とに，EGFR 陽性の患者さんを対象に，初回治療としてエルロチニブ単剤にベバシズマブを加える群と，エルロチニブ単剤群とのランダム化第Ⅱ相臨床試験の集積が日本で最近終わったところです。そういった組み合わせがEGFR-TKI 単剤以上に効果が出てくるのではと期待しています。

前門戸　EGFR-TKI への併用として化学療法よりもベバシズマブのほうが毒性面は少し軽いかもしれないということが期待されますね。

浦本　WJOG からは，EGFR 遺伝子変異陽性患者さんに対する術後補助療法をゲフィチニブと対照群(シスプラチン＋ビノレルビン併用療法)に分けた IMPACT 試験が行われていますね。

前門戸　結果が非常に待ち遠しいです。

ところでつい最近ですが，EGFR の測定法である Scopion-ARMS 法が使えるようになりました。つまり高感度法が1つ増えたことになりますが，加藤先生はどのようにお考えですか。

新しい高感度法について

加藤　Scopion-ARMS 法は従来のクランプ法やインベーダー法，サイクリーブ法などの高感度法より，さらにワンオーダー少ない検体量で EGFR 遺伝子変異を検出する方法として開発されました。微小検体や胸水，末梢血中といった腫瘍細胞の少ない場合に有用であったという研究結果が出ています。

実際には，従来の高感度法でごく少量の喀痰細胞診などでも対応できている現状から考えると，日常臨床では Scopion-ARMS 法が必要になるケースは少ないと思います。

ただ，臨床背景から EGFR 陽性が強く疑われるのに，高感度法で陰性になった場合の再検査や，腫瘍量が非常に少ないときには Scopion-ARMS 法が有効ですので，保険承認されたことは喜ばしいと思います。

前門戸　大泉先生はどのようにお考えでしょうか。NEJ グループとして，PNA-LNA クランプ法を中心に測定されてきたと思いますが。

大泉　各種の高感度法で EGFR 遺伝子変異検出能に差がないことは，既に報告されていると思います。

当施設では，組織検査よりも病理結果が早く出る場合も多いので，細胞診の検体を用いて高感度法で EGFR 遺伝子変異測定をしていますね。

前門戸　検体の提出ではホルマリンの問題などがかなり影響すると思いますが，浦本先生，そのあたりに関していかがでしょうか。

大泉　聡史先生

浦本　ホルマリンについては，従来長時間固定していたと思いますが，やはり長くても 24 時間以内で引き上げるとよいと思います。

Scopion-ARMS 法については，治療前のサンプルでも 38％ぐらい T790M 変異がみつかる報告があります。それでも EGFR-TKI で効果のある方はおられる。つまり本当に高感度化し過ぎてしまって，腫瘍の性状を反映しているのかという疑問もあります。

また，外科の立場から申し上げますと，基本的に組織を en bloc に採取できるので腫瘍の最大割面を切るようにしていますが，それが本当に腫瘍の全貌を表しているのかという問題があります。

もう1つ，遺伝子プロファイルが術前，転移出現時に本当に一致したのかという問題があります。

前門戸　逆に我々内科医としては，生検部分は腫瘍のほんの一部のため，それが腫瘍全体を反映しているかどうかということが問題でもあるのですが。

浦本　それは逆によい面もあって，腫瘍の一番端が一番活性化しているところなので，そこが腫瘍の全貌ではないかという方もおられるのですね。

胃癌の組織を中央部と端または全体に分けて分析したところ，端でも8割ぐらいは全体を把握できることが判明したという報告もありますので，肺癌と胃癌では少し違いますが，内科の先生が検体を採ることは非常に有意義なことで，だからこそ日本からよいエビデンスが出ているのだと思います。

また，長崎大学のグループは小さい腫瘍に対して，気管支鏡とエコーを使ってプローベにガイドシース(GS)を装着して鉗子を挿入して腫瘍を的確に採取されているそうですね。

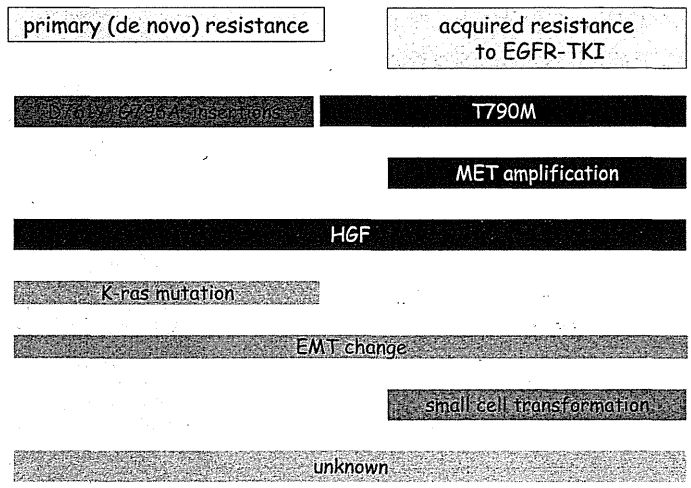

図2 耐性の分子機構

この手法は体壁を通過して採取したものを検討するBATTLE試験とは逆であり，日本の内科の先生方は非常にきめ細かく採取されるので，サンプリングのレベルが高いのではと感じています。

前門戸 つまりEGFRの新しい測定法として上市されたScopion-ARMS法は，感度は優れている可能性があるものの，通常の検体であれば従来の高感度法で十分であろうということだと思います。

そして組織中の変異の不均一性の問題を含め，偽陰性に対しては，今後重要な問題になってくると思います。

さて，EGFR-TKIをファーストライン，あるいはセカンドラインで使ったとして，単剤治療だと1年前後で耐性になるわけですが，耐性についての戦略が実は一番の課題だと思います。耐性の機序については，浦本先生，いかがでしょうか。

耐性の機序について

浦本 耐性の機序には初期耐性と獲得耐性があり，初期耐性は感受性変異が感受性を示しますので，その反対で野生型は一応耐性となります。

もう1つはKRAS遺伝子の変異です。KRAS遺伝子変異もEGFR遺伝子変異と同様肺腺癌で起こりますが，clinical characteristicsがまったく違って，EGFR遺伝子変異は非喫煙者，かつ女性に多いのですがKRAS遺伝子変異は元喫煙者で，男性に多い。あるいは，EGFR遺伝子変異は東アジアに多いけれどもKRAS遺伝子変異は欧米に多い，しかもEGFR-TKI反応率も全然違いますね。

さらに大腸癌領域で，セツキシマブはKRAS遺伝子変異を有する症例には効果がないというデータがありますが，その尤度比は6.82ですので，KRAS遺伝子変異だけをもって肺癌領域にあてはめると3.52ということで，あまり高くありません。

したがいまして，2008年のESMOにおいてMurray先生が，有名なものとしてExon20インサーション，あるいは我々が発見したG796A遺伝子変異など，他にも初期耐性があるのではないかとおっしゃっていました。

また，2012年のASCOでのトピックスは，MEK阻害薬のselumetinibです。KRAS遺伝子変異のある腫瘍を対象として，ドセタキセルに追加投与した群とドセタキセル単剤投与群のOSをみる臨床試験が行われ，OSは違いがなかったのですが，PFSと奏効率は明らかにselumetinibを入れたほうがよいという結果が出ています。

問題になっている獲得耐性については，以上のように先程来出ているT790MやMETの増幅，small cell transformation，もしくはEMT (epithelial mesenchymal transition，上皮間葉移行)があります(**図2**)。

日本人については，金沢大学の矢野聖二先生のグループが肝細胞増殖因子(HGF)の高発現が重要であるというデータを出されていました。

ただ，問題なのは，先程前門戸先生がheterogeneityのことをおっしゃいましたが，私たちの経験でも，両肺に沢山の肺転移がある症例にIC(informed consent)の後に手術を施行したところ，どこを採ってもEGFR遺伝子変異がみつかったのですが，そのうちの1個の検体のみにT790M遺伝子変異がありました。つまり同じようにみえる組織でもheterogeneityを有するものがあるということですね。

また，EMTに関して解析してみると，確かに上皮系マーカーのγプロテインが治療後に消失したり，間葉系マー

カーであるフィブロネクチンやビメンチンがTKI治療後に増強している症例がありました。

加えて，ゲフィチニブを長期投与した培養細胞中の耐性株をみると，転写因子(EGR-1)の核内移行阻害，さらにがん抑制遺伝子(PTEN)の発現低下が幾つかの検体で認められます。

