心電図

心電図（ECG）とは，心電計によって得られる心臓全体を総合した活動電流の図形記録である．図1のように，心電図の波形図はP波，PR部分，QRS波，ST部分，T波およびU波に分類される．最も大きなR波が心室の収縮を表し，2つの連続するR波の間隔をRR間隔とよぶ．1分（60秒）をRR間隔（秒）で割ったものが心拍数である．Q波の始まりからT波の終わりまでがQT間隔であり，心室の脱分極開始から再分極終了までの時間を表す．QT間隔が長くなると，トルサード・ドゥ・ポワン（TdP）とよばれる重篤な不整脈を引き起こし，突然死などのリスクが高まることが知られている．

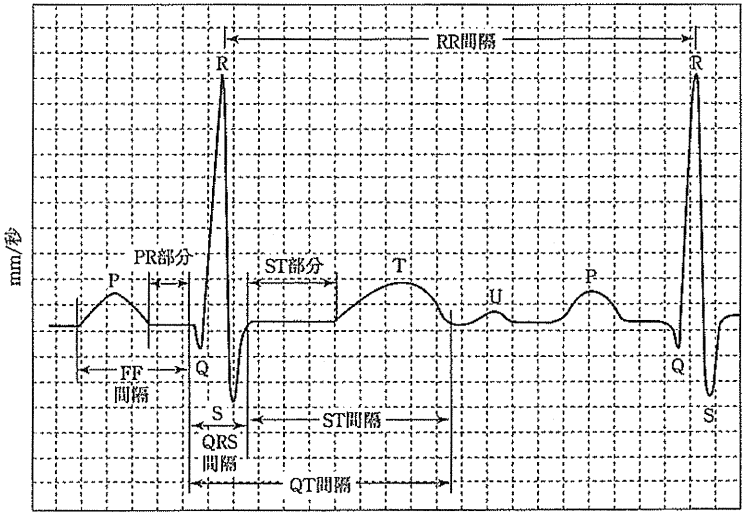

図1　心電図波形

[福島雅典監修，2006，『メルクマニュアル第18版日本語版』日経BP社，p. 625]

●薬によるQT間隔の延長　QT間隔の延長は先天性あるいは薬物誘発性であることが多い．よって，新薬開発時の臨床試験においてQT延長作用を検討することが求められている．QT延長作用が0.005秒未満であればTdPを引き起こす可能性はほとんどなく，0.02秒を超えるとその可能性が高いといわれている．

●QT間隔の補正方法　QT間隔とRR間隔には正の相関がある．個体によってRR間隔は異なり，個体内でも時点によってRR間隔は異なっているため，QT間隔を評価する際にはRR間隔の影響を取り除く必要がある．その1つの対処法がRR間隔による補正である．RR間隔が1秒，すなわち心拍数が60となるように補正したQT間隔をQTC間隔（補正されたQT間隔）とよぶ．補正方法を補正対象で分類すると，

・集団補正法：すべての人に同じ補正式を適用する．
・試験別補正法：臨床試験の対象者全体に試験固有の補正式を適用する．
・個体別補正法：個体ごとに補正式を推定して適用する．

となる．集団補正法が適用できる本質的な条件は，「個体によらずQTとRRの関係が安定かつ一定」であるが，この条件は厳密には成り立たない可能性が高いことが知られている．また，すべての補正法について，「日，時間によらずQTとRRの関係が安定かつ一定」，および「薬の投与にかかわらずQTとRRの関係が安定かつ一定」という条件が必要である．

QT間隔とRR間隔または心拍数（HR）の関係式で分類すると，

$$QT=\alpha+\beta\times RR \quad (1)$$

$$QT=\alpha+\beta\times HR \quad (2)$$

$$\log(QT)=\alpha+\beta\times\log(RR) \quad (3)$$

となる．集団補正法として最も知られている方法は式(3)の関係式を用いたBazettのQT_c間隔：$QT/RR^{1/2}$である．そのほかにも式(1)を用いた$QT_c=QT-0.514(1-RR)$，式(2)を用いた$QT_c=QT+1.87(HR-60)$，式(3)を用いた$QT/RR^{1/3}$などがある．

●QT延長作用の臨床的評価　薬の投与によってQT_c間隔が0.005秒程度延長するかどうか，という規制当局の問いに開発者は答えなければならない．したがって，QT延長作用を評価する臨床試験を計画する際には，QT_c間隔の変動要因となる個人特性（年齢，性，電解質異常，併存疾患など），個人内（日内，日間）での変動，心電図測定の信頼性，薬物の血中濃度などについて十分な検討を行い，対象，用量，投与期間，試験デザインを決定することが重要である．また，限られた対象者数で精度の高い臨床試験を行うには，上述の個体別補正法を用いてQT_c間隔を求める必要があることが示唆されている．　[手良向聡]

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[2] 厚生労働省医薬食品局審査管理課長，非抗不整脈薬におけるQT/QTc間隔の延長と催不整脈作用の潜在的可能性に関する臨床的評価について，薬食審査発1023第1号(平成21年10月23日).

腫瘍マーカー

腫瘍マーカーとは，がんの組織から血液や尿などの中に出てくる物質で，がんの目印(マーカー)になるので，そうよばれている．CEA(がん胎児性抗原)，AFP(αフェトプロテイン)，PSA（前立腺特異抗原）などが代表的であるが，そのほかにも多くの物質が腫瘍マーカーとして知られている．しかし，これらの物質はがんでない正常な組織においてもつくり出されているため，これらの物質を測定しただけで，がんの診断ができるわけではない．また，これらの物質はさまざまな臓器でつくられているため，もしCEAという腫瘍マーカーの数値が高く，がんが疑われたとしても，胃がんなのか，大腸がんなのか，肺がんなのかを正確には診断できない．確定的な診断を行うためには，画像検査などのさらに精密な検査が必要となる．現在，がんのスクリーニング（早期発見）に広範囲に使われている腫瘍マーカーの1つが前立腺がんに対するPSAである．以下，PSAの例を用いて，がんの診断の統計学的評価について解説する．

●腫瘍マーカーによる前立腺がんの診断　あなたが健康診断で血液中のPSA値を測定され，医師から「PSA値が異常ではないので，前立腺がんの可能性はありません」，もしくは「PSA値が異常です．前立腺がんの可能性があります」と告げられた場合，その可能性はどの程度であろうか．表1は，腫瘍マーカー（PSA）による診断の確かさを調べるために行われたある研究の結果である．

表1　前立腺がんのスクリーニング検査結果

	前立腺がん（組織学的診断）	
	あり	なし
PSA値異常あり（PSA陽性）	67％（感度）	3％
PSA値異常なし（PSA陰性）	33％	97％（特異度）
計	100％	100％

この研究では，血液中のPSA値が4ng/mLを超えた場合を異常あり(陽性)と判定している．このように「陽性」と「陰性」を分ける境界の値をカットオフ値とよぶ．ここで診断の確かさを表す2つの指標が，感度と特異度である．ここで感度は，

$$感度=\frac{「PSA陽性」と判定され，前立腺がんであった人の数}{前立腺がんであった人の総数}$$

と定義される．この数字から，前立腺がんであった人のうち67％がPSA陽性を示し，残りの33％の人はPSA陰性であったことがわかる．67％という感度はそれほど高くなく，PSA検査だけでは前立腺がんを見逃すことが多いといえる．一方，特異度とは，

$$特異度=\frac{「PSA陰性」と判定され，前立腺がんでなかった人の数}{前立腺がんでなかった人の総数}$$

である．この研究での特異度は97％であり，前立腺がんでなかった人の97％がPSA陰性と判定されていた．残りの3％の人は，前立腺がんではないにもかかわらず，PSA陽性と判定されていた．97％という特異度はかなり高く，PSA検査によって前立腺がんでないことはほぼ確実に判定できる．

定義からわかるように感度と特異度はそれぞれ0～1の値をとり，両方の指標がともに1であれば，完全な診断検査ということになるが，実際には測定誤差などもあり，そのような検査は存在しない．また，感度と特異度は，一方を高くしようとするともう一方が低くなる，トレードオフの関係にある．例えば，PSA検査のカットオフ値を4ng/mLから2ng/mLに下げると，PSA陽性と判定される人数が多くなり，感度は高くなる．しかし，そうすると多くの人を陽性と判定してしまうために特異度は低くなる．したがって，先のような研究から，感度と特異度のバランスを考えてPSA値の4mg/mLというカットオフ値が決定され，その値が広く用いられている．

●腫瘍マーカーの推移による再発の予測　通常，がんの大きさと腫瘍マーカーの値には関連があり，手術でがんを切除されると腫瘍マーカーの値は低くなる．よって手術後，がんが再発していないことを確認するために定期的に腫瘍マーカー検査が行われる．がんのスクリーニングのためだけではなく，進行・再発を予測するという目的にも多くの腫瘍マーカーが利用されている．その際用いられる指標としては，倍加時間（腫瘍マーカーの値が2倍になる時間）が用いられることが多い．

[手良向聡]

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ORIGINAL REPORT

Randomized Phase III Trial of Platinum-Doublet Chemotherapy Followed by Gefitinib Compared With Continued Platinum-Doublet Chemotherapy in Japanese Patients With Advanced Non–Small-Cell Lung Cancer: Results of a West Japan Thoracic Oncology Group Trial (WJTOG0203)

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This study is registered with UMIN-CTR [http://www.umin.ac.jp/ctr/index.htm, identification number C000000035].

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

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See accompanying editorial on page 713 and article on page 744

ABSTRACT

Purpose
Gefitinib is a small molecule inhibitor of the epidermal growth factor receptor tyrosine kinase. We conducted a phase III trial to evaluate whether gefitinib improves survival as sequential therapy after platinum-doublet chemotherapy in patients with advanced non–small-cell lung cancer (NSCLC).

Patients and Methods
Chemotherapy-naïve patients with advanced stage (IIIB/IV) NSCLC, Eastern Cooperative Oncology Group performance status of 0 to 1, and adequate organ function were randomly assigned to either platinum-doublet chemotherapy up to six cycles (arm A) or platinum-doublet chemotherapy for three cycles followed by gefitinib 250 mg orally once daily, until disease progression (arm B). Patients were stratified by disease stage, sex, histology, and chemotherapy regimens. The primary end point was overall survival; secondary end points included progression-free survival, tumor response, safety, and quality of life.

