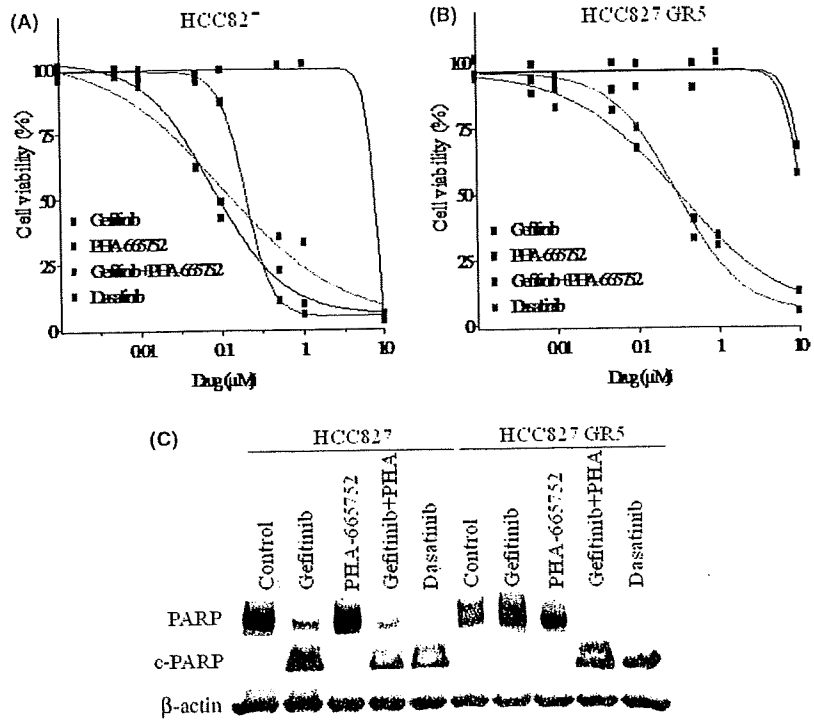

Fig. 3. Effects of dasatinib on growth and apoptosis in gefitinib-resistant non-small cell lung cancer cells with *MET* amplification. (A) HCC827 cells or (B) HCC827 GR5 cells were treated for 72 h with increasing concentrations of gefitinib alone, PHA-665752 alone, gefitinib and PHA-665752 in combination, or dasatinib alone in medium containing 10% serum, after which cell viability was assessed. Data are means of triplicates from a representative experiment and are expressed as a percentage of the value for untreated cells. (C) HCC827 and HCC827 GR5 cells were incubated for 72 h with gefitinib (1 μM) alone, PHA-665752 (1 μM) alone, gefitinib plus PHA-665752, or dasatinib (1 μM) in medium containing 10% serum. Cell lysates were then prepared and subjected to immunoblot analysis with antibodies to poly(ADP-ribose) polymerase (PARP) and to β-actin. The positions of intact PARP (116 kDa) and the 85-kDa cleavage fragment (c-PARP) are shown.

could not reduce tumor size compared with vehicle treatment (Fig. 4). In contrast, dasatinib (15 mg/kg) inhibited tumor growth in HCC827 GR5 xenografts to a significantly greater extent than did treatment with gefitinib or vehicle alone (Fig. 4). These results indicated that Src inhibitor effectively exerts anti-tumor effects in gefitinib-resistant NSCLC xenografts with *MET* amplification.

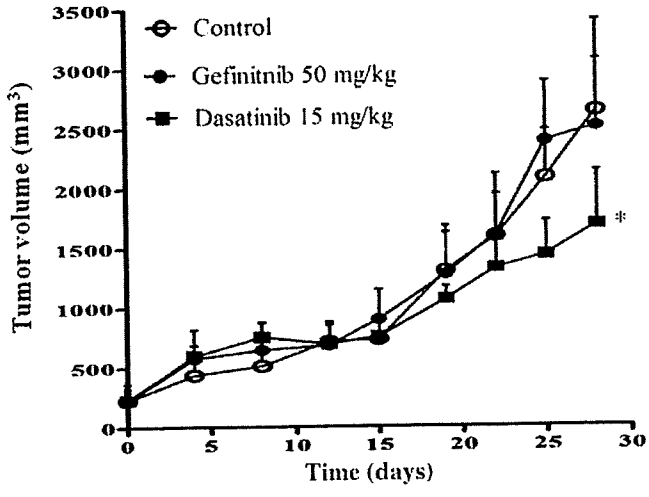

Fig. 4. Effects of dasatinib on the growth of gefitinib-resistant non-small cell lung cancer cells with *MET* amplification *in vivo*. Nude mice with tumor xenografts established by s.c. implantation of HCC827 GR5 cells were treated daily for 28 days with vehicle (control), gefitinib (50 mg/kg), or dasatinib (15 mg/kg) by oral gavage. Tumor volume was determined at the indicated times after the onset of treatment. Points indicate the mean of values from five mice per group; bars indicate SE. $*P < 0.05$ for dasatinib *versus* control or gefitinib alone (Student's *t*-test).

Discussion

The emergence of *MET* amplification induces ErbB3-dependent downstream signaling mediated by Akt and Erk that is important for cell survival and proliferation, ultimately leading to the development of gefitinib resistance, in NSCLC cells with *EGFR* mutations.[22,23] Although the combination of the specific MET inhibitor PHA-665752 and gefitinib is considered promising for overcoming gefitinib resistance due to *MET* amplification, a single-agent therapy to overcome such resistance would be more desirable.[22,23] We have shown that, in addition to MET activation, Src is markedly activated in NSCLC cells with *MET* amplification, including HCC827 GR cells. Forced expression of Src has previously been shown to result in gefitinib resistance in gallbladder adenocarcinoma cells[38] and to promote tumorigenesis in EGFR-overexpressing mammary epithelial cells.[39] In addition, MET and Src cooperate to mediate proliferation of breast cancer cells in the presence of EGFR-TKI.[34] Consistent with these previous observations, our results now suggest that Src contributes to gefitinib resistance in NSCLC cells with *MET* amplification and is a potential target molecule for overcoming such resistance.

To explore how Src activation affects MET or EGFR signaling in gefitinib-resistant NSCLC cells with *MET* amplification, we examined the effects of Src inhibitors on EGFR, ErbB3, and MET activation in both HCC827 and HCC827 GR5 cells. Gefitinib was previously shown to inhibit ErbB3 and MET activation as well as EGFR activation in the parental HCC827 cells,[22,23,40] suggestive of a functional interaction between EGFR and both ErbB3 and MET in *EGFR*-mutant NSCLC cells without *MET* amplification (Fig. 5A). In contrast, gefitinib did not inhibit ErbB3 or MET activation in HCC827 GR cells, with the combination of gefitinib and PHA-665752 being necessary to achieve inhibition of ErbB3 activation in these cells with *MET* amplification.[22,23] In addition, endogenous ErbB3 was co-immunoprecipitated with MET from HCC827 GR cells

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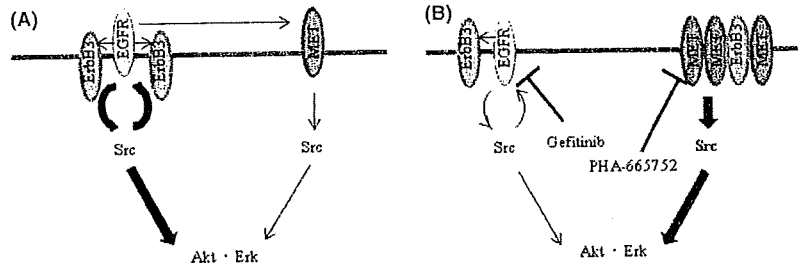

Fig. 5. Models for signaling pathways in gefitinib-sensitive non-small cell lung cancer (NSCLC) cells (A) and gefitinib-resistant NSCLC cells with acquired *MET* amplification (B). Src functions downstream of both epidermal growth factor receptor (EGFR) and MET as well as upstream of Akt and Erk signaling pathways and EGFR. However, the dependency of Src signaling is shifted from EGFR to MET and MET associates with ErbB3 after the acquisition of *MET* amplification. EGFR mediates, at least in part, activation of MET in gefitinib-sensitive NSCLC cells, whereas EGFR and MET function independently of each other in gefitinib-resistant NSCLC cells with acquired *MET* amplification. Pathways targeted by gefitinib or PHA-665752 are indicated, and the relative activities of signaling pathways are denoted by the width of the arrows.