一番の問題はこのような様々な耐性のメカニズムが1症例に重なって複雑な耐性機構となり得るということと，いまだ分っていない機序があるということだと思います。

前門戸　T790Mとの重なりについてはどうなのでしょうか。

浦本　当科のデータではT790MはHGFと重なることが多いですね。

大泉　先生，いまのお話は気管支鏡で採取された検体についてでしょうか。

浦本　殆どが手術検体で，一部気管支鏡などで採取します。

そして耐性への治療として，やはり再生検をできるだけ行います。その結果，T790Mをもつ症例のほうが生存期間が長いというデータが出ています(**図3**)。

Oxnard氏からも，今年のASCOでも，Rossell氏も同じようなデータを出しています。

恐らくT790M例は腫瘍の増殖スピードが遅い，そして効果のあるEGFR-TKIを中止すると，disease flare(EGFR-TKI中止後から次治療投与開始前までの間に，入院を要する，かつ/または死亡するような急激な病勢進行)が起こるのではないかと思っています。

実際にTKIを使ったうちの約23％がdisease flareになり，そのうち43％はT790Mがあることが報告されました。EGFR- T790M axisに依存している腫瘍は安易にTKIを中止しないほうがよいのではないかと考えています。

前門戸　ただいまdisease flareの話にも触れていただきましたが，TKIを中止した後の対応が問題ですね。

浦本　現在私たちは，第Ⅱ相臨床試験として，採血と病理検体を採りながらゲフィチニブにS1を併用する検討を続けています。

このように沢山の分子標的薬が出てくると，外科医は手術はもとより，EBUSや胸腔鏡などで多くの腫瘍組織を採れるため色々な検討ができますし，salvage therapyの可能性も広がるのではないかと感じています。

前門戸　外科的にも侵襲の少ない手法が色々開発されてきていますので，我々内科医とぜひうまくコミュニケーションを図っていただければと思います。

大泉　そうですね。転移部位も含めて複数の箇所に腫瘍ができたときはheterogeneityの問題が確かにあるかもしれません。浦本先生がおっしゃった通り，今後外科の先生と協力して癌組織を何らかの形で採取するということが重要になってくると思います。

加藤　晃史先生

前門戸　もう1つの耐性への克服として，世界的にafatinibが注目されていますが，加藤先生，どのようにお考えでしょうか。

第2世代の薬剤について

加藤　afatinibは第2世代のEGFR-TKIとして開発された薬剤です。第1世代の耐性の主たる原因であるT790M変異を克服するとされ，ゲフィチニブかエルロチニブへの耐性後の奏効率は7％でした。耐性にはT790M変異以外の機構があることから，T790M出現患者に限ればもう少し高い効果となる可能性もありますので，afatinibが上市された暁には，大泉先生がおっしゃったように，とにかく私たちは生検を使ってT790Mを証明したうえで第2世代のTKIを使うということを，臨床試験でも実地臨床でも行っていくべきだろうと考えています。

前門戸　afatinibにセツキシマブを併用するという試みもされていますが，それについてはいかがでしょう。

加藤　EGFR-TKI耐性化の機序としてT790Mの出現だけでなく，METを介するなど複数の経路があるために，単剤で耐性化を克服するのは難しいという考え方があります。耐性化後に複数経路を抑えるコンセプトで，afatinibにセツキシマブを併用する試験結果が発表されています。セツキシマブ自体はEGFR抗体ですので双方の経路を完全に抑制すれば効果が非常に上がると期待していますが，日本ではセツキシマブの開発が遅れていますので，もう少

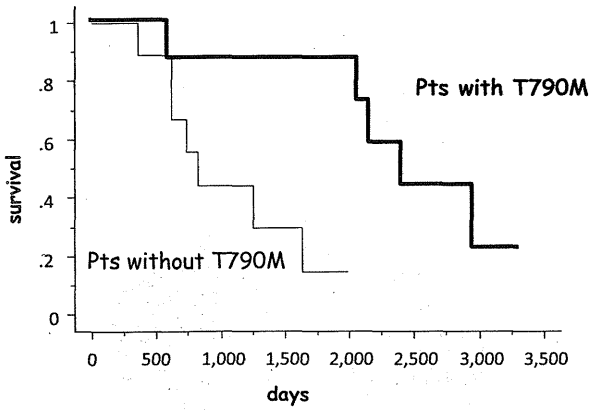

図3 Survival curves stratified by T790M of EGFR

し海外からの有用なデータが出ることを期待します。

前門戸 データで比較するとLUX-lung1，4などでも10％弱の奏効率ですが，セツキシマブを上乗せすることでT790Mの有無にかかわらず50％くらいの奏効率が得られているようですので，非常に有望な方法だとは思います。とはいえ，先程加藤先生がいわれたように様々な問題点も含んでいるということですね。

それではもう1つの薬剤として，EGFR-TKIのリチャレンジであるセカンドTKIについて，大泉先生，お願いできますか。

大泉 TKIを中止することでいわゆるdisease flareの発現もありますので，TKIを続けながら他剤を上乗せしたり，あるいは他剤を挟んで休止期間を置いてからもう1回投薬するなど色々な考え方があると思います。

再投与についての前向きな臨床試験も色々検討されていますが，我々の検討によるとPFSが約2カ月，OSは約14カ月という結果でした。他の再投与試験の報告では，奏効率は大体15～20％ぐらいです。治療戦略のオプションとして考えられます。

前門戸 今年(2012年)のASCOでも，再投与群とそうでない群のOSを比較したところ，再投与群のほうが長いというデータが先端医療センターから発表されていましたね。いまのところ再投与が有望とまではいい切れなくとも，一部の患者さんには確かに効果がある可能性がありますので，検討すべき課題だと思います。

次にEGFR遺伝子変異を有する群についてですが，まずEGFR野生型に対するエルロチニブのエビデンスについて，大泉先生，お願いします。

大泉 まずBR21試験について説明します。この試験では，PS0～3症例においてセカンドライン，サードラインでエルロチニブの有効性が検討されている点が特徴だと思います。ご存知の通り全体集団ではエルロチニブ群においてプラセボ群と比較してOSの優越性が証明されています。EGFR変異陰性群におけるサブグループ解析では，エルロチニブ群7.9カ月とプラセボ群3.3カ月と解析症例数の関係から統計学的有意差はないものの有効性はあるように考えられます。

またSATURN試験ではEGFR遺伝子変異陰性例においてエルロチニブ群でPFSとOSで優越性が証明されまして，スイッチメンテナンス療法を支持するエビデンスになっています。

EGFR遺伝子野生型に本当に効果があるのかは，偽陰性の問題もあり，個人的にはさらなる検討課題と考えています。

前門戸 NEJのグループでも，野生型の患者さんに対するエルロチニブの試験が検討されましたね。十分な奏効率を示すことはできなかったのですが，一部長いPFSを示す患者さんがおられます。今後はそういった患者さんを見分けることが重要な課題となると思います。

ところで，最近，イタリアのグループからTailor試験のデータが発表されましたね。加藤先生，解説をお願いします。

最近の試験データについて

加藤 Tailor試験を考えるうえで参考となると思いますので，まずTITAN試験からお話いたします。TITAN試験というのはEGFRの状態に関係なく，セカンドラインにおけるエルロチニブとドセタキセル，あるいはペメトレキセドとの効果の違いについて調べたものですが，OSは差がありませんでした。

PFSは，初期効果としてやはり化学療法のほうが若干高いのですが，興味深いのは長期生存者がエルロチニブ群だったことです。この状況はEGFR野生型に限っても変わらないようです。

ここでの問題点は，EGFR陰性に偽陰性が混在し，奏効者が交じっている可能性があるので，長期生存に関しては陰性のデータとはいい切れませんが，全体として有意差はなく，エルロチニブはドセタキセル，ペメトレキセドと同等の効果があるとされています。

続いて，それに反証するような形で，Tailor試験というのが組まれました。

Tailor試験はセカンドラインの薬剤として，ドセタキセルとエルロチニブを比較するという単純なデザインになっています。そこでEGFR野生型を抽出したところ，PFSはドセタキセル群のほうが非常に有用性が高かったため，今年のASCOで，セカンドラインではドセタキセルを使

うべきであると発表され，大きな議論が巻き起こりました。

先程のTITAN試験のようにPFSはドセタキセル群のほうがよいことはある程度想定されていたのですが，本来Tailor試験の主要評価項目であったOSについては最終的な解析が発表されていませんので，この段階でドセタキセルが有意であると結論づけたことは若干問題もあったと思います。

