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シンポジウム

3．抗体療法の進歩と問題点
2）固形腫瘍を標的とする抗体療法

石岡千加史

Key words：分子標的薬，抗体薬，固形腫瘍

はじめに

1946年に化学療法薬ナイトロジェン・マスタードが初めての抗悪性腫瘍薬(以下，抗がん薬)として臨床に登場して以来50年以上が経過した．現在，抗がん薬は化学療法薬，内分泌療法薬，バイオセラピーおよびがん分子標的治療薬（以下，分子標的治療薬）に分類されるが，このうち殺細胞効果を主体とする化学療法薬が長年にわたりがん薬物療法の中心を占めていた．1990年代の分子標的治療薬の登場により，化学療法では得られなかった治療成績の向上が得られるようになった．現在，多数の薬剤が複数の疾患に適応が拡大され，一部の腫瘍では飛躍的に治療成績が向上している．ここではわが国で承認された固形腫瘍に対する3種類の抗体薬について主に主要な臨床試験成績を中心に解説するとともに，がん薬物療法を取り巻く課題について取り上げる．

1．がん薬物療法における分子標的薬の位置づけ

現在，開発途上の抗がん薬と新規に承認された抗がん薬の多くは分子標的薬である．このため21世紀の抗がん薬の主役は分子標的治療薬が取って代わるものと考えられるが，現時点では固形腫瘍においては分子標的薬と化学療法薬が併用で投与される場合が多い．がん分子標的薬には，抗体薬と小分子化合物がある（図1）．小分子化合物は受容体型チロシンキナーゼの他に最近では細胞質や核内に治療標的を持つ薬剤が開発されているが，抗体薬の場合，分子標的は細胞表面の抗原，増殖因子受容体の細胞外ドメインやそのリガンドである．昨年度までに，20種類を超えるがん分子標的薬が内外市販されたがその約半数は抗体薬である．このうち固形腫瘍に対して承認された抗体薬はトラスツズマブ，ベバシズマブおよびセツキシマブ（シンポジウム後にパニツムマブが承認された)であり(表)，これら3薬は標準治療の一部として使用されている．

いしおか　ちかし：東北大学加齢医学研究所臨床腫瘍学分野，東北大学病院腫瘍内科

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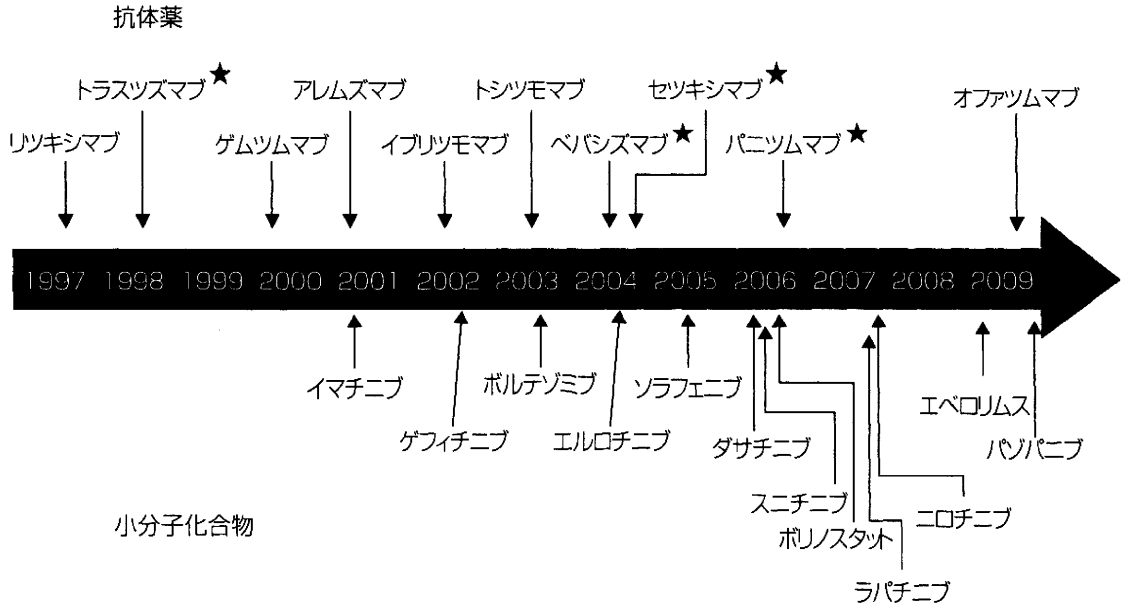

図 1

表．固形癌に対する抗体薬と本邦での適応

一般名	商品名	標的分子	適応	本邦承認年
セツキシマブ	アービタックス	EGFR	転移性大腸癌	2008
パニツムマブ	ベクチビックス	EGFR	転移性大腸癌	2010
トラスツズマブ	ハーセプチン	HER2	転移性乳癌	2001
			早期乳癌術後補助療法	2008
ベバシズマブ	アバスチン	VEGF	転移性大腸癌	2007
			非小細胞肺癌（ⅢBまたはⅣ期扁平上皮がんを除く）	2009

2. 固形腫瘍に対する抗体療法の進歩

1）トラスツズマブ

トラスツズマブは，ヒト化モノクロナル抗体であり，乳癌の25～30％を占めるHER2陽性乳癌に有効性が示され，固形腫瘍に対する初めての抗体薬として1998年米国FDAで，その3年後の2001年には日本で承認された．トラスツズマブの標的分子HER2は，ヒトEGFRファミリーの1つでリガンドを持たない分子種であり，ホモ2量体または他のEGFRファミリーとのヘテロ2量体を形成し細胞内へ細胞増殖等のシグナルを伝達する．乳癌の他，非小細胞肺癌，食道癌，胃癌，大腸癌，膀胱癌などの他の上皮系腫瘍においても遺伝子増幅による過剰発現が認められ，これらの腫瘍においてはHER2はがん細胞増殖のゲートキーパーとして作用していると考えられている．HER2は乳癌治療においてトラスツズマブの治療選択の理想的分子マーカーである．免疫組織染色法であるハーセプテストで3+か，ハーセプテストで2+かつFISH法でHER2遺伝子増幅が認める場合をHER2陽性診断する．一般的に，HER2陽性乳癌はHER2陰性乳癌よりも予後が不良である．トラスツズマブはHER2の細胞外ドメインに特異的に結合し，エフェクター細胞であるNK細胞や単球のFcγ受容体を介した抗体依存性細胞介在性細胞障害（ADCC）活性によりHER2陽性がん細胞の細胞増殖を抑制し細胞死を誘導すると考えられる．

HER2陽性転移性乳癌に対するトラスツズマブの初回治療での臨床効果は，H0648試験で初め

て示された．この無作為比較試験ではアンスラサイクリン系またはタキサン系化学療法薬による標準化学療法後にトラスツズマブを併用すると，主要評価項目である無増悪生存期間や副次的評価項目である全生存期間が延長し奏効率が向上することが明らかになった[1]．その後の複数の試験により，トラスツズマブは他の化学療法剤との併用，または単剤での有効性および化学療法増悪後の継続治療における有効性が示され，現在，HER2陽性転移性乳癌の1次治療としての地位を確立している．