Results
Between March 2003 and May 2005, 604 patients were randomly assigned. There was a statistically significant improvement in progression-free survival in arm B (hazard ratio [HR], 0.68; 95% CI, 0.57 to 0.80; $P < .001$); however, overall survival results did not reach statistical significance (HR, 0.86; 95% CI, 0.72 to 1.03; $P = .11$). In an exploratory subset analysis of overall survival by histologic group, patients in arm B with adenocarcinoma did significantly better than patients in arm A with adenocarcinoma (n = 467; HR, 0.79; 95% CI, 0.65 to 0.98; $P = .03$).

Conclusion
This trial failed to meet the primary end point of OS in patients with NSCLC. The exploratory subset analyses demonstrate a possible survival prolongation for sequential therapy of gefitinib, especially for patients with adenocarcinoma.

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INTRODUCTION

Lung cancer is the most common cancer worldwide, with an estimated 1.2 million new cases globally (12.3% of all cancers) and 1.1 million deaths (17.8% of all cancer deaths) in 2000.[1] The estimated global incidence of non–small-cell lung cancer (NSCLC) in 2000 was approximately 1 million, which accounted for approximately 80% of all cases of lung cancer.[1] Treatment of advanced NSCLC is palliative; the aim is to prolong survival without leading to deterioration in quality of life.[2] The recommended first-line treatment of advanced NSCLC currently involves up to six cycles of platinum-based combination chemotherapy, with no single combination recommended over another.[3,4] Recently, combination chemotherapy of pemetrexed plus cisplatin was significantly superior to gemcitabine plus cisplatin in nonsquamous NSCLC.[5]

Gefitinib is an orally active epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) that blocks the signal transduction pathways

implicated in the proliferation and survival of cancer cells.[6] In two phase II trials in patients with pretreated advanced NSCLC (Iressa Dose Evaluation in Advanced Lung Cancer [IDEAL] 1 and 2), gefitinib 250 mg/d showed response rates of 12% and 18% and a median survival time (MST) of 7.0 and 7.6 months in IDEAL1 and 2, respectively; in addition, the toxicity profile was not severe.[7,8] This favorable tolerability profile, coupled with a mechanism of action that is distinct from that of cytotoxic agents, provides a strong rationale for use of gefitinib in combination with standard cytotoxic regimens. Platinum-doublet chemotherapy added to gefitinib in untreated patients with NSCLC was evaluated in two large-scale, placebo-controlled, randomized trials (INTACT-1 and -2).[9,10] Gefitinib showed no survival benefit over placebo when combined with standard platinum-doublet chemotherapy in both trials. Furthermore, gefitinib did not improve time to progression or objective tumor response over chemotherapy alone. These results were disappointing and surprising because of the significant antitumor activity of gefitinib when given alone to pretreated patients with NSCLC.

First, it is possible that each of the agents is working against a susceptible subpopulation of tumor cells so that the effect is redundant rather than additive, or that one agent results in the loss of an intermediary molecule that is essential to the function of the other agent, resulting in an antagonistic effect. Second, patients included in these studies were not selected on the basis of a specific biomarker, such as target EGFR expression, gene amplification, or mutations. Clinical profiles of females, never smokers, adenocarcinoma histology, and Asian ethnicity have all been recognized as favorable subgroups that respond to gefitinib.[11-14]

Because no additive effect was observed by administering gefitinib continuously in combination with chemotherapy, possible alternatives could be the administration of gefitinib in the interval between chemotherapy cycles or as sequential treatment after chemotherapy. This could also potentially prevent the problem of drug interference or antagonism. We conducted a randomized phase III trial to evaluate whether gefitinib improves survival as sequential therapy after platinum-doublet chemotherapy in chemotherapy-naive patents with NSCLC.

PATIENTS AND METHODS

Patients

Eligible patients were 20 to 75 years of age, with histologically or cytologically confirmed stage IIIB (with malignant pleural effusion or contralateral hilar lymph node metastases) or stage IV NSCLC who had not previously received any chemotherapy. Patients who had recurrence after complete surgical resection were permitted. Patients treated with either adjuvant or neoadjuvant chemotherapy were excluded in this trial. Additional criteria included a Eastern Cooperative Oncology Group performance status of 0 to 1, and adequate organ function as indicated by WBC count $\geq$ 4,000/μL, absolute neutrophil count $\geq$ 2,000/μL, hemoglobin $\geq$ 9.5 g/dL, platelets $\geq$ 100,000/μL, AST/ALT $\leq$ 2.5 times the upper limit of normal, total bilirubin $\leq$ 1.5 mg/dL, serum creatinine $\leq$ 1.2 mg/dL, and PaO_2 in arterial blood $\geq$ 70 mmHg. Asymptomatic brain metastases were allowed provided that they had been irradiated and were clinically and radiologically stable. Patients were excluded from the study if they had radiologically and clinically apparent interstitial pneumonitis or pulmonary fibrosis. All patients provided written informed consent, and the study protocol was approved by the West Japan Thoracic Oncology Group Protocol Review Committee and the institutional review board of each participating institution.

Treatment Plan

Eligible patients were centrally registered at West Japan Thoracic Oncology Group Data Center and were randomly assigned to receive either platinum-doublet chemotherapy up to six cycles (arm A) or three cycles of platinum doublet followed by gefitinib 250 mg/d orally, until disease progression (arm B). Patients who achieved disease control (response or stable disease) treated with three cycles of platinum-doublet went for gefitinib treatment phase in arm B. Each physician selected his/her chemotherapy options before randomization. Platinum-doublet chemotherapy options included any of the following: (1) carboplatin area under the curve 6, day 1, and paclitaxel 200 mg/m^2, day 1, every 3 weeks; (2) cisplatin 80 mg/m^2, day 1, and irinotecan 60 mg/m^2, days 1, 8, 15, every 4 weeks; (3) cisplatin 80 mg/m^2, day 1, and vinorelbine 25 mg/m^2, days 1, 8, every 3 weeks; (4) cisplatin 80 mg/m^2, day 1, and gemcitabine 1,000 mg/m^2 days 1, 8, every 3 weeks; or (5) cisplatin 80 mg/m^2, day 1, and docetaxel 60 mg/m^2 day 1, every 3 weeks. The dose of carboplatin was calculated using Calvert's formula, and the glomerular filtration rate was estimated by the Cockcroft-Gaut formula. These treatment schedules and doses are used as standard platinum-doublet regimens for advanced NSCLC in Japan.[15,16]

Randomization was stratified according to the institution, type of histology (adenocarcinoma *v* nonadenocarcinoma), clinical stage (IIIB *v* IV), and selected platinum-doublet regimens with the use of a minimization procedure. Patients receiving platinum-doublet chemotherapy received standard supportive treatments, including hydration and antiemetics, according to each institutional standard guideline. After withdrawing from the trial as a result of disease progression or intolerable toxicity, any systemic treatment, including with EGFR-TKI, was permitted in both arms.

Baseline and Follow-Up Assessments

Pretreatment evaluation included a complete medical history and physical examination, a CBC with differential and platelet count, standard biochemical profile, ECG, chest radiographs, computed tomography (CT) scans of the chest, abdomen, and brain, magnetic resonance imaging, and a whole-body bone scan. During treatment, a CBC and biochemical tests were performed at least every 2 weeks. A detailed medical history was taken and a complete physical examination with clinical assessment was performed every 2 weeks to assess disease symptoms and treatment toxicity, and chest

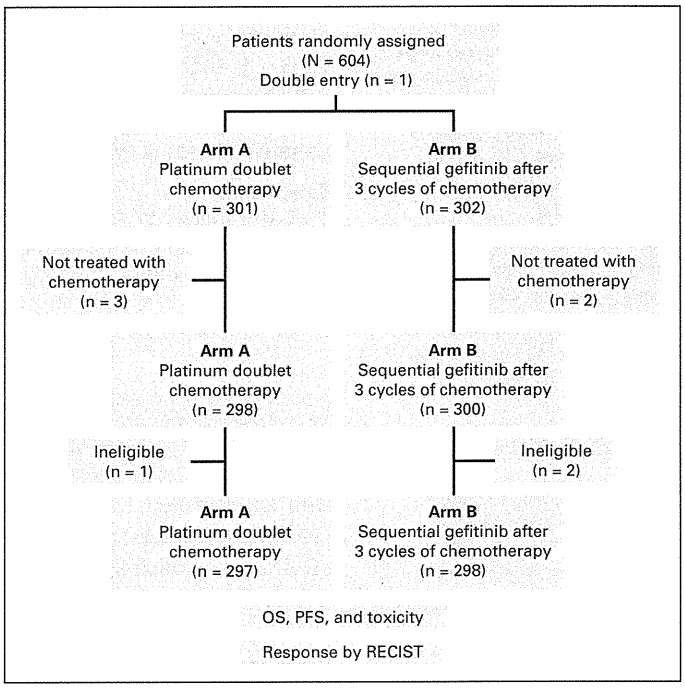

Fig 1. CONSORT diagram for the study. OS, overall survival; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors.

radiographs were done every treatment cycle. Toxicity was evaluated according to the National Cancer Institute Cancer Common Toxicity Criteria (NCI-CTC) version2.[17]

All patients were assessed for response by CT scans monthly during treatment. Response Evaluation Criteria in Solid Tumors (RECIST) were used for the evaluation of response.[18]

Disease-related symptoms were assessed using the Lung Cancer Subscale (LCS) of the Functional Assessment of Cancer Therapy-Lung quality of life instrument (version 4.0).[19] Patients were asked to complete the instrument at the time of enrollment and at 12 weeks and 18 weeks after initiation of treatment. The maximum attainable score on the LCS was 28, where the patient was considered asymptomatic.

Statistical Analysis

The primary end point was OS; secondary end points included PFS, tumor response, safety, and quality of life. Based on previous trials evaluating platinum-doublet chemotherapy, the MST was approximately a range of 8 to 11 months.[3] In IDEAL-1, which was the trial of gefitinib alone in patients with previously treated NSCLC, median time to treatment failure was 98 days.[7] This trial was designed to detect a 3-month difference in MST. To attain 80% power at a two-sided significance level of .05, assuming a MST in the chemotherapy alone arm of 9 months with 2 years of follow-up after 3 years of accrual, 225 patients in each treatment group were required. Both the OS and PFS were estimated with the Kaplan-Meier method. Comparisons of OS and PFS between arms were assessed by the stratified log-rank test. Two interim analyses were planned after half the patients were registered and at the end of registration.

At the first interim analysis, 14% of patients in arm B unexpectedly withdrew from sequential gefitinib treatment after the three cycles of platinum-doublet chemotherapy at their own request because of hearing the news of interstitial lung disease (ILD) as a result of the use of gefitinib in Japan. If 15% of patients treated with sequential gefitinib withdrew, 284 patients in each arm were required to attain an 80% power at a two-sided significance level of .05, assuming a MST of the chemotherapy alone arm of 9 months with 2 years of follow-up after 3 years of accrual. Consequently, a protocol amendment was performed in April 2004.