ただ，あくまで局所効果についてはPFSに差があるように，やはり初期効果に関してはドセタキセルのほうが高いことは殆ど私たちが理解している通りですので，エルロチニブはEGFR野生型の腫瘍縮小効果はそれほど高くない。ただし，OSに関してはドセタキセルと同等であるというのが現時点での解釈だろうと思います。

ですから野生型にはドセタキセルやペメトレキセドを上回る効果はないですけれども，同等であるというように考えるべきだろうと思います。

ところで自験例なのですが，手術検体でEGFR陰性だった患者さんにサードラインでエルロチニブを使って非常に効果があったという経験をしました。偽陰性の可能性もありましたが，それ以上調べることのできない現状にあって，EGFR陰性の患者さんにEGFR-TKIを1回も使用しないというのは，一部の患者さんの利益を損ねる可能性があるという意味で，エルロチニブはEGFR陰性に対して有効であると考えたいと思っています。

前門戸　確かに非喫煙患者さんはEGFR変異が多く含まれる集団ですので，検査法の問題がありますね。偽陰性の問題もありますし，セカンドラインでは使用可能な薬剤がかなり充実してきましたので，いずれかの段階で試したいと思います。

大泉　まったくその通りだと思います。いまの時点でのエビデンスはTailor試験のところで加藤先生がおっしゃった通りです。肺癌診療ガイドラインでも記載されていますし，エルロチニブは陰性例に対しても考慮すべき薬剤であることは間違いないと思います。

前門戸　EGFR変異，TKIに関してはかなり研究が進んできたこともあり議論し尽くされた印象をもたれている方もおられると思いますが，本日お話いただいたように様々な課題がまだ沢山ありますので，これからも日本発のエビデンスをどんどん出していければと思います。本日は活発なご討議をどうもありがとうございました。

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Updated overall survival results from a randomized phase III trial comparing gefitinib with carboplatin–paclitaxel for chemo-naïve non-small cell lung cancer with sensitive EGFR gene mutations (NEJ002)

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Background: NEJ002 study, comparing gefitinib with carboplatin (CBDCA) and paclitaxel (PTX; Taxol) as the first-line treatment for advanced non-small cell lung cancer (NSCLC) harboring an epidermal growth factor receptor (EGFR) mutation, previously reported superiority of gefitinib over CBDCA/PTX on progression-free survival (PFS). Subsequent analysis was carried out mainly regarding overall survival (OS).

Materials and methods: For all 228 patients in NEJ002, survival data were updated in December, 2010. Detailed information regarding subsequent chemotherapy after the protocol treatment was also assessed retrospectively and the impact of some key drugs on OS was evaluated.

Results: The median survival time (MST) was 27.7 months for the gefitinib group, and was 26.6 months for the CBDCA/PTX group (HR, 0.887; $P = 0.483$). The OS of patients who received platinum throughout their treatment ($n = 186$) was not statistically different from that of patients who never received platinum ($n = 40$). The MST of patients treated with gefitinib, platinum, and pemetrexed (PEM) or docetaxel (DOC, Taxotere; $n = 76$) was around 3 years.

Conclusions: No significant difference in OS was observed between gefitinib and CBDCA/PTX in the NEJ002 study, probably due to a high crossover use of gefitinib in the CBDCA/PTX group. Considering the many benefits and the risk of missing an opportunity to use the most effective agent for EGFR-mutated NSCLC, the first-line gefitinib is strongly recommended.

Key words: EGFR mutation, gefitinib, individualized treatment, lung cancer

introduction

Two pivotal studies have revealed that somatic mutations in the kinase domain of the epidermal growth factor receptor (EGFR) strongly correlate with responsiveness to gefitinib, the first EGFR tyrosine kinase inhibitor (EGFR-TKI) used to treat non-small cell lung cancer (NSCLC) [1, 2]; subsequently, several phase II studies have demonstrated the promising efficacy of individualized treatment for advanced NSCLC patients with EGFR-TKI on the basis of EGFR gene mutation status [3–10]. Subsequently, we have conducted a phase III

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study comparing gefitinib with the standard platinum doublet regimen, carboplatin (CBDCA, Nippon Kayaku, Tokyo) and paclitaxel (PTX, Bristol-Myers Squibb, Tokyo), as the first-line treatment for advanced NSCLC harboring EGFR gene mutations (NEJ002) [11]. The study revealed that gefitinib provided significantly longer progression-free survival (PFS), the primary endpoint of the study, than CBDCA/PTX. Other phase III studies also have demonstrated the superiority of EGFR-TKI over the platinum doublet regimen [12, 13]; thus EGFR-TKIs are now globally recognized as the standard first-line treatment for advanced NSCLC with sensitive EGFR mutations [14].

Regarding overall survival (OS), one of the secondary endpoints of NEJ002, the rate of events was <40% in the previous report, for which the data cutoff point was December 2009. Although our study was not powered for OS, we proceeded with this OS analysis to evaluate the long-term survival result for each treatment group. We updated the data for PFS, OS, and safety examined in a longer follow-up period and also assessed the impact of subsequent chemotherapy on OS in patients with EGFR-mutated NSCLC.

materials and methods

study design and treatment

Full details of the NEJ002 study have been published previously. Eligible patients had chemo-naïve advanced NSCLC with a sensitive EGFR mutation detected by the highly sensitive peptide nucleic acid-locked nucleic acid PCR clamp method [15]. Patients were randomly assigned (1:1) to gefitinib (250 mg/day) or CBDCA (AUC 6.0)/paclitaxel (Taxol, 200 mg/m^2) on day 1 every 3 weeks (up to six cycles). The primary endpoint of NEJ002 was to evaluate the superiority of gefitinib over CBDCA/PTX in PFS. The secondary endpoints included response rate, OS, quality of life (QOL), and safety profiles (see Supplementary data, available at *Annals of Oncology* online). Patients provided a written informed consent. The study was conducted in accordance with the Helsinki Declaration of the World Medical Association. The protocol was approved by the institutional review board of each participating institution.

updated evaluation

PFS, OS, and safety data evaluated by the Common Terminology Criteria for Adverse Events version 3.0 were re-evaluated at the data cutoff point in December 2010 for the entire intent-to-treat population ($n = 228$), which was initially unplanned. Detailed information on subsequent chemotherapy carried out after the protocol treatment was also assessed for all patients retrospectively.

statistical analysis

The Kaplan–Meier survival curves were drawn for PFS and OS and compared using a two-sided non-stratified log-rank test with a significance level of 0.05. The hazard ratio (HR, gefitinib:CBDCA/PTX) and its two-sided 95% confidence interval (CI) were calculated by Cox regression analysis including only the treatment arm as a covariate. Subgroup analyses for OS, which were shown in a forest plot, were carried out to examine the interaction effect of treatment arm with age, gender, performance status, smoking status, type of histology, and type of EGFR mutation using a Cox regression model including treatment arm, each of the clinical factors, and their interaction effects as covariates. We did not account for adjustment for multiplicity due to the repetition of subgroup analyses, because we carried out them as exploratory analyses. Other comparative analyses were evaluated on the basis of a two-sided 5% significance level and 95% CI. All analyses were carried out using SAS for Windows release 9.1 (SAS Institute Inc., Cary, NC, USA).

Results

updated PFS

Among the 224 patients assessable, the updated median PFS of the gefitinib group and that of the CBDCA/PTX group were 10.8 months and 5.4 months, respectively (HR, 0.322; 95% CI 0.236–0.438; $P < 0.001$), which was quite similar to the previous results (Table 1). The number of events for PFS at the last data cutoff (December 2010) was 98 in the gefitinib group and 101 in the CBDCA/PTX group. The rate of events for PFS slightly increased from the previous report (from 83% to 88%).

updated OS

At the last data cutoff point, the median follow-up time was 704 days (range 30–1659) and 69 death events were observed in each arm. The rate of events for OS increased from 36% in the previous report to 61% in the current study (Table 1). The MST and the 2-year survival rate were 27.7 months and 58%,

Table 1. Previous and updated results of survival

	Previous results (in 2009)		Updated results (in 2010)	
First-line treatment group	Gefitinib	CBDCA/PTX	Gefitinib	CBDCA/PTX
PFS				
Median PFS, months	10.8	5.4	10.8	5.4
Hazard ratio (95% CI)	0.296 (0.215–0.408)		0.322 (0.236–0.438)	
One-year PFS rate	42.1%	3.2%	43.8%	4.2%
Number of events (%)	87 (76%)	100 (91%)	98 (86%)	101 (92%)
Overall survival				
Median survival time, months	30.5	23.6	27.7	26.6
Hazard ratio (95% CI)	0.798 (0.517–1.232)		0.887 (0.634–1.241)	
1-year survival rate	84.7%	86.4%	85.0%	86.8%
2-year survival rate	61.4%	46.7%	57.9%	53.7%
Number of events (%)	39 (34%)	43 (38%)	69 (61%)	69 (61%)

CBDCA/PTX, carboplatin plus paclitaxel; CI, confidence interval; PFS, progression-free survival.

respectively, for the gefitinib group, and 26.6 months and 54% for the CBDCA/PTX group (HR, 0.887; 95% CI 0.634–1.241; $P = 0.483$) (Figure 1). No factor, including the type of EGFR mutation, had a substantial impact on OS between the groups (Figure 2).

safety

No additional serious adverse event (NCI-CTC grade ≥3) was reported in either group after the previous report. Briefly, the most common adverse events reported were rash and diarrhea with gefitinib, and appetite loss, sensory neuropathy, and myelotoxicities with CBDCA/PTX. The combined incidence of serious adverse events combined was significantly higher in the CBDCA/PTX group than in the gefitinib group (71.7% versus 41.2%; $P < 0.001$).