また，トラスツズマブは早期乳癌の術後補助療法としての有用性が示されている．早期乳癌の標準治療は手術と放射線治療による局所療法と周術期の全身化学療法であるが，HER2陽性早期乳癌に対する術後補助化学療法後にトラスツズマブを1年間投与すると，再発リスクと死亡リスクが約30%低下する[2,3]．その後，複数の大規模比較試験によりこの結果が検証されている．さらに，MDACC試験では，パクリタキセルからFEC療法への順次投与による術前補助化学療法にトラスツズマブを併用した術前療法は，病理学的完全奏効率を2倍以上改善し，3年無病生存率を著しく改善した[4,5]．このように，トラスツズマブは術前後を問わず，周術期補助療法として有用であると考えられる．

2009年の米国臨床腫瘍学会に発表されたToGA試験では，トラスツズマブはHER2陽性進行胃癌に対しても有効であることが示された[6]．この試験では，対象となった約3,800人の約22%の症例がHER2陽性（この場合，IHC3＋またはFISH法陽性をHER2陽性とした）で，トラスツズマブ併用群では主要評価項目の全生存期間の中央値が2.7カ月延長したほか，無増悪生存期間や奏効率についてもトラスツズマブの上乗せ効果が認められた．乳癌同様の基準でHER2陽性をIHC3＋，またはIHC2＋かつFISH法陽性で判定した場合のサブグループ解析では，HER2陽性率は全体の約16%に減るが，トラスツズマブ群の全生存期間の中央値が4.2カ月延長した．この試験は，韓国と日本が多数参加した国際共同治験であり，近い将来，欧米に遅れずに胃癌へ適応が拡大されるのと期待されている．乳癌や胃癌以外にも肺癌，食道癌，大腸癌，膀胱癌の一部はHER2陽性であり，他のHER2陽性の上皮系悪性腫瘍に対してもトラスツズマブが有効である可能があり，今後の臨床試験に期待が集まる．

2）ベバシズマブ

ベバシズマブはヒト化モノクルナル抗体で，血管新生阻害を作用機序とする初めての抗がん剤として，転移性大腸癌を対象に米国FDAでは2004年に，日本では3年遅れの2007年に承認された．ベバシズマブの標的分子は血管内皮細胞増殖因子（vascular endothelial growth factor：VEGF）である．ベバシズマブはVEGF（特にVEGF-A）を中和しVEGFR受容体のVEGFR-1とVEGFR-2を介した腫瘍血管新生を抑制する．その結果，腫瘍血管の退縮，腫瘍血管の正常化による化学療法薬の透過性亢進による腫瘍縮小や血管新生阻害による転移抑制効果をもたらすと考えられている．

未治療転移性大腸癌を対象とした第III相臨床試験において[7]，イリノテカン・フルオロウラシル・ロイコボリン併用療法（IFL療法，以前の標準化学療法）にベバシズマブを追加した群では生存期間中央値20.3カ月，無増悪生存期間中央値10.6カ月，奏効率44.8%であり，IFL療法単独群の生存期間中央値15.6カ月，無増悪生存期間中央値6.2カ月，奏効率34.8%を有意に上回り，死亡のリスクを34%減少させた．市販後のFirst-BEAT試験[8]は医師に標準化学療法を選択させる臨床試験で主要評価項目は安全性だが，副次的観察項目の無増悪生存期間ではベバシズマブ併用により10カ月を越えた．このように，ベバシズマブと標準化学療法との併用は転移性大腸癌の一次治療における標準治療として位置づけられるようになった．また，イリノテカンと並ぶ大腸癌化学療法のキードラッグであるオキサリ

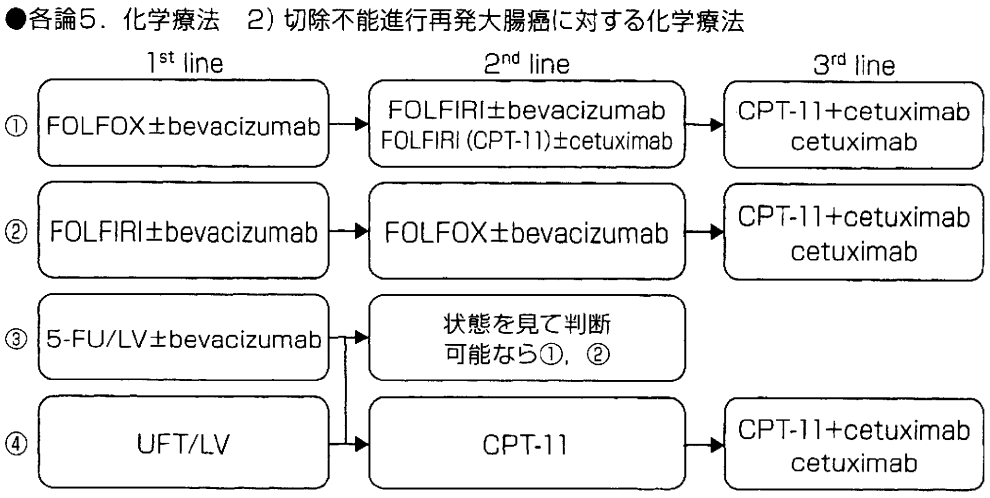

図　2

プラチンをベースにした標準化学療法(FOLFOXやCapeOx)においても，ベバシズマブは転移性大腸癌の初回治療において，主要評価項目の無増悪生存期間を延長した[9]．さらに，1次治療でイリノテカンを含む化学療法無効例に，2次治療としてオキザリプラチンを含む標準化学療法にベバシズマブを併用すると全生存期間と無増悪生存期間が延長することが示され[10]，ベバシズマブは2次治療においても化学療法への上乗せ効果が示された．2009年に改訂された大腸癌治療ガイドライン(図2)[11]では，1次および2次治療において，標準化学療法へのベバシズマブ併用が推奨されている．

ベバシズマブの有用性は肺癌においても示されている．再発または進行非小細胞肺癌（扁平上皮癌除く）を対象としたE4599試験[12]において，化学療法（カルボプラチン・パクリタキセル併用療法）にベバシズマブを追加した群は生存期間中央値12.3カ月，無憎悪生存期間中央値6.2カ月，奏効率35%であり，化学療法単独群の生存期間中央値10.3カ月，無増悪生存期間中央値4.5カ月，奏効率15%を有意に上回った．この臨床第III相試験により，これまでの非小細胞肺癌の標準治療であるプラチナ・ダブレット療法にベバシズマブを併用する治療により全生存期間中央値が約2カ月上回った．日本においては2009年に非小細胞肺癌（扁平上皮癌除く，Stage IIIB，IV，初回治療例）に適応拡大されている．

