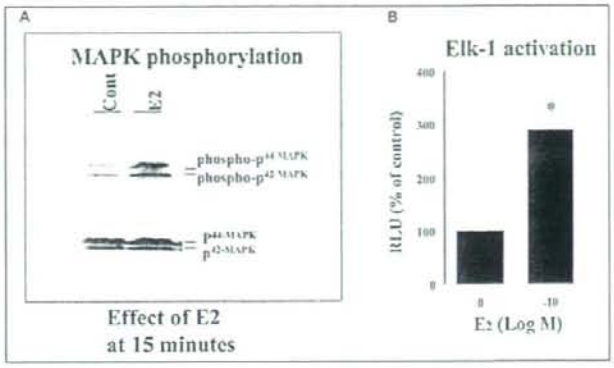

Figure 4.

A) Effect of 0.1 nM estradiol on levels of activated and total MAP kinase measured 15 min after addition of steroid. Shown on the top segment is activated MAP kinase as assessed by an antibody specific for activated MAP kinase and on the bottom segment, total MAP kinase. B) Effect of 0.1 nM estradiol on the activation of ELK-1.

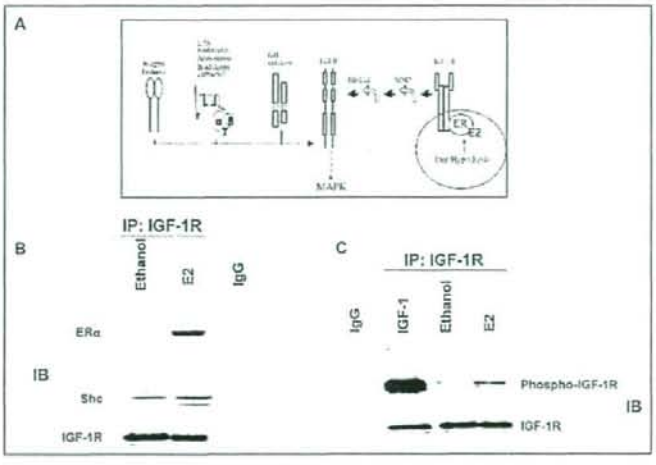

Figure 5.

A, top) Diagrammatic representation of a model in which estradiol binds to ERα which then binds to the adaptor protein, SHC. At the same time estradiol causes phosphorylation of the IGF-1-R, which provides a binding site for SHC. In this model, estradiol signals through the IGF-1-R and activates MAP kinase which then acts through Elk-1 to initiate gene transcription. B) estradiol-induced protein complex formation among ERα, SHC and IGF-1-R. MCF-7 cells were treated with vehicle, 1 ng/ml IGF-1, or E_2 at 0.1 nM for the times indicated. Lysates were immunoprecipitated with IGF-1-R antibody. The nonspecific monoclonal antibody (IgG) served as a negative control.[28] C) estradiol increases the phosphorylation of the IGF-1-R.

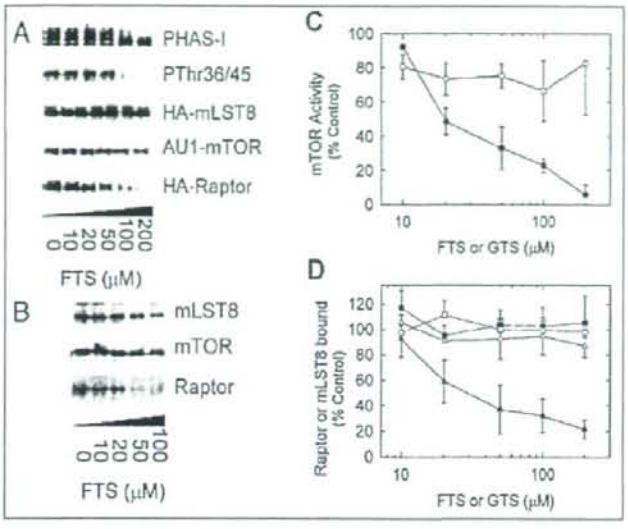

Figure 6.

Left) FTS promotes raptor dissociation and inhibits mTOR activity in cell extracts. A) 293T cells were transfected with pcDNA3 alone (vector) or with a combination of pcDNA3-AU---mTOR, pcDNA3-3-HA-raptor and pcDNA3-3HA-mLST8. Extracts of cells were incubated with increasing concentration of FTS for 30 min before AU-1-mTOR was immunoprecipitated. Samples of the immune complexes were incubated with (γ32P)-ATP and recombinant (HIS 6) PHAS-1 and then subjected to SDS-PAGE. A phosphor image of a dried gel was obtained to detect ^{32}P-PHAS1 and an immunoblot was prepared with PThr36/45 antibodies. Other samples of the immune complexes were subjected to SDS-PAGE and immunoblots were prepared with antibodies to the HA epitope or to mTOR.[2] B) Extracts of nontransfected 293T cells were incubated with increasing concentrations of FTS before mTOR was immunoprecipitated with mTab 1. A control immunoprecipitation was conducted using nonimmune IgG(Nl). Immune complexes were subjected to SDS-PAGE and immunoblots were prepared with antibodies to mLST8, mTOR and raptor.[2] Right) Relative effects of increasing concentrations of FTS and GTS on mTOR activity and the association of mTOR and raptor. Samples of extracts from 293T cells overexpressing AU1-mTOR, HA-raptor and HA-mLST8 were incubated for 1 hr with increasing concentrations of FTS (●, ◆, ■) or GTS (○, △, □) before immunopreciptations were conducted with anti-AU 1 antibodies.[2] A) mTOR kinase activity (●, ○) was determined by measuring ^{32}P incorporation into (HIS6) PHAS-1 in immune complex kinase assays performed with (γ32P)-ATP. B) The relative amounts of HA-raptor (◆,○) and HA-mLST8 (■, △) that co-immunoprecipitated with AU-1-mTOR were determined after immunoblotting with anti-HA antibodies. The results (mean values ± SE for five experiments) are expressed as percentages of the mTOR activity (C) or co-immununoprecipitating proteins (D) from samples incubated without FTS or GTS and have been corrected for the amounts of AU-1–mTOR immunopecipitated.[2] From: McMahon LP et al. J Mol Endocrinol 2005; 19(1):175–183;[2] with permission of The Endocrine Society.

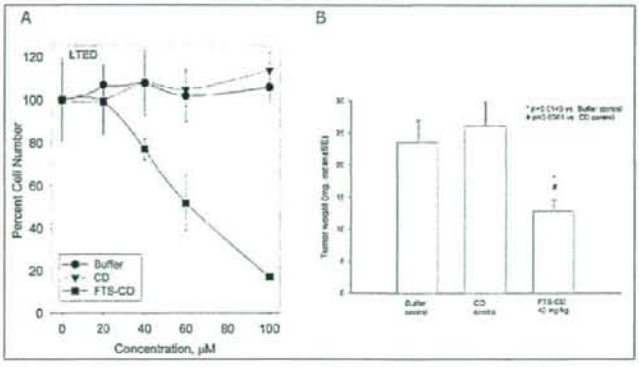

Figure 7.

