Table III. *Molecular analysis of circulating tumor cell (CTCs).*

Case	CTC (n/7.5 ml)	KRAS		RNAS extraction
		In CTC	In tissue sample	
2	2	Wild-type*	O Wild-type*	nd
3	4	NA		nd
	28	Wild-type*		nd
	73	nd	× (G13D)	NO
	18	nd		NO
	12	nd		NO
5	1	Wild-type*	O Wild-type	nd
12	1	NA	(G12V)	nd
13	1	Wild-type*	× (G13D)	nd

NA, Not amplified; nd, not done; NO, not extracted; O, match; X, no match.

the *KRAS* G13D mutation, analysis of CTC DNA from the same cases did not yield any result (Table III). The CTC DNA obtained from our examination seemed to be inadequate for *KRAS* Scorpion-ARMS analysis. We also made three attempts to obtain RNA from the CTCs captured in case 3, where the number of CTCs was 12, 18, and 73, but all failed (Table III).

Discussion

CTCs have been recently detected in various types of cancers, including colonic, breast, and prostatic cancer (11, 12). The importance of CTC analysis has been proposed, including its use as a prognostic or predictive biomarker. In this study, we examined the practical availability of CTC analysis using the CellSearch system, which involves outsourcing the analysis to a commercial laboratory. The detection rate and the number of cells identified were rather low, even in stage IV CRC. Previous studies reported detection rates of over two CTCs per 7.5 ml of blood in 30-40% of patients with metastatic CRC (4-6); in patients with metastatic breast and prostate cancer, the same rate was observed in 60% of the patients (11, 12). Our observations are similar to the former.

In general, the number of CTCs in patients with metastatic CRC seems to be lower than that observed in patients with metastatic breast cancer. The cell surface markers used in the CellSearch system (*i.e.* cytokeratin and adhesion-related EpCAM) may be less abundant in patients with metastatic CRC compared with those with metastatic breast cancer. Another possibility is that a fraction of the CTCs may transform to mesenchymal cells through epithelial mesenchymal transition (EMT). This EMT may be more frequent in CTCs from metastatic CRC than from those in metastatic breast cancer. The method used to collect CTCs may require modification according to the type of cancer. Immunomagnetic separation has been reported to improve CTC detection rates. For example, cytokeratin 20 was positive in CTCs in 92.9% of patients with metastatic CRC after column immunomagnetic separation (5).

Many reports describe a relationship between therapeutic outcomes and baseline number of CTCs or number of CTCs during therapy (5, 6, 9). However, in this study, there was no correlation between the number of CTCs during therapy and the outcomes. This observation may be due to the low detection rate of CTCs in metastatic CRC. Once CTCs are detected, the change in the number of CTCs could be a good predictive marker of ongoing treatment, as shown in our cases. In contrast to single measures of CTC number (either baseline or during therapy), changes in CTC counts during therapy could be used to determine whether to continue or change the therapy. Prospective studies should be conducted in the future to clarify these points.

CTCs are viewed as a good source of DNA and RNA for analyses (13-15). However, the DNA obtained using the CellSearch system was not suitable for *KRAS* Scorpion-ARMS analysis in this study. The PCR conditions, such as primer sequences, composition of reaction buffer, and annealing temperature, may require modification. RNA was not recovered from CTCs using the CellSearch system.

Recently, circulating DNA was shown to be useful for identifying acquired resistance to antibodies to EGFR in metastatic CRC (16). This method seems to be much more potent than CTC analysis for *KRAS* mutation detection. However, a next generation sequencer is necessary to use this method, and the balance between cost and effectiveness should be discussed before choosing this method for daily clinical use. Furthermore, CTCs may be rich in molecular information derived from RNAs or proteins rather than DNA. Analysis of these molecules may be advantageous over that of circulating DNA.

Acknowledgements

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《各論：がん腫別薬物療法》

3 大腸癌

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ポイント

- 大腸癌はわが国で年間約10万人が罹患し，4万人が死亡する主要ながんである．
- 転移を伴う全身病変としての大腸癌の治療においては薬物療法の進歩がいちじるしく，予後の改善が得られている．
- 薬物療法は術後補助化学療法と切除不能がんに対する薬物療法で目的が異なるが，近年では薬物療法後に転移巣の治癒切除が行われることも少なくない．
- 標準レジメンは殺細胞性抗がん剤，分子標的薬の組み合わせによる多剤併用療法であるが，個々の症例においては治療目標，治療のラインや患者の全身状態によって選択する必要がある．

キーワード 殺細胞性抗がん剤多剤併用療法，抗VEGF抗体薬，抗EGFR抗体薬，大腸癌治療ガイドライン

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はじめに

大腸癌（直腸・結腸癌）はわが国において罹患数は胃癌に次いで2位，死亡数では全体で3位，女性のがん死亡の1位をしめる悪性腫瘍である．本稿では近年，急速な進歩を遂げている大腸癌の補助化学療法，切除不能がんにおける薬物療法について解説する．

◉大腸癌薬物療法に用いられる薬剤

保険適応があり，実臨床で主に用いられているのは以下の薬剤である．

①殺細胞性抗がん剤：（注射薬）：5-FU（5-フルオロウラシル），5-FU＋LV（leucovorin），イリノテカン（CPT-11），オキザリプラチン（L-OHP），（経口薬）：UFT，UFT＋LV錠，capecitabine，S-1．

②分子標的薬：ベバシズマブ，セツキシマブ，パニツムマブ．

殺細胞薬としてのキードラッグは，5FU，CPT-11，L-OHPの3剤であり，切除不能大腸癌の治療では，この3剤を使い切ることが全生存期間の延長に寄与する．経口薬はいずれも5FUのプロドラッグやその配合剤である．