海外ではHER2陰性転移性乳癌の初回治療におけるベバシズマブの有用性も示されている．E2100試験[13]では，パクリタキセルに対する無増悪生存期間，全生存期間および奏効率の上乗せ効果が示された．この上乗せ効果は，他の抗がん剤であるドセタキセル，アンスラサイクリン系やカペシタビンでも示され，米国FDAでは2008年にHER2陰性転移性乳癌への使用が承認された．また，転移性腎細胞癌に対してもベバシズマブは標準治療薬のインターフェロンに対する上乗せ効果が，無増悪生存期間について示され[14]，米国FDAでは2009年に承認された．この他，米国FDAは2009年に脳腫瘍のグリオブラストーマ(膠芽腫）に対してベバシズマブを承認している．

3）セツキシマブ

セツキシマブはヒト・マウスキメラ型モノクルナル抗体で，転移性大腸癌を対象に2003年にスイスで，2004年には米国FDAで承認された．日本では5年遅れて2008年に承認された．セツキシマブの標的分子はヒト上皮成長因子受容体

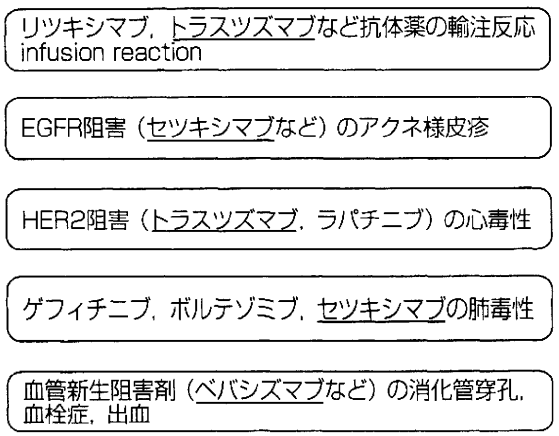

図 3

ファミリーメンバーのEpidermal Growth Factor Receptor(EGFR)である．セツキシマブは，EGFRの細胞外ドメインに特異的に結合し，EGFやTGF-α(リガンド)の結合を競合阻害することにより，EGFRの2量体形成とEGFRの自己リン酸化を阻害し，EGFRを介したRAS/MAPK系路やPI3K/AKT系へのシグナル伝達を遮断することにより，細胞増殖を抑制しアポトーシスを誘導するものと考えられている．また，EGFRの内在化やADCC活性を介した作用機序が存在すると考えられている．

セツキシマブは転移性大腸癌の既治療例に対して2008年に国内承認が得られた．その根拠となった臨床試験は，イリノテカン不応性の転移性大腸癌においてイリノテカンとの併用で治療成功期間を延長することを示したBOND試験[15]とフッ化ピリミジン，オキザリプラチン，イリノテカン不応性の転移性大腸癌において単剤で全生存期間を延長することを示したNCIC CTG CO.17試験[16]である．その後，セツキシマブは転移性大腸癌の1次治療において標準化学療法FOLFIRIとの併用で奏効率を向上し無増悪生存期間を延長することが示された（CRYSTAL試験)[17]．さらに，セツキシマブは転移性大腸癌の1次治療において標準化学療法FOLFOX4との併用で有用性が検討された（OPUS試験)[18]が，奏効率や無増悪生存期間に統計学的に有意な差を見いだせなかった．しかし，これらの臨床試験の後方視的解析では初回治療，既治療に関わらず，奏効率や生存期間の延長がみられるのはEGFRの下流のKRASをコードする*KRAS*遺伝子が野生型の症例だけであり，初回治療では，*KRAS*変異型症例ではむしろ奏効率や生存期間が悪化する傾向があることが示された．2009年版の大腸癌治療ガイドライン（図2)[11]において，セツキシマブの適応に*KRAS*遺伝子検査の実施が推奨されている．2010年から，*KRAS*遺伝子変異は抗EGFR抗体薬の不応性予測因子として*KRAS*遺伝子検査が保険適応になったほか，添付文書上の既治療例での使用制限が解除された．さらに，本シンポジウム後の2010年6月30日に大腸癌治療ガイドラインが，さらに改訂され，抗EGFR抗体薬（セツキシマブとパニツムマブ）は1次または2次治療での使用がKRAS野生型に限り推奨されるようになった[19]．*KRAS*遺伝子以外にもEGFRの下流遺伝子の*BRAF*遺伝子や*PIK3CA*遺伝子の変異が，また，EGFRのリガンドの発現やADCC活性に影響するFcγ受容体の遺伝子多型もセツキシマブの感受性を規定する可能性があると考えられる．今後，これらの分子異常が治療方針決定のための有用な分子マーカーになりうるか注目される．

3. 固形腫瘍に対する抗体療法の副作用（図3）

従来の化学療法薬と異なり分子標的薬には分子種（抗体薬か小分子化合物か）や作用機序に基づく多様な副作用がある．トラスツズマブの副作用のうち，頻度の高いものとして抗体薬特有のinfusion reactionがあり，全症例の約40%に発現する．他の注意すべき副作用に心毒性がある．早期乳癌術後補助療法に関する5つの無作為比較試験のメタ解析[20]によると，トラスツズマブの長期投与による心毒性は，1年投与で慢性心不全（NYHA III/IV）が0.6%，左室駆出率低下が3%の頻度で出現し相対リスクはそれぞれ5.59,