A) In vitro effects of FTS on cell growth. Effects of FTS complexed with cyclodextrin (CD) for solubility were compared with buffer or cyclodextrin (CD) alone on the number of LTED cells expressed as a percent of maximum number. The ordinate shows the concentration of FTS used. B) In vivo effects of FTS on cell growth. LTED cells were implanted into castrate nude mice to form xenografts. Silastic implants delivering estradiol at amounts sufficient to provide plasma levels of estradiol of 5 pg/ml were implanted. One group received buffer alone, the second cyclodextrin alone and the third FTS 40 mg/kg complexed to cyclodextrin. The effects of FTS-CD compared to CD control were statistically significant at $p = 0.0061$.

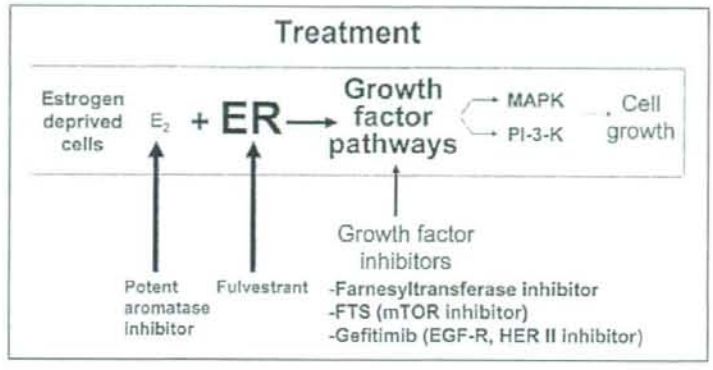

Figure 8.
Practical implications of the effects of up-regulation of growth factor pathways and development of hypersensitivity to estradiol. Potent aromatase inhibitors are useful to counteract the enhanced sensitivity to estradiol resulting from adaptation to prolonged estradiol deprivation. A pure antiestrogen such as fulvestrant can counteract the up-regulation of the ER that occurs. Growth factor inhibitors such as FTS, farnesyl-transferase inhibitors and growth factor inhibitors such as Iressa and others can be used to block up-regulation of growth factor pathways.

医療経済

サマリー

医療改革の流れの中で癌医療に携わる臨床医も医療経済への基本的な理解をもつことが重要になってきた。本項では経済学のアプローチによる医療研究の目的を導入したうえで，医療サービスの経済評価としての費用効果分析を簡単に解説し，わが国での乳癌医療の経済評価の近年の事例を紹介する。

はじめに

日本経済の成長率を上回る国民医療費の増大が続く中で，医療費適正化が医療行政の目標の1つとして掲げられ医療費の伸びの抑制が図られてきている。こうした文脈のもとで進んでいる医療改革は，癌医療にかかる大きな費用の負担のあり方に影響を及ぼし，癌専門医の日常臨床の場にまでさまざまなかたちで影を落としている。同時に，国民に医療サービスを提供するために限りある医療費をどのように使っていったらよいのかという医療改革の大きな課題に対して，経済学のアプローチによる医療研究の担う役割が期待されている。本書の読者である癌専門医あるいは研修医・学生の方々にとっても癌医療のあり方を考えるうえで医療経済への基本的な理解をもつことが重要になってきたといえよう。

しかし，医師にとって経済は比較的なじみの薄いものであるとも想像されるので，本項では，『背景』で「医療経済学入門」として，経済学のアプローチの基本を紹介したうえで，医療サービスの経済評価の結果の解釈の仕方を中心に簡単な解説を行う。『現状』では，これを踏まえたかたちで乳癌医療の経済評価の近年の事例を紹介する。さらに『問題点』では，乳癌医療の経済評価を活かす制度をめぐる問題点を簡単に論じ，最後に『展望』では，経済学の観点から医師の役割などを論じてまとめとする。

医療経済学入門

1．医療費適正化と経済学

医療費適正化という文脈のもとで経済学のアプローチによる医療研究の担う役割が期待されている理由としては，医学が主として病気や健康を扱う学問であるように，経済学が主として金銭や景気を扱う学問であるためであると理解されることが多い。医療費とはすなわち金銭であり，経済学の出番となるのだという解釈である。これは，経済学が社会科学として社会現象の解明を図る際に，物やサービスの生産や取り引きに着目することが多く，生産や取り引きの裏面には，自給自足や物々交換がほとんど行われない現代社会では，ほとんどの場合金銭の流れが伴うという事実のためであろうと思われる。しかしこの解釈は，誤りではないものの，捉え直すことができるものである。

経済学は一般に，「さまざまの有用な商品を生産するために，社会がどのように稀少性のある資源を使い，異なる集団の間にそれらの商品を配分するかについての研究である」と定義される。したがって，われわれの文脈では，経済学の医療への応用とは，さまざまな医療サービスを提供するために，社会が限りある国民医療費を使い，さまざまな病気の患者に有効な医療サービスをいかに受けてもらうかについての研究であると解することができる。つまり，物やサービスの流れに焦点を合わせれば，無尽蔵ではない医療費を使って医療が国民に行き渡るようにするためにはどうしたらよいのかということが

問題であるからこそ，経済学の出番となるのであるとも解釈できる。このように捉え直すと，医療すなわち人の命の問題を金銭の問題と結びつけようとするときに抱かれやすい直感的な倫理性への懸念を整理して考えることにも役立つ。

2．医療サービスの経済評価

医療経済学とは，医療を対象とした経済学の応用分野であり，経済学の幅広い理論と多種多様な分析手法の応用が考えられる研究領域であるが，実践的には，新薬の導入や効能追加といった新しい医療の導入に関して費用効果分析，費用効用分析，費用便益分析などの分析手法を用いた医療サービスの経済評価というスタイルの研究が多く行われてきている。また，費用効用分析は費用効果分析の中の1つのタイプと分類されることもある。これらの中では，広義の費用効果分析が比較的広く使われてきている。こうした研究報告は癌関連の学術誌にも掲載されることが多いので，以下ではこの費用効果分析（費用効用分析）の結果の解釈の仕方を簡単に解説する。

3．費用効果分析（費用効用分析）のエンドポイント

費用効果分析とは文字どおり費用と効果を同時に分析する手法である。癌専門医にとっては，効果を分析する臨床試験の分析手法はなじみがあると思われる。ここでは，臨床試験との比較からスタートして，費用効果分析の結果の読み方の基本を説明していく。

単純な新薬の臨床試験では，ある病態の患者を集め，偏りがないように2群に分け，各群に対して既存の薬物療法と新薬を使う薬物療法を施し，それぞれ効果を測定し，両群の効果の差をとって，今後同様の病態の患者に新薬を使うことの可否が判断される。つまり，

$$\text{増分効果} = \text{効果}_{\text{新薬}} - \text{効果}_{\text{既存薬}}$$

が結果のエンドポイントであり，増分効果が，正であれば新薬が医療に導入されるべきであり，負であれば導入されるべきではないと判断されることになる。

費用効果分析での効果の分析でも，臨床試験の場合と同じように増分効果が求められる。また同様に費用の分析でも，既存の薬物療法に伴う費用と新薬を使う薬物療法に伴う費用を測定し，両群の費用の差がとられる。つまり，

$$\text{増分費用} = \text{費用}_{\text{新薬}} - \text{費用}_{\text{既存薬}}$$

である。この増分費用が，正であれば新薬を使うと費用がかさむことになり，負であれば安上がりになることになる。ただし，効果の大小を無視して増分費用の符号のみから導入の可否を判断することはできない。