but not from HCC827 cells.[22,23] These previous results thus suggested that ErbB3 signaling becomes more dependent on MET than on EGFR after emergence of *MET* amplification, and that the MET-ErbB3 signaling complex is largely independent of EGFR signaling (Fig. 5B).[22,23] We have shown that Src inhibitors reduced the extent of EGFR activation in both HCC827 and HCC827 GR5 cells, consistent with previous observations showing that Src mediates EGFR activation by phosphorylating its Y845 residue.[37,41] In HCC827 GR5 cells, however, Src inhibitors did not inhibit ErbB3 or MET activation, despite it doing so in the parental HCC827 cells. These results support the notion that MET signaling is independent of EGFR signaling as a result of the shift of the dependence of ErbB3 signaling from EGFR to MET in HCC827 GR cells (Fig. 5B).[22,23]

We examined whether *MET* amplification affects the physical association between Src and either EGFR, MET, or ErbB3 by immunoprecipitation. The association between MET and Src was increased in HCC827 GR5 cells compared with that in HCC827 cells, whereas the association between EGFR and Src was reduced in HCC827 GR5 cells. These findings are consistent with our results showing that PHA-665752 blocks Src activation to a greater extent in HCC827 GR5 cells than in HCC827 cells, a pattern opposite to that for the effects of gefitinib (Fig. 5). The mechanism of increased association between MET and Src induced by acquired *MET* amplification has remained unclear. It is possible that *MET* amplification alters the protein expression which mediates binding of Src to MET. On the basis of the notion that Src is activated downstream of MET signaling in HCC827 GR cells, we examined the effects of Src inhibitors in these cells on Akt and Erk signaling pathways, both of which are known to be activated by Src.[24–26,42] We have shown that Src inhibitors markedly inhibited Akt and Erk signaling pathways in gefitinib-resistant NSCLC cells with *MET* amplification. Previous studies found that neither gefitinib nor PHA-665752 alone blocked Akt or Erk pathways in HCC827 GR cells,[22,23] with the combination of both of these agents being necessary for such inhibition, consistent with the notion that Akt and Erk pathways are dependent on both EGFR and MET signaling in these cells (Fig. 5B). We observed that gefitinib and PHA-665752 each induced a slight increase in the phosphorylation levels of Akt in HCC827 GR5 cells (Fig. 2A), possibly because EGFR and MET pathways functionally compensate for each other when either is inhibited. Our results suggest that Src functions downstream of both EGFR and MET, but that it is mainly dependent on MET signaling in HCC827 GR cells. Together, our observations explain the ability of Src inhibitors to suppress Akt and Erk activation in gefitinib-resistant NSCLC cells with *MET* amplification (Fig. 5B).

Finally, we found that Src inhibitor dasatinib also inhibited the growth of HCC827 GR5 cells as well as did combined treatment with gefitinib and PHA-665752. HCC827 GR5 cells underwent apoptosis, as detected by PARP cleavage, after treatment with dasatinib. Furthermore, dasatinib inhibited tumor growth in HCC827 GR5 xenografts to a significantly greater extent than treatment with gefitinib alone. Our present data suggest that Src inhibitors might overcome gefitinib resistance in NSCLC patients with *MET* amplification. Our findings strengthen the rationale of the ongoing clinical trial of dasatinib for NSCLC patients who no longer respond to erlotinib or gefitinib (http://www.clinicaltrials.gov). The results of this clinical trial should provide insight into the relation between the efficacy of Src inhibitors and whether gefitinib resistance is attributable to the secondary T790M mutation of *EGFR* or to acquired *MET* amplification.

Abbreviations

EGFR	epidermal growth factor receptor
NSCLC	non-small cell lung cancer
PARP	poly(ADP-ribose) polymerase
TKI	tyrosine kinase inhibitor

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ORIGINAL REPORT

Meta-Analysis of Single-Agent Chemotherapy Compared With Combination Chemotherapy As Second-Line Treatment of Advanced Non–Small-Cell Lung Cancer

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The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
Doublet chemotherapy is more effective than single-agent as first-line treatment of advanced non–small-cell lung cancer (NSCLC). As second-line treatment, several randomized trials have been performed comparing single-agent with doublet chemotherapy, but each trial had an insufficient power to detect potentially relevant differences in survival.

Methods
We performed meta-analysis of individual patient data from randomized trials, both published and unpublished, comparing single-agent with doublet chemotherapy as second-line treatment of advanced NSCLC. Primary end point was overall survival (OS). All statistical analyses were stratified by trial.

Results
Eight eligible trials were identified. Data of two trials were not available, and data of six trials (847 patients) were collected. Median age was 61 years. Performance status was 0 or 1 in 90%; 80% of patients had received previous platin-based chemotherapy. OS was not significantly different between arms ($P = .32$). Median OS was 37.3 and 34.7 weeks in the doublet and single-agent arms, respectively. Hazard ratio (HR) was 0.92 (95% CI, 0.79 to 1.08). Response rate was 15.1% with doublet and 7.3% with single-agent ($P = .0004$). Median progression-free survival was 14 weeks for doublet and 11.7 weeks for single agent ($P = .0009$; HR, 0.79; 95% CI, 0.68 to 0.91). There was no significant heterogeneity among trials for the three efficacy outcomes. Patients treated with doublet chemotherapy had significantly more grade 3 to 4 hematologic (41% *v* 25%; $P < .0001$) and grade 3 to 4 nonhematologic toxicity (28% *v* 22%; $P = .034$).

Conclusion
Doublet chemotherapy as second-line treatment of advanced NSCLC significantly increases response rate and progression-free survival, but is more toxic and does not improve overall survival compared to single-agent.

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INTRODUCTION

Cisplatin-based chemotherapy is considered standard of care worldwide for patients with advanced non–small-cell lung cancer (NSCLC).[1] At disease progression, many patients still have a good performance status (PS) and can be considered for further active treatment.

Until 2000, there was no evidence supporting the efficacy of second-line treatment, but in recent years the efficacy of several drugs in this setting has been demonstrated in phase III trials, and second-line treatment is now considered standard.[2,3]

In particular, second-line chemotherapy with docetaxel 75 mg/m^2 every 3 weeks has been proven to be effective in two phase III trials.[4,5] This treatment, indeed, prolongs overall survival (OS) compared with best supportive care, and improves some quality of life items like fatigue and pain.[4] In a individual patient data meta-analysis,[6] weekly docetaxel demonstrated similar efficacy, with a significantly lower risk of febrile neutropenia. Pemetrexed has been shown to be comparable with docetaxel, with a more favorable toxicity profile.[7] To date, no single-agent treatment has obtained better results than docetaxel.

A logical strategy for improving the efficacy of second-line treatment is to combine agents with different mechanism of action and toxicity. In first-line treatment, doublet chemotherapy is more effective

than single-agent, both in terms of objective response and OS.[8] Several randomized trials comparing a doublet with single-agent chemotherapy as second-line have been conducted in recent years.[9-15] Most of these trials were characterized by a small sample size, with inadequate statistical power to exclude potentially clinically relevant differences in efficacy.

The main objective of this meta-analysis, based on individual patient data, is to compare the efficacy of a doublet chemotherapy with single-agent treatment for the second-line treatment of advanced NSCLC, with a statistical power much higher than each trial. Data regarding activity and toxicity were also collected and analyzed.

PATIENTS AND METHODS

Identification of Eligible Trials

Published and unpublished studies were included in this meta-analysis, as previously recommended.[16]

The literature search was performed in July 2007, and updated in June 2008, to identify all randomized trials comparing single-agent and combination chemotherapy in second-line treatment of patients with advanced NSCLC. Trials evaluating a combination of a cytotoxic agent with a targeted drug, or a combination of targeted agents were not eligible. Search was performed using PubMed, EMBASE, Proceedings of American Society of Clinical Oncology, Proceedings of European Society of Medical Oncology, Proceedings of European Cancer Conference, Proceedings of World Conference on Lung Cancer, and the registry of the U.S. National Institutes of Health clinicaltrials.gov from 1997 to 2008, with the following key-words: "lung cancer", "NSCLC"; "second-line", "randomized/randomized". References of the identified articles were checked, and principal investigators were asked whether they were aware of other published or unpublished trials.