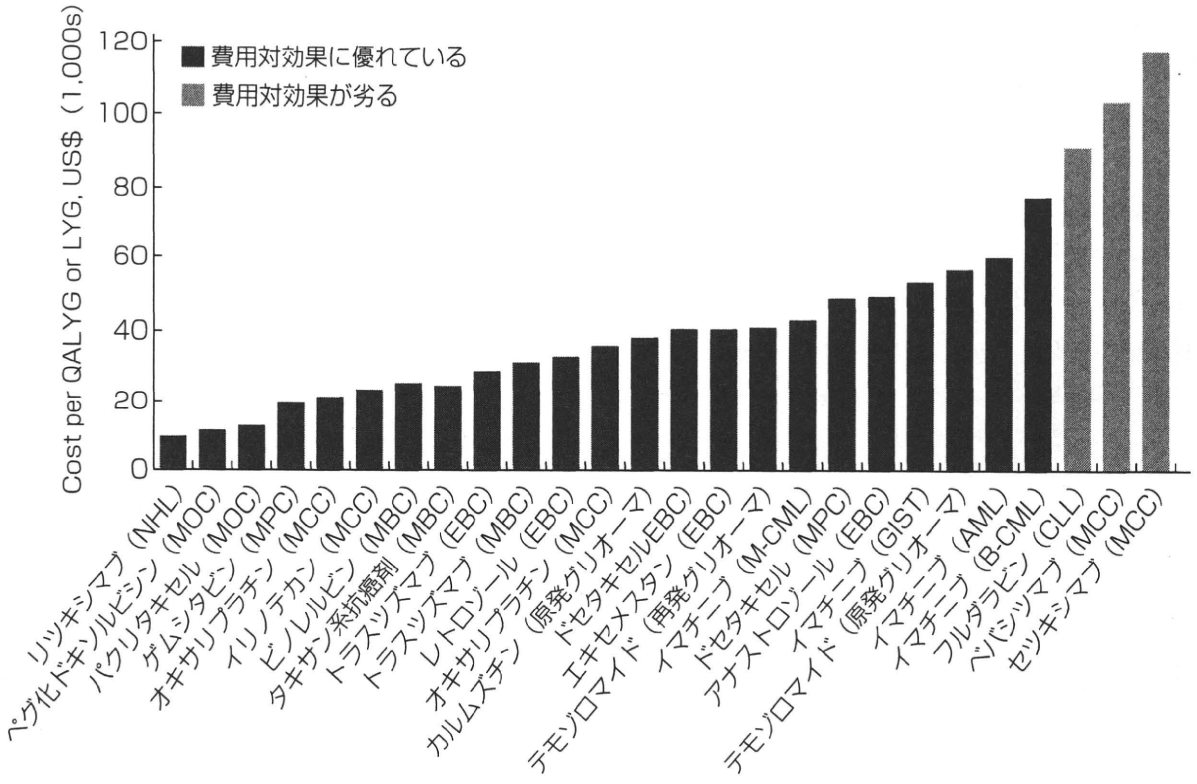

図 4

2.12と有意に高かった．ベバシズマブに特徴的な有害事象には血管新生阻害作用を持つ薬剤に特徴的な高血圧症，タンパク尿，動脈血栓症，消化管穿孔，創傷治癒遅延，腫瘍関連出血などがあり重篤な副作用の出現に常時注意を払う必要がある．セツキシマブの特徴的で高頻度の副作用にざ瘡様皮疹，皮膚乾燥などの皮膚毒性がある．国内の市販後の使用成績調査では69.4%に何らかの副作用が発症した．生命予後に影響するものは少ない．他に低マグネシウム血症，心不全，間質性肺障害，角膜炎などの眼障害がある．

4. 固形腫瘍に対する抗体療法の課題

前述のように，がん薬物療法が進歩する中で副作用は多様化している．がん分子標的薬に特徴的な副作用としてinfusion reaction，皮膚毒性，心毒性，肺毒性，消化管穿孔，血栓症や出血など多様かつ一部は重篤なものが一定の頻度で発生するため，適応に当たってはがん薬物療法専門医をはじめとする医師の専門性の向上や，チーム医療のパートナーである薬剤師や看護師の専門性の向上が課題である．また，医療施設の要件として外来化学療法の実施体制の整備に加えて，重篤な副作用に対応できる循環器内科，呼吸器内科，消化器外科，皮膚科などの他科の専門医との協力体制の確立，急性合併症に対応できる時間外の診療体制の整備など病院機能を高める必要がある．このような背景から，平成18年度から厚生労働省によって全国にがん診療連携拠点病院が指定され整備が進められているが，がん診療連携拠点病院の機能の一層の充実と近隣の医療機関との連携体制の整備が課題である．

もう一つ大きな課題に，抗がん薬とりわけ分子標的薬の高額コストの問題である．抗がん剤に関する海外の医療経済評価によると（図4）[21]，抗体薬の費用対効果はトラスツズマブやリツキシマブは優れているが，ベバシズマブやセツキシマブの費用対効果が劣っていると報告されている．このうちセツキシマブの場合，*KRAS*遺伝子変異（前述）を分子マーカーとして臨床に導入することにより費用対効果が約40%改善する

事が示されている[22]．ベバシズマブに関してはこれまで有用な分子マーカーがなく，今後の研究の成果が待たれる．21世紀になり，新規に承認される抗がん薬の多くは分子標的薬であるが，現在市販された分子標的薬のほとんどの場合，内外の承認時期の格差が3～5年に及んでいる（いわゆるドラッグ・ラグ）．最近は国際共同治験に国内でも多くの施設が参加するようになり，規制当局の審査体制の改善と併せてドラッグ・ラグ問題は解消されつつある．

おわりに

現在，分子標的薬に関しては新薬や承認薬の適応拡大の臨床開発が世界中で多数行われており，発展途上のがん薬物療法は今後益々発展すると期待される．新薬開発や適応拡大と同時に高齢化社会の進行によりがん薬物療法の適応になる患者数は年々増加の一途を辿るが，がん薬物療法を専門にする医師や医師以外の専門医療者が不足している．質の高いがん薬物療法の普及のためには専門医療者の養成が急務であり，大学医学部における腫瘍内科講座の整備を含めた若い医師の養成体制を構築する必要があると考えられる．

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SPECIAL ARTICLE

Quality of guideline development assessed by the Evaluation Committee of the Japan Society of Clinical Oncology

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Abstract
Background The Japan Society of Clinical Oncology started implementing clinical practice guidelines for cancer in 2001. It created a Guideline Committee and has published cancer-related information in collaboration with individual subspecialty cancer societies. The society then established an Evaluation Committee to assess the quality of guidelines.

Methods The quality of development and general characteristics of guidelines were reviewed using the AGREE instrument. The six standardized domain scores and 23-item crude scores were described, and items with a low median score or a wide inter-quartile range were explored. Kappa statistics for inter-rater reproducibility were also described.

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Results Domains in which the median score was >50 points in 18 guidelines developed between March 2005 and May 2009 included "scope and purpose," "rigor of development," and "clarity and presentation." Domains with a median score < 50 points were "stakeholder involvement," "applicability," and "editorial independence." Scores in all domains except "stakeholder involvement" were higher during the second half of the period than during the first half of the period, although *P* values were 0.10–0.93. Crude scores remained low for items 5, 7, 19, 20, 22, and 23, and the inter-quartile ranges of items 2, 6, 10, and 22 were wide. Kappa statistics ranged from –0.02 to 0.64, and they were especially low for items 3, 5, 7, 18, and 23.

Conclusion Guideline quality has tended to improve during the 10 years since the society started this activity. However, issues remain to be improved through continuous revisions.

Keywords Clinical practice guideline · AGREE instrument · Cancer

Introduction

The Japan Society of Clinical Oncology started implementing clinical practice guidelines (CPGs) for cancer in 2001 in collaboration with allied subspecialty societies. The society has developed summary versions of CPGs and flowcharts, and it has published them on the Internet with structured abstracts of important articles. Around 20 guidelines have been developed by subspecialty societies by November 2009, and 13 of them are presented on the society's homepage (http://www.jsco-cpg.jp/) [1].

The society established a Guideline Committee (GC) for this activity, as well as an Evaluation Committee (EC) to evaluate and ensure the quality of published guidelines. The aims of the present study were to identify issues requiring resolution from a summary of the assessment results generated by the EC.

Methods

Process before publishing the guidelines

The activity of CPG publishing and implementation in the society proceeds as follows. A subcommittee of the GC for a specific cancer writes a draft summary, algorithm, and structured abstract in accordance with the specific subspecialty society, and submits them, or sometimes a complete CPG, to the board of the GC. The board of the GC reviews and sends them to the EC. The EC evaluates them and reports the result to the chair of the GC and the members of GC subcommittee. If there is no major flaw, a homepage is developed. These tools for implementation of the CPG are then released to the public after the final approval of the GC and the board of the society.