分子標的薬のうち抗VEGF抗体，ベバシツマブは血管新生阻害剤であり，単剤では抗腫瘍効果を示さず，抗がん剤との併用により無増悪生存期間，全生存期間への上乗せ効果が証明されている．ベバシツマブの感受性と相関するバイオマーカーは見つかっていない．頻度の高い副作用として，高血圧症，たんぱく尿，鼻出血があるが，多くの場合コントロール可能であり，使いやすい併用分子標的薬である．しかし，低頻度であるが重篤になり得る副作用として血管塞栓症，消化管穿孔があり，適応に際して注意が必要である．腸管穿孔に関して，原発巣が残存していることは併用の妨げにはならないが，狭窄やがん性腹膜炎に伴う通過障害がある場合は慎重を要する．

抗EGFR抗体であるセツキシマブ，パニツムマブは，EGFRの下流の増殖シグナルを抑制す

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表　切除不能・進行・再発大腸癌に対する薬物療法選択の考え方

		一次療法	二次療法	三次療法
KRAS 変異型	多剤併用療法可能	FLOFIRI±ベバシツマブ mFOLFOX±ベバシツマブ CapeOX±ベバシツマブ	mFOLFOX±ベバシツマブ FLOFIRI±ベバシツマブ IRIS±ベバシツマブ イリノテカン±ベバシツマブ	
	多剤併用療法不能	s5FU±ベバシツマブ Caecitabine±ベバシツマブ	状態改善の場合，再検討	
KRAS 野生型	多剤併用療法可能	KRAS 変異型と同じ一次療法 FOLFIRI＋セツキシマブ mFOLFOX＋パニツムマブ	KRAS 野生型と同じ二次療法 FOLFIRI＋セツキシマブ FOLFOX＋パニツムマブ イリノテカン＋セツキシマブ or パニツムマブ FOLFOX，CapeOX（±ベバシツマブ） FLOFIRI イリノテカン単剤（±ベバシツマブ）	セツキシマブ，または パニツムマブ ±イリノテカン
	多剤併用療法不能	KRAS 変異型と同じ一次療法 セツキシマブ，またはパニツムマブ	状態改善の場合，再検討	

※文献 1～4）からまとめて作成

ることにより，単剤でも抗腫瘍効果を示す．EGFR 下流の遺伝子変異のなかで頻度の高い KRAS 変異型（大腸癌の約 40%）には無効であることが知られており，適応決定前の検査は必須である．KRAS 野生型においても効果が期待できるのは約 4 割であり，高感受性が保証されるわけではない．

❸切除不能転移・再発大腸癌の治療選択

切除不能の転移・再発大腸癌治療では，延命と QOL（Quality of Life）の最大化が目標である．NCCN やわが国の大腸癌治療ガイドラインにおいては一次療法から三次療法までの選択肢がアルゴリズムとして提示されているが，個々の症例をどのように治療していくかは腫瘍内科医の専門性が強く試される機会である．表に筆者の考え方をまとめた．

1．一次療法

KRAS 変異の有無を問わず，下記の治療は推奨される．

可能な場合には多剤併用療法が選択されるが，わが国でもっとも汎用されているのは L-OHP ベース±ベバシズマブのレジメンである．mFOLFOX6 は L-OHP，LV，5FU 急速静注，5FU46 時間持続注から構成される．5FU の代わりに経口薬の capecitabine を用いた CapeOx の効果は FOLFOX と同等と報告されている．L-OHP 投与では次第に末梢神経障害が蓄積するため，高度になる前に L-OHP を休薬し，5FU/LV（or Capesitabine）±ベバシツマブが維持療法として用いられ，その後の増悪の際には L-OHP の再導入は検討される．また，L-OHP の総投与回数が 8 回を超える頃からアレルギーの出現頻度が高くなることに留意する．

FOLFIRI±ベバシツマブは一次療法の良い選択肢である．L-OHP ベースの治療後の二次療法

としてもFOFIRIが選択されることが多いが，FOLFOXとFOLRIRIは，どちらが先行しても全生存期間に差がないとのエビデンスがある．L-OHPでは末梢神経障害，薬剤アレルギー，CPT-11では下痢や脱毛の頻度が高いことなどの毒性のプロファイルを念頭に，患者の希望も考慮したうえで一次療法を選択する．また，年齢やQOLの観点から，多剤併用療法が困難な場合には，5FU/LV（or Capecitabine）±ベバシツマブが一次療法の候補として考慮される．

2．一次療法

KRAS野生型大腸癌の場合，下記の治療は選択肢になり得る．

KRAS野生型の場合は，FOLFOX＋パニツムマブ，FOLFIRI＋セツキシマブなどの抗EGFR抗体併用が選択肢となり得る．抗EGFR抗体については二次療法，三次療法でも，また単剤でも一定の抗腫瘍効果が期待されるので，一次療法から用いる場合の明確な基準はないが，後述するようにconversion therapyを念頭に置いた肝転移治療や，腫瘍量が多く，臨床症状の速やかな改善を目指したい症例などの場合に考慮される．また，殺細胞性抗がん剤が不適の症例では一次療法として抗EGFR抗体薬単剤療法は選択肢になり得る．

3．二次療法

一次療法でキードラッグとしてL-OHP，CPT-11どちらをベースにしたかにより，その逆が二次療法として選択されることが多い．つまり，FOLFOX（CapeOx）→FOLFIRI，FOLFIRI→FOLFOX（CapeOx）が一般的に選択されている．FOLFIRIに代わりわが国で開発されたIRIS療法（S-1，CPT-11併用療法）も選択肢である[3]．また，CPT-11単剤は二次療法として選択しうるが，L-OHPの場合は単独では抗腫瘍効果を示さないので単剤投与は行われない．

ベバシツマブ併用一次療法での増悪後の同剤継続については明確なエビデンスがなかったが，2012年の米国臨床腫瘍学会（ASCO）で，二次療法での継続の優越性を示す第Ⅲ相試験の結果が報告され，抗がん剤レジメン変更後もベバシツマブ併用継続は選択肢となった[4]．

