new therapies, particularly for patients with prostate cancer and RCC (30,31). In this study, we surveyed patients with untreated Stage IV prostate cancer and RCC in Japan to determine the currently used drugs. We also calculated the proportion of new treatments in the total drug treatment and the monthly cost per month for each treatment. This study was carried out under the leadership of the Japan Clinical Oncology Group (JCOG) Health Economic Committee.

Patients and methods

A survey was conducted among physicians at JCOG-affiliated centers regarding the initial drug therapy given to patients with untreated Stage IV prostate cancer and RCC. The patients were first diagnosed with advanced cancer at JCOG institutions between April 2022 and March 2023. The number of patients in different age categories (<75 and ≥75 years) were collected separately. A Google Form questionnaire was used, and no personal patient information was collected; the survey investigated the initial treatment given.

The prostate cancer drug regimens included ADT alone (goserelin, leuprorelin or degarelix), ADT + antiandrogen (bicalutamide or flutamide), ADT + docetaxel and ADT + androgen receptor signaling inhibitor (ARSI; abiraterone, apalutamide or enzalutamide). For RCC drug therapy, the study included patients who received TKI (sunitinib, pazopanib, cabozantinib or sorafenib), IO–IO (nivolumab + ipilimumab) and IO–TKI (pembrolizumab + axitinib, avelumab + axitinib, nivolumab + cabozantinib or pembrolizumab + lenvatinib) regimens.

Drug costs were calculated according to drug prices as of September 2023. For docetaxel, avelumab and ipilimumab doses, a body weight of 59 kg and a body surface area of 1.68 m^2 were used as the standard for Japanese patients. For nivolumab + ipilimumab, the monthly cost was calculated after calculating the 12-month drug cost because the cost of treatment in the first 3 months and beyond varies. We defined high-cost and very high-cost treatments as those that cost ≥500 000 and ≥1 000 000 Japanese yen (JPY) per month, respectively, as per the definition prescribed by the JCOG Health Economics Committee.

Results

Among 44 JCOG participating centers, 38 and 36 centers provided information about the drugs they used to treat prostate cancer and RCC, respectively (Supplementary Table 1). A total of 700 patients with untreated Stage IV prostate cancer and 137 patients with Stage IV RCC were surveyed.

The main treatments that were introduced for metastatic hormone-sensitive prostate cancer (mCSPC) stratified by age and cost per month are shown in Fig. 1 and Table 1. ADT + ARSI was the most common (56%) regimen, and ADT + docetaxel was the least common (4.0%). Patients who were ≥75 years old were more likely to be treated with ADT alone than patients <75 years old (18.5% vs. 9.6%). Furthermore, patients ≥75 years old were less likely to be treated with ADT + apalutamide than those <75 years old (9.8% vs. 18.4%). Of note, ADT + ARSI was administered to 56% of all treated patients, with drug costs ranging from 272 874 to 424 746 JPY (Table 1). The cost of ADT + ARSI was 10.6–30.8-fold compared with ADT alone and ADT + antiandrogen, which are conventional treatments. Therefore, although no patients received high-cost treatments according to the definition used by this study, treatment costs for mCSPC have greatly increased. Details of drug costs for prostate cancer are described in Supplementary Table 2.

Table 2 lists the results of clinical trials on primary drug therapy for mCSPC. It summarizes the drug dose, OS, recurrence-free survival, older adult sample size and treatment duration of each clinical trial. The control treatment was ADT alone in all clinical trials except the ENZAMET trial. The LATITUDE trial included patients with high-risk mCSPC, while the other trials included all mCSPC patients. In each trial, >45% of patients were >70 years old and 20–30% were >75 years old. The previously reported median durations of treatment for ADT alone, ADT + antiandrogen, ADT + docetaxel, ADT + abiraterone, ADT + apalutamide and ADT + enzalutamide were 13.8–20.2, 13.8–20.2, 33, 25.8, 39.3 and 40.2 months, respectively (Table 2). ADT + enzalutamide had the longest median treatment duration, and the overall total treatment cost was 11 094 034 JPY. Since no head-to-head trials have compared these three ARSIs, clinicians are faced with the challenging task of choosing the most appropriate treatment for patients with mCSPC.

Figure 2 and Table 3 show the treatments that were used for metastatic renal cancer stratified by age and cost per month: TKI alone, nivolumab + ipilimumab, pembrolizumab + axitinib,

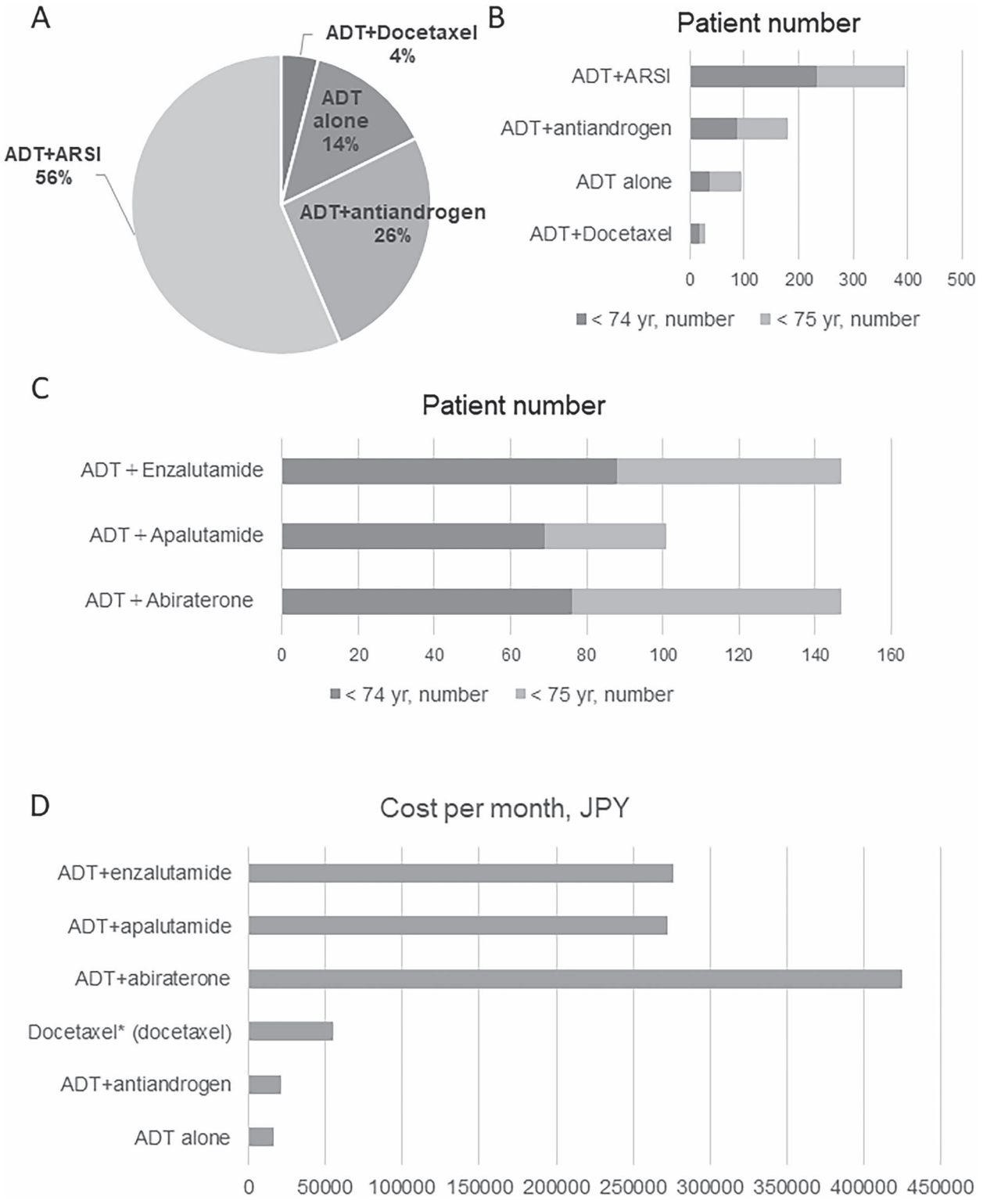


Figure 1. (A) Treatment selection for patients with untreated Stage IV prostate cancer. (B) Treatment selection (stratified by age) for patients with untreated Stage IV prostate cancer. (C) Number of patients stratified by age for each of the three ADT + ARSI treatments. (D) Treatment costs of different regimens. ADT, androgen deprivation therapy; ARSI, androgen receptor signaling inhibitor.

avelumab + axitinib, nivolumab + cabozantinib, pembrolizumab + lenvatinib were administered to 8.8, 19.3, 10.8, 9.3, 17.5 and 34.3% of patients. A higher proportion of patients >75 years of age were treated with TKIs alone than patients <75 years of age (13.5 vs. 6.9%). Moreover, patients ≥75 years of age were also more likely to receive avelumab + axitinib than those <75 (6.9 vs. 15.3%). Drug costs ranged from 623 243 to 1 616 042 JPY, all of which were high-cost treatments (>500 000 JPY). Four combination therapies were

Table 1. Number of patients by type of treatment, breakdown of patients by age, and monthly drug costs

Treatment	Age, <75 yr	Age, ≥75 yr	Total		Cost per month, JPY
ADT alone	36 (9.6%)	60 (18.5%)	96 (13.7%)		16 383
ADT+ antiandrogen	87 (23.2%)	94 (28.9%)	181 (25.9%)		21 319
ADT+ docetaxel	19 (5.1%)	9 (2.8%)	28 (4.0%)		54 693
ADT+ abiraterone	76 (20.3%)	71 (21.8%)	147 (21.0%)	ADT + ARSI (56.4%)	424 746
ADT+ apalutamide	69 (18.4%)	32 (9.8%)	101 (14.4%)		272 874
ADT+ enzalutamide	88 (23.5%)	59 (18.2%)	147 (21.0%)		275 971
Total	375 (100%)	325 (100%)	700 (100%)		

ADT, androgen deprivation therapy.

Table 2. Results of pivotal trials investigating hormone therapies for metastatic prostate cancer

	Latitude	Charrted	Enzamet	Arches	Titan
Author	Fizazi (2017, 2019)	Sweeney (2015) Kyriakopoulos (2018)	Davis (2019) Sweeney (2023)	Armstrong (2019) Armstrong (2022)	Chi (2019, 2021)
New treatment	Abiraterone + ADT	Docetaxel + ADT	Enzalutamide + ADT	Enzalutamide + ADT	Apalutamide + ADT
Dosage	1000 mg	75 mg/m^2	160 mg	160 mg	240 mg
Control	Placebo + ADT	ADT	NSAA + ADT	Placebo + ADT	Placebo + ADT
Inclusion criteria	High-risk mHSPC Gleason >8 Bone meta >3 Visceral meta	mHSPC	mHSPC	mHSPC	mHSPC
N (total)	1199	790	1125	1150	1152
N (new treatment)	597	397	563	574	525
Age (new treatment), years, median (range)	68 yr (38–89)	64 yr (36–88)	69 yr (63–74)	70 yr (46–92)	69 yr (45–94)
Elderly patients (new treatment), No. (%)	≥75 yr, 123 (20.6%)	≥70 yr, 178 (44.8%)	≥70 yr, 257 (45.6%)	≥75 yr, 170 (29.6%)	≥75 yr, 133 (25.3%)
OS, months, median, New treatment/control	53.3/36.5	57.6/47.2	NR/NR	NR/NR	NR/52.2
	HR 0.66 (95%CI 0.56–0.78)	HR 0.72 (95%CI 0.59–0.89)	HR 0.70 (95%CI 0.58–0.84)	HR 0.66 (95%CI 0.53–0.81)	HR 0.66 (95% 0.53–0.79)
PFS, months, median, New treatment/control	rPFS 33.1/14.7	cPFS 33.0/19.8	cPFS 81.0/25.0	rPFS 49.8/38.9	rPFS NR/22.1
	HR 0.46 (95%CI 0.39–0.54)	HR 0.62 (95%CI 0.51–0.75)	HR 0.45 (95%CI 0.39–0.53)	HR 0.63 (95%CI 0.52–0.76)	HR 0.48 (95% 0.39–0.60)
Treatment duration, month, median (range)					
New treatment	25.8 (IQR: 12.3–49)	NA	NA	40.2 (range 0.2–58.1)	39.3 (range 0–55.7)
Control	14.4 (IQR: 7.3–25.8)	NA	NA	13.8 (range 0.2–27.6)	20.2 (range 0.1–37.0)

c, clinical; CI, confidence interval; meta, metastasis; HR, hazard ratio; NA, not available; NR, not reached; NSAA, non-steroidal antiandrogen; OS, overall survival; PC, prostate cancer; PFS, progression-free survival; r, radiographic.

very expensive, costing >1 000 000 JPY/month, and the fifth did not strictly meet the definition of a very high-cost treatment, but was expensive, costing close to 1 000 000 JPY/month. According to the definition of this study, all patients received high-cost treatments as primary therapy for metastatic renal cancer. Furthermore, 80.4% of patients with metastatic renal cancer received very high-cost treatments, with breakdown of 81.3% of <75 years of age and 78.4% of ≥75 years of age. The details of drug costs for RCC are described in Supplementary Table 3.

Table 4 lists the results of clinical trials of metastatic RCC treatments. In all trials, the control was sunitinib alone. Four trials included ~40% of patients aged ≥65 years. In the nivolumab + ipilimumab trial, only 8.2% of the patients were aged ≥75 years. The duration of TKI alone, nivolumab + ipilimumab, pembrolizumab + axitinib, avelumab + axitinib and nivolumab + cabozantinib and pembrolizumab + lenvatinib treatments were reported as 7.3–11, 7.9, 10.4, 8.6–9.0, 14.3 and 17 months of treatment, respectively (Table 4). The pembrolizumab + lenvatinib regimen had the longest median treatment duration, and the overall total treatment cost was calculated to be 18 784 677 JPY. The lack of head-to-head trials has made it difficult for clinicians to select the first-line treatment for patients with metastatic RCC.

Discussion

Until 2015, ADT alone was the common treatment for mCSPC. However, in recent years, novel hormone therapy and chemotherapy drugs have been developed based on ADT, and clinical trials

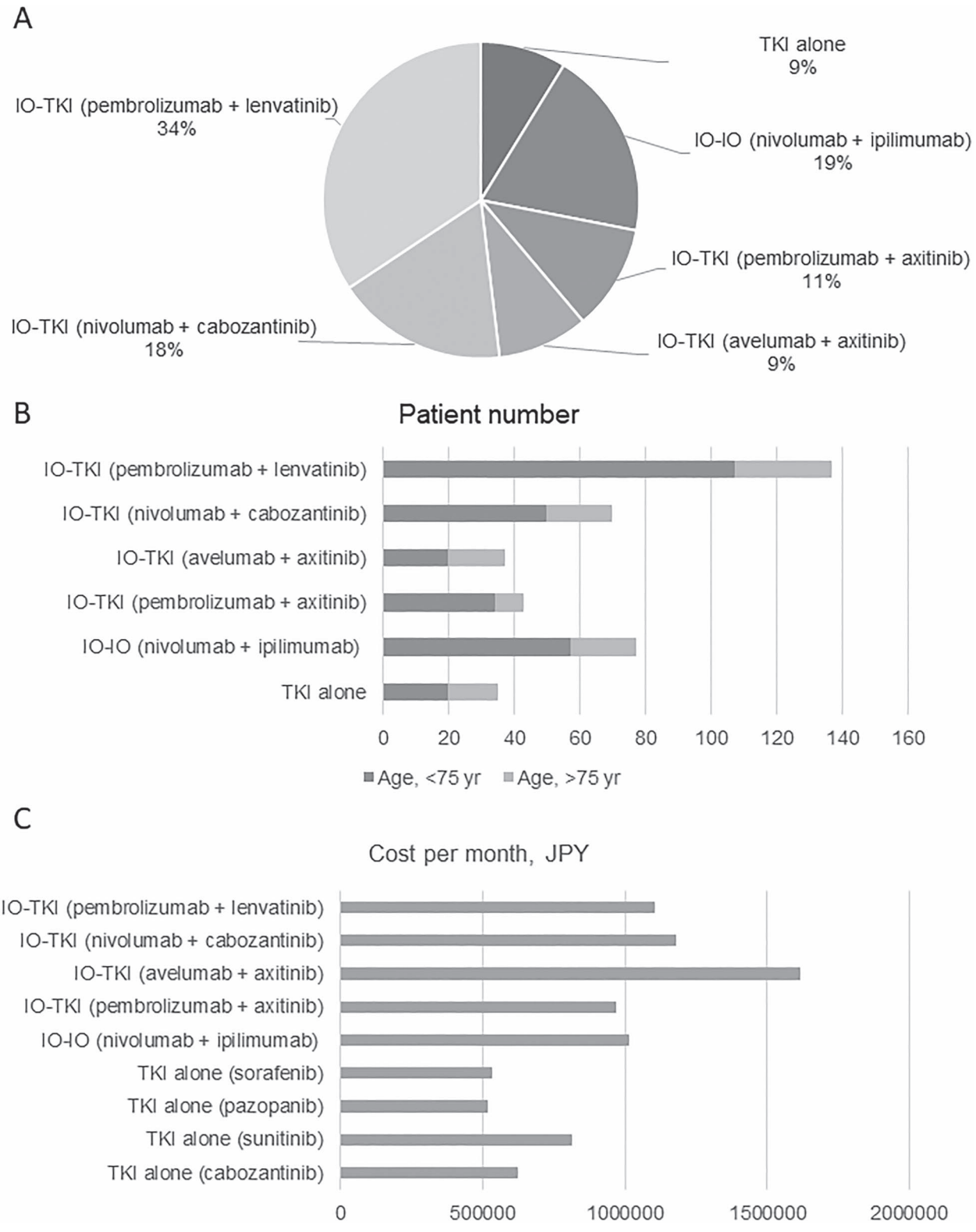


Figure 2. (A) Treatment selection for patients with untreated Stage IV renal cell carcinoma (RCC). (B) Treatment selection stratified by age for patients with untreated Stage IV RCC. TKI, tyrosine kinase inhibitor; IO, immune-oncology drug; JPY, Japanese yen.

have shown their efficacy and safety. The 2023 Japan Urological Association guidelines also weakly recommend the use of ADT + ARSI as a primary hormone therapy for mCSPC (32).

In the current survey, ADT + ARSI was introduced in 56% of patients in Japan. Three ADT + ARSI regimens are available, but the number of patients treated with ADT + apalutamide, which has

Table 3. Number of patients by type of treatment, breakdown of patients by age, and monthly drug costs

Treatment	Age, <75 yr	Age, ≥75 yr	Total	Cost per month, JPY
TKI alone	20 (6.9%)	15 (13.5%)	35 (8.8%)	623 243
IO–IO (nivolumab + ipilimumab)	57 (19.8%)	20 (18%)	77 (19.3%)	1 012 535
IO–TKI (pembrolizumab + axitinib)	34 (11.8%)	9 (8.1%)	43 (10.8%)	971 919
IO–TKI (avelumab + axitinib)	20 (6.9%)	17 (15.3%)	37 (9.3%)	1 616 042
IO–TKI (nivolumab + cabozantinib)	50 (17.4%)	20 (18%)	70 (17.5%)	1 181 236
IO–TKI (pembrolizumab + lenvatinib)	107 (37.2%)	30 (27%)	137 (34.3%)	1 104 981

TKI, tyrosine kinase inhibitor; IO, immune-oncology drug; JPY, Japanese yen

Table 4. Results of pivotal trials investigating combination therapies for metastatic renal cell carcinoma

	CheckMate 214	JAVELIN Renal 101	KEYNOTE-426	CheckMate 9ER	CLEAR
Author	Motzer (2018, 2019) Albiges (2020)	Motzer (2019) Choueiri (2020)	Rini (2019) Powles (2020)	Choueiri (2021) Motzer (2022)	Motzer (2021) Choueiri (2023)
New treatment	Ipilimumab +Nivolumab	Avelumab + Axitinib	Pembrolizumab +Axitinib	Nivolumab + Cabozantinib	Pembrolizumab +Lenvatinib
Dosage	Nivolumab (3 mg per kilogram), Ipilimumab (1 mg per kilogram)	Avelumab (a dose of 10 mg per kilogram of body weight), axitinib (5 mg twice daily)	Pembrolizumab was (a dose of 200 mg once every 3 weeks), Axitinib (a dose of 5 mg twice daily)	Nivolumab (a dose of 240 mg), cabozantinib (a dose of 40 mg once daily)	Lenvatinib (a dose of 20 mg orally once daily), pembrolizumab (a dose of 200 mg)
Control	Sunitinib	Sunitinib	Sunitinib	Sunitinib	Sunitinib
Inclusion criteria	Untreated advanced renal-cell carcinoma with a clear-cell component	Untreated advanced renal-cell carcinoma with a clear-cell component	Untreated advanced renal-cell carcinoma with a clear-cell component	Untreated advanced renal-cell carcinoma with a clear-cell component	Untreated advanced renal-cell carcinoma with a clear-cell component
IMDC risk	Intermediate/poor	All risk	All risk	All risk	All risk
N (total)	847	886	861	651	1069
N (new treatment)	425	442	432	323	355
Age (treatment), years, median (range)	62 yr (26–85)	62 yr (29–83)	62 yr (30–89)	62 yr (29–90)	64 yr (34–88)
Elderly patients (treatment), No. (%)	≥75 yr, 35 (8.2%)	≥65 yr, 171 (38.7%)	≥65 yr, 172 (39.8%)	≥65 yr, 132 (40.9%)	≥65 yr, 161 (45.4%)
OS, months, median New treatment/control	48.1/26.6	NR/NR	NR/35.7	37.7/34.3	NR/NR
	HR 0.65, 95%CI (0.54–0.78)	0.80, 95% CI (0.62–1.03	HR 0.68, 95%CI (0.55–0.85)	HR 0.70, 95%CI (0.55–0.90)	HR 0.72 95%CI (0.55–0.93)
PFS, months, median New treatment/control	11.2/8.3	13.3/8.0	15.4/11.1	16.6/8.3	23.3/9.2
	HR 0.74 (95%CI 0.62–0.88)	HR 0.69 (95% CI 0.57–0.83)	HR 0.71 (95%CI 0.60–0.84)	HR 0.56 (95%CI 0.46–0.68)	HR 0.42 (95%CI 0.34–0.52)
Treatment duration, month, median (range)					
New treatment	7.9 (2.1–21.8)	8.6 (0.5–25.3) for avelumab, 9.0 (0.02–24.9) for axitinib	10.4 (0.03–21.2)	14.3 (0.2–27.3)	17.0 (0.1–39.1)
Control	7.8 (3.5–19.6)	7.3 (0.2–23)	7.8 (0.07–20.5)	9.2 (0.8–27.6)	11.0 (0.1–40.0)

been on the insurance list for only a short time, was less than that of the other two regimens. The low percentage of older patients administered ADT + apalutamide may be due to inexperience with administration of this combination therapy. By contrast, 34% of patients receive ADT + ARSI in the USA and Europe (33,34). This indicates that the use of ARSI is more widespread in Japan than in the West possibly due to Japan's universal health insurance system, which makes the drugs available to many patients even if they are expensive. Although there was no treatment among the initial drug therapies for mCSPC in which the monthly cost exceeded 500 000 JPY, the total cost of ADT + ARSI is likely to be notably higher than other options because of the long treatment period involved.

Patients ≥75 years used ADT + antiandrogen more frequently than patients <75 (47.4 vs. 32.8%), whereas ADT + ARSI was used less frequently (49.8 vs. 62.2%). This suggests that clinicians balance efficacy and safety when choosing systemic treatment for mCSPC, considering the patient's age and medical condition. Of note, prospective data are limited due to the lack of enrollment of patients aged ≥75 years in pivotal clinical trials. However, retrospective real-world data indicate that caution is needed regarding adverse events specific to older adults, such as falls, but appropriately adjusted doses are well tolerated and provide oncologic benefits similar to those observed in younger adults (35–37). Among the three ARSIs, ADT + Abiraterone is ∼1.5-fold compared with the other two ARSIs. However, no cost-effectiveness analysis has been performed to evaluate the relative merits of these three ARSIs.

The treatment of metastatic renal cancer has reached a turning point with the development of novel therapies combining immune checkpoint inhibitors and TKIs, resulting in increased therapeutic response rates and survival. The Society for Immunotherapy of Cancer guidelines state that all patients without contraindications to immunotherapy should receive a first-line IO-based regimen (38). Due to the lack of a cost-effectiveness analysis, clinicians need to choose the best IO-based regimen based on evidence from clinical trial data, pathological findings, patient compliance, personal belief and regulatory approval.

In this survey, TKI (only), IO–IO and IO–TKI regimens were administered to 9, 19 and 72% of the patients, respectively. By contrast, a report based on a US database showed that between 2019 and 2022, TKI monotherapy decreased from 33.8 to 8.4%, while IO–IO increased from 52.8 to 57.7% and IO–TKI also increased from 13.3 to 33.9% (39,40). This indicates that the use of immune-combination therapy is more widespread in Japan than in the West due to drug availability, even for RCC drug therapy.

Notably, avelumab + axitinib therapy has the highest cost, >1.5 million JPY per month, while the costs of the other four immune-combination therapies are ∼1 million JPY per month. All of the immune-combination therapies are expensive, but there are differences in cost among them; the relative differences between the therapies are small, but the absolute differences are appreciable. The most expensive drug among the TKI monotherapy options was sunitinib, but the monthly drug costs for both TKI monotherapy options exceeded 500 000 JPY. Because conventional TKI therapy is also expensive, the cost ratio of the new therapy compared with conventional therapy for RCC is not as obvious as that of prostate cancer, but the overall cost is larger (41).

While avelumab + axitinib was prescribed the least frequently, it was prescribed the most frequently to the elderly among first-line combined immunotherapies. This may be partly due to the drug characteristics (avelumab is a PDL1 antibody) and safety profile. This combination has the lowest incidence of immune-related adverse events, hence, the increased probability of prescribing it to older adults (20). The most frequently prescribed combined immunotherapy was pembrolizumab + lenvatinib, but the frequency of prescriptions for older adults was low. This is due to the higher incidence of adverse events in prospective studies compared with other immuno-complex therapies (42), resulting in physicians being cautious about administering the therapy.

There are clinical trials that have focused on reducing the cost of expensive drugs. One of them is the low-dose abiraterone trial in which the dose of abiraterone can be reduced by taking it after a meal with non-inferior effect to the standard dose (43,44). Although no Phase III trials have been conducted, the NCCN guidelines suggest taking a quarter of the usual dose of abiraterone with a low-fat diet as an alternative when circumstances preclude taking the typical dose (45,46). The other clinical trial is related to IO-based treatment. Considering the long-lasting effect of IO-based treatment, discontinuation of IO-based therapy may help reduce side effects and the financial burden of taking these drugs. There are two ongoing prospective trials that aim to confirm the non-inferiority of discontinuation versus continuation of IO-based treatment (47,48).

This study had limitations. First, the survey was conducted over a short period of 1 year at limited JCOG participating centers and did not capture the actual treatment duration. Second, the cost of each treatment was calculated based on 1 year of treatment at the usual dose, and thus, does not consider cases in which the dose was reduced or discontinued in actual practice. However, to the best of our knowledge, this is the first report of a survey of first-line drug regimens for patients with untreated Stage IV prostate cancer and RCC patients in Japan stratified by age and treatment costs. The survey results can be used to plan future health economic studies that examine cost-effectiveness and promote the efficient use of limited resources to ensure better patient outcomes.

Conclusion

This study reports on prescription preferences and respective drug costs in Japan based on a questionnaire survey of first-line drug therapy for untreated Stage IV prostate cancer and RCC. Most Japanese patients with urologic cancers receive state-of-the-art, effective treatments, but the costs of these treatments are very high and rapidly increasing.

Supplementary Data

Supplementary data are available at *Japanese Journal of Clinical Oncology* online.

Funding

This work was supported by the Research Fund of National Federation of Health Insurance Societies and in part by the National Cancer Center Research and Development Funds (2023-J-03).

Conflict of interest statement

Takahiro Osawa has received honoraria from Ono, MSD and Takeda. Hiroshi Kitamura has received honoraria from Astellas, AstraZeneca, Bristol-Myers Squibb, Janssen, MSD and Sanof and has received research expenses from AstraZeneca, Bristol-Myers Squibb and MSD. Hiroyuki Nishiyama received honoraria from Astellas, AstraZeneca, Bristol-Myers Squibb, Ono, MSD and Merck, donations for education and research from Bayer and consultant fees from Janssen, MSD, One and AstraZeneca. The other authors have no conflicts of interest.

Author contributions

T.O., K.S. and R.M. designed the research. T.O., K.S. and R.M. collected the data. T.O. analyzed the data. T.M., Y.M., H.K., and H.N supervised the project. T.O. wrote the paper. All authors read and approved the final manuscript.

References

1. *2023 White Paper on Aging Society*. Japanese Cabinet Office, 2023. https://www8.cao.go.jp/kourei/whitepaper/w-2023/zenbun/05pdf_index.html (28 December 2023, date last accessed).

2. Statistical information by cancer type (prostate). 2019. https://ganjoho.jp/reg_stat/statistics/stat/cancer/20_prostate.html (28 December 2023, date last accessed).
3. Hospital cancer registry in Japan. https://ganjoho.jp/public/qa_links/report/hosp_c/hosp_c_reg_surv/latest.html (28 December 2023, date last accessed).
4. Huggins C, Hodges CV. Studies on prostatic cancer: I. The effect of castration, of estrogen and of androgen injection on serum phosphatases in metastatic carcinoma of the prostate. *J Urol* 2002;168:9–12. https://doi.org/10.1016/S0022-5347(05)64820-3.
5. Dunn MW, Kazer MW. Prostate cancer overview. *Semin Oncol Nurs* Elsevier 2011;27:241–50. https://doi.org/10.1016/j.soncn.2011.07.002.
6. Armstrong AJ, Szmulewitz RZ, Petrylak DP, et al. ARCHES: a randomized, phase III study of androgen deprivation therapy with enzalutamide or placebo in men with metastatic hormone-sensitive prostate cancer. *J Clin Oncol* 2019;37:2974–86. https://doi.org/10.1200/JCO.19.00799.
7. Davis ID, Martin AJ, Stockler MR, et al. Enzalutamide with standard first-line therapy in metastatic prostate cancer. *N Engl J Med* 2019;381:121–31. https://doi.org/10.1056/NEJMoa1903835.
8. Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med* 2017;377:352–60. https://doi.org/10.1056/NEJMoa1704174.
9. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *N Engl J Med* 2015;373:737–46. https://doi.org/10.1056/NEJMoa1503747.
10. Sweeney CJ, Martin AJ, Stockler MR, et al. Testosterone suppression plus enzalutamide versus testosterone suppression plus standard antiandrogen therapy for metastatic hormone-sensitive prostate cancer (ENZAMET): an international, open-label, randomised, phase 3 trial. *Lancet Oncol* 2023;24:323–34. https://doi.org/10.1016/S1470-2045(23)00063-3.
11. Kyriakopoulos CE, Chen YH, Carducci MA, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED trial. *J Clin Oncol* 2018;36:1080–7. https://doi.org/10.1200/JCO.2017.75.3657.
12. Chi KN, Chowdhury S, Bjartell A, et al. Apalutamide in patients with metastatic castration-sensitive prostate cancer: final survival analysis of the randomized, double-blind, phase III TITAN study. *J Clin Oncol* 2021;39:2294–303. https://doi.org/10.1200/JCO.20.03488.
13. Chi KN, Agarwal N, Bjartell A, et al. Apalutamide for metastatic, castration-sensitive prostate cancer. *N Engl J Med* 2019;381:13–24. https://doi.org/10.1056/NEJMoa1903307.
14. Armstrong AJ, Azad AA, Iguchi T, et al. Improved survival with enzalutamide in patients with metastatic hormone-sensitive prostate cancer. *J Clin Oncol* 2022;40:1616–22. https://doi.org/10.1200/JCO.22.00193.
15. Fizazi K, Tran N, Fein L, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2019;20:686–700. https://doi.org/10.1016/S1470-2045(19)30082-8.
16. Motzer RJ, Rini BI, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in first-line treatment for advanced renal cell carcinoma: extended follow-up of efficacy and safety results from a randomised, controlled, phase 3 trial. *Lancet Oncol* 2019;20:1370–85. https://doi.org/10.1016/S1470-2045(19)30413-9.
17. Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med* 2018;378:1277–90. https://doi.org/10.1056/NEJMoa1712126.
18. Choueiri TK, Motzer RJ, Rini BI, et al. Updated efficacy results from the JAVELIN renal 101 trial: first-line avelumab plus axitinib versus sunitinib in patients with advanced renal cell carcinoma. *Ann Oncol/ESMO* 2020;31:1030–9. https://doi.org/10.1016/j.annonc.2020.04.010.
19. Albiges L, Tannir NM, Burotto M, et al. Nivolumab plus ipilimumab versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended 4-year follow-up of the phase III CheckMate 214 trial. *ESMO Open* 2020;5:e001079. https://doi.org/10.1136/esmoopen-2020-001079.
20. Motzer RJ, Penkov K, Haanen J, et al. Avelumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2019;380:1103–15. https://doi.org/10.1056/NEJMoa1816047.
21. Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2019;380:1116–27. https://doi.org/10.1056/NEJMoa1816714.
22. Powles T, Plimack ER, Soulières D, et al. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. *Lancet Oncol* 2020;21:1563–73. https://doi.org/10.1016/S1470-2045(20)30436-8.
23. Choueiri TK, Eto M, Motzer R, et al. Lenvatinib plus pembrolizumab versus sunitinib as first-line treatment of patients with advanced renal cell carcinoma (CLEAR): extended follow-up from the phase 3, randomised, open-label study. *Lancet Oncol* 2023;24:228–38. https://doi.org/10.1016/S1470-2045(23)00049-9.
24. Choueiri TK, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med* 2021;384:829–41. https://doi.org/10.1056/NEJMoa2026982.
25. Motzer RJ, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib in first-line treatment for advanced renal cell carcinoma (CheckMate 9ER): long-term follow-up results from an open-label, randomised, phase 3 trial. *Lancet Oncol* 2022;23:888–98. https://doi.org/10.1016/S1470-2045(22)00290-X.
26. Motzer R, Alekseev B, Rha SY, et al. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. *N Engl J Med* 2021;384:1289–300. https://doi.org/10.1056/NEJMoa2035716.
27. Smith TJ, Hillner BE. Bending the cost curve in cancer care. *N Engl J Med* 2011;364:2060–5. https://doi.org/10.1056/NEJMsb1013826.
28. Sullivan R, Peppercorn J, Sikora K, et al. Delivering affordable cancer care in high-income countries. *Lancet Oncol* 2011;12:933–80. https://doi.org/10.1016/S1470-2045(11)70141-3.
29. Leighl NB, Nirmalakumar S, Ezeife DA, Gyawali B. An arm and a leg: the rising cost of cancer drugs and impact on access. *Am Soc Clin Oncol Educ Book* 2021;41:e1–e12. https://doi.org/10.1200/EDBK_100028.
30. Chien CR, Geynisman DM, Kim B, Xu Y, Shih YCT. Economic burden of renal cell carcinoma—part I: an updated review. *Pharmacoeconomics* 2019;37:301–31. https://doi.org/10.1007/s40273-018-0746-y.
31. Maganty A, Hollenbeck BK. New technology in prostate cancer and financial toxicity. *Urol Oncol Semin Orig Investig* 2023;41:376–9. https://doi.org/10.1016/j.urolonc.2023.04.014.
32. *Clinical Guideline For Prostate Cancer* [In Japanese]. MedicalReview Co., Ltd, Osaka, Japan, 2023.
33. Barata PC, Leith A, Ribbands A, et al. Real-world treatment trends among patients with metastatic castration-sensitive prostate cancer: results from an international study. *Oncologist* 2023;28:780–9. https://doi.org/10.1093/oncolo/oyad045.
34. Dodkins J, Nossiter J, Cook A, et al. Does research from clinical trials in metastatic hormone-sensitive prostate cancer treatment translate into access to treatments for patients in the "real world"? A systematic review. *Eur Urol Oncol* 2023;7:14–24. https://doi.org/10.1016/j.euo.2023.05.002.
35. Boukovala M, Spetsieris N, Efstathiou E. Systemic treatment of prostate cancer in elderly patients: current role and safety considerations of androgen-targeting strategies. *Drugs Aging* 2019;36:701–17. https://doi.org/10.1007/s40266-019-00677-6.
36. Graff JN, Baciarello G, Armstrong AJ, et al. Efficacy and safety of enzalutamide in patients 75 years or older with chemotherapy-naive metastatic castration-resistant prostate cancer: results from PREVAIL. *Ann Oncol* 2016;27:286–94. https://doi.org/10.1093/annonc/mdv542.
37. Smith MR, Rathkopf DE, Mulders PFA, et al. Efficacy and safety of abiraterone acetate in elderly (75 years or older) chemotherapy naïve patients with metastatic castration resistant prostate cancer. *J Urol* 2015;194:1277–84. https://doi.org/10.1016/j.juro.2015.07.004.
38. Rini BI, Battle D, Figlin RA, et al. The society for immunotherapy of cancer consensus statement on immunotherapy for the treatment of advanced

renal cell carcinoma (RCC). *J Immunother Cancer* 2019;7:354. https://doi.org/10.1186/s40425-019-0813-8.
39. Shah NJ, Sura SD, Shinde R, et al. Real-world treatment patterns and clinical outcomes for metastatic renal cell carcinoma in the current treatment era. *Eur Urol Open Sci* 2023;49:110–8. https://doi.org/10.1016/j.euros.2022.12.015.
40. Lai G-S, Li J-R, Wang S-S, et al. Real world treatment sequences and outcomes for metastatic renal cell carcinoma. *PloS One* 2023;18:e0294039. https://doi.org/10.1371/journal.pone.0294039.
41. Bach PB. New math on drug cost-effectiveness. *N Engl J Med* 2015;373:1797–9. https://doi.org/10.1056/NEJMp1512750.
42. Bosma NA, Warkentin MT, Gan CL, et al. Efficacy and safety of first-line systemic therapy for metastatic renal cell carcinoma: a systematic review and network meta-analysis. *Eur Urol Open Sci* 2022;37:14–26. https://doi.org/10.1016/j.euros.2021.12.007.
43. Szmulewitz RZ, Peer CJ, Ibraheem A, et al. Prospective international randomized phase II study of low-dose abiraterone with food versus standard dose abiraterone In castration-resistant prostate cancer. *J Clin Oncol* 2018;36:1389–95. https://doi.org/10.1200/JCO.2017.76.4381.
44. Szmulewitz RZ, Stadler WM, Ratain MJ. The abiraterone dosing chess match with Johnson & Johnson-Back in check. *JAMA Oncol* 2021;7:827–8. https://doi.org/10.1001/jamaoncol.2020.8087.
45. Dey T, Goyal S, Periasamy K, Madan R. Is low-dose abiraterone for prostate cancer an attractive strategy for limited resource settings? *Indian J Med Paediatr Oncol* 2022;43:040–6. https://doi.org/10.1055/s-0042-1742400.
46. NCCN guideline prostate cancer. Version 1.2023 — September 16, 2022.
47. JCOG1905: a randomized controlled phase III trial on continued or paused PD-1 pathway blockade for patients with advanced renal cell carcinoma (STOP study). 2023. https://www8.cao.go.jp/kourei/whitepaper/w-2023/zenbun/05pdf_index.html (28 December 2023, date last accessed).
48. Nomura S, Goto Y, Mizutani T, et al. A randomized phase III study comparing continuation and discontinuation of PD-1 pathway inhibitors for patients with advanced non-small-cell lung cancer (JCOG1701, SAVE study). *Jpn J Clin Oncol* 2020;50:821–5. https://doi.org/10.1093/jjco/hyaa054.

JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2024, 1–7
https://doi.org/10.1093/jjco/hyae048
Original Article

OXFORD

Original Article

Current status of the cost burden of first-line systemic treatment for patients with advanced hepatocellular carcinoma in Japan, 2021–22

Hiroshi Imaoka[1,*], Keita Sasaki[2], Ryunosuke Machida[2], Hiroaki Nagano[3], Sohei Satoi[4], Masafumi Ikeda[1], Satoshi Kobayashi[5], Taro Yamashita[6], Takuji Okusaka[7], Akio Ido[8], Etsuro Hatano[9], Haruo Miwa[10], Masaki Ueno[11], Kazuhiko Nakao[12], Satoshi Shimizu[13], Hidekazu Kuramochi[14], Ryotaro Sakamori[15], Hidetaka Tsumura[16], Naohiro Okano[17], Kazuhiko Shioji[18], Hirofumi Shirakawa[19], Noriyuki Akutsu[20], Kunihiro Tsuji[21], Hiroshi Ishii[22], Kumiko Umemoto[23], Akinori Asagi[24], Makoto Ueno[5] and on behalf of the JCOG Hepatobiliary and Pancreatic Oncology Group

[1]Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [2]Japan Clinical Oncology Group Data Center/Operations Office, National Cancer Center Hospital, Tokyo, Japan, [3]Department of Gastroenterological, Breast and Endocrine Surgery, Yamaguchi University Graduate School of Medicine, Ube, Japan, [4]Division of Pancreatobiliary Surgery, Department of Surgery, Kansai Medical University, Hirakata, Japan, [5]Department of Gastroenterology, Kanagawa Cancer Center, Yokohama, Japan, [6]Department of Gastroenterology, Kanazawa University Hospital, Kanazawa, Japan, [7]Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital, Tokyo, Japan, [8]Digestive and Lifestyle Diseases, Kagoshima University Graduate School of Medical and Dental Sciences, Kagoshima Japan, [9]Division of Hepato-Biliary-Pancreatic Surgery and Transplantation, Department of Surgery, Graduate School of Medicine, Kyoto University, Kyoto, Japan, [10]Gastroenterological Center, Yokohama City University Medical Center, Yokohama, Japan, [11]Second Department of Surgery, Wakayama Medical University, Wakayama, Japan, [12]Department of Gastroenterology and Hepatology, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan, [13]Department of Gastroenterology, Saitama Cancer Center, Saitama, Japan, [14]Department of Chemotherapy and Palliative Care, Tokyo Women's Medical University, Tokyo, Japan, [15]Department of Gastroenterology and Hepatology, NHO Osaka National Hospital, Osaka, Japan, [16]Department of Gastroenterological Oncology, Hyogo Cancer Center, Akashi, Japan, [17]Department of Medical Oncology, Kyorin University Faculty of Medicine, Tokyo, Japan, [18]Department of Internal Medicine, Niigata Cancer Center Hospital, Niigata, Japan, [19]Department of Medical Oncology, Tochigi Cancer Center, Utsunomiya, Japan, [20]Department of Gastroenterology and Hepatology, Sapporo Medical University School of Medicine, Sapporo, Japan, [21]Department of Gastroenterology, Ishikawa Prefectural Central Hospital, Kanazawa, Japan, [22]Division of Gastroenterology, Chiba Cancer Center, Chiba, Japan, [23]Department of Clinical Oncology, St. Marianna University School of Medicine, Kawasaki, Japan and [24]Department of Gastrointestinal Medical Oncology, National Hospital Organization Shikoku Cancer Center, Matsuyama, Japan

*For reprints and all correspondence: Hiroshi Imaoka, Department of Hepatobiliary and Pancreatic Oncology, National Cancer Center Hospital East, 6-5-1, Kashiwanoha, Kashiwa, Chiba 277-8577, Japan. E-mail: hiimaoka@east.ncc.go.jp

Received 13 March 2024; Editorial Decision 1 April 2024; Accepted 5 April 2024

Abstract

Background: Although recent advances in systemic therapies for hepatocellular carcinoma (HCC) have led to prolonged patient survival, the high costs of the drugs place a heavy burden on both

patients and society. The objectives of this study were to examine the treatment regimens used as first-line systemic treatment for patients with advanced HCC in Japan and to estimate the treatment costs per regimen.

Methods: For this study, we aggregated the data of patients who had received first-line systemic treatment for advanced HCC between July 2021 and June 2022. The treatment cost per month of each regimen was estimated based on standard usage, assuming an average weight of 60 kg for male patients. The data were categorized by the treatment regimen, and the treatments were categorized based on the cost into very high-cost (≥1 000 000 Japanese yen [JPY]/month), high-cost (≥500 000 JPY/month) and other (<500 000 JPY/month) treatments.

Results: Of the total of 552 patients from 24 institutions whose data were analyzed in this study, 439 (79.5%) received atezolizumab plus bevacizumab, 98 (17.8%) received lenvatinib and 15 (2.7%) received sorafenib as the first-line treatment. The treatment cost per month for each of the above regimens was as follows: atezolizumab plus bevacizumab, 1 176 284 JPY; lenvatinib, 362 295 JPY and sorafenib, 571 644 JPY. In total, 82.2% of patients received high-cost regimens, and the majority of these patients received a very high-cost regimen of atezolizumab plus bevacizumab.

Conclusions: Advances in systemic therapies for HCC have led to prolonged patient survival. However, the treatment costs are also increasing, imposing a burden on both the patients and society.

Key words: hepatocellular carcinoma, treatment cost, immune checkpoint inhibitor, tyrosine kinase inhibitor, cost burden

Introduction

Hepatocellular carcinoma (HCC) is one of the deadliest cancers known and the third leading cause of cancer death. In 2020, it is estimated that over 830 000 patients worldwide died from this disease (1). Although the incidence of HCC has declined globally, it remains one of the most commonly diagnosed cancers, with over 900 000 new patients diagnosed each year (2). One of the clinical problems associated with HCC is its resistance to systemic treatments. Patients with advanced disease (e.g. those with portal vein invasion and distant metastases) are candidates for systemic therapies, and ∼50–60% of patients will receive systemic therapy at some point during the clinical course of the disease (3). However, advanced disease carries a dismal prognosis, with an overall survival (OS) of ∼2 years (4).

There has been a rapid expansion of systemic treatment options approved by the Japan Pharmaceuticals and Medical Devices Agency (PMDA) for patients with advanced HCC, ranging from anti-vascular endothelial growth factor (VEGF) antibodies to multi-targeted tyrosine kinase inhibitors (TKIs), immune checkpoint inhibitors (ICIs) and combinations of the above. Consequently, sorafenib, lenvatinib, atezolizumab plus bevacizumab and durvalumab plus tremelimumab have come to be used as first-line treatments for HCC in Japan. While these therapeutic regimens are effective for treating advanced HCC, many patients with advanced HCC, not only in Japan but around the world, face substantial financial pressure due to medical expenses (5). Furthermore, the high costs of the treatments also place a heavy burden on the social health resources (6–8). Therefore, we performed a multicenter survey to clarify the current status of the cost burden of first-line systemic treatment of advanced HCC in Japan. The objectives of this study were to examine the treatment regimens used as first-line systemic treatment for advanced HCC and estimate the cost of treatment using each of these regimens in Japan. This study was carried out under the leadership of the Japan Clinical Oncology Group's (JCOG) Health Economic Committee.

Methods

For this study, we distributed an online questionnaire via Google Forms to institutions affiliated with the JCOG Hepatobiliary and Pancreatic Oncology Group and aggregated the treatment data obtained in response to the questionnaire. The treatment data of patients who had received first-line systemic treatment for advanced HCC between July 2021 and June 2022 were aggregated, but no patient personal data were collected. Thus, this study did not require individual consent or Institutional Review Board approval. The data of patients in different age categories (≤74 and ≥75 years) were collected separately. The treatments were categorized into very high-cost (≥1 000 000 Japanese yen [JPY]/months), high-cost (≥500 000 JPY/months) and other (<500 000 JPY/month) treatments based on the definition provided by the JCOG Health Economic Committee. The treatment cost per month of each regimen was estimated based on standard usage, that is, assuming an average weight of 60 kg for male patients treated without any skips, delays and/or dose reductions (Table 1). The standard usage protocol of each of the regimens was as follows: atezolizumab plus bevacizumab: atezolizumab 1200 mg plus bevacizumab at 15 mg/kg body weight administered intravenously every 3 weeks; lenvatinib: 12 mg/day (for patients with a body weight of ≥60 kg) or 8 mg/day (for patients with a body weight of <60 kg) administered orally and sorafenib: 400 mg administered orally twice-daily in 28-day cycles. Treatment costs were calculated based on the drug prices as of March 2024; the costs of supportive care (e.g. antiemetics and medications for adverse events) were not included.

Results

Data on a total of 552 patients who had received first-line systemic therapy for HCC between July 2021 and June 2022 were collected from 24 institutions. Of the 552 patients, 329 (59.6%) were ≤74 years old and 223 patients (40.4%) were ≥75 years old.

Table 1. Results of pivotal studies for advanced HCC and cost in Japan

Regimen	Publication year	median OS (months)	median PFS (months)	Mean dose intensity (%)	Cost[a] (JPY)
Atezolizumab plus bevacizumab (11)	2020	19.2 (9)	6.9	95 (Atezolizumab) 93 (Bevacizumab)	1 176 284
Durvalumab plus tremelimumab (13)	2022	16.43	3.78	not reported	3 806 181 (first month) 1 329 232 (after the first month)
Durvalumab (13)	2022	16.56	3.65	not reported	1 329 232
Lenvatinib (10)	2018	13.6	7.4	88	362 295
Sorafenib (9)	2008	10.7	5.5[b]	84 (12)	571 644

OS, overall survival; PFS, progression-free survival; JPY, Japanese yen. [a]The costs were calculated as the cost for body weight (60 kg) per month (30 days). [b]Time to radiologic progression.

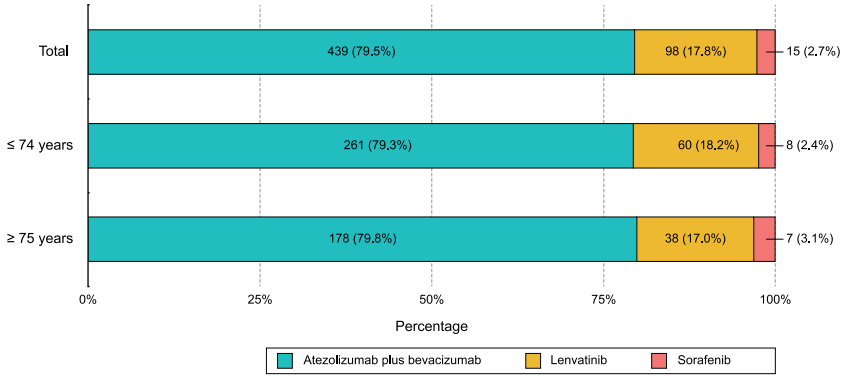


Figure 1. Bar chart presenting the percentages of patients receiving each of the major treatment regimens used as first-line systemic treatment for advanced hepatocellular carcinoma in Japan.