For symptom analysis, comparisons of LCS between arms were conducted using a linear mixed-effects model in which the missing data depend on the observed LCS, using the MIXED procedure in SAS version 9 (SAS Institute, Cary, NC).

RESULTS

Patient Characteristics

From March 2003 to May 2005, 604 patients with advanced NSCLC from 39 institutions were enrolled (Appendix, online only). Patients were randomly assigned to platinum-doublet chemotherapy up to 6 cycles (n = 302, arm A) or sequential gefitinib after three cycles of platinum-doublet chemotherapy (n = 302, arm B). One patient was double entry in arm A, and three patients in arm A and two in arm B did not receive any chemotherapy. Therefore, a total of 598 patients (298 in arm A and 300 in arm B) were included in the analysis of patients' profiles and the assessment for toxicity. In addition, three patients did not meet the entry criteria; thus, 297 patients with measurable lesions by RECIST in arm A and 298 eligible patients in arm B were assessable for OS, PFS, and response. Figure 1 shows the CONSORT diagram. Table 1 presents baseline patient characteristics and lists the platinum-doublet chemotherapy regimen selected by each physician.

Table 1. Patients' Characteristics and Selected Platinum-Doublet Chemotherapy Regimens

Parameter	Arm A		Arm B		*P*
	No. of Patients	%	No. of Patients	%	
Patients enrolled	298		300		—
Median age, years	63		62		.114
Range	35-74		25-74		
Sex					
Male	191	34.6	192	64.0	.981
Female	107	67.8	108	36.0	
ECOG PS					
0	103	30.8	90	30.0	.778
1	195	69.2	210	70.0	
Histology					
Adenocarcinoma	232	77.9	237	79.0	.733
Nonadenocarcinoma	66	22.1	63	21.0	
Clinical stage					
IIIB	54	18.1	55	18.3	.946
IV	244	81.9	245	81.7	
Smoking status					
Smoker	202	67.8	210	70.0	.559
Nonsmoker	96	32.2	90	30.0	
Selected platinum-doublet chemotherapy regimens					
CP	193	64.8	195	65.0	.987
IP	8	2.7	10	3.3	
VP	44	14.8	45	15.0	
GP	45	15.1	42	14.0	
DP	8	2.7	8	2.7	

NOTE. Differences between two arms were tested by χ^2 test, excluding age (Wilcoxon test), ECOG PS.
Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; CP, carboplatin and paclitaxel; IP, irinotecan and cisplatin; VP, vinorelbine and cisplatin; GP, gemcitabine and cisplatin; DP, docetaxel and cisplatin.

Treatment Delivery

The median number of chemotherapy cycles was three (range, 1 to 6) in arm A, and three (range, 1 to 3) in arm B. One hundred seventy-two patients (57.3%) in arm B were treated with gefitinib after completion of three cycles of platinum-doublet. The median treatment duration of gefitinib was 69.5 days, and the maximum treatment duration was 1,324 days. As presented in Figure 2, EGFR-TKIs, which included gefitinib, erlotinib, and vandetanib, were used in 54.5% and 75.2% of patients in arm A and B, respectively, at any time during treatment of NSCLC. In arm B, gefitinib treatment did not take place because of early disease progression before the completion of three cycles of platinum-doublet chemotherapy in 93 patients (31.2%), and 33 (11.1%) in arm B rejected the use of gefitinib after platinum-doublet because of publication of a news report about gefitinib-induced ILD.

Treatment Efficacy

At the time of final analysis, 247 (83.2%) and 232 patients (78.0%) had died in arm A and arm B, respectively. The MST was 12.9 months for chemotherapy alone and 13.7 months for chemotherapy followed by gefitinib (hazard ratio [HR] according to Cox's regression model, 0.86; 95% CI, 0.72 to 1.03; $P = .11$ stratified log-rank test, Fig 3A). The PFS was 4.3 months in arm A and 4.6 months in arm B (HR, 0.68; 95% CI, 0.57 to 0.80; $P < .001$, Fig 3B).

When exploratory subset analysis were performed, sequential therapy with gefitinib after three cycles of platinum-doublet chemotherapy prolonged OS significantly in the subset of patients with adenocarcinoma (HR, 0.79; 95% CI, 0.65 to 0.98; $P = .03$; Fig 4A). There was no significant difference in OS due to the small subset of patients with nonadenocarcinoma (HR, 1.24; 95% CI, 0.85 to 1.79; $P = .25$; Fig 4B). In addition to the OS plots, the PFS plots for adenocarcinoma and nonadenocarcinoma were showed in Figure 4C and 4D, respectively. Furthermore, results of the subset analysis were summarized for forest plots in Figure 5. Another subset of smokers had a survival advantage with chemotherapy followed by gefitinib over chemotherapy alone. There was no difference between the two treatment groups in the subset of never smokers. Never smokers with NSCLC had a prolonged survival of about 23.5 months in arm A and 21.7 months in arm B.

The overall response rate was 29.3% for chemotherapy alone and 34.2% for chemotherapy followed by gefitinib. There was no significant difference between treatment arms ($P = .20$; Fisher's exact test). The overall disease control rate (response and stable disease) were 71.0% and 75.5% in arm A and in arm B, respectively ($P = .22$).

Toxicity

Toxicity was assessed according to NCI-CTC version 2 in all patients who received at least one treatment cycle of platinum-doublet chemotherapy (Table 2). Grade 3 or 4 anemia developed in 21.8% of patients in arm A and 13.3% of patients in arm B. There was a significant difference between the two arms ($P = .006$). Grade 3 or 4

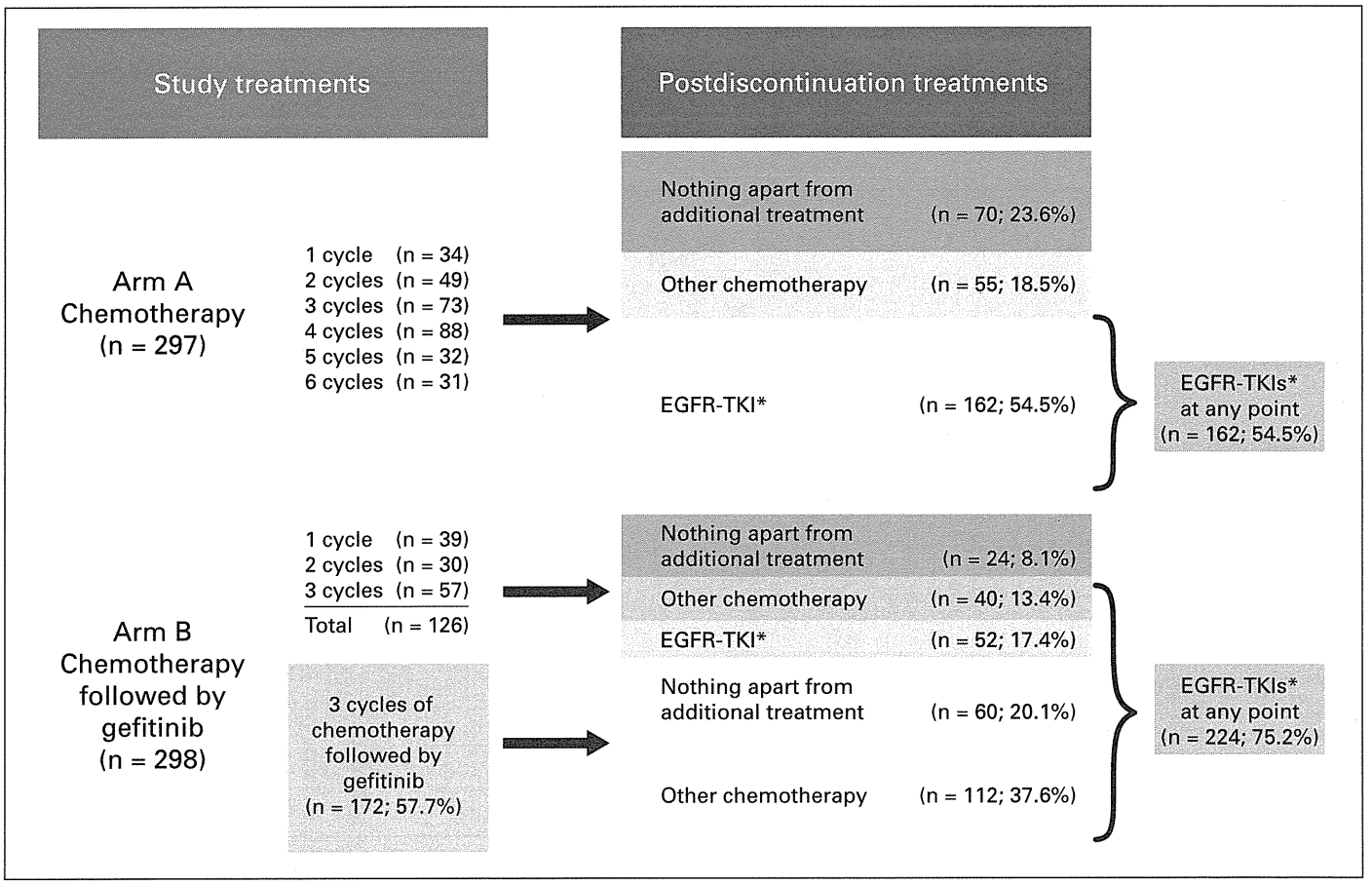

Fig 2. Exposure to active epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), including postdiscontinuation treatments in the full analysis set population (n = 595).