KRAS野生型の大腸癌の二次療法における，抗EGFR抗体併用に関しては，CPT-11＋セツキシマブや，一次療法がL-OHPベースの場合のFOLFIRI＋パニツムマブの有効性が示されている．一次治療で抗EGFR抗体併用療法が行われた症例における二次療法の分子標的薬併用に関してはエビデンスが少ないが，ベバシツマブ併用は選択肢になり得る．

4．三次療法

KRAS野生型の大腸癌において，二次療法までに抗EGFR抗体が用いられていない場合には，（セツキシマブまたはパニツムマブ）±CPT-11が推奨される．CPT-11は，前治療で用いられている場合でも，併用可能であればそのメリットがある．

◉Conversion therapy：薬物療法で縮小した肝転移の切除

切除不能の肝転移が薬物療法効果によりにR0切除可能と再判断された場合は，肝転移切除は推奨される．特定のレジメンを推奨するエビデンスはないが，直接効果が高いことなどから，肝転移単独の場合はFOLFOXが選択されていることが多い．抗EGFR抗体に関しては，CELIM試験で，KRAS野生型大腸癌の肝転移にFOLFOX，FOLFIRIにセツキシマブを併用したレジメン後に高いR0切除率が報告されたが，前向きの比較試験は存在しない．

◉治癒切除後の結腸癌における補助化学療法

R0切除が行われたStage Ⅲ大腸癌には再発抑制，予後改善の目的で術後補助化学療法が推奨される．フルオロウラシルによる補助療法として，①5FU＋LV療法（注射），②UFT/LV療法（経口），③カペシタビン（経口）が，L-OHP併用療法として④mFOLFOX6（注射，持続注），⑤CapOX（経口，注射併用）が用いられている．Stage Ⅲ結腸癌における欧米の標準治療はL-

OHP 併用療法である．まだわが国における長期成績はないが，筆者は少なくとも Stage Ⅲb の症例には積極的に L-OHP 併用療法を用いている．考慮される投与期間はいずれの場合も 6ヵ月が原則であるが，L-OHP の蓄積性の末梢神経障害が残存する場合があるので，治療目標と減量・休薬のリスクベネフィットについては患者と話し合い続ける必要がある．

●バイオマーカー開発と個別化医療

がんの増殖シグナルに代表される分子機構の解明と新規分子標的薬の開発が進んでいる．一方で，個々の症例での有効性をより鋭敏に予測するための新規バイオマーカー開発は，毒性制御の面からも，費用対効果の面からも重要である．腫瘍内科医は個別化医療時代のこうした課題を理解しながら，実地医療の選択を考えていく必要がある．

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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%; $P < 0.001$).

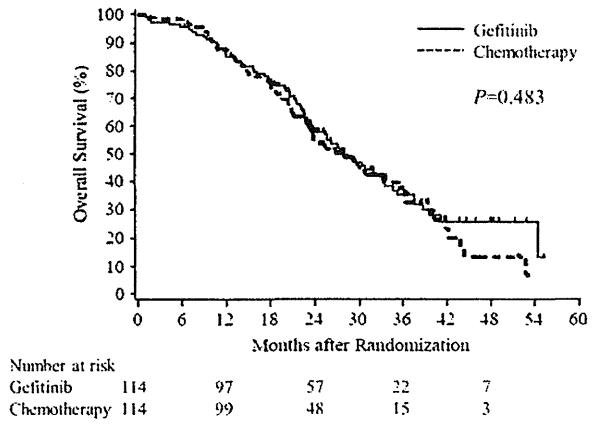

Figure 1. Kaplan–Meier curves for updated overall survival (OS) in the intent-to-treat population of NEJ002.

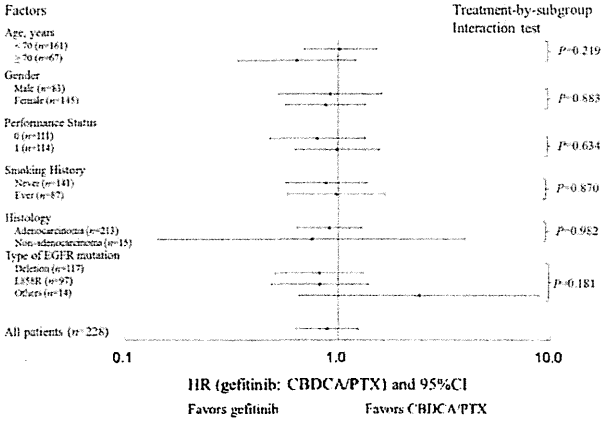

Figure 2. Forest plot of updated overall survival (OS) by clinical factors and the type of epidermal growth factor receptor (EGFR) mutation. Hazard ratio (HR) <1 implies a lower risk of death for patients treated with first-line gefitinb.