Study Quality

Each study was assessed for quality and potential bias using a structured checklist based on the Method for Evaluating Research and Guideline Evidence criteria.[17] Study characteristics were quality of randomization, blinding, outcome measures, measure assessment, arm comparability, loss to follow-up, and intention to treat analysis. An overall quality score was assigned to each

Table 1. Characteristics of the Six Randomized Trials Included in the Meta-Analysis

Parameter	Study					
	Takeda et al[9]	Georgoulias et al[10]	Georgoulias et al[11]	Wachters et al[12]	Gebbia et al[14]	Smit et al[15]
Phase of the study	III	II*	II*	II	III	II*
Treatment dose and schedule						
Single-agent arm	Docetaxel 60 mg/m^2 day 1 every 3 weeks	Irinotecan 300 mg/m^2 day 1 every 3 weeks	Cisplatin 80 mg/m^2 day 1 every 3 weeks	Docetaxel 75 mg/m^2 day 1 every 3 weeks	Docetaxel 33.3 mg/m^2 days 1, 8, 15 every 4 weeks	Pemetrexed 500 mg/m^2 day 1 every 3 weeks
Combination arm	Docetaxel 60 mg/m^2 day 8 + gemcitabine 800 mg/m^2 days 1 and 8 every 3 weeks	Gemcitabine 1,000 mg/m^2 days 1 and 8 + irinotecan 300 mg/m^2 day 8 every 3 weeks	Cisplatin 80 mg/m^2 day 8 + irinotecan 110 mg/m^2 day 1, 100 mg/m^2 day 8, every 3 weeks	Docetaxel 60 mg/m^2 day 1 + irinotecan 200 mg/m^2 day 1 every 3 weeks	Docetaxel 30 mg/m^2 days 1, 8, 15 every 4 weeks + gemcitabine 800 mg/m^2 days 1 and 8 every 4 weeks or vinorelbine 20 mg/m^2 days 1 and 8 every 4 weeks or capecitabine 1,300 mg/m^2 days 5 to 18 every 4 weeks	Pemetrexed 500 mg/m^2 day 1 every 3 weeks + carboplatin AUC5 day 1 every 3 weeks
Primary end point	Overall survival	Overall survival	Overall survival	Response rate	Overall survival	Time to progression
Planned sample size	284	144	130	106	375	240
Actual sample size	130	147	139	108	84	240
Start of the accrual	January 2002	September 1999	July 1999	October 2000	May 2005	October 2005
End of the accrual	April 2003	December 2001	November 2002	January 2003	December 2006	May 2007
Median follow-up, weeks	90.4	59.4	91.6	74.3	70.7	64.0
Trial quality (MERGE criteria)	B1	B1	B1	B1	B1	B1
Eligibility criteria						
Age	20-75	≥ 18	≥ 18	≥ 18	18-75	≥ 18
Performance status	ECOG 0-1	WHO 0-2	WHO 0-2	ECOG 0-2	ECOG 0-2	ECOG 0-2
Previous lines of chemotherapy	1	1-2	1-2	1	1	≥ 1
Previous treatment	Platin based	Platin based	Taxane + gemcitabine	Platin- or nonplatin-based	Platin based	Relapse > 3 months after platin based

Abbreviations: AUC5, area under the time concentration curve 5; MERGE, Method for Evaluating Research and Guideline Evidence; ECOG, Eastern Cooperative Oncology Group.
*Defined randomized phase II, sample size was actually calculated according to phase III design, with formal comparison between treatment arms.

study: A (low risk of bias), B1 (low to moderate risk of bias), B2 (moderate to high risk of bias), C (high risk of bias).

Before performing the analyses, data of each published study were carefully checked and verified for coherence with the original publications; database quality was excellent for all studies.

Statistical Methods

All the analyses were performed according to the intention-to-treat principle. All the analyses were stratified by trial. All tests were two sided.

Primary end point was OS, defined as the time between date of random assignment and date of death, or last date of follow-up for censored patients. OS curves were estimated using the Kaplan-Meier technique and compared using the stratified log-rank test. Median follow-up was calculated according to the inverted Kaplan-Meier technique.[18]

Because meta-analysis was based on individual patient data, heterogeneity of treatment effect among trials on OS was assessed by likelihood ratio of two trial-stratified models, one with trial-specific treatment estimates and one with overall treatment estimate, as suggested by Smith et al.[19] Under the null hypothesis of no heterogeneity, this statistic follows approximately a χ^2 distribution on $J - 1$ *df* (where J is the total number of trials).[19]

Findings of the meta-analysis are depicted in classical Forest plots, with point estimates and 95% CIs for each trial and overall; size of the squares is proportional to study size.

Further exploratory analyses were performed in the subgroups based on the main baseline patients characteristics, to describe possible heterogeneity of treatment effect. Interaction test was also performed.

Secondary end points were progression-free survival (PFS), objective response rate (RR), and toxicities.

PFS was defined as the time between date of random assignment and date of progression, or date of death for patients dead without progression, or last date of follow-up for censored patients. PFS was analyzed likewise OS.

RR was compared using the stratified Mantel-Haenszel χ^2 test for combining 2×2 tables and the Breslow-Day test was used to detect differences in treatment effect among the trials.[20] For RR, patients obtaining complete response or partial response were considered as responders, and all others as nonresponders.

Toxicity variables were dichotomized as severe (grade 3 to 4) and no/mild (grades 0 to 2). Toxicity rates were compared using the stratified exact tests; the Zelen exact test was used to detect differences in toxicity effects among the six trials[20] and the pooled odds ratio (OR) with 95% CI was estimated by means of exact method.

Statistical analyses were performed using SAS 8.2 (SAS Institute, Cary, NC) and graphs using R 2.4.1 (R Foundation for Statistical Computing, Vienna, Austria) software packages. Exact tests were performed using StatXact 7 (Cytel Software, Cambridge, MA).

RESULTS

Characteristics of the Trials

Eight trials were eligible, for a total of 1,372 patients: three trials were conducted in Greece,[10,11,13] two in the Netherlands,[12,15] one in Japan,[9] one in Italy,[14] and one in Canada, the United States, and Poland (GlaxoSmithKline, data on file, courtesy of P. Legenne). As of February 2009, six trials have already been published as full-length articles[9-14]; one was presented at the 2008 Annual Meeting of the American Society of Clinical Oncology,[15] and one is still unpublished.

Individual patient data from one trial,[13] despite the efforts of the principal investigator who moved to another institution, were not available. We also did not obtain individual patient data from the

Table 2. Characteristics of the Patients Analyzed (N = 847)

Characteristic	Single Agent (n = 428)		Combination (n = 419)		Total (N = 847)	
	No.	%	No.	%	No.	%
Median age, years	61		60		61	
Range	34-78		34-84		34-84	
Sex						
Male	326	76	324	77	650	77
Female	102	24	95	23	197	23
Histologic type						
Adenocarcinoma	204	48	182	43	386	46
Squamous	124	29	132	32	256	30
Large cell	49	11	60	14	109	13
Non-small cell unspecified	30	7	31	7	61	7
Other	2	1	—		2	< 1
Unknown	19	6	14	3	33	4
Performance status						
0	130	30	128	31	258	30
1	250	58	253	60	503	59
2	48	11	38	9	86	10
Previous chemotherapy						
Cisplatin	240	56	239	57	479	57
Carboplatin	103	24	106	25	209	25
Platin based	342	80	332	79	674	80
Docetaxel	143	33	156	37	299	35
Paclitaxel	22	5	25	6	47	6
Gemcitabine	253	59	200	48	453	53
Vinorelbine	29	7	38	9	67	8
Response to first line						
Responders	210	49	203	48	413	49
Non-responders	213	50	212	51	425	50
Unknown	5	1	4	1	9	1

unpublished SKF104864-615 trial (unpublished results), although GlaxoSmithKline, sponsor of the trial, kindly provided us with a summary of final results. Eventually individual data were obtained from six trials, accounting for 63% of the potentially eligible patients (863 of 1,372). Main characteristics of the six trials are described in Table 1. Four were randomized phase II trials,[10-12,15] but in three of these[10-11,15] sample size was actually calculated according to a classical phase III design, with a formally planned comparison between treatment arms. The Japanese trial[9] was terminated early, because of high incidence of interstitial lung disease (ILD) and three treatment-related deaths (5%) due to ILD in the combination arm. In the Italian trial,[14] patients were randomly assigned in a 3:1:1 ratio to three arms: A, docetaxel; B, docetaxel plus gemcitabine or plus vinorelbine; C, docetaxel plus capecitabine. For this meta-analysis, arms B and C were grouped. The trial was stopped prematurely, blind to results, because the recruitment rate was extremely slower than expected.

Single agent consisted of docetaxel (three trials), irinotecan (one trial), cisplatin (one trial), pemetrexed (one trial). In all trials, patients assigned to combination chemotherapy were treated with the addition of a second drug to the one administered as single-agent. Except Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose trial 7,[15] which evaluated pemetrexed plus carboplatin in patients already treated with platin-based therapy, all the trials evaluated drugs not received by the patients as first-line treatment.