費用効果分析では，費用と効果を同時に評価するために，さらに増分効果と増分費用の比をとって結果としてまとめられる。これは増分費用効果比（incremental cost-effectiveness ratio；ICER）と呼ばれる。つまり，

$$\text{増分費用効果比} = \frac{\text{増分費用}}{\text{増分効果}} = \frac{\text{費用}_{\text{新薬}} - \text{費用}_{\text{既存薬}}}{\text{効果}_{\text{新薬}} - \text{効果}_{\text{既存薬}}}$$

であり，これが費用効果分析のプライマリー・エンドポイントともいうことができる指標である。

4．増分効果，増分費用，増分費用効果比の意義

ここで，これらの増分効果，増分費用，増分費用効果比をみてどのような判断を下すことができるのかということが問題になるが，まず図1をみていただきたい。

これは，費用効果平面と呼ばれる図で，増分効果と増分費用をプロットすることができる二次元の平面である。ここでは例として第Ⅳ象限に☆印が示してある。これは「増分効果が正で新薬の効果が既存薬を上回っている」ということであり，臨床試験，すなわち効果の分析のみの結果からはこの新薬は医療に導入されるべきであると判断されるであろう。一方で，「増分費用は負で新

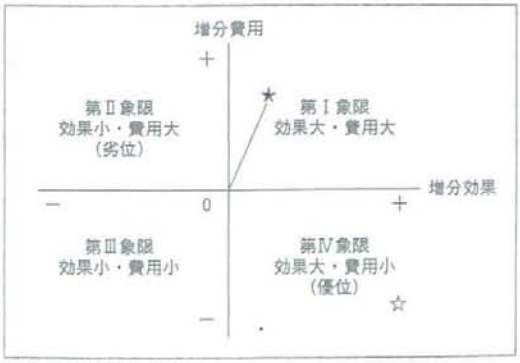

図1　費用効果平面

薬を使うほうが安上がりになる」ということでもあり，費用の分析のみの結果からも，国民のかかるさまざまな病気の治療を限りある医療費で負担しなければならないという前提に立てば，節約された医療費を他に回すことができるなどとも考えられ，新薬を導入するべきではないかと示唆されるであろう。このように考えてくると，増分効果と増分費用が第Ⅳ象限にプロットされるような結果が得られた場合は，費用と効果を同時に評価した結果として新薬が導入されるべきであるという判断が得られる。このような場合に新薬は既存薬に対して優位であると表現される。

次に，増分効果と増分費用が第Ⅱ象限にプロットされるような結果が得られた場合について考えてみよう。この場合は，新薬では「既存薬を上回るような効果は得られないうえに費用もかさむ」ということになる。費用効果分析の結果として費用と効果の両面から新薬を導入するべきではないという判断が得られる。このような場合に新薬は既存薬に対して劣位であると表現される。

これらのように優位あるいは劣位の結果が得られた場合には，費用効果分析の結果について増分費用と増分効果の符号を考えるだけで導入の可否の判断を下すことができる。しかし，第Ⅰ象限や第Ⅲ象限にプロットされるような結果が得られた場合には増分費用と増分効果の符号を考えるだけでは判断を下すことができない。

実は，われわれが考えてきている新薬の導入の可否を検討する文脈では，図1に★印で示したように第Ⅰ象限に結果がプロットされる。つまり，新薬の「効果は大きい(増分効果正)が費用はかさむ(増分費用正)」ときに，これを導入するべきか否かを考えなければならない場合が多い。効果が大きいのに新薬の普及を控えるという選択が考慮される理由は，多種多様な新薬すべてを普及させる費用を負担することは難しく，小さな費用で大きな効果が得られる新薬を選び出して優先すべきではないのであろうかとか，費用がかさむ新薬を普及させると，保健医療システムの中でめぐりめぐって医療費が回ってこないために，効果が大きく安上がりな治療があるのに受けることができない患者が生じてしまわないであろうかというような懸念などを考えることができるであろう。こうした場合の結果の解釈は，増分費用効果比の大きさ，つまり原点0と★印を結んだ線分の傾きの大きさによることになる。

図1をみれば容易に想像がつくように，この傾きは費用と効果の測定単位に依存して変わるものである。しかし，費用効果分析では費用の測定単位には金銭，つまり円，効果の測定単位には生存の延長年数，つまり年が広く用いられている。さらに後者に関しては生存期間の生活の質の調整を加えて測定したほうが望ましいとされており，質調整生存年(quality-adjusted life-years；QALYs)という単位で延長年数が測られることがある。QALYsとは，完全な健康状態に「1」，死亡状態に「0」，病気によって生活の質が損なわれた状態に「1よりも小さい」ウエイトを付けて生存の延長年数に生活の質の低下を加味するもので，図2の網掛け部の面積として示すことができる概念である。このとき使われるウエイトは特定の健康状態で過ごす生活に対する個人や社会の好みに応じて決められるものであり，こうした好みは経済学では効用とも呼ばれる。このために生活の質の調整を加えずに効果の測定を行った経済評価を狭義の費用効果分析とし，生活の質の調整を加えて測定を行ったものを費用効用分析として区別することがある。

このように円と年という測定単位が用いられると，線分の傾き，すなわち増分費用効果比は，新薬を使って「1人の生存を1年(QALYsで測られた場合は完全な健康で過ごす1年換算)延ばすためには何円これまで以上に支払わなければならないのか」を表したものとして解釈することができる。この値の評価の仕方は人によってさまざまであろう。この新薬を待ち望んでいた患者，他の

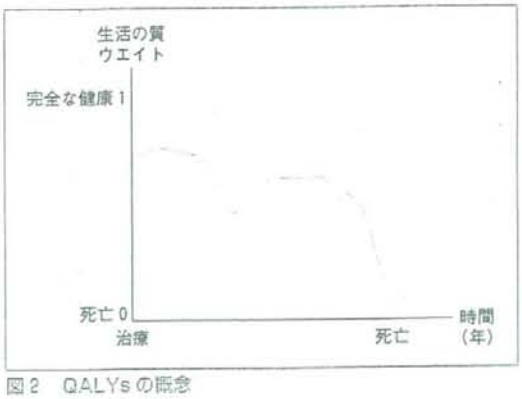

図2　QALYsの概念

病気の患者，健康な人などの中には，喜んで支払いたいと思う者もいれば，とても支払う気持ちになれないと思う者もいるであろう。しかし，費用効果分析の結果の解釈の仕方としては，社会が新薬や新しい治療法の医療への導入によって1人の生存を1年延ばすために追加的にいくらまで支払う意思があるのかという基準を立てて，増分費用効果比と比較することによって，新薬の導入の可否が判断される。この基準の値については，諸国の社会のあり様によって異なるが，わが国では，600万円程度であろうという報告がある。先進諸国での研究報告事例や医療行政上の判断もほぼ同じような値が基準とされてきているが，必ずしも明確に定まっているわけではない。