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

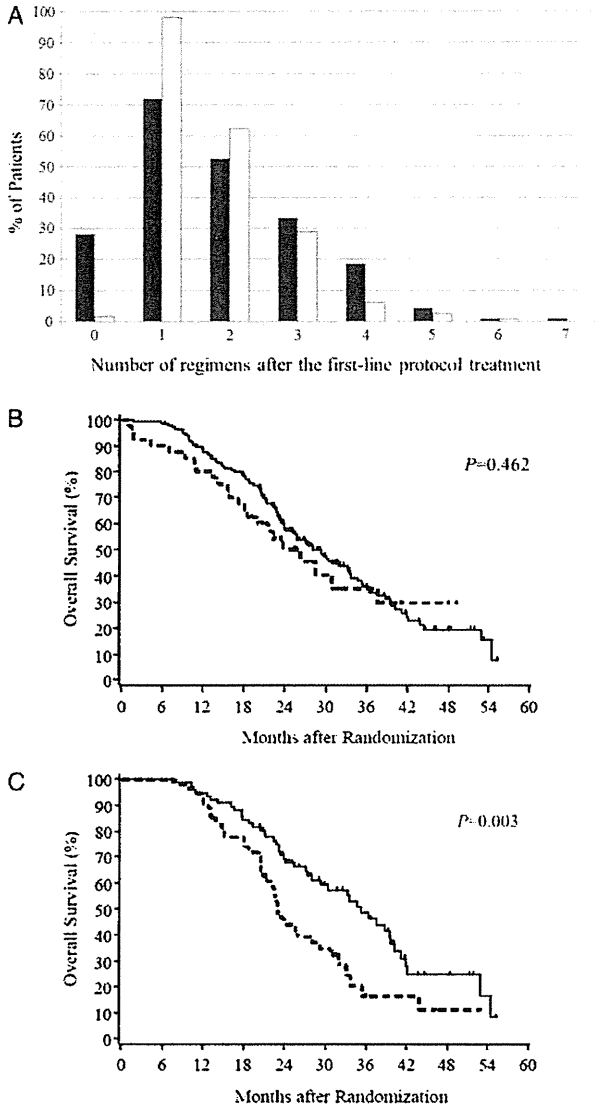

Figure 3. Evaluation of the impact of subsequent treatment on overall survival (OS) in NEJ002. The number of regimens that patients received after the first-line treatment with gefitinib (black bar) and that with chemotherapy (white bar) (A). The OS of patients treated with whichever line of gefitinib 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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Pemetrexed-based chemotherapy in patients with advanced, ALK-positive non-small cell lung cancer

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Background: Anaplastic lymphoma kinase (ALK)-positive non-small-cell lung cancer (NSCLC) is highly responsive to crizotinib. To determine whether ALK-positive NSCLC is also sensitive to pemetrexed, we retrospectively evaluated progression-free survival (PFS) of ALK-positive versus ALK-negative patients who had been treated with pemetrexed-based chemotherapy for advanced NSCLC.

Patients and methods: We identified 121 patients with advanced, ALK-positive NSCLC in the USA, Australia, and Italy. For comparison, we evaluated 266 patients with advanced, ALK-negative, epidermal growth factor receptor (EGFR)-wild-type NSCLC, including 79 with KRAS mutations and 187 with wild-type KRAS (WT/WT/WT). We determined PFS on different pemetrexed regimens.

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Quality of Life with Gefitinib in Patients with *EGFR*-Mutated Non-Small Cell Lung Cancer: Quality of Life Analysis of North East Japan Study Group 002 Trial

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ABSTRACT

Background. **For non-small cell lung cancer (NSCLC) patients with epidermal growth factor receptor (*EGFR*) mutations, first-line gefitinib produced a longer progression-free survival interval than first-line carboplatin plus paclitaxel but did not show any survival advantage in the North East Japan 002 study. This report describes the quality of life (QoL) analysis of that study.**

Methods. **Chemotherapy-naïve patients with sensitive *EGFR*-mutated, advanced NSCLC were randomized to receive gefitinib or chemotherapy (carboplatin and paclitaxel). Patient QoL was assessed weekly using the Care Notebook, and the primary endpoint of the QoL analysis was time to deterioration from baseline on each of the physical, mental, and life well-being QoL scales. Kaplan–Meier probability curves and log-rank tests were employed to clarify differences.**

Results. **QoL data from 148 patients (72 in the gefitinib arm and 76 in the carboplatin plus paclitaxel arm) were analyzed. Time to defined deterioration in physical and life well-being significantly favored gefitinib over chemotherapy (hazard ratio [HR] of time to deterioration, 0.34; 95% confidence interval [CI], 0.23–0.50; $p < .0001$ and HR, 0.43; 95% CI, 0.28–0.65; $p < .0001$, respectively).**

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Conclusion. **QoL was maintained much longer in patients treated with gefitinib than in patients treated with standard chemotherapy, indicating that gefitinib should be considered as the standard first-line therapy for advanced *EGFR*-mutated NSCLC in spite of no survival advantage.**
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Introduction

Dysregulation of protein kinases is frequently observed in cancer cells. Therefore, protein kinases are attractive targets in the development of anticancer drugs such as small molecule inhibitors that block binding of ATP to the catalytic domain of the tyrosine kinase. In 2004, three groups of researchers reported that activating mutations of the epidermal growth factor receptor gene (*EGFR*) were present in a subset of non-small cell lung cancer (NSCLC) tumors, and that tumors with *EGFR* mutations were highly sensitive to EGFR tyrosine kinase inhibitors (TKIs) [1–3]. Since then, our multiple phase II studies confirmed a striking response to EGFR TKIs in this population [4–8].

In phase III NSCLC trials, EGFR TKIs such as gefitinib or erlotinib were compared with conventional chemotherapies initially in unselected patients [9–11], next on the basis of clinical characteristics [12], and subsequently using molecular selection [13–16]. Among them, the pivotal phase III study North East Japan (NEJ) 002 compared gefitinib with chemotherapy in first-line therapy for patients with NSCLC with mutated *EGFR* and confirmed, as the primary endpoint, that the progression-free survival (PFS) interval in the gefitinib group was significantly longer than that in the carboplatin plus paclitaxel group (10.8 months versus 5.4 months, hazard ratio [HR], 0.30; $p < .001$) [13]. A subgroup analysis of the Iressa® Pan-Asia Study (IPASS) [12] and similar phase III studies—the West Japan Thoracic Oncology Group 3405 trial [14], the OPTIMAL trial [15], and European Randomised Trial of Tarceva versus Chemotherapy [16]—also demonstrated a superior PFS outcome in patients treated with EGFR TKIs than in those treated with standard chemotherapies. However, the IPASS and NEJ 002 trials showed identical overall survival (OS) outcomes using gefitinib and chemotherapy in the first-line treatment of NSCLC patients harboring sensitive *EGFR* mutations [17, 18].