The details of the treatment regimens these patients received were as follows: atezolizumab plus bevacizumab, 439 patients (79.5%); lenvatinib, 98 patients (17.8%) and sorafenib, 15 patients (2.7%) (Fig. 1). Of the 329 patients who were ≤74 years old, 261 (79.3%) received atezolizumab plus bevacizumab, 60 (18.2%) received lenvatinib and 8 (2.4%) received sorafenib. Of the total 223 patients who were ≥75 years old, 178 (79.8%) received atezolizumab plus bevacizumab, 38 (17.0%) received lenvatinib and 7 (3.1%) received sorafenib.

The details of the treatment costs per month for each regimen were as follows: atezolizumab plus bevacizumab, 1 176 284 JPY; lenvatinib, 362 295 JPY and sorafenib, 571 644 JPY (Table 1). In all, 82.2% of patients received high-cost treatments, and 79.5% received the very high-cost treatment of atezolizumab plus bevacizumab. Similarly, 83.0% of patients received high-cost treatments, and 79.8% received the very high-cost treatment in elderly patients.

Discussion

In the present study, using data obtained from a multicenter survey, we clarified the current status of the cost burden of first-line systemic treatment for advanced HCC in Japan. Over 80% of patients received high-cost treatments (atezolizumab plus bevacizumab or sorafenib), of which the majority received very-high-cost treatment (atezolizumab plus bevacizumab). This finding was nearly identical among both the age groups (≤74 and ≥75 years) of HCC patients included in the analysis. Advances in systemic therapies for HCC have led to prolonged patient survival. However, they are also leading to healthcare economic issues, including increased treatment costs.

In recent years, the landscape of advanced HCC treatment has changed dramatically (Table 1), primarily with the advent of targeted therapies and immunotherapy. The initial era of systemic therapy for advanced HCC was dominated by single-agent treatment with sorafenib, following its approval by the PMDA in 2009; this approval was granted on the basis of data from the phase III SHARP trial, which demonstrated an OS benefit in the treatment arm over the placebo arm (9). Around a decade later, the phase III REFLECT trial showed the non-inferiority of lenvatinib, a multikinase inhibitor with activities against both VEGFR and FGFR, as compared with sorafenib (10). Although lenvatinib failed to yield superior OS, it demonstrated activity and a statistically significantly improved progression-free survival (PFS) and objective response rate. Thus, lenvatinib is generally preferred over sorafenib for the systemic treatment of patients with HCC. Now, a new era of ICI therapy has begun. In the phase III IMbrave150 trial, atezolizumab plus bevacizumab (an anti-PD-L1 inhibitor and anti-VEGF antibody, respectively) were demonstrated to show substantial OS and PFS benefits as compared with sorafenib (11,12). The toxicity profile of the patients treated with atezolizumab plus bevacizumab was also manageable; based on this evidence, the PMDA approved this combination treatment in 2020. Subsequently, the phase III HIMALAYA trial demonstrated the superiority of durvalumab plus tremelimumab over sorafenib as a first-line systemic treatment for advanced HCC. Similarly, durvalumab monotherapy can also be considered in this setting, being

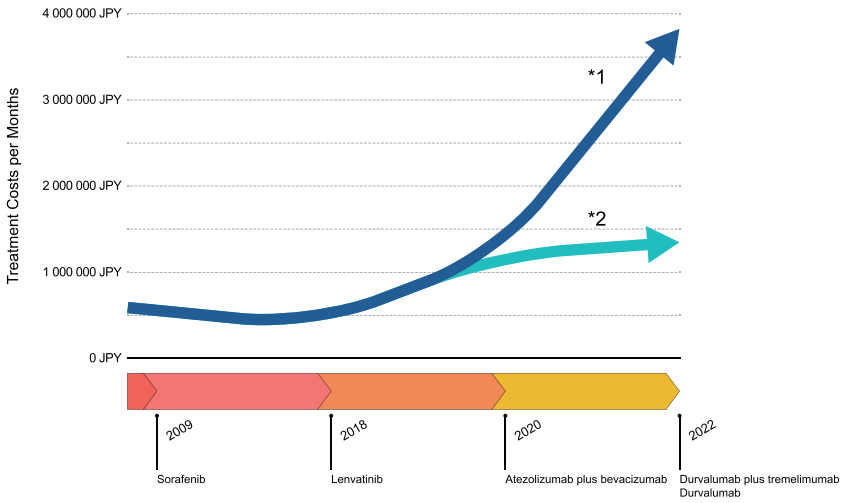


Figure 2. History of approved treatment regimens for advanced hepatocellular carcinoma and their costs in Japan. JPY, Japanese yen; ∗1, Durvalumab plus tremelimumab; ∗2, Durvalumab monotherapy.

non-inferior to sorafenib and having a more favorable toxicity profile (13). Consequently, a paradigm shift from the use of TKIs to the use of ICIs for the treatment of HCC has led to prolonged survival of the patients, but also a significant increase in treatment costs.

We did not examine the treatment costs of durvalumab and tremelimumab, which began to be reimbursed by national health insurance only in 2023; if this combination of ICIs were also to be included, the derived treatment costs could increase further (Fig. 2). There is a lack of robust head-to-head trial data to compare the efficacy and safety of atezolizumab plus bevacizumab and durvalumab plus tremelimumab. Thus, there is currently no consensus on the use of atezolizumab plus bevacizumab, durvalumab and tremelimumab for the treatment of advanced HCC. Additionally, many ongoing trials still use TKIs as controls since trials comparing TKIs and ICIs were initiated almost simultaneously, and several trials have not yet reported their results (Table 2). The growth of ICI-based regimens may confuse clinicians in making treatment decisions in the future (14). However, given the efficacy data (median OS, 19.2 months for atezolizumab plus bevacizumab versus 16.43 months for durvalumab and tremelimumab) and treatment costs per month (1 176 284 JPY for atezolizumab plus bevacizumab versus 3 806 181 JPY for durvalumab and tremelimumab) of the two combination treatments, durvalumab and tremelimumab are unlikely to be cost-effective due to similar survival benefits and much higher treatment costs. Such cost-effectiveness considerations may help clinicians in making optimal decisions regarding the treatment of advanced HCC. Therefore, further randomized trials and cost-effectiveness analyses of these regimens are warranted.

Another problem in relation to the treatment costs of advanced HCC is the advancing age of the patients. With the aging of the population in developed countries, patients with HCC are also aging. One epidemiological report based on the SEER registry data showed that although the incidence of HCC is decreasing among younger patients, it continues to increase among elderly patients, in both men and women of all races/ethnicities (15). This phenomenon could affect the health care system through two scenarios. First, as the proportion of the aging population increases, the proportion that pays taxes and premiums to finance the system decreases. The treatment cost is financed not only by governmental revenues but also by insurance premiums imposed on employers and employees. This means that the younger generation will have to bear a greater cost burden in the future. Second, elderly patients face higher health risks, including adverse events caused by the systemic treatments themselves, and require a greater amount of care than younger patients. Japan's insurance system maintains a low patient copayment rate for medical expenses. However, in recent years, the rate has been raised to control the growing cost burden among elderly patients. Despite these efforts, the socioeconomic burden continues to increase since the high-cost medical care system sets an upper limit on the total amount of medical expenses per month, even for elderly patients. Several studies have reported that systemic treatments are equally effective in elderly patients. For example, Li et al. (16) reported from a *post hoc* analysis of the IMbrave150 trial that the atezolizumab plus bevacizumab arm, showed a prolonged OS and PFS as compared with the sorafenib arm even among elderly patients (≥75 years old). However, the aforementioned risks could lead to reduced cost-effectiveness in elderly patients (17–19). When considering the cost burden of systemic therapy for HCC and making treatment decisions, it is necessary to evaluate not only the effectiveness but also the cost-effectiveness of the available therapeutic strategies.

Currently, many clinical trials are being conducted to explore effective treatment options (Table 2). The majority of these trials are of combination regimens with ICIs: anti-PD-1/PD-L1 antibody, anti-CTLA-4 antibody, anti-TIGIT antibody and anti-LAG-3 antibody. Furthermore, several late-phase trials are underway to evaluate the efficacy of triplet therapies, including ICIs and TKIs, with the expectation of higher anti-tumor efficacies. Another trend of the ongoing clinical trials is to examine the expansion of the indications of ICIs. Several trials of ICIs in combination with local and adjuvant treatments are underway (Table 2), and some have reported positive results. In the phase III EMERALD-1 trial assessing transarterial chemoembolization (TACE) in combination with durvalumab and/or bevacizumab versus TACE plus placebo, the TACE with durvalumab plus bevacizumab arm showed a statistically significantly better PFS as compared with the TACE plus placebo arm in patients with intermediate-stage HCC (20). The IMbrave050 trial evaluated the efficacy of atezolizumab plus bevacizumab in the adjuvant setting in patients with HCC with high-risk features after curative resection or ablation (21). The study was the first successful phase III trial to show improved recurrence-free survival after curative treatment in patients

Table 2. Ongoing major clinical trials for advanced hepatocellular carcinoma

Trial name and/or ID	Investigational treatment	Control	Phase	Primary end points	Treatment line
Advanced stage					
Checkmate 9DW NCT04039607	Nivolumab (anti-PD-1 antibody) plus ipilimumab (anti-CTLA-4 antibody)	Sorafenib (TKI) or lenvatinib (TKI)	III	OS	First-line
IMbrave152 NCT05904886	Tiragolumab (anti-TIGIT antibody) plus atezolizumab (anti-PD-L1 antibody) + bevacizumab (anti-VEGF antibody)	Atezolizumab plus bevacizumab	III	OS & PFS	First-line
NCT04183088	Tislelizumab (anti-PD-1 antibody) plus regorafenib (TKI)	–	II	ORR & PFS	First-line
NCT03680508	Cobolimab (TIM-3 binding antibody) plus dostarlimab (anti-PD-1 antibody)	–	II	ORR	First-line
TRIPLET NCT05665348	Atezolizumab plus bevacizumab plus ipilimumab	Atezolizumab plus bevacizumab	II/III	ORR & OS	First-line
RELATIVITY-106 NCT05337137	Relatlimab (anti-LAG-3 antibody) plus nivolumab plus bevacizumab	Nivolumab plus bevacizumab	I/II	ORR	First-line
NCT04194775	Nofazinlimab (anti-PD-1 antibody) plus lenvatinib	Lenvatinib	III	OS	First-line
NCT04523493	Toripalimab (anti-PD-1 antibody) plus lenvatinib	Lenvatinib	III	OS	First-line
NCT03605706	SHR-1210 (anti-PD-1 antibody) plus FOLFOX4	SHR-1210	III	OS	First-line
NCT03764293	SHR-1210 (anti-PD-1 antibody) plus apatinib (TKI)	Sorafenib	III	OS & PFS	First-line
NCT04720716	IBI310 (anti-CTLA-4 antibody) plus sintilimab (anti-PD-1 antibody)	Sorafenib	III	ORR & OS	First-line
NCT04723004	Toripalimab (anti-PD-1 antibody) plus bevacizumab	Sorafenib	III	OS & PFS	First-line
NCT05408221	Rulonilimab (anti-PD-1 antibody) plus lenvatinib	Lenvatinib	II/III	ORR	First-line
IMbrave-251 NCT04770896	Atezolizumab plus sorafenib or lenvatinib	Sorafenib or lenvatinib	III	OS	Second-line
Intermediate stage					
EMERALD-3 NCT05301842	TACE plus durvalumab (anti-PD-L1 antibody) plus tremelimumab (anti-CTLA-4 antibody) and/or lenvatinib	TACE	III	PFS	
CheckMate 74 W NCT04340193	TACE plus nivolumab and/or ipilimumab	TACE	III	OS & Time to TACE progression	
IMPACT jRCTs051230037	TACE plus atezolizumab plus bevacizumab	Atezolizumab plus bevacizumab	III	OS	
ABC-HCC NCT04803994	Atezolizumab plus bevacizumab	TACE	III	Time to failure of treatment strategy	
Adjuvant setting					
CheckMate 9DX NCT03383458	Nivolumab	Placebo	III	RFS	
KEYNOTE-937 NCT03867084	Pembrolizumab (anti-PD-1 antibody)	Placebo	III	RFS	
EMERALD-2 NCT03847428	Durvalumab and/or bevacizumab	Durvalumab	III	RFS	

TKI, tyrosine kinase inhibitor; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; TACE, transarterial chemoembolization; RFS, recurrence-free survival.

with HCC. These combination therapies of ICIs in combination with local and adjuvant therapies may improve the prognosis of patients with HCC, but they can also be expected to further increase the treatment costs.

The expansion of the indications of expensive immunotherapy regimens raises significant concerns about the current and future treatment costs worldwide. Due to the rising treatment costs, new oncology products frequently fail to meet the willingness-to-pay

threshold, or in other words, the maximum price a cancer patient is willing to pay for his/her treatment (22). Zou et al. (5) reported that the treatment for HCC places a significant economic burden on the patients and their families. Su et al. (23) reported that atezolizumab plus bevacizumab treatment was unlikely to be a cost-effective option as compared with sorafenib in patients with advanced HCC. The PMDA does not take cost-effectiveness into consideration when making approval decisions, so that cost-effectiveness analyses often end up only as academic exercises (22). To effect a change in this scenario, the oncology community should consider the cost-effectiveness of treatments in their guidelines and daily practices. In addition, the pricing and payment systems should be reformed in order to reduce the cost burden on the patients and society.

Other potential measures to improve the situation include promoting the use of less expensive but equally effective drugs. The use of biosimilars can improve cost-effectiveness. Although the development of biosimilars with large molecular weights is difficult due to technical difficulties, bevacizumab biosimilars have also received approval in Japan for the treatment of metastatic colorectal cancer, non-small cell lung cancer and breast cancer. Although convincing evidence is often thought to be lacking for biosimilars, over the past few years, a number of reports have demonstrated their benefits. A network meta-analysis showed that atezolizumab plus bevacizumab and sintilimab plus IBI305, a bevacizumab biosimilar, showed comparable efficacy (24). The rapid approval of such biosimilars for HCC is expected to reduce the treatment costs. In recent years, ICIs have been manufactured at a lower cost in China. Liu (25) reported that tislelizumab, an anti-PD-1 antibody, is the most cost-effective first-line systemic treatment agent for advanced HCC. Considering their cost-effectiveness, such drugs could be useful treatment options.

The present study had some limitations. The first was that this survey covered only institutions affiliated with the JCOG. In Japan, HCC treatment is not exclusively confine of oncologists but is also performed by hepatologists who oversee antiviral and local therapies. Therefore, the study data may not reflect the overall systemic treatment trends for HCC in Japan. The second limitation was that this study was a hospital-based study based on estimates of the proportion of patients who received the major systemic treatment regimens at each of the participating institutions. Patient-level data (e.g. duration of treatment, drug discontinuations and dose reductions) were not collected in this study. Therefore, our survey data cannot be used to assess the individual cost-effectiveness of the treatment regimens.

Conclusion

In ~80% of patients with advanced HCC in Japan, the first-line systemic treatment prescribed was atezolizumab plus bevacizumab, a treatment regimen categorized as a very high-cost (≥1 000 000 JPY/month) treatment. Advances in systemic therapies for HCC have led to prolonged patient survival but are also expected to lead to increased treatment costs and a heavy cost burden on patients and society in the future.

Acknowledgements

The authors would like to express their sincere appreciation to the members of the JCOG Data Center and JCOG Operations Office for their support.

Authors' contributions

Hiroshi Imaoka (Conceptualization, Collection and assembly of data, Data curation, Formal analysis, Methodology, Supervision, Writing–original draft, Writing–review & editing), Sohei Satoi (Collection and assembly of data, Supervision), Hiroaki Nagano (Collection and assembly of data, Supervision), Satoshi Kobayashi (Collection and assembly of data), Taro Yamashita (Collection and assembly of data), Takuji Okusaka (Collection and assembly of data), Akio Ido (Collection and assembly of data), Etsuro Hatano (Collection and assembly of data), Kazuhiko Shioji (Collection and assembly of data, Methodology), Haruo Miwa (Collection and assembly of data), Masaki Ueno (Collection and assembly of data), Kazuhiko Nakao (Collection and assembly of data), Satoshi Shimizu (Collection and assembly of data), Hidekazu Kuramochi (Collection and assembly of data), Ryotaro Sakamori (Collection and assembly of data), Hidetaka Tsumura (Collection and assembly of data), Naohiro Okano (Collection and assembly of data), Keita Sasaki (Methodology, Writing–review & editing), Hirofumi Shirakawa (Collection and assembly of data), Noriyuki Akutsu (Collection and assembly of data), Kunihiro Tsuji (Collection and assembly of data), Hiroshi Ishii (Collection and assembly of data), Kumiko Umemoto (Collection and assembly of data), Akinori Asagi (Collection and assembly of data), Ryunosuke Machida (Methodology, Writing–review & editing), Masafumi Ikeda (Supervision, Writing–review & editing), and Makoto Ueno (Supervision, Writing–review & editing)

Funding

This work was supported in part by the National Cancer Center Research and Development Funds (2023-J-03) and Research Fund of National Federation of Health Insurance Societies (Kenpo-ren).

Conflict of interest statement

Hiroshi Imaoka has received research funding from Ono Pharmaceutical; and honoraria from AstraZeneca. Sohei Satoi received research fundings from Boston Scientific, Nihon Servier and Amino-Up Company. Masafumi Ikeda has received consulting fees from AbbVie, AstraZeneca, Bayer, Chugai, Eisai, Eli Lilly Japan, MSD and Ono Pharmaceutical; and honoraria from Abbott, AstraZeneca, Bayer, Bristol Myers Squibb, Chugai, Eisai, Eli Lilly Japan, Gilead, MSD, Sumitomo Dainippon and Takeda; research fundings from AstraZeneca, Bristol Myers Squibb, Chugai, Eisai, Eli Lilly Japan, MSD, Ono Pharmaceutical, Merck Serono and Novartis. Satoshi Kobayashi has received honoraria from AstraZeneca, Eisai, Chugai Pharma, Takeda and Eli Lilly Japan. Etsuro Hatano has received honoraria from Chugai, AstraZeneca and Eisai; and other financial or non-financial interests from Chugai and Eisai. Satoshi Shimizu has received grant from AstraZeneca, Incyte, Delta-Fly Pharma and Nihon Servier. Naohiro Okano has received honoraria from Taiho Pharmaceutical, Eli Lilly Japan, Eisai, Bayer Yakuhin, Chugai, Ono Pharmaceutical, Daiichi Sankyo, AstraZeneca, MSD, Incyte and Nihon Servier; and medical writing support from J-Pharma. Hiroshi Ishii has received honoraria from AstraZeneca, Ono Pharma, Chugai, Takeda and Eli Lilly Japan; and is a member of Data Safety Monitoring Board or Advisory Board for Ono Pharma.

Makoto Ueno has received honoraria from Taiho Pharmaceutical, AstraZeneca, Yakult Honsha, MSD, Nihon Servier, Ono Pharmaceutical, Incyte, Chugai, Boehringer Ingelheim, J-pharma, Daiichi Sankyo, Eisai, Takeda and Novartis; and research fundings from

Taiho Pharmaceutical, AstraZeneca, MSD, Nihon Servier, Ono Pharmaceutical, Incyte, Chugai, Boehringer Ingelheim, J-pharma, Eisai, Novartis, Astellas Pharma, Delta Fly Pharma, Novocure and Chiome Bioscience.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71:209–49. https://doi.org/10.3322/caac.21660.
2. Amini M, Looha MA, Zarean E, Pourhoseingholi MA. Global pattern of trends in incidence, mortality, and mortality-to-incidence ratio rates related to liver cancer, 1990-2019: a longitudinal analysis based on the global burden of disease study. *BMC Public Health* 2022;22:604. https://doi.org/10.1186/s12889-022-12867-w.
3. Singal AG, Kanwal F, Llovet JM. Global trends in hepatocellular carcinoma epidemiology: implications for screening, prevention and therapy. *Nat Rev Clin Oncol* 2023;20:864–84. https://doi.org/10.1038/s41571-023-00825-3.
4. Reig M, Forner A, Rimola J, et al. BCLC strategy for prognosis prediction and treatment recommendation: the 2022 update. *J Hepatol* 2022;76:681–93. https://doi.org/10.1016/j.jhep.2021.11.018.
5. Zou H, Li M, Lei Q, et al. Economic burden and quality of life of hepatocellular carcinoma in greater China: a systematic review. *Front Public Health* 2022;10:801981. https://doi.org/10.3389/fpubh.2022.801981.
6. Smith TJ, Hillner BE. Bending the cost curve in cancer care. *N Engl J Med* 2011;364:2060–5. https://doi.org/10.1056/NEJMsb1013826.
7. Sullivan R, Peppercorn J, Sikora K, et al. Delivering affordable cancer care in high-income countries. *Lancet Oncol* 2011;12:933–80. https://doi.org/10.1016/S1470-2045(11)70141-3.
8. Leighl NB, Nirmalakumar S, Ezeife DA, Gyawali B. An arm and a leg: the rising cost of cancer drugs and impact on access. *Am Soc Clin Oncol Educ Book* 2021;41:1–12. https://doi.org/10.1200/EDBK_100028.
9. Llovet JM, Ricci S, Mazzaferro V, et al. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008;359:378–90. https://doi.org/10.1056/NEJMoa0708857.
10. Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial. *The Lancet* 2018;391:1163–73. https://doi.org/10.1016/S0140-6736(18)30207-1.
11. Finn RS, Qin S, Ikeda M, et al. Atezolizumab plus bevacizumab in unresectable hepatocellular carcinoma. *N Engl J Med* 2020;382:1894–905. https://doi.org/10.1056/NEJMoa1915745.
12. Cheng AL, Qin S, Ikeda M, et al. Updated efficacy and safety data from IMbrave150: atezolizumab plus bevacizumab vs. sorafenib for unresectable hepatocellular carcinoma. *J Hepatol* 2022;76:862–73. https://doi.org/10.1016/j.jhep.2021.11.030.
13. Abou-Alfa GK, Lau G, Kudo M, et al. Tremelimumab plus durvalumab in unresectable hepatocellular carcinoma. *NEJM Evidence* 2022;1. https://doi.org/10.1056/EVIDoa2100070.
14. Bristol Myers Squibb announces checkmate -9DW trial evaluating Opdivo (nivolumab) plus Yervoy (ipilimumab) meets primary endpoint of overall survival for the first-line treatment of advanced hepatocellular carcinoma. News release. *Bristol Myers Squibb* 2024. (20 March 2024, date last accessed); https://tinyurl.com/5n75mafe.
15. Rich NE, Yopp AC, Singal AG, Murphy CC. Hepatocellular carcinoma incidence is decreasing among younger adults in the United States. *Clin Gastroenterol Hepatol* 2020;18:242–248.e5. https://doi.org/10.1016/j.cgh.2019.04.043.
16. Li D, Toh HC, Merle P, et al. Atezolizumab plus bevacizumab versus Sorafenib for unresectable hepatocellular carcinoma: results from older adults enrolled in the IMbrave150 randomized clinical trial. *Liver Cancer* 2022;11:558–71. https://doi.org/10.1159/000525671.
17. Muss HB, Berry DA, Cirrincione C, et al. Toxicity of older and younger patients treated with adjuvant chemotherapy for node-positive breast cancer: the cancer and Leukemia group B experience. *J Clin Oncol* 2007;25:3699–704. https://doi.org/10.1200/JCO.2007.10.9710.
18. Hurria A, Togawa K, Mohile SG, et al. Predicting chemotherapy toxicity in older adults with cancer: a prospective multicenter study. *J Clin Oncol* 2011;29:3457–65. https://doi.org/10.1200/JCO.2011.34.7625.
19. Extermann M, Boler I, Reich RR, et al. Predicting the risk of chemotherapy toxicity in older patients: the chemotherapy risk assessment scale for high-age patients (CRASH) score. *Cancer* 2012;118:3377–86. https://doi.org/10.1002/cncr.26646.
20. Lencioni R, Kudo M, Erinjeri J, et al. EMERALD-1: a phase 3, randomized, placebo-controlled study of transarterial chemoembolization combined with durvalumab with or without bevacizumab in participants with unresectable hepatocellular carcinoma eligible for embolization. *J Clin Oncol* 2024;42:LBA432–LBA. https://doi.org/10.1200/JCO.2024.42.3_suppl.LBA432.
21. Qin S, Chen M, Cheng AL, et al. Atezolizumab plus bevacizumab versus active surveillance in patients with resected or ablated high-risk hepatocellular carcinoma (IMbrave050): a randomised, open-label, multicentre, phase 3 trial. *Lancet* 2023;402:1835–47. https://doi.org/10.1016/S0140-6736(23)01796-8.
22. Garber AM, McClellan MB. Satisfaction guaranteed–"payment by results" for biologic agents. *N Engl J Med* 2007;357:1575–7. https://doi.org/10.1056/NEJMp078204.
23. Su D, Wu B, Shi L. Cost-effectiveness of atezolizumab plus bevacizumab vs sorafenib as first-line treatment of unresectable hepatocellular carcinoma. *JAMA Netw Open* 2021;4:e210037. https://doi.org/10.1001/jamanetworkopen.2021.0037.
24. Xie E, Yeo YH, Scheiner B, et al. Immune checkpoint inhibitors for child-Pugh class B advanced hepatocellular carcinoma: a systematic review and meta-analysis. *JAMA Oncol* 2023;9:1423–31. https://doi.org/10.1001/jamaoncol.2023.3284.
25. Liu K, Zhu Y, Zhu H. Immunotherapy or targeted therapy as the first-line strategies for unresectable hepatocellular carcinoma: a network meta-analysis and cost-effectiveness analysis. *Front Immunol* 2022;13:1103055. https://doi.org/10.3389/fimmu.2022.1103055.

JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2024, 1–6
https://doi.org/10.1093/jjco/hyae089
Original Article

OXFORD

Original Article

High cost of chemotherapy for gynecologic malignancies

Nobutaka Takahashi[1,*], Toshiyuki Seki[2], Keita Sasaki[3], Ryunosuke Machida[3], Mitsuya Ishikawa[4], Mayu Yunokawa[5], Ayumu Matsuoka[6], Masahiro Kagabu[7], Satoshi Yamaguchi[8], Kengo Hiranuma[9], Junki Ohnishi[10] and Toyomi Sato[11]

[1]Department of Gynecology, Shizuoka Cancer Center, Shizuoka, Japan, [2]Department of Obstetrics and Gynecology, The Jikei University School of Medicine, Tokyo, Japan, [3]Japan Clinical Oncology Group Data Centre/Operations Office, National Cancer Centre Hospital, Tokyo, Japan, [4]Department of Gynecology, National Cancer Center Hospital, Tokyo, Japan, [5]Department of Gynecologic Oncology, Cancer Institute Hospital of Japanese Foundation for Cancer Research, Tokyo, Japan, [6]Department of Reproductive Medicine, Graduate School of Medicine, Chiba University, Chiba, Japan, [7]Department of Obstetrics and Gynecology, Iwate Medical University School of Medicine, Iwate, Japan, [8]Department of Gynecologic Oncology, Hyogo Cancer Center, Akashi, Japan, [9]Department of Obstetrics and Gynecology, Juntendo University, Tokyo, Japan, [10]Department of Gynecology, National Cancer Center Hospital East, Kashiwa, Japan and [11]Department of Obstetrics and Gynecology, Faculty of Medicine, University of Tsukuba, Tsukuba, Japan

*Corresponding author. Department of Gynecology, Shizuoka Cancer Center, Sunto-gun, Shizuoka 411-8777, Japan. E-mail: n.takahashi@scchr.jp

Received 13 March 2024; Editorial Decision 2 July 2024; Accepted 6 July 2024

Abstract

Background: The prognosis of gynecological malignancies has improved with the recent advent of molecularly targeted drugs and immune checkpoint inhibitors. However, these drugs are expensive and contribute to the increasing costs of medical care.

Methods: The Japanese Clinical Oncology Group (JCOG) Health Economics Committee conducted a questionnaire survey of JCOG-affiliated facilities from July 2021 to June 2022 to assess the prevalence of high-cost regimens.

Results: A total of 57 affiliated facilities were surveyed regarding standard regimens for advanced ovarian and cervical cancers for gynecological malignancies. Responses were obtained from 39 facilities (68.4%) regarding ovarian cancer and 37 (64.9%) concerning cervical cancer, with respective case counts of 854 and 163. For ovarian cancer, 505 of 854 patients (59.1%) were treated with regimens that included PARP inhibitors, costing >500 000 Japanese yen monthly, while 111 patients (13.0%) received treatments that included bevacizumab, with costs exceeding 200 000 Japanese yen monthly. These costs are ~20 and ~10 times higher than those of the conventional regimens, respectively. For cervical cancer, 79 patients (48.4%) were treated with bevacizumab regimens costing >200 000 Japanese yen per month, ~10 times the cost of conventional treatments.

Conclusions: In this survey, >70% of patients with ovarian cancer were treated with regimens that included poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors or bevacizumab; ~50% of patients with cervical cancer were treated with regimens containing bevacizumab. These treatments were ~10 and ~20 times more expensive than conventional regimens, respectively. These

findings can inform future health economics studies, particularly in assessing cost-effectiveness and related matters.

Key words: poly (adenosine diphosphate-ribose) polymerase inhibitors, molecular targeted therapy, carcinoma, gynecologic oncology, cost-effectiveness

Introduction

Similar to other carcinomas, chemotherapy is the primary treatment strategy for advanced gynecologic malignancies. Despite treatment advancements, the median survival time for cervical cancer with distant metastasis remains <12 months with cytotoxic combination therapy alone [1]. Ovarian cancer is the fifth leading cause of cancer-related deaths among women [2]. Advanced gynecologic malignancies have been treated using platinum-based regimens such as cisplatin [3–5].

Paclitaxel plus carboplatin (TC) therapy has become the standard of care for advanced ovarian cancer since the advent of paclitaxel, remaining unchanged for a long time [6,7]. Following the introduction of bevacizumab (Bev), a molecularly targeted agent, TC plus Bev, and subsequent Bev maintenance therapy, emerged as the next standard of care for advanced ovarian cancer [8,9]. With the introduction of Bev, progression-free survival (PFS) has been extended, although it has not improved overall survival (OS). Furthermore, with the introduction of poly (adenosine diphosphate-ribose) polymerase inhibitors (PARPi), PFS has been extended, and TC plus PARPi maintenance therapy has become a new treatment option [10,11]. The advent of PARPi has significantly extended PFS and marginally extended OS (84% vs. 80% at 36 months [10], 84% vs. 77% at 24 months [11]) in the overall population. The current standard chemotherapy for advanced ovarian cancer is primarily TC plus Bev, followed by Bev maintenance therapy or TC plus PARPi maintenance therapy (Table 1).

For advanced cervical cancer, paclitaxel plus cisplatin (TP) therapy has been the standard of care in combination with cytotoxic anticancer agents [12]. Similar to ovarian cancer, TP or TC plus Bev have become the standard of care with the introduction of Bev with the extension of PFS and OS. [13,14] (Table 2). The programmed death receptor (PD)-1 inhibitor pembrolizumab (Pem), an immune checkpoint inhibitor, has been introduced as a new treatment option [15]. The PFS and OS benefit brought about by Bev was further extended by the advent of Pem. The current standard chemotherapy for advanced cervical cancer predominantly involves TP plus Bev and Pem or TC plus Bev and Pem. Notably, Pem was not included in this survey because it was not covered by insurance for cervical cancer until after September 2022.

One challenge posed by advances in the treatment of these cancers is economic toxicity. For example, Bev costs >200 000 Japanese yen (JPY) per month at a standard dosage, whereas PARPi costs >500 000 JPY per month at a standard dosage.

In Japan, the universal health insurance system typically permits the use of expensive drugs, if approved, without special restrictions. However, the pressure on medical costs from these drugs poses a concern, potentially leading to future financial strain on healthcare finances and even bankruptcy [16–18].

In the future, integrating health economic evaluations into clinical research will be crucial to increasing treatment value, managing costs effectively, maintaining treatment quality, and ensuring treatment affordability and sustainability.

Therefore, we conducted a questionnaire survey in Japanese Clinical Oncology Group (JCOG)-affiliated facilities to assess the current status of high-cost medical care in Japan. This study was conducted under the supervision of the JCOG Health Economic Committee.

Materials and methods

We conducted an online questionnaire survey (Google form) of patients with Stages 3 and 4 ovarian cancer and Stage 4b cervical cancer at 57 JCOG-affiliated facilities. Patients targeted for this survey were first diagnosed with advanced ovarian or cervical cancer at JCOG institutions between July 2021 and June 2022. We gathered information on first-line chemotherapy regimens used for each patient without collecting any personal patient data. The number of patients in different age categories (≤74 and ≥75 years) was collected separately. Moreover, costs for supportive care, such as antiemetics or granulocyte-colony stimulating factor (G-CSF), were not included.

For this study, high-cost medical care was defined as >500 000 JPY per month, whereas very high-cost medical care was defined as >1 million JPY per month by the JCOG Health Economics Committee. The personal data of patients were not collected. Thus, this study did not require individual consent or Institutional Review Board approval [19].

Regimens

Ovarian cancer

The regimens studied for advanced ovarian cancer were predetermined as the standard of care before the study began. These regimens were selected by the attending physician based on the patient's background, including homologous recombination deficiency and breast cancer susceptibility (BRCA) status [10,20], and disease status (e.g. presence of tumor invasion into the intestinal tract).

·Paclitaxel + Carboplatin → Niraparib maintenance therapy

·Paclitaxel + Carboplatin → Olaparib maintenance therapy

·Paclitaxel + Carboplatin + Bevacizumab → Bevacizumab maintenance therapy

·Paclitaxel + Carboplatin + Bevacizumab → Olaparib + Bevacizumab maintenance therapy

The primary results of these regimens in the trials are shown in Table 1.

Cervical cancer

The current standard of care for advanced or recurrent cervical cancer is TC plus Bev plus pembrolizumab; however, pembrolizumab was not covered by insurance until September 2022. As the regimen

Table 1. Primary outcomes of advanced ovarian cancer regimens

Regimen	Reference number (publication year)	Main results (median PFS; months)	Main results (OS)	Median cycles or dose completion proportion
TC → Niraparib maintenance	[11] (2019)	Niraparib 13.8 Placebo 8.2	Niraparib 84% Placebo 77% (at 24 months)	177/484 (36.5%) received at data cut off
TC → Olaparib maintenance	[10] (2018)	Olaparib 56.0 Placebo 13.8	Olaparib 84% Placebo 80% (at 36 months)	123/260 (47.3%) completed at the 2-year mark
TC + Bev → Bev maintenance	[8,9] (2011)	Bev 14.1 Placebo 10.3	Bev 39.7 Placebo 39.3 (months)	A median of 16–17 cycles
TC + Bev → Bev + Olaparib maintenance	[16] (2019)	Olaparib + Bev 37.2 Placebo 17.7	Data are immature	196/537 (36.4%) completed at the 2-year mark

TC, paclitaxel + carboplatin; Bev, Bevacizumab; PFS, progression-free survival; OS, overall survival.

Table 2. Main results of advanced cervical cancer regimen

Regimen	Reference number (publication year)	Main results (median PFS; months)	Main results (OS)	Median cycles or dose completion ration
TC + Bev → Bev maintenance[a]	[14] (2020)	Bev 10.9	Bev 25.0 (months, median)	a median of nine cycles
TP + Bev → Bev maintenance	[13] (2013)	Bev 8.2 Placebo 5.9	Bev 17.0 Placebo 13.3 (months)	a median of seven cycles
TC or TP + Pem + Bev → Pem + Bev maintenance	[15] (2021)	Pem 10.4 Placebo 8.2	Pem 50.4% Placebo 40.4% (at 24 months)	a median of 18 cycles

TC, paclitaxel + carboplatin; TP, paclitaxel + cisplatin; Bev, Bevacizumab; Pem, Pembrolizumab; PFS, progression-free survival; OS, overall survival.
[a]Single-arm Phase II study.

was not covered by insurance in 2021, the regimens listed below were included in this study.

·Paclitaxel + Cisplatin + Bevacizumab → Bevacizumab maintenance therapy

·Paclitaxel + Carboplatin + Bevacizumab → Bevacizumab maintenance therapy

The primary results of these regimens in the trials are shown in Table 2.

The cost of the regimen was calculated based on a height of 157 cm and weight of 55 kg, with a body surface area of 1.552 m^2 [21,22]. The carboplatin dose was calculated using Jelliffe formula at an area under the curve of 5 or 6. The cost of each drug is presented in Table S1.

Calculation of costs of each regimen of ovarian cancer*

·Paclitaxel + Carboplatin → Niraparib maintenance therapy

*Paclitaxel(175 mg/m^2) + Carboplatin (AUC = 6) → Niraparib × 200 mg daily × 30 days

·Paclitaxel + Carboplatin → Olaparib maintenance therapy

* Paclitaxel (175 mg/m^2) + Carboplatin (AUC = 6) → Olaparib × 600 mg daily × 30 days

·Paclitaxel + Carboplatin + Bevacizumab → Bevacizumab maintenance therapy

*Paclitaxel (175 $mg/m^{2)}$ + Carboplatin (AUC = 6) + Bevacizumab (15 mg/kg) every 3 weeks → Bevacizumab (15 mg/kg) every 3 weeks

·Paclitaxel + Carboplatin + Bevacizumab → Olaparib + Bevacizumab maintenance therapy

*Paclitaxel (175 $mg/m^{2)}$ + Carboplatin (AUC = 6) + Bevacizumab (15 mg/kg) every 3 weeks → Olaparib × 600 mg daily × 30 days + Bevacizumab (15 mg/kg) every 3 weeks

Calculation of costs of each regimen of cervical cancer*

·Paclitaxel + Carboplatin + Bevacizumab → Bevacizumab maintenance therapy

*Paclitaxel (175 $mg/m^{2)}$ + Carboplatin (AUC = 5) + Bevacizumab (15 mg/kg) every 3 weeks → Bevacizumab (15 mg/kg) every 3 weeks

·Paclitaxel + Cisplatin + Bevacizumab → Bevacizumab maintenance therapy

*Paclitaxel (135 $mg/m^{2)}$ + Cisplatin (50 mg/m^2) + Bevacizumab (15 mg/kg) every 3 weeks → Bevacizumab (15 mg/kg) every 3 weeks

Results

Questionnaires were distributed to 57 JCOG-affiliated facilities, and responses were received from 39 centers (68.4%) for ovarian cancer and 37 centers (64.9%) for cervical cancer.

The number of patients with ovarian cancer during the study period was 854 (Figure 1), of whom 616 (72.1%, 616/854) were eligible for the study regimen. The most common regimen for ovarian cancer was TC plus niraparib maintenance, involving a total of 267 patients (31%, 267/854). The second most common regimen was TC plus Bev, followed by Bev plus olaparib maintenance, with 170 patients (20%, 170/854). TC plus Bev after Bev maintenance was administered to 111 patients (13%, 111/854). TC plus olaparib maintenance therapy was administered to 68 patients (8%, 68/854). Chemotherapy-alone regimens, including TC and dose-dense TC, were administered to 238 patients (28%, 238/854). Of the 616 patients, 542 (87.9%, 542/616) were under 75 years old, while 74 (12.1%, 74/616) were 75 years or older. Therefore, according to the definition used in this study, 505 patients (59.1%, 505/854) received high-cost medical care as primary therapy. Among the 542

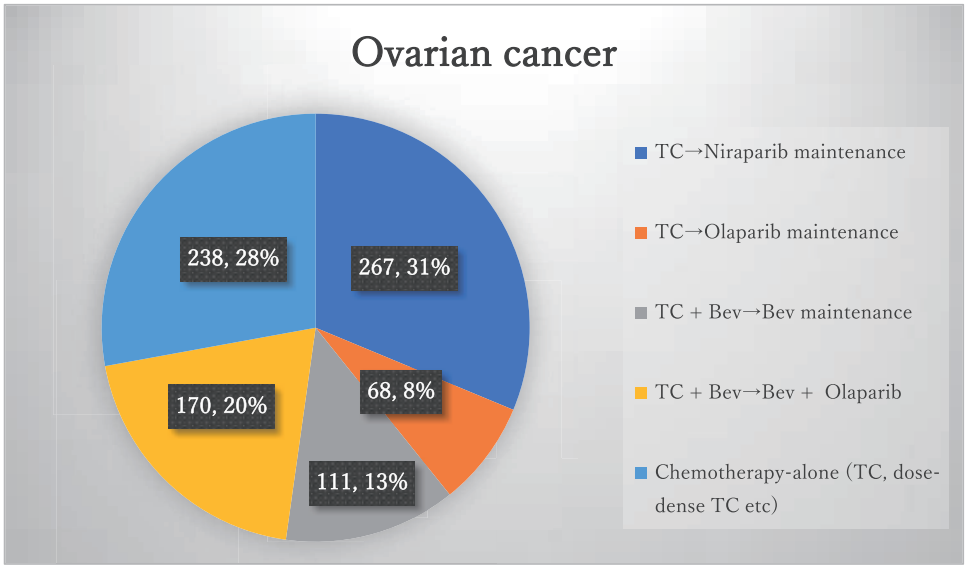


Figure 1. Results of the questionnaires for ovarian cancer TC, paclitaxel + carboplatin; Bev, bevacizumab.

Table 3. Cost of advanced ovarian cancer regimens

Treatment	Age, <75 yr	Age, >75 yr	Total	Cost per month, JPY
TC → Niraparib maintenance	231 (27%)	36 (4%)	267 (31%)	27 561 → 558 960
TC → Olaparib maintenance	64 (7.5%)	4 (0.5%)	68 (8%)	27 561 → 574 560
TC + Bev → Bev maintenance	89 (10.5%)	22 (2.5%)	111 (13%)	264 222 → 236 661
TC + Bev → Bev + Olaparib maintenance	158 (18.5%)	12 (1.5%)	170 (20%)	264 222 → 811 221
TC	n/s	n/s	n/s	27 561

TC, paclitaxel + carboplatin; Bev, Bevacizumab; n/s not surveyed.

younger patients, 453 (83.5%, 453/542) received high-cost medical care. Among the 72 older patients, 52 (72.2%, 52/72) received high-cost medical care. Regimens containing Bev were 10 times as costly as conventional TC, with no significant OS benefit. Similarly, regimens containing PARPi were 20 times as costly as conventional TC, with no significant OS benefit. The cost of each regimen and its classification as high cost are presented in Table 3.

During the study period, 163 patients were diagnosed with cervical cancer (Figure 2), and 79 (49.0%) received the study regimen. The most common regimen for cervical cancer was TC plus Bev, followed by Bev maintenance, with 60 patients (36.8%). TC plus Bev, followed by Bev maintenance, was administered to 19 patients (11.6%). Among these 79 patients, 72 (91.1%, 72/79) were under the age of 75, while seven (8.9%) were over 75. Regimens containing Bev were 10 times as costly as conventional TP or TC, with an OS benefit of several months. The costs of each regimen and their classification as high costs are listed in Table 4.

Discussion

Responses were received from 39 out of 57 centers (68.4%) for ovarian cancer and from 37 centers (64.9%) for cervical cancer. For ovarian cancer, high-cost medical care was applicable to 505 (82.1%) of the 615 patients. In addition, 52 (72.2%) received high-cost medical care among the 72 older patients. The trials of PARPi added to chemotherapy alone have shown only marginally prolonged OS (84% vs. 80% at 36 months [10], 84% vs. 77% at 24 months [11]) in the overall population, suggesting that from a cost-effectiveness perspective, the indication of these regimens would be controversial, especially in older patients [10,11].

PARPi introduction has made maintenance therapy with PARPi a standard treatment for ovarian cancer. More cases of TC plus niraparib than TC plus olaparib in this study may be attributed to olaparib being restricted to BRCA-positive patients due to insurance coverage, while niraparib can be used regardless of BRCA status. Considering that the patient was previously monitored only following TC therapy, the introduction of a cytotoxic anticancer drug raised medical costs by ~600 000 JPY per month, potentially for up to 2 or 3 years of maintenance therapy. Prolonged PFS associated with maintenance therapy incurs significant costs [23]. Although the healthcare system differs from that of Japan, generous reimbursement by public insurance could lead to overtreatment and waste of medical resources. High-cost medical care was also provided to patients aged 75 years and older in this study. Considering their prognosis and adverse events, we should consider criteria when administering expensive drugs that allow only a marginal prolongation of OS. The cost of medical care in Japan continues to increase yearly, and measures are required to reduce those costs. The use of biosimilars can be one of those measures [18]. Biosimilars differ from the original drugs, although their clinical efficacy is almost equal to that of the original drugs. They are inexpensive, making them suitable drugs for reducing medical care costs. Biosimilars of Bev have already been used for several carcinomas [24,25].

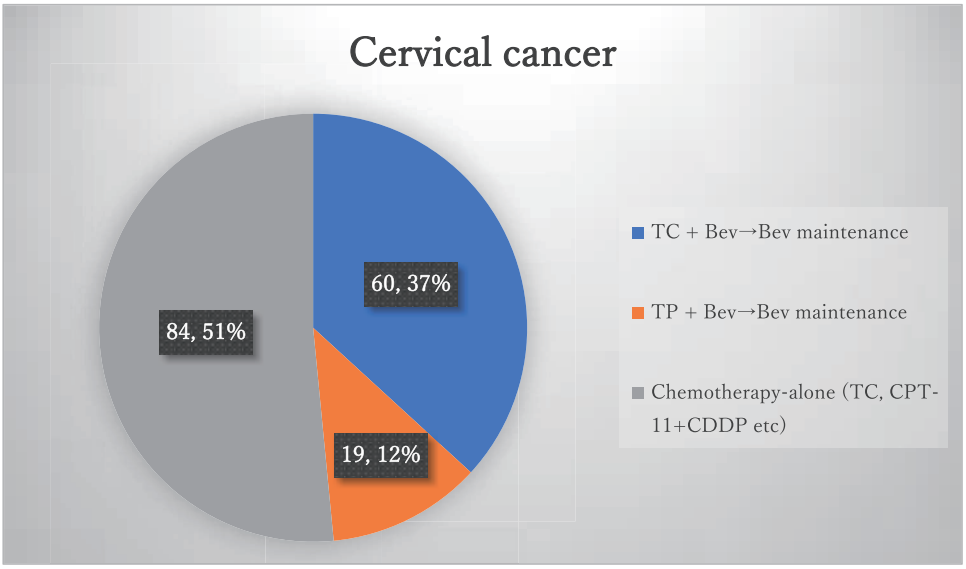


Figure 2. Results of the questionnaires for cervical cancer, TC, paclitaxel + carboplatin; TP, paclitaxel + cisplatin; Bev, bevacizumab.

Table 4. Cost of advanced cervical cancer regimens

Treatment	Age, <75 yr	Age, >75 yr	Total	Cost per month, JPY
TC + Bev → Bev maintenance	54 (33%)	6 (4%)	60 (37%)	256 974 → 236 661
TP + Bev → Bev maintenance	18 (11.4%)	1 (0.6%)	19 (12%)	254 446 → 236 661
TC	n/s	n/s	n/s	24 115
TP	n/s	n/s	n/s	17 785

TC, paclitaxel + carboplatin; TP, paclitaxel + cisplatin; Bev, Bevacizumab; n/s not surveyed.

None of the patients with cervical cancer received high-cost treatments as defined by the JCOG committee, although the regimens were ∼200 000 JPY more expensive per month than conventional chemotherapy alone. However, this study excluded patients who received pembrolizumab because it was not covered by insurance in Japan at the time of the study. PD-1 inhibitors, including pembrolizumab, are now indicated for gynecological malignancies, alongside their indications for other cancer types. Four-drug combination therapy consisting of TC plus Bev plus this agent is currently one of the standard treatments for advanced cervical cancer [15]. The estimated cost of this regimen exceeds 600 000 JPY, which corresponds to the high cost of this study (Table S3). Therefore, the proportion of patients receiving high-cost medical care may have increased if this agent was included in the survey.

In cervical cancer, the trial of pembrolizumab added to chemotherapy alone has shown prolonged OS (50.4% vs. 40.4% at 24 months), suggesting that from a cost-effectiveness perspective, these regimens' indication in all patients, including older patients, is controversial. The use of Bev biosimilar in ovarian cancer is also expected to reduce costs; therefore, the development of biosimilars for PD-1 inhibitors and PARPi is expected to advance.

The standard treatments of gynecological cancers are decided by PFS elongation, and thus include drugs without OS benefit (Bev for ovarian cancer) or with OS benefit with only marginal OS benefit (PARPi for ovarian cancer). These drugs, however, bring a 10- to 20-fold increase in treatment costs, questioning the sustainability of cancer care.

This study had several limitations. This survey was conducted over a limited period at JCOG-affiliated facilities. Individual patient data were not collected; therefore, the actual dosing periods, drug discontinuations, or dose reduction could not be considered. In addition, they were not evaluated using measures such as the incremental cost-effectiveness ratio of the most recent PAPRi and ICI treatment regimens.

Conclusion

More than 70% of patients with ovarian cancer received regimens containing PARP inhibitors or Bev, and ∼50% of patients with cervical cancer received regimens containing Bev, which were ∼10 or ∼20 times more expensive than conventional regimens, respectively. Japanese patients with gynecological cancers receive state-of-the-art therapies, but the associated costs have increased substantially. The results of this study may be used in future health economics studies examining cost-effectiveness and other issues.

Acknowledgements

We would like to thank Editage for English language editing.

Supplementary data

Supplementary data is available at *Japanese Journal of Clinical Oncology* online.

Conflict of interest

The authors declare no conflict of interest.

Funding

This work was supported by the Research Fund of the National Federation of Health Insurance Societies (Kenpo-ren) and the National Cancer Center Research and Development Funds (2023-J-03).