Methodological Quality of the Trials

In all studies, most evaluation criteria from the checklist are fulfilled with overall quality score B1 (Table 1; ie, all included studies were of sufficiently high quality to consider the risk of bias as low to moderate). The main drawback of all studies was the lack of blinding, which is a common practice in clinical trials in advanced cancer because of difficulties of blinding to different infusion times, schedules, and toxicities. Lack of blinding is unlikely to affect OS, but could potentially bias secondary end points (PFS, RR, toxicity). All studies had a time-to-event primary outcome, with the exception of Wachters et al study,[12] that had RR as a primary end point. Definitions of the primary outcome were detailed in all trials. Allocation concealment was always adequate. Treatment groups were balanced for the most relevant baseline characteristics (age, PS, stage, histology, response to first-line treatment), although these characteristics were not always considered as stratification factors. For all trials, complete data were available for intention-to-treat analysis, and reasons for the exclusion of a few patients were carefully accounted for and are described later. In particular, a very small percentage of patients were completely lost to follow-up after random assignment in two trials.[10,11]

Main Results

Overall, 847 of the 863 originally randomly assigned patients were eligible for the meta-analysis (Appendix Fig A1, online only). Fifteen patients were excluded from two trials[10,11] because of complete absence of information in the study database. One patient was excluded because of ineligible histology (small-cell lung cancer). Of the 847 eligible patients, 428 patients (50.5%) had been assigned to a single agent, and 419 were assigned to doublet (49.5%). Main characteristics of the 847 patients are described in Table 2. Median age was 61 years (range, 34 to 84). Most of the patients were males (77%), had a good PS (0 or 1 in 90%), and had previously received a first-line platin-based treatment (80%).

Median follow-up was 74.0 weeks (71.7 weeks in single-agent arm, and 74.4 weeks in combination arm). Overall survival curves of patients according to treatment arms are shown in Figure 1. Overall, 642 deaths were recorded (76%), with median survival equal to 37.3 weeks for doublet, and 34.7 weeks for single agent. Corresponding hazard ratio (HR) was 0.92 (95% CI, 0.79 to 1.08; $P = .32$ at log-rank test stratified by trial). The 6-month survival rates were 62.9% and 61.6%, and the 1-year survival rates were 34.4% and 31.8%, for combination and single agent chemotherapy, respectively. As shown in Figure 2, there was no evidence of heterogeneity among the six trials ($P = .87$; I^2 0%). Exploratory survival analysis by subgroups is shown in Figure 3; there was no evidence of heterogeneity among subgroups of treatment effect around the overall effect.

PFS curves of patients according to treatment assigned are shown in Figure 1. Overall, 805 progressions were recorded (95%), with median PFS equal to 14.0 weeks and 11.7 weeks for doublet and single-agent chemotherapy, respectively. The corresponding HR was 0.79 (95% CI, 0.68 to 0.91; $P = .0009$ at log-rank test stratified by trial). Six-month PFS rates were 27.2% and 18.1%, and the 1-year PFS rates were 6.5% and 5.5% for patients assigned to combination and single-agent chemotherapy, respectively. Forest plot of treatment effect on

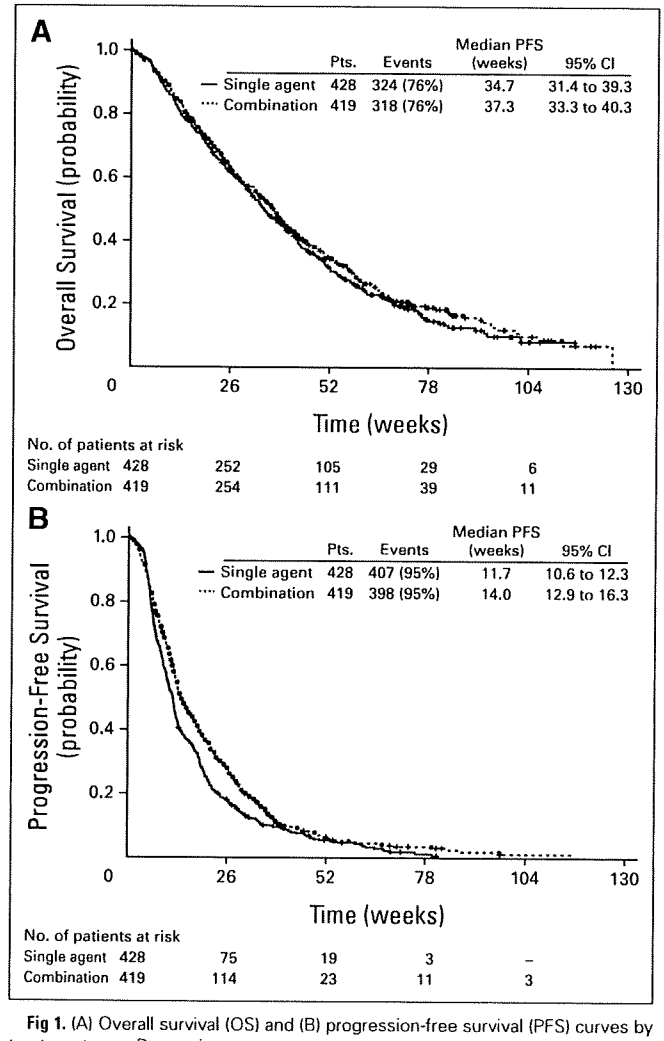

Fig 1. (A) Overall survival (OS) and (B) progression-free survival (PFS) curves by treatment arm. Pts, patients.

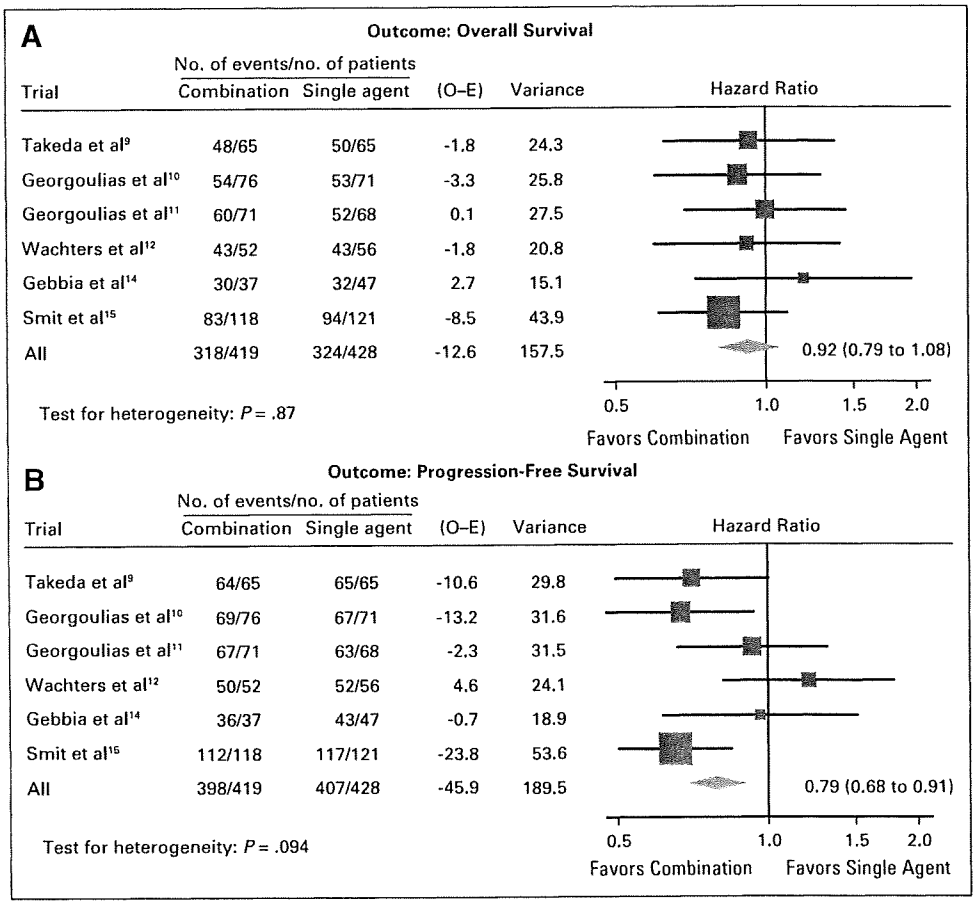

Fig 2. Forest plot of treatment effect on (A) overall survival and (B) progression-free survival. (O–E), observed events minus expected events.

PFS is shown in Figure 2. There was no statistically significant heterogeneity among the six trials ($P = .094$; I^2 47%) and among subgroups (Fig 3).

Further posthoc analyses were performed to study interaction between trial characteristics and treatment effect (Appendix Table A1, online only). Trials were classified according to the single-agent drug (docetaxel[9,12,14] *v* other drug[10,11,15]), or according to the dose planned in doublet arm (same dose of the single-agent drug[9-11,15] *v* reduced dose[12,14]). Interaction tests for OS were not significant. PFS was significantly longer with doublet only when single-agent drug was used at the same dose in the doublet arm.

Objective RR was increased with doublet: 7.3% versus 15.1%, with single-agent and doublet, respectively ($P = .0004$). The test for heterogeneity was borderline significant ($P = .06$; I^2 50%). Exact odds ratio of RR was 2.24 (95% CI, 1.43 to 3.53; Appendix Fig A2, online only).