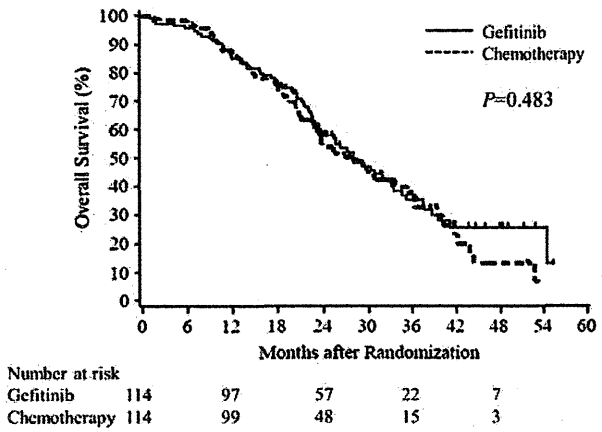

Figure 1. Kaplan–Meier curves for updated overall survival (OS) in the intent-to-treat population of NEJ002.

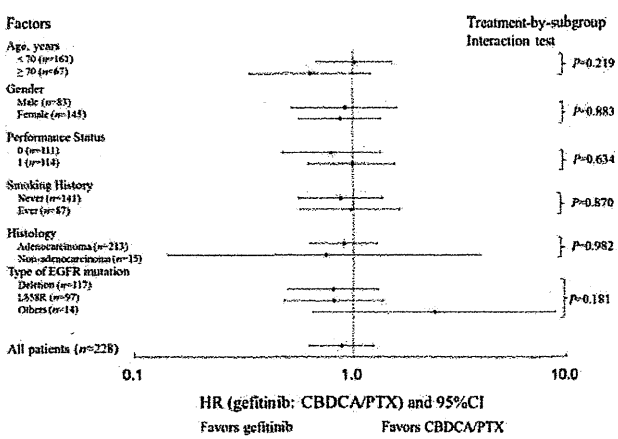

Figure 2. Forest plot of updated overall survival (OS) by clinical factors and the type of epidermal growth factor receptor (EGFR) mutation. Hazard ratio (HR) <1 implies a lower risk of death for patients treated with first-line gefitinb.

post-protocol chemotherapy

The chemotherapy regimens employed in NEJ002 are summarized in Table 2. Regarding the number of subsequent regimens, >50% of patients had received third-line chemotherapy or more, which was quite compatible with general practice in Japan (Figure 3A).

In the gefitinib group, 82 patients (72%) received at least one subsequent regimen. Among these, 74 patients (65%) were treated with the platinum doublet regimen including a crossover use of CBDCA/TXL in 59 patients (52%). Some patients received pemetrexed (PEM) combined with a platinum agent because it became available for the treatment of NSCLC in Japan in May 2009. Twelve patients went back on gefitinib and 32 received erlotinib in one of their later-line treatments. Among the 32 patients who received no subsequent regimen, 12 (11%) had been still treated with their first-line gefitinib at the data cutoff point (8 patients had still maintained their response to gefitinib, while 4 had continued gefitinib after the documentation of disease progression, in accordance with the patient's wishes). There were various reasons why the other 20 patients (18%) did not receive any subsequent regimens: deterioration of PS due to the progression of NSCLC ($n = 11$), interstitial lung disease due to gefitinib treatment ($n = 3$), exacerbation of co-morbidities ($n = 2$), or in accordance with the patient's wishes ($n = 4$). On the other hand, 113 patients (99%) in the CBDCA/PTX group had received at least one subsequent regimen, of whom 112 (98%) had moved to gefitinib.

The standard second-line chemotherapeutic agents PEM or docetaxel (DOC, Sanofi-Aventis K.K., Tokyo), which are used for advanced NSCLC, were used in 29% and 25% of patients in the gefitinib group, respectively, and in 16% and 19% of those in the CBDCA/PTX group, respectively. More than >20% of patients in both the arms received other agents such as irinotecan, S-1, gemcitabine, vinorelbine, or amrubicin as third- or later-line chemotherapy.

evaluation of the impact of key drugs on OS

To examine the impact of the platinum agent on OS of patients with EGFR-mutated NSCLC, we compared the OS of patients who received both gefitinib and a platinum agent in their treatment ($n = 186$) with that of patients who had never received a platinum agent ($n = 40$) in NEJ002. We found no significant difference between the OS of each group (Figure 3B). The number of patients who received a platinum agent but had not received gefitinib was only two in NEJ002.

We then assessed the impact of standard second-line agents (PEM and DOC) on OS. We divided patients who had received third-line or more in NEJ002 ($n = 131$) into two groups: the first group received EGFR-TKI, platinum agent, and PEM or DOC (P/D group, $n = 76$), and the second group received EGFR-TKI, platinum agent, but neither PEM nor DOC (no P/D group, $n = 55$). The MST of the P/D group was significantly longer than that of the no P/D group (34.8 months versus 22.6 months, $P = 0.003$) (Figure 3C).

Table 2. Summary of regimens for entire treatment in NEJ002

	Second-line *n* (%)	Third- or later-line *n* (%)	Total *n* (%)
First-line gefitinib group (*n* = 114)			
EGFR-TKI	8 (7.0)	34 (29.8)	114 (100)
Gefitinib	2 (1.8)	10 (8.8)	114 (100)
Erlotinib	6 (5.3)	26 (22.8)	32 (28.1)
Chemotherapy	74 (64.9)	52 (45.6)	76 (66.7)
Platinum based	71 (62.3)	11 (9.6)	74 (64.9)
CBDCA/PTX[a]	56 (49.2)	3 (2.6)	59 (51.8)
Platinum/PEM[b]	11 (9.6)	4 (3.5)	15 (13.2)
PEM (monotherapy)	2 (1.8)	16 (14.0)	18 (15.8)
DOC	0	28 (24.6)	28 (24.6)
Others[c]	1 (0.9)	26 (22.8)	27 (23.7)
First-line CBDCA/PTX group (*n* = 114)			
EGFR-TKI	109 (95.6)	42 (36.8)	112 (98.2)
Gefitinib	109 (95.6)	8 (7.0)	112 (98.2)
Erlotinib	0	33 (28.9)	33 (28.9)
BIBW2992	0	2 (1.8)	2 (1.8)
Chemotherapy	3 (2.7)	52 (45.6)	114 (100)
Platinum based	2 (1.8)	9 (7.9)	114 (100)
CBDCA/PTX	1 (0.9)	1 (0.9)	114 (100)
Platinum/PEM	0	4 (3.5)	4 (3.5)
PEM (monotherapy)	0	14 (12.3)	14 (12.3)
DOC	1 (0.9)	21 (18.4)	22 (19.3)
Others[c]	0	26 (22.8)	26 (22.8)

CBDCA/PTX, carboplatin plus paclitaxel; PEM, pemetrexed; EGFR-TKI, epidermal growth factor receptor tyrosine kinase inhibitor; DOC, docetaxel.
[a]Includes two CBDCA/PTX plus bevacizumab.
[b]Includes one CBDCA/PEM plus bevacizumab.
[c]Includes irinotecan, S-1, gemcitabine, vinorelbine, and amrubicine.

discussion

Although the NEJ002 study met its primary endpoint, in that gefitinib was superior to CBDCA/PTX in PFS, OS data were also important in evaluating the efficacy of the entire treatment including the regimens investigated. The current updated analysis demonstrated that the treatment course initiated with gefitinib achieved OS at least equivalent to a traditional treatment course initiated with a platinum doublet regimen for patients with advanced NSCLC harboring a sensitive EGFR mutation. Since the median follow-up time increased from 17 months in the previous report to 23 months in the current analysis, the OS results should become more accurate. We have already reported that the QOL was significantly better in the gefitinib group than in the CBDCA/PTX group in NEJ002 [16]. Moreover, gefitinib attained a high response rate, rapid improvement of symptoms, and exhibited low toxicity. Taking these factors together, we recommend the use of gefitinib as the first-line treatment.