References

1. Friedlander M, Grogan M. Guidelines for the treatment of recurrent and metastatic cervical cancer. *Oncologist* 2002;7:342–7. https://doi.org/10.1634/theoncologist.2002-0342.
2. Siegel RL, Miller KD, Wagle NS., et al. Cancer statistics, 2023. *CA Cancer J Clin* 2023;73:17–48. https://doi.org/10.3322/caac.21763.
3. Lambert HE, Berry RJ. High dose cisplatin compared with high dose cyclophosphamide in the management of advanced epithelial ovarian cancer (FIGO stages III and IV): report from the North Thames cooperative group. *Br Med J (Clin Res Ed)* 1985;290:889–93. https://doi.org/10.1136/bmj.290.6472.889.
4. Piccart MJ, Bertelsen K, James K et al. Randomized intergroup trial of cisplatin-paclitaxel versus cisplatin-cyclophosphamide in women with advanced epithelial ovarian cancer: three-year results. *J Natl Cancer Inst* 2000;92:699–708, https://doi.org/10.1093/jnci/92.9.699.
5. Thigpen JT, Blessing JA, DiSaia PJ., et al. A randomized comparison of a rapid versus prolonged (24 hr) infusion of cisplatin in therapy of squamous cell carcinoma of the uterine cervix: a Gynecologic Oncology Group study. *Gynecol Oncol* 1989;32:198–202. https://doi.org/10.1016/S0090-8258(89)80033-2.
6. Ozols RF, Bundy BN, Greer BE., et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group study. *J Clin Oncol* 2003;21:3194–200. https://doi.org/10.1200/JCO.2003.02.153.
7. du Bois A, Lück HJ, Meier W., et al. A randomized clinical trial of cisplatin/paclitaxel versus carboplatin/paclitaxel as first-line treatment of ovarian cancer. *J Natl Cancer Inst* 2003;95:1320–9. https://doi.org/10.1093/jnci/djg036.
8. Burger RA, Brady MF, Bookman MA., et al. Incorporation of bevacizumab in the primary treatment of ovarian cancer. *N Engl J Med* 2011;365:2473–83. https://doi.org/10.1056/NEJMoa1104390.
9. Perren TJ, Swart AM, Pfisterer J., et al. A phase 3 trial of bevacizumab in ovarian cancer. *N Engl J Med* 2011;365:2484–96. https://doi.org/10.1056/NEJMoa1103799.
10. Moore K, Colombo N, Scambia G., et al. Maintenance olaparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med* 2018;379:2495–505. https://doi.org/10.1056/NEJMoa1810858.
11. González-Martín A, Pothuri B, Vergote I., et al. Niraparib in patients with newly diagnosed advanced ovarian cancer. *N Engl J Med* 2019;381:2391–402. https://doi.org/10.1056/NEJMoa1910962.
12. Moore DH, Blessing JA, McQuellon RP., et al. Phase III study of cisplatin with or without paclitaxel in stage IVB, recurrent, or persistent squamous cell carcinoma of the cervix: a gynecologic oncology group study. *J Clin Oncol* 2004;22:3113–9. https://doi.org/10.1200/JCO.2004.04.170.
13. Tewari KS, Sill MW, Long HJ., et al. Improved survival with bevacizumab in advanced cervical cancer. *N Engl J Med* 2014;370:734–43. https://doi.org/10.1056/NEJMoa1309748.
14. Redondo A, Colombo N, McCormack M., et al. Primary results from CECILIA, a global single-arm phase II study evaluating bevacizumab, carboplatin and paclitaxel for advanced cervical cancer. *Gynecol Oncol* 2020;159:142–9. https://doi.org/10.1016/j.ygyno.2020.07.026.
15. Colombo N, Dubot C, Lorusso D., et al. Pembrolizumab for persistent, recurrent, or metastatic cervical cancer. *N Engl J Med* 2021;385:1856–67. https://doi.org/10.1056/NEJMoa2112435.
16. Sullivan R, Peppercorn J, Sikora K., et al. Delivering affordable cancer care in high-income countries. *Lancet Oncol* 2011;12:933–80. https://doi.org/10.1016/S1470-2045(11)70141-3.
17. Smith TJ, Hillner BE. Bending the cost curve in cancer care. *N Engl J Med* 2011;364:2060–5. https://doi.org/10.1056/NEJMsb1013826.
18. Leighl NB, Nirmalakumar S, Ezeife DA., et al. An arm and a leg: the rising cost of cancer drugs and impact on access. *Am Soc Clin Oncol Educ Book* 2021;41:e1–12. https://doi.org/10.1200/EDBK_100028.
19. Eba J, Nakamura K. Overview of the ethical guidelines for medical and biological research involving human subjects in Japan. *Jpn J Clin Oncol* 2022;52:539–44. https://doi.org/10.1093/jjco/hyac034.
20. Ray-Coquard I, Pautier P, Pignata S., et al. Olaparib plus bevacizumab as first-line maintenance in ovarian cancer. *N Engl J Med* 2019;381:2416–28. https://doi.org/10.1056/NEJMoa1911361.
21. Mikami M, Shida M, Shibata T., et al. Impact of institutional accreditation by the Japan Society of Gynecologic Oncology on the treatment and survival of women with cervical cancer. *J Gynecol Oncol* 2018;29:e23. https://doi.org/10.3802/jgo.2018.29.e23.
22. Machida H, Matsuo K, Yamagami W., et al. Trends and characteristics of epithelial ovarian cancer in Japan between 2002 and 2015: a JSGO-JSOG joint study. *Gynecol Oncol* 2019;153:589–96. https://doi.org/10.1016/j.ygyno.2019.03.243.
23. Penn CA, Wong MS, Walsh CS. Cost-effectiveness of maintenance therapy based on molecular classification following treatment of primary epithelial ovarian cancer in the United States. *JAMA Netw Open* 2020;3:e2028620. https://doi.org/10.1001/jamanetworkopen.2020.28620.
24. Lai SP, Wang SY, Chan AL., et al. Cost-effectiveness and drug wastage of bevacizumab biosimilar with or without chemotherapy for platinum-resistant recurrent ovarian cancer. *Expert Rev Pharmacoecon Outcomes Res* 2024;24:541–9. https://doi.org/10.1080/14737167.2024.2319605.
25. Cheung WY, Samimi S, Ma K., et al. Real-world safety and effectiveness of a bevacizumab biosimilar (ABP 215) in metastatic colorectal cancer patients in Canada. *Clin Colorectal Cancer* 2024;23:46–57.e4. https://doi.org/10.1016/j.clcc.2023.10.007.

JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2024, 1–9
https://doi.org/10.1093/jjco/hyae094
Original Article

OXFORD

Original Article

High-cost treatments for advanced lung cancer in Japan (Lung Cancer Study Group of the Japan Clinical Oncology Group)

Kageaki Watanabe[1,*], Keita Sasaki[2], Ryunosuke Machida[2], Junichi Shimizu[3], Yuki Yamane[4], Motohiro Tamiya[5], Shin Saito[6], Yuji Takada[7], Kiyotaka Yoh[8], Hiroshige Yoshioka[9], Haruyasu Murakami[10], Satoru Kitazono[11], Yasuhiro Goto[12], Hidehito Horinouchi[13] and Yuichiro Ohe[13]

[1]Department of Thoracic Oncology and Respiratory Medicine, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, 3-18-22, Honkomagome, Bunkyo-ku, Tokyo, 113-8677, Japan, [2]JCOG Data Center/Operations Office, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan, [3]Department of Thoracic Oncology, Aichi Cancer Centre Hospital, 1-1, Kanokoden, Chikusa-ku, Nagoya, Aichi, 464-8681, Japan, [4]Department of Thoracic Oncology, Saitama Cancer Center, 780, Komuro, Ina, Kitaadachi, Saitama, 362-0806, Japan, [5]Department of Thoracic Oncology, Osaka International Cancer Institute, 3-1-69 Otemae, Chuo-ku, Osaka, 541-8567, Japan, [6]Department of Pulmonary Medicine, Sendai Kousei Hospital, 4-15 Hirosemachi, Aoba-ku, Sendai, 980-0873, Japan, [7]Department of Respiratory Medicine, Itami City Hospital, 1-100, Koyanoike, Itami, Hyogo, 664-8540, Japan, [8]Department of Thoracic Oncology, National Cancer Center Hospital East, 6-5-1, Kashiwanoha, Kashiwa, Chiba, 277-8577, Japan, [9]Department of Thoracic Oncology, Kansai Medical University Hospital, 2-3-1, Shinmachi, Hirakata City, Osaka, 573-1191, Japan, [10]Division of Thoracic Oncology, Shizuoka Cancer Center, 1007 Shimonagakubo, Nagaizumi-cho, Sunto-gun, Shizuoka, 411-8777, Japan, [11]Department of Thoracic Medical Oncology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, 3-8-31 Ariake, Koto-ku, Tokyo, 135-8550, Japan, [12]Department of Respiratory Medicine, Fujita Health University School of Medicine, 1-98 Dengakugakubo, Kutsukake-cho, Toyoake, Aichi, 470-1192, Japan and [13]Department of Thoracic Oncology, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan

*Corresponding author. Department of Thoracic Oncology and Respiratory Medicine, Tokyo Metropolitan Cancer and Infectious Diseases Center, Komagome Hospital, 3-18-22 Bunkyo-ku, Tokyo 113-8677, Japan.
E-mail: kageaki_watanabe@tmhp.jp

Received 17 April 2024; Editorial Decision 8 July 2024; Accepted 10 July 2024

Abstract

Background: The treatment of lung cancer has made dramatic progress in the past decade, but due to the high cost of drugs, the total pharmaceutical cost has been rising explosively. There are currently no data available in Japan on which regimens are used, to what extent they are used, and what their total cost is.

Methods: Sixty Japanese centers belonging to the Lung Cancer Study Group of the Japan Clinical Oncology Group were surveyed for information about the first-line treatment for advanced lung cancer in practice from July 2021 to June 2022. Three types of cancer were included: driver gene mutation-negative NSCLC, EGFR mutation-positive NSCLC, and extensive-stage small cell lung cancer (ES-SCLC).

Results: Recent treatment costs for ICIs or ICI plus chemotherapy were about 20–55 times higher than those for conventional chemotherapy. Of the 3738 patients with driver gene aberration-negative NSCLC, 2573 (68.8%) received treatments with monthly cost of 500 000 Japanese yen (JPY) or more; 2555 (68.4%) received ICI therapy. Of the 1486 patients with EGFR mutation-positive NSCLC, 1290 (86.8%) received treatments with a monthly cost of 500 000 JPY or more; 1207 (81.2%) received osimertinib. ICI treatments with a monthly cost of 500 000 JPY or more were administered to 607 (56.3%) of 1079 patients with ES-SCLC. Elderly NSCLC patients received slightly more high-cost treatment than younger patients.
Conclusion: Recent treatments cost many times more than conventional chemotherapy. This study revealed that high-cost treatments were widely used in advanced lung cancer and some of high-cost treatments were used despite the lack of clear evidence. Physicians should pay attention to the cost of treatments they use.

Key words: high-cost treatment, immune checkpoint inhibitor, nonsmall cell lung cancer, epidermal growth factor receptor mutation-positive non-small cell lung cancer, extensive-stage small cell lung cancer

Introduction

Cancer treatment has made great progress over the past decade with the advent of various, molecularly targeted drugs and immune checkpoint inhibitors (ICIs). However, these drugs are expensive, and the total pharmaceutical cost for cancer treatment continues to rise explosively. Owing to their high cost, these drugs are sometimes said to be 'financially toxic' and have become a social problem in both developing and developed countries, including Japan [1–4]. In Japan, this trend in the increasing cost of treatments is particularly pronounced due to the aging population. The Japan Clinical Oncology Group (JCOG) Health Economics Committee is currently grappling with these issues.

The cost problems could be divided to two aspects. First, recent treatments cost many times more than conventional chemotherapy. Second, some drugs cost far more than others of the same class without clear benefit in efficacy or toxicity, and physicians are indifferent to cost. This led to use of low-value (similar efficacy, similar toxicity, no head-to-head comparison data, only higher cost) treatments, which makes waste and burden to society. These low-value treatments for lung cancer include durvalumab (as opposed to atezolizumab) in small cell lung cancer (SCLC) and ramucirumab plus epidermal growth factor receptor—tyrosine kinase inhibitor (EGFR-TKI) (as opposed to bevacizumab plus EGFR-TKI) in epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC).

To understand the details of the use of expensive drugs in the treatment of lung cancer, the Lung Cancer Study Group of the JCOG conducted a survey to determine which drugs were currently being used in clinical practice.

Lung cancer yearly affects approximately 126 000 individuals, causing 75 000 deaths in Japan [5]. Lung cancer is also the leading cause of cancer-related deaths in men and the second leading cause of cancer-related deaths in women [5]. Lung cancer comprises NSCLC and SCLC. The former has many driver gene mutations, such as EGFR gene mutation and anaplastic lymphoma kinase (ALK) fusion gene translocation, and the cost of the molecularly targeted drugs, which are most commonly used in their treatment, is reimbursed under the Japanese National Health Insurance scheme [6]. For this reason, these drugs are widely used in clinical practice. In addition, six types of ICI, namely, the anti-programmed cell death-1 (PD-1) antibodies, pembrolizumab and nivolumab, the anti-programmed cell death-ligand 1 (PD-L1) antibodies, atezolizumab and durvalumab, and the anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibodies, ipilimumab, and tremelimumab, are widely used to treat driver gene mutation-negative NSCLC and extensive-stage SCLC (ES-SCLC). Their cost is likewise covered by National Health Insurance, leading to the wide use of these drugs in clinical practice.

While costly medications are extensively utilized in the treatment of lung cancer, comprehensive data regarding their utilization, extent of usage, and associated expenses are currently unavailable in Japan. Consequently, we conducted a retrospective study to ascertain the utilization patterns of high-cost treatments for advanced lung cancer treatment in Japan.

Materials and methods

The present study surveyed 60 Japanese health centers belonging to the Lung Cancer Study Group of the JCOG to determine which regimens were being used as first-line treatment for advanced or recurrent lung cancer between July 2021 and June 2022. The survey covered the following, three disease categories: driver gene mutation and translocation-negative or indeterminate type NSCLC; EGFR mutation-positive NSCLC; and ES-SCLC; all of which are widely treated with high-cost regimens. In the survey, data on the total number of patients receiving one of these first-line treatment regimens and their age (74 years or younger, 75 years or older) were collected. Treatment regimens were tabulated for those listed in the Japanese Lung Cancer Society Guideline (2022 ed.) [7], and those not listed were classified as 'other'. Individual patient data, including detailed histology, number of doses, treatment duration, efficacy (response, progression-free survival (PFS), overall survival (OS), adverse events, and quality of life were not investigated. Patients treated by investigational agents were excluded, but those who had participated in clinical trials such as the JCOG trials were included. Each center investigated these data categories retrospectively, entered their findings into a Google form format, and tabulated the results. Treatment costs were calculated on a monthly and total cost basis. Costs were calculated assuming a typical patient (70-year-old male, height 170 cm, weight 60 kg, body surface area 1.7 m^2, Cr 0.8 mg/dl, Ccr 72.9 ml/min [Cockcroft-Gault]) receiving treatment. The total treatment cost was calculated by multiplying the cost of a single dose, the median number of

administrations, and the number of persons receiving the drug. The price of the medications as of 1 April 2024 was used to calculate the cost. Pembrolizumab, nivolumab, ipilimumab, and atezolizumab cost 214 498 JPY (Japanese Yen)/100 mg, 469 104 JPY/360 mg, 419 578 JPY/50 mg, and 563 917 JPY/1200 mg, respectively. If a generic version of a drug was available, the lowest price was used. The JCOG Health Economics Committee defined treatments that cost more than 500 000 JPY per month as high-cost treatments and treatments that cost more than 1 million JPY per month as very high-cost treatments.

Results

Responses were received from all 60 centers belonging to the Lung Cancer Study Group of the JCOG. Table 1 shows a list of the high-cost treatments and very high-cost treatments. The cost of recent treatment with ICIs or ICI plus chemotherapy for NSCLC is approximately 19.3 to 38.7 times more expensive than conventional chemotherapy, carboplatin plus paclitaxel. The cost of recent treatment with osimertinib monotherapy or erlotinib plus ramucirumab for EGFR mutation-positive NSCLC is 6.8 times and 15.3 times more expensive than conventional drug, gefitinib. The cost of recent treatment with ICI plus chemotherapy for ES-SCLC is approximately 33.5 to 54.7 times more expensive than conventional chemotherapy, carboplatin plus etoposide (Table 1).

Driver gene mutation and translocation-negative NSCLC

In total, 3738 patients were treated; of these, 2330 (62.3%) were aged 74 years or younger, 1057 (28.3%) were aged 75 years or older, and 351 (9.4%) were unknown; 2555 patients (68.4%) received an ICI, and 832 (22.3%) did not. Of the ICI used, pembrolizumab, nivolumab plus ipilimumab, and atezolizumab was administered to 1504 (40.2%), 718 (19.2%), and 333 (8.9%) patients, respectively. The regimens consisted of pembrolizumab monotherapy (n = 605, 16.2%), carboplatin + pemetrexed + pembrolizumab (n = 497, 13.3%), nivolumab + ipilimumab (n = 349, 9.3%), carboplatin + pemetrexed (n = 302, 8.1%), carboplatin + nab-paclitaxel (n = 238, 6.4%), and carboplatin + pemetrexed + nivolumab + ipilimumab (n = 221, 5.9%) (Table 2).

In terms of age, 1749 (75.1%) patients aged 74 years or younger received ICI treatment, 806 (76.3%) patients aged 75 years or older received ICI treatment, with the proportion of patients aged 75 years or older being slightly greater. About, 308 (29.1%) patients aged 75 years or older received pembrolizumab monotherapy and 173 (16.4%) patients received nivolumab plus ipilimumab. The proportion of patients receiving these regimens was significantly greater in those aged 75 years or older than in those aged 74 years or younger. In contrast, the percentage of chemotherapy + ICI was lower in those aged 75 or older.

At six-weeks of ICI treatment, the cost (based on 60 kg body weight) of pembrolizumab, nivolumab + ipilimumab, and atezolizumab was 857 992 JPY, 1 450 002 JPY, and 1 127 834 JPY, respectively. The monthly cost was 623 066 JPY, 1 052 978 JPY, and 819 022 JPY, respectively. Assuming that each patient received the median number of ICI doses given in a clinical trial [8–16], the total treatment cost of ICI therapy was estimated to be 6.34 billion JPY for a pembrolizumab-based regimen, 4.32 billion JPY for a nivolumab + ipilimumab-based regimen, and 2.18 billion JPY for an atezolizumab- based regimen. Furthermore, 2573 (68.8%) patients received high-cost treatments, and 1013 (27.1%) patients received very high-cost treatments (Tables 1 and 2).

EGFR mutation-positive NSCLC

In total, 1486 patients were treated; of these, 908 patients (61.1%) were aged 74 years or younger, 516 patients (34.7%) were aged 75 years or older, and 62 (4.2%) were of unknown age. By regimen, 1207 (81.2%) patients received osimertinib, 83 (5.6%) received erlotinib + ramucirumab, and 81 (5.5%) received afatinib. Osimertinib was administered to 758 patients (83.5%) aged 74 years or younger and 449 patients (87.0%) aged 75 years or older, with the proportion of patients aged 75 years or older being significantly greater. As of 1 April 2024, the price of an 80 mg tablet of osimertinib was 18 540.2 JPY; thus, the cost of this drug per month per patient was 565 476 JPY, making osimertinib a high-cost drug. Assuming that osimertinib was administered until the median PFS of 18.9 months [17], the total cost of treatment per patient was 10 687 000 JPY. In the present survey, the total cost of this regimen was estimated to be 12.8 billion JPY. In contrast, the price of a 250 mg tablet of gefitinib, a first-generation EGFR-TKI, was 2715.3 JPY. Thus, the cost of gefitinib per month per patient was 82 817 JPY. Assuming that gefitinib was administered until the median PFS of 10.2 months [17], total cost of this regimen per patient was 844 700 JPY. In summary, 1290 (86.8%) patients received high-cost treatments, and 83 (5.6%) patients received very high-cost treatments (Tables 1 and 3).

ES-SCLC

In total, 1079 patients were treated, 686 (63.6%) patients were aged 74 years or younger, 377 (34.9%) patients were aged 75 years or older, and 16 (1.5%) were of unknown age. ICI was administered to 607 (56.3%) patients but not to 472 (43.7%) patients. The most commonly administered regimen was carboplatin + etoposide (n = 381, 35.3%), followed by carboplatin + etoposide + durvalumab (n = 290, 26.9%), carboplatin + etoposide + atezolizumab (n = 222, 20.6%), and cisplatin + etoposide + durvalumab (n = 95 patients, 8.8%). By age, more patients aged 75 years or older received carboplatin + etoposide than patients aged 74 years or younger (n = 191, 50.7% and n = 190, 27.7%, respectively). Conversely, fewer of the former than of the latter age-group received cisplatin + etoposide + durvalumab (n = 1, 0.3% and n = 94, 13.7%). There was no difference in the proportion of patients receiving carboplatin + etoposide + ICI by age Table 4.

The number of ICI doses was assumed to be the median number of ICI doses given in a clinical trial [18,19]. The cost of carboplatin (area under the curve [AUC] = 5, day 1) + etoposide (80 mg/m^2, days 1–3) was 17 338 JPY per cycle and 69 352 JPY per four cycles of chemotherapy for a total cost of about 26.4 million JPY. For carboplatin (AUC = 5, day 1) + etoposide (80 mg/m^2, days 1–3) + durvalumab (1500 mg/body, day 1), the cost was 947 800 JPY per cycle and 6 582 586 JPY for seven ICI doses for a total cost of about 1.91 billion JPY. For cisplatin (80 mg/m^2, day 1) + etoposide (100 mg/m^2, days 1–3) + durvalumab (1500 mg/body, day 1), the cost was 949 666 JPY per cycle and 6 724 478 JPY for seven ICI doses for a total cost of 638.8 million JPY. One cycle of carboplatin (AUC = 5, day 1) + etoposide (100 mg/m^2, days 1–3) + atezolizumab (1200 mg/body, day 1) cost 581 255 JPY, and seven ICI doses cost 4 016 771 JPY for a total cost of 891.7 million JPY. Cisplatin or carboplatin + etoposide + durvalumab were considered very

Table 1. List of high-cost treatments and very high-cost treatments in lung cancer

Regimen	Treatment cost per 3 weeks (JPY)	Treatment cost per month (JPY)	High-cost treatment	Very high-cost treatment
NIVO + IPI	725 001	1 052 978	○	○
CBDCA + PEM + NIVO + IPI	814 534	1 183 014	○	○
CDDP + PEM + NIVO + IPI	815 660	1 184 649	○	○
CBDCA + PTX + NIVO + IPI	747 252	1 085 295	○	○
Pembrolizumab	428 996	623 066	○	
CBDCA + PEM + Pembrolizumab	518 529	753 102	○	
CDDP + PEM + Pembrolizumab	519 655	754 737	○	
CBDCA + nab-PTX + Pembrolizumab	726 521	1 055 185	○	○
CBDCA + PTX + Pembrolizumab	451 247	655 383	○	
Atezolizumab	563 917	819 022	○	
CBDCA + nab-PTX + Atezolizumab	861 442	1 251 142	○	○
CBDCA + PEM + Atezolizumab	654 343	950 355	○	
CDDP + PEM + Atezolizumab	654 576	950 694	○	
CBDCA + PTX + BEV + Atezolizumab	681 876	990 344	○	
CBDCA + PTX + BEV	117 959	171 321		
CDDP + GEM + necitumumab	487 474	707 998	○	
CBDCA + PEM	89 533	130 036		
CDDP + PEM	90 659	131 671		
CBDCA + nab-PTX	297 525	432 120		
CBDCA + PTX	22 251	32 317		
Osimertinib	389 344	565 476	○	
Gefitinib	57 021	82 817		
Erlotinib	212 293	308 331		
Afatinib	181 213	263 191		
Dacomitinib	172 859	251 058		
Erlotinib + Bevacizumab	308 001	447 335		
Erlotinib + Ramucirumab	870 330	1 264 050	○	○
Gefitinib + CBDCA + PEM	146 554	212 853		
CBDCA + ETP + Atezolizumab	581 255	844 204	○	
CBDCA + ETP + Durvalumab	947 800	1 376 567	○	○
CDDP + ETP + Durvalumab	948 926	1 378 202	○	○
CDDP + irinotecan	17 593	25 552		
CDDP + ETP	19 204	27 892		
CBDCA + ETP	17 338	25 181		

Abbreviations: JPY, Japanese Yen; NIVO, nivolumab; IPI, ipilimumab; CBDCA, carboplatin; PEM, pemetrexed; CDDP, cisplatin; PTX, paclitaxel; nab-PTX, nab-paclitaxel; BEV, bevacizumab; GEM, gemcitabine; ETP, etoposide. "○" is placed in the appropriate treatment.
Costs were calculated assuming a typical patient (70-year-old male, height 170 cm, weight 60 kg, body surface area 1.7 m^2, Cr 0.8 mg/dl, Ccr 72.9 ml/min [Cockcroft-Gault]). The price of the medications as of 1 April 2024 was used to calculate the treatment cost.

high-cost drugs and were used in 35.7% of patients with ES-SCLC. Carboplatin + etoposide + atezolizumab was considered a high-cost regimen and was used in 20.6% of patients with ES-SCLC. Six hundred seven (56.3%) patients were treated with high-cost treatments, and 385 (35.7%) patients were treated with very high-cost treatments (Tables 1 and 4).

Discussion

No studies have to date have provided a real-world cost analysis of lung cancer treatments in Japan. The present study surveyed 60 centers belonging to the Lung Cancer Study Group of the JCOG, a leading lung cancer treatment group in Japan. The survey revealed which regimens were used in clinical practice and to what extent they were used at all 60 centers while also estimating the approximate cost of the treatments.

The large number of patients with lung cancer and the high cost of many drugs are contributing to increasing the total cost of treatments. The cost of treatments for driver gene mutation and translocation-negative NSCLC, EGFR mutation-positive NSCLC, and ES-SCLC was 12.84 billion JPY, 12.8 billion JPY, and 3.44 billion JPY, respectively.

The efficacy of each ICIs and ICI-containing treatments has been proven by comparison with chemotherapy, which has been the standard of care. However, comparative data between various ICIs and ICI-containing treatments are not fully available. As a result, physicians use ICIs and ICI-containing treatments for their patients lacking adequate selection criteria.

The cost of treatments for driver gene mutation and translocation-negative NSCLC was particularly high because ICI is the mainstay of treatment. Pembrolizumab, the cheapest of the three ICI, was the most used but is nonetheless expensive.

Table 2. List of treatments for driver gene mutation and translocation-negative NSCLC

Regimen (Treatment cost per month, JPY)	Number (%)	≤74 yrs (%)	≥75 yrs (%)	ICI total (%)
NIVO + IPI regimen				
NIVO + IPI	349	176	173	718
(1 052 978)	(9.3)	(7.6)	(16.4)	(19.2)
NIVO + IPI + CBDCA + PEM	221	189	32	
(1 183 014)	(5.9)	(8.1)	(3.0)	
NIVO + IPI + CDDP + PEM	25	24	1	
(1 184 649)	(0.7)	(1.0)	(0.1)	
NIVO + IPI + CBDCA + PTX	123	102	21	
(1 085 295)	(3.3)	(4.4)	(2.0)	
PEMBRO regimen				
PEMBRO	605	297	308	1504
(623 066)	(16.2)	(12.7)	(29.1)	(40.2)
PEMBRO + CBDCA + PEM	497	388	109	
(753 102)	(13.3)	(16.7)	(10.3)	
PEMBRO + CDDP + PEM	81	79	2	
(754 737)	(2.2)	(3.4)	(0.2)	
PEMBRO + CBDCA + nab-PTX	167	116	51	
(1 055 185)	(4.5)	(5.0)	(4.8)	
PEMBRO + CBDCA + PTX	154	128	26	
(655 383)	(4.1)	(5.5)	(2.5)	
ATEZO regimen				
ATEZO	24	15	9	333
(819 022)	(0.6)	(0.6)	(0.9)	(8.9)
ATEZO + CBDCA + nab-PTX	128	83	45	
(1 251 142)	(3.4)	(3.6)	(4.3)	
ATEZO + CBDCA + PEM	48	28	20	
(950 355)	(1.3)	(1.2)	(1.9)	
ATEZO + CDDP + PEM	6	4	2	
(950 694)	(0.2)	(0.2)	(0.2)	
ATEZO + CBDCA + PTX + BEV	127	120	7	
(990 344)	(3.4)	(5.2)	(0.7)	
Regimen without ICI				
CBDCA + PTX + BEV	50	37	13	832
(171 321)	(1.3)	(1.6)	(1.2)	(22.3)
CDDP + GEM + NECI	18	18	0	
(707 998)	(0.5)	(0.8)	(0)	
CBDCA + PEM	302	212	90	
(130 036)	(8.1)	(9.1)	(8.5)	
CDDP + PEM	43	43	0	
(131 671)	(1.2)	(1.8)	(0)	
CBDCA + nab-PTX	238	144	94	
(432 120)	(6.4)	(6.2)	(8.9)	
CBDCA + PTX	181	127	54	
(32 317)	(4.8)	(5.5)	(5.1)	
Other	351	NE	NE	
	(9.4)			
Total	3738	2330	1057	

Abbreviations: NSCLC, non-small cell lung cancer; JPY, Japanese Yen; ICI, immune checkpoint inhibitor; NIVO, nivolumab; IPI, ipilimumab; CBDCA, carboplatin; PEM, pemetrexed; CDDP, cisplatin; PTX, paclitaxel; PEMBRO, pembrolizumab; nab-PTX, nab-paclitaxel; ATEZO, atezolizumab; BEV, bevacizumab; GEM, gemcitabine; NECI, necitumumab; NE, not evaluable.

For EGFR mutation-positive NSCLC, there is a problem that despite being in the same class and having the same efficacy and safety, the costs vary widely; EGFR-TKI plus angiogenesis inhibitors (bevacizumab or ramucirumab) is an example [20,21]. Treatment with ramucirumab plus erlotinib is 2.8 times more expensive than treatment with bevacizumab plus erlotinib, even though the efficacy and safety are almost identical. It would be difficult to justify the use of high-cost treatment without documented superiority in efficacy and/or safety to a less costly alternative. There is no single reason why the more expensive treatment should be chosen.

EGFR mutation-positive NSCLC accounted for about 80% of all the cases treated with osimertinib, and the total cost was correspondingly high. It is obvious that protracted therapy with expensive, oral, anticancer drugs will result in correspondingly higher costs.

Table 3. List of treatments for EGFR mutation-positive NSCLC

Regimen (Treatment cost per month, JPY)	Number (%)	≤74 yrs (%)	≥75 yrs (%)
Osimertinib	1207	758	449
(565 476)	(81.2)	(83.5)	(87.0)
Gefitinib	31	14	17
(82 817)	(2.1)	(1.5)	(3.3)
Erlotinib	16	12	4
(308 331)	(1.1)	(1.3)	(0.8)
Afatinib	81	62	19
(263 191)	(5.5)	(6.8)	(3.7)
Dacomitinib	1	1	0
(251 058)	(0.1)	(0.1)	(0)
Erlotinib + Bevacizumab	3	3	0
(447 335)	(0.2)	(0.3)	(0)
Erlotinib + Ramucirumab	83	56	27
(1 264 050)	(5.6)	(6.2)	(5.2)
Gefitinib + CBDCA + PEM	2	2	0
(212 853)	(0.1)	(0.2)	(0)
Other	62	NE	NE
	(4.2)		
Total	1486	908	516

Abbreviations: EGFR, epidermal growth factor receptor; JPY, Japanese Yen; NSCLC, non-small cell lung cancer; CBDCA, carboplatin; PEM, pemetrexed; NE, not evaluable.

Table 4. List of treatments for ES-SCLC

Regimen (Treatment cost per month, JPY)	Number (%)	≤74 yrs (%)	≥75 yrs (%)
CBDCA + ETP + Atezolizumab	222	149	73
(844 204)	(20.6)	(21.7)	(19.4)
CBDCA + ETP + Durvalumab	290	185	105
(1 376 567)	(26.9)	(27.0)	(27.9)
CDDP + ETP + Durvalumab	95	94	1
(1 378 202)	(8.8)	(13.7)	(0.3)
CDDP + irinotecan	8	7	1
(25 552)	(0.7)	(1.0)	(0.3)
CDDP + ETP	67	61	6
(27 892)	(6.2)	(8.9)	(1.6)
CBDCA + ETP	381	190	191
(25 181)	(35.3)	(27.7)	(50.7)
Other	16	NE	NE
	(1.5)		
Total	1079	686	377

Abbreviations: ES-SCLC, extensive-stage small cell lung cancer; JPY, Japanese Yen; CBDCA, carboplatin; CDDP, cisplatin; ETP, etoposide; NE, not evaluable.

Comparison of the efficacy and cost of osimertinib and gefitinib, extending the median PFS of 8.7 months and median OS of 6.8 months in patients with EGFR mutation-positive NSCLC would cost 9 842 000 JPY per patient [17].

The percentage of patients with ES-SCLC receiving ICI therapy was 56.3%, which was lower than that of patients with NSCLC. In addition, about half the patients older than 75 years did not receive ICI therapy possibly because SCLC is a smoking-related cancer and therefore occurs more often in patients with poor pulmonary status, making the drug less effective for prolonging PFS and OS than in cases of NSCLC. Using atezolizumab to extend the median PFS by 0.9 months and the median OS by 2.0 months increased the cost of therapy to 3 950 000 JPY per patient [19]. Using durvalumab to extend the median PFS by 0.8 months and the median OS by 2.6 months increased the cost of therapy to 6 510 000 JPY per patient [18].

Atezolizumab and durvalumab are the same PD-L1 inhibitor. The efficacy and safety of treatment with carboplatin plus etoposide plus atezolizumab in the Impower133 trial and platinum plus etoposide plus durvalumab in the CASPIAN trial are nearly identical [18,19]. Slight differences in trial design and slight differences in results between the two trials are not inadequate to select one over the other. The only major and clear difference is cost, with the cost of durvalumab combination therapy being approximately 1.6 times the cost of atezolizumab combination therapy. However, durvalumab combination therapy was used about 1.7 times more than

atezolizumab combination therapy in this study. This fact demonstrates how indifferent physicians are to the cost of treatment. It would be difficult to justify the use of high-cost treatment without documented superiority in efficacy and/or safety to a less costly alternative. There is no single reason why the more expensive treatment should be chosen.

The long-term response and long-term survival rate can be achieved in a small percentage of ES-SCLC patients using an ICI combination regimen. In the future, patient selection will hopefully be made more efficient using biomarkers and newly developed treatment strategies.

In addition, the actual total treatment cost may be higher than the results of this study have shown. One reason for this may be that in Japanese clinical practice, ICIs and target-based drugs continue to be used beyond progressive disease; i.e. the high frequency of their use cannot be justified by the current evidence. The appropriate duration of ICIs dosing is currently under investigation in the JCOG 1701 trial to evaluate the benefit of discontinuing ICI therapy after one year in NSCLC patients who have responded to ICI therapy [22]. There have also been several dose-optimization studies of target-based drugs, and the efficacy of low-dose EGFR-TKI therapy has been reported [23–26]. All of these trials are very appropriate strategies to control treatment costs.

This study has several limitations. First, the accurate cost of drugs for lung cancer treatment in Japan was not determined because lung cancer treatment is also conducted at other treatment centers besides the 60 centers belonging to the Lung Cancer Study Group of the JCOG. Second, the duration of drug administration, efficacy, and side effects of each regimen, which might impact the total treatment cost, were not investigated at all. Since ICI therapy aims to achieve a long-term response, it is incorrect to assume that the number of ICI doses used in a cost estimate is equivalent to the median number of ICI doses administered in a clinical trial. Third, the cost of cancer treatment involves not only the cost of the drugs mentioned above, but also that of ancillary drugs, such as antiemetics and granulocyte colony-stimulating factor (G-CSF), as well of countermeasures for adverse events. Since these treatment costs were not investigated, the actual, total treatment cost of lung cancer therapy is unknown. Fourth, cost-effectiveness analysis in medical care is generally done using quality adjusted life years (QALY) [27]. However, the present survey did not examine the patients' quality of life. A more thorough cost-effectiveness analysis for lung cancer awaits future research.

Lung cancer was a disease with an extremely poor prognosis until about ten years ago. Over the past decade, treatments and the prognosis have greatly improved [28]. At the same time, however, drug costs have drastically increased. The present survey revealed the scale of this increase. Currently, ICI and molecularly targeted drugs in lung cancer treatment are mainly administered in the advanced stage, but if they should come to be used widely at the perioperative stage, their treatment cost may be expected to increase even more.

Pharmaceutical company are also focusing their attention on the development of expensive drugs and are hesitant to produce inexpensive drugs. As a result, there is a new problem in the US: drug-shortage crisis for classical but essential anti-cancer agents such as platinum and etoposide [29–31].

Efforts to optimize drug use, including drug costs, in cancer treatment are already underway mainly in Europe [32]. The issues surrounding the cost of health care, including the cost of drugs, must be addressed by all parties involved in providing health care services, including the government, regulatory authorities, academia, the pharmaceutical industry, patients, and physicians. To develop better treatments, the 'financial toxicity' of high medical costs must be seriously addressed.

Conclusion

Recent treatments for advanced lung cancer cost about 20–55 times more than conventional chemotherapy. This study revealed that high-cost treatments were widely used in driver gene mutation and translocation-negative NSCLC, EGFR mutation-positive NSCLC, and ES-SCLC, and that some high-cost treatments were used despite the lack of clear evidence, because physicians are indifferent to the cost. Inappropriate high-cost treatments make waste and burden to society. Physicians should pay attention to the cost of treatments they use. The results of this study will serve as a benchmark for future cost-effectiveness analyses of lung cancer treatments.

Acknowledgements

We thank all the investigators who participated in the study, in particular, the researchers and staff of the 60 centers belonging to the Lung Cancer Study Group:
Department of Respiratory Medicine, National Hospital Organization Asahikawa Medical Center; Department of Respiratory Medicine, National Hospital Organization Hokkaido Cancer Center; Department of Respiratory Medicine, Hokkaido University Hospital; Division of Pulmonary Medicine, Department of Internal Medicine, Iwate Medical University School of Medicine; Department of Respiratory Medicine, Miyagi Cancer Center; Department of Pulmonary Medicine, Sendai Kousei Hospital; Department of Respiratory Medicine, Akita Kousei Medical Center; Division of Thoracic Oncology, Department of Medical Oncology, Tochigi Cancer Center; Department of Pulmonary Medicine and Clinical Immunology, Dokkyo Medical University School of Medicine; Division of Respiratory Medicine, Gunma Prefectural Cancer Center; Department of Thoracic Oncology, Saitama Cancer Center; Department of Thoracic Oncology, National Cancer Center Hospital East; Department of Medical Oncology, Funabashi Municipal Medical Center; Department of Thoracic Oncology, National Cancer Center Hospital; Department of Medical Oncology, Kyorin University Faculty of Medicine; Department of Thoracic Oncology and Respiratory Medicine, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital; Respiratory Medicine, National Center for Global Health and Medicine; Division of Medical Oncology, Department of Medicine, Showa University School of Medicine; Division of Respiratory Diseases, Department of Internal Medicine, Jikei University School of Medicine; Department of Thoracic Medical Oncology, The Cancer Institute Hospital of Japanese Foundation for Cancer Research; Department of Respiratory Medicine, Japanese Red Cross Medical Center; Department of Respiratory Medicine, Juntendo University Graduate School of Medicine; Department of Respiratory Medicine, Toho University Omori Medical Center Department of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School; Division of Medical Oncology, Department of Internal Medicine, Teikyo University School of Medicine; Department of Thoracic Oncology of Kanagawa Cancer Center; Department of Respiratory Medicine, Yokohama Municipal Citizen's Hospital; Department of Respiratory Medicine, Kitasato University School of Medicine; Department of Internal Medicine, Niigata Cancer Center Hospital; Department of Respiratory Medicine and Infectious Diseases, Niigata University Graduate School of Medical and Dental Sciences; Department of Hematology and Medical Oncology, Shinshu University School of Medicine; Department of Respiratory Medicine and Medical Oncology, Gifu Municipal Hospital; Division of Thoracic Oncology, Shizuoka Cancer Center; Department of Thoracic Oncology, Aichi Cancer Center; Department of Respiratory Medicine, National Hospital Organization, Nagoya Medical Center; Department of Respiratory Medicine, Nagoya University Graduate School of Medicine Department of Respiratory Medicine, Fujita Health University School of Medicine; Department of Respiratory Medicine, Kyoto University Hospital; Department of Clinical Oncology, Graduate

School of Medicine, Osaka Metropolitan University; Department of Medical Oncology, Kindai University Faculty of Medicine; Department of Thoracic Oncology, Osaka International Cancer Institute; Department of Thoracic Oncology, National Hospital Organization Kinki-Chuo Chest Medical Center; Department of Respiratory Medicine, Osaka General Medical Center; Department of Clinical Oncology, Osaka City General Hospital; Department of Thoracic Oncology, Kansai Medical University Hospital; Department of Respiratory Medicine and Hematology, Hyogo Medical University School of Medicine; Respiratory Division, Department of Internal Medicine, Itami City Hospital; Internal Medicine III, Wakayama Medical University; Department of Respiratory Medicine, Kurashiki Central Hospital; Department of Respiratory Medicine, Japanese Red Cross Okayama Hospital; Department of Respiratory Medicine, Hiroshima University Hospital; Department of Medical Oncology, Yamaguchi-Ube Medical Center; Department of Respiratory Medicine and Rheumatology, Tokushima University; Department of Thoracic Oncology and Medicine, National Hospital Organization Shikoku Cancer Center; Department of Thoracic Oncology, National Hospital Organization Kyushu Cancer Center; Department of Respiratory Medicine, NHO Kyushu Medical Center; Division of Respirology, Neurology, and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine; Department of Respiratory Medicine, Graduate School of Medical Sciences, Kyushu University; Department of Respiratory Medicine, Nagasaki University Graduate School of Biomedical Sciences; Department of Respiratory Medicine, Kumamoto University Hospital; and we also thank James R. Valera for his assistance with editing this manuscript.

CRediT statement

Kageaki Watanabe, Keita Sasaki, Ryunosuke Machida, Junichi Shimizu, Yuki Yamane, Motohiro Tamiya, Shin Saito, Yuji Takada, Kiyotaka Yoh, Hiroshige Yoshioka, Haruyasu Murakami, Satoru Kitazono, Yasuhiro Goto, Hidehito Horinouchi, Yuichiro Ohe all contribute significantly to this study.

Conceptualization: Kageaki Watanabe, Keita Sasaki, Ryunosuke Machida.

Data curation: Kageaki Watanabe, Keita Sasaki, Ryunosuke Machida.

Formal analysis: Kageaki Watanabe.

Funding acquisition: None.

Investigation: Kageaki Watanabe, Hidehito Horinouchi.

Methodology: Kageaki Watanabe, Keita Sasaki, Ryunosuke Machida, Hidehito Horinouchi.

Project administration: Kageaki Watanabe, Keita Sasaki, Ryunosuke Machida.

Resources: 60 Japanese centers belonging to the Lung Cancer Study Group.

Software: None.

Supervision: Yuichiro Ohe.

Validation: None.

Visualization: None.

First draft: Kageaki Watanabe.

Review & editing: Kageaki Watanabe, Keita Sasaki, Ryunosuke Machida, Junichi Shimizu, Yuki Yamane, Motohiro Tamiya, Shin Saito, Yuji Takada, Kiyotaka Yoh, Hiroshige Yoshioka, Haruyasu Murakami, Satoru Kitazono, Yasuhiro Goto, Hidehito Horinouchi, Yuichiro Ohe.

Supplementary data

Supplementary data is available at *Japanese Journal of Clinical Oncology* online.

Conflict of interest

Kageaki Watanabe received honoraria from AstraZeneca, Chugai Pharmaceutical, Merck Biopharma, Amgen, Novartis Pharma, Bristol-Meyers Squibb, MSD, Nippon Boehringer Ingelheim, Ono Pharmaceutical, RIKEN GENESIS, Sysmex Corporation, Pfizer, Taiho Pharmaceutical, Takeda Pharmaceutical, and Guardant Health outside the submitted work. Junichi Shimizu received honoraria from Taiho Pharmaceutical, Takeda Pharmaceutical, Chugai Pharmaceutical, MSD, AstraZeneca, Novartis, Pfizer, Amgen, Merck outside the submitted work. Motohiro Tamiya received Consulting fees from Pfizer and honoraria from Pfizer, Ono Pharmaceutical, Takeda Pharmaceutical, AstraZeneca, Chugai Pharmaceutical, MSD, Eli Lilly, Bristol-Mayers, Amgen outside the submitted work. Kiyotaka Yoh received grants or contracts from Abbvie, Amgen, AstraZeneca, Boehringer Ingelheim, Chugai, Daiichi Sankyo, Lilly, MSD, Pfizer, Taiho, Takeda and consulting fees from Boehringer Ingelheim and honoraria for lectures from Abbvie, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, Janssen, Kyowa kirin, Lilly, Merck Serono, Novartis, Ono, Otsuka, Taiho, Takeda outside the submitted work. Hiroshige Yoshioka received research funding from Daichi Sanko, AstraZeneca, Janssen Pharmaceutical, MSD, Novartis Pharma, Delta Fly Pharma, Boehringer Ingelheim, and consulting fees from Delta Fly Pharma and honoraria for lectures from Eli Lilly, Chugai Pharmaceutical, MSD, AstraZeneca, Boehringer Ingelheim, Taiho Pharmaceutical, Ono Pharmaceutical, Bristol-Myers Squibb, Novartis Pharma, Kyowa Kirin, Nippon Kayaku, Otsuka Pharmaceutical, Amgen, Pfizer, Nipro Pharma, Daiichi Sankyo, Merck Biopharma outside the submitted work. Haruyasu Murakami received research grant and funding from Chugai pharma, AstraZeneca, AbbVie, Daiichi Sankyo, IQvia, Taiho Pharmaceutical, Bayer and honoraria from Chugai pharma, Daiichi Sankyo, AstraZeneca, Takeda, Amgen, Ono Pharmaceutical, Bristol-Myers Squibb Japan, MSD, Pfizer, Novartis, Lilly Japan, Taiho Pharmaceutical, Eisai, Nihonkayaku and participated on a Data Safety Monitoring Board or Advisory Board of Chugai pharma, GAIA BioMedicine, Daiichi Sankyo, Takeda, Kyowa Kirin outside the submitted work. Satoru Kitazono received honoraria for lectures from Chugai Pharmaceutical, Ono Pharmaceuticals, Janssen Pharmaceutical, Eli Lilly Japan outside the submitted work. Yasuhiro Goto received grants or contracts from Teijin Pharma Limited, and honoraria from Taiho Pharmaceutical, Nippon Boehringer Ingelheim, Chugai Pharmaceutical, MSD, AstraZeneca, GlaxoSmithKline, Pfizer, Takeda Pharmaceutical outside the submitted work. Hidehito Horinouchi received grants or contracts from AstraZeneca, Roche/Chugai Pharmaceutical, MSD, Abbvie, Bristol-Myers Squibb, Ono Pharmaceutical, and Daiichi Sankyo and honoraria from AstraZeneca, Roche/Chugai Pharmaceutical, MSD, Abbvie, Bristol-Myers Squibb, and Ono Pharmaceutical outside the submitted work. Yuichiro Ohe received grants or contracts from AstraZeneca, Chugai, Eli Lilly, LOXO Kirin, Sumitomo, Pfizer, Taiho, Novartis, Takeda, kissei, Daiichi-Sankyo, Janssen, LOXO, and honoraria from AstraZeneca, Chugai, Eli Lilly, ONO, BMS, Boehringer Ingelheim, Bayer, Pfizer, MSD, Taiho, Nippon Kayaku, Kyowa Hakko Kirin, Eisai, Daiichi-Sankyo, and payment for expert testimony from AstraZeneca, Chugai, ONO, BMS, Kyorin, Celltrion, Amgen, Nippon Kayaku, Boehringer Ingelheim, AnHeart Therapeutics Inc. PharmaMar outside the submitted work. Keita Sasaki, Ryunosuke Machida, Yuki Yamane, Shin Saito, Yuji Takada declare that they have no conflicts of interest to disclose.

Funding

This study was supported in part by the Research Fund of National Federation of Health Insurance Societies (Kenpo-ren) and the National Cancer Center Research and Development Fund (2023-J-03).