When the OS time is identical in the two arms, improvements in quality of life (QoL) and disease-related symptoms are among the key goals of treatment for NSCLC. However, there has been no prospective report describing QoL in NSCLC patients with sensitive *EGFR* mutations who were treated using an EGFR TKI. This QoL analysis was prospectively conducted as a secondary endpoint in the NEJ 002 study.

Methods

This study was performed in accordance with the Helsinki Declaration (1964, amended in 2000) of the World Medical Association. The participating institutions received approval from their institutional ethics review boards. The details regarding patient eligibility and treatment were described previously [13]. Briefly, eligibility stipulated the presence of advanced NSCLC harboring a sensitive *EGFR* mutation, the absence of the resistant *EGFR* mutation T790M, no history of chemotherapy, and age ≤75 years. *EGFR* mutation status was examined using the peptide nucleic acid-locked nucleic acid polymerase chain reaction (PNA-LNA PCR) clamp method [19]. Eligible patients were randomly assigned to receive either gefitinib (at a dose of 250 mg/day orally) or standard chemotherapy. Standard chemotherapy consisted of paclitaxel (at a dose of 200 mg/m^2 i.v.) and carboplatin (area under the concentration–time curve of 6), both administered on the first day of every 3-week cycle. Randomization was balanced by institution, sex, and stage. The primary endpoint was the PFS interval; secondary endpoints included the OS time, response rate, toxic effects, and QoL.

QoL Assessment

The Care Notebook (supplemental online Fig. 1) [20], which has been previously validated and reported [21, 22], was used to assess QoL. The Care Notebook is a self-administered, cancer-specific questionnaire that asks about cancer patients' conditions during 1 week regarding 24 items that are structured in multidimensional scales. The questionnaire consists of three major scales: physical well-being, mental well-being, and life well-being. These major scales are divided into several subscales. Physical well-being has three multi-item subscales, which are appetite loss (items P3, P4, P7), constipation (P6, P8), and fatigue (P9, P10), and three single-item measures, which are pain (item P1), shortness of breath (item P2), and sleeping trouble (P5). Mental well-being has three multi-item subscales, which are anxiety (M1, M2), irritation (M3, M5), and depression (M4, M6). Life well-being has three multi-item subscales, which are daily functioning (L1, L2), social functioning (L3, L4), and subjective QoL (L5–L8), which consists of peace of mind (L5), feeling of happiness (L6), QoL functioning (L7), and satisfaction with daily life (L8). Each item is asked using one word or a short phrase and employs an 11-point linear analog scale (0–10). A score of 10 in physical well-being and mental well-being indicates the heaviest burden. A score of 10 in life well-being indicates the best possible function or QoL; thus, the polarity of the data for life well-being was reversed before the analysis so that a greater score indicated a poorer QoL in all items of the questionnaire.

Seventy sheets of the Care Notebook were bundled as a booklet. Patients started answering the questionnaire before starting therapy and answered it once a week during first-line treatment. After completion of the questionnaire, the booklets were collected by the patients' doctors and sent to the QoL data center (Saitama Medical University).

Statistical Analyses

The primary endpoint in the QoL analysis, which was prospectively defined in the protocol of the clinical trial, was the time from random assignment of treatment to deterioration in the

following, which are clinically relevant and are frequently observed in patients with advanced NSCLC: (a) pain and shortness of breath (P1 and P2), (b) anxiety (M1 and M2), and (c) daily functioning (L1 and L2). From previous studies [23, 24], deterioration was recognized when the score changed from baseline by one of 11 points (9.1%) in a direction indicating a worse QoL at any timepoint. This primary analysis was performed for 20 weeks after the initiation of first-line therapy. All patients who had a baseline plus at least one follow-up QoL assessment were included in the time-to-deterioration analysis. Patients who had not deteriorated were censored at the time of the last QoL questionnaire completion. Kaplan–Meier curves and the log-rank test were used to compare the time to deterioration in each subscale between the two treatment arms. Also, more severe deterioration was defined as a score change of three of 11 points (27.3%) [23, 24].

In addition, we performed a secondary analysis using QoL data according to the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) standard method [25]. During the initial 20 weeks from the start of treatment, we first checked whether or not the scores showed an improvement at any time in a subscale by ≥9.1% (one point or more) from baseline. In such cases, the response was judged to be "improved" even if the scores were initially or subsequently below the lower boundary, that is, −9.1%. If the response was not classified as improved, we next checked whether or not the scores showed a worsening in a subscale by ≥−9.1% from baseline, resulting in the response being classified as "worsened." In cases that were classified as neither improved nor worsened, the response was classified as "stable." A χ^2 test was used for comparisons between the two arms.

Results

Summary of Clinical Outcomes

In the NEJ 002 study [13], 230 patients who had sensitive *EGFR* mutations were enrolled and were randomly assigned to either gefitinib (n = 115) or carboplatin plus paclitaxel (n = 115), and 114 and 110 patients, respectively, were included in the PFS analysis (Fig. 1). Patients in the gefitinib arm had a significantly longer PFS time (median PFS time, 10.8 months versus 5.4 months; HR, 0.30; 95% CI, 0.22–0.41; $p < .001$) and a higher response rate (73.7% versus 30.7%; $p < .001$) than patients in the chemotherapy arm. Second-line gefitinib was administered to 98.2% of patients in the carboplatin plus paclitaxel arm after disease progression. As a result, the median OS time was 27.7 months in the gefitinib arm and 26.6 months in the chemotherapy arm, with the difference in survival time not statistically significant (p = .48) [18]. The most common adverse events of any grade were rash (71.1%) and aspartate aminotransferase or alkaline phosphatase elevation (55.3%) in the gefitinib arm and neutropenia (77.0%), anemia (64.6%), appetite loss (56.6%), and sensory neuropathy (54.9%) in the chemotherapy arm [13].

Baseline QoL

Of the 224 patients, the QoL booklets of 163 patients (73%) were collected by their doctors and sent to the QoL data center.