結果の解釈としては600万円程度を目安として，増分費用効果比が下回った場合は新薬を使った薬物療法は費用対効果に優れ医療費の使い方として効率性が高く医療に導入するべきだと示唆されると解され，逆に上回った場合は費用対効果の観点からは導入されるべきだとは示唆されないと解される。

最後に第Ⅲ象限に結果がプロットされる，つまり「効果は小さい(増分効果負)が費用は安上がり(増分費用負)」という場合に関しては，既存薬の効果のほうが優れているのにその使用を控えるべきであるというような判断は現実的にありえないというような理由から，結果の解釈の仕方にはコンセンサスがない。このような結果が意義をもつと考えられるのは，たとえば集団検診でのスクリーニング方法を決めるために費用効果分析を行った場合などであろう。

5．注意点

費用効果分析の結果として得られた増分効果，増分費用，増分費用効果比を上述のように解釈して新薬や効能追加の可否を判断することができるのは，そのような判断を正当化するために経済学の理論基盤から要請される正しいやり方で分析が行われていることが前提である。この前提を確認するためには，理論と方法論の正しい理解に基づいて分析全体の批判的吟味を行って個別の報告の質を評価することが必須である。たとえば，ここまでの簡単な説明では費用の測定は単純に医療費を合計することのように解されるかもしれないが，本来は医療制度によって規定された金銭の流れの合計ではなく，対象となる医療を提供するために社会全体のあらゆる個人や組織が創いた全資源の最大価値という意味での社会的機会費用を測ってはじめて判断を下すことが正当化できるのである。したがって，近似として医療費の合計をとることに伴う問題を理解したうえで判断を下すことが重要である。この他にも留意しなければならないポイントはいくつもあるが，入門からさらに一歩踏み込もうという方には，末尾の文献欄に成書等を示す。

わが国での乳癌医療の経済評価の近年の事例を表1にまとめた。高額な遺伝子検査である21-gene RT-PCRの導入，薬価のきわめて高いトラスツズマブの術後補助療法への適応拡大，ジェネリック医薬品が利用できるタモキシフェンに代えて薬価が高額なアロマターゼ阻害薬のレトロゾールの使用など，「効果は大きい(増分効果正)が費用はかさむ(増分費用正)」と予想される文脈で，評価が行われてきている。これら3つの事例では，いずれも新しい医療を導入するべきであるという結論が得られている。

わが国では，表1に挙げた事例以外にも乳癌検診プログラムなどを対象とした経済評価の報告例があるが，それらは方法論的に問題をはらんでいると考えられるので，表1からは除外した。

このように費用効果分析は社会や保健医療システム全体のレベルで新しい医療を導入するべきか否かという判断に資するものである。しかし，わが国では新薬や新しい医療技術の導入の可否に関して，その増分費用効果比を考慮に入れて判断する制度にはなっていない。この点に関して諸外国をみると，イギリス，オーストラリア，カナダの一部の州などでは，新薬や効能追加時に，承認や保険適用，また公的に提供される医療の中での使用の推奨などに関する政策決定が，費用効果分析の結果を取り入れて行われている。たとえばイギリスでは，NICE (National Institute for Health and Clinical Excellence)と

表1　わが国での乳癌医療の経済評価の近年の事例

著者	論文題目	発表学術誌	評価内容
Kondo, et al (2007)[1]	Economic evaluation of 21-gene reverse transcriptase-polymerase chain reaction assay in lymph-node-negative, estrogen-receptor-positive, early-stage breast cancer in Japan.	Breast Cancer Res Treat [Epub]	リンパ節転移陰性ホルモン感受性乳癌の術後化学療法の使用決定に21-gene RT-PCR検査を導入することは費用対効果に優れる(ICER：124～300万円/QALY)。
Shiroiwa, et al (2007)[2]	The model-based cost-effectiveness analysis of 1-year adjuvant trastuzumab treatment; Based on 2-year follow-up HERA trial data.	Breast Cancer Res Treat 109：559-566	Her 2 陽性乳癌の術後補助療法でのトラスツズマブ使用を導入することは費用対効果に優れる(ICER：220～330万円/年)。
Okubo, et al (2005)[3]	Cost-effectiveness of letrozole versus tamoxifen as first-line hormonal therapy in treating postmenopausal women with advanced breast cancer in Japan.	Gan To Kagaku Ryoho 32：351-363	閉経後ホルモン感受性転移・再発乳癌の一次治療でタモキシフェンに代えてレトロゾール使用を導入することは費用対効果に優れる(ICER：55万円/年)。

ICER：incremental cost-effectiveness ratio(増分費用効果比)

いう公的機関が，新しい医療の有効性に加えて費用対効果も鑑みて，その導入の可否を勧告している。同様な機関はフランスやドイツでも設立されている。したがって，医療経済学の立場からは，わが国でこのような社会的な意思決定のルールづくりが進んでいないことは問題であると考えられる。

本項をここまで読み進めていただいた読者の方々の中には次のような2つの感想をおもちになる方もいるのではないかと想像する。これらを簡単に論じることで結びとしたい。

まず，「600万円という基準がピンとこない」という感想である。この値は国民の平均的な価値判断を推定したものである。しかし，すでに触れたように癌患者に対して癌の新薬の価値を尋ねれば600万円よりもずっと大きな値が得られるであろう。患者の気持ちのわかる癌専門医なら同様に大きな値を思い浮かべるであろう。実際，米国の癌専門医に増分費用効果比の判断基準値を聞いたある研究では，広く使われている5万ドル(≒600万円)に対して30万ドルという結果が得られたと報告されている。しかし，費用のかさむ新しい医療が次々と生み出される中で，患者と医師が一緒になって請求書を無制限に医療保険につけ回し続ければ，国民全体から集めた保険料では支払いきれなくなってしまうであろう。この悪循環を断ち切るために医療経済学の立場からは，患者ではなく医師のほうが専門家として，眼前の患者の背後にいる別の患者や，いつ病気になるかわからない健常者たちも抱いている医療の安定的な提供への願いを考慮に入れて，請求書の内容を厳選する判断を下すことが，医師の社会的な役割の1つだと期待されるわけである。医師は確かに眼前の1人の患者の立場に立って医療を行うべきではあるが，同時に広く国民から集めた国民医療費を使って医療を提供する限りにおいては，社会的な立場から最適な医療を考えることも期待されるのである。

もう1つは，「医療費適正化というきわめて複雑で多様な側面をもつ問題を考えるうえで，新しい医療の導入の増分費用効果比をみているだけで解決につながるのか？」という感想である。確かに本項で解説した費用効果分析は新しい医療の導入の効率性のみを検討するものである。しかし，最初に触れたように「さまざまな医療サービスを提供するために，社会が限りある国民医療費を使い，さまざまな病気の患者に有効な医療サービスをいかに受けてもらうかについての研究」としての経済学の医療への応用には，本項で主に解説してきた医療サービスの経済評価を超えた広がりがある。こうした点に関心をもたれる方には，以下に示す成書等に当たられることお勧めする。

(近藤正英)