A summary of grade 3 to 4 adverse effects is reported in Table 3. Combination chemotherapy is characterized by a significantly higher incidence of neutropenia, anemia, thrombocytopenia, emesis, and diarrhea. Patients treated with doublet had significantly more grade 3 to 4 hematologic (25% *v* 41%; $P < .0001$) and grade 3 to 4 nonhematologic toxicity (22% *v* 28%; $P = .034$). Heterogeneity among studies was found for some adverse effects, possibly due to the different drugs and doses used.

DISCUSSION

This individual patient data meta-analysis shows no significant difference in OS between doublet and single-agent chemotherapy as second-line treatment of patients with advanced NSCLC. This meta-analysis, with 847 patients and 642 events, has a statistical power of 80% of recognizing a HR of 0.8 for combination chemotherapy. Our data show that doublets determine a statistically significant increase in RR and in PFS. This increase in activity does not translate in increase in OS compared with single-agent treatment. This appears to be coherent with the results described in the different setting of first-line chemotherapy of advanced NSCLC, where much larger differences in RR and in time to progression are needed to predict a significant survival benefit.[21]

Systematic reviews and meta-analyses have been increasingly used in recent years, as a precious instrument of assessing and interpreting the results from different clinical trials conducted on the same topic. The object of this meta-analysis represents a good topic for this approach because limited sample size of each trial did not allow adequate power to detect potentially clinically relevant differences in efficacy between the two strategies. Four trials were phase II randomized trials,[10-12,15] although three of these[10-11,15] were designed as classical phase III trials. Classically, phase II randomized trials should not be planned to formally compare the treatments, but

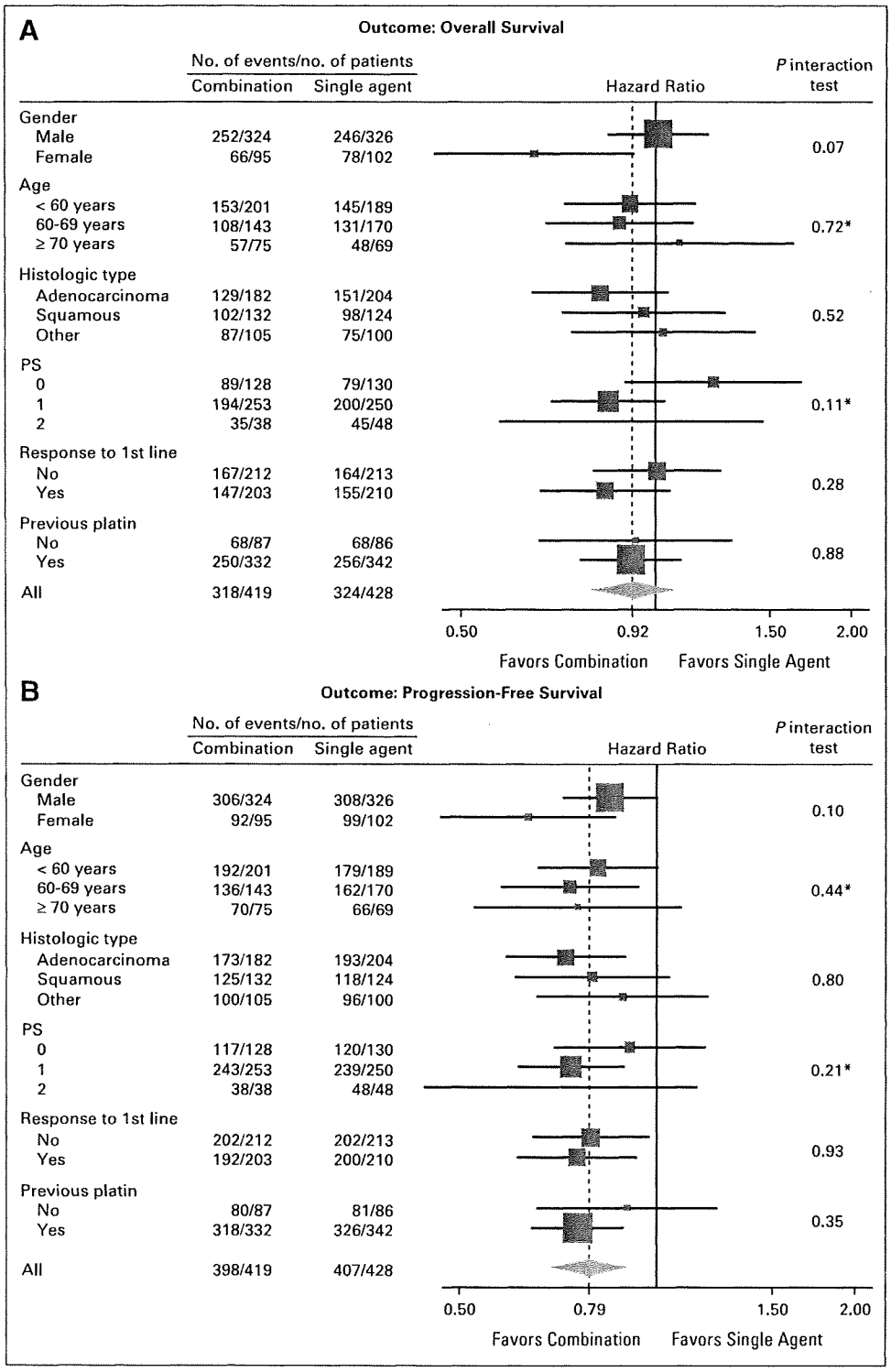

Fig 3. Treatment effect on (A) overall survival and (B) progression-free survival within major patient subgroups. *Trend test.

they can be considered when conducting an individual patient data meta-analysis, because treatment was assigned randomly, and information on OS, primary end point of the meta-analysis, was collected prospectively.

A relevant limitation of this meta-analysis is the difference in treatment schedules among the trials. In three trials, patients assigned to single-agent arm received docetaxel, although in a different schedule: 75 mg/m^2 every 3 weeks,[12] 60 mg/m^2 every 3 weeks,[9] and 33 mg/m^2 weekly.[14] These trials were also different for the drug added to docetaxel in the combination arm. Different single agents were used in two studies enrolling patients who had already received docetaxel as first-line treatment: irinotecan[10] or cisplatin.[11] These differences in

Table 3. Summary of Grade 3-4 Adverse Effects By Treatment

Adverse Effect	No. of Patients With Available Data	Single Agent		Combination		Exact OR	95% CI	P*	P for Homogeneity†
		No.	%	No.	%				
Neutropenia	786	95	24	136	35	2.04	1.38 to 3.04	.0002	.0002
Febrile neutropenia	839	31	7	31	7	1.00	0.57 to 1.76	.99	.032
Anemia	839	9	2	37	9	4.47	2.08 to 10.70	< .0001	.17
Thrombocytopenia	839	7	2	40	10	6.24	2.71 to 16.76	< .0001	.51
Any hematologic	839	106	25	172	41	2.62	1.83 to 3.79	< .0001	.015
Nausea/vomiting	839	12	3	23	6	1.94	0.91 to 4.36	.081	.85
Mucositis	839	2	< 1	1	< 1	0.48	0.01 to 9.31	.62	.99
Diarrhea	839	20	5	42	10	2.28	1.25 to 4.28	.006	.0004
Constipation	839	7	2	3	1	0.42	0.07 to 1.86	.22	.30
Cardiovascular	710	3	1	5	1	1.85	0.35 to 12.04	.49	.66
Pulmonary	700	9	3	10	3	1.15	0.40 to 3.29	.82	.064
Neurological	839	4	1	5	1	1.28	0.27 to 6.50	.75	.67
Liver	839	6	1	6	1	1.01	0.27 to 3.84	.99	.40
Renal	839	—	—	1	< 1	—	—	.48	—
Any nonhematologic	839	92	22	118	28	1.43	1.02 to 2.00	.034	.036

NOTE. Toxicity analysis performed on 839 patients (841 patients received at least one administration of chemotherapy; toxicity data not available in two patients).
Abbreviation: OR, odds ratio.
*Exact text stratified by trial.
†Exact test for homogeneity of ORs.

treatment schedules contribute to increase the clinical heterogeneity of the meta-analysis. However, differently from statistical heterogeneity, which makes the interpretation of a meta-analysis more problematic, clinical heterogeneity may improve the generalizability of the observed results. Which is to say that the consistent absence of efficacy when different doublets are compared with single-agent, although limited by the small number of trials, represents strong evidence against this strategy. All studies tested as second-line treatment drugs different from those received as first line, with the exception of one trial,[15] that tested the addition of carboplatin to pemetrexed in patients who had already received platin-based treatment. However, meta-analysis performed excluding this trial did not produce significant differences in OS (data not shown).