The review in the EC

The EC has ten members, including a chair and four members from outside the society. All members individually review drafts under evaluation before attending a meeting where all members reach a consensus-based final assessment.

The AGREE instrument [2] was used for reviews that focus on the process of CPG development and the general characteristics of the CPGs, but not on the validity of specific statements. The AGREE instrument is a comprehensive tool for evaluation whose validity and reproducibility have been investigated [3, 4]. The EC did not require revision of the content and format of the draft after review, but revisions were expected for a subsequent version. The EC previously presented the appropriate methods for developing evidence-based CPGs to the GC.

Method of review

The present study summarizes the results of the review of the CPGs by the EC.

The AGREE instrument consists of 23 items that assess six domains of the CPG development process: "scope and purpose" (items 1–3), "stakeholder involvement" (items 4–7), "rigor of development" (items 8–14), "clarity and presentation" (items 15–18), "applicability" (items 19–21), and "editorial independence" (items 22–23). For each item, a crude score of 1–4 is assigned based on the reviewers' certainty of fulfilling the requirements of the items and the quantity of information contained in the CPG. A standardized domain score is calculated for the 6 domains after summing and adjusting the crude scores into a scale from 0 to 100 points. A global assessment could be given, but such global assessments were not recorded for all CPGs. Global quality was described as an aggregated score determined from the summation of all domain scores, although AGREE does not suggest using this strategy for global assessment.

The distributions of the crude scores for the items were determined. Low-score items in which the medians were ≤2 and dispersed items, for which the inter-quartile range of the crude score was 1–4, were identified. The dispersed items contained CPGs with both low and high scores, which led to the supposition that they could be easily improved.

Kappa statistics were calculated for each item to determine inter-rater reproducibility [5, 6]. Low kappa values

indicate a trend toward the item scoring differently among raters. When calculating kappa, crude scores of 1 and 2, as well as those of 3 and 4, were combined into one level. The EC used only one representative score based on consensus for evaluation at meetings and did not use the individual crude scores from which the kappa values were derived.

When members thought that determining a score was difficult, the committee used its own criteria to standardize

Table 1 Guidelines that have been reviewed by the evaluating committee

Type of cancer	Title	Version
Stomach[a]	Japanese Gastric Cancer Association: guidelines for the diagnosis and treatment of carcinoma of the stomach, April 2004 edition	2
Liver[b]	The Japan Society of Hepatology:[c] "clinical practice guidelines for hepatocellular carcinoma:" evidence-based clinical guidelines for the diagnosis and treatment of hepatocellular carcinoma in Japan (the print/web version)	1
GIST[a]	Japanese Gastric Cancer Association, Japan Society of Clinical Oncology, Japanese Study Group on GIST: clinical practice guidelines for gastrointestinal stromal tumors (GIST) in Japan	1
Oral cancer	Japan Society for Oral Tumors: clinical practice guidelines for oral cancer	1
Uterine cervix	The Japan Society of Gynecologic Oncology: treatment guidelines for cervical cancer, 2007 edition	1
Uterine body	The Japan Society of Gynecologic Oncology: treatment guidelines for uterine body cancer, 2006 edition	1
Children's leukemia	The Japanese Society of Pediatric Hematology: guidelines for the treatment of childhood leukemia/lymphoma, 2007 edition	1
Esophagus[d]	The Japan Esophageal Society: guidelines for the diagnosis and treatment of esophageal cancer	2
Kidney[d]	The Japanese Urological Association: clinical practice guidelines for managing renal carcinoma and the digest edition (web version)	1
Pancreas[d]	Japan Pancreas Society: evidence-based clinical practice guidelines for pancreatic cancer	1
Colon[d]	Japanese Society for Cancer of the Colon and Rectum: guidelines for the treatment of colon cancer, 2005 edition	1
Biliary tract[d]	Japanese Society of Hepato-Biliary-Pancreatic Surgery: clinical practice guidelines for the management of biliary tract and ampullary carcinomas (the print and web digest version)	1
Head and neck	Japan Society for Head and Neck Cancer: clinical practice guidelines for head and neck cancer	1
Breast[a]	The Japanese Breast Cancer Society: evidence-based clinical practice guidelines of the Japanese Breast Cancer Society (5 volumes) and web version	1
	1. Systemic therapy	
	2. Surgery	
	3. Radiation therapy	
	4. Screening and diagnosis	
	5. Epidemiology and prevention	
Lung	The Japan Lung Cancer Society: clinical practice guidelines for lung cancer, revised edition	2
Skin[d]	The Japanese Skin Cancer Society: clinical practice guidelines for the management of cutaneous malignancies	1
Ovary[d]	The Japan Society of Gynecologic Oncology: ovarian cancer treatment guidelines, 2004 edition	1
Ovary	The Japan Society of Gynecologic Oncology: ovarian cancer treatment guidelines, 2007 edition	2

Order in table reflects the list in the homepage of the Japan Society of Clinical Oncology (order of Japanese 50 sounds)

[a] Presentation was partly funded by the Scientific Study for the Third Term Comprehensive Control Research for Cancer of the Ministry of Health, Labour, and Welfare in 2007

[b] Development was funded by the Scientific Study for Supporting Clinical Practice Guidelines of the Ministry of Health, Labour, and Welfare in 2002–2003

[c] On October 2009

[d] Development and presentation was partly funded by the Scientific Study for the Research on the Medical Safety and Health Technology Assessment of the Ministry of Health, Labour, and Welfare in 2005–2006

Table 2 Domain scores determined using the AGREE instrument for clinical practice guidelines

Domain	Total ($n = 18$)		The first half, March 2005–March 2007 ($n = 10$)		The second half, April 2007–May 2009 ($n = 8$)		P value[a]
	Median	IQR[b]	Median	IQR	Median	IQR	
Scope and purpose	72.2	66.7–100	66.7	55.5–100	83.3	66.7–100	0.38
Stakeholder involvement	41.7	16.7–50.0	43.1	25.0–58.3	41.7	29.2–50.0	0.93
Rigor of development	66.7	38.9–83.3	44.4	16.7–72.2	72.2	61.1–86.1	0.13
Clarity and presentation	75.0	58.3–91.7	70.8	33.3–91.7	83.3	70.8–100	0.18
Applicability	33.3	0–66.6	16.7	0–33.3	50.0	25.0–66.7	0.10
Editorial independence	0	0–50.0	0	0–0	33.3	0–50.0	0.12
Aggregated	56.3	36.5–69.8	48.6	28.6–58.7	65.9	54.8–71.4	0.11

[a] Comparison of scores between the first half of the period and the second half of the period was tested using the Wilcoxon rank-sum test

[b] Inter-quartile range

the score among its members. Item 13 indicates a requirement for an external review of the CPG. This item was not scored because review by the EC is compatible with this. Item 21 requires the CPG to present key review criteria for monitoring or audit. This item was also omitted from scoring because quality indicators for measuring adherence to CPGs have not been developed.