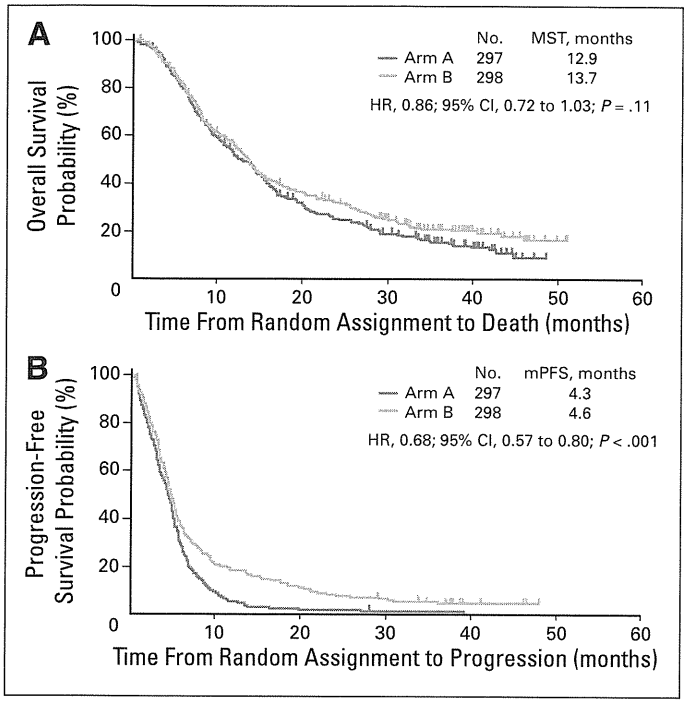

Fig 3. (A) Overall survival and (B) progression-free survival (n = 598). MST, median survival time; HR, hazard ratio; mPFS, median progression-free survival.

thrombocytopenia occurred in 10.7% of patients in arm A and 6.3% of patients in arm B, but differences did not reach significance ($P = .054$). Conversely, grade 3 or 4 AST/ALT elevation in arm B was severer than in arm A ($P = .002$). Severe ILD induced by gefitinib, which many patients feared developing, was observed in two patients in this study.

Disease-Related Symptoms Assessment

All 595 patients completed baseline LCS questionnaires; questionnaire completion rates were 81.0% at 12 weeks and 70.3% at 18 weeks. LCS data were missing in 111 surveys because of death or severe impairment of the patient's general condition; this accounted for 6.2% of the total number of surveys scheduled. The adjusted mean of initial summed scores of LCS were 20.3 for arm A and 20.6 for arm B, respectively. The adjusted LCS scores at 12 and 18 weeks were 21.0 and 20.9 for arm A, and 21.8 and 21.2 for arm B, respectively. Sequential gefitinib seemed to provide better symptom relief, although differences did not reach statistical significance ($P = .10$).

DISCUSSION

Sequential gefitinib therapy after three cycles of standard platinum-doublet chemotherapy showed no survival benefit over platinum-doublet chemotherapy up to six cycles in previously untreated patients with advanced NSCLC. However, sequential gefitinib was associated with significantly prolonged PFS. Recently, positive results with maintenance or sequential chemotherapy have been reported in clinical trials in PFS or time to progression; however, OS was not significantly lengthened.[20,21] More recently, pemetrexed administered to NSCLC patients without progression after four cycles of first-line treatment with platinum-doublet provided significant improvement in PFS compared with placebo (HR, 0.60; 95% CI, 0.49 to 0.73; $P < .00001$).[22]

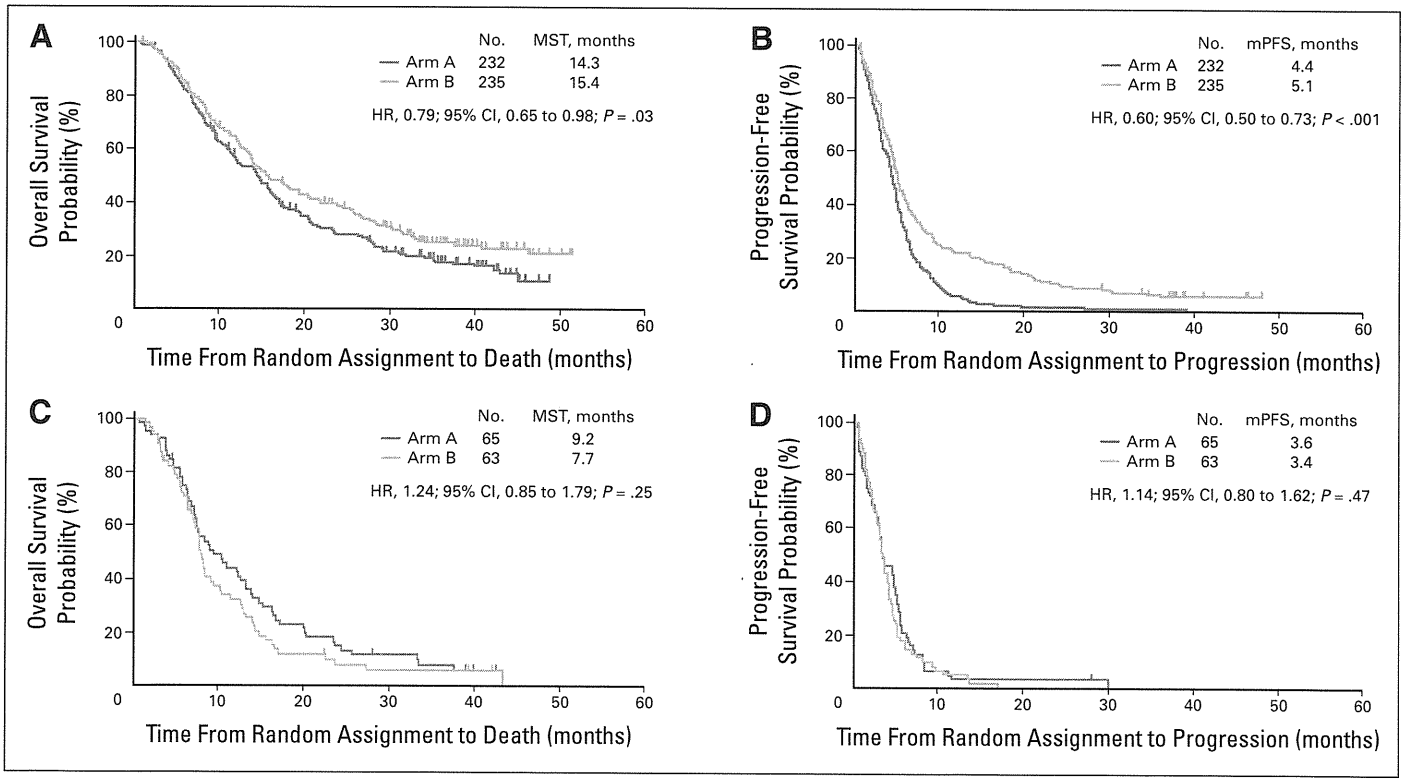

Fig 4. (A) Overall survival in the subset groups of patients with adenocarcinoma (n = 467), (B) progression-free survival in the subset groups of patients with adenocarcinoma (n = 467), (C) overall survival in the subset groups of patients with nonadenocarcinoma (n = 128), and (D) progression-free survival in the subset groups of patients with nonadenocarcinoma (n = 128). MST, median survival time; HR, hazard ratio; mPFS, median progression-free survival.

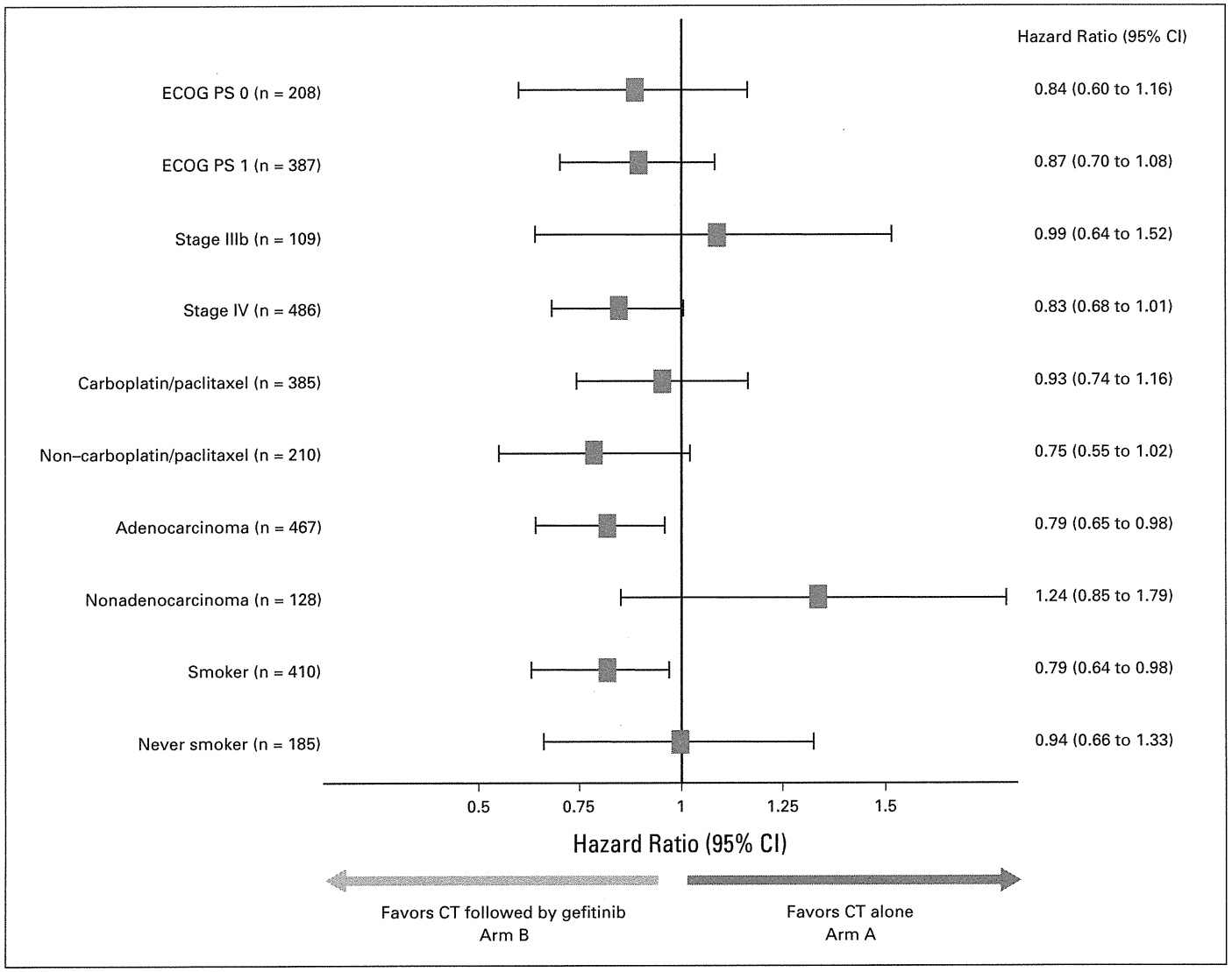

Fig 5. Forest plot subgroup analysis according to patients' backgrounds. CT, chemotherapy; ECOG PS, Eastern Cooperative Oncology Group performance status.