References

1. Qasim Hussaini SM, Gupta A, Dusetzina SB. Financial toxicity of cancer treatment. *JAMA Oncol* 2022;8:788. https://doi.org/10.1001/jamaoncol.2021.7987.
2. Smith TJ, Hillner BE. Bending the cost curve in cancer care. *N Engl J Med* 2011;364:2060–5. https://doi.org/10.1056/NEJMsb1013826.
3. Sullivan R, Peppercorn J, Sikora K. et al. Delivering affordable cancer care in high-income countries. *Lancet Oncol* 2011;12:933–80. https://doi.org/10.1016/S1470-2045(11)70141-3.
4. Leighl NB, Nirmalakumar S, Ezeife DA. et al. An arm and a leg: the rising cost of cancer drugs and impact on access. *Am Soc Clin Oncol Educ Book* 2021;41:e1–12. https://doi.org/10.1200/EDBK_100028.
5. *National Cancer Center Cancer Information Service*. https://ganjoho.jp. Last date accessed on May 2024.
6. Tan AC, Tan DSW. Targeted therapies for lung cancer patients with oncogenic driver molecular alterations. *J Clin Oncol* 2022;40:611–25. https://doi.org/10.1200/JCO.21.01626 Epub 5 Jan 2022.
7. *The Japanese lung cancer society guideline for non-small cell lung cancer, stage IV*. https://www.haigan.gr.jp/guideline/2022/. Last date accessed on May 2024.
8. Hellmann MD, Paz-Ares L, Bernabe Caro R. et al. Nivolumab plus Ipilimumab in advanced non-small-cell lung cancer. *N Engl J Med* 2019;381:2020–31. https://doi.org/10.1056/NEJMoa1910231.
9. Paz-Ares L, Ciuleanu TE, Cobo M. et al. First-line nivolumab plus ipilimumab combined with two cycles of chemotherapy in patients with non-small-cell lung cancer (CheckMate 9LA): an international, randomised, open-label, phase 3 trial. *Lancet Oncol* 2021;22:198–211. https://doi.org/10.1016/S1470-2045(20)30641-0.
10. Reck M, Rodríguez-Abreu D, Robinson AG. et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. *N Engl J Med* 2016;375:1823–33. https://doi.org/10.1056/NEJMoa1606774.
11. Gandhi L, Rodríguez-Abreu D, Gadgeel S. et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med* 2018;378:2078–92. https://doi.org/10.1056/NEJMoa1801005.
12. Paz-Ares L, Luft A, Vicente D. et al. Pembrolizumab plus chemotherapy for squamous non-small-cell lung cancer. *N Engl J Med* 2018;379:2040–51. https://doi.org/10.1056/NEJMoa1810865.
13. Herbst RS, Giaccone G, de Marinis F. et al. Atezolizumab for first-line treatment of PD-L1-selected patients with NSCLC. *N Engl J Med* 2020;383:1328–39. https://doi.org/10.1056/NEJMoa1917346.
14. West H, McCleod M, Hussein M. et al. Atezolizumab in combination with carboplatin plus nab-paclitaxel chemotherapy compared with chemotherapy alone as first-line treatment for metastatic non-squamous non-small-cell lung cancer (IMpower130): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol* 2019;20:924–37. https://doi.org/10.1016/S1470-2045(19)30167-6.
15. Nishio M, Barlesi F, West H. et al. Atezolizumab plus chemotherapy for first-line treatment of nonsquamous NSCLC: results from the randomized phase 3 IMpower132 trial. *J Thorac Oncol* 2021;16:653–64. https://doi.org/10.1016/j.jtho.2020.11.025.
16. Socinski MA, Jotte RM, Cappuzzo F. et al. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. *N Engl J Med* 2018;378:2288–301. https://doi.org/10.1056/NEJMoa1716948.
17. Soria JC, Ohe Y, Vansteenkiste J. et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med* 2018;378:113–25. https://doi.org/10.1056/NEJMoa1713137.
18. Paz-Ares L, Dvorkin M, Chen Y. et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. *Lancet* 2019;394:1929–39. https://doi.org/10.1016/S0140-6736(19)32222-6.
19. Horn L, Mansfield AS, Szczęsna A. et al. First-line Atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. *N Engl J Med* 2018;379:2220–9. https://doi.org/10.1056/NEJMoa1809064.
20. Seto T, Kato T, Nishio M. et al. Erlotinib alone or with bevacizumab as first-line therapy in patients with advanced non-squamous non-small-cell lung cancer harbouring EGFR mutations(JO25567): an open-label, randomised, multicentre, phase 2 study. *Lancet Oncol* 2014;15:1236–44. https://doi.org/10.1016/S1470-2045(14)70381-X.
21. Nakagawa K, Garon EB, Seto T. et al. Ramucirumab plus erlotinib in patients with untreated, EGFR-mutated, advanced non-small-cell lung cancer(RELAY): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2014;15:1236–44. https://doi.org/10.1016/S1470-2045(14)70381-X.
22. Nomura S, Goto Y, Mizutani T. et al. A randomized phase III study comparing continuation and discontinuation of PD-1 pathway inhibitors for patients with advanced non-small-cell lung cancer (JCOG1701, SAVE study). *Jpn J Clin Oncol* 2020;50:821–5. https://doi.org/10.1093/jjco/hyaa054.
23. Yamada K, Aono H, Hosomi Y. et al. A prospective, multicentre phase II trial of low-dose erlotinib in non-small cell lung cancer patients with EGFR mutations pretreated with chemotherapy: thoracic oncology research group 0911. *Eur J Cancer* 2015;51:1904–10. https://doi.org/10.1016/j.ejca.2015.06.120.
24. Miyamoto S, Azuma K, Ishii H. et al. Low-dose Erlotinib treatment in elderly or frail patients with EGFR mutation-positive non-small cell lung cancer: a Multicenter phase 2 trial. *JAMA Oncol* 2020;6:e201250. https://doi.org/10.1001/jamaoncol.2020.1250.
25. Noro R, Igawa S, Bessho A. et al. A prospective, phase II trial of monotherapy with low-dose afatinib for patients with EGFR, mutation-positive, non-small cell lung cancer: thoracic oncology research group 1632. *Lung Cancer* 2021;161:49–54. https://doi.org/10.1016/j.lungcan.2021.08.007.
26. Tsukita Y, Taguri M, Goto Y. et al. Multi-institutional study of osimertinib dose-optimization in non-small cell lung cancer patients with EGFR activating mutation aged 70 years or older ('MONEY' trial). *Jpn J Clin Oncol* 2024;54:730–4. https://doi.org/10.1093/jjco/hyae032.
27. Spencer A, Rivero-Arias O, Wong R. et al. The QALY at 50: one story many voices. *Soc Sci Med* 2022;296:114653. https://doi.org/10.1016/j.socscimed.2021.114653.
28. Ariyasu R, Kakuto S, Miyadera K. et al. Real-world outcome analysis of patients with stage IV NSCLC treated with tyrosine kinase and immune checkpoint inhibitors. *JTO Clin Res Rep* 2023;4:100524. https://doi.org/10.1016/j.jtocrr.2023.100524.
29. Yang YT, Socal M, Bennett CL. Addressing the drug-shortage crisis in oncology. *JAMA Oncol* 2024;10:155–6. https://doi.org/10.1001/jamaoncol.2023.5722.
30. Hantel A, Spence R, Camacho P. et al. ASCO ethical guidance for the practical management of oncology drug shortages. *J Clin Oncol* 2024;42:358–65. https://doi.org/10.1200/JCO.23.01941.
31. Jenei K, Lythgoe MP, Vokinger KN. Shortages of essential cancer medicines: who is responsible and what are the possible solutions? *Lancet Oncol* 2024;25:23–6. https://doi.org/10.1016/S1470-2045(23)00470-9.
32. Hirsch I, Goldstein DA, Tannock IF. et al. Optimizing the dose and schedule of immune checkpoint inhibitors in cancer to allow global access. *Nat Med* 2022;28:2236–7. https://doi.org/10.1038/s41591-022-02029-1.

JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2024, 1–7
https://doi.org/10.1093/jjco/hyae109
Original Article

OXFORD

Original Article

Status of incremental costs of first-line treatment recommended in Japanese clinical guidelines for metastatic breast cancer patients

Tsuguo Iwatani[1,*], Keita Sasaki[2], Ryunosuke Machida[2], Tadahiko Shien[1], Fumikata Hara[3], Tomomi Fujisawa[4], Yuko Takano[5], Yoshie Kobayashi[6], Michiyo Saimura[7], Kei Koizumi[8], Mitsuo Terada[9], Shinsuke Sasada[10], Kanako Saito[11], Miwa Sumiyoshi[12] and Hiroji Iwata[13]

[1]Department of Breast and Endocrine Surgery, Okayama University Hospital, Okayama, Japan, [2]Japan Clinical Oncology Group Data Center/Operations Office, National Cancer Center Hospital, Tokyo, Japan, [3]Department of Breast Oncology, Aichi Cancer Center, Nagoya, Japan, [4]Department of Breast Oncology, Gunma Prefectural Cancer Center, Gunma, Japan, [5]Department of Clinical Oncology and Chemotherapy, Nagoya University Hospital, Nagoya, Japan, [6]Department of Breast Oncology, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, Kure, Japan, [7]Department of Surgery, Kitakyushu Municipal Medical Center, Kitakyushu, Japan, [8]Department of Surgery 1, Divisions of Breast Surgery, Hamamatsu Medical University School of Medicine, Hamamatsu, Japan, [9]Department of Breast Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan, [10]Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan, [11]Department of Medical Oncology, Mie University Hospital, Mie, Japan, [12]Department of Breast Surgery, Hiroshima City Hiroshima Citizens Hospital, Hiroshima, Japan and [13]Department of Medical Research and Developmental Strategy, Nagoya City University, Graduate School of Medical Sciences, Nagoya, Japan

*For reprints and all correspondence: Department of Breast and Endocrine Surgery, Okayama University Hospital, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558 Japan. E-mail: tiwatani@okayama-u.ac.jp

Received 19 June 2024; Editorial Decision 30 July 2024; Accepted 7 August 2024

Abstract

Background: The increasing incidence and prevalence of breast cancer alongside diagnostic and treatment technology advances have produced a debate about the financial burden cancer places on the healthcare system and concerns about access.

Methods: This study was conducted at 51 hospitals belonging to the Breast Cancer Study Group of the Japan Clinical Oncology Group using a web-based survey. The survey period conducted from July 2021 to June 2022. The study population included patients with metastatic breast cancer who received the related treatment as their first-line therapy. The proportion of patients who selected that regimen as their first-line treatment was tabulated. The total cost increase for each current standard therapy in comparison to conventional treatments was calculated.

Results: A total of 702 patients (pts) were surveyed. Of those enrolled, 342 (48.7%) received high-cost treatment [estimated monthly drug costs exceeding ~500 000 Japanese Yen (JPY)]. Of these, 16 pts (4.7%) were receiving very high-cost treatment, amounting to more than 1 000 000 JPY per month. Fifty three (15.5%) of the patients who received high-cost treatment were 75 years of age or older. Of these, 1 pt (0.3%) were receiving very high-cost treatment. Analyses of incremental costs by current drugs showed that abemaciclib was costly with total additional cost of 6 365 670 JPY per patient. The total additional cost of the regimen per patient that included palbociclib was the second highest at 4011248 JPY, followed by atezolizumab at 3209033 JPY.

Conclusions: The findings indicate that evaluating the financial implications of high-cost treatments requires considering not only drug prices but also analysis of total cost increase.

Key words: breast cancer, cost, incremental cost, guideline

Background

Breast cancer is the second most commonly diagnosed cancer worldwide and one of the leading causes of cancer-related mortality. In 2022, more than 2.2 million individuals worldwide were diagnosed with breast cancer, and more than 666 000 patients died (1). In Japan, more than 90 000 patients were diagnosed with cancer in 2022, with more than 17 000 deaths (2). Cancer's increasing incidence and prevalence, as well as diagnostic and treatment technology advances, have prompted a public debate about the financial burden cancer places on the healthcare system and concerns about access. New cancer drugs are expensive, and their prices are rising rapidly. For instance, in the USA in 2012, the average cost of treating a patient with a new cancer drug was ~US$89 000 per year (3). By 2016–17, this amount had nearly doubled to US$174 000 (4). One factor may be the 'individualization' of treatments, which refers to the use of a treatment only for a subpopulation of patients with characteristics that potentially predict that the treatment will be effective. If only a small proportion of the total number of patients has characteristics known to be necessary for therapeutic efficacy, the market size will necessarily be limited because only a small number of patients will receive treatment. Consequently, a higher cost per patient may be required to recoup the costs of drug development.

The cost of cancer care is a significant concern and challenge in countries with well-developed healthcare systems (5–11). For example, an analysis of healthcare spending in 27 European Union (EU) countries revealed that higher healthcare spending in Western than in Eastern European countries was associated with both higher cancer incidence and lower cancer mortality, particularly for breast cancer (12).

Similar to the EU countries, breast cancer statistics in Japan are characterized by high prevalence and low mortality rates (13). National healthcare expenditure in fiscal year (FY) 2019 was 44389.5 billion Japanese Yen (JPY), an increase of 994.6 billion JPY from the previous year. Regarding healthcare expenditures for medical treatment by injury and disease category, neoplasms (tumors) accounted for 4745.9 billion JPY (14.9%), following the cost of cardiovascular diseases. The healthcare cost for breast cancer amounted to 390.9 billion JPY, which was the third largest after lung and colorectal cancers. The healthcare cost for breast cancer was 254.6 billion JPY in 2009, and this figure increased by about 140 billion JPY during the 10 years to 2019 (14).

The Japanese healthcare system offers universal health coverage and a multi-payer system. The reimbursement prices for medicines were constant across Japan, although they changed over time. Because the public insurer pays the majority of medical costs, an increase in breast cancer medical costs will affect the Japanese healthcare system.

We therefore conducted a multicenter survey to ascertain the incremental cost of the first-line treatment recommended in the Japanese clinical guidelines for patients with metastatic breast cancer (MBC). The Japan Clinical Oncology Group (JCOG) Health Economics Committee oversaw this study.

Objectives

This study's objective was to examine the regimens used in Japan as first-line systemic treatment for MBC and to estimate the incremental treatment cost using each of these novel, high-cost regimens in comparison with traditional regimens, and to ascertain the current financial burden on public health expenditures associated with advances in breast cancer care.

Materials and methods

Data collection

This survey was conducted at 51 hospitals belonging to the Breast Cancer Study Group of the JCOG using a web-based survey. One representative from each hospital was asked to respond to the survey. The survey period spanned 1 year, from July 2021 to June 2022. The number of patients who received high-cost treatments during this period was also examined. The study population included patients with MBC who had receive treatment as their first-line therapy. The regimens were recommended in the Guidelines for Breast Cancer Treatment (edited by the Japanese Breast Cancer Society) (15). Regimens were established for each breast cancer subtype, including hormone receptor (HR) positive human epidermal growth factor receptor 2 negative (HR + HER2-), HER2-positive (HER2+), and triple-negative (TN). The study also included drugs for patients with pathogenic mutations in the BRCA1/2 gene.

In accordance with the aforementioned criteria, the following treatments were included in the analysis: nonsteroidal aromatase inhibitors (NSAI) in combination with cyclin-dependent kinase 4/6 inhibitors (CDKIs) (palbociclib and abemaciclib) for HR + HER2- breast cancer (16–22); and trastuzumab in combination with trastuzumab and docetaxel (Tmab+Pmab+DTX) for HER2+ breast cancer (23). The TN subtype adopted regimens that incorporate immune checkpoint inhibitors (ICIs) with four established regimens: nab-paclitaxel (nab-PTX) + atezolizumab, nab-PTX + pembrolizumab, PTX + pembrolizumab, and carboplatin (CBDCA) + gemcitabine (GEM) + pembrolizumab (24,25). Olaparib, a poly ADP-ribose polymerase inhibitor, was included as a regimen for patients with BRCA1/2 gene pathogenic variants (26).

Analytical methods

Medical expenditures were tabulated as monthly drug costs, excluding supportive medications, such as antiemetics and antiallergic medications. The proportion of patients who selected that regimen as their first-line treatment was tabulated, and differences in the proportion of patients who selected the high-cost regimen were examined using an age of 75 years as the cutoff.

Medical expenditures were based on the official drug prices in Japan as of 2023. The monthly drug costs were tabulated excluding supportive medications, such as antiemetics and antiallergic drugs. The regimens were categorized into very high-cost (≥1 000 000 JPY/month), high-cost (≥500 000 JPY/month), and other (< 500 000 JPY/month) treatments defined by the JCOG Health Economics Committee in this survey.

The proportion of patients who selected that regimen as their primary treatment was tabulated, and differences in the proportion of patients who selected the high-cost regimen were examined using an age of 75 years as the cutoff. We then tabulated the median course of administration from the literature on pivotal trials that provided the basis for regimen reimbursement (16–26). Subsequently, the total cost increase for each high-cost regimen as compared with the control arm of the pivotal trial (the conventional standard of care) was calculated, based on drug prices and incremental median progression-free interval (see below). For drugs administered on a per-body surface area basis, the dose was calculated based on the average physique of Japanese women, assuming a height of 160 cm and a weight of 60 kg (1.622 m^2).

Cost calculation

All costs associated with this survey are presented in terms of drug costs per month. First, for a treatment cycle of 28 days, the drug cost for this one cycle was calculated as the cost of the drug. For a treatment cycle of 21 days, the annual cost was calculated assuming 18 cycles of treatment per year, and this was divided by 12 to obtain the cost per month.

To ascertain the current financial burden on public health expenditures, incremental cost analysis was conducted. The incremental cost analysis was based on the drug cost per month calculated in this manner. The incremental cost per month was defined as the difference between the cost of the novel treatment regimen and the cost of the comparator. Finally, the clinical benefit [progression free survival (PFS) gained in months] of the novel treatment regimens derived from the clinical trial results was multiplied by the incremental cost per month to calculate total cost increase, assuming that the novel treatment was administered for the period of the median PFS.

Results

Responses were received from 30 of the 51 institutions (59%). A total of 702 patients (pts) were surveyed: HR + HER2- type, 405 patients; HER2+, 145 patients; TN type, 127 patients; and BRCA1/2+ type, 25 patients. Of all enrolled patients, 342 (48.7%) received high-cost treatment and 16 (4.7%) received very high-cost treatment. In this survey, nab-PTX+ atezolizumab was classified as very high-cost treatment. The most prevalent breast cancer subtype was the HR + HER2- type, accounting for 27.8% of all cases. The next most prevalent subtype was HER2+, which accounted for 12.3% of all cases. The TN type was the third most common, accounting for 7.1% of all cases, whereas the BRCA1/2+ type was the least prevalent, accounting for 1.6% of all cases. In a survey per breast cancer subtypes, the largest percentage of patients treated with high-cost treatment regimens were of the HER2+ type (59.3%), followed by the HR + HER2- type (48.1%), BRCA1/2+ type (44.0%), and TN type (39.3%) (Fig. 1 and Table 1).

An analysis of the implementation of high-cost treatment regimens by age revealed that 53 (15.5%) of the 342 patients who received high-cost treatment were 75 years of age or older (Table 2). Of 53 elderly patients who received high-cost therapy, 40 were treated with NSAI+CDKIs. Only two patients received regimens that included ICIs. Of these, 1 patient (0.3%) were receiving very high-cost treatment (≥1 000 000 JPY/month).

Table 3 presents the median extended PFS and associated incremental costs from the pivotal study for each treatment. The treatments with the highest incremental cost per month were regimens that ICIs: nab-PTX + atezolizumab, 1 180 586 JPY, nab-PTX + pembrolizumab, 932 682 JPY, CBDCA+GEM+pembrolizumab, 681 792, and JPY and PTX + pembrolizumab,. 669 126 JPY. Conversely, the lowest incremental cost per month was observed for CDKIs, at 481581 JPY for abemaciclib and 437 848 JPY for palbociclib.

A study on the incremental cost of the drug was conducted, assuming that treatment could be continued for the median duration of PFS based on clinical trial results. The results indicate that abemaciclib was the most costly with total additional cost of 6365670JPY per patient. Then, the incremental cost of palbociclib was 4 011 248 JPY. The incremental cost of the regimen that included atezolizumab was the third highest, at 3209033 JPY. Conversely, the lowest incremental cost administered for median PFS was olaparib, which was compared to eribulin mesylate, at 766368 JPY.

Discussion

The results of this survey provide a comprehensive overview of the status of first-line treatment regimens and associated costs for MBC based on the Japanese healthcare system. One regimen was identified as being matched to very high-cost regimens among recent first-line treatments. High-cost treatments, such as CDKIs, were used for a substantial number of patients, particularly those under 74 years of age.

The first discussion concerns the status of high-cost treatments for MBC patients in Japan. The lack of a clear definition of what constitutes high-cost treatment has led to defining it as a regimen with drug costs exceeding an average of 500 000 JPY per month (equivalent to 6 million JPY per year). Given that the average annual income per salaried employee working throughout the year was 4.58 million JPY according to the National Tax Agency's "Statistical Survey of Private Salaries for 2021," our definition is ∼1.31 times that amount (27). Accordingly, our survey revealed that 48.7% of patients selected the high-cost treatment recommended as the first-line treatment for MBC in the practice guidelines (Fig. 1 and Table 1). This outcome may be attributed to physicians selecting treatment options without being fully aware of the associated drug costs. This discrepancy in the perception of medical cost explanations was observed by Saeki et al. (28) in their study of financial toxicity in Japanese patients with breast cancer. It examined the extent to which physicians and patients explained the medical costs. Specifically, the study reported that physicians "explained medical costs to their patients," while a higher percentage of patients reported that "physicians did not explain medical costs to them." Consequently, we suggest that the cost of drugs be incorporated into practice guidelines to facilitate communication between healthcare providers and patients regarding the financial implications of drug therapies. Then, from the standpoint of regulating pharmaceutical expenditures, it would be advantageous to incorporate data regarding the accessibility and costs of generic drugs and biosimilars.

The second issue concerns the proportion of older patients receiving high-cost treatment. Elderly individuals frequently present with comorbidities, suggesting considerable interindividual variability in organ function, cognitive function, and social living environments. It is also crucial to evaluate life expectancy. Jolly et al. reported that 21% of elderly breast cancer patients died of causes other than breast cancer within 5 years (29). The proportion of elderly participants in clinical trials is relatively low. When treating elderly patients,

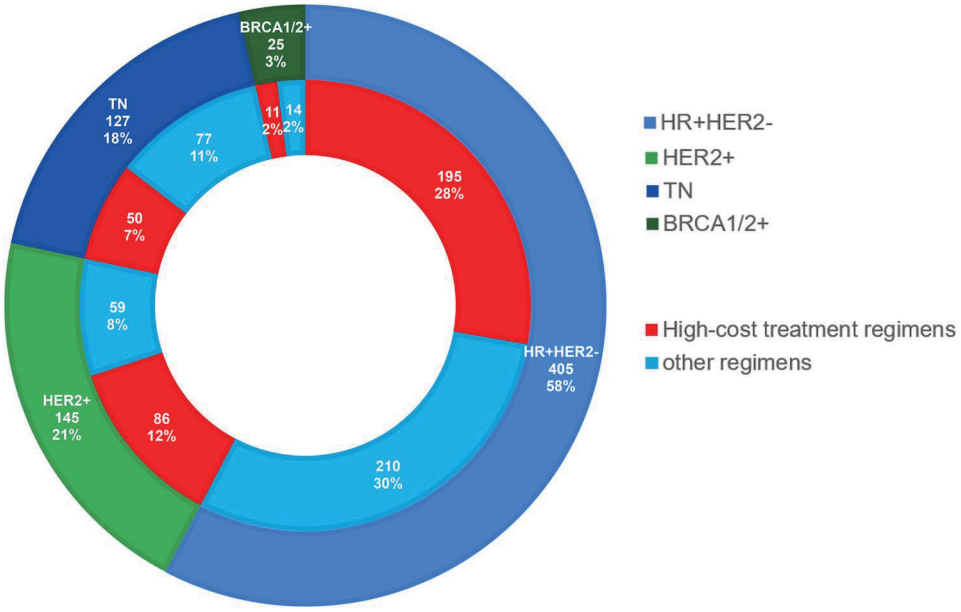


Figure 1. Proportion of high-cost regimens per subtype hormone receptor-positive HER2-negative (HR+HER2-), HER2-positive (HER2+), TN, and a pathogenic variant of the BRCA1/2 gene (BRCA1/2+).

Table 1. Status of application of regimens by breast cancer subtype

Subtype	First line treatment regimen	Number of patients by high-cost treatment
HR + HER2-	[a]NSAI+CDKIs	195 (27.8%)
	others	210 (29.9%)
HER2+	[a]Tmab+Pmab+DTX	86 (12.3%)
	others	59 (8.4%)
TN	[a]nab-PTX+ atezolizumab	16 (2.3%)
	[a]nab-PTX+ pembrolizumab	1 (0.1%)
	[a]PTX+ pembrolizumab	4 (0.6%)
	[a]CBDCA+ GEM+ pembrolizumab	29 (4.1%)
	others	77 (11.0%)
BRCA1/2+	[a]olaparib	11 (1.6%)
	others	14 (2.0%)
Total		702

Hormone receptor-positive HER2-negative (HR + HER2-), HER2-positive (HER2+), and TN, non-steroidal aromatase inhibitor (NSAI), CDKIs, trastuzumab + pertuzumab + docetaxel (Tmab+Pmab+DTX), nab-paclitaxel (nab-PTX), paclitaxel (PTX), carboplatin (CBDCA), gemcitabine (GEM), a pathogenic variant of the BRCA1/2 gene (BRCA1/2+).
[a]High-cost regimens.

physicians must meticulously ascertain the treatment indications and proactively manage adverse events at the outset based on a comprehensive geriatric assessment and effective comorbidity management, despite the limited evidence available.

In fact, we found that only 15.5% of the high-cost patients were older than 75 years. The most common high-cost treatment was for HR + HER2- type MBC, which accounted for 40 cases (11.7%). A report examining the age and frequency of adverse events for CDKIs for HR + HER2- type (30), Tmab+Pmab+DTX for HER2+ type (31), and ICIs for TN type (32) revealed an increased frequency of adverse events in the elderly for all regimens. The reasons why clinicians avoid high-cost treatment for the elder patients are thought to be complex, but the high incidence of adverse events in this demographic may be a contributing factor.

The final issues for consideration are the drug price and the incremental cost of obtaining the clinical benefit identified in the clinical study. Our study revealed that the drug with the highest incremental cost per month was atezolizumab. This was followed by regimens containing pembrolizumab. The rationale for this might attributed to the high drug price, despite the transient efficacy of ICIs, which ranged from 2.5 to 4.1 months. Then, as demonstrated in Table 3, in examining drug price and clinical efficacy, the greatest incremental cost in achieving clinical efficacy was not for atezolizumab, which has the highest drug cost, but for abemaciclib, a CDKIs. The next most significant incremental cost was pembrolizumab, followed by palbociclib and atezolizumab. These results show that when a high-cost treatment is introduced, the healthcare provider focuses on the drug price; however, we need to consider the incremental cost, including

Table 2. Status of high-cost treatment indications for elderly patients

Subtype	First line treatment regimen	Number of <75 years old patients using high-cost treatment	Number of ≥75 years old patients using high-cost treatment	Number of patients by high-cost treatment
HR + HER2-	NSAI+CDKIs	155 (45.3%)	40 (11.7%)	195 (57.0%)
HER2+	Tmab+Pmab+DTX	75 (21.9%)	11 (3.2%)	86 (25.1%)
TN	nab-PTX+ atezolizumab	15 (4.4%)	1 (0.3%)	16 (4.7%)
	nab-PTX+ pembrolizumab	1 (0.3%)	0	1 (0.3%)
	PTX+ pembrolizumab	4 (1.2%)	0	4 (1.2%)
	CBDCA+ GEM+ pembrolizumab	28 (8.2%)	1 (0.3%)	29 (8.5%)
BRCA1/2+	olaparib	11 (3.2%)	0	11 (3.2%)
Total		289 (84.5%)	53 (15.5%)	342

hormone receptor-positive HER2-negative (HR + HER2-), HER2-positive (HER2+), and TN, NSAI, CDKIs, trastuzumab + pertuzumab + docetaxel (Tmab+Pmab+DTX), nab-paclitaxel (nab-PTX), paclitaxel (PTX), carboplatin (CBDCA), gemcitabine (GEM), a pathogenic variant of the BRCA1/2 gene (BRCA1/2+).

Table 3. Analysis of the incremental costs required to obtain the benefits of pivotal trials

Subtype	Comparator	Cost of comparator/-month	Novel treatment regimen	Cost of novel treatment regimen/-month	Clinical benefit Median PFS	Incremental cost/month	Incremental cost administered for median PFS
HR+ HER2-	NSAI	6531JPY	NSAI+CDKIs (palbociclib)	437848JPY	9.3 months gained	431317JPY	4011248JPY
	NSAI	6531JPY	NSAI+CDKIs (Abemaciclib)	481581JPY	13.4 months gained	475050JPY	6365670JPY
HER2+	Tmab+DTX	159179JPY	Tmab+Pmab+DTX	486093JPY	6.3 months gained	326914JPY	2059558JPY
TN	nab-PTX	361485JPY	nab-PTX+ atezolizumab	1180586JPY	2.5 months gained	819101JPY	3209033JPY
	nab-PTX	361485JPY	nab-PTX+ pembrolizumab	932682JPY	4.1 months gained	571197JPY	2341908JPY
	PTX	25635JPY	PTX+ pembrolizumab,	669126JPY		643491JPY	2638313JPY
	CBDCA+GEM	38298JPY	CBDCA+ GEM+ pembrolizumab	681792JPY		643494JPY	2638325JPY
BRCA 1/2+	capecitabine	39720JPY	olaparib	574560JPY	2.8 months gained	534840JPY	1497552JPY
	eribulin mesylate	300857JPY				273703JPY	766368JPY
	vinorelbine	24042JPY				550518JPY	1541450JPY

HR, human epidermal growth factor receptor 2 (HER2), TN, a pathogenic variant of the BRCA1/2 gene (BRCA1/2+), NSAI, CDKIs, trastuzumab + pertuzumab + docetaxel (Tmab+Pmab+DTX), nab-paclitaxel (nab-PTX), paclitaxel (PTX), carboplatin (CBDCA), gemcitabine (GEM).

the length of the clinical benefit. Additionally, when evaluating the budget impact of high-cost drugs, it is crucial to consider the number of patients for whom the drugs are indicated. As shown in Tables 1 and 2, the regimens with the greatest number of patients treated at a high cost were those combining NSAI and CDKIs in patients with HR + HER2-type MBC. This indicates that CDKIs have the greatest financial burden impact on public health expenditures among breast cancer drugs because of their high incremental costs and the large number of patients for whom they are indicated. In addition, from a clinical standpoint, as Griggs et al. have asserted (33), the dearth of data directly comparing the efficacy and safety of multiple CDKI options renders it challenging for clinicians to select between them with any degree of certainty.

This study has several limitations. The first is the study's comprehensiveness. It was conducted exclusively at centers participating in the JCOG Breast Cancer Group. Consequently, this study does not represent all the breast cancer treatment centers in Japan. Given that individual data were not collected, the cost calculation was based on the assumption of a standard Japanese female patient with breast cancer. The survey period was short. Drug costs in Japan are subject to regular reviews, which may result in future fluctuations in estimated costs. Furthermore, the guidelines in the 2022 edition are subject to future updates, given the evolving nature of first-line treatment. It should be noted that, as the present study is not a cost-effectiveness analysis of treatment regimens, but rather a survey of the current situation, the results cannot be used as a basis for clinicians to

make decisions about which treatment regimen to choose in clinical practice.

Our study is the first to report on the current status of high-cost medical care recommended by practice guidelines for the first-line treatment of patients with MBC in Japan. It is imperative to continue our research efforts, because we anticipate the emergence of more innovative and costly pharmaceuticals for the treatment of breast cancer in the near future. For instance, with respect to the treatment strategy for CDKIs, which our research has demonstrated to be costly, it is advisable to encourage clinical research such as the SONIA trial (34), which seeks to optimize the treatment strategy for CDKIs.

Acknowledgements

The authors would like to express their gratitude to the members of the JCOG Data Center and JCOG Operations Office for their support, and following researchers who participated in the study and provided data: Dr Kazuya Miyoshi (National Hospital Organization Fukuyama Medical Center), Dr Noriko Maeda (Yamaguchi University Hospital), Dr Akira Matsui (National Hospital Organization Tokyo Medical Center), Dr Minoru Miyashita (Tohoku University Hospital), Dr Mariko Kikuchi (Kitasato University Hospital), Dr Mai Okazaki (University of Tsukuba Hospital), Dr Michiko Tsuneizumi (Shizuoka General Hospital), Dr Shin Ogita (St. Luke's International Hospital), Dr Mikiko Kasahara (Kansai Medical University Hospital), Dr Satomi Watanabe (Kindai University Hospital), Dr Sayuri Watanabe (National Hospital Organization Nagoya Medical Center), Dr Yumiko Koi (National Hospital Organization Kyushu Cancer Center), Dr Masakazu Kagawa (Yao Municipal Hospital), Dr Miyuki Kitahara (Ibaraki Prefectural Central Hospital, Ibaraki Cancer Center), Prof. Takashi Hojo (Saitama Medical Center, Saitama Medical University), Dr Hikaru Nakagami (Aichi Cancer Center), Dr Emi Tokuda (Fukushima Medical University), Dr Hiroyuki Yasojima (National Hospital Organization Osaka National Hospital), and Dr Mina Takahashi (National Hospital Organization Shikoku Cancer Center).

Conflict of interest

Tsuguo Iwatani received honoraria from Eisai outside of the submitted work. Tadahiko Shien received honoraria from Daiichi-Sankyo, Chugai, Eli Lilly, MSD, Eisai, Kyowa-Kirin, AstraZeneca, Gilliad, and Pfizer outside of the submitted work. Fumikata Hara received honoraria from Daiichi-Sankyo, Chugai, Eli Lilly, MSD, Kyowa-Kirin, and Pfizer outside of the submitted work. Kei Koizumi received honoraria from Chugai and Pfizer outside of the submitted work. Kanako Saito received honoraria from Daiichi-Sankyo, Chugai, Eli Lilly, MSD, Eisai, Kyowa-Kirin, AstraZeneca, and Pfizer outside of the submitted work. Hiroji Iwata received grants from Chugai, Daiichi Sankyo, AstraZeneca; consulting fees from Daiichi Sankyo, Chugai, AstraZeneca, Eli Lilly, MSD, Pfizer, Giliead; and honoraria from Daiichi Sankyo, Chugai, AstraZeneca, Eli Lilly, MSD, Pfizer, Taiho, Kyowa Kirin outside of the submitted work.

Funding

This work was supported by the Research Fund of the National Federation of Health Insurance Societies and, in part, by the National Cancer Center Research and Development Funds (2023-J-03).

References

1. World Health Organization. *GLOBOCAN breast fact sheet 2022*. International Agency for Research on Cancer. World Health Organization. Lyon, France. https://gco.iarc.who.int/media/globocan/factsheets/cancers/20-breast-fact-sheet.pdf (March 2024, date last accessed).
2. World Health Organization. *GLOBOCAN Japan fact sheet 2022*. International Agency for Research on Cancer. World Health Organization. Lyon, France. https://gco.iarc.who.int/media/globocan/factsheets/populations/392-japan-fact-sheet.pdf (March 2024, date last accessed).
3. Siddiqui M, Rajkumar SV. The high cost of cancer drugs and what we can do about it. *Mayo Clin Proc* 2012;87:935–43. https://doi.org/10.1016/j.mayocp.2012.07.007.
4. Carrera PM, Kantarjian HM, Blinder VS. The financial burden and distress of patients with cancer: understanding and stepping-up action on the financial toxicity of cancer treatment. *CA Cancer J Clin* 2018;68:153–65. https://doi.org/10.3322/caac.21443.
5. Singleterry J. *The costs of cancer. Addressing patient costs 2017. American Cancer Society cancer action network*. American Cancer Society. Washington, DC, USA. https://www.acscan.org/sites/default/files/Costs of Cancer - FinaFWeb.pdf. (March 2024, date last accessed).
6. Bullock AJ, Hofstatter EW, Yushak ML, Buss MK. Understanding patients' attitudes toward communication about the cost of cancer care. *J Oncol Pract* 2012;8:e50–8. https://doi.org/10.1200/JOP.2011.000418.
7. Bestvina CM, Zullig LL, Yousuf ZS. The implications of out-of-pocket cost of cancer treatment in the USA: a critical appraisal of the literature. *Future Oncol* 2014;10:2189–99. https://doi.org/10.2217/fon.14.130.
8. Shih YT, Xu Y, Liu L, et al. Rising prices of targeted oral anticancer medications and associated financial burden on medicare beneficiaries. *J Clin Oncol* 2017;35:2482–9. https://doi.org/10.1200/JCO.2017.72.3742.
9. Hunter WG, Zafar SY, Hesson A, et al. Discussing health care expenses in the oncology clinic: analysis of cost conversations in outpatient encounters. *J Oncol Pract* 2017;13:e944–56. https://doi.org/10.1200/JOP.2017.022855.
10. Kaisaeng N, Harpe SE, Carroll NV. Out-of-pocket costs and oral cancer medication discontinuation in the elderly. *J Manag Care Spec Pharm* 2014;20:669–75. https://doi.org/10.18553/jmcp.2014.20.7.669.
11. Doshi JA, Li P, Huo H, Pettit AR, Armstrong KA. Association of patient out-of-pocket costs with prescription abandonment and delay in fills of novel oral anticancer agents. *J Clin Oncol* 2018;36:476–82. https://doi.org/10.1200/JCO.2017.74.5091.
12. Ades F, Senterre C, de Azambuja E, et al. Discrepancies in cancer incidence and mortality and its relationship to health expenditure in the 27 European Union member states. *Ann Oncol* 2013;24:2897–902. https://doi.org/10.1093/annonc/mdt352.
13. *Statistical information by cancer type; breast*. https://ganjoho.jp/reg_stat/statistics/stat/cancer/14_breast.html (March 2024, date last accessed).
14. *Portal site for Japanese government statistics*. https://www.e-stat.go.jp/stat-search/files?page=1&layout=datalist&toukei=00450032&tstat=000001020931&cycle=8&tclass1=000001210900&tclass2=000001210901&stat_infid=000040112149&tclass3val=0 (March 2024, date last accessed).
15. *Breast Cancer Clinical Practice Guidelines edited by the Japanese Breast Cancer Society*. https://jbcs.xsrv.jp/guideline/2022/y_index/ (March 2024, date last accessed).
16. Finn RS, Martin M, Rugo HS, et al. Palbociclib and letrozole in advanced breast cancer. *N Engl J Med* 2016;375:1925–36. https://doi.org/10.1056/NEJMoa1607303.
17. Rugo HS, Finn RS, Diéras V, et al. Palbociclib plus letrozole as first-line therapy in estrogen receptor-positive/human epidermal growth factor receptor 2-negative advanced breast cancer with extended follow-up. *Breast Cancer Res Treat* 2019;174:719–29. [Epub 2019 Jan 10]. https://doi.org/10.1007/s10549-018-05125-4.
18. Slamon DJ, Diéras V, Rugo HS, et al. Overall survival with palbociclib plus letrozole in advanced breast cancer. *J Clin Oncol* 2024;42:994–1000. [Epub 2024 Jan 22]. https://doi.org/10.1200/JCO.23.00137.
19. Goetz MP, Toi M, Campone M, et al. MONARCH 3: Abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol* 2017;35:3638–46. [Epub 2017 Oct 2]. https://doi.org/10.1200/JCO.2017.75.6155.
20. Johnston S, Martin M, Di Leo A, et al. MONARCH 3 final PFS: a randomized study of abemaciclib as initial therapy for advanced breast cancer. *NPJ Breast Cancer* 2019;5:5. 10.1038/s41523-018-0097-z.
21. Johnston S, O'Shaughnessy J, Martin M, et al. Abemaciclib as initial therapy for advanced breast cancer: MONARCH 3 updated results in

prognostic subgroups. *NPJ Breast Cancer* 2021;7:80. https://doi.org/10.1038/s41523-021-00289-7.

22. Goetz MP, Toi M, Huober J., Sohn JH, Trédan O, Park I, Campone M, Chen SC, Manso LM, Paluch-Shimon S, Freedman OC, Andre V, Saha A, van Hal G, Shahir A, Iwata H, Johnston SRD, O'Shaughnessy J, Pivot X, Tolaney S, Hurvitz S, Llombart A GS01-12: MONARCH 3: final overall survival results of abemaciclib plus a nonsteroidal aromatase inhibitor as first-line therapy for HR+. *HER2- advanced breast cancer.* Cancer Res. San Antonio, TX, 2024, 84:GS01-12. https://doi.org/10.1158/1538-7445.SABCS23-GS01-12.
23. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med* 2015;372:724–34. https://doi.org/10.1056/NEJMoa1413513.
24. Emens LA, Adams S, Barrios CH, et al. First-line atezolizumab plus nab-paclitaxel for unresectable, locally advanced, or metastatic triple-negative breast cancer: IMpassion130 final overall survival analysis. *Ann Oncol* 2021;32:983–93. [Epub 2021 Jul 1]. Erratum in: Oncol A. 2021 Aug 2. Erratum. In: Ann Oncol 1650;32:2021 Dec. 10.1016/j.annonc.2021.05.355.
25. Cortes J, Cescon DW, Rugo HS, et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. *Lancet* 2020;396:1817–28. https://doi.org/10.1016/S0140-6736(20)32531-9.
26. Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. *N Engl J Med* 2017;377:523–33. [Epub 2017 Jun 4]. Erratum in: N Engl J Med 2017;377:523–33. 10.1056/NEJMoa1706450.
27. National Survey of Private Salaries. https://www.nta.go.jp/publication/statistics/kokuzeicho/minkan/top.htm (March 2024, date last accessed).
28. Saeki S, Iwatani T, Kitano A, et al. Society. Factors associated with financial toxicity in patients with breast cancer in Japan: a comparison of patient and physician perspectives. *Breast Cancer* 2023;30:820–30. [Epub 2023 Jun 13]. Erratum in: Breast cancer 2023 Jul 3;: PMID: 37310584. https://doi.org/10.1007/s12282-023-01476-z.
29. Jolly T, Williams GR, Jones E, Muss HB. Treatment of metastatic breast cancer in women aged 65 years and older. *Womens Health (Lond)* 2012;8:455–71. quiz 470–1. https://doi.org/10.2217/WHE.12.18.
30. Howie LJ, Singh H, Bloomquist E, et al. Outcomes of older women with hormone receptor-positive, human epidermal growth factor receptor-negative metastatic breast cancer treated with a CDK4/6 inhibitor and an aromatase inhibitor: an FDA pooled analysis. *J Clin Oncol* 2019;37:3475–83. [Epub 2019 Sep 27]. https://doi.org/10.1200/JCO.18.02217.
31. Miles D, Baselga J, Amadori D, et al. Treatment of older patients with HER2-positive metastatic breast cancer with pertuzumab, trastuzumab, and docetaxel: subgroup analyses from a randomized, double-blind, placebo-controlled phase III trial (Cleopatra). *Breast Cancer Res Treat* 2013;142:89–99. [Epub 2013 Oct 16]. https://doi.org/10.1007/s10549-013-2710-z.
32. Schmid P, Rugo HS, Adams S, et al. Atezolizumab plus nab-paclitaxel as first-line treatment for unresectable, locally advanced or metastatic triple-negative breast cancer (IMpassion130): updated efficacy results from a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2020;21:44–59. [Epub 2019 Nov 27]. https://doi.org/10.1016/S1470-2045(19)30689-8.
33. Griggs JJ, Wolf AC. Cyclin-dependent kinase 4/6 inhibitors in the treatment of breast cancer: more breakthroughs and an embarrassment of riches. *JCO* 2017;35:2857–9. https://doi.org/10.1200/JCO.2017.73.9375.
34. Sonke GS, van Ommen - Nijhof A, Wortelboer N, et al. Primary outcome analysis of the phase 3 SONIA trial (BOOG 2017-03) on selecting the optimal position of cyclin-dependent kinases 4 and 6 (CDK4/6) inhibitors for patients with hormone receptor-positive (HR+), HER2-negative (HER2-) advanced breast cancer (ABC). *J Clin Oncol* 2023;41: LBA1000-LBA1000. https://doi.org/10.1200/JCO.2023.41.17_suppl.LBA1000.

JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2024, 1–7
https://doi.org/10.1093/jjco/hyae104
Original Article

OXFORD

Original Article

A real-world survey on expensive drugs used as first-line chemotherapy in patients with HER2-negative unresectable advanced/recurrent gastric cancer in the stomach cancer study group of the Japan clinical oncology group

Tomohiro Nishina[1,*], Narikazu Boku[2], Yukinori Kurokawa[3], Keita Sasaki[4], Ryunosuke Machida[4] and Takaki Yoshikawa[5]

[1]Department of Gastrointestinal Medical Oncology, NHO Shikoku Cancer Center, Ehime, Japan, [2]Department of Oncology and General Medicine, IMSUT Hospital, Institute of Medical Science, University of Tokyo, Tokyo, Japan, [3]Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, Osaka, Japan, [4]Japan Clinical Oncology Group Data Center/Operations Office, National Cancer Center Hospital, Tokyo, Japan and [5]Department of Gastric Surgery, National Cancer Center Hospital, Tokyo, Japan

*For reprints and all correspondence: Department of Gastrointestinal Medical Oncology, National Hospital Organization Shikoku Cancer Center, 160 Kou, Minamiumemoto-machi, Matsuyama, Ehime 791-0280, Japan.
E-mail: nishina.tomohiro.nj@mail.hosp.go.jp

Received 17 April 2024; Editorial Decision 25 July 2024; Accepted 8 August 2024

Abstract

Background: Molecular-targeted drugs and immune checkpoint inhibitors have been developed for various malignant diseases, thereby improving clinical outcomes. However, these drugs are expensive, and few studies have assessed their actual use and costs in Japan. This study aimed to survey the use and costs of first-line chemotherapy for advanced/recurrent gastric cancer (AGC) in real-world settings.

Methods: The survey included patients with human epidermal growth factor receptor type2 (HER2)-negative AGC who initiated first-line chemotherapy from January 2022 to December 2022 at the participating 92 institutions in the Japan Clinical Oncology Group. Data on the regimens were collected using Google Forms. A regimen that costs >500 000 Japanese yen (JPY) per month was defined as expensive.

Results: Data on chemotherapy regimens were collected from 2173 patients at all 92 institutions between March 2023 and May 2023. We analyzed 2113 patients who underwent the chemotherapy with recommended regimens and conditionally recommended regimens according to the Japanese Gastric Cancer Treatment Guidelines sixth edition. The expensive regimens were triplet chemotherapy with fluoropyrimidine (S-1 or capecitabine or 5-fluorouracil/levofolinate), oxaliplatin, and nivolumab. Their monthly costs ranged from 767 648 to 771 046 JPY. Nivolumab-containing regimens cost more than 20 times the price of conventional chemotherapy with fluoropyrimidine and oxaliplatin. These regimens were used in 1416 (67%) of 2113 patients: in 71% of patients aged ≤74 years and in 59% of patients aged ≥75 years.

Conclusion: The regimens with >20-fold cost of conventional chemotherapy were used as first-line chemotherapy in two-thirds of patients and more than half even in the elderly population with

HER2-negative AGC. This finding is important for future health economic studies on drug cost-efficacy.

Key words: gastric cancer, real-world survey, chemotherapy, nivolumab, cost

Introduction

Gastric cancer is a relevant global health issue, with a high burden in Eastern Asia, Eastern Europe, and South America. It is the fifth most common cancer worldwide and the third leading cause of cancer-related mortality (1).

The prognosis of unresectable advanced/recurrent gastric cancer (AGC) is generally poor. The median survival time of patients who did not receive chemotherapy was reported as 3–5 months (2,3). Since a couple of randomized, controlled trials confirmed survival benefits of systemic chemotherapy compared with the best supportive care (2,3), systemic chemotherapy should be primarily considered for patients with AGC.

In the Japanese Gastric Cancer Treatment Guidelines sixth edition (4), first-line chemotherapy is categorized into the recommended regimens that are the standard of care, and the conditionally recommended regimens that are the options for patients unfit for the standard treatment due to various reasons in routine clinical practice.

In terms of first-line chemotherapy for human epidermal growth factor receptor type2 (HER2)-negative AGC (~80% of AGC cases), various combinations of fluoropyrimidine and platinum are recognized as recommended regimens based on the results of phase III studies (5–8). Several trials evaluated the addition of molecular-targeted agents, such as vascular endothelial growth factor inhibitors, epidermal growth factor receptor inhibitors, and mesenchymal–epithelial transition inhibitors to the combination of fluoropyrimidine and platinum-based agents. However, these combinations, except for vascular endothelial growth factor inhibitor, could not show survival benefits (9–11). Recently, the CheckMate 649 and ATTRACTION-4 trials have shown that the addition of nivolumab can prolong patient survival (12,13). Consequently, combinations of fluoropyrimidine and oxaliplatin plus nivolumab have become one of the recommended regimens by the Japanese Gastric Cancer Treatment Guidelines sixth edition (4).

Although nivolumab is effective against various types of cancers, it is expensive. The increased use of nivolumab in gastric cancer treatment may have a substantial impact not only on personal costs but also on healthcare budgets both at the national and institutional levels. However, in Japan, due to the universal health insurance system, medical professionals seldom pay attention to a high-medical cost. The issue of high-cost healthcare is widely recognized as a significant problem in high-income countries (14–16).

To ensure the sustainability of the health insurance system and from the perspective of improving the quality of medical care and enhancing patient quality of life, the appropriate use of expensive drugs in cancer treatment should be considered. However, a real-world survey on the actual usage of expensive treatments has not been sufficiently conducted. To collect and analyze the important fundamental data, the Japan Clinical Oncology Group (JCOG) Health Economics Committee conducted a survey on the use of expensive medical treatments for unresectable recurrent cancers, focusing on first-line chemotherapy. The current study aimed to discuss about the utilization of expensive drugs as first-line chemotherapy for AGC based on the results of the real-world survey.

Materials and methods

Target patients of the survey

The survey included patients who initially received first-line chemotherapy for HER2 negative AGC from January 2022 to December 2022 at the participating institutions in the JCOG Stomach Cancer Study Group. Patients who recurred at least 6 months after last administration of preoperative/postoperative adjuvant chemotherapy were eligible.

Targeted chemotherapy regimens in the survey

The chemotherapy regimens targeted by this survey were first-line chemotherapy for HER2-negative cancer categorized as recommended regimens and conditionally recommended regimens according to the Japanese Gastric Cancer Treatment Guidelines sixth edition (4). The recommended regimens were S-1 and cisplatin, S-1 and oxaliplatin (SOX), capecitabine and cisplatin (XP), capecitabine and oxaliplatin (CapeOX), and 5-FU/levofolinate calcium (LV) with oxaliplatin (FOLFOX), SOX plus nivolumab, CapeOX plus nivolumab, and FOLFOX plus nivolumab. The conditionally recommended regimens were 5-FU and cisplatin, 5-FU/LV, 5-FU/LV and paclitaxel, and S-1 and docetaxel. In addition to the specified regimens, the other regimens used in clinical practice were categorized as others. For the recommended and conditionally recommended chemotherapy, excluding the others, the patients were divided according to age ($\leq$74 vs. $\geq$75 years) at treatment initiation.

Survey methods

Data on first-line regimens used for each patient were collected from each institution using Google Forms. No personal patient data were collected. Thus, this study did not require individual consent or Institutional Review Board approval.

Calculation method for the regimen costs

The regimen costs were calculated assuming as a standard body type with height of 165 cm, weight of 60 kg, and body surface area of 1.66 m^2. For medications with generic alternatives, the drug with a lower price was used. The regimen costs were calculated based on the prices as of 1 February 2024. The monthly regimen costs were calculated as the cost for 4 weeks. For example, in a regimen where one cycle is given every 3 weeks, the cost for one cycle was multiplied by 4/3 to calculate it as the cost for 4 weeks.