There is a conservative opinion which states that the platinum doublet regimen should still be used as the first-line treatment for advanced NSCLC. This is because there has been no prospective study showing superiority of first-line EGFR-TKI over platinum doublet regimens for OS. Furthermore, some retrospective analyses have suggested that EGFR-TKI might be similarly effective in EGFR-mutated NSCLC regardless of the line at which it is used [17]. However, it is very important to recognize from our study that, though almost 100% of patients in the CBDCA/PTX group crossed over to gefitinib, the OS curve of the first-line gefitinib group was not inferior to that of the CBDCA/PTX group. While the risk associated with missing the administration of platinum agents after first-line gefitinib may be of concern, our *post-hoc* analysis suggested that the impact of the platinum agent on OS would not be larger than that of EGFR-TKI for patients with EGFR-mutated NSCLC. Figure 3B shows the MST of patients treated without platinum to be >2 years, which is a quite favorable result compared with previous historical data obtained when EGFR-TKI was not available. Thus, we feel that it is a concern if the chance to use gefitinib is missed when chemotherapy is carried out as the first-line treatment. The extremely high crossover rate in NEJ002 is hard to attain in general practice. In fact, only 51.5% of patients in the first-line CBDCA/PTX group received subsequent EGFR-TKI in the IPASS study [12]. Thus, we strongly recommend that the best drug should be used in the first instance.

Patients in the first-line gefitinib group tend to be treated with PEM or DOC monotherapy more intensively; this was because we supposed that some of these did not receive platinum doublet treatment for various reasons. However, we consider that the ideal treatment strategy for appropriate patients is to make use of available standard drugs. The most important finding in the *post-hoc* analysis shown in Figure 3C was that patients treated with EGFR-TKIs, platinum, and

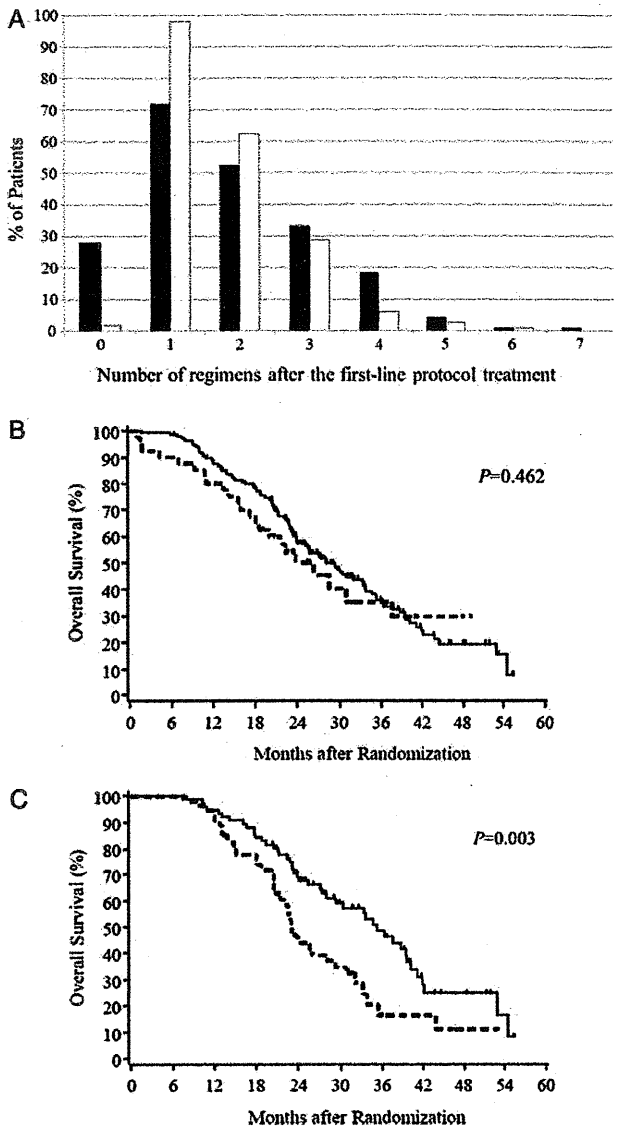

Figure 3. Evaluation of the impact of subsequent treatment on overall survival (OS) in NEJ002. The number of regimens that patients received after the first-line treatment with gefitinib (black bar) and that with chemotherapy (white bar) (A). The OS of patients treated with whichever line of gefitinib but not platinum (a dotted line) and those treated with both gefitinib and platinum (a solid line) (B). The OS of patients treated with gefitinib, platinum, with pemetrexed (PEM) and/or docetaxel (DOC; a solid line), and those treated with gefitinib, platinum but neither pemetrexed nor docetaxel (a dotted line) (C).

PEM/DOC achieved MST of around 3 years even though they had systemically advanced disease; however, the analysis may not conclusively show the difference between the two groups because they were not randomly assigned. This suggests that patients with EGFR-mutated NSCLC and with good PS enough to complete many lines of treatment may further benefit from a proper use of the above mentioned 'key drugs'. Although PEM and DOC were equally recognized as standard second-line agents at the time of the NEJ002 study [18], we now consider PEM to be more appropriate for EGFR-mutated NSCLC where adenocarcinoma is much common [14]. Since at least 14 patients (12%) failed to move to subsequent chemotherapy and ~20% of patients had never received platinum agents or PEM after their disease progressed in the gefitinib group, we think there may be a room for improvement of OS in these populations. Thus, we are now investigating a new treatment strategy, in which the first-line gefitinib is combined with CBDCA and PEM, for patients with EGFR-mutated NSCLC (UMIN000002789).

There are some limitations in the current analysis. First, the sample size of NEJ002 had inadequate power for evaluation of the difference in OS between the two groups. Since death events in one-third of patients have not yet occurred, the true OS curve may change slightly from that shown in this report. A meta-analysis combining several phase III studies and comparing EGFR-TKI with platinum doublet in an EGFR-mutated NSCLC population would be warranted. Second, the *post-hoc* analysis on subsequent chemotherapies may have been biased, because post-protocol treatments were not restricted under the NEJ002 protocol; however, they were very similar to those used in general practice in Japan. In addition, the unplanned comparative analysis between the subgroups shown in Figure 3B and C cannot draw definitive conclusions. It may be difficult to find whether the additive effect of platinum agents or PEM/DOC or good PS itself, that enabled patients to receive those agents irrespective of chemotherapy effects, influenced survival prolongation in the superior group more directly. However, we believe that they give us some interesting suggestions for future investigations such as that underway in our new study.

The reason there was no significant difference in OS between the first-line gefitinib group and the first-line CBDCA/PTX group in NEJ002 was very likely a high rate of crossover use of gefitinib in the CBDCA/PTX group. Considering the many benefits from EGFR-TKI use and the risk of missing an opportunity to use the most effective agent for treatment of EGFR-mutated NSCLC, the first-line gefitinib is strongly recommended in general practice for this population.

funding

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disclosure

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ORIGINAL ARTICLE

Bevacizumab plus chemotherapy for advanced non-squamous non-small-cell lung cancer with malignant pleural effusion

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Abstract
Purpose The presence of malignant pleural effusion (MPE) indicates a poorer prognosis for patients with non-small-cell lung cancer (NSCLC) and impairs their quality of life. Because vascular endothelial growth factor (VEGF) is the key mediator MPE production, we evaluated the efficacy and safety of chemotherapy plus bevacizumab, an anti-VEGF antibody, in non-squamous NSCLC patients with MPE, especially regarding the control of pleural effusions.
Methods From November 1, 2009 to September 30, 2011, medical charts of 13 consecutive patients with MPE who received bevacizumab plus chemotherapy as the initial or secondary treatment were retrospectively analyzed.
Results Of the 13 patients, 6 did not undergo pleurodesis, 3 were unsuccessfully treated by pleurodesis, 2 had encapsulated pleural effusion, and 2 had no re-expansion of the lung. Twelve patients (92.3 %) achieved MPE control lasting >8 weeks following bevacizumab plus chemotherapy. Five of 10 patients with measurable lesions had confirmed partial responses. Of 3 patients without measurable lesions, one had confirmed CR. Median progression-free survival time without re-accumulation of MPE was 312 days. Grade 3 or 4 neutropenia, thrombocytopenia, hypertension, or proteinuria was observed in 2, 2, 1, or 1 patient, respectively.
Conclusions This is the first study to report that bevacizumab plus chemotherapy is highly effective for the management of MPE in non-squamous NSCLC patients. Prospective clinical trials are warranted to investigate the efficacy of bevacizumab for MPE.