It was the first randomized, double-blind, placebo controlled trial to demonstrate a significant OS prolongation for maintenance treatment with pemetrexed in patients with advanced NSCLC (HR, 0.79; 95% CI, 0.65 to 0.95; $P = .012$).[22] The results of the Sequential Erlotinib in Unresectable NSCLC (SATURN) study, which was a randomized, double-blind, placebo controlled trial with erlotinib as maintenance, were presented this year. Erlotinib maintenance treatment had improvement in PFS of 41% compared with placebo.[23] Maintenance or sequential chemotherapy strategy after standard treatment has lately been receiving considerable attention. As a result, our trial was considered a consolidation therapy using other agent without progression after front-line treatment rather than maintenance.

Although the median number of chemotherapy cycles was three in both arms, 47.5% of patients received more than four cycles in Arm A. The number of treatment cycles was lower in Japanese than in whites; however, comparability was to be kept between the two arms in this randomized trial. These results were consistent with Japanese data on the median number of cycles of platinum-doublet chemotherapy.[15]

Toxicity results were consistent with previous Japanese studies of advanced NSCLC patients who received platinum-doublet chemotherapy.[15,16] Furthermore, no significant severe adverse events were seen that were not predictable from the safety profiles of gefitinib in sequential therapy after platinum-doublet chemotherapy. Recently published data suggested that gefitinib might be associated with ILD in Japanese patients[11]; however, in our study, the overall incidence of ILD was less than 1%, and no imbalance was identified between the two treatment arms in terms of ILD.

It was interesting that sequential gefitinib therapy had a significant survival prolongation in patients with adenocarcinoma histology (HR, 0.79; 95% CI, 0.65 to 0.98; $P = .03$). There was no difference also in PFS or OS for patients with nonadenocarcinoma. It was possible that these patients just did not benefit from an ineffective therapy of sequential gefitinib. In patients with NSCLC, adenocarcinoma histology, nonsmoker, and Japanese or Asian ethnicity are favorable predictive factors for a response to gefitinib treatment.[11-14] When the analysis was performed in the most favorable subset population that responded to gefitinib—that is, among those with both adenocarcinoma histology and nonsmokers—the MST was 23.5 months in arm A and 25.1 months and in arm B, respectively. Indeed, more than three quarters of the patients with favorable profiles in arm A received gefitinib after the protocol treatment, because physicians recognized

Table 2. Toxicity According to National Cancer Institute Common Toxicity Criteria Version 2

Toxicity	Arm A (n = 298)				Arm B (n = 300)				χ^2 Test *P* for Grade 3 + 4
	Grade 3		Grade 4		Grade 3		Grade 4		
	No.	%	No.	%	No.	%	No.	%	
Hematologic									
Leukopenia	98	32.9	21	7.0	97	32.3	14	4.7	.461
Neutropenia	90	30.2	136	45.6	79	26.3	133	44.3	.153
Febrile neutropenia	33	11.1	5	1.7	38	12.8	0	0	.297
Anemia	57	19.1	8	2.7	35	11.7	5	1.7	.006
Thrombocytopenia	32	10.7	0	0	18	6.0	1	0.3	.054
Nonhematologic									
Anorexia	43	14.4	0	0	33	11.0	2	0.7	.316
AST/ALT	11	3.7	1	0.3	32	10.7	0	0	.002
Constipation	25	8.4	0	0	20	6.7	1	0.3	.631
Creatinine	1	0.3	0	0	0	0	0	0	.315
Diarrhea	6	2.0	0	0	5	1.7	0	0	.152
Dyspnea	3	1.0	5	1.7	4	1.3	5	1.7	.816
Fatigue	22	7.4	7	2.3	18	6.0	4	1.3	.294
Hypersensitivity	1	0.3	1	0.3	2	0.7	2	0.7	.417
Infection	36	12.1	1	0.3	26	8.7	0	0	.135
Nausea	38	12.8	0	0	29	9.7	0	0	.232
Neuropathy									
Motor	5	1.7	1	0.3	4	1.3	1	0.3	.991
Sensory	12	4.0	1	0.3	7	2.3	0	0	.260
Performance status	27	9.1	8	2.7	23	7.7	9	3.0	.676
Pneumonitis (ILD)	2	0.7	0	0	4	1.3	0	0	.417
Rash	2	0.7	0	0	1	0.3	0	0	.559
Stomatitis/pharingitis	0	0	0	0	2	0.7	0	0	.482
Vomiting	12	4.0	1	0.3	15	5.0	2	0.7	.465

Abbreviation: ILD, interstitial lung disease.

these patients were more likely to respond to gefitinib. Patients who were nonsmokers with adenocarcinoma in arm A resulted in subsequent gefitinib therapy as well as in arm B.

Activating mutations in the gene for *EGFR* appear in a subset of adenocarcinoma of lung cancer.[24,25] A higher response to EGFR-TKIs is noted in specific subgroups that include females, never smokers, patients with adenocarcinoma histology, and East Asians.[12] Higher EGFR mutation rates are also noted in these subgroups and are also related to a better response to EGFR-TKIs[24,25] and longer survival.[12] Patients with these mutations exhibit objective response rates in the range of 75% to 95%.[12-14,26,27]

Patients included in this study were not selected on the basis of the target *EGFR* mutation status, because when this study was planned, we had not recognized the *EGFR* mutation as a predictive factor to respond to gefitinib. In Japanese patients with adenocarcinoma, a higher incidence of *EFGR* mutations, are estimated compared with white patients. It seems that more than 40% of Japanese patients with adenocarcinoma have an *EGFR* mutation.[12] Complex results in this study can be explained by analyzing the *EGFR* mutation status of participating patients. It may be important to select patients who are known to receive a clinical benefit with treatment using an EGFR-TKI.

In conclusion, this trial failed to meet the primary end point of OS in patients with advanced NSCLC. The exploratory subset analyses demonstrate a possible survival prolongation for sequential therapy of gefitinib, especially for patients with adenocarcinoma. Further investigations are warranted to confirm the best sequential therapy after platinum-based chemotherapy for patients with advanced NSCLC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Transarterial chemotherapy alone versus transarterial chemoembolization for hepatocellular carcinoma: A randomized phase III trial☆

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See Editorial, pages 981–983

***Background/Aims*: Transcatheter arterial chemoembolization (TACE) is a combination of transarterial infusion chemotherapy (TAI) and embolization, and has been widely used to treat patients with hepatocellular carcinoma (HCC). However, since the impact of adding embolization on the survival of patients treated with TAI had never been evaluated in a phase III study, we conducted a multi-center, open-label trial comparing TACE and TAI to assess the effect of adding embolization on survival.**

***Methods*: Patients with newly diagnosed unresectable HCC were randomly assigned to either a TACE group or a TAI group. Zinostatin stimalamer was injected into the hepatic artery, together with gelatin sponge in the TACE group and without gelatin sponge in the TAI group. Treatment was repeated when follow-up computed tomography showed the appearance of new lesions in the liver or re-growth of previously treated tumors.**

***Results*: Seventy-nine patients were assigned to the TACE group, and 82 were assigned to the TAI group. The two groups were comparable with respect to their baseline characteristics. At the time of the analysis, 51 patients in the TACE group and 58 in the TAI group had died. The median overall survival time was 646 days in the TACE group and 679 days in the TAI group ($p = 0.383$).**

***Conclusions*: The results of this study suggest that treatment intensification by adding embolization did not increase survival over TAI with zinostatin stimalamer alone in patients with HCC.**

Keywords: **Zinostatin stimalamer; Survival benefit; Overall survival; Lipiodol emulsion; Gelatin sponge**

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Abbreviations: HCC, hepatocellular carcinoma; AFP, α-fetoprotein; TACE, transarterial chemoembolization; TAI, transarterial infusion chemotherapy; SMANCS, zinostatin stimalamer; CT, computed tomography; TE, therapeutic effect; SMA, styrene maleic acid; NCS, neocarzinostatin.

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1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancers worldwide and a major cause of cancer mortality [1]. Although the screening of populations with a high risk of HCC using ultrasonography and serum α-fetoprotein (AFP) measurements have recently increased the number of candidates for effective local treatments such as hepatic resection and local ablation therapy, many patients exhibit HCCs that are unsuitable for local treatments at the time of the initial diagnosis or at the time of recurrence after local treatment. In these patients, transcatheter arterial chemoembolization (TACE) has been widely used, because TACE induces a marked antitumor effect in HCC.

Several randomized controlled studies have been conducted to assess the survival benefit of TACE compared with conservative therapy [2–9], and an improvement in survival with TACE has been shown in two recent phase III studies [7,8], in both of which TACE was compared with no treatment, and in two meta-analyses [10,11]. However, the impact of adding embolization on the overall survival of patients treated with transarterial infusion chemotherapy (TAI) has never been evaluated in a randomized controlled phase III study. We conducted a multi-centre, open-label trial to compare the effects of TACE and TAI alone to clarify the possible benefits of treatment intensification using embolization in addition to infusion chemotherapy. In this study, zinostatin stimalamer (SMANCS) was selected as the chemotherapeutic agent for use with both TACE and TAI. SMANCS is a lipophilic anti-cancer agent that dissolves in lipiodol to form a stable solution, retaining selectively in HCC. TAI with SMANCS has been widely used in clinical practice to treat patients with advanced HCC in Japan, because it has been reported to have fewer deleterious effects than TACE, especially on liver function, and to have an antitumor effect superior to TAI with other water-soluble agents in non-randomized studies [12,13].

2. Methods

Consecutive new patients with HCC were eligible if they had no indications for resection and/or local ablation therapy. The diagnosis was confirmed histologically and/or clinically using angiography and computed tomography (CT). Each patient was required to meet the following criteria: intrahepatic lesions that showed tumor staining by angiography and those in which the total size was less than 50% of the entire liver; adequate hematological function (white blood cells $\geqslant 3000/mm^3$, platelets $\geqslant 50{,}000/mm^3$, and hemoglobin $\geqslant 9.0$ g/dL), adequate hepatic function (serum total bilirubin $\leqslant 2.0$ mg/dL, serum albumin $\geqslant 3.0$ g/dL, serum AST [aspartate aminotransferase] $\leqslant 5$ times the upper limit of normal, serum ALT [alanine aminotransferase] $\leqslant 5$ times the upper limit of normal); adequate renal function (serum creatinine < the upper limit of normal, and serum blood urea nitrogen < the upper limit of normal); an Eastern Cooperative Oncology Group performance status of 0–1; an age of between 20 and 74 years of age; technically eligible for intra-arterial therapy; and written informed consent. Patients were excluded if they met any of the following criteria: a history of allergy to iodine-containing agents and/or contrast material; concomitant malignancy; a history of anti-cancer treatment for HCC; extrahepatic metastasis or tumor thrombus in the portal vein and/or the hepatic vein; intrahepatic arteriovenous shunting; ascites and/or pleural effusion not controlled by diuretics; pregnant or lactating woman and fertile patients not using effective contraception; myocardial infarction within the previous 6 months; or any serious physical and/or mental conditions. The study was performed in accordance with the Declaration of Helsinki, and approved by the ethics committee of each participating center. The study was investigator-designed and investigator-driven, and it received no support from any pharmaceutical companies.