Information on third-line treatment was available for three trials,[9-11] with similar rates in both arms, so it is unlikely that subsequent treatment could have masked the impact of combination chemotherapy on OS.

Despite our efforts to retrieve all existing evidence, individual patient data from two trials were not available for this meta-analysis. The Greek randomized phase II trial, conducted in 130 patients pretreated with platin-based chemotherapy, tested docetaxel versus docetaxel plus irinotecan.[13] Despite higher RR and longer PFS, doublet produced similar survival compared with single agent: median OS was 6.5 months with combination and 6.4 months with single-agent, and 1-year survival was 37% and 34%, respectively. As for the SKF-104864/615 trial, it was a registrative phase III trial sponsored by GlaxoSmithKline, comparing docetaxel plus topotecan versus docetaxel (unpublished results). Based on the interim analysis, study was discontinued after 395 patients, since the probability of demonstrating a survival benefit for experimental arm was too low to justify continuation. There were increased rates of adverse events with combination, without significant difference in efficacy: median OS was 28.6 weeks with single agent and 30.7 weeks with combination (unpublished data, courtesy of GlaxoSmithKline). Therefore results of both unavailable studies are in the same direction of our meta-analysis. Considering this evidence, and our efforts to identify other unpublished trials, it seems unlikely that meta-analysis results might be conditioned by publication bias.

Of course, toxicity is particularly relevant in second-line treatment of advanced NSCLC, given the potential negative impact on benefit/risk ratio and quality of life. Our results confirm that combination chemotherapy is associated with a significant increase in some toxicities. The Japanese trial[9] was terminated early because of high incidence of ILD and three treatment-related deaths due to ILD in the combination arm. In our pooled analysis, combination chemotherapy determined a significant increase in severe hematologic and nonhematologic toxicity. Some of these toxicities (like afebrile neutropenia) may not necessarily represent an increase in patient distress, but others (like anemia or diarrhea) can significantly impair quality of life. Heterogeneity among studies was actually present in the occurrence of several toxicities. In particular, severe neutropenia was particularly high in both arms of the Japanese study[9], as expected for pharmacogenetic differences, and was higher for single-agent arm in the study by Wachters et al,[12] where patients assigned to combination received prophylactic granulocyte colony-stimulating factor. In two studies,[9,10] febrile neutropenia was more common with single agent, but this can be probably explained by the higher use of prophylactic growth factors in the combination arm. Finally, occurrence of severe diarrhea was clearly higher in the arms with irinotecan,[10-12] but sensitivity analysis showed that, after the exclusion of the corresponding two trials, the difference in diarrhea rates disappeared.

With the described limitations, this meta-analysis gives much more solid results than single trials. There were no survival differences between the two strategies, and the absence of significant heterogeneity, among the trials and among subgroups, reinforces these finding. Prolongation of PFS could be judged a worthwhile result if considered to be itself a relevant benefit for the patient, regardless of the survival

improvement. However, this meta-analysis demonstrates a prolongation of PFS of about 2 weeks that, although statistically significant, does not appear to be clinically substantial.

In conclusion, randomized evidence available for this individual patient data meta-analysis does not support the use of combination chemotherapy as second-line treatment for patients with NSCLC, based on a increase in toxicity without any gain in survival.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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original article

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Phase III trial of docetaxel plus gemcitabine versus docetaxel in second-line treatment for non-small-cell lung cancer: results of a Japan Clinical Oncology Group trial (JCOG0104)

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Background: This trial evaluated whether a combination of docetaxel and gemcitabine provides better survival than docetaxel alone in patients with previously treated non-small-cell lung cancer (NSCLC).

Patients and methods: Eligibility included pathologically or cytologically proven NSCLC, failure of one platinum-based regimen, performance status of zero or one, 20–75 years old, and adequate organ function. Patients received docetaxel 60 mg/m^2 (day 1) or docetaxel 60 mg/m^2 (day 8) and gemcitabine 800 mg/m^2 (days 1 and 8), both administered every 21 days until disease progression.

Results: Sixty-five patients participated in each arm. This trial was terminated early due to an unexpected high incidence of interstitial lung disease (ILD) and three treatment-related deaths due to ILD in the combination arm. Docetaxel plus gemcitabine compared with docetaxel-alone patients experienced similar grade and incidence of toxicity, except for ILD. No baseline factor was identified for predicting ILD. Median survival times were 10.3 and 10.1 months (one-sided $P = 0.36$) for docetaxel plus gemcitabine and docetaxel arms, respectively.

Conclusion: Docetaxel alone is still the standard second-line treatment for NSCLC. The incidence of ILD is higher for docetaxel combined with gemcitabine than for docetaxel alone in patients with previously treated NSCLC.

Key words: docetaxel, gemcitabine, non-small-cell lung cancer, platinum-refractory, second-line chemotherapy

original article

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 ~1 million, which accounted for ~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 four cycles of platinum-based combination chemotherapy, with no single combination recommended over others [3]. Although this treatment improves survival rates, a substantial proportion of patients do progress and should be offered second-line treatment. With unsurpassed efficacy compared with other chemotherapeutic regimens or best supportive care [4, 5], docetaxel alone is the current standard as second-line chemotherapy for advanced NSCLC. The recommended regimen of docetaxel 75 mg/m^2 given i.v. every 3 weeks as second-line therapy has been associated with median survival times of 5.7–7.5 months [4, 5] and is also associated with better quality-of-life outcomes compared with best supportive care [2]. Docetaxel monotherapy for recurrent NSCLC after platinum-based chemotherapy has several limitations, however, including low response rates (7–11%), brief duration of disease control, and minimal survival advantage [4, 5].

Gemcitabine is also active against recurrent NSCLC after platinum-based chemotherapy [6]. Gemcitabine 1000 mg/m^2 once a week for 3 weeks every 28 days produced a 19% response rate in a phase II trial, and it shows significant activity mainly

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in patients previously responsive to chemotherapy [6]. Single-agent gemcitabine has a low toxicity profile and is well tolerated [6].

Docetaxel and gemcitabine have distinct mechanisms of action and nonoverlapping toxic effects except for neutropenia. Many studies of the combination of docetaxel and gemcitabine have been conducted in first- and second-line settings [7–16]. The following doses and schedule have been adopted in most studies: docetaxel 80–100 mg/m^2 on day 1 or 8 and gemcitabine 800–1000 mg/m^2 on days 1 and 8 or on days 1, 8, and 15. Furthermore, most studies required use of prophylactic granulocyte colony-stimulating factor (G-CSF) support.

In Japan, however, the recommended dose of docetaxel is 60 mg/m^2 every 3 weeks [17, 18]. Several studies to confirm the dose and schedule of this combination without prophylactic G-CSF support have been conducted in Japan [19–21]. Two studies recommended docetaxel 60 mg/m^2 on day 8 and gemcitabine 800 mg/m^2 on days 1 and 8, and another study recommended docetaxel 50 mg/m^2 on day 8 and gemcitabine 1000 mg/m^2 on days 1 and 8, without prophylactic G-CSF support, every 3 weeks. These studies demonstrated the consistent promising efficacy of this combination regimen. An objective response was observed in 28%–40% of patients, with a median survival time of 11.1–11.9 months and a 1-year survival rate of 41%–47%.

We conducted a multicenter, randomized, phase III trial to evaluate whether the combination regimen of docetaxel and gemcitabine provides better survival than docetaxel alone in patients with previously treated NSCLC.

patients and methods

patient selection

Eligible patients were 20–75 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 failed one platinum-based chemotherapy regimen previously. Patients who had received gemcitabine or docetaxel were excluded. Additional inclusion criteria included a Eastern Cooperative Oncology Group performance status of zero to one, and adequate organ function as indicated by white blood cell count ≥4000/μl, absolute neutrophil count ≥2000/μl, hemoglobin ≥9.5 g/dl, platelets ≥100 000/μl, aspartate aminotransferase (AST)/alanine amonotransferase (ALT) ≤2.5 times the upper limit of normal, total bilirubin ≤1.5 mg/dl, serum creatinine ≤1.2 mg/dl, and PaO_2 in arterial blood ≥70 torr. Asymptomatic brain metastases were allowed provided that they had been irradiated and were clinically and radiologically stable. Prior thoracic radiotherapy was allowed provided that treatment was completed at least 12 weeks before enrollment. 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 Japan Clinical Oncology Group (JCOG) Clinical Trial Review Committee and the institutional review board of each participating institution.

treatment plan and dose modifications

Eligible patients were centrally registered at JCOG Data Center and were randomly assigned to either docetaxel 60 mg/m^2 as a 60-min i.v. infusion on day 1 or docetaxel 60 mg/m^2 as a 60-min i.v. infusion on day 8 plus gemcitabine 800 mg/m^2 as a 30-min i.v. infusion on days 1 and 8, using a minimization method with institutions and response to prior chemotherapy (progressive disease or not) as balancing factors. Patients receiving docetaxel were administered standard dexamethasone premedication (8 mg orally at the day before, on the day, and the day after docetaxel administration) as previously reported [7] and 50 mg of diphenhidramine 30 min before docetaxel administration. Recombinant human G-CSF was not given prophylactically. Chemotherapy cycles were repeated every 3 weeks until disease progression. Docetaxel was given before gemcitabine in the docetaxel plus gemcitabine regimen.