Results

The EC started reviewing CPGs in March 2005, and 18 of them had been reviewed by May 2009 (Table 1). Table 2 shows the standardized domain scores of these CPGs. The domains with median scores > 50 points during the entire period of review were "scope and purpose," "rigor of development," and "clarity and presentation." The median scores for "stakeholder involvement," "applicability," and "editorial independence" were <50 points. All domain scores except "stakeholder involvement" were higher during the second half of the period than during the first half of the period, although the P values were 0.10—0.93.

Figure 1 shows the distribution of crude scores for each item in all CPGs. Item numbers with median crude scores $\leq$ 2.0 were 5 (emphasizing patients' perspectives), 7 (pre-test before publication), 19 (discussion about potential organizational barriers), 20 (considering cost implications), 22 (editorial independence from funding body), and 23 (records of conflicts of interest). The item numbers with widely distributed crude scores were 2 (description of clinical questions), 6 (target users defined clearly), 10 (presentation of methods for formulating recommendations), and 22 (editorial independence from funding body).

Table 3 shows the inter-rater reproducibility for each item. The kappa statistics were –0.02 to 0.64, and the null hypothesis that the consistency of the results occurred by chance alone could not be rejected for items 3 (target patients described specifically), 5 (emphasizing patients' perspectives), 7 (pre-test before publication), 18 (tools for application), and 23 (records of conflicts of interest).

Discussion

The present report describes the results of continuous evaluation of CPGs assembled by the Japan Society of Clinical Oncology. Changes in standardized domain scores indicated that the methods and organization for developing CPGs have improved slightly, although the differences were not statistically significant and the number of CPGs assessed was small. The domains with median scores > 50 points were "scope and purpose" (items 1–3), "rigor of development" (items 8–14), and "clarity and presentation" (items 15–18). Domains with median scores < 50 points were "stakeholder involvement" (items 4–7), "applicability" (items 19–21), and "editorial independence" (items 22–23). Developers must consider these findings when developing new guidelines or revising those that have been already established. For individual items, low scores were observed in items 5, 7, 19, 20, 22, and 23.

Item 5 emphasizes patients' perspectives. The values of individual patients with cancer should be considered in clinical decision making. Several guidelines seemed to specifically recommend a single option without providing alternatives. Representatives of patients or paramedical staff should be involved in these processes.

Item 7 addresses the pilot use of the CPG before formal publication. When a pilot is not used to improve the quality of the CPG, early feedback about its validity, implementation, and impact on routine practice after publication should be obtained.

Item 19 addresses potential organizational barriers. Alternatives should be discussed when barriers interfere with CPG implementation.

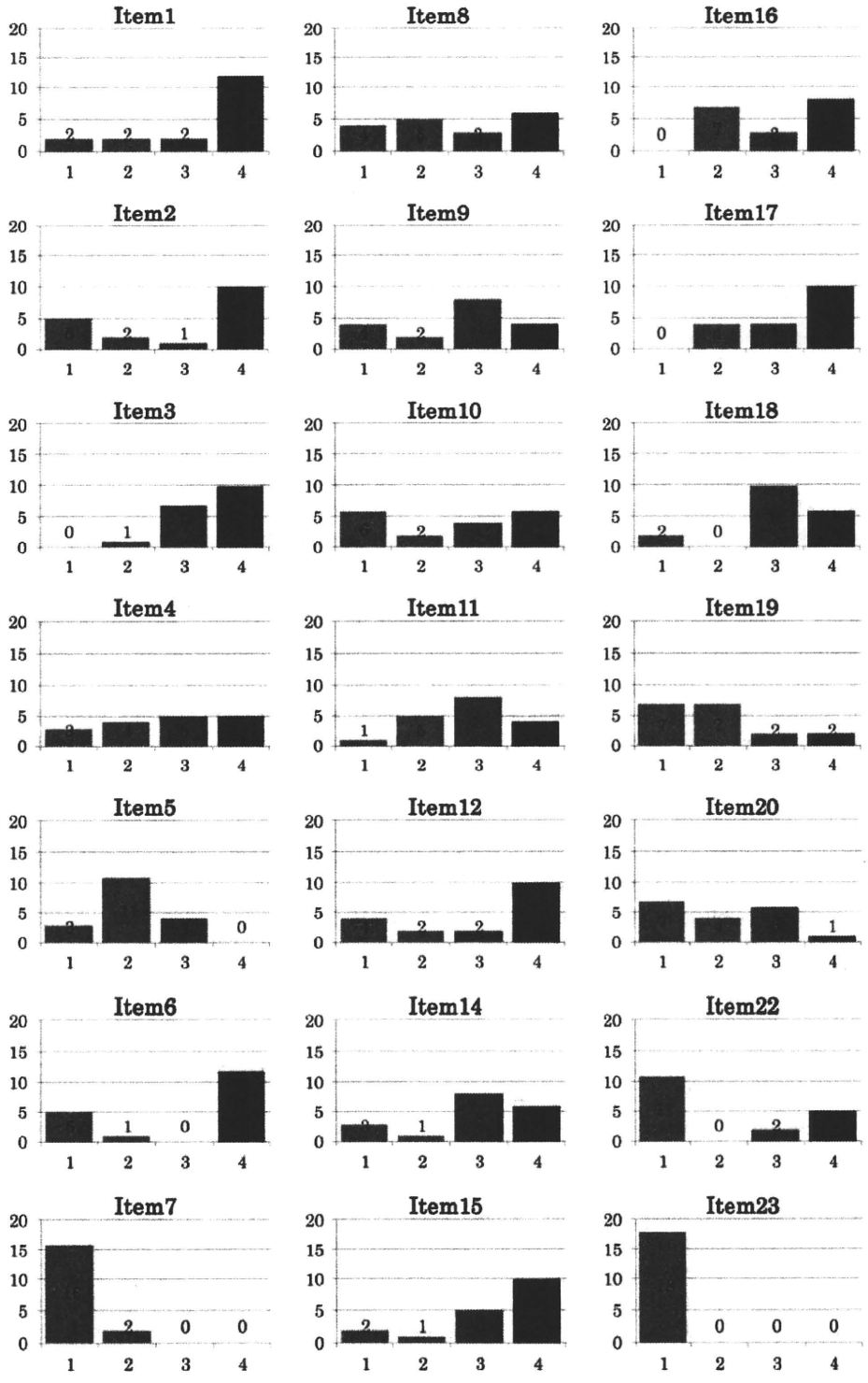

Fig. 1 Distribution of crude scores for each item. Crude scores of each item were reached by consensus after discussion in a committee meeting and are not simple means or medians of scores supplied by individual members of the Evaluation Committee

Item 20 refers to cost issues. The clinical practice of oncology must be individualized because it is based on patient status and value judgments. In general, the issue of cost is important, especially in preventive medicine and in the long-term management of prevalent chronic disorders such as hypertension or dyslipidemia. Cost is more urgent in preventive medicine than for oncologists whose patients have cancer.