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（以上，50音順）

Cost-effective treatment options in first-line therapy for advanced breast cancer in Japan

Masahide Kondo and Masakazu Toi[†]

Concern regarding the economic aspect of cancer care has been increasing in the face of mounting healthcare expenditure in Japan. The need, not only for effective, but also for efficient treatment options in breast cancer care have been recognized in a broader context. In clinical practice, treatment options in first-line therapy for advanced breast cancer have become similar to those in Western countries in the past 5 to 10 years in the context of so-called 'evidence-based medicine' employing clinical evidence; whereas evidence of cost-effectiveness has been less acknowledged. Limited economic evidence suggests that current Japanese practice in first-line hormonal therapy is cost-effective. However, the efficiency of other options, such as chemotherapy, remains unknown. The expanding use of an expensive molecular-targeting agent, trastuzumab, has great implications for a treatment algorithm for breast cancer as well as for cost-effectiveness of care. Trastuzumab, of which use in first-line therapy was not found to be cost-effective in Western countries, is expected to be used for a number of HER2-overexpressing primary breast cancers in Japan. The extension of indication of this single agent would increase national healthcare expenditure by 0.1%. The authors believe explicit discussion on value for money of new expensive drugs would be unavoidable, not only among health policy makers, but also leading breast cancer specialists in Japan in the near future.

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CONTENTS

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Breast cancer has become one of the leading causes of death and morbidity in Japan. It is the fifth largest cause of death from cancers of major sites among females after stomach, lung, colon and liver. Mortality is rising continuously [1], although its age-adjusted mortality standardized to world population (8.3/10,000 population) is lower than those in Northern America (19.2) or Western Europe (22.3), according to an international comparison by the International Agency for Research on Cancer in 2002 [2]. The latest estimated incidence of breast cancer among females standardized to world population (33.8/100,000 in 1998) is the highest among cancers for major sites and is rising continuously [3]. The number of incident cases in 1999 was 36,139, which is remarkably larger than 11,123 in 1975; and the age-adjusted incidence standardized to Japan's standard population increased 2.14-times during the same period [4]. Notable increases among the younger generation implies that it could become as high as those in Northern America (99.4) or Western Europe (84.6) [2] in the near future [3]. Although there is no established estimate for the number of advanced breast cancer cases, a proportion of cases with metastasis or invasion among newly diagnosed cases reported from a well-organized cancer registration (38.5%) [5], and unavoidable expectation of recurrence among early cases suggest that a number of cases are subject to first-line therapy for advanced breast cancer.

The increasing number of breast cancer cases combined with the use of resource-consuming therapies has grave implications for healthcare resources in Japan. Healthcare expenditure for cancer as a whole is reported to be US$283 billion, which accounts for 11.4% of the national healthcare expenditure in 2002. This is increasing steadily both in amount and

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share [6]. The breakdown for breast cancer is estimated to be US$18 billion, accounting for 8.5% of healthcare expenditure for all cancers [7].

These increasing trends, which are commonly observed in industrialized countries, demand not only effective, but also efficient or cost-effective, treatment strategies for breast cancer.

Breast cancer is a solid carcinoma developed from the mammary gland. It is, however, widely acknowledged as a systemic disease, especially in the case of advanced breast cancer that requires combined modality therapy. It is also characterized by the involvement of sex hormones in its pathophysiology. Chemotherapy and endocrine therapy play major roles in its treatment, along with surgery and radiation therapy. Innovative – often expensive – antitumor and hormonal agents have been intensively developed and introduced widely in industrialized countries, including Japan.

This review, therefore, will focus on drug therapy strategies for advanced breast cancer and will discuss current options for first-line therapy in light of cost–effectiveness in Japan. Major drugs used in breast cancer treatment are summarized in BOX 1.

Box 1. Major drugs used in breast cancer treatment

Hormonal drug

- Antiestrogen
  - Tamoxifen
  - Toremifene
- Gestogen
  - Progesterone
  - MPA
- LH-RH analog
  - Goserelin
  - Leuprolide
- Selective estrogen receptor modifier
  - Fulvestrant*
- Aromatase inhibitor
  - Anastrozole
  - Letrozole*
  - Exemestane
  - Fadrozole

Anticancer drug

- Alkylating agent
  - Cyclophosphamide
- Metabolic antagonist
  - Folate metabolism antagonist
    - Methotrexate
  - Pyrimidine metabolism antagonist
    - 5-FU
    - 5'DFUR
    - Capecitabine
    - UFT
- Mitotic inhibitor
  - Vinca alkaloid
    - Vinorelbine
  - Taxane
    - Paclitaxel
    - Docetaxel
- Antitumor antibiotic
  - Anthracycline
    - Doxorubicin

Human monoclonal antibody

- Trastuzumab

*Not yet made available in Japan.
5-FU: 5-fluorouracil; 5'DFUR: 5'-deoxy-5-fluorouridine; MPA: Medroxyprogesterone acetate; UFT: Uracil and tegafur.

Treatment strategies for advanced breast cancer

Treatment strategies for breast cancer in Japan are arguably harmonizing with global standards with the recent development of a series of guidelines.

A consensus that evidence-based therapy should be provided for patients, despite the evidence being evaluated by breast cancer specialists in Western countries and, therefore, there are probably some unknown ethnic differences [8], has been rapidly formulated in the last 5–10 years. When there was a sudden interest in so-called 'evidence-based medicine' in the Japanese medical arena in the late 1990s [9], wide clinical practice variations in breast cancer treatment are acknowledged and the development of guidelines for breast cancer treatment was launched. The variations were surveyed by breast cancer specialists [10,11] and efforts were made to establish a consensus. The first guideline was published as a report of the Ministry of Health, Labor and Welfare funded research in 2003 [12], which was then revised by the Japanese Breast Cancer Society in 2004 [13]. In 2005, the Japan Society of Clinical Oncology published a guideline for appropriate drug use in the treatment of breast cancer [14]. The voice of the patient groups strongly supported the creation of such guidelines for good clinical practice.

The treatment strategy for advanced breast cancer in the latest guidelines [14] is summarized in FIGURE 1. Clearly, this is consistent with National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology [15,101], and its development was based on Hortobagyi's algorithm [16].