Dose adjustments were based mainly on hematologic parameters. The doses of docetaxel and gemcitabine were reduced by 10 and 200 mg/m^2, respectively, in subsequent cycles if chemotherapy-induced febrile neutropenia, grade 4 anemia, grade 4 thrombocytopenia, grade 4 leukopenia, or grade 4 neutropenia lasting for >3 days occurred in the absence of fever. Dose reductions were maintained for all subsequent cycles. Patients requiring more than one dose reduction were off-protocol treatment.

baseline and follow-up assessments

Pretreatment evaluation included a complete medical history and physical examination, a complete blood count (CBC) test with differential and platelet count, standard biochemical profile, electrocardiogram, chest radiographs, computed tomographic scans of the chest, abdomen, and brain, magnetic resonance imaging, and a whole-body bone scan. During treatment, a CBC and biochemical tests were carried out weekly. A detailed medical history was taken and a complete physical examination with clinical assessment was carried out weekly to assess disease symptoms and treatment toxicity, and chest radiographs were done every treatment cycle. Toxicity was evaluated according to the National Cancer Institute Cancer—Common Toxicity Criteria Version 2 [22].

All patients were assessed for response by computed tomography scans after every two cycles of chemotherapy. Response Evaluation Criteria in Solid Tumors (RECIST) were used for the evaluation of response [23].

The progression-free survival (PFS) was calculated from the day of randomization until the day of the first evidence of disease progression or death. If the patient had no progression, PFS was censored at the day when no clinical progression was confirmed. Overall survival (OS) was measured from the day of randomization to death.

Disease-related symptoms were evaluated and scored at baseline and 6 weeks after the start of treatment with the seven-item Lung Cancer Subscale (LCS) of the Functional Assessment of Cancer Therapy-Lung version 4 [24], which were translated from English to Japanese. The questionnaire entries were listed as follows: 'I have been short of breath', 'I am losing weight', 'My thinking is clear', 'I have been coughing', 'I have a good appetite', 'I feel tightness in my chest', and 'Breathing is easy for me'. Patients scored using a five-point Likert scale (0–4) by themselves. The maximum attainable score of the LCS was 28, where the patient was considered to be asymptomatic.

statistical analysis

The primary endpoint was OS; secondary endpoints were PFS, the overall response rate, disease-related symptoms, and toxicity profile. Based on previous trials evaluating the docetaxel [4, 5] and docetaxel plus gemcitabine [19–21] regimens, the present study was designed to detect a 12% difference of 1-year survival rate. To attain an 80% power at a one-sided significance level of 0.05, assuming 1-year survival of docetaxel arm as 35% with 1 year of follow-up after 2 years of accrual, 284 patients (142 per each arm) were required. Analyses were to be carried out with all randomized patients. Both the OS and PFS were estimated with the Kaplan–Meier method. The comparisons of OS and PFS between arms were assessed by the stratified log-rank test with a factor used at randomization, response to prior chemotherapy. Two interim analyses were planned after half of the patients were registered and the end of registration.

For the symptom analysis, changes of LCS from initial score were compared between arms using analysis of covariance with initial score as a covariate.

All analyses were carried out with SAS software release 8.2 (SAS Institute, Cary, NC).

results

This trial was terminated early due to the unexpected high incidence of interstitial lung disease (ILD) and three treatment-related deaths due to ILD in the combination arm, which were identified by the Adverse Event Reporting system.

patient characteristics

From January 2002 to September 2003, 130 patients with NSCLC who had failed prior platinum-based chemotherapy from 32 institutions were enrolled (Appendix). These patients were randomly assigned to docetaxel alone (n = 65) or docetaxel plus gemcitabine (n = 65). One patient died as a result of rapid progressive disease before chemotherapy administration, and one patient did not meet the entry criteria in the docetaxel arm. In addition, one patient did not meet the entry criteria in the docetaxel plus gemcitabine arm. All patients were included in the analysis of survival and PFS, and 64 docetaxel and 65 docetaxel plus gemcitabine patients were assessable for toxicity. Fifty-nine patients with measurable lesions by RECIST in the docetaxel arm and 57 eligible patients in docetaxel plus gemcitabine arm were assessable for response (Figure 1). Table 1 presents baseline patient characteristics.

The median number of cycles was 3 (range 0–6) and 2 (range 1–8) in the docetaxel and docetaxel plus gemcitabine arms, respectively. The median interval between cycles was 22 days for both arms.

toxicity

This trial was terminated early due to the unexpected high incidence of ILD and three treatment-related deaths (4.6%) due to ILD in the docetaxel plus gemcitabine arm. These events were identified by the Adverse Event Reporting system. Thirteen (20.0%) patients receiving combination treatment suffered from all grades of ILD, whereas only two (3.1%) patients receiving docetaxel alone suffered from grades 1–2 ILD. Grades 2–4 ILD occurred in 16.9% of docetaxel plus gemcitabine patients, an unexpected high incidence rate. No risk factors were identified contributing to these pulmonary adverse events.

Toxicity was assessed in all patients who received at least one treatment cycle and in all cycles (Table 2). Overall, grades 3–4 neutropenia occurred in 55 docetaxel patients (85.9%) and 53 docetaxel plus gemcitabine patients (81.5%). Grades 3–4 anemia occurred in two patients (3.1%) and 12 patients (18.5%) treated with docetaxel alone and docetaxel plus

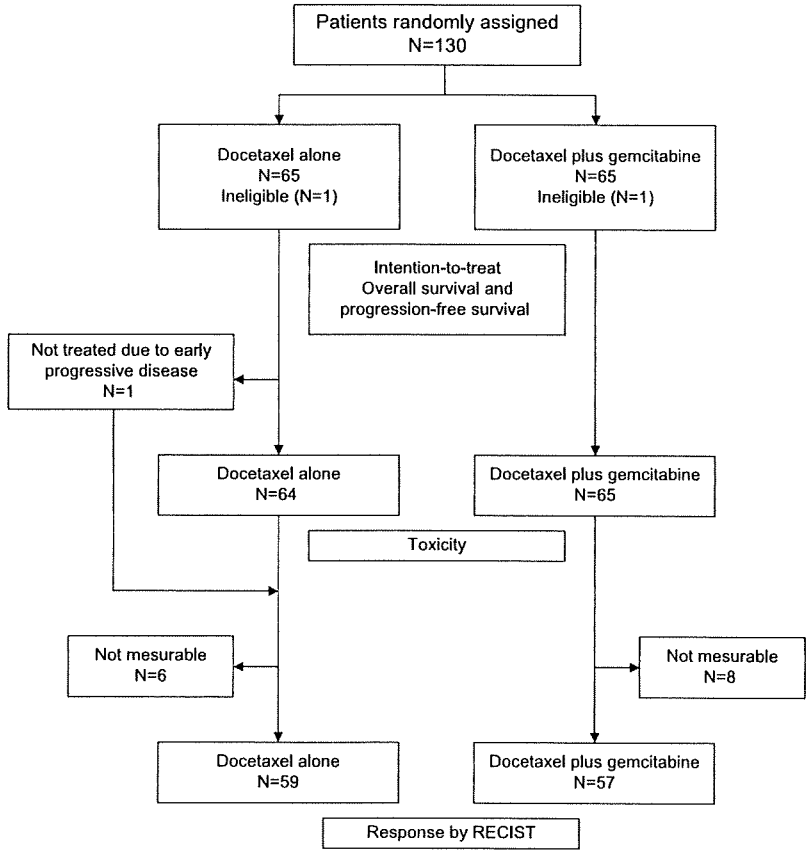

Figure 1. CONSORT diagram for the study.

gemcitabine, respectively. Sixteen patients treated with docetaxel (25.0%) and 11 patients with docetaxel plus gemcitabine (16.9%) developed febrile neutropenia. All required antibiotic treatment and G-CSF; however, no patient died. One patient in the docetaxel plus gemcitabine arm developed anaphylatic shock immediately after administration of docetaxel at the second cycle. Grades 2–4 ALT elevation was more frequent with docetaxel plus gemcitabine than with docetaxel (20.0% versus 4.7%). Grades 2–4 non-neutropenic infection occurred more often with docetaxel plus gemcitabine than with docetaxel (21.5% versus 15.6%). Grades 2–4 ILD was more frequent with docetaxel plus gemcitabine than with docetaxel (16.9% versus 1.6%). Other toxic effects were relatively mild (Table 2). Overall, docetaxel plus gemcitabine was more toxic than docetaxel, however, well tolerated except for ILD in docetaxel plus gemcitabine arm.