Table 3 Inter-rater reproducibility of each item

Item	Kappa[a]	*P* value	Item	Kappa[a]	*P* value
1	0.23	<0.01	12	0.31	<0.01
2	0.64	<0.01	14	0.49	<0.01
3	0.00	0.49	15	0.15	<0.01
4	0.37	<0.01	16	0.20	<0.01
5	−0.02	0.61	17	0.15	<0.01
6	0.34	<0.01	18	0.05	0.18
7	0.04	0.23	19	0.19	<0.01
8	0.33	<0.01	20	0.28	<0.01
9	0.35	<0.01	22	0.14	0.01
10	0.33	<0.01	23	0.05	0.20
11	0.18	<0.01			

[a] Kappa statistics express agreement of several raters above the expected value

Item 22 requires editorial independence from funding bodies. The source of financial support should be documented. If pharmaceutical companies are the source, then the procedure for maintaining editorial independence should also be documented.

Item 23 asks about records of conflicts of interest. None of the CPGs described records for conflicts of interest, although the impact of CPGs on routine practice is substantial. Concern about conflicts of interest is increasing in Japan, where medical journals have not managed this issue as foreign journals have. The Japan Society of Clinical Oncology and the Japan Society of Medical Oncology have developed the "Clinical Oncology Research Conflict of Interest Policy (ver. 1)" [7, 8]. According to this policy, all members of the society must report their status regarding conflict of interest when they report and publish in the society, and these reports are centrally reviewed. This procedure must be followed when CPGs are developed, and records about conflicts of interest should be explicit.

The distribution of crude scores was wide for items 2, 6, 10, and 22, for which the same item scored low and high in several CPGs. Improving these points might not be difficult, although guideline-specific conditions might be involved. The involvement of experts specialized in the field of guidelines will be useful. Item 2 requires clear descriptions of clinical questions. When "Clinical Question" is first described for each CPG topic, it may help focus readers to understand the content more easily. This format of clinical question is preferable. Item 6 asks for a clear definition of the target users. It is important to define that clearly when developing and using CPGs. Item 10 addresses an explicit document that describes the methods of formulating recommendations; however, many CPGs did not provide this information. The impact of an assessment of benefits and harms after a systematic review on formulating a recommendation should be addressed. If disagreement about a recommendation arises, the methods used to reach consensus should be described.

Although the EC has reviewed a dozen CPGs, this report has some challenging issues as limitations. First, the inter-rater reproducibility of several items of the AGREE instrument was poor. Previous studies have identified good validity and reproducibility [3, 4], but we found that reproducibility was not easily achieved in our setting. Although AGREE is a good method of evaluation, the scoring remains subjective. We did not directly use the crude scores of individual members to reach the final assessment. Nevertheless, low reproducibility means that judgment by a member using the AGREE items is not a simple matter. Among low-score items, the score of items 5, 7, and 23 might be influenced by a difficult evaluation. Consensus will be achieved if the committee has criteria for scoring that maintain the original concept of the AGREE items.

Second, common scoring methods are not applicable to all CPGs, because solid evidence is not available in some fields of cancer. Although all CPGs of the society are related to cancer, each type of cancer has specific characteristics. AGREE itself does not recommend establishing a threshold to differentiate CPGs of "good" or "bad" quality.

The activity of CPG development is continuous, and CPGs of the subspecialty societies and the published material of the society (http://www.jsco-cpg.jp/) will be revised sequentially. These guidelines have also been published on the homepages of the subspecialty societies and of the Medical Information Network Distribution Service (MINDS), thus bringing the CPGs closer not only to medical professionals but also to patients. The activities of publishing and implementing CPGs within the society over the first decade seem to have begun well. Efforts to improve quality must be maintained, and users, including patients, should be able to easily understand the contents.

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Conflict of interest statement M. Toi received honoraria from GlaxoSmithKline. The other authors have no conflict of interest.

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ORIGINAL ARTICLE

Gefitinib or Chemotherapy for Non–Small-Cell Lung Cancer with Mutated EGFR

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ABSTRACT

BACKGROUND

Non–small-cell lung cancer with sensitive mutations of the epidermal growth factor receptor (EGFR) is highly responsive to EGFR tyrosine kinase inhibitors such as gefitinib, but little is known about how its efficacy and safety profile compares with that of standard chemotherapy.

METHODS

We randomly assigned 230 patients with metastatic, non–small-cell lung cancer and EGFR mutations who had not previously received chemotherapy to receive gefitinib or carboplatin–paclitaxel. The primary end point was progression-free survival; secondary end points included overall survival, response rate, and toxic effects.

RESULTS

In the planned interim analysis of data for the first 200 patients, progression-free survival was significantly longer in the gefitinib group than in the standard-chemotherapy group (hazard ratio for death or disease progression with gefitinib, 0.36; P<0.001), resulting in early termination of the study. The gefitinib group had a significantly longer median progression-free survival (10.8 months, vs. 5.4 months in the chemotherapy group; hazard ratio, 0.30; 95% confidence interval, 0.22 to 0.41; P<0.001), as well as a higher response rate (73.7% vs. 30.7%, P<0.001). The median overall survival was 30.5 months in the gefitinib group and 23.6 months in the chemotherapy group (P=0.31). The most common adverse events in the gefitinib group were rash (71.1%) and elevated aminotransferase levels (55.3%), and in the chemotherapy group, neutropenia (77.0%), anemia (64.6%), appetite loss (56.6%), and sensory neuropathy (54.9%). One patient receiving gefitinib died from interstitial lung disease.

CONCLUSIONS

First-line gefitinib for patients with advanced non–small-cell lung cancer who were selected on the basis of EGFR mutations improved progression-free survival, with acceptable toxicity, as compared with standard chemotherapy. (UMIN-CTR number, C000000376.)

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NON–SMALL-CELL LUNG CANCER IS A major cause of death from cancer. The use of cytotoxic chemotherapy is associated with a response rate of 20 to 35% and a median survival time of 10 to 12 months among patients with advanced non–small-cell lung cancer.[1,2] Gefitinib is an orally administered tyrosine kinase inhibitor of the epidermal growth factor receptor (EGFR). In two phase 2 studies of patients with previously treated non–small-cell lung cancer, the response rate was 9 to 19%.[3,4] In subsequent phase 3 trials, the noninferiority of gefitinib as compared with docetaxel with respect to overall survival was shown in one study (hazard ratio, 1.02)[5] but not another (hazard ratio, 1.12).[6] Meanwhile, demographic and clinical factors such as Asian race, female sex, nonsmoking status, and adenocarcinoma were shown to be predictive of the efficacy of gefitinib, warranting a large comparative trial (First Line Iressa vs. Carboplatin/Paclitaxel in Asia [IPASS]; ClinicalTrials.gov number, NCT00322452) in which patients were selected in accordance with these factors.[7]

In May 2004, two pivotal studies showed that the presence of somatic mutations in the kinase domain of EGFR strongly correlates with increased responsiveness to EGFR tyrosine kinase inhibitors in patients with non–small-cell lung cancer.[8,9] It was later found that subgroups of patients with non–small-cell lung cancer who had sensitivity to gefitinib had a high incidence of EGFR mutations. In Japan, 30% or more of patients with mutated-EGFR non–small-cell lung cancer are male or have a history of smoking.[10,11] Therefore, we hypothesized that selecting patients on the basis of EGFR mutations rather than clinical factors would result in a population with a greater sensitivity to gefitinib.