Patients who met the eligibility criteria were provisionally registered before undergoing angiography. After confirmation of technical eligibility and reconfirmation of indications for the protocol intra-arterial treatments in regard to tumor status, including the number of tumors, their vascularity, and vascular invasion based on the angiographic findings, confirmatory registration was completed by each participating investigator. Central randomization to either a TACE group or TAI group was performed by using a telephone randomization system with stratification according to AFP level and treatment center. First, participants were stratified according to AFP level into a group with levels less than 400 ng/mL and a group with levels of 400 ng/mL or more. The group with AFP levels less than 400 ng/mL was further stratified according to treatment center. Randomization was achieved using a computer-generated allocation by permutation of blocks in equal proportions.

The treatments were performed by the participating investigators at 10 Japanese centers. Zinostatin stimalamer (SMANCS; Astellas Pharm Inc., Tokyo, Japan)/lipiodol emulsion (1 mg/mL) was injected slowly under fluoroscopic monitoring into the artery feeding the HCC using a catheter in a superselective manner in both the TACE and the TAI groups. The emulsion was prepared by suspending the SMANCS in lipiodol and shaking just before injection. The volume of the emulsion, up to a maximum of 6 mL (containing 6 mg of SMANCS), was adjusted according to the tumor size and tumor distribution. In the patients in the TACE group, gelatin sponge particles were utilized after the injection of the SMANCS-lipiodol emulsion. Treatment was repeated when a follow-up CT examination showed new lesions in the liver or re-growth of previously treated tumors. Treatment was discontinued if the size of the tumor treated had increased by more than 25% one month after the previous treatment; if there were any vascular contraindications, any exclusion criteria, or any severe adverse effects (defined as grade 4 leucopenia, grade 4 neutropenia, or grade 3 febrile leucopenia/neutropenia, a serum total bilirubin elevation of more than or equal to 5.0 mg/dL, a serum creatinine elevation of more than or equal to 1.5 times the upper normal limit, or grade 3 or greater non-hematological toxicity excluding nausea, vomiting, anorexia, pain, fever, hyperglycemia, fatigue, and serum transaminase elevation), or if the patient so requested.

The primary outcome measure was survival calculated from the date of randomization. Secondary outcome measures were tumor response and toxicity. Antitumor effect was evaluated by CT performed 1 month after the completion of treatment and every 3–4 months thereafter according to the response evaluation criteria proposed by the panel of experts of the Liver Cancer Study Group of Japan [14], which resemble the criteria proposed by the European Association for the Study of the Liver (EASL) Panel of Experts on HCC [15]. Tumor size was measured using the sum of the products of the perpendicular longest diameters of all measurable lesions. In the response evaluation criteria, lipiodol accumulation in the tumors is regarded as an indication of necrosis because significant positive correlations have been reported between lipiodol accumulation observed on CT images and the necrotic regions in resected tumors examined pathologically after TACE and after TAI with SMANCS [13,16,17]. Therapeutic effect V (TE V) is defined as the disappearance or 100% necrosis of all tumors, TE IV as a more than a 50% reduction in tumor size and/or more than 50% necrosis, and TE III as a more than 25% reduction and/or more than 25% necrosis. TE I is defined as a more than 25% increase in tumor size. TE II is defined as disease not qualifying for classification as TE V, IV, III, or I. The serum AFP level of each patient was also measured 1 month after treatment and every 3–4 months thereafter. Toxicity was assessed according to the criteria of the Japan Society for Cancer

Therapy [18], whose criteria are essentially the same as the WHO criteria [19]. The follow-up period was defined in the protocol as 2 years after the enrollment of the last patient.

2.1. Statistical analysis

Based on our previous phase II studies, in which we reported a 2-year survival rate of 80% in patients treated with TACE and of 60% in patients treated with TAI, 70 patients were required in each group to achieve a 90% power to detect superior survival in the TACE group by using a two-sided alpha level of 5% [13,20]. After sensitivity analyses of combinations of survival parameters, we targeted the recruitment of 80 patients in each group. All analyses were conducted based on the intention-to-treatment principle. Survival curves were calculated from the day of randomization using the Kaplan–Meier method and compared using the log-rank test. Comparisons between groups were made using the Wilcoxon test for continuous variables and Fisher's exact test for categorical variables. Analyses were conducted using SAS ver. 8.

3. Results

Between October 1999 and June 2003, 222 patients were provisionally enrolled in the study at 10 Japanese centers (Fig 1). Sixty-one of the 222 patients were excluded because of ineligibility for intra-arterial treatment based on the angiographic findings or withdrawal of consent; too few or too many definitive tumors that required reconsideration of the treatment strategy (46), tumor thrombus in the portal vein (3), tumors without sufficient tumor staining (3), intrahepatic arteriovenous shunting (2), allergy to contrast material (1), and withdrawal of consent (6). The most common reason for exclusion was having too few definitive tumors (37/61). The patients who were excluded because of having too few definitive tumors had been considered eligible based on the detection of several small hypervascular nodules on pre-treatment CT imaging that were diagnosed as HCC, but treatment had been switched to local ablation therapy or monitoring based on angiographic findings suggesting that the nodules represented dysplastic nodules. All of the patients who withdrew consent requested TACE for their treatments. The remaining 161 patients were allocated randomly to the TACE group (79 patients) or the TAI group (82 patients). Follow-up was continued through to June 17, 2005, two years after the enrollment of the last patient. Although the baseline data of some eligible patients did not meet the eligibility criteria after they were enrolled, the study protocol permitted initiation of treatment when according to the judgment of the investigator, treatment could be performed safely. Two patients had a pre-treatment serum albumin level that was below the eligibility criterion, but there were no statistically significant differences in baseline characteristics between the two groups (Table 1).

3.1. Treatment

The total number of treatment courses was 170 with a mean of 2.2 courses per patient (range, 1–9 courses) in the TACE group and 193 with a mean of 2.4 courses (range, 1–6 courses) in the TAI group. Eight patients in the TACE group and two patients in the TAI group were scheduled for the continuation of protocol treatment as of the date of the last follow-up. The remaining 71 patients in the TACE group and 80 patients in the TAI group had discontinued treatment. The reasons for treatment discontinuation were similar in both groups (Table 2).

3.2. Survival

At the time of the final analysis, 51 patients in the TACE group and 58 patients in the TAI group had died. Seven patients in the TACE group and eight in the TAI group were lost to follow-up after the cessation of protocol treatment. The median overall survival time was 646 days in the TACE group and 679 days in the TAI group. The estimated 2-year survival rate was 48.2% for the TACE group and 49.6% for the TAI group. No significant difference in survival was seen between the two groups ($p = 0.383$, Fig. 2).

3.3. Antitumor effect

The tumor response on CT was determined in 156 patients (77 in the TACE group and 79 in the TAI group). In the TACE group, there were 8 TE V, 29 TE IV, 31 TE III, 7 TE II, and 2 TE I responses. In the TAI group, there were 5 TE V, 22 TE IV, 30 TE III, 21 TE II, and 1 TE I response. The proportion of patients with TE V or IV among the measurable patients was not significantly different between the TACE group and the TAI group (48.1% vs. 34.2%; $p = 0.11$). There was no significant difference between the two groups in the proportion of patients with a pre-treatment AFP level > 200 ng/mL whose AFP level decreased by more than half (16.5% vs. 13.4%; $p = 0.66$).

3.4. Toxicity

Hematological toxicity was relatively mild and transient in both groups, although 2 patients (2.6%) in the TACE group and 3 (3.7%) in the TAI group developed grade 4 thrombocytopenia (Table 3). Major non-hematological toxicities were hyperbilirubinemia, elevations in serum liver enzymes, fever and abdominal pain in both groups. The grade of elevated ALT levels was significantly higher in the TACE group than in the TAI group, although there were no significant differences in any other toxicities between the two groups. No treatment-related death was observed in either group. Two patients in the TACE group and six in the TAI group manifested a grade 1–2 allergic reaction immediately after injection of the SMANCS-lipiodol emulsion. Shivering in the form of trembling of the whole body lasting

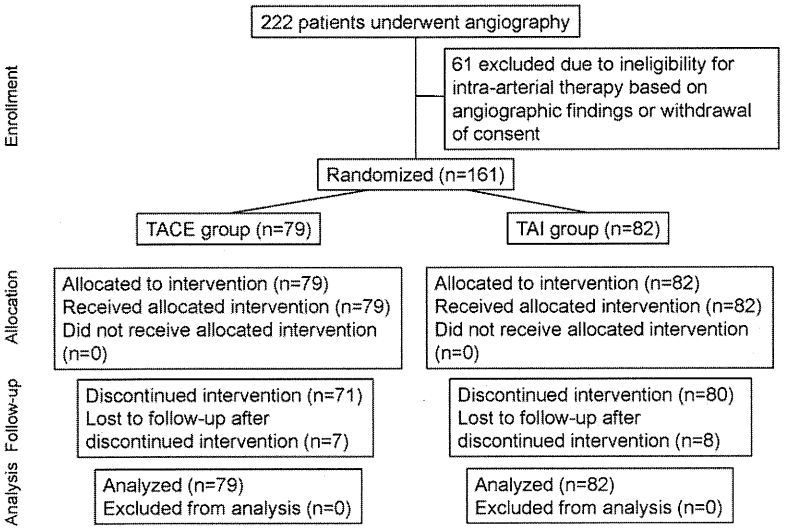

Fig. 1. Study flow diagram.

several minutes after the injection was noted in 12 patients in the TACE group and 14 patients in the TAI group, and it was thought to have been caused by SMANCS.

4. Discussion

We initiated this randomized study in 1999 because the impact of adding embolization on overall survival

Table 1
Baseline characteristics.