Treatment options in first-line therapy for advanced breast cancer

The guideline clearly identifies two types of first-line therapies, depending on the nature of the disease: hormonal therapy for hormone-responsive and non life-threatening disease, and chemotherapy for hormone-unresponsive or life-threatening disease; however, it leaves the use of human epithelial growth factor receptor (HER)2-overexpression screening and trastuzumab unclear in the strategy. Furthermore, the guideline identifies two subtypes of first-line hormonal therapy depending on the menopausal status. For premenopausal disease, combined therapy with a luteinizing hormone releasing hormone (LH-RH) analog (e.g., goserelin 3.6 mg/4 weeks or leuprolide 11.25 mg/12 weeks) and tamoxifen (20 mg) is strongly recommended compared with

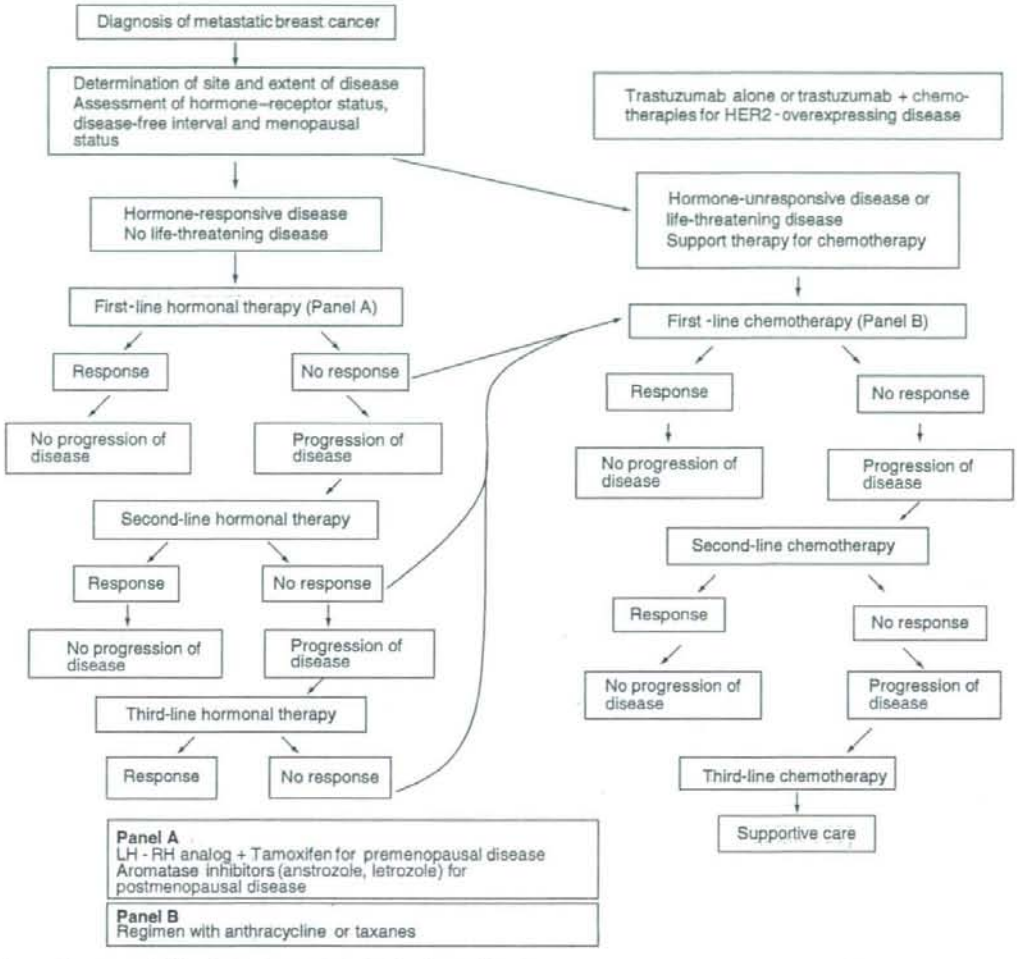

Figure 1. Japanese guidelines for treatment strategies for advanced breast cancer.
LH-RH: Luteinizing hormone-releasing hormone; HER2: human epithelial growth factor receptor type 2.

single-agent therapy with ovarian function inhibitors or tamoxifen. For postmenopausal disease, aromatase inhibitors, anastrozole or letrozole, are strongly recommended compared with selective estrogen receptor modifiers or progesterone. As first-line chemotherapy, regimens with anthracycline or taxanes are recommended based on results from randomized trials and systematic reviews. Suggested regimens are doxorubicin and cyclophosphamide (AC), cyclophosphamide, doxorubicin and 5-fluorouracil (CAF) and doxorubicin and paclitaxel (AT).

In practice, however, treatment options in first-line therapy are not totally consistent with those recommended in guidelines due to two factors: use of trastuzumab and variation of preoperative or postoperative adjuvant therapy. Trastuzumab is one of the most innovative agents introduced into breast cancer treatment since the 1990s, which is famous as an example of the product of genome-based drug discovery. It is a human monoclonal antibody, targeting HER2, and its use, combined with chemotherapy for advanced breast cancer, has been proven effective in several clinical trials [17]. Assessment of HER2-overexpressing status is routinely performed following a guideline formed by the Pathology Committee of Trastuzumab in 2001 [18] and, presently, regimens including trastuzumab are usually applied as first-line therapy for HER2-overexpressing disease. Current treatment strategy for advanced breast cancer in practice, taking HER2-overexpression status into account, is shown in FIGURE 2.

For non life-threatening and hormone-responsive disease, single-agent therapy is often chosen regardless of HER2-overexpression status, which is in accordance with Hortobagyi's algorithm.

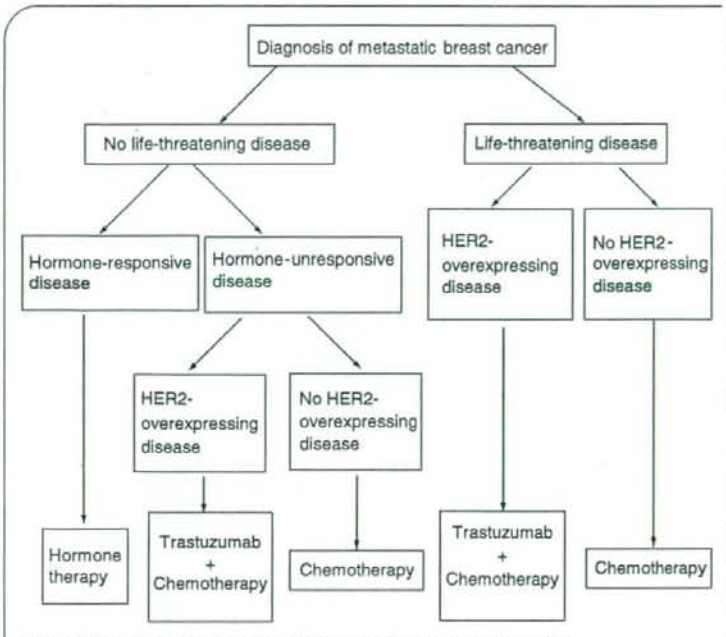

Figure 2. Current treatment strategies for advanced breast cancer in practice.
HER2: Human epidermal growth factor receptor 2.

Yet, combined therapy is sometimes used with other agents, such as trastuzumab, for HER2-overexpressing disease or oral FUs for non-HER2-overexpressing disease. The latter regimen may be a notable difference between Japanese and Western practice. Although there is no sufficient high-level evidence, there is a consensus that the regimen is effective based on Japanese long-term experiences of using oral FUs. (e.g., effectiveness of tamoxifen, uracil and tegafur [UFT] [19] or tamoxifen, cyclophosphamide and 5´deoxy-5-fluorouridine [DFUR] [20] in adjuvant therapy has been demonstrated).