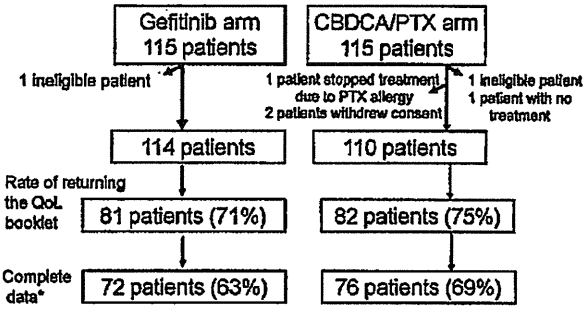

Figure 1. Patient disposition.

*The complete dataset was defined as having both a pretreatment measurement (baseline) and measurement(s) after starting the treatment during first-line therapy.

Abbreviations: CBDCA, carboplatin; PTX, paclitaxel; QoL, quality of life.

The rates of compliance among these 73% of patients were similar in the two arms. Of the 163 patients, 15 patients failed to provide complete information on their QoL prior to first-line therapy (nine patients in the gefitinib arm and six patients in the chemotherapy arm). Seventy-two patients (63%) in the gefitinib arm and 76 patients (69%) in the chemotherapy arm were investigated in this QoL analysis (Fig. 1). Demographics and disease characteristics were found to be well balanced in the two arms and were similar to those for the primary PFS analysis [13] (Table 1). Most patients had an Eastern Cooperative Oncology Group performance status (PS) score of 0 or 1 at the time of enrollment. Toxicity profiles for the patients in the QoL analysis were also similar to those for the patients in the PFS analysis [13].

Before the initiation of treatment, patients in both arms had similar baseline QoL scores on all subscales (Table 2). They had a low burden of physical well-being, but impairment was seen in the anxiety subscale (mean score, 40.5 and 40.8 in the gefitinib and carboplatin plus paclitaxel arms, respectively).

Time to Deterioration in QoL

In terms of the minimal clinically important difference in QoL, previous studies indicated that patients perceived a 5%–7% change in the scores on QoL questionnaires as clinically significant [23, 24]. The NCIC CTG recommends a 10% change as the value for clinical significance [25]. In the primary analysis of QoL in the NEJ 002 trial, deterioration was recognized when the score changed from baseline by one in 11 points (9.1%) or more in a direction indicating worse QoL at any timepoint. This criterion was chosen on the basis of our previous study, which estimated content validity by performing interviews with cancer patients (unpublished results). The times to 9.1% deterioration for pain and shortness of breath, anxiety, and daily functioning are summarized in Figure 2A. Significant differences between treatment arms were observed in deterioration of pain and shortness of breath (HR, 0.34; 95% CI, 0.23–0.50; $p < .0001$) and daily functioning (HR, 0.43; 95% CI, 0.28–0.65; $p < .0001$). There was no significant difference in anxiety between arms (HR, 0.72; 95% CI, 0.46–1.13; p = .14).

Table 1. Characteristics of patients in QoL analysis

Characteristic	Gefitinib ($n = 72$), n (%)	CBDCA/PTX ($n = 76$), n (%)	p-value
Gender			
Male	24 (33%)	29 (38%)	.608[a]
Female	48 (67%)	47 (62%)	
Mean age (range), yrs	63.0 (43–75)	62.2 (35–74)	.576[b]
Smoking status			
Never	51 (71%)	46 (61%)	.227[a]
Ever	21 (29%)	30 (39%)	
Performance status score, 0/1/2	40/32/0	43/32/1	.959[c]
Histology, adenocarcinoma/other	67/5	74/2	.495[a]
Stage, IIIB/IV/postoperative	10/52/10	15/52/9	.621[a]
Type of mutation			
Deletion	37 (51%)	36 (47%)	.616[a]
L858R	31 (43%)	36 (47%)	
Other	4 (6%)	4 (6%)	

Characteristics of patients investigated in the QoL analysis had no significant differences between arms.
[a]Fisher's exact test.
[b]t-test.
[c]Wilcoxon test.
Abbreviations: CBDCA, carboplatin; PTX, paclitaxel; QoL, quality of life.

Table 2. Baseline QoL scores

	Gefitinib		CBDCA/PTX	
Measure	Mean points	SD	Mean points	SD
Physical well-being	11.2	13.5	10.4	12.0
Appetite loss	6.8	13.0	5.9	11.5
Constipation	7.5	14.1	8.0	12.3
Pain and shortness of breath	13.5	23.2	10.5	18.5
Mental well-being	27.6	26.2	25.0	20.6
Anxiety	40.8	31.3	40.5	24.6
Irritation	18.3	25.2	14.3	20.4
Depression	23.5	27.9	20.0	24.3
Life well-being	26.4	19.3	22.9	17.1
Daily functioning	31.1	27.0	25.5	22.8
Social functioning	13.4	18.4	10.4	13.8
Subjective QoL	30.5	23.0	29.4	21.2

A 0–10 linear analog rating was changed to 0–100 points. For physical and mental well-being, a score of 100 represents the highest burden of symptoms. For life well-being, a score of 100 represents the worst possible function or QoL by changing the score polarity. There were no significant differences in scale and subscale scores between arms before starting first-line therapies.
Abbreviations: CBDCA, carboplatin; PTX, paclitaxel; QoL, quality of life; SD, standard deviation.

From previous reports [23, 24], a change in QoL score >20%, indicating more severe QoL deterioration, was also investigated. Figure 2B summarizes the time to a 27.3% (three of 11 points) deterioration in pain and shortness of breath, anxiety, and daily functioning. Patients who received gefitinib had a significantly longer time to deterioration than patients who received carboplatin plus paclitaxel for pain and shortness of breath (HR, 0.28; 95% CI, 0.17–0.46; $p < .0001$) and daily functioning (HR, 0.32; 95% CI, 0.17–0.59; $p < .0001$) as well as anxiety (HR, 0.44; 95% CI, 0.22–0.87; $p = .01$), for which a significant difference was not observed in the analysis of a 9.1% deterioration (see above).