No. of patients		79	82
Age, year	Median (range)	65.0 (42–74)	67.0 (44–74)
Gender	Male	61 (77.2%)	70 (85.4%)
Performance status	0	76 (96.2%)	77 (93.9%)
	1	3 (3.8%)	5 (6.1%)
HBsAg	+	11 (13.9%)	7 (8.5%)
HCVAb	+	57 (72.2%)	60 (73.2%)
Alcohol abuse	+	33 (41.8%)	28 (34.1%)
Albumin, g/dL	Median (range)	3.6 (2.8–4.6)	3.6 (3.0–4.6)
Total bilirubin, mg/dL	Median (range)	1.0 (0.4–2.0)	0.9 (0.3–2.0)
AST, IU/L	Median (range)	63 (16–243)	69 (18–232)
ALT, IU/L	Median (range)	60 (12–184)	60 (10–213)
Prothrombin time, %	Median (range)	80 (41–129)	78.5 (43–111)
Platelet count, $\times 10^9$/L	Median (range)	110 (48–280)	120 (44–290)
	$<100 \times 10^9$/L	29 (36.7%)	28 (34.1%)
Ascites	+	3 (3.8%)	3 (3.7%)
Stage*	I	2 (2.5%)	4 (4.9%)
	II	18 (22.8%)	17 (20.7%)
	III	28 (35.4%)	25 (30.5%)
	IV-A	31 (39.2%)	36 (43.9%)
Tumor distribution	Unilateral	40 (50.6%)	36 (43.9%)
	Bilateral	39 (49.4%)	46 (56.1%)
Maximum tumor diameter, mm	Median (range)	35 (10–330)	35 (12–350)
Number or tumors	1	13 (16.5%)	11 (13.4%)
	2–5	43 (54.4%)	52 (63.4%)
	6	23 (29.1%)	19 (23.2%)
AFP, ng/ml	Median (range)	68.3 (2.8–79170)	93.8 (3.1–40,000)
	$\geqslant$400 ng/ml	26 (32.9%)	27 (32.9%)
Serum creatinine, mg/dL	Median (range)	0.7 (0.4–1.3)	0.8 (0.5–1.1)

Abbreviations: AFP, α-fetoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HBsAg, hepatitis B surface antigen; HCVAb, hepatitis C virus antibody.
Alcohol abuse was defined as ethanol intake $\geqslant$80 g/day for $\geqslant$5 years.
* According to the staging system of the Liver Cancer Study Group of Japan.

Table 2
Reasons for treatment discontinuation.

	TACE group		TAI group	
Ineffectiveness of protocol treatment	10	13%	10	12%
Adverse event caused by protocol treatment				
Elevation of serum creatinine level	1	1%	1	1%
Elevation of alkaline phosphatase level	2	3%	2	2%
Dyspnea	0	0%	1	1%
Hypotension	1	1%	1	1%
Shivers	0	0%	1	1%
Abdominal pain	0	0%	2	2%
Ascites	1	1%	0	0%
Deterioration before subsequent protocol treatment				
Extrahepatic metastasis	4	5%	7	9%
Portal vein thrombosis	6	8%	3	4%
Tumor rupture	2	3%	0	0%
Ascites	9	11%	11	13%
Liver dysfunction	9	11%	11	13%
Poor general condition	2	3%	2	2%
Other disease	1	1%	6	7%
Technical problem preventing subsequent protocol treatment	13	16%	9	11%
Patient's request	10	13%	11	13%
Indication for tumor ablation	1	1%	2	2%
Protocol treatment ongoing	7	9%	2	2%
Total	79		82	

for patients with advanced HCC treated with TAI had not been fully evaluated and because the efficacy of TACE was still being debated at that time in various countries. Moreover, several differences in TACE methods had been noted between clinical practice in East Asian countries, including Japan, and randomized studies conducted in Europe, including differences in the selection of embolization materials, anti-cancer agents and their doses, in treatment intervals, and in patient characteristics such as tumor stage and liver function. In this study, in which our TACE method was introduced, we selected SMANCS as a chemotherapeutic agent for both TACE and TAI. SMANCS is an anti-cancer drug that has been approved by the Japanese government for administration with lipiodol into the artery feeding HCC, and TAI with SMANCS has been widely used instead of TACE in many hospitals because of its favorable antitumor effect and mild toxicity profile.

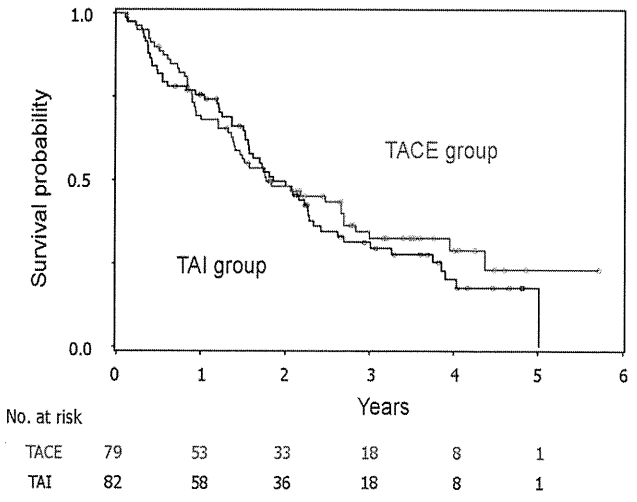

Fig. 2. Survival curves in the TACE group and in the TAI group.

This study did not confirm any significant survival advantage of TACE over TAI. A German group also reported that adding transient occlusion using degradable starch microspheres improved neither tumor response nor survival for patients treated with TAI using cisplatin and doxorubicin in a randomized phase II trial [21]. Llovet and Bruix showed that survival benefits were identified with TACE (doxorubicin or cisplatin) but not with embolization alone in their meta-analysis [11]. The survival benefit of TACE can be ascribed to the combination of embolization and chemotherapy.

It could be argued that the absence of a significant difference in survival rates between the TACE group and TAI group in this study is attributable to our methodological strategy for selecting SMANCS as the anti-cancer agent, because the agent may have produced favorable results in the TAI group. SMANCS is a high molecular weight chemical conjugate of a synthetic copolymer of styrene maleic acid (SMA) and the anti-cancer antibiotic protein, neocarzinostatin (NCS) [22,23]. SMANCS is lipophilic and dissolves in lipiodol to form a stable emulsion (SMANCS-lipiodol), which prevents rapid washout of SMANCS into plasma from trapped lipiodol. Furthermore, because of the enhanced permeability of the tumor vasculature and/or poor lym-

Table 3
Adverse events.

	TACE group						TAI group					
	Grade 3		Grade 4		Grade 1–4		Grade 3		Grade 4		Grade 1–4	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Hematological toxicity												
Leukocytes	1	1	0	0	27	34	0	0	0	0	26	32
Neutrophils	1	0	0	0	14	18	0	0	0	0	15	18
Hemoglobin	1	1	–		25	32	0	0	–		23	28
Platelets	10	13	2	3	54	68	10	12	3	4	57	70
Non-hematological toxicity												
Total bilirubin	21	27	0	0	60	76	15	18	0	0	62	76
Alkaline phosphatase	2	3	0	0	53	67	2	2	0	0	63	77
Aspartate aminotransferase	33	42	0	0	77	97	23	28	0	0	79	96
Alanine aminotransferase	28	35	0	0	73	92	16	20	0	0	77	94
Creatinine	0	0	0	0	13	16	0	0	0	0	16	20
Abdominal pain	0	0	0	0	55	70	2	2	0	0	50	61
Nausea/vomiting	1	1	–		43	54	0	0	–		39	48
Diarrhea	0	0	0	0	2	3	0	0	0	0	4	5
Fever	2	3	0	0	69	87	1	1	0	0	66	80
Shivers	0	0	0	0	12	15	1	1	0	0	14	17
Allergy	0	0	0	0	2	3	0	0	0	0	6	7
Ascites	1	1	–		3	4	0	0	–		0	0
Dyspnea	0	0	0	0	0	0	0	0	1	1	1	1
Hypotension	1	1	0	0	1	1	1	1	0	0	1	1

A 'dash' (–) indicates the grade was not available.

phatic drainage from the tumor interstitium, macromolecular agents like SMANCS are retained more selectively within tumors [24,25]. In fact, experimental studies have shown that tumor-systemic drug concentration ratios as high as 1000 can be achieved using TAI with SMANCS-lipiodol. Thus, the selective delivery of a long-lasting or slow-release anti-cancer agent may have had a sufficient antitumor effect and survival-prolonging efficacy in the TAI group even if embolization had not been used in combination.

The infrequent protocol treatment repetition in this study is another possible reason for the lack of any difference in survival between the two groups, because the average number of protocol treatments was only 2.2 courses in the TACE group and 2.4 in the TAI group, and thus the maximum anti-cancer potential may not have been achieved. We speculated that the choice of SMANCS was partly responsible for the infrequent repetition because hepatic vascular complications, such as the obstruction of the hepatic artery and the arterio-portal shunt, have been reported as adverse reactions specific to SMANCS [26]. These complications are often followed by liver dysfunction, ascites, and technical problems with regard to subsequent protocol treatment, which were the major reasons for treatment discontinuation in this study. The enrollment of many patients with far-advanced HCC in the present phase III study may have been another reason for the small number of treatment repetitions and the subsequent poor survival: the proportion of patients with a pre-treatment AFP level >200 ng/mL was 40% in the phase III study and 24% in the phase II study. Both the antitumor response and the overall survival of the TACE group were poorer than our expectations: the 2-year survival rate in the TACE group was 48.2% in the present study, as opposed to 79% in the phase II study of TACE with SMANCS.

In conclusion, the results of this study suggest that treatment intensification by adding embolization did not increase the survival of HCC patients over SMANCS transarterial chemotherapy alone. The results of this study also showed no significant differences in toxicity, except for an ALP elevation, between the two groups treated with SMANCS. It should be emphasized that the negative results in this study may be attributable to our methodological strategy for selecting SMANCS and the enrollment of many patients with far-advanced HCC. The infrequent treatment repetition and the favorable results of TAI with SMANCS are speculated to be reasons for the lack of any difference in survival between the two groups. Furthermore, the results of this study must be interpreted with caution because current TACE protocols have evolved thanks to the implementation of updated devices including new embolic agents and improved catheters. Additional studies will be required to determine whether the results obtained in this trial are consistent with the results of transarterial treatment with chemotherapeutic agents other than SMANCS and with updated procedures, although it would be difficult to conduct such studies because many consider TACE to be the standard treatment based on the positive results obtained in two recent randomized studies in which doxorubicin or cisplatin was used

[7,8]. There is a more pressing need for the establishment of new and more active treatment strategies that are superior to conventional TACE to improve the dismal prognosis of this disease.

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ORIGINAL ARTICLE

A phase II study of uracil-tegafur plus doxorubicin and prognostic factors in patients with unresectable biliary tract cancer

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Abstract

Purpose The purpose of this study was to clarify the safety and efficacy of combination chemotherapy of uracil-tegafur (UFT) and doxorubicin (UFD regimen), and to identify the prognostic factors in patients with unresectable advanced biliary tract cancer who received systemic chemotherapy.