The choice of agent in hormonal therapy is highly dependent on agents used in adjuvant therapy. Recently, there has been a remarkable shift in the choice of agents used in adjuvant therapy, which is quite similar to that in NCCN guidelines. Combined therapies with a LH–RH analog and tamoxifen for premenopausal disease, and aromatase inhibitors for postmenopausal disease, have quickly become the first choices in adjuvant therapy. Increasing numbers of patients are expected to receive these regimens as adjuvant therapy. Consequently, another anti-estrogen agent such as toremifene (40–120 mg/body) is used as first-line hormonal therapy for recurrent breast cancer after adjuvant therapy with a LH–RH analog and tamoxifen if the patient is still premenopausal. Toremifene was officially approved for postmenopausal disease, but its use for premenopausal disease has become common practice. If the patient is postmenopausal, aromatase inhibitors are used. Aromatase inhibitors, such as anastrozole (1 mg/body) or exemestane (2.5 mg/body), are chosen as letrozole has not yet been made available in Japan. Medroxyprogesterone acetate (MPA) is not chosen in first-line therapy and only used after second-line therapy.

For primary postmenopausal disease, the aromatase inhibitor most frequently used as an agent for adjuvant therapy is anastrozole. This is probably due to an appreciation of results from the arimidex, tamoxifen and combination therapy (ATAC) trial [21]. Exemestane is often used as a replacement for tamoxifen, and less frequently used as the very first agent. Once letrozole becomes available it may be used for node-positive disease more preferably, acknowledging the results from Breast International Group (BIG)-1 trial [22]. There are some specialists who view three aromatase inhibitors as almost similar, and primarily use exemestane. It is expected that the choice among aromatase inhibitors could become more individualized according to the bone or vascular toxicity, in the near future. Consequently, aromatase inhibitors are used in first-line hormonal therapy if tamoxifen was used in the adjuvant setting. The choice of agents is controversial if one of the aromatase inhibitors was already used in adjuvant therapy. Occassionally, another aromatase inhibitor is chosen, since there is low-level evidence of effectiveness for this regimen [23]. However, antiestrogen agents, such as tamoxifen, are more frequently chosen, althouth there is no sufficient evidence for the benefit of this regimen. There remains a wide variation in choice by specialists. MPA is not chosen in first-line therapy and only used after second-line therapy. Fulvestrant or pure antiestrogen is not used in Japan, since it has not been made available.

For HER2-overexpressing disease, chemotherapy, including trastuzumab (4 mg/kg loading dose; 2 mg/kg weekly), is usually applied regardless of life-threatening status. Trastuzumab monotherapy is also used for patients with relatively small burden of metastatic tumors, such as local lymph node recurrence and small-size lung metastases. A combined therapy with taxanes (e.g., weekly paclitaxel 80–100 mg/m^2 or docetaxel 60–70 mg/m^2 three-times weekly) is used for most patients, while single-agent therapy with trastuzumab is sometimes used for patients with only minor metastasis. For HER2-overexpressing and hormone-responsive disease, trastuzumab is sometimes combined with tamoxifen or aromatase inhibitors, although there is little supportive evidence for the use of these regimens. Combined use with other agents, such as vinorelbine or capacitabine, is still very limited. It is worth noting that, in Japanese practice, once trastuzumab is administered to a patient, it is usually continued through to supportive care coupled with various regimens. National Health Insurance reimburses accompanying costs. Trastuzumab is even used in patients for whom an individualized strategy is

applied. For example, it is often reused for patients with brain metastasis after appropriate local treatment, such as radiation or surgery, even though many remain controversial.

The chemotherapy regimen is also highly dependent on agents used in adjuvant therapy. In practice, risk categorization is often made according to St Gallen-based consensus [22], and the choice of agents is often made according to NCCN-based guidelines [15,101]. Anthracycline is quite often used for high-risk cases, such as node-positive disease. It is also used for most intermediate-risk cases. Yet, it is less often used for hormone-responsive and node-negative cases in Japan. Taxanes are used mostly for node-positive and hormone-unresponsive disease. There is a notable variation among specialists in the usage of taxanes for node-positive and hormone-responsive disease, although the choice of this regimen is limited. The choice of taxane for node-negative disease is even more limited (node negative disease consists of 50–60% of primary breast cancer; hormone-responsive disease 60–70% in Japan). The choice of anthracycline or taxanes is becoming less frequent for those aged 60 years and over, and frequency is minimized for 70 years and over. With regards to dosage, there are two types of practices: experts in highly-specialized hospitals usually administer a dose comparable to NCCN guidelines, and a number of physicians in community hospitals tend to administer lower (-20 to -30%) doses. Consequently, the choice in first-line therapy is anthracycline, if anthracycline was not used in adjuvant therapy; taxanes, if anthracycline was used in adjuvant therapy; or an alternative taxane agent, capecitabine, UFT or other oral FUs, if taxane was already used with anthracycline in adjuvant therapy. In using taxanes, regimens that avoid toxicity are generally preferred: weekly paclitaxel, for example, docetaxel is usually used in q3 regimen with 60–70 mg/m^2. Although the officially approved regimen of capecitabine in Japan is slightly different from that in Western countries, total dose is almost the same and Western regimen is also used in common practice. There are wider variations in the following therapies.

Cost-effectiveness

Concern regarding the economic aspect of cancer care has been increasing in Japan [24], along with the growing interest in providing evidence-based care. The former, however, seems to have less impact on treatment strategy or options for breast cancer. There is no explicit statement of consideration on efficiency of interventions in the development of the above mentioned guidelines. They are developed solely based on clinical evidence of effectiveness. There is no evidence that clinical options in practice, described previously, are influenced by any concern for resources.

There are at least two types of obstacles when discussing cost-effective options in the healthcare system, including breast cancer treatment. One is a supply side problem, that is: deficiency of economic evidence based on decent evaluation or cost–effectiveness analysis. Another is a demand side problem, that is: utilization of economic evidence on cost–effectiveness of interventions, which will be discussed later.

Economic evidence of intervention is deficient in a number of areas, including breast cancer, in Japan. With regards to the cost–effectiveness of options in therapy for breast cancer, there are currently only two referable economic evaluations, both of which describe options in first-line therapy for advanced postmenopausal disease, as summarized in TABLE 1.

Cost–effectiveness of letrozole versus tamoxifen was evaluated and the incremental cost–effectiveness ratio of choosing letrozole as first-line, instead of tamoxifen, was found to be

Table 1. Economic evidence on first-line therapy for advanced breast cancer in Japan.

	Okubo and colleagues [25]	Inoue and colleagues [26]
Comparison	Letrozole vs tamoxifen as first-line hormonal therapy in treating postmenopausal women with advanced breast cancer	Anastrozole vs fadrozole as first-line hormonal therapy in treating postmenopausal women with advanced breast cancer
Type of analysis	Cost–effectiveness analysis	Cost–effectiveness analysis
Perspective and year of costing	Payer's (insurers and patients) perspective in 2003	Payer's (insurers and patients) perspective in 2002
Model used	Markov lifetime treatment pathways	Markov lifetime treatment pathways
Time period	Lifetime	Lifetime
Source of clinical data	Mouridsen and colleagues [27]	Systematic review of published trials [28–34].
Resources accounted for	Direct medical cost born by health insurance and patient	Direct medical cost born by health insurance and patient
Discounting	3% annually for life years and resources	5% annually for resources
(ICER)	US$4969 per life-year gained (letrozle over tamoxifen)	US$1900 per life-year gained (anastrozole over fadrozole)
Sensitivity analysis?	Yes. Fifth percentile ICER = letrozole dominant; 95th percentile ICER = US$21,005	Yes. One-way and two-way: results robust

ICER: Incremental cost–effectiveness ratio.