Proportion of Patients with Improved, Stable, or Worsened QoL

Table 3 details the QoL responses according to three categories (improved, stable, worse) defined in Methods. The χ^2 test indicated that the QoL subscales of appetite loss ($p = .014$), constipation ($p < .0001$), and pain and shortness of breath ($p < .0001$) favored gefitinib over standard chemotherapy, leading to superiority of the gefitinib group on the physical well-being scale ($p < .0001$). A similar trend was observed for the QoL subscales of daily functioning ($p = .007$), social functioning ($p = .035$), and subjective QoL ($p = .042$), leading to superiority of the gefitinib group on the life well-being scale ($p < .0001$). The subscale of the mental well-being scale did not show any significant difference between the treatment arms ($p = .458$).

Discussion

This QoL analysis clearly demonstrated superior QoL in NSCLC patients with mutated *EGFR* receiving gefitinib, com-

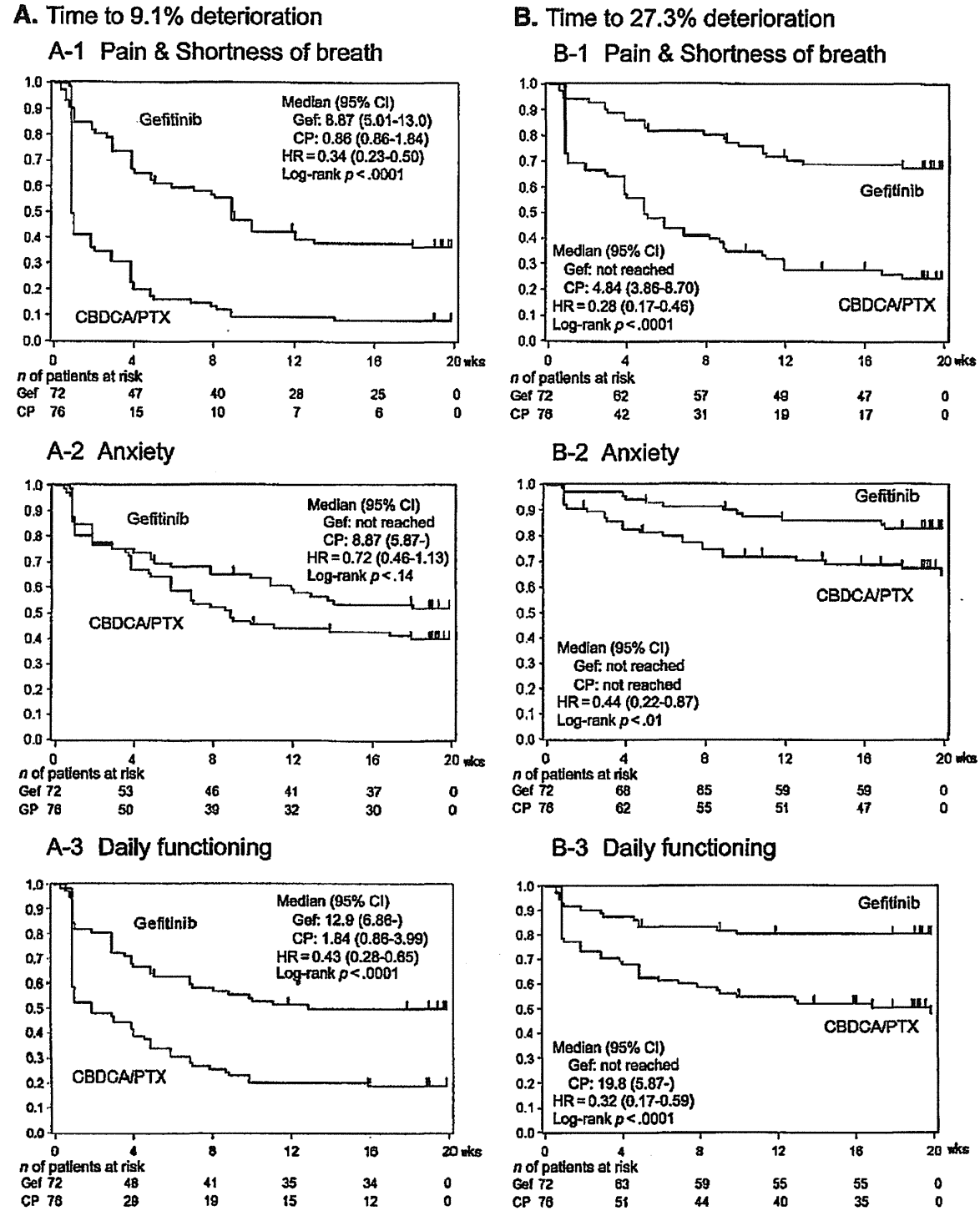

Figure 2. Time to deterioration of QoL. **(A):** Time to a 9.1% QoL deterioration for pain and shortness of breath **(A-1)**, anxiety **(A-2)**, and daily functioning **(A-3)** **(B):** Time to a 27.3% QoL deterioration for pain and shortness of breath **(B-1)**, anxiety **(B-2)**, and daily functioning **(B-3)**.

Abbreviations: CBDCA, carboplatin; CI, confidence interval; CP, carboplatin plus paclitaxel; Gef, gefitinib; HR, hazard ratio; PTX, paclitaxel; QoL, quality of life.