Definition of expensive chemotherapy

The definitions of expensive chemotherapy were proposed by the JCOG Health Economics Committee. High-cost chemotherapy was

Table 1. Treatment regimens and costs

Regimen	One cycle	Drugs and dosage	Monthly cost
SOX + Nivolumab	3 wks	S-1: 120 mg/day, Days 1–14 Oxaliplatin: 130 mg/m^2, Day 1 Nivolumab: 240 mg, Day 1	771 046 JPY
CapeOX + Nivolumab	3 wks	Capecitabine: 2000 mg/m^2/day, Days 1–14 Oxaliplatin: 130 mg/m^2, Day 1 Nivolumab: 240 mg, Day 1	767 648 JPY
FOLFOX + Nivolumab	2 wks	5-Florouracil: 400 mg/m^2, Day 1 and 1200 mg/m^2, Days 1–2 Levofolinate: 200 mg/m^2, Day 1 Oxaliplatin: 85 mg/m^2, Day 1 Nivolumab: 240 mg, Day 1	770 392 JPY
SOX	3 wks	S-1: 120 mg/d, Days 1–14 Oxaliplatin: 130 mg/m^2, Day 1	35 199 JPY
CapeOX	3 wks	Capecitabine: 2000 mg/m^2/day, Days 1–14 Oxaliplatin: 130 mg/m^2, Day 1	31 799 JPY
FOLFOX	2 wks	5-Florouracil: 400 mg/m^2, Day 1 and 1200 mg/m^2, Days 1–2 Levofolinate: 200 mg/m^2, Day 1 Oxaliplatin: 85 mg/m^2, Day 1	37 582 JPY
S-1 + Cisplatin	5 wks	S-1: 120 mg/day, Days 1–21 Cisplatin: 60 mg/m^2, Day 8	19 766 JPY
Capecitabine + Cisplatin	3 wks	Capecitabine: 2000 mg/m^2/day, Days 1–14 Cisplatin: 80 mg/m^2, Day 1	25 353 JPY
5-FU + Cisplatin	4 wks	5-Fluorouracil: 800 mg/m^2, Days 1–5 Cisplatin: 80 mg/m^2, Day 1	14 472 JPY
5-FU/l-LV	6 wks	5-Florouracil: 600 mg/m^2, Days 1, 8, 15, and 22 Levofolinate: 250 mg/m^2, Days 1, 8, 15, and 22	21 758 JPY
5-FU/l-LV + Paclitaxel	4 wks	5-Florouracil: 600 mg/m^2, Days 1, 8, 15, and 22 Levofolinate: 250 mg/m^2, Days 1, 8, 15, and 22 Paclitaxel: 80 mg/m^2, Days 1, 8, 15, and 22	49 806 JPY
S-1	6 wks	S-1: 120 mg/day, Days 1–28	16 319 JPY
S-1 + Docetaxel	3 wks	S-1: 120 mg/day, Days 1–14 Docetaxel: 140 mg/m^2, Day 1	23 014 JPY

SOX, S-1 + oxaliplatin; CapeOX, capecitabine + oxaliplatin; FOLFOX, 5-FU/Levofolinate with oxaliplatin; 5-FU, 5-Fluorouracil; l-LV, Levofolinate; JPY, Japanese yen; wks, weeks.

defined as expensive if costing >500 000 Japanese yen (JPY) per month and ultra-expensive if costing >1 000 000 JPY per month.

Results

Status of the real-world survey

The survey was conducted between March 2023 and May 2023, and responses were obtained from all 92 institutions participating in the Stomach Cancer Study Group of the JCOG.

Regimen costs

Table 1 shows the list of medication costs for each regimen per month. None of the regimens were classified as ultra-expensive. The regimens considered expensive were the combinations of fluorouracil and oxaliplatin (SOX, CapeOX, or FOLFOX) plus nivolumab. Their cost ranged from 767 648 to 771 046 JPY per month. On the other hand, the cost of the conventional chemotherapy regimens (S-1 or capecitabine or 5-FU/LV and oxaliplatin) ranged from 31 799 to 37 182 JPY per month. Nivolumab-containing regimens cost more than 20 times the higher price of conventional chemotherapy.

Real-world survey results

The total number of patients surveyed was 2173. Sixty patients treated with the regimen other than those described in the treatment guideline were excluded from the analysis because the details of the regimen costs and patient's age were not obtained. We analyzed 2113 patients who underwent the chemotherapy with recommended regimens and conditionally recommended regimens according to the Japanese Gastric Cancer Treatment Guidelines sixth edition (4).

Figure 1 shows the details of the chemotherapy regimens of all patients and the proportion of patients receiving expensive regimens. Further, 1894 (90%) patients received fluoropyrimidine and oxaliplatin (SOX or CapeOX or FOLFOX)-based treatments. The nivolumab combination regimens were as follows: SOX plus nivolumab (n = 1014, 48%), CapeOX plus nivolumab (n = 114, 5%), and FOLFOX plus nivolumab (n = 288, 14%). Totally, 1416(67%) of 2113 patients received expensive regimens.

Figure 2 shows the details of the regimens according to age; 713(34%) of 2113 patients were aged ≥75 years. The proportions of patients receiving fluoropyrimidine and oxaliplatin (SOX or CapeOX or FOLFOX)-based chemotherapy were 93% in patients aged ≤74 years and 82% in those aged ≥75 years. The proportion of patients receiving expensive regimens in the ≤74-year-old age group

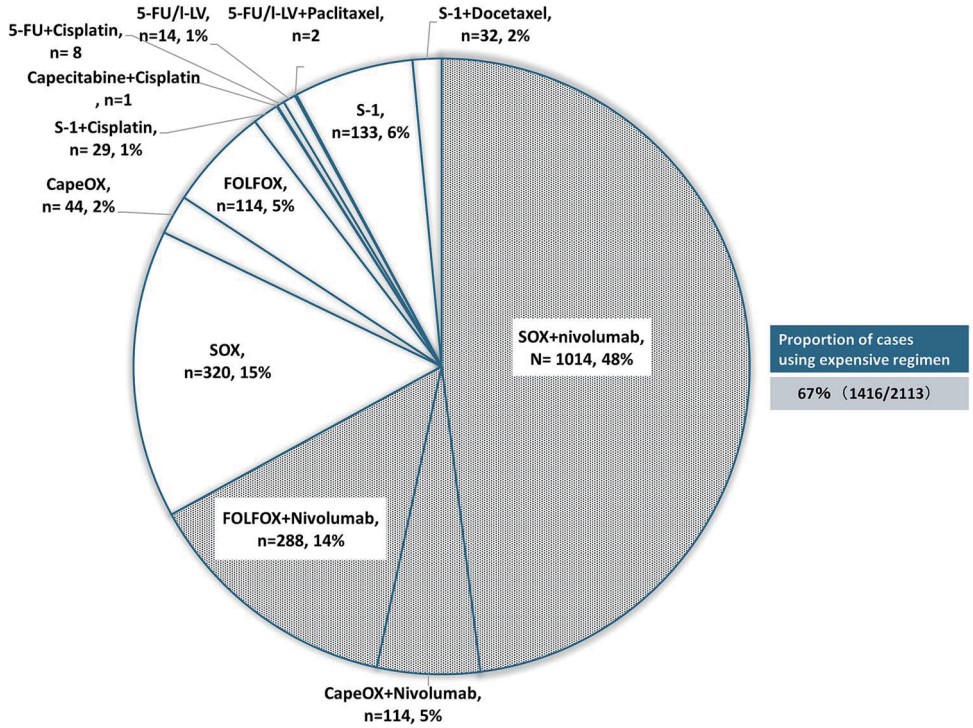


Figure 1. Chemotherapeutic regimens of all patients and the proportion of patients receiving expensive regimens. The gray shaded area of the graph represents expensive regimens. SOX, S-1 + oxaliplatin; CapeOX, capecitabine + oxaliplatin; FOLFOX, 5-fluorouracil/levofolinate with oxaliplatin; 5-FU, 5-fluorouracil; l-LV, levofolinate.

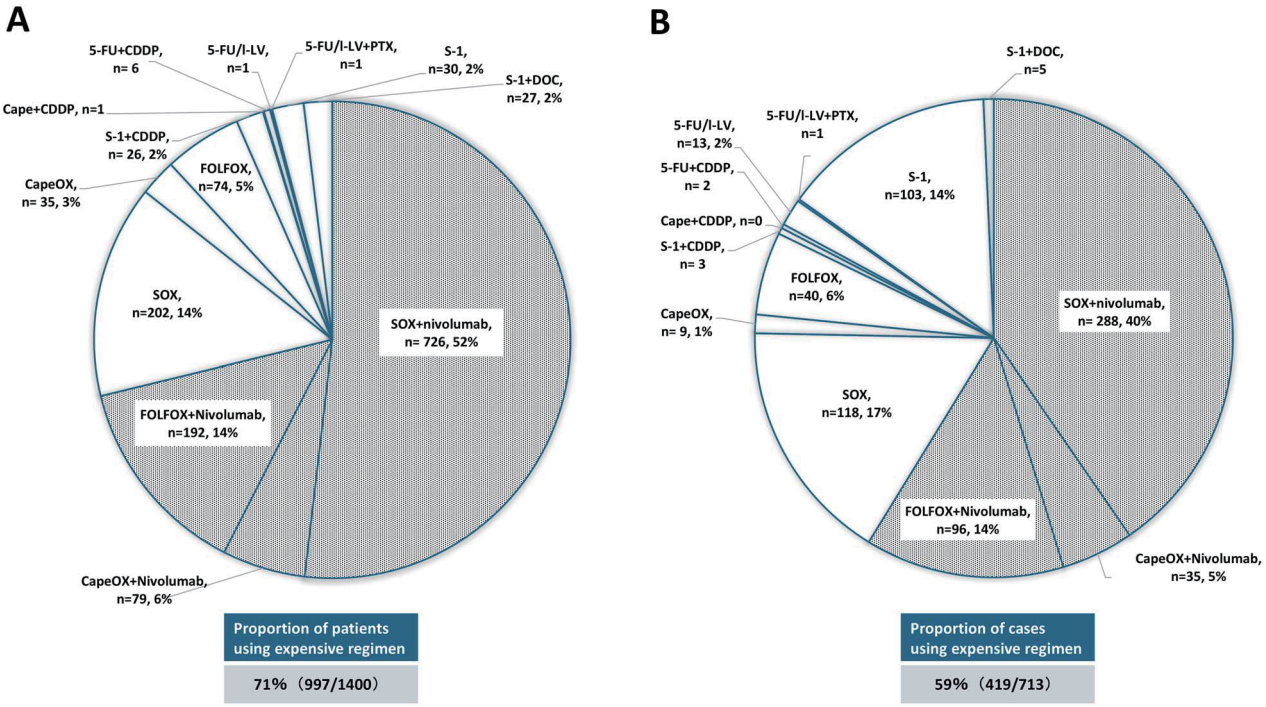


Figure 2. Subgroup data of the chemotherapeutic regimens of all patients and the proportion of patients receiving expensive regimens according to age: (A) ≤74 years old and (B) ≥75 years old. The gray shaded area of the graph represents expensive regimens. SOX, S-1 + oxaliplatin; CapeOX, capecitabine + oxaliplatin; FOLFOX, 5-fluorouracol/levofolinate with oxaliplatin; 5-FU, 5-fluorouracil; l-LV, levofolinate; cape, capecitabine; CDDP, cisplatin; DOC, docetaxel; PTX, paclitaxel.

was higher than that in the ≥75-year-old age group (71% vs. 59%; Fig. 2A and B).

Discussion

This real-world survey conducted by the Stomach Cancer Study Group of the JCOG evaluated the use of first-line chemotherapy for HER2-negative AGC. It was shown that 67% of patients received regimens with nivolumab, which were qualified as expensive treatments with monthly drug expenses exceeding 500 000 JPY. To the best of our knowledge, no real-world survey has assessed the use of expensive treatments as first-line chemotherapy for AGC.

Nivolumab has been clinically used in Japan since it was proven to prolong survival in patients with AGC receiving third- or later-line treatment compared with placebo based on the ATTRACTION-2 trial (17). In the CheckMate 649 trial, as first-line chemotherapy for HER2-negative AGC, the median overall survival was 13.8 months in the nivolumab plus chemotherapy group and 11.6 months in the chemotherapy alone group (hazard ratio 0.80; $P < .0002$). Based on these findings, a combination of nivolumab with the doublet chemotherapy is recommended as the first-line treatment for HER2 negative AGC patients in the treatment guidelines in December 2021 (4).

In subgroup analyses of programmed death ligand 1 (PD-L1) expression in the CheckMate 649 trial, the relationship of the combined positive scores with progression-free survival and OS was examined. Results showed that the hazard ratios for OS in patients with a combined positive score (CPS) of <5 and ≥5 were 0.94 and 0.70, respectively, indicating a limited additional survival benefit in patients with a CPS of <5. The ATTRACTION-4 trial showed a significant improvement in PFS, but not in OS (13). Thus, one of the reasons for no significant difference in the ATTRACTION-4 trial was considered to be that immune checkpoint inhibitors were used as the posttreatment in 27% of the placebo group, resulting in substantially longer OS of the placebo group compared with other trials. Based on these findings, the following comment has been made in the gastric cancer treatment guidelines (4), 'The survival benefit of adding nivolumab to chemotherapy in patients with a PD-L1 CPS of <5 has not been clearly elucidated. However, the risk–benefit balance of chemotherapy alone versus in combination with nivolumab should be considered based on the patient's condition. Consequently, either treatment can be selected according to the patient's informed consent'. The Japanese Gastric Cancer Treatment Guidelines state that there are no reviewed reports on the cost increase associated with the use of immune checkpoint inhibitors in first-line treatment for AGC, making it difficult to evaluate (4).

From the perspective of physicians, the combination proportion of nivolumab (67%) in the real-world setting is reasonable. This is because in first-line chemotherapy plus nivolumab for patients with PD-L1 CPS of ≥5, the 3-year survival proportions of those receiving nivolumab plus chemotherapy versus chemotherapy alone were 21% versus 10% reported in a 3-year follow-up in the CheckMate 649 trial (18). Although recent advances in chemotherapy for AGC prolonged survival, it is difficult to obtain a cure by chemotherapy alone. The current goals of palliative chemotherapy are not only to prolong survival but also to delay the manifestation of the disease-related symptoms. From this perspective, a regimen containing nivolumab, which provides an additive effect of ∼10% in response rate regardless of CPS status, is considered beneficial for patients, and there are no other effective combination therapies available for HER2-negative patients at the time of this survey.

At present, the official price of nivolumab (over ¥700 000/month) is at least 20 times higher than that of SOX (∼¥35 000/month). If SOX plus nivolumab were continued without dose reduction and interruption for 6.3 months, which is the median duration of nivolumab treatment in the ATTRACTION-4 trial, the median total costs would reach ∼¥4.85 million, and most of them (95%) are occupied with nivolumab costs. From the individual patient's point of view, the actual payment per month would be approximately from ¥8000 to ¥260 000 according to the personal income, when patients use the Japanese medical insurance system and the High-Cost Medical Expense Benefit system. Thus, thanks to these national medical insurance systems, most patients and physicians select the best first-line chemotherapy regimen recommended without a concern of medical cost pressure.

According to the payer's perspective in Japan, the cost-efficacy of nivolumab for AGC has been evaluated. Previous studies using data from ATTRACTION-4 and ATTRACTION-2 reported that the use of nivolumab as third- or later-line treatment is considered to be cost-effective, but its application in combination with chemotherapy as a first-line treatment is not cost-effective (19). Previous studies analyzing the CheckMate 649 data found that even in patients with a CPS of ≥5, the cost exceeded the cost-effectiveness threshold of USD 75 000–150 000/quality-adjusted life year in Japan. Therefore, it is not cost-effective (20). In patients with a CPS of <5, it is important to contemplate the cost–benefit and to select the use of nivolumab in patients that can have more effective results based on biomarkers.

According to the NCCN Guidelines for Older Adult Oncology, elderly patients are classified into fit, vulnerable, and unfit categories based on their life expectancy, decision-making ability, treatment goals, and risk of side effects (21). For fit patients who satisfy the eligibility criteria of clinical trials, a chemotherapy regimen similar to that for younger patients is recommended in the Japanese Gastric Cancer Treatment Guidelines (4). However, for vulnerable or unfit patients, high-level evidence is scarce. The diverse conditions of these patients make it challenging to establish clear recommendations (4). In this survey, the use of nivolumab in adults aged ≥75 years was lower than that in younger adults aged ≤74 years. This result is reasonable because some elderly patients may not be qualified for platinum-based agents. In the post-marketing survey of nivolumab monotherapy, the risk of treatment-related adverse events was higher in elderly patients, while the possibility of response was also higher (22). The incidence of immune-related adverse events increases with the use of nivolumab combination regimen as first-line treatment for AGC (12,13). However, there are no established biomarkers for efficacy and immune-related adverse events. Recently, a randomized phase II trial (WJOG8315G) targeting first-line treatment for patients aged 70 and older compared S-1 monotherapy with SOX. This study suggested that the comprehensive Geriatric Assessment (G8), which evaluates the overall health status of elderly patients, may be useful in selecting appropriate chemotherapy regimens (23). In the future, the utility of these assessment tools in treatment selection needs to be validated. Japan, with its rapidly aging population, faces several critical issues in providing healthcare for the elderly. The cost-efficacy perspective in determining the appropriateness of nivolumab combination regimens for elderly patients is still lacking. When assessing the financial impact of systemic treatments for AGC and deciding on a treatment plan, it is important to consider not just the efficacy and safety, but also the cost-effectiveness of the therapeutic options.

As for the cost reduction, there are two ongoing phase III trials that aim to confirm the non-inferiority comparing continuation versus cessation of immune-checkpoint inhibitors for patients with non-small cell lung cancer (24) and renal cell carcinoma (25). If treatment can be paused without compromising efficacy, this can potentially reduce treatment-related adverse events, improve patients' quality of life, and result in significant healthcare savings.

The current study had several limitations. First, the survey was conducted over a limited period (1 year) at JCOG-affiliated institutions. Second, individual patient data were not collected. Thus, the actual treatment duration and therapy discontinuation or dose reduction could not be considered. Third, the lack of PD-L1 (CPS) data did not confirm whether nivolumab was used in the appropriate population.

Conclusion

Sixty-seven percent of patients and more than half of the elderly population in Japan received expensive regimens as first-line chemotherapy for HER2-negative AGC. This information can be utilized in the planning of health economic studies that examine future cost-effectiveness from the perspective of physicians.

Acknowledgements

We would like to thank the members of the JCOG Stomach Cancer Group who cooperated with us in this survey of high-cost treatments.

Conflict of interest: T.N. received personal fees from Taiho, Chugai, Ono Pharmaceutical, Bristol Myers Squibb, Daiichi-Sankyo, Eli Lilly, Astellas and MSD, outside the submitted work.

N.B. reports personal fees Bristol Myers Squibb, Ono Pharmaceutical, Taiho Pharmaceutical, Eli Lilly, Daiichi-Sankyo, outside the submitted work. Y.K., R.M., and K.S. have no conflict of interest. T.Y. reports personal fees from Ono Pharmaceutical, Bristol Myers Squibb, MSD, Daiichi-Sankyo, Astellas, Taiho, and Chugai, outside the submitted work.

Funding

This work was supported in part by the Research Fund of National Federation of Health Insurance Societies (Kenpo-ren) and the National Cancer Center Research and Development Funds (2023-J-03).

References

1. Aaron PT, Theresa Nguyen W, Hashem BE. Global burden of gastric cancer: epidemiological trends, risk factors, screening and prevention. *Nat Rev Clin Oncol* 2023;20:338–49. https://doi.org/10.1038/s41571-023-00747-0.
2. Murad AM, Santiago FF, Petroianu A, Rocha PRS, Rodrigues MAG, Rausch M. Modified therapy with 5-fluorouracil, doxorubicin, and methotrexate in advanced gastric cancer. *Cancer* 1993;72:37–41. https://doi.org/10.1002/1097-0142(19930701)72:1<37::AID-CNCR2820720109>3.0.CO;2-P.
3. Glimelius B, Ekström K, Hoffman K, et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. *Ann Oncol* 1997;8:163–8. https://doi.org/10.1023/A:1008243606668.
4. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2021 (6th edition). *Gastric Cancer* 2023;26:1–25. https://doi.org/10.1007/s10120-022-01331-8.
5. Boku N, Yamamoto S, Shirao K, et al. Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. *Lancet Oncol* 2009;10:1063–9. https://doi.org/10.1016/S1470-2045(09)70259-1.
6. Koizumi W, Narahara H, Hara T, et al. S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. *Lancet Oncol* 2008;9:215–21. https://doi.org/10.1016/S1470-2045(08)70035-4.
7. Cunningham D, Starling N, Rao S, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med* 2008;358:36–46. https://doi.org/10.1056/NEJMoa073149.
8. Yamada Y, Higuchi K, Nishikawa K, et al. Phase III study comparing oxaliplatin plus S-1 with cisplatin plus S-1 in chemotherapy-naïve patients with advanced gastric cancer. *Ann Oncol* 2015;26:141–8. https://doi.org/10.1093/annonc/mdu472.
9. Yoon HH, Bendell JC, Braiteh FS, et al. Ramucirumab combined with FOLFOX as front-line therapy for advanced esophageal, gastroesophageal junction, or gastric adenocarcinoma: a randomized, double-blind, multicenter phase II trial. *Ann Oncol* 2016;27:2196–203. https://doi.org/10.1093/annonc/mdw423.
10. Lordick F, Kang YK, Chung HC, et al. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. *Lancet Oncol* 2013;14:490–9. https://doi.org/10.1016/S1470-2045(13)70102-5.
11. Shah MA, Bang YJ, Lordick F, et al. Effect of fluorouracil, leucovorin, and oxaliplatin with or without onartuzumab in HER2-negative, MET-positive gastroesophageal adenocarcinoma: the MET-gastric randomized clinical trial. *JAMA Oncol* 2017;3:620–7. https://doi.org/10.1001/jamaoncol.2016.5580.
12. Janjigian YY, Shitara K, Moehler M, et al. First-line nivolumab plus chemotherapy versus chemotherapy alone for advanced gastric, gastrooesophageal junction, and oesophageal adenocarcinoma (CheckMate 649): a randomised, open-label, phase 3 trial. *Lancet* 2021;398:27–40. https://doi.org/10.1016/S0140-6736(21)00797-2.
13. Kang YK, Chen LT, Ryu MH, et al. Nivolumab plus chemotherapy versus placebo plus chemotherapy in patients with HER2-negative, untreated, unresectable advanced or recurrent gastric or gastro-oesophageal junction cancer (ATTRACTION-4): a randomised, multicentre, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2022;23:234–47. https://doi.org/10.1016/S1470-2045(21)00692-6.
14. Thomas JS, Bruce EH. Bending the cost curve in cancer care. *New Engl J Med* 2011;364:2060–5. https://doi.org/10.1056/NEJMsb1013826.
15. Sullivan R, Peppercorn J, Sikora K, et al. Delivering affordable cancer care in high-income countries. *Lancet Oncol* 2011;12:933–80. https://doi.org/10.1016/S1470-2045(11)70141-3.
16. Leighl NB, Nirmalakumar S, Ezeife DA, Gyawali B. The rising cost of cancer drugs and impact on access. *Am Soc Clin Oncol Educ Book* 2021;41:1–12. https://doi.org/10.1200/EDBK_100028.
17. Kang YK, Boku N, Satoh T, et al. Nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2017;390:2461–71. https://doi.org/10.1016/S0140-6736(17)31827-5.
18. Janjigian YY, Ajani JA, Moehler M, et al. First-line nivolumab plus chemotherapy for advanced gastric, gastroesophageal junction, and esophageal adenocarcinoma: 3-year follow-up of the phase III CheckMate 649 trial. *J Clin Oncol* 2024;42:JCO2301601. https://doi.org/10.1200/JCO.23.01601.
19. Kashiwa M, Matsushita R. Difference in cost-effectiveness between first-line and third-line or later nivolumab therapy in patients with HER2-negative, unresectable, advanced or recurrent gastric or gastro-esophageal junction cancer in Japan. *Biol Pharm Bull* 2022;45:895–903. https://doi.org/10.1248/bpb.b22-00150.

20. Morimoto K, Moriwaki K, Shimozuma K, Nakayama T. Cost-effectiveness analysis of nivolumab plus chemotherapy vs chemotherapy for patients with unresectable advanced or metastatic HER2-negative gastric or gastroesophageal junction or esophageal adenocarcinoma in Japan. *J Gastroenterol* 2023;58:1188–97. https://doi.org/10.1007/s00535-023-02041-3.
21. VanderWalde N, Jagsi R, Dotan E, et al. NCCN guidelines insights: older adult oncology, version 2.2016. *J Natl Compr Canc Netw* 2016;14:1357–70. https://doi.org/10.6004/jnccn.2016.0146.
22. Yamaguchi K, Boku N, Muro K, et al. Real-world safety and effectiveness of nivolumab in Japanese patients with unresectable advanced or recurrent gastric/gastroesophageal junction cancer that has progressed after chemotherapy: a postmarketing surveillance study. *Gastric Cancer* 2022;25:245–53. https://doi.org/10.1007/s10120-021-01244-y.
23. Makiyama A, Shoji H, Kawakami H, et al. A randomized phase II study comparing S-1 plus oxaliplatin with S-1 monotherapy for elderly patients with advanced gastric cancer: WJOG8315G. *Ann Oncol* 2023;34:S1390. https://doi.org/10.1016/j.annonc.2023.09.139.
24. Nomura S, Goto Y, Mizutani T, et al. A randomized phase III study comparing continuation and discontinuation of PD-1 pathway inhibitors for patients with advanced non-small-cell lung cancer (JCOG1701, SAVE study). *Jpn J Clin Oncol* 2020;50:821–5. https://doi.org/10.1093/jjco/hyaa054.
25. JCOG1905: a randomized controlled phase III trial on continued or paused PD-1 pathway blockade for patients with advanced renal cell carcinoma (STOP study). 2023. https://www8.cao.go.jp/kourei/whitepaper/w-2023/zenbun/05pdf_index.html (28 December 2023, date last accessed).

JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2024, 1–8
https://doi.org/10.1093/jjco/hyae110
Original Article

OXFORD

Original Article

Real-world treatment costs of first-line treatment for metastatic colorectal cancer: a survey of the JCOG colorectal cancer study group

Atsuo Takashima[1], Megumi Ishiguro[2], Keita Sasaki[3], Ryunosuke Machida[3], Fumio Nagashima[4], Jun Imaizumi[5], Tetsuya Hamaguchi[6], Yoshiyuki Yamamoto[7], Toshiki Masuishi[8], Masako Asayama[9], Hideki Ueno[10], Katsunori Shinozaki[11], Toshihiro Kudo[12], Nozomu Machida[13], Hiroshi Matsuoka[14], Hideyuki Ishida[15], Toshifumi Yamaguchi[16], Hitoshi Nogami[17], Takeshi Yamada[18], Naoki Takegawa[19], Yosuke Kito[20], Yuko Tonoike[21], Ryoichi Sawada[22], Shunsuke Tsukamoto[23], Yukihide Kanemitsu[23] and Colorectal Cancer Study Group (CCSG) of the Japan Clinical Oncology Group (JCOG)

[1]Division of Gastrointestinal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan, [2]Health Science Research & Development Center, Tokyo Medical and Dental University, Tokyo, Japan, [3]Japan Clinical Oncology Group Data Center /Operations Office, National Cancer Center Hospital, Tokyo, Japan, [4]Department of Medical Oncology, Kyorin University Faculty of Medicine, Tokyo, Japan, [5]Department of Gastroenterological Surgery, Gunma Prefectural Cancer Center, Gunma, Japan, [6]Department of Gastroenterological Oncology, Saitama Medical University International Medical Center, Saitama, Japan, [7]Department of Gastroenterology, University of Tsukuba Hospital, Tsukuba, Japan, [8]Department of Clinical Oncology, Aichi Cancer Center Hospital, Aichi, Japan, [9]Department of Gastroenterology, Saitama Cancer Center, Saitama, Japan, [10]Department of Surgery, National Defense Medical College, Saitama, Japan, [11]Division of Clinical Oncology, Hiroshima Prefectural Hospital, Hiroshima, Japan, [12]Department of Medical Oncology, Osaka International Cancer Institute, Osaka, Japan, [13]Department of Gastroenterology, Kanagawa Cancer Center, Yokohama, Japan, [14]Department of Surgery, Fujita Health University School of Medicine, Toyoake, Japan, [15]Department of Pathology, Saitama Medical Center, Saitama Medical University, Saitama, Japan, [16]Cancer Chemotherapy Center, Osaka Medical and Pharmaceutical University, Osaka, Japan, [17]Department of Surgery, Niigata Cancer Center Hospital, Niigata, Japan, [18]Department of Gastroenterological Surgery, Nippon Medical School, Tokyo, Japan, [19]Department of Gastroenterology, Hyogo Cancer Center, Akashi, Hyogo, Japan, [20]Department of Medical Oncology, Ishikawa Prefectural Central Hospital, Ishikawa, Japan, [21]Department of Medical Oncology, Nagaoka Chuo General Hospital, Niigata, Japan, [22]Division of Gastroenterology and Hepatology, Department of Internal Medicine, The Jikei University School of Medicine, Tokyo, Japan and [23]Department of Colorectal Surgery, National Cancer Center Hospital, Tokyo, Japan

*For reprints and all correspondence: Division of Gastrointestinal Medical Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. Tel.: +81-335422511, Fax: +81-335423815; E-mail: atakashi@ncc.go.jp

Received 11 June 2024; Editorial Decision 30 July 2024; Accepted 3 August 2024

Abstract

Background: Although treatment outcomes for metastatic colorectal cancer (mCRC) have dramatically improved over the past few decades, drug costs have also significantly increased. This study aimed to investigate which first-line treatment regimens for mCRC are actually used (frequency) in Japanese practice and at what cost.

Methods: We collected data on patients with mCRC who received first-line treatment at 37 institutions of the Japan Clinical Oncology Group Colorectal Cancer Study Group from July 2021 to June 2022, and calculated the cost of regimens. The cost per month of each regimen was estimated based on standard usage, assuming a patient with a weight of 70 kg and a body surface area of 1.8 m^2. We categorized the regimens into very high-cost (≥1 000 000 Japanese yen [JPY]/month), high-cost (≥500 000 JPY/month), and others (<500 000 JPY/month).

Results: The study included 1880 participants, 24% of whom were ≥ 75 years. Molecular targeted containing regimens were received by 78% of the patients. The most frequently used regimen was the doublet regimen (fluoropyrimidine with either oxaliplatin or irinotecan) plus bevacizumab (43%), followed by doublet plus cetuximab or panitumumab (21%). The cost of molecular targeted drugs-containing regimens (ranging from 85 406 to 843 602 JPY/month) is much higher than that of only cytotoxic drug regimens (ranging from 17 672 to 51 004 JPY/month). About 16% received high-cost treatments that included panitumumab-containing regimens and pembrolizumab (17% of patients aged ≤74 years and 11% of patients aged ≥75 years).

Conclusion: About 16% of mCRC patients received first-line treatment with regimens costing >500 000JPY/month, and molecular targeted drugs being the main drivers of cost.

Key words: chemotherapy, colorectal cancer, treatment cost, cost of illness, financial toxicity

Introduction

Colorectal cancer (CRC) is a common cancer that affects both men and women worldwide (1). Its incidence increases with age (2). According to the GLOBOCAN database 2022 (3), CRC is the third most frequently diagnosed cancer and the second leading cause of cancer deaths, responsible for almost 1.92 million new diagnoses and 0.93 million deaths globally (3). In 2022, CRC was the second leading cause of cancer deaths and the most frequent cancer site in Japan, with an estimated 5400 deaths and 158 200 incidences (4).

For patients with unresectable metastatic CRC (mCRC), systemic therapy, including cytotoxic drugs, molecular targeted agents, and immunotherapy, is the global standard treatment (5–7). In the 1990s, fluorouracil (FU) was the only key drug available for systemic therapy for mCRC, which had a median survival time (MST) of almost 1 year (8–10). As of 2024, over 20 key drugs are available in Japan, and they are used as part of both first-line and later line treatments. In the global guidelines, four or more lines is described as the standard treatment (5–7).

For first-line treatment, the standard regimens of cytotoxic drugs are doublet or triplet chemotherapy with fluoropyrimidine (FU), oxaliplatin (OX), and/or irinotecan (IRI). Based on the *RAS*/*BRAF* status and tumor sidelines, the molecular targeted drugs of bevacizumab (BEV), cetuximab (CET), or panitumumab (PANI) were combined with cytotoxic regimens. Pembrolizumab was used as the first-line treatment for patients with microsatellite instability-high (MSI-high) and/or mismatch repair deficient (dMMR) mCRC. Recently, it was reported that the MST was >30 months for patients receiving first-line treatment. Although more aggressive surgical resection of the metastatic sites has also contributed to longer survival, it is clear that the prognosis is improving over time with the availability of more effective anticancer drugs (11–13).

At the same time, these dramatic advances are causing a marked increase in healthcare costs (14). In addition to the increased number of available regimens, the high price of newly introduced drugs is impacting healthcare costs (14,15). Patients with mCRC, not only in Japan but worldwide, face significant financial problems due to increasing medical costs (16–18). Additionally, the high costs of treatments place an enormous burden on social health resources. Dr. Schrag D. highlighted the cost problem for CRC in 2004 and suggested cost-effectiveness analysis parallel to clinical trials as one solution (19). While drug prices continue to rise, such analyses have been implemented in Western countries. However, in Japan, physicians have limited interest in healthcare costs and few reports on mCRC healthcare costs.

The Japan Clinical Oncology Group (JCOG) established a Health Economics Committee to address healthcare costs in March 2022. The first task of this committee was to conduct a multicenter survey to clarify the cost of first-line treatment of metastatic cancer in Japan. The objectives of this study were to examine the real-world treatment regimens used as first-line treatment for mCRC and estimate the cost of treatment using each of these regimens in the JCOG Colorectal Cancer Study Group.

Methods

Patients and data collection

We retrospectively collected data on mCRC patients from the JCOG Colorectal Cancer Study Group. Patients who received first-line

Table 1. Chemotherapy regimens.

Regimens	Molecularly targeted drug	Total n = 1880	%	Age ≤ 74 years n = 1436	%	Age ≥ 75 years n = 444	%
FU monotherapy	none	52	2.7	22	1.5	30	6.8
	BEV	141	7.5	57	4	84	18.9
	Anti-EGFR antibody	8	0.4	7	0.5	1	0.2
	CET	5		0		0	
	PANI	3		2		1	
Doublet	none	333	17.7	249	17.3	84	18.9
	BEV	813	43.2	647	45.1	166	37.4
	Anti-EGFR antibody	395	21	333	23.2	62	14
	CET	119		99		20	
	PANI	276		234		42	
Triplet	none	15	0.8	14	1	1	0.3
	BEV	99	5.3	91	6.3	8	1.8
	Anti-EGFR antibody	4	0.2	4	0.3	0	
	CET	3		3		0	
	PANI	1		1		0	
Pembrolizumab		20	1.1	12	0.8	8	1.8

FU, fluoropyrimidine; Doublet, fluoropyrimidine with either oxaliplatin or irinotecan; Triplet, fluoropyrimidine with oxaliplatin and irinotecan, BEV, bevacizumab; CET, cetuximab; EGFR, epidermal growth factor receptor; PANI, panitumumab.

palliative treatment for unresectable colorectal cancer diagnosed between July 2021 and June 2022 were included in this study. We distributed an online questionnaire via Google Forms to institutions affiliated with the JCOG Colorectal Cancer Study Group and aggregated the treatment data of first-line regimens obtained in response to the questionnaire. This study did not involve the use of personal data and therefore did not require individual consent or institutional review board approval.

Treatment regimens and calculation of costs

The collected cytotoxic regimens consisted of FU-monotherapy (fluorouracil plus calcium levofolinate [5-FU/l-LV], capecitabine [CAPE], tegafur gimeracil oteracil potassium[S1]), doublet regimens (FOLOFX [5-FU/l-LV+ OX], CAPOX [CAPE+OX], SOX [S1 + OX], FOLFIRI [5-FU/l-LV + IRI], CAPIRI [CAPE+IRI], SIR [S1 + IRI]), and triplet regimens (FOLFOXIRI [5-FU/l-LV + OX+IRI]). Molecular targeted drugs including BEV, CET, and PANI, with or without cytotoxic regimens, were also collected. Pembrolizumab monotherapy, which was approved in JAPAN in Aug 2021 for first-line treatment of mCRC, was included in the collection of immunotherapies. The data of patients in different age categories (≤74 years and ≥ 75 years) were collected separately for each regimen.

The cost of treatment for each regimen per month (4 weeks) was estimated based on standard usage and drug prices as of April 2024. In cases where generic or biosimilar drugs were available, the costs of the generic or biosimilar agents were also calculated, and the cost calculation was based on the lower price. This assumes a male patient with an average weight of 70 kg and a body surface area of 1.8 m^2, receiving treatment without any skips, delays, or dose reductions. In this study, only the cost of chemotherapy drugs was calculated, and costs for supportive care (i.e. antiemetic drugs) were not considered.

The regimens were categorized into very high-cost (≥1 000 000 Japanese yen [JPY]/month), high-cost (≥500 000 JPY/month), and others (<500 000 JPY/month) treatments based on the definition provided by the JCOG Health Economic Committee.

Results

A total of 37 institutions among 60 institutions of the JCOG Colorectal Cancer Study Group provided information. The 37 participating institutions are shown at the end of this article. The total number of eligible patients was 1880, of whom 1436 (76%) were < 74 years old and 444 (24%) were ≥ 75 years old.

Table 1 and Figure 1 show the frequency of regimen. Regarding cytotoxic regimens, 11% (201/1880) of the patients received FU monotherapy, while 82% (1541/1880) received doublet regimens and 6% (118/1880) received triplet regimens. Molecular targeted containing regimens were received by 78% (1460/1880) of the patients. The most frequently used regimen was doublet plus BEV (43%), followed by doublet plus anti-epidermal growth factor receptor (EGFR) of CET or PANI (21%) and doublet without molecular targeted drugs (18%). Doublet plus BEV and doublet plus anti-EGFR antibody of CET or PANI were more common in patients aged ≤74 years (64%, 1146/1436) than in patients aged ≥75 years (51%, 228/444). On the other hand, FU monotherapy plus BEV was commonly administered to patients aged ≥75 years (19%, 84/444).

Table 2 describes the cost of each regimen per month and the number of patients who received it. Table 3 lists the details of the treatment regimens and the cost per month for each regimen. Figure 2 displays the costs of representative cytotoxic regimens, molecular targeted drugs, and pembrolizumab for both original medicine and generic or biosimilar. The cost of molecular targeted drugs-containing regimens (ranging from 85 406 to 843 602 JPY/month) is much higher than that of only cytotoxic drug regimens (ranging from 17 672 to 51 004 JPY/month). The most expensive molecularly targeted drug regimen of FOLFOXIRI+PANI is ∼50 times more expensive than the cheapest cytotoxic regimen of 5-FU/l-LV. An anti-EGFR antibody of PANI was 2 times more expensive than CET (792 598 JPY/month vs. 396 164 JPY/month).

PANI-containing regimens and pembrolizumab were classified as high-cost regimens. Three hundred patients (16%) received high-cost regimens (PANI-containing regimens, n = 280 patients [15%]; pembrolizumab, n = 20 [1%]). High-cost regimens were administered to

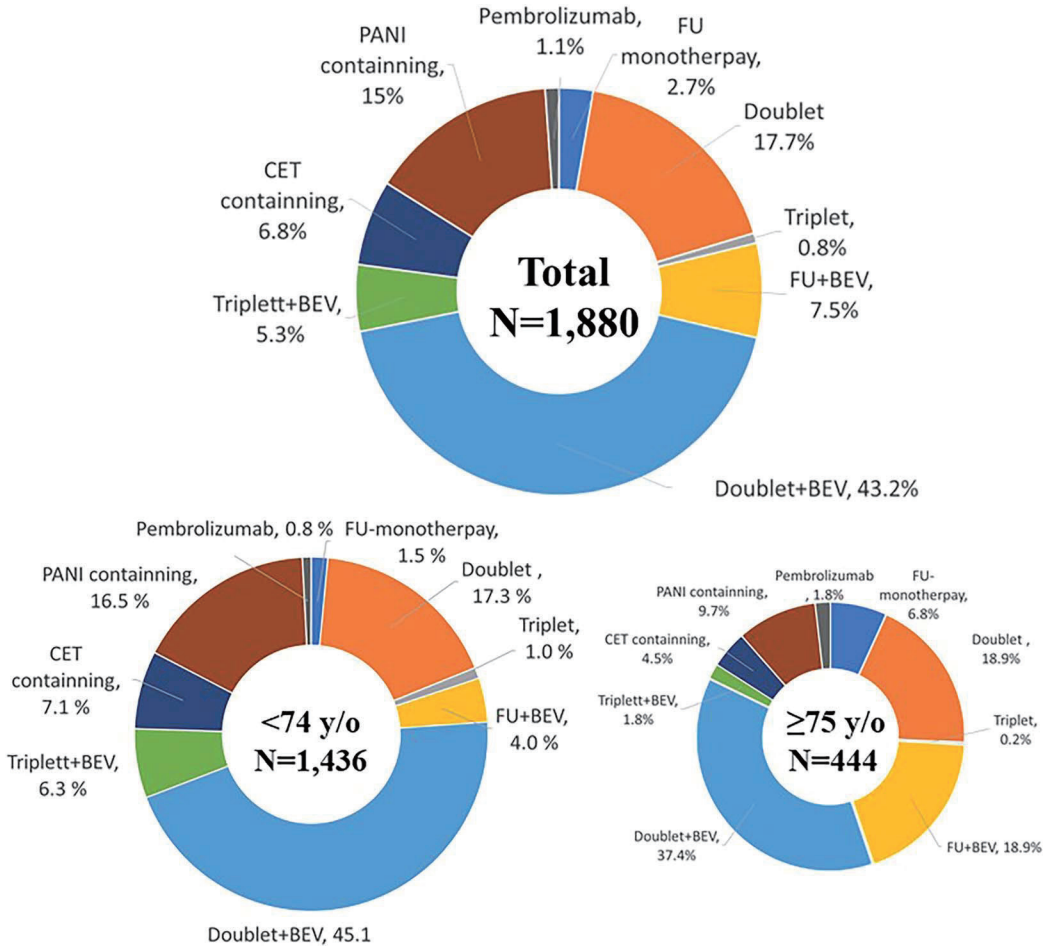


Figure 1. Frequency of regimens. FU, fluoropyrimidine; doublet, fluoropyrimidine with either oxaliplatin or irinotecan; triplet, fluoropyrimidine with oxaliplatin and irinotecan, BEV, bevacizumab; CET, cetuximab; EGFR, epidermal growth factor receptor; PANI, panitumumab.

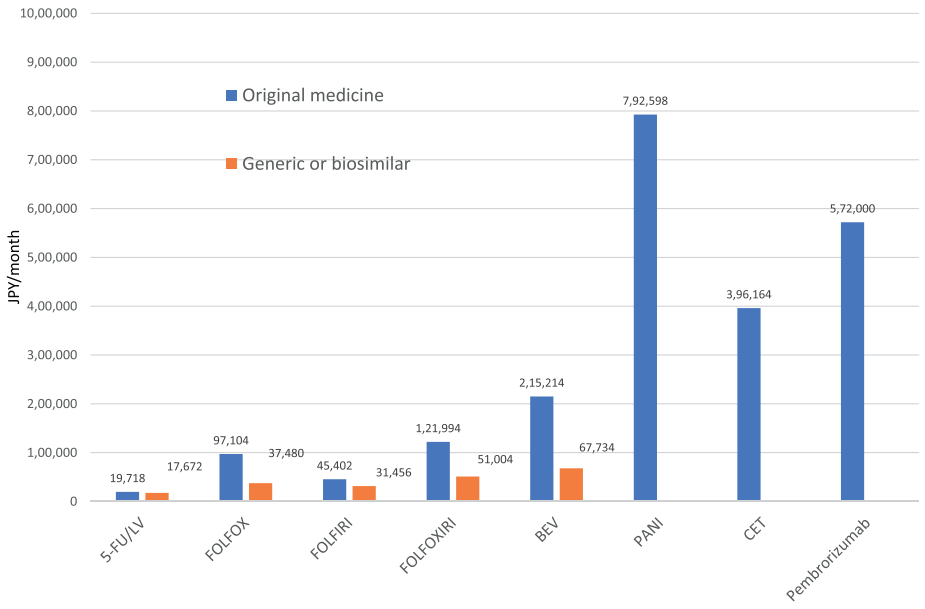


Figure 2. Cost of each regimen per month. 5-FU/l-LV, 5-fluorouracil plus calcium levofolinate; FOLFOX, fluorouracil plus calcium levofolinate plus oxaliplatin; FOLFIRI, fluorouracil plus calcium levofolinate plus irinotecan; FOLFOXIRI, fluorouracil plus calcium levofolinate plus oxaliplatin plus irinotecan; BEV, bevacizumab; CET, cetuximab; PANI, panitumumab; JPY, Japanese yen.

Table 2. Number of patients and cost of each regimen.

Regimens	Molecular targeted drug	Total n = 1880	%	Age ≤ 74 years n = 1436	%	Age ≥ 75 years n = 444	%	Cost per month (JPY)
5-FU/l-LV	none	12	0.6	5	0.3	7	1.6	17 672
	BEV	20	1.1	10	0.7	10	2.3	85 406
	CET	2	0.1	2	0.1	0	0.0	413 836
	PANI	2	0.1	1	0.1	1	0.2	810 270
CAPE	none	36	1.9	16	1.1	20	4.5	15 888
	BEV	115	6.1	44	3.1	71	16.0	85 406
S1	none	4	0.2	1	0.1	3	0.7	14 649
	BEV	6	0.3	3	0.2	3	0.7	82 383
	CET	3	0.2	3	0.2	0	0.0	410 813
	PANI	1	0.1	1	0.1	0	0.0	807 247
FOLFOX	none	138	7.3	101	7.0	37	8.3	37 480
	BEV	318	16.9	243	16.9	75	16.9	105 214
	CET	90	4.8	73	5.1	17	3.8	433 644
	PANI	240	12.8	199	13.9	41	9.2	830 078
CAPOX	none	161	8.6	122	8.5	39	8.8	30 499
	BEV	364	19.4	293	20.4	71	16.0	98 233
SOX	none	12	0.6	9	0.6	3	0.7	31 529
	BEV	27	1.4	23	1.6	4	0.9	99 263
FOLFIRI	none	15	0.8	13	0.9	2	0.5	31 456
	BEV	50	2.7	42	2.9	8	1.8	99 190
	CET	29	1.5	26	1.8	3	0.7	427 620
	PANI	36	1.9	35	2.4	1	0.2	824 054
CAPIRI	none	1	0.1	1	0.1	0	0.0	22 853
	BEV	9	0.5	8	0.6	1	0.2	90 587
S1 + IRI	none	6	0.3	3	0.2	3	0.7	22 853
	BEV	45	2.4	38	2.6	7	1.6	90 587
FOLFOXIRI	none	15	0.8	14	1.0	1	0.2	51 004
	BEV	99	5.3	91	6.3	8	1.8	118 738
	CET	3	0.2	3	0.2	0	0.0	447 168
	PANI	1	0.1	1	0.1	0	0.0	843 602
Pembrolizumab	none	20	1.1	12	0.8	8	1.8	572 000

BEV, bevacizumab; CAPE, capecitabine; CET, cetuximab; CAPIRI, capecitabine plus irinotecan; CAPOX, capecitabine plus oxaliplatin; FOLFIRI, fluorouracil plus calcium levofolinate plus irinotecan; FOLFOX, fluorouracil plus calcium levofolinate plus oxaliplatin; FOLFOXIRI, fluorouracil plus calcium levofolinate plus oxaliplatin plus irinotecan; 5-FU/l-LV, 5-fluorouracil plus calcium levofolinate; IRI, irinotecan; JPY, Japanese yen; PANI, panitumumab; SOX, S1 plus oxaliplatin.

17% (249/1436) of patients aged ≤74 years and 11% (51/444) of patients aged ≥75 years.

Discussion

The results of this study provide a comprehensive overview of the current landscape of first-line treatment regimens and associated costs for mCRC based on the Japanese healthcare system. Although no patients received very high-cost regimens as first-line treatment, sixteen percent of patients, particularly those aged ≤74 years, received high-cost treatments, and molecular targeted drugs being the main drivers of cost.

The regimens that were classified as high-cost treatments were PANI-containing regimens and pembrolizumab. The PARADIGM (20) and KEYNOTE-177 (21) trials were pivotal phase III trials evaluating the efficacy of high-cost regimens. The PARADIGM trial showed that in patients with left-sided RAS wild-type mCRC, the addition of PANI to FOLFOX significantly improved OS relative to BEV. The MST was 37.9 months with PANI versus 34.3 months with BEV (hazard ratio [HR], 0.82; 95.798% CI, 0.68–0.99; $P = 0.03$). The estimated median total costs based on mPFS were 10 874 022 JPY (830 078 JPY/month × 13.1 months) for FOLFOX+PANI and 1 252 047 JPY (105 214 JPY/month × 11.9 months) for FOLFOX+BEV. The difference in MST between the PANI and BEV regimens was ∼3.6 months, with the cost being ∼8.7 times higher (a difference of 10 million JPY). The KEYNOTE-177 trial (20) showed the survival benefit of pembrolizumab compared with standard regimens, including FOLFOX or FOLFIRI with or without BEV/CET, for MSI-high or dMMR mCRC. At the final analysis of the KEYNOTE-177 trial, the HR of OS was 0.74 (95% CI 0.53-1.03; $P = 0.036$, MST, not reached vs. 36.7 months). The estimated median total costs were 6 349 200 JPY (572 000 JPY/month × 11.1 months) for pembrolizumab and 2 471 771 JPY (433 644 JPY/month × 5.7 months) for FOLOFX+CET which had the highest cost among the standard regimens. The hazard ratio for OS was 0.74 in patients treated with pembrolizumab in comparison to those treated with standard regimens, but the cost was ∼2.6 times higher, resulting in a difference of 3.9 million JPY. Both PANI and pembrolizumab are the key drugs for treating mCRC. However, addressing the financial burden of these treatments is essential for the benefit of all patients.