US$4969 per life-year gained [24]. Although there is no established criteria of a favorable level of cost–effectiveness ratio in Japan, that is, how much extra money the nation is willing to pay for gaining extra improvement in outcome, a study suggested that US$50,000 (6 million yen) per quality-adjusted life year gained is the social maximum willingness-to-pay for a new therapy [35]. With this criterion, the use of letrozole as first-line therapy can be judged as a favorable option. Cost–effectiveness of anastrozole versus fadrozole was also evaluated and the incremental cost–effectiveness ratio of choosing anastrozole as first-line therapy was found to be approximately US$1900 per life-year gained [26]. This can also be judged as a favorable option. Both economic evidences, coincidently, suggest the same choice as recommended in the guidelines or chosen in practice. The former demonstrates cost–effectiveness of the use of letrozole in first-line therapy for postmenopausal disease recommended in the guidelines. The latter demonstrates cost–effectiveness of the preferred use of anastrozole among aromatase inhibitors in practice. Therefore, it can be said that cost-effective options are recommended and practiced in first-line hormonal therapy for postmenopausal disease. However, the cost–effectiveness of options in hormonal therapy for premenopausal disease, or chemotherapy with and without trastuzumab remains unknown.

Trastuzumab is routinely administered to advanced HER2-overexpressing disease, which accounts for approximately 20–30% of all cases in first-line therapy, as described previously. Although trastuzumab has been proven effective for advanced breast cancer [36], it is remarkably expensive as an agent used in first-line therapy. One dose (150 mg) is priced as high as US$700 in Japan, and the standard regimen requires huge amounts of extra healthcare expenditure, approximately US$40,000 per patient per year, in addition to the cost of conventional endocrine therapy and chemotherapy. Therefore, from a viewpoint of economic evaluation, it is interesting to evaluate the cost–effectiveness of the use of trastuzumab for advanced breast cancer. However, thus far, no economic evidence has been reported in Japan. Recently, the use of trastuzumab in the treatment of advanced breast cancer was found to not be cost-effective in economic evaluations carried out in Norway [37] and Belgium [38]. Although due caution is needed in transferring these findings into the Japanese context [39], these findings at least imply that the use of trastuzumab as first-line therapy might not be cost-effective in Japan following economic evaluation. If this is the case, the option suggested by the economic evaluation would contradict the option in current guidelines and practices based on clinical evidence. Japanese practice of prolonged administration of trastuzumab supported by National Health Insurance, for example, might need reconsideration. However, currently there is no sign of opening explicit discussion about these issues. This is probably not a problem unique to Japan. The problem of how to utilize trastuzumab in a treatment strategy taking cost–effectiveness into account would also be emerging in other industrialized countries.

Summary & conclusions

In general, there are few differences in the therapeutic strategy for breast cancer, either primary disease or advanced disease, between Western countries and Japan. In common practice, however, a minor difference might exist as lower dosages of chemotherapy tend to be applied, particularly for anthracyclines, and oral FUs are used more frequently in Japan compared with other countries. Practice of less toxic agents, such as hormonal therapy and trastuzumab treatment, is more or less the same, as suggested by international guidelines or consensus.

Evidence of cost–effectiveness regarding options in first-line therapy for advanced breast cancer in Japan is very limited. Available evidence suggests that cost-effective options are recommended and practiced in hormonal therapy for postmenopausal disease. Cost–effectiveness of the other options in first-line therapy remains unclear. The cost of trastuzumab and the recent report on cost–effectiveness of trastuzumab used in first-line therapy in Western counties imply that current options in Japan might not be cost-effective. However, cost–effectiveness of options as a whole would be quite similar to those in Western countries.

Expert commentary & five-year view

In the long term, increasing numbers of molecular-targeting agents will be developed and incorporated into clinical practice of breast cancer treatment in Japan, as well as in other countries. The public and media are paying close attention to this field. For example, the remarkable effect of trastuzumab in preventing recurrence in primary breast cancer patients was introduced very quickly to the public through the media after the information was released in a scientific congress [40]. Many investigators expect that trastuzumab will be approved for primary breast cancer treatment in a short while and it could change the practice of breast cancer treatment dramatically, as its therapeutic impact is huge. Although the HER2-positive subgroup is not large (only approximately 15–20% of primary breast cancer), investigators or physicians may take into consideration its status, as with hormone receptor status in hormonal therapy, when determining primary breast cancer treatment. It certainly influenced the treatment strategy of non-HER2-overexpressing cancers, and it also elicits a significant change in the treatment algorithm of advanced or metastatic diseases. Although other new molecular-targeting agents have not yet been approved for breast cancer in Japan, it is not difficult to imagine that a similar or greater impact to trastuzumab will be made by these new agents.

As mentioned earlier, there is a demand-side problem in realizing cost-effective options in the healthcare system in Japan. Less appreciation of pharmacoeconomics compared with so-called 'evidence-based medicine' in Japan's medical arena may be accountable, since there is no explicit regulation on drugs, in terms of cost–effectiveness, in Japan. Drugs are approved and listed for National Health Insurance in terms of safety and efficacy, and even price is set based on efficacy and international comparison only. There is no institution similar to the National Institute for Health and Clinical Evidence in the UK, which produces influential recommendations on physician's decision

making based on economic evidence as well as clinical evidence, in Japan's healthcare system. Even health policy makers have not given cost–effectiveness any clear role in the health system, nor do leading breast cancer specialists who formulate guidelines. Thus, it is quite natural for a breast cancer specialist who actually faces a patient to make clinical decisions based solely on clinical evidence and to pay little concerns to societal resource problems. The voice of the suffering patients saying that they should have better access to the latest treatment supports this practice.

However, imminent extension of the indication of trastuzumab to primary breast cancer will have the greatest implication for healthcare resources in Japan. Treating approximately 20% of incident cases – 7300 per year – would add an extra US$292 million per year to national healthcare expenditure, which is equivalent to 0.1% of the total healthcare expenditure. This is a huge amount for the impact of a single agent. Additionally, it is predictable that similar, extremely expensive, new drugs will be developed in succession. We believe explicit discussion on value for money of these new drugs will be unavoidable in the near future, not only among health policy makers but also among leading specialists developing guidelines.

Key issues

- Breast cancer is rapidly increasing in Japan.
- Healthcare expenditure for cancer care is increasing.
- Not only, effective but also efficient, treatment options in breast cancer care are required.
- Japanese practice has become similar to the global standard in the context of evidence-based medicine; pharmacoeconomics is less appreciated.
- Limited economic evidence suggests current practice is cost-effective.
- Resource-consuming trastuzumab seems to not be cost-effective in first-line therapy.
- New molecular-targeting agents will drastically change treatment options.
- Extension of the indication of trastuzumab for primary breast cancer will make explicit discussion about cost–effectiveness unavoidable.

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