Table 3. QoL response

Measure	Gefitinib, *n*			CBDCA/PTX, *n*			*p*-value
	Improved	Stable	Worse	Improved	Stable	Worse	
Physical well-being	18	28	26	16	10	50	<.0001
Appetite loss	13	21	38	14	8	54	.014
Constipation	16	24	32	23	6	47	<.0001
Pain and shortness of breath	21	18	33	16	3	57	<.0001
Mental well-being	33	16	23	40	11	25	.458
Anxiety	48	8	16	57	6	13	.535
Irritation	27	18	27	27	11	38	.181
Depression	35	15	22	36	10	30	.346
Life well-being	38	22	12	32	8	36	<.0001
Daily functioning	40	10	22	30	4	42	.007
Social functioning	23	28	21	16	22	38	.035
Subjective QoL	41	15	16	38	8	30	.042

In a secondary analysis of QoL responses, patients were classified as improved (>9.1%), stable (<9.1%, >−9.1%), or worsened (<−9.1%) for all scales and subscales according to the National Cancer Institute of Canada Clinical Trials Group standard QoL analysis framework.
The χ^2 test was used to compare the distributions of these three categories between two treatment arms.
Abbreviations: CBDCA, carboplatin; PTX, paclitaxel; QoL, quality of life.

pared with patients receiving chemotherapy. Better QoL in patients receiving gefitinib further endorses the preference of gefitinib as the first-line therapy for patients with NSCLC with mutated *EGFR* despite a lack of difference in OS outcomes. Accordingly, integration of QoL analyses into a clinical trial should be considered, because maintenance of a good QoL solidifies the clinical efficacy of the treatment being investigated. In addition, this analysis also highlights the importance of QoL endpoints in randomized trials analyzing PFS outcomes, because OS outcomes may be affected by subsequent therapies.

QoL recorded by patients in a self-reported form accurately demonstrated how the patients felt about their QoL during treatment. As soon as chemotherapy with carboplatin plus paclitaxel was started, a striking difference in QoL was observed (Fig. 2A). It seems reasonable that physical well-being deteriorated with chemotherapy in a high proportion of patients, considering that >95% of patients had a PS score of 0–1, a fact that is probably reflected by the low scoring in the baseline scores of physical well-being and daily functioning, with the majority of patients scoring <30. The NCIC CTG recommended matrix (Table 2) also showed that physical well-being was stable or improved in 60% of patients in the gefitinib group. In sharp contrast, scores for physical well-being deteriorated in 75% of patients in the chemotherapy group. This better QoL in the gefitinib group will help patients to maintain social activities, continue to work, and enjoy spending time with their families.

When patients were treated with gefitinib monotherapy in other trials, QoL and symptom improvement were rapid and were correlated with tumor response and survival [26, 27]. In the BR.21 study using unselected patients, another EGFR TKI, erlotinib, also improved tumor-related symptoms and important aspects of QoL such as physical functioning [28]. Post hoc investigations in the IPASS study employing selection by background indicated that QoL was better in the gefitinib group than in the chemotherapy group for patients with *EGFR*-mutated NSCLC [29]. Taken together with our first prospective QoL analysis of patients with *EGFR*-mutated NSCLC, EGFR TKI therapy provides an advantage in terms of improving QoL and symptoms over conventional cytotoxic agents.

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) [30] and Functional Assessment of Cancer Therapy (FACT)–General [31] have been used in many clinical trials to assess the QoL of patients worldwide, and we have developed and validated Japanese versions of these tests for use mainly in clinical studies with the original developers [32, 33]. The Care Notebook [20–22] was originally developed in the 1990s for clinical practice and has a notebook-style format to collect valid and reliable QoL information repeatedly. The NEJ 002 study lacked sufficient support from clinical research coordinators, and doctors had to personally administer QoL questionnaires to patients and pick them up after the answers were completed. Therefore, we chose the Care Notebook, which has good results concerning concurrent validity with the EORTC QLQ-C30 and FACT–Spiritual Well-being [22], for QoL investigation on a weekly basis instead of the above gold standard questionnaires. More than 3,000 Care Notebooks were collected during the initial 20 weeks of treatment in this study, and this method might be the first success of a QoL investigation on a weekly basis for advanced cancer patients in a phase III trial.

This study has some limitations. First, compliance with the QoL survey was modest. Missing data in the QoL investigation

were found to be institution dependent. Namely, the doctors in some institutions did not give the Care Notebook to patients or did not pick it up after the answers were completed. However, randomization of the study treatments was stratified by institution, and therefore, the effects of selection bias might not be large. Both arms had similar patient characteristics (Table 1) and similar baseline QoL scores (Table 2). Although compliance was modest, this QoL difference between arms may represent that in the overall population. Secondly, because the primary endpoint of the NEJ 002 study focused on the PFS interval after first-line treatment, the QoL analysis also focused on patients treated during first-line treatment, and, therefore, the investigation period for the primary QoL analyses was relatively short (20 weeks) to reduce the effects of second-line treatment. Finally, the patients in this QoL analysis were a selected population—patients with a PS score of 0–1 whose tumor had *EGFR* mutation—which might potentially influence the QoL outcomes. However, in another study, namely the NEJ 001 study [7], which employed *EGFR* mutation-positive patients with an extremely poor PS, 68% of the patients improved from a PS score ≥3 at baseline to a PS score ≤1 with gefitinib therapy. Although no QoL investigation was conducted in the NEJ 001 study because of the patients being in extremely poor condition, the striking PS score improvement might have been related to improved QoL. This indicates that EGFR TKIs might universally ameliorate the QoL of patients with *EGFR*-mutated NSCLC, irrespective of their PS scores or symptomatic burdens.

Summary

The QoL analysis of the NEJ 002 study clearly demonstrated that gefitinib maintained patient QoL longer than carboplatin plus paclitaxel during first-line treatment. A longer PFS interval with a better QoL during first-line treatment is valuable for advanced NSCLC patients with limited survival times. Although the OS time for patients first treated using gefitinib was not significantly different from that of patients treated using chemotherapy, the first-line use of gefitinib for advanced NSCLC harboring *EGFR* mutations is strongly recommended.

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This study is registered in University Hospital Medical Information (UMIN) Network Clinical Trial Registry (identification number, UMIN C000000376).

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