Keywords Non-small-cell lung cancer · Bevacizumab · VEGF · Malignant pleural effusion · Personalized therapy

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Introduction

Malignant pleural effusion (MPE) occurs in approximately 15 % of lung cancer patients and is a significant problem during the entire course of patient management [1, 2]. Intrapleural therapy by means of a chest tube, using sclerosing or chemotherapeutic agents, has been widely used for the treatment for symptomatic MPE. Intrapleural injections of sclerosing agents, for example talc and OK-432 (a preparation of *Streptococcus pyogenes*), as well as pleurodesis and chemotherapeutic agents such as bleomycin, are currently in use. Prospective studies of intrapleural therapy with talc or bleomycin for MPEs reported that the success rate for controlling pleural effusions was 37–84 % at 3 months from the start of treatment [3–8]. One study suggested that pleurodesis together with OK-432 was more effective than intrapleural injections of bleomycin or cisplatin and etoposide, but the 4-week pleural effusion-free survival rate was only 75.8 % [9]. Thus, the efficacy of current intrapleural therapy is poor and must be improved. Furthermore, intrapleural therapy is unsuitable for patients without full lung re-expansion after chest tube drainage. To

date, there are no reports of successful treatment by intrapleural therapy in patients without full lung re-expansion after tube drainage.

VEGF plays an essential role in malignant effusion formation [10–14]. It is a potent growth factor for endothelial cells and not only induces the formation of new blood vessels, but also accelerates vascular permeability. Cancer cells invade the pleural cavity or metastasize to it, and their proliferation results in the production of large amounts of VEGF, a factor 50,000 times more potent than histamine in causing vascular permeability. Thus, VEGF is thought to induce effusion formation and accumulation [15, 16]. Consistent with this, the level of VEGF is high in malignant effusions from various malignancies, including mesotheliomas, breast, and lung cancers [13, 17–21]. Accordingly, the inhibition of VEGF activity with bevacizumab, a recombinant humanized monoclonal antibody to VEGF, may lead to improved management of MPE. Bevacizumab, neutralizing the biologic activity of VEGF, reduces the vascularization of tumors and may prevent MPE accumulation.

The main purpose of the study was to evaluate the efficacy and safety of bevacizumab plus chemotherapy for controlling MPE.

Patients and methods

Patients

We retrospectively reviewed the medical charts of all non-squamous NSCLC patients with MPEs who received bevacizumab plus chemotherapy from November 1, 2009 to September 30, 2011 at Nippon Medical School and Tsuboi Cancer Center Hospital. Of 35 NSCLC patients treated with bevacizumab plus chemotherapy, 13 had MPE. In this term, there were 85 NSCLC patients with MPE. Except for 13 patients treated with bevacizumab, 31, 22, and 19 patients received only chemotherapy or epidermal growth factor receptor tyrosine-kinase inhibitor, or intrapleural therapy, or thoracentesis, respectively. MPE was defined as cytologically proven or exudative, and no other cause such as heart failure or atelectasis was present.

Clinical assessments

Response rate (RR), disease control rate (DCR), pleural effusion control rate (PECR), progression-free survival time (PFS) without re-accumulation of MPE, and the adverse events of treatment were analyzed. We defined re-accumulation as an unequivocal increase compared to baseline MPE on a chest radiograph or a computed tomography scan. The antitumor effect was evaluated according to the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). The response rate was taken as the percentage of patients who had a complete response (CR) or partial response (PR). The disease control rate was the summed percentage of patients with CR, PR, and stable disease (SD). The pleural effusion control rate (PECR) was defined as the percentage of patients without re-accumulation of MPE for eight weeks from the start of treatment. Because the objective evaluation of PR had to be done after at least 8 weeks of treatment, the pleural effusion was evaluated by computed tomography at that time. All patients except one, who had acute progressive disease with re-accumulation of MPE, received a CT scan at 8 weeks or later. Progression-free survival time (PFS) without re-accumulation of MPE was calculated from the time of starting bevacizumab-based therapy until the day on which pleural effusion increased again regardless of whether or not other aspects of the disease progressed, or the day of death regardless of cause. For the assessment of adverse events, the National Cancer Institute Common Terminology Criteria for Adverse Events grading system was used (CTCAE, version 4.0). The Kaplan–Meier method was employed to estimate PFS without re-accumulation of MPE.

Results

Patients' characteristics

The characteristics of the 13 patients are shown in Table 1. Six patients did not undergo chest tube drainage or pleurodesis with sclerosing agents. Three patients treated with intrapleural OK-432 had subsequent re-accumulation of MPE. Two patients had encapsulated pleural effusion and two patients had no re-expansion of the affected lung after tube drainage. In these four patients with abundant pleural effusion for a long time, pleurodesis failed. They were also evaluated in the study.

Bevacizumab-based chemotherapy was first-line treatment in 10 patients and secondary chemotherapy in the remaining three. All patients received carboplatin to area under the curve (AUC) of 6 (Calvert's formula), bevacizumab 15 mg/kg and paclitaxel 200 mg/m^2, pemetrexed 500 mg/m^2, or docetaxel 60 mg/m^2 on day 1. Pemetrexed or docetaxel was administered as a part of the clinical study. Three patients were practically treated with second-line chemotherapy chosen at attending physicians, plus bevacizumab. The patients treated with pemetrexed were supplemented with folic acid and vitamin B_{12}. All chemotherapy cycles were repeated every three weeks for up to six cycles. Patients who had not progressed on the above protocols received bevacizumab 15 mg/kg or bevacizumab 15 mg/kg plus pemetrexed 500 mg/m^2 as maintenance

Table 1 Characteristic of patients with malignant pleural effusions

Variable	First line	Second line
Patients, *n*	10	3
Gender, *n*		
Male	7	1
Female	3	2
Age (yr)		
Median	65.5	62
Range	41–75	61–78
ECOG PS, *n*		
0	5	0
1	4	2
2	1	1
Histology, *n*		
Adenocarcinoma	6	3
The other	4	0
EGFR mutation, *n*		
Positive	1	1
Negative	9	2
Regimen of combined chemotherapy, *n*		
CBDCA + PEM	5	1
CBDCA + PTX	3	2
CBDCA + DTX	2	0

n number of patients, *ECOG PS* Eastern Cooperative Oncology Group performance status, *EGFR* epidermal growth factor receptor, *CBDCA* carboplatin, *PEM* pemetrexed, *PTX* paclitaxel, *DTX* docetaxel

therapy every three weeks until disease progression. If necessary, doses were reduced and the start of treatment was delayed, as appropriate. Three patients had received previous chemotherapy, including one with an epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitor (EGFR-TKI). Chemotherapy regimens were as follows: carboplatin plus pemetrexed, $n = 6$; carboplatin plus paclitaxel, $n = 5$, carboplatin plus docetaxel, $n = 2$.

Efficacy

Of the 13 patients, 12 controlled their pleural effusions (overall PECR, 92 %). The treatment was successful in one of the two patients without re-expansion of the affected lung after tube drainage (Table 2). The only patient whose MPE could not be controlled had an enormous mass on his mediastinum with a great deal of MPE; the affected lung had not re-expanded after tube drainage. His cancer progressed rapidly to aggravate his condition and resulted in his death 53 days after the start of treatment.

Of the 10 patients with measurable lesions, 5 had confirmed PR, 4 SD, and 1 progressive disease (PD). Of the 3 patients without measurable lesions, one had a confirmed CR and 2 had non-CR/non-PD with reduction in MPE.

Table 2 Summary of pleural effusion control

	n	Successful number of patients in pleural effusion control, *n*	PECR (%)
Patients unsuccessfully treated with pleurodesis	3	3	100
Patients treated without pleurodesis	6	6	100
Patients with encapsulated effusions	2	2	100
Patients without full lung expansion following tube drainage.	2	1	50
Total	13	12	92

n number of patients, *PECR* pleural effusion control rate

Median PFS without re-accumulation of MPE was 312 days as shown in Fig. 1.