Methods Patients with histologically or cytologically confirmed, measurable biliary tract cancer, including intrahepatic or extrahepatic cholangiocarcinoma, gallbladder cancer, and ampullary cancer, who were not suitable candidates for surgery, were eligible for the study. Patients received oral UFT at 300 mg/m^2 per day divided into two doses on days 1–14 and intravenous doxorubicin at 30 mg/m^2 on day 1. This cycle was repeated every 21 days. The relationship between the patient characteristics and the prognosis was examined. Univariate and multivariate analyses were conducted to identify the prognostic factors associated with survival.

Results Sixty-one patients from 12 institutions were enrolled in the late phase II study between April 2005 and March 2006. Of the 61 patients, 4 patients had partial responses, for an objective response rate of 6.6% (95% CI: 1.8–15.9%); 28 patients had stable disease, 27 had progressive diseases, and 2 patients were not evaluated. The median progression-free survival was 1.6 months, and the overall median survival time was 6.5 months. In the 85 patients who received this UFD chemotherapy in previous and late phase II studies, multivariate analysis revealed the ECOG performance status 1 ($P = 0.001$), gallbladder as the

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primary cancer site ($P = 0.014$), T-factor 4 of the TNM classification ($P = 0.035$), and elevated serum lactate dehydrogenase levels ($P = 0.043$) as being associated with a significantly shorter survival.

Conclusions Combination chemotherapy of UFT and doxorubicin had minimum activity against advanced biliary tract cancer. Performance status was identified as the most important prognostic factor in patients who received systemic chemotherapy.

Keywords Biliary tract cancer · Systemic chemotherapy · Uracil-tegafur · Doxorubicin · Phase II study · Prognostic factor

Introduction

Biliary tract cancer consists of cholangiocarcinoma (CC), gallbladder cancer (GBC), and ampullary cancer (AC) [1]; intrahepatic cholangiocarcinoma is often included in clinical trials for biliary tract cancer. Each type of cancer has characteristic features, and the treatment strategy and prognosis are different. This heterogeneity has made it difficult to conduct and evaluate chemotherapy for biliary tract cancer. Biliary tract cancer is relatively uncommon in western countries, but it is a common cause of cancer-related death in Asia. In Japan, the mortality is estimated to be 16,000 deaths annually [2]. While surgery currently remains the only potentially curative treatment, most patients are found to have an unresectable advanced stage of disease. Although patients with unresectable disease receive various palliative treatments, including systemic chemotherapy, the prognosis remains extremely poor.

A previous report showed improved survival in patients with biliary tract cancer treated with 5-fluorouracil (5-FU)-based chemotherapy compared to the best supportive care [3]. Efforts have been made to develop promising regimens for biliary tract cancer using clinical trials of systemic chemotherapy [4]. In various reports on chemotherapy for biliary tract cancer, fluoropyrimidines have been considered as the basis of chemotherapy [5–7]. Furthermore, cisplatin or anthracycline antitumor antibiotic agents such as doxorubicin and epirubicin have been used as combination chemotherapy with 5-FU [8–10]. Recently, clinical trials of gemcitabine show moderate activity against biliary tract cancers, and gemcitabine-based regimens have been investigated [11–22]. However, no standard chemotherapy has currently been identified that can clearly prolong survival.

In Japan, until 2006, only three anticancer agents—uracil–tegafur (UFT), doxorubicin, and cytarabine—had been approved by the Ministry of Health, Labour, and Welfare for biliary tract cancer. Uracil-tegafur is an orally administered drug that is a combination of uracil and tegafur in a 4:1 molar concentration ratio. Tegafur is a 5-FU prodrug that is hydroxylated and converted to 5-FU by hepatic microsomal enzymes. Uracil prevents degradation of 5-FU by inhibiting dihydropyrimidine dehydrogenase, which leads to an increased level of 5-FU in plasma and tumor tissues [23, 24]. Doxorubicin is an anthracycline antibiotic that induces various biologic effects and has one of the widest spectra of antitumor activity against lymphomas, leukemias, soft tissue sarcomas, and a variety of carcinomas. Because, UFT + doxorubicin is the only doublet regimen currently covered by health insurance in Japan, we investigated the combination of UFT and doxorubicin (the UFD regimen) in patients with unresectable advanced biliary tract cancer as an early phase II study in 2004. In that study, the UFD showed modest activity; the response rate was 12.5%, the median progression-free survival (PFS) was 2.5 months, and the median overall survival (OS) was 7.6 months [25]. To examine the safety and efficacy in a larger number of patients, a multicenter late phase II study was conducted in a Japanese chemotherapy study group for biliary tract and pancreatic cancers. The objectives of the study were to evaluate response rate, toxicity, PFS, and OS. As an additional exploratory analysis, we examined the prognostic factors in patients with unresectable biliary tract cancer who had received the UFD regimen in the early and current phase II studies.

Patients and methods

Patient eligibility

The eligibility criteria for enrollment in this late phase II study were: (1) histologically or cytologically confirmed biliary tract cancer consisting of intrahepatic CC (ICC), extrahepatic CC (ECC), GBC, or AC; (2) measurable disease on computed tomography (CT) or magnetic resonance imaging (MRI); (3) unresectable disease; (4) no prior chemotherapy; (5) age $\geq$ 20 years, with a set upper limit of 74 years according to another Japanese trials of gemcitabine and S-1 [13, 26]; (6) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; (7) adequate bone marrow function (leukocyte count $\geq$ 4,000 cells/mm^3, platelet count $\geq$ 100,000 cells/mm^3, and hemoglobin $\geq$ 9.0 g/dL), renal function (serum creatinine concentration $\leq$ upper limit of normal range), and hepatic function [serum bilirubin level $\leq$ 2.0 mg/dL, serum albumin level $\geq$ 3.0 g/dL, and serum aspartate transaminase (AST) and alanine transaminase (ALT) levels $\leq$ 2.5 times the upper limit of normal range]; (8) life expectancy $\geq$ 8 weeks; and (9) written informed consent from the patient. Percutaneous biliary drainage was performed in patients with obstructive jaundice and these patients were

required to have serum bilirubin levels of ≤ 3.0 mg/dL, and serum AST and ALT levels ≤ 5 times the upper limit of normal before enrollment. Exclusion criteria were: serious complications such as active infection, active gastrointestinal ulcer, cardiac disease, or renal disease; central nervous system metastasis; marked pleural effusion or ascites; symptomatic interstitial pneumonitis; and pregnancy or lactation for women. This study was approved by the local institutional review boards at all participating centers.

In addition, prognostic factors were analyzed in patients treated with the UFD regimen in the earlier and current phase II studies. The eligibility criteria for enrollment in the previous study were the same as those mentioned above for the current study, except that the upper age limit of 74 years for enrollment was not set.

Treatment methods

Uracil-tegafur was administered orally at a dose of 300 mg/m^2 per day (400 mg/day in patients with body surface < 1.50 m^2 and 500 mg/body per day in patients with body surface $\geq$ 1.50 m^2) divided into two dosages, for 14 consecutive days followed by 1 week of rest. Doxorubicin was given as a 10-min intravenous infusion on day 1 of each cycle at a dose of 30 mg/m^2. This cycle was repeated every 21 days provided that patients had recovered sufficiently from the drug-related side effects.

Patients continued to receive additional courses of this regimen until a maximum of 15 courses, evidence of disease progression, or the appearance of unacceptable toxicity. When hematological toxicity greater than grade 3 or nonhematological toxicity greater than grade 2 was observed, treatment was delayed until the toxicity subsided to grade 1 or less. If the daily dose of UFT was considered to be intolerable, the dose was reduced by 100 mg/day (one capsule/day). In general, patients were treated as outpatients and admitted to the hospital only for management of toxicities and disease-related complications.

Assessment of response and toxicity

Physical examination, complete blood cell counts, serum chemistries, and urinalysis were performed at baseline and at least twice in 3 weeks after initiating treatment. Patients underwent dynamic CT or MRI to evaluate response at 4–6-week intervals after the start of treatment. Computed tomography or MRI was performed by obtaining contiguous transverse sections using the helical scanning method at a section thickness of 5 mm. Tumor response was assessed using the Response Evaluation Criteria in Solid Tumors [27]. Objective responses were confirmed by a second evaluation performed at least 4 weeks later. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

Study designs

The primary end point of this study was the overall response rate and the secondary endpoints were adverse events, OS, and PFS. In this study, the threshold response rate was defined as 5%, the expected response rate was set as 15%, and a sample size of 40 would ensure that there was a 74% power at a one-sided significance level of 5% in the late phase II study. The accrual period was set at 1 year and follow-up period was set at 1 year. When 40 patients were enrolled, the enrollment was extended until the end of the accrual time to improve the statistical power.

Factors analyzed

Twenty-three clinical variables were chosen at the time of study enrollment for the univariate and multivariate analyses. Each variable was divided into two categories as follows: age (<64 or $\geq$64 years), sex (male or female), PS (0 or 1), pretreatment (surgery or no treatment), biliary drainage (yes or no), diagnosis (GBC or non-GBC including ICC, ECC, and AC), white blood cell count (<8,000 or $\geq$8,000/mL), hemoglobin level (<11.0 or $\geq$11.0 g/dL), platelet count (<150,000 or $\geq$150,000/mL), serum total bilirubin level (<2.0 or $\geq$2.0 mg/dL), serum albumin level (<3.5 or $\geq$3.5 g/dL), serum lactate dehydrogenase (LDH) level (<300 or $\geq$300 IU/L), serum AST and ALT levels (<40 or $\geq$40 IU/L), serum alkaline phosphatase (<400 or $\geq$400 IU/L), size of maximum targeted tumor (<60 mm or $\geq$60 mm), T-factor of TNM classification (Tx-3 or T4) [1], extent of disease (locally advanced and local recurrence after surgery, or metastatic), liver metastasis (presence or absence), ascites or peritoneal dissemination (presence or absence), lymph node metastasis (presence or absence), serum carcinoembryonic antigen (CEA) level (<10 or $\geq$10 ng/mL), and serum carbohydrate antigen 19-9 (CA 19-9) level (<1,000 or $\geq$1,000 U/mL). The size of the primary tumor was measured by enhanced CT. Peritoneal dissemination was defined as recognition of peritoneal nodules in CT scans or accumulation of ascites.

Statistical analysis

Progression-free survival was calculated from the first day of treatment until evidence of tumor progression, clinical progression, or death due to any cause. Overall survival was calculated from the first day of treatment until death due to any cause. Survival data were analyzed using the Kaplan–Meier method. The tumor response, toxicity, and survival were evaluated on an intention-to-treat basis.