Our previous prospective, phase 2 studies of gefitinib therapy in patients with advanced non–small-cell lung cancer and EGFR mutations[12-14] revealed a response rate of more than 70% and progression-free survival of 9 to 10 months. We also developed a rapid, sensitive method for detecting sensitive EGFR mutations: the peptide nucleic acid–locked nucleic acid (PNA-LNA) polymerase-chain-reaction (PCR) clamp method.[15] We then undertook a phase 3 study comparing gefitinib and standard carboplatin–paclitaxel chemotherapy in patients who had advanced non–small-cell lung cancer with sensitive EGFR mutations and who had not previously received chemotherapy.

METHODS

PATIENT POPULATION

This multicenter, randomized, phase 3 trial was approved by the institutional review board of each participating center. Eligibility criteria included the presence of advanced non–small-cell lung cancer harboring sensitive EGFR mutations, the absence of the resistant EGFR mutation T790M (in which threonine at amino acid 790 is substituted by methionine), no history of chemotherapy, and an age of 75 years or younger (because a benefit of a platinum-based regimen in patients >75 years of age is not established). Table 1 in the Supplementary Appendix (available with the full text of this article at NEJM.org) lists the detailed eligibility and exclusion criteria. The authors attest to the fidelity of the article to the full protocol and statistical-analysis plan.

DETECTION OF *EGFR* MUTATIONS

Cytologic or histologic specimens were examined for *EGFR* mutations by means of the PNA-LNA PCR clamp method. Briefly, genomic DNA fragments containing mutation hot spots of the *EGFR* gene were amplified with the use of a PCR assay in the presence of a peptide nucleic acid clamp primer synthesized from a peptide nucleic acid with a wild-type sequence. This method results in preferential amplification of the mutant sequence, which is then detected by a fluorescent primer that incorporates locked nucleic acids to increase the specificity. As a result, a mutant *EGFR* sequence is detected in specimens that contain 100 to 1000 excess copies of wild-type *EGFR* sequence. The sensitivity and specificity of the PNA-LNA PCR clamp method are 97% and 100%, respectively.[15,16]

STUDY DESIGN AND TREATMENT

Before randomization, patients were stratified according to sex, clinical stage of non–small-cell lung cancer (IIIB, IV, or postoperative relapse), and institution. Eligible patients were randomly assigned to receive either gefitinib (at a dose of 250 mg per day orally) or standard chemotherapy. The standard chemotherapy consisted of paclitaxel (at a dose of 200 mg per square meter of body-surface area, given intravenously over a 3-hour period) and carboplatin (at a dose equivalent to an area under the concentration–time curve [AUC] of 6, given intravenously over a 1-hour period), both administered on the first day of every 3-week cycle. The

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carboplatin dose in milligrams was calculated by means of the Calvert formula (AUC × [the calculated creatinine clearance in milliliters per minute+25]; www.freekinetics.com/auccalc1.htm). The glomerular filtration rate was estimated according to the Cockcroft–Gault method ([140−age in years] × [actual weight in kilograms] ÷ [72 × serum creatinine level in milligrams per deciliter {× 0.85 in women}]). Chemotherapy was continued for at least three cycles. Gefitinib was administered until disease progression, development of intolerable toxic effects, or withdrawal of consent.

CLINICAL ASSESSMENTS

Assessments made before enrollment are summarized in Table 2 in the Supplementary Appendix. Assessment of the tumor for a response to treatment was performed by means of computed tomography (CT) every 2 months. Unidirectional measurements were adopted on the basis of the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.0).[17] Progression-free survival was evaluated for the period from the date of randomization to the date when disease progression was first observed or death occurred. Treatment response and progression-free survival were determined by external review of the CT films by experts who were not aware of the treatment assignments. Overall survival was evaluated for the period from the date of randomization to the date of death. Toxic effects were assessed according to the National Cancer Institute Common Terminology Criteria (NCI-CTC, version 3.0; http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf).

STATISTICAL ANALYSIS

The primary end point was progression-free survival, as a measure of the superiority of gefitinib over carboplatin–paclitaxel. From our previous data, we hypothesized that the progression-free survival with gefitinib was 9.7 months; from the results of the Iressa NSCLC Trial Assessing Combination Treatment (INTACT),[18] we hypothesized that the progression-free survival with standard chemotherapy was 6.7 months. We estimated that a total of 230 events would be needed for the study to have a power of 80% to confirm the superiority of gefitinib over standard chemotherapy, with the use of a log-rank test and a two-sided significance level of 5%. Setting the duration of enrollment to 2 years with a minimum follow-up period of 6 months, we initially planned to enroll 320 patients.

Kaplan–Meier survival curves were drawn for progression-free survival and were compared by means of a log-rank test. Hazard ratios (and 95% confidence intervals) were calculated with the use of a Cox proportional-hazards analysis. Prespecified adjustment factors included sex and clinical stage.

Secondary end points included overall survival, response rate, time to the deterioration of performance status (Eastern Cooperative Oncology Group [ECOG] performance status score of ≥3, capability of only limited self-care, or confinement to a bed or chair for >50% of waking hours[19]), and toxic effects. Overall survival and the time to ECOG performance status score of 3 or more were analyzed in the same way as progression-free survival. The response rate and rate of toxic effects were compared between the two groups with Fisher's exact test and the Wilcoxon test, respectively. Each analysis was performed with the use of a two-sided, 5% significance level and a 95% confidence interval by means of SAS for Windows software (release 9.1, SAS Institute).

One interim analysis was planned to analyze the primary end point (significance level, P=0.003). The Lan–DeMets method was used to adjust for multiple comparisons. The O'Brien–Fleming type alpha-spending function was also used.

RESULTS

PATIENT CHARACTERISTICS

The study was begun in March 2006. The preplanned interim analysis was performed 4 months after the 200th patient was enrolled (May 2009); it showed a significant difference in progression-free survival between the two treatment groups (P<0.001), and the independent data and safety monitoring committee recommended termination of the study. Therefore, the study was stopped at the end of May 2009.[20]

In total, 230 patients were enrolled from 43 institutions in Japan (Fig. 1). Half (115 patients) were randomly assigned to receive gefitinib and half to receive carboplatin–paclitaxel. Two patients were excluded because they were found to be ineligible. In the chemotherapy group, 1 patient was not evaluated for safety, owing to lack of receipt of the study drugs, and 3 others were excluded from the analysis of progression-free survival.

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