Safety

Table 3 shows the grade 3 or 4 adverse events that occurred in this study. Grade 4 neutropenia was seen in 2 patients and grade 3 thrombocytopenia in another two. Grade 3 hypertension and proteinuria occurred in one patient. No thrombosis or bleeding of any grade was observed in this study.

Discussion

Our study demonstrated that bevacizumab plus chemotherapy is effective for the management of MPE. Of the 13 patients treated with bevacizumab plus chemotherapy, the overall pleural effusion control rate (PECR) was 92 % and progression-free survival time without re-accumulation of MPE was 312 days.

An experimental study reported that animals pretreated with anti-VEGF antibody showed significant reduction in pleural fluid accumulation after pleurodesis [22]. Several other animal studies showed that intraperitoneal administration of anti-VEGF antibodies caused impressive and often complete remission of local fluid accumulation in mice with malignant ascites [23–27]. A clinical report has shown that intravenous injection of bevacizumab was highly successful and safe in two patients with malignant ascites caused by colorectal cancer and adenocarcinoma of unknown origin; these patients had markedly decreased plasma VEGF levels on treatment [28]. Two other studies reported that malignant ascites accumulation was successfully diminished in a small number of patients treated by intravenous or intraperitoneal injections of bevacizumab [29, 30]. However, to the best of our knowledge, no clinical

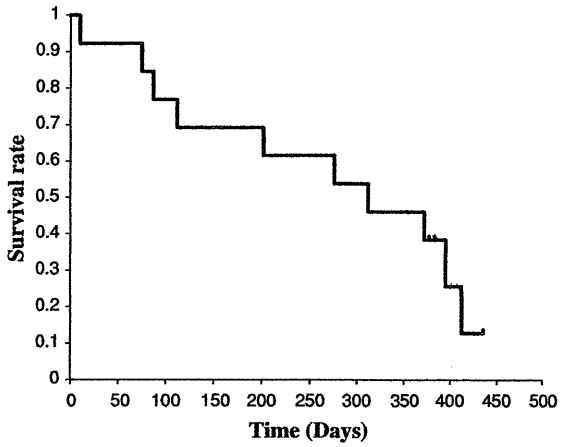

Fig. 1 Kaplan–Meier curve of progression-free survival without re-accumulation of malignant pleural effusion

Table 3 Number of patients with drug-related severe adverse events (CTCAE version 4.0)

	Grade 3	Grade 4
Leukopenia	1	1
Neutropenia	0	2
Thrombocytopenia	2	0
Hypertension	1	0
Proteinuria	1	0

CTCAE the National Cancer Institute Common Terminology Criteria for Adverse Events

studies showing that bevacizumab is effective in pleural effusion control have been published.

Several randomized studies indicated that bevacizumab combined with chemotherapy improved PFS in advanced non-squamous NSCLC patients [31, 32]. The E4599 study which compared carboplatin plus paclitaxel with or without bevacizumab demonstrated a 2-month increase in median OS with the addition of bevacizumab to chemotherapy, but adverse events, including toxicity-associated deaths, were significantly increased [31]. However, the planned confirmatory Avastin in Lung (AVAiL) study which compared cisplatin plus gemcitabine with or without bevacizumab failed to show an OS benefit [32, 33]. Thus, the role of bevacizumab in the treatment for advanced non-squamous NSCLC patients is controversial. It is crucial to identify biomarkers for selecting suitable patients in order to improve efficacy and safety, but there are none currently available for bevacizumab treatment. In recent years, evidence has emerged that personalized therapy improves the outcome of patients with advanced NSCLC. As biomarkers predicting efficacy and safety of bevacizumab are absent, the clinical condition of patients may have to act as a surrogate marker for treatment with this antibody. Bevacizumab plus chemotherapy might be an optimal individual treatment for non-squamous NSCLC patients with MPE.

The present study has several limitations. First, it was retrospective and had a small sample size. Second, the chemotherapy regimens that were used differed according to the patients' condition. Finally, the vague end point was determined, because there was no consensus definition of MPE control. For this reason, the efficacy of treatment should be interpreted with caution. However, consecutive patients with MPE who received bevacizumab and chemotherapy were evaluated. It is notable that bevacizumab plus chemotherapy succeeded even in one of the patients without full lung re-expansion after tube drainage.

Conclusion

In conclusion, our analysis suggests that bevacizumab plus chemotherapy might be a new personalized therapeutic option for non-squamous NSCLC patients with MPE. In particular, these findings may be relevant to treating patients for whom pleurodesis is not successful and who fail to fully expand the lung after tube drainage. To confirm these results, prospective studies are needed. The North-East Japan study group (NEJ) has started two prospective studies aimed at evaluating the efficacy of bevacizumab plus carboplatin and pemetrexed in chemo-naïve patients with non-squamous NSCLC and MPE. In one of the two studies, the treatment is being performed in the patients without tube drainage; in the other study, treatment is being carried out in patients with re-accumulation of MPE after pleurodesis, or in those without re-expansion of the affected lung after tube drainage. The results of these ongoing trials should help resolve this issue.

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Conflict of interest Akihiko Gemma has received lecture fees from Chugai Pharmaceutical Company. The other authors indicated no potential conflicts of interest.

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私はこう治療する

今月のテーマ

GGN（ground glass nodule）の診断と治療

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胸部CT検診の普及に伴い，胸部X線では同定困難な小型結節陰影が発見される機会が増えている．すりガラス状結節陰影（ground glass nodule;GGN）の取り扱いは，時に難しいことがある．GGNに対する診断と治療のアプローチについて概説する．

GGNとは

肺結節は，最大径3 cm以下の円形，あるいは，辺縁が不整な吸収値上昇領域である[1]．すりガラス陰影は，thin slice CT（TS-CT）上において，内部に肺血管や気管支の辺縁を認める吸収値である[1]．肺結節は，TS-CT上の肺結節の性状により，均一なすりガラス陰影（pure ground glass opacity;pure GGO），一部軟部組織吸収値を含むすりガラス陰影（mixed GGO），軟部組織吸収値を呈する陰影（solid nodule）に分類される．2011年，肺腺癌の国際分類が改訂され，そこでは，pure ground-glass nodule（GGN），part-solid noduleの用語を使用しているため，pure GGOをpure GGNに，mixed GGOをpart-solidと表記することが，CT検診学会で提唱されている[1]．典型的な画像を**図1**に示す．

GGNの病理：野口分類と腺がんの新国際分類

TS-CT上のGGNは，異形腺腫様過形成または肺腺癌である頻度が高い．1995年Noguchiらは，外科的に切除した2 cm以下の末梢発生の小型肺腺癌をreplacement type growthとnon-replacement type growthに大別し，それぞれを3種類に亜分類した[2]（**表1**）．Type A～Cはがん細胞が肺胞に沿って増殖する形態で，肺胞が保たれているため腫瘍内に空気が含まれる．一方で，type D-Fはがん細胞が重積し，肺胞を破壊しながら増殖し，腫瘍内に空気が含まれない．type A，Bではがんは上皮内に限局し，上皮内がん（adenocarcinoma in situ;AIS）と考えられており，type Cとなると間質に浸潤のある浸潤がんになる．これらの病理分類はTS-CT上の画像所見とよい相関があり，Noguchi type AはGGN，type B，CはGGNないしpartial solid所見を呈し，type D，E，Fはsolid nodule所見を呈することが多い．腺がんの瘢痕部分は，TS-CT上，充実成分の一部として観察され，partial solid所見を呈する．

2011年，世界肺癌学会（International Association for the Study of Lung Cancer;IASLC），アメリカ胸部疾患学会（American Thoracic Society;ATS），欧州呼吸器学会（European Respiratory Society;ERS）が共同で，新しい肺腺癌分類を発表した．ここでは，BACという名称が廃止され，従来のBACは，Adenocarcinoma in situ（AIS），Minimal invasive adenocarcinoma（MIA），Invasive adenocarcinoma，lepidic predominantに分類された[3]．Noguchi A，BがAISに，Noguchi A，BとCの中間型がMIAに，Noguchi Cが