Table 3. Calculation of cost of chemotherapy regimens.

	Regimen	Drugs	Dose		Duration	Cost per cycle (JPY)		Cost per month (JPY)	
						Original	Generic or biosimilar	Original	Generic or biosimilar
Cytotoxic regimens									
FU monotherapy	5-FU/l-LV	5-FU (bolus)	400 mg/m^2		q2	9859	8836	19 718	17 672
		5-FU (civ)	2400 mg/m^2						
		l-LV	200 mg/m^2						
	CAPE		4200 mg/day	day 1-14	q3	26 479	11 916	35 305	15 888
	S1		120 mg/day	day 1-14	q3	27 468	10 987	36 624	14 649
Doublet	FOLFOX	5-FU (bolus)	400 mg/m^2		q2	48 552	18 740	97 104	37 480
		5-FU (civ)	2400 mg/m^2						
		l-LV	200 mg/m^2						
		oxaliplatin	85 mg/m^2						
	CAPOX	CAPE	3600 mg/day	day 1-14	q3	73 809	22 874	98 412	30 499
		oxaliplatin	130 mg/m^2						
	SOX	S-1	120 mg/day	day 1-14	q3	78 580	23 647	104 773	31 529
		oxaliplatin	130 mg/m^2						
	FOLFIRI	5-FU (bolus)	400 mg/m^2		q2	22 701	15 728	45 402	31 456
		5-FU (civ)	2400 mg/m^2						
		l-LV	200 mg/m^2						
		irinotecan	150 mg/m^2						
	CAPIRI	CAPE	3600 mg/day	day 1-14	q3	54 453	17 140	72 604	22 853
		irinotecan	150 mg/m^2						
	S1 + IRI	S-1	120 mg/day	day 1-14	q3	40 310	17 879	53 747	23 838
		irinotecan	150 mg/m^2						
Triplet	FOLFOXIRI	5-FU (bolus)	400 mg/m^2		q2	60 997	25 502	121 994	51 004
		5-FU (civ)	2400 mg/m^2						
		l-LV	200 mg/m^2						
		oxaliplatin	85 mg/m^2						
		irinotecan	150 mg/m^2						
Molecular targeted drugs									
	BEV		5 mg/kg		q2	107 607	33 867	215 214	67 734
			7.5 mg/		q3	165 027	51 817	220 036	69 089
	PANI		6 mg/kg		q2	396 299	-	792 598	-
	CET		250 mg/m^2		q1	99 041	-	396 164	-
Immunotherapy									
	Pembrolizumab		200 mg		q3	429 000	-	572 000	-

FU, fluoropyrimidine; Doublet, fluoropyrimidine with either oxaliplatin or irinotecan; Triplet, fluoropyrimidine with oxaliplatin and irinotecan, l-LV, calcium levofolinate; 5-FU, 5-fluorouracil; BEV, bevacizumab; CAPE, capecitabine; CET, cetuximab; CAPIRI, capecitabine plus irinotecan; CAPOX, capecitabine plus oxaliplatin; FOLFIRI, fluorouracil plus calcium levofolinate plus irinotecan; FOLFOX, fluorouracil plus calcium levofolinate plus oxaliplatin; FOLFOXIRI, fluorouracil plus calcium levofolinate plus oxaliplatin plus irinotecan; 5-FU/l-LV, fluorouracil plus calcium levofolinate; IRI, irinotecan; JPY, Japanese yen; PANI, panitumumab; SOX, S1 plus oxaliplatin.

The cost of cytotoxic regimens for first-line treatment, including FU-monotherapy, doublet, and triplet, is similar, ranging from 17 672 JPY/month to 51 004 JPY/month. On the other hand, the cost of molecularly targeted drugs is quite different and much more expensive than cytotoxic regimens, ranging from 67 734 JPY/month to 792 598 JPY/month. While adding these molecularly targeted drugs to cytotoxic regimens has undoubtedly improved survival for patients with mCRC, the cost implications are substantial. Moreover, the cost of PANI and CET, which belong to the same class of anti-EGFR antibodies, is twice as high for PANI compared with CET (792 598 JPY/month vs. 396 164 JPY/month). There is currently no clear evidence comparing the efficacy and toxicities between these two drugs. This raises questions about the sustainability of healthcare systems and whether all eligible patients will have access to these therapies.

Japan faces unique challenges due to its 'high-cost medical expense benefit system' (22), which may inadvertently discourage cost-conscious medical practice. Under this system, when the amount of the copayment at a hospital or clinic in one month exceeds the maximum copayment amount, the excess amount is paid by the public medical insurance. As a result, the patient pays the same amount regardless of which drug is used, as long as a certain amount is spent. In addition, there is a system in place to ensure that scientifically effective treatments are covered by insurance and reimbursed without cost-effectiveness analyses. These factors could potentially lead to a preference for more expensive treatment

options without a thorough consideration of cost-effectiveness. The healthcare cost burden is already close to bankruptcy, and there is an urgent need for serious discussion and concrete action by healthcare providers, patients, payers, and other stakeholders toward a realistic solution to this problem.

We propose several practical solutions. Firstly, promote the use of generic drugs and biosimilars. Switching from the expensive drug bevacizumab to a biosimilar can reduce costs by 150 000 JPY per month This difference is even greater than the cost of the most expensive cytotoxic drug regimens like FOLFOXIRI. Secondly, it's important to include health economic evaluations in future clinical trials and discuss appropriate endpoints. Lastly, we believe that it's crucial for prescribing physicians to take healthcare costs into account. Currently, physicians rarely consider costs when deciding on treatment. Including cost information in treatment guidelines and displaying drug costs in electronic medical records can raise cost awareness among physicians.

Despite the insights gained from this study, several limitations should be acknowledged. Firstly, the retrospective nature of data collection may introduce inherent biases and limit the generalizability of findings. Furthermore, the frequency of pembrolizumab usage might be underestimated as it was approved during the survey period. Secondly, the study focused on first-line treatment regimens and did not explore subsequent lines of therapy or long-term cost implications. Recent standard treatment of mCRC typically involves using four or more lines of treatment. In addition, many of the later regimens involve very expensive molecular targeted drugs. Compared with front-line treatment, later treatment has shorter OS, making it easier to achieve statistically significant differences even if the absolute difference is minimal. It would be particularly important to include cost-effectiveness evaluations in later regimens. Additionally, the cost calculations were based on standard usage assumptions only for anti-cancer drugs and the prices within a specific time-frame, which may not reflect real-world variability in treatment patterns and costs. Moreover, the lack of patient-level outcome data linked to cost limits the ability to conduct a detailed cost-effectiveness analysis, which is crucial to inform policy and clinical practice.

Conclusion

This study illuminates the utilization and cost of first-line treatment options for mCRC in Japan. It emphasizes the need for sustainable strategies to ensure fair access to innovative therapies amid the global increase in healthcare costs. Future research, including cost-effectiveness analysis, should continue to explore the evolving landscape of mCRC treatment to optimize patient care and healthcare resource allocation.

Acknowledgements

List of Facilities responding to the questionnaire: The 37 participating institutions of the JCOG Colorectal Cancer Study Group; Yamagata Prefectural Central Hospital, Tochigi Cancer Center, Gunma Prefectural Cancer Center, National Defense Medical College, Saitama Cancer Center, Saitama Medical University International Medical Center, Saitama Medical Center, Saitama Medical University, National Cancer Center Hospital, Kyorin University Faculty of Medicine, Tokyo Metropolitan Cancer and Infectious diseases Center Komagome Hospital, Tokyo Medical and Dental University Hospital, Jikei University Hospital, Toho University Ohashi Medical Center, Nippon Medical School Hospital, Tokai University School of Medicine, Kanagawa Cancer Center, Niigata Cancer Center Hospital, Nagaoka Chuo General Hospital, Ishikawa Prefectural Central Hospital, Gifu University School of Medicine, Aichi Cancer Center Hospital, Fujita Health University, Osaka International Cancer Institute, Osaka Medical and Pharmaceutical University, Minoh City Hospital, Kansai Rosai Hospital, Hyogo Medical University, Hyogo Cancer Center, Himeji Red Cross Hospital, Hiroshima Prefectural Hospital, Hiroshima City North Medical Center Asa Citizens Hospital, Fukuyama City Hospital, National Hospital Organization Shikoku Cancer Center, Kochi Health Sciences Center, Kurume University School of Medicine, Kumamoto University Hospital, and Oita University Hospital.

Conflict of interest

M.I., K.S., R.S., J.I., Y.Y., H.U., K.S., N.M., H.M., H.I., T.Y., H.N., T.Y., N.T., Y.T., R.S., S.T., and Y.K. have no conflict of interest. A.T. received institutional grants from MSD, AstraZeneca, Amgen, Eisai, Bristol-Myers Squibb, and Ono Pharmaceutical outside the submitted work and received honoraria for lectures from Lilly, Ono Pharmaceutical, Taiho Pharmaceutical, Chugai Pharma, Takeda, and Merck Serono, outside the submitted work. Fumio Nagashima received institutional grants from Yakult Honsha and Astellas Pharma outside the submitted work. T. H. received institutional grants from Taiho, Chugai Pharm, Ono Pharmaceutical, Astellas Pharma, BeiGene, AstraZeneca, Pfizer, Bristol Myer Squibb, Incyte Japan outside the submitted work, and received honoraria for lectures from Chugai, Takeda, Ono, Lilly, Bayer Merck, Taiho, Yakult, Bristol-Myers Squibb, Bayer, and Daiichi-Sankyo, outside the submitted work. T.M. received institutional grants from MSD, Daiichi Sankyo, Ono, Novartis, Amgen, Syneos Health Clinical, Boehringer-Ingelheim, Pfizer, Cimic Shift Zero, and Eli Lilly outside the submitted work, and received honoraria for lectures from Takeda, Chugai, Merck Bio Pharm, Taiho, Bayer, Lilly Japan, Yakult Honsha, Sanofi, Daiichi Sankyo, Ono, Bristol myers squibb, Nippon Kayaku, and MSD outside the submitted work. M.A. received institutional grants from Seagen, Sysmex, and Isofol Medical AB outside the submitted work and received honoraria for lectures from Ono Pharmaceutical, Takeda, Merk Serono, Eli Lilly, and Taiho outside the submitted work. T.K. received institutional grants from Astellas Pharma, Amgen, Daiichi Sankyo, Incyte Biosciences Japan, MSD, Novartis Pharma, Ono Pharmaceutical, and Pfizer, outside the submitted work. Y.K. received honoraria for lectures from Taiho Pharmaceutical, Ono Pharmaceutical, and Daiichi Sankyo, outside the submitted work.

Funding

This work was supported in part by the Research Fund of National Federation of Health Insurance Societies (Kenpo-ren) and the National Cancer Center Research and Development Funds (2023-J-03).

References

1. Sung H, Ferlay J, Siegel RL., et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71:209–49. https://doi.org/10.3322/caac.21660.
2. Yancik R. Population aging and cancer: a cross-national concern. *Cancer J* 2005;11:437–41. https://doi.org/10.1097/00130404-200511000-00002.
3. Bray F, Laversanne M, Sung H., et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2024;74:229–63. https://doi.org/10.3322/caac.21834.

4. Foundation for Promotion of Cancer Research. *Cancer statistics in Japan 2024*. https://ganjoho.jp/public/qa_links/report/statistics/2024_en.html (20 May 2024, date last accessed).
5. Benson AB, Venook AP, Al-Hawary MM., et al. Colon cancer, version 2.2021, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2021;19:329–59. https://doi.org/10.6004/jnccn.2021.0012.
6. Yoshino T, Arnold D, Taniguchi H., et al. Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO-ESMO initiative endorsed by CSCO, KACO, MOS. *SSO and TOS Ann Oncol* 2018;29:44–70. https://doi.org/10.1093/annonc/mdx738.
7. Hashiguchi Y, Muro K, Saito Y., et al. Japanese Society for Cancer of the colon and rectum (JSCCR) guidelines 2019 for the treatment of colorectal cancer. *Int J Clin Oncol* 2020;25:1–42. https://doi.org/10.1007/s10147-019-01485-z.
8. Nordic Gastrointestinal Tumor Adjuvant Therapy Group. Expectancy or primary chemotherapy in patients with advanced asymptomatic colorectal cancer: a randomized trial. *J Clin Oncol* 1992;10:904–11. https://doi.org/10.1200/JCO.1992.10.6.904.
9. Scheithauer W, Rosen H, Kornek GV, Sebesta C, Depisch D. Randomised comparison of combination chemotherapy plus supportive care with supportive care alone in patients with metastatic colorectal cancer. *BMJ* 1993;306:752–5. https://doi.org/10.1136/bmj.306.6880.752.
10. Simmonds PC. Palliative chemotherapy for advanced colorectal cancer: systematic review and meta-analysis. Colorectal cancer collaborative group. *BMJ* 2000;321:531–5. https://doi.org/10.1136/bmj.321.7260.531.
11. Renouf DJ, Lim HJ, Speers C., et al. Survival for metastatic colorectal cancer in the bevacizumab era: a population-based analysis. *Clin Colorectal Cancer* 2011;10:97–101. https://doi.org/10.1016/j.clcc.2011.03.004.
12. Jawed I, Wilkerson J, Prasad V, Duffy AG, Fojo T. Colorectal cancer survival gains and novel treatment regimens: a systematic review and analysis. *JAMA Oncol* 2015;1:787–95. https://doi.org/10.1001/jamaoncol.2015.1790.
13. Chan S, Tannenbaum D, Horn R., et al. Overall survival in phase 3 clinical trials and the surveillance, epidemiology, and end results database in patients with metastatic colorectal cancer, 1986-2016: a systematic review. *JAMA Netw Open* 2022;5:e2213588. https://doi.org/10.1001/jamanetworkopen.2022.13588.
14. Wilson BE, Booth CM, Sullivan R., et al. Global application of National Comprehensive Cancer Network resource-stratified guidelines for systemic treatment of colon cancer: a population-based, customisable model for cost, demand, and procurement. *Lancet Oncol* 2023;24:682–90. https://doi.org/10.1016/S1470-2045(23)00183-3.
15. Seal BS, Sullivan SD, Ramsey S., et al. Medical costs associated with use of systemic therapy in adults with colorectal cancer. *J Manag Care Pharm* 2013;19:461–7. https://doi.org/10.18553/jmcp.2013.19.6.461.
16. Davis R, Trickey A, Abrahamse P, Kato I, Ward K, Morris AM. Association of cumulative social risk and social support with receipt of chemotherapy among patients with advanced colorectal cancer. *JAMA Netw Open* 2021;4:e2113533. https://doi.org/10.1001/jamanetworkopen.2021.13533.
17. Eaglehouse YL, Seabury SA, Aljehani M., et al. Chemotherapy treatment costs and clinical outcomes of colon cancer in the U.S. military health system's direct and private sector care settings. *Mil Med* 2023;188:e3439–46. https://doi.org/10.1093/milmed/usad132.
18. Gorey KM, Haji-Jama S, Bartfay E, Luginaah IN, Wright FC, Kanjeekal SM. Lack of access to chemotherapy for colon cancer: multiplicative disadvantage of being extremely poor, inadequately insured and African American. *BMC Health Serv Res* 2014;14:133. https://doi.org/10.1186/1472-6963-14-133.
19. Schrag D. The price tag on progress–chemotherapy for colorectal cancer. *N Engl J Med* 2004;351:317–9. https://doi.org/10.1056/NEJMp048143.
20. Watanabe J, Muro K, Shitara K., et al. Panitumumab vs bevacizumab added to standard first-line chemotherapy and overall survival among patients with RAS wild-type, left-sided metastatic colorectal cancer: a randomized clinical trial. *JAMA* 2023;329:1271–82. https://doi.org/10.1001/jama.2023.4428.
21. Diaz LA Jr, Shiu KK, Kim TW., et al. Pembrolizumab versus chemotherapy for microsatellite instability-high or mismatch repair-deficient metastatic colorectal cancer (KEYNOTE-177): final analysis of a randomised, open-label, phase 3 study. *Lancet Oncol* 2022;23:659–70. https://doi.org/10.1016/S1470-2045(22)00197-8.
22. Ministry of Health, Labour and Welfare. *High-cost medical expense benefit (Japanese)*. https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iryouhoken/juuyou/kougakuiryou/index.html (20 July 2024, date last accessed).

JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2024, 1–8
https://doi.org/10.1093/jjco/hyae117
Original Article

OXFORD

Original Article

Frequency of use and cost in Japan of first-line palliative chemotherapies for recurrent or metastatic squamous cell carcinoma of the head and neck

Kazuki Yokoyama[1], Koichiro Wasano[2,*], Keita Sasaki[3], Ryunosuke Machida[3], Mitsuhiko Nakahira[4], Koji Kitamura[5], Tomofumi Sakagami[6], Naohiro Takeshita[7,8], Akira Ohkoshi[9], Motoyuki Suzuki[10], Ichiro Tateya[11], Yohei Morishita[8], Mariko Sekimizu[12], Masahiro Nakayama[13], Taiji Koyama[14], Hirofumi Shibata[15], Satoru Miyamaru[16], Naomi Kiyota[14], Nobuhiro Hanai[17] and Akihiro Homma[18]

[1]Department of Head and Neck, Esophageal Medical Oncology, National Cancer Center Hospital, Tokyo, Japan, [2]Department of Otolaryngology-Head and Neck Surgery, Tokai University School of Medicine, Isehara, Japan, [3]Japan Clinical Oncology Group Data Center/Operations Office, National Cancer Center Hospital, Tokyo, Japan, [4]Department of Otolaryngology, Saitama Medical University International Medical Center, Hidaka, Japan, [5]Department of Head and Neck Surgery, Osaka International Cancer Institute, Osaka, Japan, [6]Department of Otolaryngology, Head and Neck Surgery, Kansai Medical University, Osaka, Japan, [7]Department of Head and Neck Medical Oncology, National Cancer Center Hospital East, Kashiwa, Japan, [8]Department of Otorhinolaryngology, Head and Neck Surgery, Jikei University Hospital, Tokyo, Japan, [9]Department of Otolaryngology-Head and Neck Surgery, Tohoku University Hospital, Sendai, Japan, [10]Department of Otolaryngology-Head and Neck Surgery, Osaka University Graduate School of Medicine, Osaka, Japan, [11]Department of Otolaryngology-Head and Neck Surgery, School of Medicine, Fujita Health University, Toyoake, Japan, [12]Department of Otolaryngology, Head and Neck Surgery, Keio University School of Medicine, Tokyo, Japan, [13]Department of Otolaryngology, Head and Neck Surgery, University of Tsukuba, Tsukuba, Japan, [14]Department of Medical Oncology and Hematology, Cancer Center, Kobe University Hospital, Kobe, Japan, [15]Department of Otolaryngology, Head and Neck Surgery, Gifu University Graduate School of Medicine, Gifu, Japan, [16]Department of Otolaryngology-Head and Neck Surgery, Kumamoto University Graduate School of Medicine, Kumamoto, Japan, [17]Department of Head and Neck Surgery, Aichi Cancer Center Hospital, Nagoya, Japan and [18]Department of Otolaryngology-Head and Neck Surgery, Faculty of Medicine, Graduate School of Medicine, Hokkaido University, Sapporo, Japan

*For reprints and all correspondence: Koichiro Wasano, Department of Otolaryngology-Head and Neck Surgery, Tokai University School of Medicine, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan. E-mail: wasano@tokai.ac.jp

Received 2 May 2024; Editorial Decision 6 August 2024; Accepted 10 August 2024

Abstract

Background: Over the last decade, novel anticancer drugs have improved the prognosis for recurrent or metastatic squamous cell carcinoma of the head and neck (RM-SCCHN). However, this has increased healthcare expenditures and placed a heavy burden on patients and society. This study investigated the frequency of use and costs of select palliative chemotherapy regimens in Japan.

Methods: From July 2021 to June 2022 in 54 healthcare facilities, we gathered data of patients diagnosed with RM-SCCHN and who had started first-line palliative chemotherapy with one of eight commonly used regimens. Patients with nasopharyngeal carcinomas were excluded. The number of patients receiving each regimen and the costs of each regimen for the first month and per year were tallied.

Results: The sample comprised 907 patients (674 were < 75 years old, 233 were ≥ 75 years old). 330 (36.4%) received Pembrolizumab monotherapy, and 202 (22.3%) received Nivolumab monotherapy. Over 90% of patients were treated with immune checkpoint inhibitors as monotherapy or in combination with chemotherapy. Treatment regimens' first-month costs were 612 851–849 241 Japanese yen (JPY). The cost of standard palliative chemotherapy until 2012 was about 20 000 JPY per month. The incremental cost over the past decade is approximately 600 000–800 000 JPY per month, a 30- to 40-fold increase in the cost of palliative chemotherapy for RM-SCCHN.

Conclusion: First-line palliative chemotherapy for RM-SCCHN exceeds 600 000 JPY monthly. Over the last decade, the prognosis for RM-SCCHN has improved, but the costs of palliative chemotherapy have surged, placing a heavy burden on patients and society.

Key words: palliative chemotherapy, head and neck cancer, immune checkpoint inhibitor, cost, health expenditures

Introduction

Head and neck cancer (HNC) was the seventh most common cancer worldwide in 2020, comprising 870 000 diagnosed cases and contributing to 440 000 deaths per year, accounting for 4.5% of all cancer deaths (1). Squamous cell carcinoma (SCC) accounts for more than 90% of HNC (2). Approximately 10% of the patients with SCC of the head and neck (SCCHN) present with distant metastases at initial diagnosis (3). Most SCCHN patients are diagnosed with localized disease and undergo surgery or radiation therapy with or without platinum-based chemotherapy. Despite improvements in diagnosis and treatment, at least 50% of patients with locally advanced SCCHN develop recurrent and/or metastatic disease within 3 years of treatment (4,5). In patients with recurrent or metastatic SCCHN (RM-SCCHN), palliative chemotherapy is the treatment of choice when salvage surgery or radiation therapy is not indicated. Combination therapy comprising platinum (cisplatin or carboplatin) + 5-fluorouracil (5-FU) has been used as the standard of care for a long time. The EXTREME trial showed that adding cetuximab to the platinum +5-FU regimen improved overall survival (OS) (Table 1) (6). Since the approval of cetuximab for RM-SCCHN in 2012, this combined cetuximab/platinum +5-FU regimen has been the standard of first-line palliative chemotherapy until recently.

In ovarian cancer, a shorter interval between prior platinum-based chemotherapy and recurrence (platinum-free interval; PFI) is associated with poor prognosis (7,8). Recurrence at PFI ≥6 months is defined as 'platinum-sensitive' disease, while recurrence at PFI <6 months is defined as 'platinum-refractory' or 'platinum-resistant' disease (9,10). The terms 'platinum-sensitive' and 'platinum-refractory' have been used for RM-SCCHN also (11,12).

Platinum-refractory RM-SCCHN has a poor prognosis, having a median survival time of 5–6 months (13–15). In the phase III trial, CheckMate 141 (16), Nivolumab significantly improved OS, showing a median OS of 7.7 months compared to 5.1 months for the treatment of physician's choice (TPC) group after 2 years of long-term follow-up (Table 1) (17,18). Based on these findings, in 2017, nivolumab was approved by the Japanese National Health Insurance system and was regarded as the standard of care for platinum-refractory RM-SCCHN.

KEYNOTE-040 was a randomized phase III trial that compared pembrolizumab against TPC in patients with platinum-refractory RM-SCCHN (19). The results of the KEYNOTE-040 trial reported a significant improvement with pembrolizumab (HR, 0.80; 95% CI, 0.65-0.98) (Table 1).

Another randomized phase III trial that compared pembrolizumab to platinum +5-FU + cetuximab (EXTREME regimen) and pembrolizumab + chemotherapy (platinum +5-FU) was conducted in platinum-sensitive RM-SCCHN patients (20). In this trial, called the KEYNOTE-048, pembrolizumab monotherapy was superior in OS in the CPS ≥ 20 group and CPS ≥ 1 group. Pembrolizumab was also superior in the pembrolizumab + chemotherapy group in OS in the CPS ≥ 1 group. In the ITT group, pembrolizumab was non-inferior to the EXTREME regimen group in OS, and the pembrolizumab + chemotherapy group was non-inferior and superior to the EXTREME regimen group (Table 1). In 2019, the Japanese National Insurance system approved pembrolizumab/platinum +5-FU combination therapy and pembrolizumab monotherapy for platinum-sensitive RM-SCCHN patients. In the Japanese Clinical Practice Guidelines for Head and Neck Cancer (2022), pembrolizumab + platinum +5-FU is recommended for all patients, and pembrolizumab monotherapy is recommended for patients with CPS ≥ 1 (21).

Since the approval of cetuximab in 2012, followed by nivolumab in 2017 and pembrolizumab in 2019, the prognosis for patients with RM-SCCHN has improved. Likewise, numerous molecularly targeted therapies and ICIs have been approved for other types of cancers (22,23). These approvals have come at a significant cost. Expenditures in Japan's healthcare system increased from 30 trillion Japanese yen (JPY) in 2000 to 46 trillion JPY in 2022. In general, novel anticancer drugs are expensive and increase healthcare costs (24–26). This trend is expected to continue with continued progress in anticancer drug development. However, little attention has been paid to rising medical costs in this area. Although a few cost-effectiveness studies have been conducted for some cancers recently in Japan (27–30), we know of no comprehensive studies on the costs of palliative chemotherapy for many other cancers, including RM-SCCHN in Japan. Moreover, to the best of our knowledge, no previous focused reports have appeared on this issue.

Table 1. Results of pivotal studies for RM-SCCHN

	EXTREME	Checkmate 141	KEYNOTE-040	KEYNOTE-048
Author	Vermorken (2008)	Ferris (2016) (2018)	Cohen (2019)	Burtness (2019, 2022) Harrington (2022)
New treatment	Cetuximab +CDDP/CBDCA +5-FU	Nivolumab	Pembrolizumab	Pembrolizumab ± CDDP/CBDCA +5-FU
Control	CDDP/CBDCA +5-FU	MTX or DTX or cetuximab	MTX or DTX or cetuximab	Cetuximab +CDDP/CBDCA +5-FU
Inclusion criteria	Platinum-sensitive RM-SCCHN	Platinum-refractory RM-SCCHN	Platinum-refractory RM-SCCHN	Platinum-sensitive RM-SCCHN
Age, years (new treatment)	56 (37–80)	59 (29–83)	60 (55–66)	Pembrolizumab alone: 62 (56–68) Pembrolizumab + chemo: 61 (55–68)
Elderly patients, years (new treatment) No.(%)	≥65: 39 (18)	≥75: 12 (5)	≥75: 19 (8)	not available
OS, months, median (95%CI) (new treatment)	10.1 (8.6–11.2)	7.7 (5.7–8.8)	8.4 (6.4–9.4)	ITT Pembrolizumab alone: 11.5 (10.3–13.5) Pembrolizumab + chemo: 13.0 (10.9–14.7) CPS < 1 Pembrolizumab alone: 7.9 (4.7–13.6) Pembrolizumab + chemo: 11.3 (9.5–14.0) CPS 1–19 Pembrolizumab alone: 10.8 (9.0–12.6) Pembrolizumab + chemo: 12.7 (9.4–15.3) CPS ≥ 20 Pembrolizumab alone: 14.9 (11.5–20.6) Pembrolizumab + chemo: 14.7 (10.3–19.3)
OS, months, median (95%CI) (control)	7.4 (6.4–8.3)	5.1 (4.0–6.2)	6.9 (5.9–8.0)	ITT vs. Pembrolizumab alone: 10.7 (9.3–12.1) vs. Pembrolizumab + chemo: 10.7 (9.3–11.7) CPS < 1 vs. Pembrolizumab alone: 11.3 (9.1–15.9) vs. Pembrolizumab + chemo: 10.7 (8.5–15.9) CPS 1–19 vs. Pembrolizumab alone: 10.1 (8.7–12.1) vs. Pembrolizumab + chemo: 9.9 (8.6–11.5) CPS ≥ 20 vs. Pembrolizumab alone: 10.8 (8.8–12.8) vs. Pembrolizumab + chemo: 11.1 (9.2–13.0)
New treatment/control HR (95%CI:)	0.80 (0.64–0.99)	0.68 (0.54–0.86)	0.80 (0.62–098)	ITT Pembrolizumab alone: 0.81 (0.68–0.97) Pembrolizumab + chemo: 0.71 (0.59–0.85) CPS < 1 Pembrolizumab alone: 1.51 (0.96–2.37) Pembrolizumab + chemo: 1.21 (0.76–1.94) CPS 1–19 Pembrolizumab alone: 0.86 (0.66–1.12) Pembrolizumab + chemo: 0.71 (0.54–0.94) CPS ≥ 20 Pembrolizumab alone: 0.58 (0.44–0.78) Pembrolizumab + chemo: 0.60 (0.45–0.82)

RM-SCCHN, recurrent or metastatic squamous cell carcinoma of the head and neck; CDDP, cisplatin; CBDCA, carboplatin; 5-FU, 5-fluorouracil; MTX, methotrexate; DTX, docetaxel; ITT, intention to treat; CPS, combined positive score; chemo, chemotherapy; CI, confidence interval; HR, hazard ratio.

On March 5, 2022, therefore, the Japan Clinical Oncology Group (JCOG) established the Health Economics Committee (HEC) to address these issues. The first mandate of this committee was to determine which palliative chemotherapy regimens are used most frequently in the Japanese healthcare system and how much they cost. This study was conducted in JCOG Head and Neck Cancer Study Group (JCOG-HNCSG) member or affiliated institutions.

Methods

Patients

We retrospectively collected data from 39 member institutions and 15 affiliated institutions of the JCOG-HNCSG. Participating institutions are listed in the Supplementary Material. The inclusion criteria were as follows: (1) a diagnosis of recurrent or metastatic SCCHN, (2) SCCHN with a clinical stage of IVc, and (3) SCCHN treated with first-line palliative chemotherapy according to one of eight regimens (see below) during the period from July 2021 to June 2022. Patients diagnosed with nasopharyngeal carcinoma were excluded from this study. Clinical staging was classified according to the 8th edition of the Union for International Cancer Control-TNM classification.

Treatment regimens

Included patients received one of the following eight chemotherapy regimens: (1) pembrolizumab alone; (2) nivolumab alone; (3) pembrolizumab + cisplatin (CDDP) + 5-fluorouracil (5-FU); (4) pembrolizumab + carboplatin (CBDCA) + 5-FU; (5) cetuximab + CDDP +5-FU (EXTREME regimen); (6) cetuximab + CBDCA +5-FU (EXTREME regimen); (7) CBDCA + paclitaxel (PTX) + cetuximab (PCE regimen); or (8) any other clinical trial regimen not listed here.

Scope of data collection

Responsible person(s) at each participating institution received an online questionnaire survey, which was used to tally the study information. The following data were collected: type of regimen each patient received as first-line palliative chemotherapy and each patient's demographic information (i.e. gender, age, etc.). Next, the patients' data were grouped into two age categories (<75 and ≥ 75 years), and the number of patients in each group was recorded. The patients' personal data were not collected or stored.

Treatment costs

The first month and annual costs of treatment were calculated separately using the standard and regulated market prices for the drugs in each regimen in Japan as of March 1, 2024 (Table 2). Doses of treatment regimens were calculated according to a patient height of 165 cm, weight of 60 kg, and body surface area of 1.615 m^2. The dose of carboplatin was calculated as follows:

$$\text{Dose (mg)} = \text{target AUC} \times (\text{GFR} + 25),$$

where AUC is the calculated 'area under the blood concentration-time curve,' and GRF is the glomerular filtration rate. GFR was calculated using the Cockcroft-Gault formula (31) for a male having a serum creatinine level of 0.7 and an age of 60 years.

For the pembrolizumab + platinum +5-FU and the EXTREME regimens, costs were calculated assuming that pembrolizumab and cetuximab were administered as single agents for 6 cycles within 1 year. For the PCE regimen, after 6 cycles, CBDCA was discontinued, and PTX and cetuximab were continued at a dose of 80 mg/m^2 of PTX and 250 mg/m^2 of cetuximab in a 28-day cycle. PTX and cetuximab were administered on days 1, 8, and 15 for 1 year.

The first-month cost of all regimens was calculated separately by dividing the cost of the first cycle by the number of days in that cycle and multiplying the result by 30. Assuming pembrolizumab was administered for 17.3 cycles per year, the cost per year of pembrolizumab was calculated by multiplying the cost of one cycle by 17.3. Likewise, assuming nivolumab was administered for 26 cycles per year, the cost per year of nivolumab was calculated by multiplying the cost of one cycle by 26. The cost per year of pembrolizumab + platinum +5-FU was calculated by summing the total cost of the first six cycles of the combination therapy and the remaining 11.3 cycles of pembrolizumab monotherapy. The cost per year of the EXTREME regimen was also calculated by summing the total cost of the first 6 cycles of combination therapy and the remaining 11.3 cycles of cetuximab monotherapy. The cost per year of the PCE regimen was also calculated by summing the total cost of the first 6 cycles of CBDCA + PTX + cetuximab therapy and the remaining 8.5 cycles of PTX + cetuximab therapy.

It should be noted that our cost analysis included only the cost of the chemotherapy agents themselves. The cost of treatment administration and supportive care, such as antiemetic medications, were not included. The HEC of Japan defines high-cost medical care as care costing 500 000 JPY or more per month, and very-high-cost medical care as care costing 1 000 000 JPY or more per month.

Results

All 54 institutions provided data for the analysis to meet the mandate of the HEC, which was to survey which palliative chemotherapy regimens are used most frequently in the Japanese healthcare system to treat RM-SCCHN and how much these regimens cost. The total number of eligible patients was 907; 673 were < 75 years old and 233 were ≥ 75 years old. Of the 906 patients, 29 participated in the clinical trial but their treatment details were not included in the survey questionnaire.

Overall, the most used regimen was pembrolizumab monotherapy, accounting for 36.4% of the cases (Table 3); for patients ≥75 years, pembrolizumab monotherapy accounted for 56.7% of the cases. The second most used regimen was nivolumab monotherapy, accounting for 22.3% of the cases. Of the 906 patients, more than 90% received ICI as a monotherapy or in combination with another therapy. ICI monotherapy was used more frequently in patients ≥75 years than in patients <75 years. In contrast, combination chemotherapy with ICI was used more frequently in patients <75 years. The least frequently used regimens were those that did not use ICI as a first-line therapy, accounting for 7.6% of the cases, and those used in the EXTREME trial, accounting for only 1.7% of the cases.

The monthly costs of all regimens were between 612 851 JPY and 849 241 JPY. Per our definition and that of the HEC of Japan, this is considered to be high-cost medical care. The annual costs of all regimens were between 7 and 10 million JPY.

The standard treatment for RM-SCCHN until 2012, the platinum +5-FU regimen, costs about 20 000 JPY per month. Now, the incremental cost over the last decade is approximately 600 000 to 800 000 JPY per month, a 30- to 40-fold increase in the cost of palliative chemotherapy for RM-SCCHN.

Table 2. Surveyed chemotherapy regimens and their calculated costs

Regimen	Agent	Vial size(s) (mg)	Price (JPY)	Dosing schedules	Median OS In pivotal trials (months)	First-month costs (JPY)	Annual costs (JPY)
Pembrolizumab	Pembrolizumab	100	214 498	200 mg/body, Q3W 400 mg/body, Q6W	CPS < 1: 7.9 CPS1–19: 10.8 CPS ≥20: 14.8	612 851	7 421 630
Nivolumab	Nivolumab	240	366 405	240 mg/body, Q2W 480 mg/body, Q4W	7.7	785 153	9 526 530
CDDP +5-FU + Pembrolizumab	CDDP	50 10	3175 740	100 mg/m^2, Q3W, up to 6 cycles	CPS < 1: 11.3[a] CPS1–19: 12.7 CPS ≥ 20: 14.7	634 504	7 512 572
	5-FU	1000 250	519 255	4000 mg/m^2, Q3W, up to 6 cycles			
	Pembrolizumab	100	214 498	200 mg/body, Q3W			
CBDCA +5-FU + Pembrolizumab	CBDCA	450 150	5846 2491	AUC 5, Q3W, up to 6 cycles	CPS < 1: 11.3[a] CPS1–19: 12.7 CPS ≥ 20: 14.7	630 692	7 496 564
	5-FU	1000 250	519 255	4000 mg/m^2, Q3W, up to 6 cycles			
	Pembrolizumab	100	214 498	200 mg/body, Q3W			
CDDP +5-FU + Cetuximab	CDDP	50 10	3175 740	100 mg/m^2, Q3W, up to 6 cycles	10.7[b]	836 807	8 819 519
	5-FU	1000 250	519 255	4000 mg/m^2, Q3W, up to 6 cycles			
	Cetuximab	500 100	166 678 35 287	400 mg/m^2, first week 250 mg/m^2, Q1W thereafter			
CBDCA +5-FU + Cetuximab	CBDCA	450 150	5846 2491	AUC 5, Q3W, up to 6 cycles	10.7[b]	832 995	8 796 096
	5-FU	1000 255	519 255	4000 mg/m^2, Q3W, up to 6 cycles			
	Cetuximab	500 100	166 678 35 287	400 mg/m^2, first week 250 mg/m^2, Q1W thereafter			
PTX + CBDCA + Cetuximab	PTX	150 30	5105 1852	100 mg/m^2, day1,8, Q3W, up to 6 cycles	14.7	849 241	7 594 495
	CBDCA	450 150	5846 2491	AUC 2.5, days 1and 8, Q3W, up to 6 cycles			
	Cetuximab	500 100	166 678 35 287	400 mg/m^2, first week 250 mg/m^2, Q1W thereafter			
Reference							
CDDP +5-FU	CDDP	50 10	3175 740	100 mg/m^2, Q3W, up to 6 cycles	7.3	21 652	129 912
	5-FU	1000 250	519 255	4000 mg/m^2, Q3W, up to 6 cycles			
CBDCA +5-FU	CBDCA	450 150	5846 2491	AUC 5, Q3W, up to 6 cycles	8.3	17 841	107 046
	5-FU	1000 250	519 255	4000 mg/m^2, Q3W, up to 6 cycles			

JPY, Japanese Yen; OS, overall survival; CDDP, cisplatin; CBDCA, carboplatin; 5-FU, 5-fluorouracil; PTX, paclitaxel; Q3W, once every 3 weeks; Q1W, once every week.
[a]OS data for both CDDP and CBDCA were not available. [b]OS data for both CDDP and CBDCA were not available.

Table 3. Number of head and neck cancer patients receiving each regimen

Regimen	First-month costs (JPY)	Total (n = 907) No. (%)	<75 years (n = 674) No. (%)	≥75 years (n = 233) No. (%)
Pembrolizumab	612 851	330 (36.4)	198 (29.4)	132 (56.7)
Nivolumab	785 153	202 (22.3)	158 (2.4)	44 (18.9)
CDDP +5-FU + Pembrolizumab	634 504	153 (16.9)	139 (20.6)	14 (6.0)
CBDCA +5-FU + Pembrolizumab	630 692	125 (13.8)	95 (14.1)	30 (12.9)
PTX + CBDCA + Cetuximab	849 241	53 (5.8)	48 (7.1)	5 (2.1)
Clinical trial	–	29 (3.2)	24 (3.6)	5 (2.1)
CDDP +5-FU + Cetuximab[a]	836 807	8 (0.9)	6 (0.9)	2 (0.9)
CBDCA +5-FU + Cetuximab[a]	832 995	7 (0.8)	6 (0.9)	1 (0.4)

CDDP, cisplatin; CBDCA, carboplatin; 5-FU, 5-fluorouracil; ICI, immune checkpoint inhibitor; PTX, paclitaxel.
[a]EXTREME trial.

Discussion

To the best of our knowledge, this is the first study to conduct a broad survey of the frequency of different palliative chemotherapy regimens for the treatment of RM-SCCHN and their costs in the Japanese healthcare system. Our survey of patients being treated at 39 member JCOG-HNCSG healthcare facilities and 15 affiliated facilities revealed that over 90% of the first-line palliative chemotherapy regimens included ICI and that all of these met the criteria for high-cost medical care having a monthly cost of more than 500 000 JPY. However, we found differences in these results when the data were analyzed according to patient age.

Our findings that ICIs were used widely as the first-line treatment for RM-SCCHN are consistent with recommendations of the 2022 Japanese Clinical Practice Guidelines for Head and Neck Cancer (21). Prior to 2022, the previous standard treatment for RM-SCCHN was a selection of one of the regimens of the EXTREME trial (6). As our current survey showed, the EXTREME regimens are rarely used as first-line palliative chemotherapy. Only about 30% of patients in our survey younger than 75 years old received ICI monotherapy, while patients 75 years and older accounted for nearly 80% of the cases receiving ICI monotherapy. One reason for this disparity may be that elderly patients are expected to be less tolerant of cytotoxic anticancer agents. Thus, they may be more likely to choose ICI monotherapy rather than ICI combination therapy. In general, regimens composed of ICI or molecular targeting agents are more expensive than regimens lacking these agents. Our survey also revealed that the regimens composed of cetuximab plus platinum-based chemotherapy were more expensive than regimens containing ICI. This is partly because cetuximab is typically administered more often, i.e. on a weekly basis.

There was no available data in Japan on the cost-effectiveness of the various treatments for RM-SCCHN. However, such studies have been conducted in the US, UK, China, Switzerland, and Argentina, among others (32–39). These studies evaluated the cost-effectiveness of different ICI monotherapies, and some concluded they were cost-effective, but others concluded they were not. In general, cost-effectiveness is evaluated by comparing an incremental cost-effectiveness ratio (ICER) to the willingness-to-pay (WTP) (40). ICER represents the incremental cost between two treatment approaches divided by the incremental effectiveness (measured with quality-adjusted life year [QALY]). QALY is a product of a patient's health utility over survival time (41). Health utility measures quality of life and ranges from 0 (death) to 1 (perfect health). If the ICER is less than the WTP, the treatment is considered 'cost-effective' (40).

It is difficult to compare the cost-effectiveness of the same regimens across countries, because extrapolating foreign cost-effectiveness studies into the Japanese healthcare system is fraught with problems. These include fundamental differences in healthcare systems and implementation of care, variations in drug prices among countries, fluctuations in the drug prices over time, and differences between WTP and ICER thresholds (42). These metrics are significantly influenced by each country's social and economic situations (41). To assess the future cost-effectiveness of palliative chemotherapy for RM-SCCHN, it is crucial to discuss the WTP and ICER thresholds for anticancer drugs in Japan, which typically range from 5 to 15 million JPY/QALY (43). Ongoing WTP surveys need to be conducted because gross domestic product fluctuations affect ICER thresholds (43). Therefore, since the present study was merely a survey of the number of RM-SCCHN patients who received palliative chemotherapy and estimates of the drug costs of their treatment regimens, it is impossible to draw conclusions about cost-effectiveness without knowing the ICER thresholds and WTP.

To address the cost issue, it is important to have not only cost-effectiveness studies but also cost-control studies, such as those investigating less expensive treatments or shorter treatment durations. However, there are no such reports currently.

Regardless of several useful findings in our study, our survey had several limitations. First, because our survey did not collect data on the actual dosage of the drugs and whether the drugs were discontinued or reduced, the calculated costs do not reflect the actual costs of the chemotherapeutic drugs administered to the patients. Furthermore, the cost of therapy administration and imaging, treatment for adverse events, supportive care, and end-of-life care were not included in our survey and were thus not computed. Hence, the treatment regimen costs we computed might be underestimated. Third, we did not collect CPS data in this study, and since CPS will be essential for the choice of ICI alone or in combination with chemotherapy, the analysis including CPS could have provided a more profound discussion. Fourth, only eight pre-selected regimens were assessed in the present study, and the survey did not include patients who started treatment with S-1 or PTX + cetuximab. Thus, our findings do not fully reflect all the possible palliative chemotherapy regimens used in Japan for RM-SCCHN.

Conclusion

In Japan, the first-line palliative chemotherapy for RM-SCCHN is costly at more than 600 000 JPY per month, which is 30–40 times

higher than it was until 2012. The incremental cost is approximately 600 000–800 000 JPY per month. Over the last decade, the prognosis for RM-SCCHN has improved, but the costs of palliative chemotherapy have surged, placing a heavy burden on patients and society.

Supplementary data

Supplementary data are available at *Japanese Journal of Clinical Oncology* online.

Acknowledgements

Institutions belonging to the JCOG Head and Neck Cancer Study Group and affiliated institutions of this group joined in this survey.

Author contributions

KY, KW, KS, and RM (conception and design); JT, KS, AO, AN, HY, SS, MN, NT, KY, AS, FI, MS, RO, YM, AS, KK, DS, KE, YO, DN, AW, IT, HN, HS, CS, TT, KT, MS, KK, TS, YI, HM, TK, NA, TH, NM, ST, TN, MM, NM, SM, KY, MN, FM, YK, YT, MF, YT, SF, AH, TK, KK, SM, and SS (study materials and/patients); KY and KW (data collection); KY and KW (data analysis and interpretation). All authors contributed to the writing of this manuscript, approved the final version of this manuscript, and are accountable for this study.

Conflict of interest

Dr. Koichiro Wasano has received grants from the following entities outside of the submitted work: MEXT/JSPS KAKENHI; Kyorin Pharmaceutical Co., Ltd.; Nihon Cochlear Co., Ltd.; and MakiChie Co., Ltd. Dr. Naomi Kiyota has received grants from the following entities outside of the submitted work: Ono Pharmaceutical; Bristol-Meyers Squibb; Astra Zeneca Co., Ltd.; Chugai Pharmaceutical Co., Ltd.; Boehringer-Ingelheim; Bayer; Lilly; GSK; Adlai Nortye; and Abbvie. Dr. Kiyota is also a member of the advisory board of Ono Pharmaceutical Co., Ltd. and Adlai Nortye, and has received honoraria from Bayer; Ono Pharmaceutical Co., Ltd.; Bristol-Meyers Squibb; Merck Biopharma; Astra-Zeneca Co., Ltd.; Eisai; Lilly; Novartis; and Merck Sharp & Dohme. Dr. Nobuhiro Hanai has received research funding from MSD, Adlai Nortye USA Inc., and has received honoraria from Rakuten Medical. Dr. Akihiro Homma has received grants and/or personal fees from the following entities outside the submitted work. Grants: Japan AMED and the National Cancer Center Research and Development Fund; Taiho Pharmaceutical Co., Ltd.; ONO Pharmaceutical Co., Ltd.; KYORIN Pharmaceutical Co., Ltd.; Eisai and Mitsubishi Tanabe Pharma; Otsuka Pharmaceutical Factory; Iwasakidenshi Co., Ltd.; and Torii Pharmaceutical Co., Ltd. Personal fees: Taiho Pharmaceutical Co., Ltd.; ONO Pharmaceutical Co., Ltd.; KYORIN Pharmaceutical Co., Ltd.; Eisai and Mitsubishi Tanabe Pharma; Bristol-Myers Squibb K.K.; Merck; Bayer Yakuhin; Eli Lilly Japan; Sanofi; Rakuten Medical; Meiji Pharma; Demant Japan K.K.; and MSD K.K. Dr. Taiji Koyama has received honoraria from Shionogi, Merck Biopharma, Nihon Medi-Physics. Dr. Mitsuhiko Nakahira has received honoraria from Ono Pharmaceutical Co., Ltd.; Eisai, Tokyo-igakusha. Dr. Naohiro Takeshita has received honoraria from Merck Biopharma, Eisai. Dr. Kazuki Yokoyama has received honoraria from Merck Biopharma. Dr. Ichiro Tateya has received honoraria from Intuitive Surgical, Taiho Pharmaceutical Co., Ltd.; KYORIN Pharmaceutical Co., Ltd.; Olympus Co., Ltd.; Rakuten Medical Co., Merck BioPharma, Hisamitsu Pharmaceutical Co., Ltd.; Taisho Pharmaceutical Holdings CO., Ltd.; Meiji Seika pharma CO., Ltd. The remaining authors declare no conflicts of interest related to this study.

Funding

This work was supported in part by the Research Fund of National Federation of Health Insurance Societies (Kenpo-ren) and the National Cancer Center Research and Development Funds (2023-J-03).

Data availability statement

The de-identified data reported in this study will be made available upon reasonable request made to the corresponding author.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71:209–49. https://doi.org/10.3322/caac.21660.
2. Vigneswaran N, Williams MD. Epidemiologic trends in head and neck cancer and aids in diagnosis. *Oral Maxillofac Surg Clin North Am* 2014;26:123–41. https://doi.org/10.1016/j.coms.2014.01.001.
3. Pisani P, Airoldi M, Allais A, et al. Metastatic disease in head & neck oncology. *Acta Otorhinolaryngol Ital* 2020;40:S1–S86. https://doi.org/10.14639/0392-100X-suppl.1-40-2020.
4. Lacas B, Carmel A, Landais C, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 107 randomized trials and 19,805 patients, on behalf of MACH-NC group. *Radiother Oncol* 2021;156:281–93. https://doi.org/10.1016/j.radonc.2021.01.013.
5. Chow LQM. Head and neck cancer. *N Engl J Med* 2020;382:60–72. https://doi.org/10.1056/NEJMra1715715.
6. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 2008;359:1116–27. https://doi.org/10.1056/NEJMoa0802656.
7. Colombo N, Gore M. Treatment of recurrent ovarian cancer relapsing 6-12 months post platinum-based chemotherapy. *Crit Rev Oncol Hematol* 2007;64:129–38. https://doi.org/10.1016/j.critrevonc.2007.04.004.
8. Markman M, Rothman R, Hakes T, et al. Second-line platinum therapy in patients with ovarian cancer previously treated with cisplatin. *J Clin Oncol* 1991;9:389–93. https://doi.org/10.1200/JCO.1991.9.3.389.
9. Japan Society for Head and Neck Cancer. *Japanese Clinical Practice Guidelines for Head and Neck Cancer 2022 [In Japanese]*. Tokyo: Kanehara & Co., Ltd, 2022.
10. NCCN Clinical Practice Guidelines in Oncology. *Ovarian cancer continue including fallopian tube cancer and primary peritoneal cancer version 1*. 2024; https://www.nccn.org/professionals/physician_gls/pdf/ovarian.pdf (accessed March 30, 2024.).
11. Horichi Y, Matsui H, Yamamura Y, Iwae S. Platinum resistance and sensitivity in recurrent/metastatic head and neck squamous cell carcinoma. *Auris Nasus Larynx* 2023;51:132–7. https://doi.org/10.1016/j.anl.2023.05.005.
12. Yokota T, Homma A, Kiyota N, et al. Immunotherapy for squamous cell carcinoma of the head and neck. *Jpn J Clin Oncol* 2020;50:1089–96. https://doi.org/10.1093/jjco/hyaa139.
13. Machiels JP, Haddad RI, Fayette J, et al. Afatinib versus methotrexate as second-line treatment in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck progressing on or after platinum-based therapy (LUX-Head & Neck 1): an open-label, randomized phase 3 trial. *Lancet Oncol* 2015;16:583–94. https://doi.org/10.1016/S1470-2045(15)70124-5.