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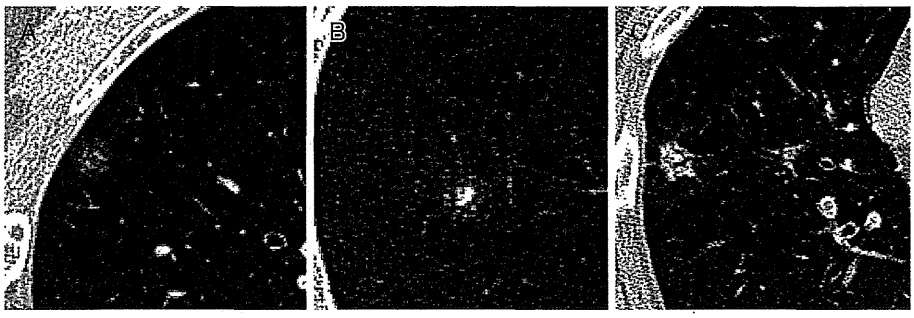

図1　末梢小型肺癌のHR-CT
A:pure GGN，B:part solid GGN，C:solid nodule

表1　野口分類

replacement type growth	
type A	localized bronchioloalveolar carcinoma（LBAC）
type B	LBAC with foci of collapse of alveolar structure
type C	LBAC with foci of active fibroblastic proliferation
non-replacement type growth	
type D	poorly differentiated adenocarcinoma
type E	tubular adenocarcinoma
type F	papillary adenocarcinoma with compressive and destructive growth

（文献2）より作成）

Invasive adenocarcinoma，lepidic predominantにそれぞれ対応するものと考えられる．

GGNの予後

GGNの予後は病理像による．野口分類A，Bではリンパ節転移がなく，手術成績は良好で，5年生存率は100%である．type Cになると28%がリンパ節転移を有するようになり，5年生存率は74.8%と減少する[2]．また，線維芽細胞の増殖巣が線維化巣全体の10%以下の場合，type C'と分類され，5年生存率は100%とされる[4]．肺腺癌の新分類では，AIS（野口分類A，Bに相当），MIA（MinamiらのC'に相当[4]）であれば，完全切除されれば，5年生存率は100%である．

GGOの経過観察

結節の性状により，経過観察の方法が異なる（図2）．

1．pure GGNの場合

大きさが15 mm以上であれば，手術を含めた確定診断を行う．15 mm未満の場合は，TS-CTにて3か月，12か月，24か月後と経過観察を行い，①増大あるいは濃度上昇，②内部に5 mm以上のsolid成分が出現した場合には確定診断を実施する．24か月後不変の場合年1回の経過観察CTを実施する．

2．part-solidの場合

15 mm以上の場合は，確定診断をつける．15 mm以下の場合，炎症性病変の可能性もあるため，3か月後のTS-CTにて縮小や消失していない場合は確定診断をつける．

3．solid noduleの場合

10 mm以上の場合，原則として確定診断を実施する．TS-CT上で大きさが5 mm以上10 mm未満の場合，喫煙者は非喫煙者と比較して腫瘍倍加時間が短いため，間隔を変えて経過観察する．

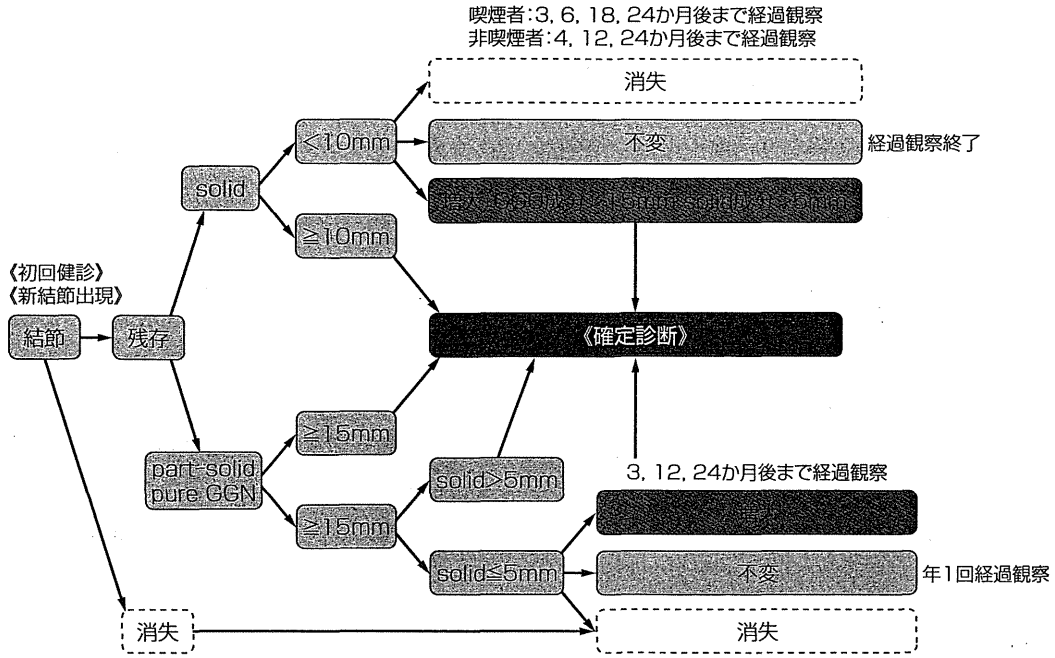

図2　GGNの経過観察
（文献1）より作成）

すなわち，喫煙者では3，6，12，18，24か月後まで，非喫煙者では，4，12，24か月まで経過観察を行う．画像所見で肺内リンパ節転移が強く疑われるならば，大きさにかかわらず3か月後の経過観察を行い，不変であれば，12か月後まで経過観察を行う．

4．経過観察中に新しい結節を認めた場合

新しい結節がsolid noduleで10 mm以上であれば確定診断を実施し，10 mm未満であれば，喫煙者の場合は1，3，6，12か月後，非喫煙者であれば1，4，12か月と経過観察をし，不変の場合は，1年ごとに健診を行う．part-solidやpure GGNの場合は，4か月後で消失や縮小していない場合，かつpart-solidの場合，solidの成分の増大がない場合は12か月後に経過観察する．12か月後でも不変の場合は年ごとでの経過観察とする[1]．

確定診断

GGNの確定診断には，病理診断が必須である．気管支鏡検査，CTガイド下生検などが試みられる．超音波気管支鏡やガイドシースの併用によりGGNに対する術前確定診断率も上昇傾向にあるが，100%の確定診断は得られないため，胸腔鏡手術による診断，治療を一期的に実施することが多い．

GGNに対する手術

GGNが肺癌と診断された場合，および，肺癌が疑われるが他の検査により病理診断が困難な場合には，手術適応である．ただし，GGNの予後は一般的に良好であり，患者の年齢，performance status（PS），肺機能，合併疾患の有無などを考慮したうえで，手術適応となるかを検討する．肺葉切除が肺癌の根治治療としては標準的である．肺葉切除群と縮小手術群（区域・部分切除）を比較した，Lung Cancer Study Group（LCSG）による第3相試験（1995年）では，縮小手術群で有意に局所再発率が高く，予後不良である[5]．しかし，GGNを示す非浸潤癌の発見の

頻度が高くなってきており，LCSGの結果が，GGNに当てはまるかは不明であり，縮小手術の妥当性も議論されるようになってきている．2cm以下のpure GGNの場合は，術中迅速診断にて病理学的にAAHやtype A，Bであれば，リンパ節転移がなく予後良好なことが期待されるため，肺楔状切除や部分切除で治癒する可能性が高い[2]．Okadaらが2006年に報告した多施設共同前向試験では，2cm以下の肺癌に対して肺葉切除と縮小手術（区域切除）を行い，5年生存割合は縮小手術（区域切除）群と肺葉切除群で同様で，局所再発にも差がないとされ，縮小手術の有用性が示されている[6]．

おわりに

1993年東京から「肺がんをなくす会」で始まった低線量CT肺がん検診は，2010年アメリカでの大規模ランダム化比較試験（National Lung Screening Trial）により，喫煙者肺癌による死亡率を20%低減させることが証明された[7]．TS-CTによる画像診断と詳細な病理所見の対比により，上皮内癌ないし微少浸潤，肺胞置換，lepidic pattern進展形式を呈する予後良好な肺腺癌の存在が明らかとなり，胸腔鏡による縮小手術が可能となった．この分野における日本の貢献は大きいが，CT検査被曝により約3%の上乗せ発がん率を危惧する報告もある[8]．画像診断が必ずしも病理像と一致しない場合や，経過観察中の思わぬ増大，患者判断による経過観察からの脱落などの問題もあり，GGN治療方針の決定においては，EBMもさることながら，患者との十分な情報共有が必須と考える．

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