14. Saloura V, Cohen EE, Licitra L, et al. An open-label single-arm, phase II trial of zalutumumab, a human monoclonal anti-EGFR antibody, in patients with platinum-refractory squamous cell carcinoma of the head and neck. *Cancer Chemother Pharmacol* 2014;73:1227–39. https://doi.org/10.1007/s00280-014-2459-z.
15. Machiels J-P, Subramanian S, Ruzsa A, et al. Zalutumumab plus best supportive care versus best supportive care alone in patients with recurrent or metastatic squamous-cell carcinoma of the head and neck after failure of platinum-based chemotherapy: an open-label, randomised phase 3 trial. *Lancet Oncol* 2011;12:333–43. https://doi.org/10.1016/S1470-2045(11)70034-1.
16. Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab for recurrent squamous-cell carcinoma of the head and neck. *N Engl J Med* 2016;375:1856–67. https://doi.org/10.1056/NEJMoa1602252.
17. Ferris RL, Blumenschein G Jr, Fayette J, et al. Nivolumab vs investigator's choice in recurrent or metastatic squamous cell carcinoma of the head and neck: 2-year long-term survival update of CheckMate 141 with analyses by tumor PD-L1 expression. *Oral Oncol* 2018;81:45–51. https://doi.org/10.1016/j.oraloncology.2018.04.008.
18. Kiyota N, Hasegawa Y, Takahashi S, et al. A randomized, open-label, phase III clinical trial of nivolumab vs. therapy of investigator's choice in recurrent squamous cell carcinoma of the head and neck: a subanalysis of Asian patients versus the global population in checkmate 141. *Oral Oncol* 2017;73:138–46. https://doi.org/10.1016/j.oraloncology.2017.07.023.
19. Cohen EEW, Soulières D, Le Tourneau C, et al. Pembrolizumab versus methotrexate, docetaxel, or cetuximab for recurrent or metastatic head-and-neck squamous cell carcinoma (KEYNOTE-040): a randomised, open-label, phase 3 study. *The Lancet* 2019;393:156–67. https://doi.org/10.1016/S0140-6736(18)31999-8.
20. Burtness B, Harrington KJ, Greil R, et al. Pembrolizumab alone or with chemotherapy versus cetuximab with chemotherapy for recurrent or metastatic squamous cell carcinoma of the head and neck (KEYNOTE-048): a randomised, open-label, phase 3 study. *The Lancet* 2019;394:1915–28. https://doi.org/10.1016/S0140-6736(19)32591-7.
21. Homma A, Ando M, Hanai N, et al. Summary of Japanese clinical practice guidelines for head and neck cancer - 2022 update edited by the Japan society for head and neck cancer. *Auris Nasus Larynx* 2023;51:174–88. https://doi.org/10.1016/j.anl.2023.07.003.
22. Min HY, Lee HY. Molecular targeted therapy for anticancer treatment. *Exp Mol Med* 2022;54:1670–94. https://doi.org/10.1038/s12276-022-00864-3.
23. Shiravand Y, Khodadadi F, Kashani SMA, et al. Immune checkpoint inhibitors in cancer therapy. *Curr Oncol* 2022;29:3044–60. https://doi.org/10.3390/curroncol29050247.
24. Saluja R, Arciero VS, Cheng S, et al. Examining trends in cost and clinical benefit of novel anticancer drugs over time. *J Oncol Pract* 2018;14:e280–94. https://doi.org/10.1200/JOP.17.00058.
25. Vokinger KN, Hwang TJ, Grischott T, et al. Prices and clinical benefit of cancer drugs in the USA and Europe: a cost-benefit analysis. *Lancet Oncol* 2020;21:664–70. https://doi.org/10.1016/S1470-2045(20)30139-X.
26. da Veiga CRP, da Veiga CP, Drummond-Lage AP. Concern over cost of and access to cancer treatments: a meta-narrative review of nivolumab and pembrolizumab studies. *Crit Rev Oncol Hematol* 2018;129:133–45. https://doi.org/10.1016/j.critrevonc.2018.07.002.
27. Sugiura K, Hiratsuka H, Oshima G, Aiko S. Cost-effectiveness analysis of pembrolizumab in patients with treatment-refractory metastatic colorectal cancer in Japan. *Jpn J Clin Oncol* 2023;53:691–7. https://doi.org/10.1093/jjco/hyad050.
28. Konishi T, Fujiogi M, Michihata N, et al. Cost-effectiveness analysis of trastuzumab monotherapy versus adjuvant chemotherapy plus trastuzumab in elderly patients with HER2-positive early breast cancer. *Jpn J Clin Oncol* 2022;52:1115–23. https://doi.org/10.1093/jjco/hyac107.
29. Takushima Y, Igarashi A, Yoshihara H, Shitara K, Doi T. Cost-effectiveness of trifluridine/tipiracil against nivolumab for heavily pretreated metastatic gastric cancer in Japan. *Jpn J Clin Oncol* 2021;51:1383–90. https://doi.org/10.1093/jjco/hyab086.
30. Okumura H, Inoue S, Naidoo S, Holmstrom S, Akaza H. Cost-effectiveness analysis of enzalutamide for patients with chemotherapy-naive metastatic castration-resistant prostate cancer in Japan. *Jpn J Clin Oncol* 2021;51:1319–29. https://doi.org/10.1093/jjco/hyab071.
31. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31–41. https://doi.org/10.1159/000180580.
32. Wurcel V, Chirovsky D, Borse R, Altuna JI, Carabajal F, Gandhi J. Cost-effectiveness of Pembrolizumab regimens for the first-line treatment of recurrent or metastatic head and neck squamous cell carcinoma in Argentina. *Adv Ther* 2021;38:2613–30. https://doi.org/10.1007/s12325-021-01656-3.
33. Haddad R, Cohen EEW, Venkatachalam M, et al. Cost-effectiveness analysis of nivolumab for the treatment of squamous cell carcinoma of the head and neck in the United States. *J Med Econ* 2020;23:442–7. https://doi.org/10.1080/13696998.2020.1715414.
34. Liu M, Han S, Zheng B, et al. Cost-effectiveness analysis of pembrolizumab in the treatment of advanced recurrent metastatic head and neck squamous cell carcinoma in China and the United States. *Cancer Manag Res* 2019;Volume 11:9483–93. https://doi.org/10.2147/CMAR.S226243.
35. Xin W, Ding H, Fang Q, et al. Cost-effectiveness of pembrolizumab for treatment of platinum-resistant recurrent or metastatic head and neck squamous cell carcinoma in China: an economic analysis based on a randomised, open-label, phase III trial. *BMJ Open* 2020;10:e038867. https://doi.org/10.1136/bmjopen-2020-038867.
36. Ward MC, Shah C, Adelstein DJ, et al. Cost-effectiveness of nivolumab for recurrent or metastatic head and neck cancer. *Oral Oncol* 2017;74:49–55. https://doi.org/10.1016/j.oraloncology.2017.09.017.
37. Hirschmann A, Lupatsch JE, Schwenkglenks M, et al. Cost-effectiveness of nivolumab in the treatment of head and neck cancer. *Oral Oncol* 2018;87:104–10. https://doi.org/10.1016/j.oraloncology.2018.10.032.
38. Tringale KR, Carroll KT, Zakeri K, Sacco AG, Barnachea L, Murphy JD. Cost-effectiveness analysis of nivolumab for treatment of platinum-resistant recurrent or metastatic squamous cell carcinoma of the head and neck. *J Natl Cancer Inst* 2018;110:479–85. https://doi.org/10.1093/jnci/djx226.
39. Zargar M, McFarlane T, Chan KKW, Wong WWL. Cost-effectiveness of nivolumab in recurrent metastatic head and neck squamous cell carcinoma. *Oncologist* 2018;23:225–33. https://doi.org/10.1634/theoncologist.2017-0277.
40. Shiroiwa T, Sung YK, Fukuda T, Lang HC, Bae SC, Tsutani K. International survey on willingness-to-pay (WTP) for one additional QALY gained: what is the threshold of cost effectiveness? *Health Econ* 2010;19:422–37. https://doi.org/10.1002/hec.1481.
41. Prieto L, Sacristan JA. Problems and solutions in calculating quality-adjusted life years (QALYs). *Health Qual Life Outcomes* 2003;1:80. https://doi.org/10.1186/1477-7525-1-80.
42. Schwarzer R, Rochau U, Saverno K, et al. Systematic overview of cost-effectiveness thresholds in ten countries across four continents. *J Comp Eff Res* 2015;4:485–504. https://doi.org/10.2217/cer.15.38.
43. Hasegawa M, Komoto S, Shiroiwa T, Fukuda T. Formal implementation of cost-effectiveness evaluations in Japan: a unique health technology assessment system. *Value Health* 2020;23:43–51. https://doi.org/10.1016/j.jval.2019.10.005.

JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2024, 1–9
https://doi.org/10.1093/jjco/hyae116
Original Article

OXFORD

Original Article

Cost of medical care for malignant brain tumors at hospitals in the Japan Clinical Oncology Group brain-tumor study group

Kazuya Motomura[1,*], Keita Sasaki[2], Narushi Sugii[3], Shigeru Yamaguchi[4], Hirotaka Inoue[5], Akito Oshima[6], Kazuhiro Tanaka[7], Yoshihiro Otani[8], Mitsuaki Shirahata[9], Ichiyo Shibahara[10], Motoo Nagane[11], Shunsuke Tsuzuki[12], Tomoo Matsutani[13], Yoshihiro Tsukamoto[14], Noriyuki Kijima[15], Kenichiro Asano[16], Makoto Ohno[17], Akihiro Inoue[18], Yohei Mineharu[19], Keisuke Miyake[20], Yuta Mitobe[21], Mitsuto Hanihara[22], Yu Kawanishi[23], Shoichi Deguchi[24], Masato Saito[25], Ryosuke Matsuda[26], Kenta Ujifuku[27], Hideyuki Arita[28], Yuichi Sato[29], Shinji Yamashita[30], Ushio Yonezawa[31], Junya Yamaguchi[1], Yasutomo Momii[32], Takahiro Ogawa[33], Atsushi Kambe[34], Shigeo Ohba[35], Junya Fukai[36], Norihiko Saito[37], Masashi Kinoshita[38], Koichiro Sumi[39], Ryohei Otani[40], Takeo Uzuka[41], Noriyoshi Takebe[42], Shinichiro Koizumi[43], Ryuta Saito[1], Yoshiki Arakawa[19], Yoshitaka Narita[17] and the Members of Japan Clinical Oncology Group Brain Tumor Study Group (JCOG-BTSG)

[1]Department of Neurosurgery, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Japan, [2]JCOG Data Center/Operations Office, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo, Japan, [3]Department of Neurosurgery, University of Tsukuba Hospital, 2-1-1 Amakubo, Tsukuba, Japan, [4]Department of Neurosurgery, Faculty of Medicine, Hokkaido University, North 15, West 7, Kita-ku, Sapporo, Japan, [5]Department of Neurosurgery, Graduate School of Medical Sciences, 1-1-1, Honjo, Chuo-ku, Kumamoto University, Kumamoto, Japan, [6]Department of Neurosurgery, Yokohama City University, 3-9, Fukuura, Kanazawa, Yokohama, Japan, [7]Department of Neurosurgery, Kobe University Hospital, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe, Japan, [8]Department of Neurological Surgery, Okayama University Faculty of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, kita-ku, Okayama, Japan, [9]Department of Neurosurgery/Neuro-oncology, Saitama Medical University International Medical Center, 1397-1 Yamane, Hidaka, Saitama, Japan, [10]Department of Neurosurgery, Kitasato University School of Medicine, 1-15-1, Kitasato, Minami-ku, Sagamihara, Japan, [11]Department of Neurosurgery, Kyorin University Faculty of Medicine, 6-20-2 Shinkawa, Mitaka, Tokyo, Japan, [12]Department of Neurosurgery, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, Japan, [13]Department of Neurological Surgery, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuou-ku, Chiba, Japan, [14]Department of Neurosurgery, Brain Research Institute, Niigata University, 1-757 Asahimachi-dori, Chuo-ku, Niigata, Japan, [15]Department of Neurosurgery, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, Osaka, Japan, [16]Department of Neurosurgery, Hirosaki University Graduate School of Medicine, Zaifu-cho 5, Hirosaki, Japan, [17]Department of Neurosurgery and Neuro-Oncology, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo, Japan, [18]Department of Neurosurgery, Ehime university school of medicine, 454, Shitsukawa, Toon, Ehime, Japan, [19]Department of Neurosurgery, Kyoto University Graduate School of Medicine, 54 Kawahara-cho Shogoin Sakyo-ku, Kyoto, Japan, [20]Department of Neurological Surgery, Kagawa University Faculty of Medicine, 1750-1 Ikenobe, Miki-cho, Kita-gun, Kagawa, Japan, [21]Department of Neurosurgery, Yamagata

University Hospital, 2-2-2, Iida-Nishi, Yamagata, Japan, [22]Department of Neurosurgery, University of Yamanashi, 1110 Shimokato, Chuo, Yamanashi, Japan, [23]Department of Neurosurgery, Kochi Medical School, Kochi University, Kohasu, Oko-cho, Nankoku, Kochi, Japan, [24]Department of Neurosurgery, Shizuoka Cancer Center, Shimonagakubo 1007, Nagaizumi, Sunto-gun, Shizuoka, Japan, [25]Department of Neurosurgery, Asahikawa Medical University, 2-1-1-1 Midorigaoka Higashi, Asahikawa, Japan, [26]Department of Neurosurgery, Nara Medical University, Shijo-cho 840, Kashihara, Nara, Japan, [27]Department of Neurosurgery, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki, Japan, [28]Department of Neurosurgery, Osaka International Cancer Institute, 3-1-69, Otemae, Chuo-ku, Osaka, Japan, [29]Department of Neurosurgery, Iwate Medical University School of Medicine, 2-1-1 Idai-dori, Yahaba, Shiwa, Iwate, Japan, [30]Department of Neurosurgery, Miyazaki University, 5200 Kihara Kiyotake, Miyazaki, Japan, [31]Department of Neurosurgery, Hiroshima University Hospital, 1-2-3 Minamiku Kasumi, Hiroshima, Japan, [32]Department of Neurosurgery, Oita University Faculty of Medicine, 1-1 Idaigaoka Hasama-machi Yufu, Oita, Japan, [33]Department of Neurosurgery, Kyoto Prefectural University of Medicine, 465 Kajii-cho, Kawaramachi-Hirokoji, Kamigyo-ku, Kyoto, Japan, [34]Department of Brain and Neurosciences, Division of Neurosurgery, Faculty of Medicine, Tottori University, 36-1 Nishi-cho, Yonago, Tottori, Japan, [35]Department of Neurosurgery, Fujita Health University, 1-98Dengakugakubo, Kutsukake-cho, Toyoake, Aichi, Japan, [36]Department of Neurological Surgery, Wakayama Medical University School of Medicine, 811-1 Kimiidera, Wakayama, Japan, [37]Department of Neurosurgery, Toho University Ohashi Medical Center, 2-22-36, Ohashi, Meguro, Tokyo, Japan, [38]Department of Neurosurgery, Kanazawa University, 13-1 Takara-machi, Kanazawa, Japan, [39]Department of Neurological Surgery, Nihon University School of Medicine, 30-1 Oyaguchikamicho, Itabashi-ku, Tokyo, Japan, [40]Department of Neurosurgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, 3-18-22 Honkomagome, Bunkyo-ku, Tokyo, Japan, [41]Department of Neurosurgery, Dokkyo Medical University Hospital, 880 Kitakobayashi, Mibu-machi, Shimotsuga-gun, Tochigi, Japan, [42]Department of Neurosurgery, Medical Research Institute Kitano Hospital, PIIF Tazuke-kofukai, 2-4-20 Ohgimachi, Kita-ku, Osaka, Japan and [43]Department of Neurosurgery, Hamamatsu University School of Medicine, 1-20-1, Handayama, Higashi-ku, Hamamatsu, Shizuoka, Japan

*For reprints and all correspondence: Kazuya Motomura, Department of Neurosurgery, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan. E-mail: kmotomura@med.nagoya-u.ac.jp
Received 27 April 2024; Editorial Decision 5 August 2024; Accepted 21 August 2024

Abstract

Background: This study aimed to investigate what treatment are selected for malignant brain tumors, particularly glioblastoma (GBM) and primary central nervous system lymphoma (PCNSL), in real-world Japan and the costs involved.

Methods: We conducted a questionnaire survey regarding treatment selections for newly diagnosed GBM and PCNSL treated between July 2021 and June 2022 among 47 institutions in the Japan Clinical Oncology Group-Brain Tumor Study Group. We calculated the total cost and cost per month of the initial therapy for newly diagnosed GBM or PCNSL.

Results: The most used regimen (46.8%) for GBM in patients aged ≤74 years was 'Surgery + radiotherapy concomitant with temozolomide'. This regimen's total cost was 7.50 million JPY (Japanese yen). Adding carmustine wafer implantation (used in 15.0%), TTFields (used in 14.1%), and bevacizumab (BEV) (used in 14.5%) to the standard treatment of GBM increased the cost by 1.24 million JPY for initial treatment, and 1.44 and 0.22 million JPY per month, respectively. Regarding PCNSL, 'Surgery (biopsy) + rituximab, methotrexate, procarbazine, and vincristine (R-MPV) therapy' was the most used regimen (42.5%) for patients of all ages. This regimen incurred 1.07 million JPY per month. The three PCNSL regimens based on R-MPV therapy were in ultra-high-cost medical care (exceeding 1 million JPY per month).

Conclusions: Treatment of malignant brain tumors is generally expensive, and cost-ineffective treatments such as BEV are frequently used. We believe that the results of this study can be used to design future economic health studies examining the cost-effectiveness of malignant brain tumors.

Key words: glioblastoma, primary central nervous system lymphoma, treatment regimen, high-cost medical care, cost

Introduction

Glioblastoma (GBM) is one of the most malignant primary brain tumors and diffusely infiltrates the central nervous system (1,2). In Japan, GBM is a rare cancer, accounting for 1.68 cases of 100 000 people per year (3). Postoperative concomitant chemoradiotherapy with temozolomide (TMZ) and adjuvant TMZ are the standard treatments for GBM worldwide (4), with a median overall survival (OS) period of 14.6 months (5).

As GBM has the poor prognosis, treatment development is currently underway to determine what to add to TMZ to prolong survival for GBM. Firstly, carmustine wafer implantation (Gliadel) is an intracavity sustained-release formulation containing carmustine, a nitrosourea alkylating antineoplastic agent, implanted on the resection surface during the resection of malignant gliomas (6). Secondly, bevacizumab (BEV) is another drug approved for GBM treatment. Although there are two randomized controlled trials (AVAglio and RTOG0805) on BEV in combination with TMZ plus chemoradiotherapy for newly diagnosed GBM, it is not considered the standard of care for newly diagnosed GBM, mainly because two large placebo-controlled phase III trials showed no significant differences in OS, and this has not been approved for use in newly diagnosed GBM in any country other than Japan. Thirdly, the NovoTTF-100A system is a portable device that generates a low-intensity, intermediate-frequency alternating electric field called a tumor-treating field (TTF), which is believed to kill cancer cells by inhibiting their replication (7). However, the actual treatment selections for GBM in the real world as well as their associated costs have not been fully investigated.

According to the Report of the Brain Tumor Registry of Japan (2005–2008) (5), primary central nervous system lymphoma (PCNSL) accounts for 4.9% (814 per 4 years) of all primary brain tumors, and the incidence of PCNSL has been increasing in recent years. Currently, the standard treatment for PCNSL is HD-MTX-based remission induction therapy and consolidation therapy with high-dose cytarabine (AraC) or WBRT. The 2-year survival rate of patients treated with rituximab + MTX + procarbazine + vincristine (R-MPV), which is a combination of HD-MTX-based multiple agent remission induction therapy and HD-AraC, consolidation pharmacotherapy, and 23.4 Gy of reduced dose whole brain radiation, was 90% (8).

In addition to the standard treatment for these malignant brain tumors, further therapeutic development should be conducted to enable prolonged survival and may achieve a cure in the future. However, the high development costs of these new drugs render them costly. Japan has a universal health insurance system that significantly reduces patients' out-of-pocket expenses, even when medical costs are high (9). The reduced costs come from insurance premiums and taxes paid by Japanese citizens. As the cost of medical care continues to increase, the burden on the public is approaching its limit. In the future, it will be necessary to consider drug costs and the effects of treatment choices on patient outcomes and the effects on healthcare costs and the use of limited healthcare resources from a broad perspective. Particularly, the burden of cancer continues to grow, and the disease is becoming a major economic burden for all industrialized countries (10,11). Therefore, the Japan Clinical Oncology Group (JCOG) Health Economic Committee considered that it was necessary to discuss sustainable medical care for the next generation of patients.

In the present study, we conducted a survey at a hospital in the JCOG-BTSG to reveal the treatment options available for GBM and PCNSL among malignant brain tumors and the medical costs for each regimen. This study aimed to investigate what treatment are available for malignant brain tumors, particularly GBM and PCNSL, in real-world Japan and the costs involved. It was led by the JCOG Health Economic Committee.

Materials and methods

A questionnaire survey

A questionnaire survey was conducted at 47 JCOG-BTSG-registered centers to determine the initial treatment regimens used for malignant brain tumors that are not curable: (1) newly diagnosed GBM and (2) PCNSL. The survey was conducted using Google Form, which included the name of the facility and the name of the researchers. The lists of initial treatment regimens established in the questionnaire survey items are shown in Tables 1 (newly diagnosed GBM) and Table 2 (PCNSL). There were 11 treatment regimens for GBM and eight treatment regimens for PCNSL (Tables 1 and 2). The content of each treatment regimen was extracted from regimens used mainly in Japan. In the survey, the total number of patients receiving each treatment was collected, but individual patient data were not collected. The number of patients who were treated with each regimen was divided by 'age ≤ 74 years/≥ 75 years (at the start of treatment)' in the survey. The study period covered cases of newly diagnosed GBM or PCNSL from July 2021 to June 2022 at each institution.

Calculation of the cost of each treatment for malignant brain tumors

This study calculated the total cost of the initial therapy for newly diagnosed GBM and PCNSL (not including the cost of maintenance therapy). Medical costs were calculated based on Japanese receipt scores. Monthly cost was calculated based on the treatment duration for each treatment regimen. Among the treatments, we defined 'high-cost medical care' as treatments of ≥0.5 million JPY per month and 'ultra-high-cost medical care' as treatments of ≥1 million JPY per month, as defined by the JCOG Health Economics Committee.

Results

General information

Questionnaires were collected from patients with newly diagnosed GBM or PCNSL treated between April 2022 and March 2023 from 47 JCOG-BTSG registries. The questionnaires collected from patients with newly diagnosed GBM received responses from 42 of all 47 JCOG-BTSG-registered centers (89.4%). In contrast, the survey for PCNSL received responses from 39 of the 47 JCOG-BTSG-registered centers (83.0%). Among these centers, the total numbers of patients surveyed for GBM and PCNSL were 733 and 258, respectively. In Japan, the Center for Cancer Genomics and Advanced Therapeutics offers a next-generation sequencing-based comprehensive genomic profiling test for patients with malignant brain tumors. This test targets patients with GBM or PCNSL. The cost is 0.56 million JPY (12).

Results of a survey of treatment regimens used for newly diagnosed GBM

Overall, 733 GBM cases were reported, of which 530 GBM cases were reported for those aged ≤74 years and 203 GBM cases were reported for those aged ≥75 years. The proportions of elderly and non-elderly patients receiving each treatment regimen for newly diagnosed GBM are shown in Fig. 1 and Table 1. The most used regimen for GBM in patients aged ≤74 years was 'Surgery + radiotherapy

Table 1. Initial treatment regimens for newly diagnosed GBM surveyed in the questionnaire.

Treatment regimens	74 years old or younger		75 years old or older	
	No. of patients (n = 530)	(%)	No. of patients (n = 203)	(%)
Surgery + RT (60Gy/30fr)	5	1.0	14	6.9
Surgery + RT (60Gy/30fr) + TMZ	248	46.8	16	7.9
Surgery + RT (60Gy/30fr) + TMZ + Carmustine wafer implantation	57	10.8	6	3.0
Surgery + RT (60Gy/30fr) + TMZ + TTFields	56	10.6	3	1.5
Surgery + RT (60Gy/30fr) + TMZ + Carmustine wafer implantation + TTFields	29	5.5	0	0
Surgery + RT (40Gy/15fr) + TMZ	40	7.6	117	57.7
Surgery + RT (25Gy/5fr) + TMZ	14	2.7	22	10.9
Surgery + RT (60Gy/30fr) + TMZ + BEV	54	10.2	24	11.9
Surgery + RT (60Gy/30fr) + TMZ + BEV + Carmustine wafer implantation	12	2.3	1	0.5
Surgery + RT (60Gy/30fr) + TMZ + BEV + TTFields	10	1.9	0	0
Surgery + RT (60Gy/30fr) + TMZ + BEV + Carmustine wafer implantation + TTFields	5	1.0	0	0
Number of facilities that responded to the survey: 42 of the 47 JCOG-BTSG-registered centers (89.4%)				

Abbreviation: RT, radiation therapy; TMZ, temozolomide, TTFields, tumor-treating fields; BEV, bevacizumab.

Table 2. Initial treatment regimens for newly diagnosed PCNSL surveyed in the questionnaire.

Treatment regimens	74 years old or younger		75 years old or older	
	No. of patients (n = 172)	(%)	No. of patients (n = 86)	(%)
Surgery (biopsy) + HD-MTX therapy	11	6.4	12	14.0
Surgery (biopsy) + HD-MTX therapy + Tirabrutinib	2	1.2	3	3.5
Surgery (biopsy) + HD-MTX therapy + ASCT/HDC	3	1.8	0	0
Surgery (biopsy) + HD-MTX therapy + WBRT	7	4.1	5	5.9
Surgery (biopsy) + R-MPV therapy	73	42.5	46	53.5
Surgery (biopsy) + R-MPV therapy + Tirabrutinib	12	7.0	8	9.4
Surgery (biopsy) + R-MPV therapy + ASCT/HDC	19	11.1	0	0
Surgery (biopsy) + R-MPV therapy + WBRT	45	26.2	12	14.0
Number of facilities that responded to the survey: 39 of the 47 JCOG-BTSG-registered centers (83.0%)				

Abbreviation: HD-MTX, high-dose methotrexate; WBRT, whole brain radiotherapy; R-MPV, rituximab, methotrexate, procarbazine, and vincristine; ASCT/HDC, autologous stem cell transplantation/high-dose chemotherapy.

(RT) (60 Gy/30 fr) + TMZ,' (248/530 cases, 46.8%), which is the standard treatment for non-elderly patients with GBM. The next most used regimen was 'Surgery + RT (60 Gy/30 fr) + TMZ' plus (1) carmustine wafer implantation or (2) TTFields, or (3) BEV, which were almost equally used. In contrast, the most used regimen for GBM in patients aged ≥75 years was 'Surgery + RT (40 Gy/15 fr) + TMZ' (117/203 cases, 57.7%), which is the standard treatment for elderly patients with GBM. The next most used regimens were 'Surgery + RT (60 Gy/30 fr) + TMZ plus BEV' (24/203 cases, 11.9%), and 'Surgery + RT (25 Gy/5 fr) + TMZ' (22/203 cases, 10.9%), which were performed as clinical trials. 'Carmustine wafer implantation' and 'TTFields' tended not to be used in elderly patients with GBM. Overall, the percentages of carmustine wafer implantation, TTFields, and BEV used were 110/733; 15.0%, 103/733; 14.1%, and 106/733; 14.5%, respectively.

Comparison of the cost of each treatment regimen used for newly diagnosed GBM

The cost of treatment for eight of the 11 regimens for GBM used in the survey was investigated (Table 3). Among all 733 GBM patients, 521 patients (71.1%) were in the 'high-cost medical care' group, while 116 (15.8%) were in the 'ultra-high-cost medical care' group. As divided to age groups, 471/530 (88.9%) patients ≤74 years belonged to the 'high-cost medical care' group, while 112/530 (21.1%) were in the 'ultra-high-cost medical care' group. Among patients ≥75 years, 50/203 (24.6%) were in the 'high-cost medical care' group, compared to 4/203 (2.0%) in the 'ultra-high-cost medical care' group with a low percentage.

The total cost of 'Surgery + RT (60 Gy/30 fr) + TMZ', the standard treatment for GBM in non-elderly patients as initial treatment, was 7.50 million JPY, including 1.32 million JPY for surgery and 1.00 million JPY for radiation therapy. One course of maintenance therapy cost 0.15 million JPY per month for TMZ maintenance therapy. The cost of 'Surgery + RT (60 Gy/30 fr) + TMZ (standard of care)' for the first 6 months, 1 year, and up to 12 courses of TMZ maintenance therapy is shown in Table 3. Adding carmustine wafer implantation to the standard treatment of GBM in non-elderly patients increased the cost by 1.24 million JPY for initial treatment, adding TTFields increased the cost by 1.44 million JPY per month, and adding BEV increased the cost by 0.22 million JPY per a month. 'Surgery + RT (60 Gy/30 fr) + TMZ' (standard of care), adding 'TTFields regimen,'

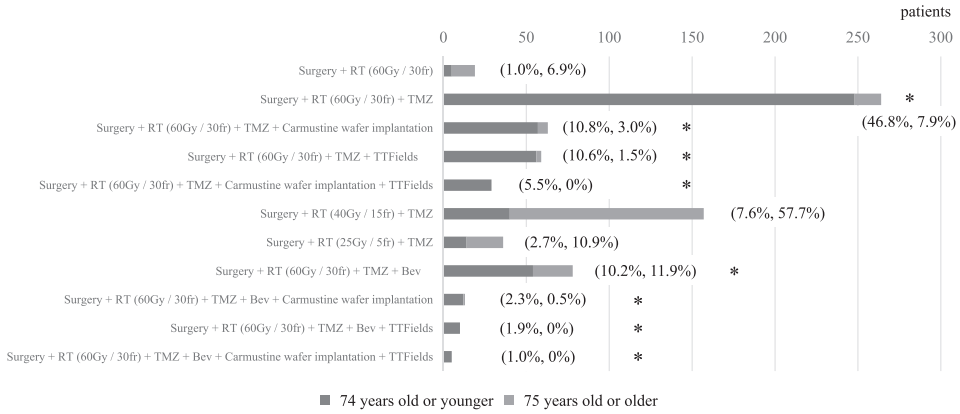


Fig. 1. The proportion of each regimen for newly diagnosed GBM, selected by JCOG-participating physicians, according to the age group. Percentages show the proportion of patients receiving the regimen in each age groups (<75 years or > 75 years). The bold star highlights the regimens with high- or ultra-high- cost.

Table 3. Total cost of each treatment regimen and monthly cost for newly diagnosed GBM.

Treatment	Surgery cost (million JPY)	Cost for the first 6 months of treatment (including 3 courses of TMZ maintenance therapy) (million JPY)	Cost for the first 1 year of treatment (including 9 courses of TMZ maintenance therapy) (million JPY)	Cost for initial treatment without recurrence +12 courses of TMZ maintenance therapy (million JPY)	Cost per month (million JPY)	high-cost medical care	ultra-high-cost medical care
Surgery + RT (60Gy/30fr) + TMZ (Standard of care) (JCOG0911)	1.32	7.95	8.85	9.3	0.74	○	
Surgery + RT (60Gy/30fr) + TMZ + Carmustine wafer implantation (JCOG1703)	1.32	9.19	10.09	10.54	0.84	○	
Surgery + RT (60Gy/30fr) + TMZ + TTFields	1.32	12.27	21.81	26.58	1.82	○	○
Surgery + RT (60Gy/30fr) + TMZ + Carmustine wafer implantation + TTFields	1.32	13.51	23.05	27.82	1.92	○	○
Surgery + RT (60Gy/30fr) + TMZ + BEV	1.32	8.61	10.83	12.31	0.9	○	
Surgery + RT (60Gy/30fr) + TMZ + BEV + Carmustine wafer implantation	1.32	9.85	12.07	13.55	1.01	○	○
Surgery + RT (60Gy/30fr) + TMZ + BEV + TTFields	1.32	12.93	23.79	29.59	1.98	○	○
Surgery + RT (60Gy/30fr) + TMZ + BEV + Carmustine wafer implantation + TTFields	1.32	14.17	25.03	30.83	2.09	○	○

Abbreviation: RT, radiation therapy; TMZ, temozolomide; TTFields, tumor-treating fields; BEV, bevacizumab; JCOG, Japan Clinical Oncology Group.

'carmustine wafer implantation + TTFields regimen,' 'BEV + carmustine wafer implantation + TTFields regimen,' 'BEV + carmustine wafer implantation + TTFields regimen,' and 'BEV + carmustine wafer implantation + TTFields regimen' were regimens for ultra-high-cost medical care.

Results of a survey of treatment regimens used for PCNSL

A total of 258 PCNSL cases were reported, of which 172 were reported in patients aged ≤74 years and 86 were reported in patients aged ≥75 years. The proportions of elderly and non-elderly patients in each treatment regimen for PCNSL are shown in Fig. 2 and Table 2. 'Surgery (biopsy) + R-MPV therapy' was the commonly used regimen for patients with PCNSL of all ages (119/258 cases, 46.1%). As the European Association of Neuro-Oncology guidelines state that RT should be avoided in elderly patients with PCNSL (13), 'Surgery (biopsy) + R -MPV therapy + WBRT' was the second most common treatment regimen. Autologous stem cell transplantation high-dose chemotherapy was not performed in patient with PCNSL aged >75 years.

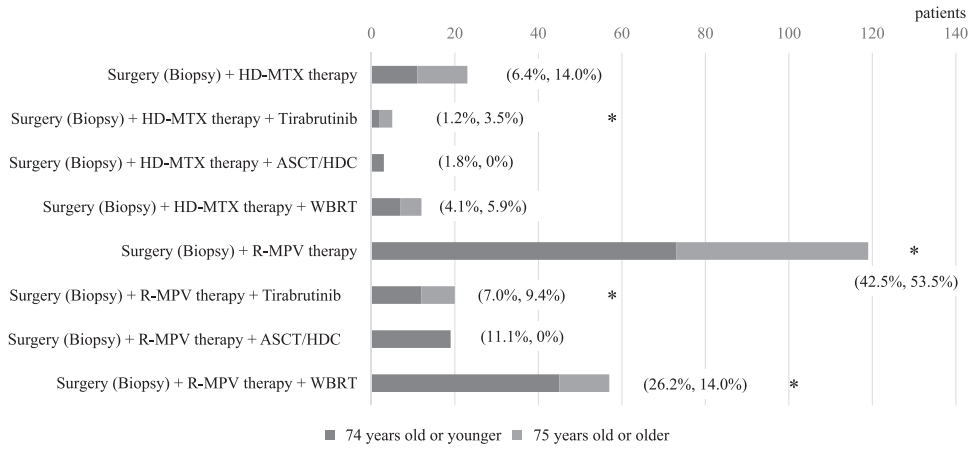


Fig. 2. The proportion of each regimen for newly diagnosed PCNSL, selected by JCOG-participating physicians, according to the age group. Percentages show the proportion of patients receiving the regimen in each age groups (<75 years or > 75 years). The bold star highlights the regimens with high- or ultra-high-cost.

Table 4. Total cost of each treatment regimen and monthly cost for newly diagnosed PCNSL.

Treatment	Surgery (biopsy) cost (million JPY)	Cost for the first 6 months of treatment (Cost for initial treatment without recurrence) (million JPY)	Cost per month (million JPY)	high-cost medical care	ultra-high-cost medical care
Surgery (biopsy) + HD-MTX therapy (Previous standard of care, JCOG1114)	0.2	2	0.33		
Surgery (biopsy) + HD-MTX therapy + Tirabrutinib	0.2	4.73	0.79	○	
Surgery (biopsy) + HD-MTX therapy + WBRT	0.2	2.9	0.48		
Surgery (biopsy) + R-MPV therapy	0.2	6.4	1.07	○	○
Surgery (biopsy) + R-MPV therapy + Tirabrutinib	0.2	8.22	1.37	○	○
Surgery (biopsy) + R-MPV therapy + WBRT (Standard of care)	0.2	7.9	1.32	○	○

Abbreviation: HD-MTX, high-dose methotrexate; WBRT, whole brain radiotherapy; R-MPV, rituximab, methotrexate, procarbazine, and vincristine; JCOG, Japan Clinical Oncology Group.

Comparison of the cost of each treatment regimen used for PCNSL

The total cost of six of the eight regimens for PCNSL used in the survey was investigated (Table 4). Among the 258 patients with PCNSL, 201 (77.9%) were in the 'high-cost medical care' group, while 196 (76.0%) were in the 'ultra-high-cost medical care' group. Among patients ≤74 years, 132/172 (76.7%) were in the 'high-cost medical care' group, compared to 130/172 (75.6%) in the 'ultra-high-cost medical care' group. In contrast, among patients ≥75 years, 69/86 (80.2%) were in the 'high-cost medical care' group, compared to 66/86 (76.7%) in the 'ultra-high-cost medical care' group.

The most frequently used regimen at the JCOG-BTSG-registered centers was 'Surgery (biopsy) + R-MPV therapy,' with a total cost of 6.4 million JPY and 1.07 million JPY per month. The cost of the stereotactic brain tumor biopsy surgery was 0.2 million JPY. Regarding chemotherapy, MTX therapy (two courses) cost 0.7 million JPY per month, R-MPV therapy (two courses) cost 1.4 million JPY per month, and tirabrutinib cost 0.91 million JPY per month. The three regimens based on R-MPV therapy involved ultra-high-cost medical care, with a monthly cost exceeding 1 million JPY. In contrast, adding tirabrutinib to HD-MTX or R-MPV therapy resulted in an increase in 0.91 million JPY per month.

Discussion

Both GBM and PCNSL are rare brain tumors with poor prognoses. Although these tumors are treated with what is considered the standard care, little consideration has been given to the cost of the standard treatment itself, the cost of new drugs added to the standard treatment, and the cost-benefit ratio of these new drugs (14,15). Furthermore, clinical trials for the development of new therapies in Japan have not been conducted in a cost-benefit manner. In this study, we investigated the treatment regimens used for GBM and PCNSL at JCOG-BTSG-registered centers with the most experience in treating brain tumors in Japan and the cost of these regimens.

The standard treatment for GBM is 'Surgery + RT (60 Gy/30 fr) + 6–12 cycles of TMZ' (4,16). In our series, this regimen was also the commonly used regimen for GBM patients with 264 of 733 cases (36.0%). In the current study, 15.0% (110/733) of the patients with GBM were treated with carmustine wafer implantation. However, there are not many prospective randomized clinical trials that compare these treatment regimen with groups of patients treated with other agents. Although there are some reports from retrospective studies [17–19), there is still no evidence that carmustine wafer implantation in GBM leads to a prolonged prognosis. We

are currently awaiting the results of a randomized phase III study, JCOG1703 (16), for newly diagnosed maximally resected GBM comparing carmustine wafer implantation followed by chemoradiotherapy with TMZ with chemoradiotherapy alone (16). While it remains to be seen how carmustine wafer implantation during surgery much improves the prognosis for of patients with GBM will improve with carmustine wafer implantation during surgery, we should firmly consider the 1.24 million JPY increase over standard therapy. Therefore, this drug is not generally used for GBM in routine practice before the results of the phase III trial, making it less available than it should be.

For GBM, the following two treatments (TTFields and BEV) are representative of prospective randomized clinical trials. A randomized phase III trial was conducted to evaluate the efficacy of the TTFields in newly diagnosed GBM (20). A total of 695 patients with GBM were randomized to receive TMZ maintenance with TTFields or maintenance with TMZ alone after completion of the initial treatment with the Stupp regimen. In patients with newly diagnosed GBM, the median OS period was significantly prolonged by 4.9 months in the TTFields group compared with TMZ alone (20.9 months vs. 16.0 months). A prolonged OS benefit of 4.9 months for TTFields must be considered for cost-effectiveness, considering that the cost per month for TTFields is 1.44 million JPY. A French research group performed a cost-effectiveness analysis of TTFields (21). The analysis using the Markov model showed that the addition of TTFields to the standard treatment with TMZ increased the life expectancy by 4.08 months (0.34 life-years gained (LYG)) and the cost per patient by €185 476. The incremental cost-effectiveness ratio (ICER) was €549 909/LYG. Therefore, this study emphasizes that the current cost of TTFields has an ICER that is significantly high to be cost-effective. However, other research groups tested different models and concluded that TTF remains a less cost-effective intervention, significantly hindering its dissemination to potentially eligible patients (22). Thus, given that TTFields are costly, there is a difference in opinion as to whether they are cost-effective. In the present study, 14.1% (103/733) of patients with GBM were treated with TTF. In Japan, the use of TTF increases the monthly amount by 1 440 000 JPY, with the ICER estimated at 17280000JPY/LYG (incremental cost: 5875200JPY; incremental effectiveness: 0.34 LYG). Therefore, it is considered to be a less cost-effective treatment since it far exceeds the willingness-to-pay (WTP) threshold in Japan (7.5 million yen/QALY).

In the AVAglio study, compared chemoradiotherapy with TMZ plus BEV (23) and chemoradiotherapy with TMZ plus placebo in patients with newly diagnosed GBM, the median OS period was not significantly different at 16.8 and 16.7 months, respectively. Another randomized controlled trial of BEV in combination with chemoradiotherapy with TMZ for newly diagnosed GBM is the RTOG0805 trial (24) showed no difference in OS between BEV-treated (median survival, 15.7 months) and placebo-treated patients (median survival, 16.1 months). Therefore, BEV is not considered the standard of care for newly diagnosed GBM worldwide, partly because of the lack of significant OS differences in two large placebo-controlled phase III trials. However, the use of BEV for newly diagnosed GBM has been inconsistently approved by insurance in Japan. Even in the JCOG-BTSG registry, 106/733 (14.5%) patients with newly diagnosed GBM were treated with BEV despite a lack of OS prolongation (Fig. 1). One of the reasons why BEV is often used in Japan is that 49.2% of patients newly diagnosed with GBM in Japan have a Karnofsky performance status (KPS) of ≤70 and BEV is used to improve performance status of patients. Some patients with GBM with low KPS may benefit from additional BEV treatment with RT + TMZ, but considering that BEV costs 0.22 million JPY per month, the use of BEV for newly diagnosed GBM should be discouraged, at least for patients with high performance status in Japan.

Three to five cycles of HD-MTX have been the standard care for PCNSL in Japan for a long time (25), and the JCOG-BTSG conducted the JCOG1114 study comparing HD-MTX + WBRT versus HD-MTX + TMZ + WBRT plus adjuvant MTX (26). Based on the results of several clinical trials for PCNSL (8,27,28), R-MPV is considered the standard of care for PCNSL in the JCOG-BTSG, and some clinical trials are ongoing. 'Surgery (biopsy) + R-MPV therapy' was the most used regimen at the JCOG-BTSG centers in patients with PCNSL aged ≤74 years (73/172 cases, 42.5%) and in patients with PCNSL aged ≥75 years (46/86 cases, 53.5%). R-MPV therapy, the standard treatment for PCNSL, belongs to the 'ultra-high-cost medical care' group, indicating that the cost of the standard treatment itself is high. If another therapy is added to this standard therapy, the cost will naturally be even higher. Because there are no results of clinical trials comparing it with R-MPV therapy, it is difficult to discuss the cost-effectiveness of PCNSL treatment regimens; however, there are some reports of the cost-effectiveness of PCNSL treatment regimens (29,30). A retrospective study on the cost-effectiveness of rituximab plus methotrexate with AraC (R-MA regimen) has been reported (30). Thirty-seven patients who received the R-M regimen showed good OS at low costs. The International Extranodal Lymphoma Study Group-32 randomized patients with PCNSL into three groups: methotrexate-AraC, methotrexate-AraC-rituximab, and methotrexate-AraC-thiotepa-rituximab (MATRix) as induction therapy. The MATRix regimen significantly improved complete remission (29). The MATRix regimen had a 3.05 quality-adjusted life year (QALY) gain at an additional cost of $75 513, with an ICER of $24 758/QALY gain (29). Thus, the MATRix regimen appears to be the optimal induction therapy for PCNSL patients, both clinically and economically.

In the treatment of newly-diagnosed GBM, TMZ plus BEV had no significant difference in median OS period compared to TMZ alone. Thus, in the present study, if the 76 patients treated with 'Surgery + RT (60 Gy/30 fr) + TMZ + BEV Surgery + RT (60 Gy/30 fr + TMZ + BEV)', assuming those patients survived 12 months, the cost of BEV could be reduced by 200.64 million JPY, considering an increase of 0.22 million JPY per month in the cost of BEV. Since Japan's estimated medical cost in 2022 is 46 trillion JPY, this represents a 0.004% reduction in medical costs.

One limitation is that this survey did not cover all brain tumor treatment centers in Japan, only those registered with the JCOG-BTSG. The treatment selections for malignant brain tumors at non-JCOG participating centers may differ from those at JCOG participating centers that have experts in malignant brain tumors. Therefore, the results may differ if the disease population increases. In addition, because the survey period was limited to 1 year, the possibility of bias cannot be denied. Additionally, individual patient data for GBM and PCNSL were not collected. Thus, this study did not consider information, such as the actual duration of administration, drug discontinuation, or dose reduction in individual cases. Therefore, we may not have been able to accurately assess the cost-benefit ratio of each regimen for each disease. Therefore, future prospective clinical trials on GBM and PCNSL should evaluate treatment regimens and cost-benefits. There are still no ongoing surveys or studies for cost containment for malignant brain tumors. Considering the increasing healthcare costs in Japan, healthcare professionals should have a perspective for cost-effectiveness optimization for malignant brain tumors.

Conclusions

In the present study, we investigated the types of treatment regimens used for GBM or PCNSL and the proportion of elderly/non-elderly patients in each treatment at JCOG-BTSG-registered centers in Japan and provided information on the cost per month of each treatment regimen and whether it was high-cost or ultra-high-cost medical care. Treatment of malignant brain tumors is generally expensive, and substantial number of patients are treated by high-cost drugs with unproven or denied benefit. Although this study analyzed only survival time, it is important to discuss the maintenance of Performance Status or Quality of life of patients in the future. We believe that the results of this study can be used to design future health economic studies examining the cost-effectiveness of malignant brain tumors, particularly GBM and PCNSL.

Conflict of Interest

The authors declare that they have no conflicts of interest.

Funding

This work was supported in part by the Research Fund of National Federation of Health Insurance Societies (Kenpo-ren) and the National Cancer Center Research and Development Fund (2023-J-03).

Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

References

1. Broekman ML, Maas SLN, Abels ER, Mempel TR, Krichevsky AM, Breakefield XO. Multidimensional communication in the microenvirons of glioblastoma. *Nat Rev Neurol* 2018;14:482–95. https://doi.org/10.1038/s41582-018-0025-8.
2. Motomura K, Natsume A, Kishida Y, et al. Benefits of interferon-β and temozolomide combination therapy for newly diagnosed primary glioblastoma with the unmethylated MGMT promoter: a multicenter study. *Cancer* 2011;117:1721–30. https://doi.org/10.1002/cncr.25637.
3. Narita Y. Incidence of brain tumors in Japan. *Nippon Rinsho* 2023;81:7–11.
4. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. *N Engl J Med* 2005;352:987–96. https://doi.org/10.1056/NEJMoa043330.
5. Report of Brain Tumor Registry of Japan. Brain Tumor Registry of Japan (2005-2008) 14th edition. *Neurol Med Chir (Tokyo)* 57:9–102. https://doi.org/10.2176/nmc.sup.2017-0001.
6. Brem H, Mahaley MS Jr, Vick NA, et al. Interstitial chemotherapy with drug polymer implants for the treatment of recurrent gliomas. *J Neurosurg* 1991;74:441–6. https://doi.org/10.3171/jns.1991.74.3.0441.
7. Stupp R, Wong ET, Kanner AA, et al. NovoTTF-100A versus physician's choice chemotherapy in recurrent glioblastoma: a randomised phase III trial of a novel treatment modality. *Eur J Cancer* 2012;48:2192–202. https://doi.org/10.1016/j.ejca.2012.04.011.
8. Morris PG, Correa DD, Yahalom J, et al. Rituximab, methotrexate, procarbazine, and vincristine followed by consolidation reduced-dose whole-brain radiotherapy and cytarabine in newly diagnosed primary CNS lymphoma: final results and long-term outcome. *J Clin Oncol* 2013;31:3971–9. https://doi.org/10.1200/JCO.2013.50.4910.
9. Ito M. Health insurance systems in Japan: a neurosurgeon's view. *Neurol Med Chir (Tokyo)* 2004;44:617–28. https://doi.org/10.2176/nmc.44.617.
10. Sullivan R, Peppercorn J, Sikora K, et al. Delivering affordable cancer care in high-income countries. *Lancet Oncol* 2011;12:933–80. https://doi.org/10.1016/S1470-2045(11)70141-3.
11. Smith TJ, Hillner BE. Bending the cost curve in cancer care. *N Engl J Med* 2011;364:2060–5. https://doi.org/10.1056/NEJMsb1013826.
12. Omura T, Takahashi M, Ohno M, et al. Clinical application of comprehensive genomic profiling tests for diffuse gliomas. *Cancers (Basel)* 2022;14:2454. https://doi.org/10.3390/cancers14102454.
13. Hoang-Xuan K, Deckert M, Ferreri AJM, et al. European Association of Neuro-Oncology (EANO) guidelines for treatment of primary central nervous system lymphoma (PCNSL). *Neuro Oncol* 2023;25:37–53. https://doi.org/10.1093/neuonc/noac196.
14. Messali A, Hay JW, Villacorta R. The cost-effectiveness of temozolomide in the adjuvant treatment of newly diagnosed glioblastoma in the United States. *Neuro Oncol* 2013;15:1532–42. https://doi.org/10.1093/neuonc/not096.
15. Prica A, Chan K, Cheung M. Combined modality therapy versus chemotherapy alone as an induction regimen for primary central nervous system lymphoma: a cost-effectiveness analysis. *Neuro Oncol* 2014;16:1384–91. https://doi.org/10.1093/neuonc/nou057.
16. Kadota T, Saito R, Kumabe T, et al. A multicenter randomized phase III study for newly diagnosed maximally resected glioblastoma comparing carmustine wafer implantation followed by chemoradiotherapy with temozolomide with chemoradiotherapy alone; Japan clinical oncology group study JCOG1703 (MACS study). *Jpn J Clin Oncol* 2019;49:1172–5. https://doi.org/10.1093/jjco/hyz169.
17. Westphal M, Hilt DC, Bortey E, et al. A phase 3 trial of local chemotherapy with biodegradable carmustine (BCNU) wafers (Gliadel wafers) in patients with primary malignant glioma. *Neuro Oncol* 2003;5:79–88. https://doi.org/10.1093/neuonc/5.2.79.
18. Brem H, Piantadosi S, Burger PC, et al. Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The polymer-brain tumor treatment group. *Lancet* 1995;345:1008–12. https://doi.org/10.1016/S0140-6736(95)90755-6.
19. Bock HC, Puchner MJ, Lohmann F, et al. First-line treatment of malignant glioma with carmustine implants followed by concomitant radiochemotherapy: a multicenter experience. *Neurosurg Rev* 2010;33:441–9. https://doi.org/10.1007/s10143-010-0280-7.
20. Stupp R, Taillibert S, Kanner A, et al. Effect of tumor-treating fields plus maintenance Temozolomide vs maintenance Temozolomide alone on survival in patients with glioblastoma: a randomized clinical trial. *JAMA* 2017;318:2306–16. https://doi.org/10.1001/jama.2017.18718.
21. Bernard-Arnoux F, Lamure M, Ducray F, Aulagner G, Honnorat J, Armoiry X. The cost-effectiveness of tumor-treating fields therapy in patients with newly diagnosed glioblastoma. *Neuro Oncol* 2016;18:1129–36. https://doi.org/10.1093/neuonc/now102.
22. Connock M, Auguste P, Dussart C, Guyotat J, Armoiry X. Cost-effectiveness of tumor-treating fields added to maintenance temozolomide in patients with glioblastoma: an updated evaluation using a partitioned survival model. *J Neurooncol* 2019;143:605–11. https://doi.org/10.1007/s11060-019-03197-w.
23. Chinot OL, Wick W, Mason W, et al. Bevacizumab plus radiotherapy-temozolomide for newly diagnosed glioblastoma. *N Engl J Med* 2014;370:709–22. https://doi.org/10.1056/NEJMoa1308345.
24. Gilbert MR, Dignam JJ, Armstrong TS, et al. A randomized trial of bevacizumab for newly diagnosed glioblastoma. *N Engl J Med* 2014;370:699–708. https://doi.org/10.1056/NEJMoa1308573.
25. Hiraga S, Arita N, Ohnishi T, et al. Rapid infusion of high-dose methotrexate resulting in enhanced penetration into cerebrospinal fluid and intensified tumor response in primary central nervous system lymphomas. *J Neurosurg* 1999;91:221–30. https://doi.org/10.3171/jns.1999.91.2.0221.

26. Mishima K, Nishikawa R, Narita Y, et al. Randomized phase III study of high-dose methotrexate and whole-brain radiotherapy with/without temozolomide for newly diagnosed primary CNS lymphoma: JCOG1114C. *Neuro Oncol* 2023;25:687–98. https://doi.org/10.1093/neuonc/noac246.
27. Omuro A, Correa DD, DeAngelis LM, et al. R-MPV followed by high-dose chemotherapy with TBC and autologous stem-cell transplant for newly diagnosed primary CNS lymphoma. *Blood* 2015;125:1403–10. https://doi.org/10.1182/blood-2014-10-604561.
28. Shah GD, Yahalom J, Correa DD, et al. Combined immunochemotherapy with reduced whole-brain radiotherapy for newly diagnosed primary CNS lymphoma. *J Clin Oncol* 2007;25:4730–5. https://doi.org/10.1200/JCO.2007.12.5062.
29. Beca JM, Raza K, Mow E, Keech J, Kouroukis CT. Cost-effectiveness analysis of rituximab with methotrexate, cytarabine and thiotepa for the treatment of patients with primary central nervous system lymphoma. *Leuk Lymphoma* 2020;61:1097–107. https://doi.org/10.1080/10428194.2020.1711902.
30. Yuan X, Yu T, Huang Y, et al. Rituximab with high-dose methotrexate is effective and cost-effective in newly diagnosed primary central nervous system lymphoma. *Sci Rep* 2022;12:21541. https://doi.org/10.1038/s41598-022-24922-y.

JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2024, 54(10), 1059–1061
https://doi.org/10.1093/jjco/hyae131
Editorial

OXFORD

Editorial

Confronting the problems we had hoped to avoid

Key words: cost, immune-checkpoint, inhibitors, target-based, drugs, sustainability, health care, system

As early as 2004, Dr Deborah Schrag of the Memorial Sloan Kettering Cancer Center, New York, warned of the rising costs of cancer care (1). Dr Schrag pointed out that the median survival time of advanced colorectal cancer patients was notably improved, almost doubled in the last decade, thanks to the advent of new anticancer agents, such as irinotecan, oxaliplatin, bevacizumab and cetuximab. However, the progress was accompanied by a 340-fold increase in drug costs (1).

In 2004, some target-based drugs, such as imatinib, gefitinib and erlotinib were available. In retrospect, however, this was just the end of the beginning. The epidermal growth factor receptor (EGFR)-activating mutation, the true target of EGFR tyrosine kinase inhibitors (TKIs), was discovered that year. Anaplastic lymphoma kinase (ALK) fusion in lung cancer was not reported until 2007. In 2004, we did not have, or even know of, immune-checkpoint inhibitors (ICIs). We did not have antibody-drug conjugates. Nor did we know CAR-T.

Even before we began to use the full armamentarium we now have, in 2011, researchers from Europe and North America issued a statement warning that the skyrocketing cost of cancer care would endanger its affordability, even in high-income countries (2). Please note that this was 3 years before nivolumab was launched. They concluded that 'the cancer profession and industry should take responsibility and not accept a substandard evidence base and an ethos of very small benefit at whatever cost; rather, we need delivery of fair prices and real value from new technologies' (2). Has their recommendation been widely heeded? Probably not.

In Japan, medical costs in 2021 exceeded 45 trillion Japanese yen (JPY), a 4.8% increase compared to 2020 and ~a 35% increase compared to 2004. We used 8.18% of our Gross Domestic Product (GDP) on medical care, which was 7.99% and 6% in 2020 and 2004, respectively (3). Medical costs in Japan have more than tripled since 1986, when one of the authors (H.K.) graduated from medical school, while Japanese GDP has stagnated over the past three decades. When the other author (T.K.) graduated from medical school in 1967, Japan's medical costs were <4 trillion JPY, ~3.5% of the GDP. Is such an increase sustainable? Definitely not.

But why is this happening? Medical cost increases are mainly driven by two factors: progress in medicine, such as the advent of new drugs, and the aging population. Nobody is to blame for either of them—and nobody can stop them. However, if left unchecked, we will soon witness a total collapse of our healthcare system. The Japanese public insurance system allows us to spend as much money as necessary to treat our patients. Although the Japanese constitution guarantees the right to maintain 'the minimum' standard of living, we have provided 'optimum' medical care for everyone. It is highly unlikely that we can go on as we have, due, alas, to a lack of money.

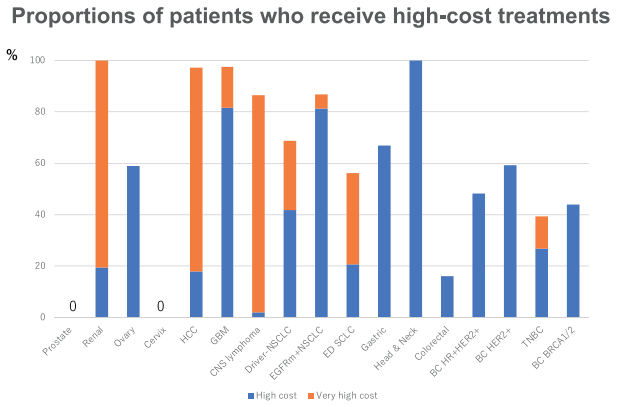


Figure 1. Proportions of patients who receive treatments at monthly costs of 500 000 JPY and 1 000 000 JPY, according to tumor type.

What can we do? To be honest with you, we do not know. Then what should we do? First, we need to understand the situation for what it is. We physicians did not care about money and tried to ignore inconvenient truths. However, understanding ourselves and understanding what we are doing is the first step to we need to take. How much money do we spend on the care of our patients? Unfortunately, we are no longer living in a world where every expense can be justified in the name of 'patient care'. We need to look at how we can curb this excessive use of resources. But first, we have to understand what we are actually doing.

In a series of articles accompanying this Editorial, nine subgroups of the Japan Cooperative Oncology Group (JCOG) conducted investigations on first-line treatment selections during 2021–2022 and their associated costs in a total of 17 cancer types (4–12). A total of 15 564 patients (29% of them are aged 75 years old or more) were surveyed in probably one of the largest surveys of this kind in the 2020s and certainly the first ever in Japan. Although there are substantial variations according to each specific cancer, we could observe several common features from the data.

First, the monthly cost is high both in absolute and relative terms. Among the 17 tumor types, a median of 59% of the patients (1QR: 44% to 3QR: 87%) received treatments with monthly costs of 500 000 JPY or more. A total of 17% of the patients received treatments with monthly costs of 1 000 000 JPY or more (Fig. 1). As compared to conventional chemotherapy, which was the standard of care 10–15 years ago, there were 10- to 50-fold cost increases.

Elderly patients received high-cost treatments less frequently, although this was apparently due to concerns over toxicities rather than cost. In fact, high-cost regimens such as nivolumab +

ipilimumab in non-small cell lung cancers (7) or nivolumab/pembrolizumab in head and neck cancers (12) are more frequently used in patients of 75 years or older.

Some 'effective' drugs such as androgen receptor signaling inhibitors for prostate cancer and CDK4/6 inhibitors for breast cancer are used for extended periods, because of longer progression-free survival, leading to high total (not only monthly) costs (4,11). This kind of phenomenon was previously reported on pertuzumab, an anti-HER2 antibody (13).

The 'benefits' of the high-cost treatments were highly variable. It could be substantial (such as EGFR-TKIs in EGFR-mutated non-small cell lung cancer), marginal [such as nivolumab to gastric cancer (8)], or nonexistent [such as bevacizumab to glioblastoma (11)]. In most of the cases, lack of adequate benefit does not affect the drug price, since it is the result of an indication-extension trial, and the price had already been determined at the original indication approval.

Oftentimes, more than one drugs of the same class are available. This includes androgen receptor signaling inhibitors for prostate cancer (4), ICIs and TKIs for renal cell carcinoma (4), ICIs for hepatocellular carcinoma (6), ICIs, TKIs and anti-vascular-endothelial growth factor antibodies for lung cancers (7), CDK4/6 inhibitors for breast cancer (10,14) and anti-EGFR and anti-VEGR antibodies in colon cancer (9). Drug prices can vary greatly among the same class, despite exhibiting the same efficacy and toxicities. This again is mainly a result of an indication-extension trial and the price having already been determined at the time of the original indication approval. For example, both ramucirumab and bevacizumab are available for second-line treatments for colorectal cancers, with almost identical efficacy and toxicities, but ramucirumab is many times more expensive than bevacizumab (15–17). The use of ramucirumab in colorectal cancers is strongly discouraged in the literature (15,16), with the speculation that the pharmaceutical company wants to maintain the high price for the lead indication of gastric cancer (17).

We all sense that cancer care is unsustainable and soon to become unaffordable, but there is no easy way out. We are very reluctant to discuss cost-effectiveness. For example, suppose you find a report that the incremental cost-effectiveness ratio for the treatment you are going to give to your patient is 500 000 US dollars per quality-adjusted life year, far exceeding the willing-to-pay threshold of any country, including Japan. But could you 'abandon' the patient, just because it is too expensive? Could you explain this to your patient? Human life is 'priceless', isn't it? How can we balance our duties to patients versus society? (18,19) In addition, cost-effectiveness analyses reports are not reliable. Industry-sponsored studies are far more likely to give 'cost-effective' reports (20). What can we believe?

Still, there should be something we could do, or at least something we could start with. For example, we could move away from the idea of 'care at any cost' and stop using expensive drugs, which provide no clear additional benefit. This can be done without any discussion on cost-effectiveness, since there is no (additional) 'effectiveness'. These drugs include bevacizumab for glioblastoma [as one of the JCOG reports pointed out (11)], or ramucirumab for colorectal cancer (15–17). Ramucirumab can be substituted with bevacizumab, or even better, by bevacizumab biosimilar, which is a much less expensive alternative, without any compromise in efficacy.

As a next step, perhaps we could initiate some discussions. Panitumumab and cetuximab, both anti-EGFR antibodies, are used in Rat sarcoma virus (RAS)-wild colorectal cancer, with similar efficacies (9). Panitumumab is double the price of cetuximab. The only difference appears to be that panitumumab is administered bi-weekly, whereas cetuximab is given weekly. Does this difference, which amounts to a matter of convenience for the patients, justify the huge increase in cost? Or simply, how about giving cetuximab bi-weekly? We have talked about efficacy, toxicity and convenience. It is time to add cost to our list of discussion points.

Last but not the least, we should perform more and more research on treatment optimization. The dosage of modern cancer drugs might be suboptimally determined, by adopting classic dose-increase studies with cytotoxic agents (21). Food and Drug Administration (FDA) has launched an initiative, Project Optimus, to reform the dose optimization and dose selection paradigm (https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus). In addition to dose reduction, many trials evaluate de-escalation strategies, including shortened duration, longer intervals and more (21–26). Some studies have been launched in Japan, including those conducted at JCOG (27).

Life is priceless. But our resources are limited. We have to use the limited resources wisely to treat our patients who are all mortal. We used to believe that it was not our responsibility to think about cost, resources, affordability and sustainability. In fact, it is. If we are to avoid the collapse of the Japanese Health Insurance System, we need to start thinking seriously about medical costs. We hope you can agree on this.

*Hideo Kunitoh**
Department of Medical Oncology, Japanese Red Cross Medical Center, Tokyo, Japan
Tadao Kakizoe
Japan Cancer Society, Tokyo, Japan

**For reprints and all correspondence: Hideo Kunitoh, Department of Medical Oncology, Japanese Red Cross Medical Center 4-1-22 Hiro-o, Shibuya-ku, Tokyo 150-8935, Japan.*
E-mail: hideokunito@gmail.com

Conflict of interest

None declared.

Funding

None declared.

Disclaimer

Dr Kunitoh is the Editor-in-Chief, and Dr Kakizoe is the Emeritus Editor-in-Chief of JJCO.

However, the opinions expressed in the Editorials are their personal opinions and do not necessarily reflect the views of the journal or publisher.

References

1. Schrag D. The price tag on progress – chemotherapy for colorectal cancer. *N Engl J Med* 2004;351:317–9. https://doi.org/10.1056/NEJMp048143.
2. Sullivan R, Peppercorn J, Sikora K, et al. Delivering affordable cancer care in high-income countries. *Lancet Oncol* 2011;12:933–80. https://doi.org/10.1016/S1470-2045(11)70141-3.
3. Ministry of Health, Labor and Welfare (MHLW). Overview of national healthcare expenditure in 2021 24 October 2023. https://www.mhlw.go.jp/toukei/saikin//hw/k-iryohi/21/dl/kekka.pdf (in Japanese), 29 August 2024, date last accessed.
4. Osawa T, Sasaki K, Machida R, et al. Real-world treatment trends for patients with advanced prostate cancer and renal cell carcinoma and their

cost—a survey in Japan. *Jpn J Clin Oncol* 2024;54:1062–70. https://doi.org/10.1093/jjco/hyae045.
5. Takahashi N, Seki T, Sasaki K, et al. High cost of chemotherapy for gynecologic malignancies. *Jpn J Clin Oncol* 2024;54:1078–83. https://doi.org/10.1093/jjco/hyae089.
6. Imaoka H, Sasaki K, Machida R, et al. Current status of the cost burden of first-line systemic treatment for patients with advanced hepatocellular carcinoma in Japan, 2021–22. *Jpn J Clin Oncol* 2024;54:1071–77. https://doi.org/10.1093/jjco/hyae048.
7. Watanabe K, Sasaki K, Machida R, et al. High-cost treatments for advanced lung cancer in Japan (lung cancer study Group of the Japan Clinical Oncology Group). *Jpn J Clin Oncol* 2024;54:1084–92. https://doi.org/10.1093/jjco/hyae094.
8. Nishina T, Boku N, Kurokawa Y, et al. A real-world survey on expensive drugs used as first-line chemotherapy in patients with HER2-negative unresectable advanced/recurrent gastric cancer in the stomach cancer study group of the Japan clinical oncology group. *Jpn J Clin Oncol* 2024;54:1100–6. https://doi.org/10.1093/jjco/hyae104. JJCO-24-0273.R1.
9. Takashima A, Ishiguro M, Sasaki K, et al. Real-world treatment costs of first-line treatment for metastatic colorectal cancer: a survey of the JCOG colorectal cancer study group. *Jpn J Clin Oncol* 2024;54:1107–14. https://doi.org/10.1093/jjco/hyae110. JJCO-24-0420.R1.
10. Iwatani T, Sasaki K, Machida R, et al. Current status of the cost burden of first-line systemic treatment for patients with advanced hepatocellular carcinoma in Japan, 2021–22. *Jpn J Clin Oncol* 2024;54:1093–99. https://doi.org/10.1093/jjco/hyae109.
11. Motomura K, Sasaki K, Sugii N. et al. Cost of medical care for malignant brain tumors at hospitals in the Japan clinical oncology group brain-tumor study group. *Jpn J Clin Oncol* 2024;54:1123–31. https://doi.org/10.1093/jjco/hyae116. JJCO-24-0307.R2.
12. Yokoyama K, Wasano K, Sasaki K, et al. Frequency of use and cost in Japan of first-line palliative chemotherapies for recurrent or metastatic squamous cell carcinoma of the head and neck. *Jpn J Clin Oncol* 2024;54:1115–22. https://doi.org/10.1093/jjco/hyae117. JJCO-24-0315.R1.
13. Durkee BY, Qian Y, Pollom EL, et al. Cost-effectiveness of pertuzumab in human epidermal growth factor receptor 2-positive metastatic breast cancer. *J Clin Oncol* 2015;34:902–9. https://doi.org/10.1200/JCO.2015.62.9105.
14. Griggs JJ, Wolff AC. Cyclin-dependent kinase 4/6 inhibitors in the treatment of breast cancer: more breakthroughs and an embarrassment of riches. *J Clin Oncol* 2017;35:2857–9. https://doi.org/10.1200/JCO.2017.73.9375.
15. Effing SMA, Gyawali B. Assessing the risk-benefit profile of ramucirumab in patients with advanced solid tumors: a meta-analysis of randomized controlled trials. *EClinicalMedicine* 2020;25:100458. https://doi.org/10.1016/j.eclinm.2020.100458.
16. Goldstein DA, El-Rayes BF. Considering efficacy and cost, where dose ramucirumab fit in the management of metastatic colorectal cancer? *Oncologist* 2015;20:981–2. https://doi.org/10.1634/theoncologist.2015-0028.
17. Bach PB. Ramucirumab for colon cancer and the problem of rising prices independent of benefits. *Oncologist* 2015;20:983–4. https://doi.org/10.1634/theoncologist.2015-0257.
18. Goldstein DA. The ethical and practical challenges of value-based cancer care at the patient's bedside. *JAMA Oncol* 2016;2:860–1. https://doi.org/10.1001/jamaoncol.2016.0535.
19. Kumar P, Moy B. The cost of cancer care-balancing our duties to patients versus society: are they mutually exclusive? *Oncologist* 2013;18:347–9. https://doi.org/10.1634/theoncologist.2013-0078.
20. Haslam A, Lythgoe MP, Greenstreet Akman E, Prasad V. Characteristics of cost-effectiveness studies for oncology drugs approved in the United States from 2015-2020. *JAMA Netw Open* 2021;4:e2135123. https://doi.org/10.1001/jamanetworkopen.2021.35123.
21. CLPO H, Mehra N, Maliepaard M, et al. Dose selection of novel anticancer drugs: exposing the gap between selected and required doses. *Lancet Oncol* 2024;25:e340–51. https://doi.org/10.1016/S1470-2045(24)00134-7.
22. Malmberg R, Zietse M, Dumoulin DW, et al. Alternative dosing strategies for immune checkpoint inhibitors to improve cost-effectiveness; a special focus on nivolumab and pembrolizumab. *Lancet Oncol* 2022;23:e552–61. https://doi.org/10.1016/S1470-2045(22)00554-X.
23. Shapiro CL. Bigger isn't always better : the ESMO dose de-intensification guideline framework. *Ann Oncol* 2022;33:672–3. https://doi.org/10.1016/j.annonc.2022.05.001.
24. Trapani D, Franzoi MA, Burstein HJ, et al. Risk- adapted modulation through de-intensification of cancer treatments: an ESMO classification. *Ann Oncol* 2022;33:702–12. https://doi.org/10.1016/j.annonc.2022.03.273.
25. Tannock IF, Ratain MJ, Goldstein DA, Lichter AS, Rosner GL, Saltz LB. Near-equivalence: generating evidence to support alternative cost-effective treatments. *J Clin Oncol* 2021;39:950–5. https://doi.org/10.1200/JCO.20.02768.
26. Piccart MJ, Hilbers FS, Bliss JM, et al. Road map to safe and well-designed de-escalation trials of systemic adjuvant therapy for solid tumors. *J Clin Oncol* 2020;38:4120–9. https://doi.org/10.1200/JCO.20.01382.
27. Nomura S, Goto Y, Mizutani T, et al. A randomized phase III study comparing continuation and discontinuation of PD-1 pathway inhibitors for patients with advanced non-small-cell lung cancer (JCOG 1701, SAVE study). *Jpn J Clin Oncol* 2020;50:821–5. https://doi.org/10.1093/jjco/hyaa054.

JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2024, 1–6
https://doi.org/10.1093/jjco/hyae032
Clinical Trial Note

OXFORD

Clinical Trial Note

Multi-institutional study of osimertinib dose-optimization in non-small cell lung cancer patients with EGFR activating mutation aged 70 years or older ('MONEY' trial)

Yoko Tsukita[1,*], Masataka Taguri[2], Yasushi Goto[3], Yukio Hosomi[4], Tomonori Mizutani[5], Kageaki Watanabe[4], Kiyotaka Yoh[6], Satoshi Takahashi[7], Kaoru Kubota[8] and Hideo Kunitoh[9]

[1]Department of Respiratory Medicine, Tohoku University Graduate School of Medicine, Sendai, Japan, [2]Department of Health Data Science, Tokyo Medical University, Tokyo, Japan, [3]Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan, [4]Department of Thoracic Oncology and Respiratory Medicine, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan, [5]Department of Medical Oncology, Kyorin University Faculty of Medicine, Tokyo, Japan, [6]Department of Thoracic Oncology, National Cancer Center Hospital East, Chiba, Japan, [7]Department of Thoracic Surgery, Tokyo Medical University, Tokyo, Japan, [8]Department of Pulmonary Medicine and Oncology, Graduate School of Medicine, Nippon Medical School, Tokyo, Japan and [9]Department of Chemotherapy, Japan Red Cross Medical Center, Tokyo, Japan

*For reprints and all correspondence: Yoko Tsukita, Department of Respiratory Medicine, Tohoku University Graduate School of Medicine, 1-1 Seiryo-machi, Aoba-ku, Sendai 980 8574 Japan. E-mail: y-tsukita@rm.med.tohoku.ac.jp

Received 5 December 2023; Editorial Decision 26 February 2024; Accepted 1 March 2024

Abstract

Osimertinib is the standard of care for patients with epidermal growth factor receptor-activating mutation-positive non-small cell lung cancer. Dose-toxicity has been previously reported, but no dose–response data within the range of 20–240 mg daily (mg/d). Thus, the current 80 mg/d dosing might be too high for elderly Japanese patients with an average body weight of only 50 kg, resulting in excessive toxicity and cost. We therefore initiated a study to investigate whether osimertinib at 40 mg/d is non-inferior to 80 mg/d in patients with advanced or recurrent epidermal growth factor receptor-activating mutation-positive non-small cell lung cancer aged ≥70 years, using a regression discontinuity design. Osimertinib is administered at 40 mg/d for body weight ≤50 kg, and 80 mg/d for body weight >50 kg. The primary endpoint is progression-free survival. Sample size is 550 patients, based on a non-inferiority margin of the progression-free survival hazard ratio 1.333, 0.10 one-sided type I error and 80% power.

Key words: osimertinib, dose-optimization, non-small cell lung cancer, epidermal growth factor receptor activating mutation, regression discontinuity design

Introduction

The cost of medical care in Japan is rising steadily, and the sustainability of the healthcare insurance system is a concern (1). In particular, insurance reimbursement for high-cost drugs such as immune checkpoint inhibitors and molecular-targeted drugs is having a significant impact.

Osimertinib, with the fourth highest sales of pharmaceuticals in Japan in 2022 (2), is the standard of care for patients with epidermal growth factor receptor-activating mutation-positive (EGFRm+) non-small cell lung cancer (NSCLC). In the FLAURA trial comparing osimertinib to first-generation EGFR-TKIs, median progression-free survival (PFS) and overall survival (OS) were significantly prolonged with osimertinib relative to first-generation EGFR-TKIs (PFS: 13.9 vs. 10.2 months, OS: 36.8 vs. 31.8 months) (3,4). Furthermore, osimertinib was associated with a lower incidence of skin rash, diarrhoea and liver dysfunction adverse events compared with first- and second-generation EGFR-TKIs, although interstitial lung diseases (ILD) are a concern (5). Therefore, osimertinib is actively administered to elderly patients who would not be suitable for cytotoxic anti-cancer drugs. Since osimertinib was recently approved for 3-year adjuvant therapy (6), further increases in prescriptions are expected in the near future.

Dosage setting in the development of anti-cancer drugs, even for drugs with novel mechanisms of action, is based on conventional escalation studies and maximum tolerated doses. However, this approach could result in excessive doing of molecular targeted agents such as osimertinib. In Phase I/II study (AURA trial) for NSCLC harbouring EGFRm with disease progression previously treated with EGFR-TKI (7), response rates of osimertinib were similar for 20, 40, 80, 160 and 240 mg daily doses. Regarding safety, adverse events leading to discontinuation were reported in 11.5% of patients on 40 mg daily and 22.7% for 80 mg daily. Furthermore, a pharmacokinetic study analyzing a total of 780 patients from the AURA trial, the AURA2 trial and healthy volunteers showed no evidence of a relationship between osimertinib exposure and probability of objective response, duration of response or best percentage change in target lesion size. However, it showed a linear relationship between exposure and the occurrence of rash or diarrhoea (8). These results suggest that the efficacy of 40 and 80 mg daily is likely to be equivalent, but that toxicity is lower at 40 mg. Although we were unable to find any papers specifically addressing differences in osimertinib toxicity according to patients' body weights (BW), it would be natural to presume that the body size of the patient would be associated with osimertinib PK. Therefore, patients with low BW would likely derive greater benefit (lower toxicities) from lower doses.

Elderly patients are seldom included in clinical trials for drug development, and therefore conventional dosing may be too high for these patients because of concerns about increased toxicity and decreased quality of life (QOL). A Japanese retrospective study of first-line osimertinib therapy in 132 patients aged ≥75 years reported that 44 (40.9%) required dose reduction because of adverse events, the most common reasons being fatigue, skin rash and diarrhoea (9). The incidence of ILD was 17.4% with 9.1% of patients having Grade 3 or higher, which was more frequent than in the Japanese population in the FLAURA trial (10). The rate of treatment discontinuation because of adverse events was 26.5%. Median PFS was 19.4 months, with no significant difference between patients with or without dose reduction. That study thus suggested that osimertinib 80 mg daily was more toxic and probably overdosed for elderly patients.

Based on the above rationales, we hypothesize that osimertinib at 40 mg daily instead of the current standard dosing of 80 mg daily might improve risk- and cost-benefits with maintaining efficacy in elderly patients, especially those with a low BW. Efficacy and safety of low starting doses of first- and second-generation EGFR-TKIs have been reported, but these were single arm Phase II trials (11–13). It has not been elucidated whether optimizing the dosage of osimertinib ameliorates toxicities, including financial issues, and improves QOL whilst maintaining efficacy.

The main hypothesis of the present study is that osimertinib 40 mg daily is non-inferior to 80 mg daily in terms of PFS in elderly patients with low BW. A randomized controlled trial to test this hypothesis is not feasible because of the large sample size required and patients' reluctance to be randomized. Furthermore, since the objective of this study is to optimize the dose according to BW, it would be inefficient to uniformly randomize all patients. Therefore, we adopted a regression discontinuity design with BW as the continuous assignment variable. The threshold for treatment decision was 50 kg and the usefulness of osimertinib dose optimization in patients weighing 50 kg or less will be examined.

The Japan Red Cross Medical Center Review Board approved the study protocol in July 2023, and patient enrolment began on 20 September 2023. This study has the potential to contribute to reducing toxicity and improving QOL in elderly patients, as well as reducing the cost of medical care. This trial is necessary to move away from the conventional 'more is better' approach to cancer treatment and to take the first step towards more patient-centred and sustainable cancer treatments in an ageing society.

Protocol digest of this study

Objectives

The aim of this study was to investigate whether the efficacy of osimertinib 40 mg daily is non-inferior to conventional 80 mg daily in elderly Japanese patients with EGFRm+ NSCLC, with a small body-size.

Study design

Regression discontinuity design (14–16), with BW as the assignment variable. The threshold for treatment decision is 50 kg. Those who declined to be assigned by BW are to be treated with conventional dose of 80 mg daily ('fuzzy' regression discontinuity), but would be included in the analysis as allocated. The schema of this study is shown in Fig. 1.

Endpoints

The primary end-point is PFS, defined as the time from receiving the first dose of osimertinib to the diagnosis of disease progression, death from any cause or the last day of follow-up. The secondary end-points are OS, time to treatment failure (TTF), response rate, adverse events and QOL. OS is defined as the time from receiving the first dose of osimertinib to death from any cause, or the last day of follow-up. TTF is defined as the time from receiving the first dose of osimertinib to the diagnosis of disease progression, death from any cause, discontinuation of the protocol treatment or initiation of post-treatment. If none of the above events occurs, TTF is censored at the last day of follow-up. Response rate is defined as the proportion of complete or partial responses amongst the eligible patients, based on Response Evaluation Criteria in Solid Tumors version 1.1. Safety

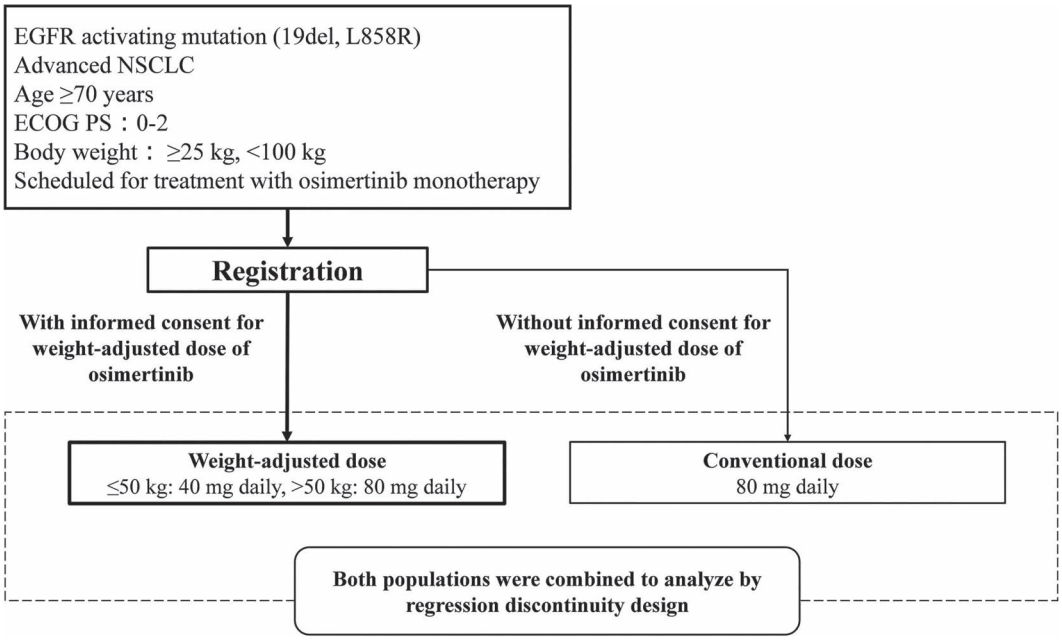


Figure 1. Design of the MONEY trial.

is assessed on the basis of adverse events graded according to the National Cancer Institute-Common Toxicity Criteria version 5.0. QOL is assessed on the basis of EuroQol 5 dimensions 5-level.

Inclusion criteria

1. Histologically or cytologically confirmed NSCLC.
2. EGFR exon 19 deletion or L858R point mutation-positive (any diagnostic method is acceptable).
3. Clinical Stage IIIB, IIIC without an indication for definitive thoracic radiotherapy, Stage IV or post-operative or post-radiotherapy recurrent disease (the stage will be defined based on the UICC International Union for Tumors Lung Classifications 2017, 8th edition).
4. Patients scheduled for treatment with osimertinib monotherapy.
5. No history of systemic therapy for lung cancer in this study (patients with recurrent disease that worsened during or after adjuvant chemotherapy, excluding EGFR-TKI, can be enrolled).
6. Aged 70 years or older at the time of enrolment.
7. Eastern Cooperative Oncology Group performance status, 0, 1 or 2.
8. BW at least 25 and <100 kg.
9. Patients without measurable lesions are acceptable.
10. No symptomatic brain metastasis, meningeal metastasis or spinal metastasis that requires radiotherapy or surgery.
11. Adequate function of major organs allowing osimertinib treatment.
12. Patients who are currently participating or will participate in other clinical trials or observational studies can participate with permission.
13. Written informed consent.

Exclusion criteria

1. Infectious disease requiring systemic treatment.
2. ILD on chest computed tomography.
3. History of synchronous or metachronous malignancies that affect the assessment of the primary endpoint.
4. Psychiatric illnesses or symptoms that affect the patient's activities of daily living.
5. Poorly controlled diabetes mellitus, hypertension, congestive heart failure, unstable angina, severe arrhythmia, cerebrovascular disease, etc.
6. Women who are pregnant, possibly pregnant, within 28 days postpartum or breastfeeding.
7. Other ineligible status judged by the attending physician.

Treatment

Osimertinib monotherapy, with 40 mg daily for those with BW of ≤50 kg or 80 mg daily for those with BW > 50 kg. Patients who declined to be assigned by BW are to be treated with the conventional dose of 80 mg daily. Osimertinib to be continued until death, disease progression or intolerable toxicity.

Follow-up

All randomized patients will be followed up for at least 2 years after the completion of patient accrual. Radiographic tumour evaluations are performed and assessed, according to Response Evaluation Criteria in Solid Tumors (version 1.1), by each investigator at least every 12 weeks over the follow-up period.

Decision rule

If PFS shows no significant discontinuity at the BW 50 kg threshold, osimertinib 40 mg daily would be non-inferior to 80 mg daily and optimal for patients weighting 50 kg or less. Better QOL in the 40 mg group is also anticipated. If non-inferiority is not demonstrated, 80 mg daily dose would remain the standard.

Statistical considerations

We assume a median PFS of 20 months in both arms and setting a non-inferiority margin at a hazard ratio of 1.333 (ensuring that

the median PFS in the osimertinib 40 mg arm is not shorter than 15 months). Under a 1:1 allocation ratio, an accrual period of 2.5 years, a follow-up period of 2 years, a one-sided significance level of 0.1 and a power of 80%, the required total sample size for a standard randomized controlled trial is 299. Considering the regression discontinuity design, we should multiply the design effect (DE) by the aforementioned sample size of 299. Under the assumption that BW is normally distributed and its median is at the threshold, DE is 1.654 (14). Thus, the required sample size is estimated to be $299 \times 1.654 = 497$ cases, and we plan to register 550 participants, allowing for a 10% drop-out.

In the analysis of the primary endpoint (PFS), Kaplan–Meier plots will be constructed for each group, and the median survival time and its 95% confidence interval will be calculated. The primary analysis will be conducted fitting a Cox proportional hazards model based on a regression discontinuity design, as follows:

$$h(t) = h_0(t)\exp\left(\alpha X + \beta Z + \gamma XZ\right) \quad \text{(A)}$$

where $h(t)$ is a the hazard function at time point t, $h_0(t)$ is the baseline hazard, X is an indicator variable taking the value 1 for BW to be $\leq$50 kg and 0 otherwise. Z represents the continuous variable of {BW (kg) − 50}. The estimate of $\exp(\alpha)$ is the hazard ratio for the 80 mg group compared with the 40 mg group. The 80% confidence interval for this estimate and the one-sided P value based on the Wald test with the null hypothesis of a hazard ratio of 1.333 will be computed.

To confirm that the statistical assumptions of the regression discontinuity design are met (15,16), a histogram of BW will be created. Summary statistics for major baseline prognostic factors will be calculated for each group. To assess comparability of two groups at the threshold, we use regression models similar to the model (A) and the balance of prognostic factors at the threshold will be assessed using standardized mean differences (SMDs). Specifically, for each continuous prognostic factor, we use the following linear regression model:

$$E\left[W|X,Z\right] = \delta + \alpha X + \beta Z + \gamma XZ \quad \text{(B)}$$

where W is the prognostic factor divided by $\sqrt{\left(S_0^2 + S_1^2\right)/2}$ where S_0^2 and S_1^2 are the standard deviations of W for the 40 and 80 mg arms, respectively. For each binary prognostic factor, we use the following logistic regression model:logit

$$E\left[W|X,Z\right] = \delta + \alpha X + \beta Z + \gamma XZ \quad \text{(C)}$$

For model (B), SMD is α. To calculate SMD for model (C), we define p_0 as expit(δ) and p_1 as expit($\delta + \alpha$) where $\text{expit}(k) = 1/(1 + \exp(-k))$. Then, SMD is calculated by $\left(p_1 - p_0\right) / \sqrt{\left\{p_1\left(1-p_1\right) + p_0\left(1-p_0\right)\right\}/2}$. Similar to models (B and C), categorical factors >2 categories are modelled by multinomial logistic regression and SMDs are calculated using a procedure similar to that of binary factors. For any prognostic factors found to be imbalanced (absolute SMD exceeding 0.25 between groups at the threshold), a post hoc adjusted analysis based on the Cox proportional hazards model will be conducted.

To obtain a valid treatment effect estimate, the assumed model (A) must be correctly specified. As a sensitivity analysis, we also conduct an analysis based on the following Cox model considering possibly non-linear associations for weight:

$$h(t) = h_0(t)\exp\left(\alpha X + g_0(Z) + Xg_1(Z)\right)$$

where $g_0(Z)$ and $g_1(Z)$ are restricted cubic spline functions whose nots are placed at 0.05, 0.50, 0.95 percentiles for each group.

In the main analysis, we will classify those who declined to the assigned treatment as allocated according to the intention-to-treat (ITT) principle. However, ITT analysis tends to be anti-conservative in demonstrating non-inferiority. Thus, an additional per-protocol analysis will also be conducted.

Interim analysis and monitoring

All statistical analyses will be conducted at the Department of Health Data Science, Tokyo Medical University. Periodic monitoring will be performed every year by the steering committee to evaluate study progress and to improve the quality of the data. Although no formal interim analysis is planned for this study, the steering committee evaluates the accrual rate, BW distribution, patients' consent status and clinical response to the therapy according to the dose at registration of 100 patients to confirm the feasibility and validity of the study.

Participant institutions (from north to south)

National Hospital Organization Hokkaido Cancer Center, Akita Kousei Medical Center, Yamagata Prefectural Central Hospital, Tohoku University Graduate School of Medicine, Niigata Cancer Center Hospital, University of Tsukuba Hospital, Tochigi Cancer Center, Dokkyo Medical University Hospital, Gunma Prefectural Cancer Center, National Hospital Organization Shibukawa Medical Center, Kasukabe Medical Center, National Cancer Center Hospital, Toranomon Hospital, Tokyo Saiseikai Central Hospital, Nippon Medical School Hospital, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, NTT Medical Center Tokyo, Showa University Hospital, Toho University Omori Medical Center, Japan Red Cross Medical Center, Tokyo Medical University Hospital, Center Hospital of the National Center for Global Health and Medicine, Tokyo Metropolitan Police Hospital, Kyorin University Hospital, Tokai University Hachioji Hospital, Yokohama Municipal Citizen's Hospital, Kanagawa Cancer Center, Fujisawa City Hospital, Kurobe City Hospital, Kanazawa University Hospital, Shinshu University Hospital, Gifu Municipal Hospital, Hamamatsu University Hospital, Nagoya University Hospital, Kansai Electric Power Hospital, Osaka Medical and Pharmaceutical University Hospital, Kansai Medical University Hospital, Hyogo Prefectural Amagasaki General Medical Center, Tottori University Hospital, Okayama University Hospital, Fukuyama City Hospital, Hiroshima Prefectural Hospital, Hiroshima University Hospital, National Hospital Organization Kure Medical Center and Chugoku Cancer Center, National Hospital Organization Shikoku Cancer Center, Ehime University Hospital, Saiseikai Imabari Hospital, National Hospital Organization Kyushu Medical Center, Shin Koga Hospital, Nagasaki University Hospital, National Hospital Organization Okinawa National Hospital.

Acknowledgements

NAI assisted with editing the English language.

Funding

This research was supported by Japan Agency for Medical Research and Development (AMED) under Grant Number JP23ck0106893h0001, by the Research Fund of National Federation of Health Insurance Societies and by Comprehensive Support Project for Oncology Research by Public Health Research Foundation, a Japanese non-profit public interest incorporated foundation.

Conflict of interest statement

Yoko Tsukita reports honoraria from AstraZeneca, Taiho Pharmaceutical, Eli Lilly, MSD, Eisai, Chugai Pharmaceutical, Daiichi Sankyo, Bristol-Meyers Squibb and Nippon Boehringer Ingelheim outside the submitted work. Yasushi Goto reports grants to institution from Abbvie, Eli Lilly, Pfizer, Bristol Myers Squibb, Ono Pharmaceutical, Novartis, Kyorin, DaiichiSankyo, Novartis and Preferred Network; honoraria and participation on advisory board of Eli Lilly, Chugai, Taiho Pharmaceutical, Boehringer Ingelheim, Ono Pharmaceutical, Bristol Myers Squibb, Pfizer, MSD and Novartis; honoraria from Merck and Thermo Fischer; participation on advisory board of AstraZeneca, Guardant Health Inc., Illumina and DaiichiSankyo; Leadership of Caner Net Japan, JAMT outside the submitted work. Yukio Hosomi reports honoraria from AstraZeneca, Eli Lilly Japan, Taiho Pharmaceutical, Chugai Pharmaceutical, Ono Pharmaceutical, Bristol-Myers Squibb, Kyowa Kirin, Nippon Kayaku, Takeda, Eisai, Novartis and Pfizer outside the submitted work. Tomonori Mizutani reports honoraria from Chugai Pharmaceutical and AstraZeneca outside the submitted work. Kageaki Watanabe reports Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai Pharmaceutical, Merck Biopharma, MSD, Novartis Pharma, Ono Pharmaceutical, Riken Genesis, Sysmex Corporation and Takeda Pharmaceutical outside the submitted work. Kiyotaka Yoh reports grants to institution from Abbvie, Amgen, AstraZeneca, Boehringer Ingelheim, Chugai, Daiichi Sankyo, Lilly, MSD, Pfizer, Taiho and Takeda; consulting fees from Boehringer Ingelheim; honoraria from Abbvie, Amgen, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, Janssen, Kyowa Kirin, Lilly, Merck Serono, Novartis, Ono, Otsuka, Taiho and Takeda outside the submitted work. Satoshi Takahashi reports honoraria from AstraZeneca, Bristol Myers Squibb Japan, Chugai Pharma, Kyowa Kirin, Lilly Japan, MSD, Nippon Kayaku, Taiho Pharmaceutical and Takeda outside the submitted work. Kaoru Kubota reports honoraria from Taiho Pharmaceutical, Ono Pharmaceutical, Chugai Pharmaceutical, AstraZeneca, Pfizer, Shionogi, Nihon Kayaku, Kyowa Kirin, Boehringer Ingelheim, Eli Lilly, Bristol-Meyers Squibb, Sawai, Takeda, Merck and Novartis; leadership of Japan Association of Medical Translation outside the submitted work. Hideo Kunitoh repots consulting fees from Daiichi-Sankyo; honoraria from Taiho Pharmaceutical, Daiichi-Sankyo, MSD, Johnson & Johnson and AstraZeneca outside the submitted work.

Registration number

This trial has been registered in the UMIN Clinical Trials Registry as UMIN000038683.

References

1. *Overview of National Health Care Expenditures [Internet]*. Ministry of Health, Labour and Welfare; 2020 [cited 2023 November 1]. Available from: https://www.mhlw.go.jp/toukei/saikin/hw/k-iryohi/20/dl/data.pdf.
2. *Pharmaceutical Market Statistics [Internet]*. IQVIA; 2023 [cited 2023 November 1]. Available from: https://www.iqvia.com/-/media/iqvia/pdfs/japan/topline-marketdata/2023/toplinedata_fy_2022.pdf.
3. Soria JC, Ohe Y, Vansteenkiste J, et al. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med* 2018;378:113–25. https://doi.org/10.1056/NEJMoa1713137.
4. Ramalingam SS, Vansteenkiste J, Planchard D, et al. Overall survival with osimertinib in untreated, EGFR-mutated advanced NSCLC. *N Engl J Med* 2020;382:41–50. https://doi.org/10.1056/NEJMoa1913662.
5. Tsukita Y, Inoue A. First-line therapy in non-small cell lung cancer patients with EGFR activating mutations: a consideration of the clinical position of osimertinib based on the subset of Japanese patients in the FLAURA study. *Jpn J Clin Oncol* 2022;52:405–10. https://doi.org/10.1093/jjco/hyac012.
6. Wu YL, Tuboi M, He J, et al. Osimertinib in resected EGFR-mutated non-small-cell lung cancer. *N Engl J Med* 2020;383:1711–23. https://doi.org/10.1056/NEJMoa2027071.
7. Janne PA, Yang JCH, Kim DW, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med* 2015;372:1689–99. https://doi.org/10.1056/NEJMoa1411817.
8. Brown K, Comisar C, Witjes HJ, et al. Population pharmacokinetics and exposure-response of osimertinib in patients with non-small cell lung cancer. *Br J Clin Pharmacol* 2017;83:1216–26. https://doi.org/10.1111/bcp.13223.
9. Yamamoto G, Asahina H, Honjo O, et al. First-line osimertinib in elderly patients with epidermal growth factor receptor-mutated advanced non-small cell lung cancer: a retrospective multicenter study (HOT2002). *Sci Rep* 2021;11:23140. https://doi.org/10.1038/s41598-021-02561-z.
10. Ohe Y, Imamura F, Nogami N, et al. Osimertinib versus standard-of-care EGFR-TKI as first-line treatment for EGFRm advanced NSCLC: FLAURA Japanese subset. *Jpn J Clin Oncol* 2019;49:29–36. https://doi.org/10.1093/jjco/hyy179.
11. Miyamoto S, Azuma K, Ishii H, et al. Low-dose erlotinib treatment in elderly or frail patients with EGFR mutation-positive non-small cell lung cancer: a multicenter phase 2 trial. *JAMA Oncol* 2020;6:e201250. https://doi.org/10.1001/jamaoncol.2020.1250.
12. Imai H, Kaira K, Suzuki K, et al. A phase II study of afatinib treatment for elderly patients with previously untreated advanced non-small-cell lung cancer harboring EGFR mutations. *Lung Cancer* 2018;126:41–7. https://doi.org/10.1016/j.lungcan.2018.10.014.
13. Yokoyama T, YoshiokaH FD, et al. A phase II study of low starting dose of afatinib as first-line treatment in patients with EGFR mutation-positive non-small-cell lung cancer (KTORG1402). *Lung Cancer* 2019;135:175–80. https://doi.org/10.1016/j.lungcan.2019.03.030.
14. Schochet PZ. Statistical power for regression discontinuity designs in education evaluations. *J Educ Behav Stat* 2009;34:238–66. https://doi.org/10.3102/1076998609332748.
15. Bor J, Moscoe E, Mutevedzi P, Newell ML, Bärnighausen T. Regression discontinuity designs in epidemiology: causal inference without randomized trials. *Epidemiology* 2014;25:729–37. https://doi.org/10.1097/EDE.0000000000000138.
16. Moscoe E, Bor J, Bärnighausen T. Regression discontinuity designs are underutilized in medicine, epidemiology, and public health: a review of current and best practice. *J Clin Epidemiol* 2015;68:122–33. https://doi.org/10.1016/j.jclinepi.2014.06.021.

医療保障総合政策調査・研究基金事業
高額医薬品の適正使用の推進のための調査研究
報告書

令和７年３月

健康保険組合連合会
〒107-0052　東京都港区赤坂 8-5-26
住友不動産青山ビル西館内
https://www.kenporen.com/