Table 1. Patient characteristics

	D arm		DG arm	
	No. of patients	%	No. of patients	%
Patients enrolled	65		65	
Age, years				
Median	62		60	
Range	34–75		34–74	
Gender				
Male	48	73.8	51	78.5
Female	17	26.2	14	21.5
ECOG PS				
0	20	30.8	21	32.3
1	45	69.2	44	67.7
Histology				
Squamous	19	29.2	22	33.8
Adenocarcinoma	40	61.5	40	61.5
Large cell	4	6.2	3	4.6
Others	2	3.1	0	0
Best response of prior chemotherapy				
CR	2	3.1	0	0
PR	38	58.5	40	61.5
SD	20	30.8	19	29.2
PD	5	7.7	6	9.2

D, docetaxel; DG, docetaxel plus gemcitabine; ECOG PS, Eastern Cooperative Oncology Group performance status; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

treatment efficacy

The overall response rate for docetaxel alone was 6.8% [95% confidence interval (CI) 1.9% to 16.5%] and 7.0% for docetaxel plus gemcitabine (95% CI 2.0% to 17.0%). There was no significant difference between treatment arms ($P = 0.71$; Fisher's exact test).

At the time of this analysis, 50 docetaxel patients (76.9%) and 48 docetaxel plus gemcitabine patients (73.8%) had died. The median survival time was 10.1 months for docetaxel alone and 10.3 months for docetaxel plus gemcitabine (one-sided $P = 0.36$ stratified log-rank test; Figure 2A). The respective 1-year survival rate was 43.1% (95% CI 31.0% to 55.1%) for docetaxel and 46.0% (95% CI 33.8% to 58.1%) for docetaxel plus gemcitabine.

The median PFS time was 2.1 and 2.8 months for docetaxel and docetaxel plus gemcitabine, respectively (one-sided $P = 0.028$ stratified log-rank test; Figure 2B).

Table 2. Hematological and non-hematological toxicity

	D arm ($n = 64$)					DG arm ($n = 65$)				
	NCI-CTC grade					NCI-CTC grade				
Hematological	0–1	2	3	4	3–4%	0–1	2	3	4	3–4%
Anemia	27	35	2	0	3.1	21	32	9	3	18.5
Leukopenia	9	14	29	12	64.1	11	12	32	10	64.6
Neutropenia	7	2	15	40	85.9	8	4	19	34	81.5
Thrombocytopenia	64	0	0	0	0	43	14	8	0	12.3
Non-hematological	0–1	2	3	4	2–4%	0–1	2	3	4	2–4%
Allergic reaction	64	0	0	0	0	59	5	1	0	9.2
Alopecia	45	18	–	–	28.1	49	14	–	–	21.5
ALT	61	2	1	0	4.7	52	10	3	0	20.0
Diarrhea	61	3	0	0	4.7	60	3	2	0	7.7
Edema	63	1	0	0	1.6	64	1	0	0	1.5
Fatigue	56	5	2	1	12.5	56	7	1	1	13.8
Febrile neutropenia	48	–	16	0	25.0	54	–	11	0	16.9
Infection with grades 3–4 neutropenia	59	–	5	0	7.8	56	–	9	0	13.8
Infection without neutropenia	54	8	2	0	15.6	51	4	9	1	21.5
Nausea	55	7	2	–	14.1	55	6	4	–	15.4
Neuropathy	62	2	0	0	3.1	62	2	0	1	4.6
Pneumonitis (ILD)	63	1	0	0	1.6	54	3	7	1	16.9
Stomatitis	61	3	0	0	4.7	60	5	0	0	7.7

D, docetaxel; DG, docetaxel plus gemcitabine; NCI-CTC, National Cancer Institute—Cancer Common Toxicity Criteria; ALT, alanine aminotransferase; ILD, interstitial lung disease.

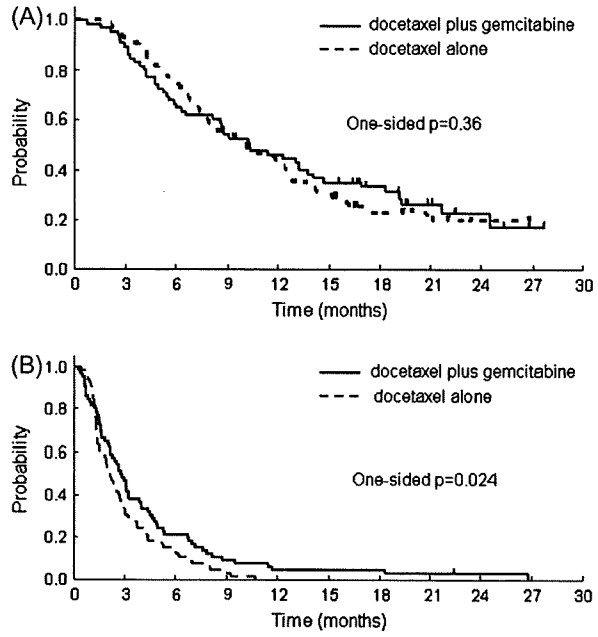

Figure 2. Overall survival (A) and progression-free survival (B) by treatment arm.

disease-related symptom assessment

Patients' compliance with disease-related symptom assessment was 100% at baseline and 95.4% at 6 weeks later. Compliance rates were not different between the arms ($P = 1.00$). LCS data were missing in four surveys due to death or severe impairment of the patient's general condition; this accounted for 1.5% of the total number of surveys scheduled. Mean LCS at baseline and 6 weeks were shown in Table 3. There were no significant differences in the LCS changes from baseline to 6 weeks between docetaxel and docetaxel plus gemcitabine arms ($P = 0.61$).

discussion

This trial was terminated early due to the unexpected high incidence of ILD and three treatment-related deaths due to ILD in the docetaxel plus gemcitabine arm. Our findings seem to indicate that the combination of docetaxel and gemcitabine may be associated with a higher incidence of pulmonary adverse events compared with docetaxel alone, especially in patients with previously treated NSCLC.

Pulmonary toxicity following chemotherapeutic agents, including ILD, has been well recognized for many years. In most cases, this toxicity is mild and self-limiting. However, the mechanism of developing drug-induced ILD is uncertain, and risk factors for developing this disorder have not been identified. In terms of combination therapy with docetaxel and gemcitabine for advanced NSCLC, there were few reports about the incidences of ILD at the time this study was planned. A phase I study of patients with transitional cell carcinoma evaluated thrice-weekly doses of docetaxel given on day 1 plus gemcitabine given on days 1 and 15 and showed that pulmonary toxicity occurred in three of five patients and was

Table 3. Disease-related symptom assessment

Lung Cancer Subscale	D arm	DG arm
Baseline		
Number	$n = 65$	$n = 65$
Mean ± SD	19.0 ± 5.48	19.7 ± 5.25
6 weeks later		
Number	$n = 62$	$n = 62$
Mean ± SD	18.1 ± 5.56	18.9 ± 5.05
Difference		
Mean ± SD	−1.11 ± 3.81	−0.99 ± 4.49

D, docetaxel; DG, docetaxel plus gemcitabine; SD, standard deviation.

the cause of death in one [25]. Recently, some reports have been published about the high incidence of ILD due to the combination regimen of docetaxel and gemcitabine in patients with NSCLC [13, 26, 27], including the present study (Table 4). In Japanese population, ILD is a very complex issue in treatment of patients with lung cancer. Epidermal growth factor tyrosine kinase inhibitor gefitinib is developing ILD significantly in Japanese patients with NSCLC [28]. It is uncertain why ILD is developing more in Japanese patients with NSCLC than the Western patients. Ethnic difference may be one of the explanations for this occurrence. The combination of gemcitabine and docetaxel is associated with a high incidence of severe pulmonary toxicity. The regimen should not be used outside a clinical trial.

The median survival times of 10.1 and 10.3 months and estimated 1-year survival rates of 43.1% and 46.0% with docetaxel alone and docetaxel plus gemcitabine, respectively, suggest that adding gemcitabine to docetaxel did not provide any increased efficacy in patients with previously treated NSCLC. Interestingly, the combination regimen of docetaxel plus gemcitabine significantly improved the median PFS time ($P = 0.028$). Possible reasons for failing to detect a significant difference between survival curves may include an insufficient occurrence of documented events as a result of the study population comprising patients with relatively good prognosis, in addition to a high proportion of patients subsequently receiving third-line therapy. During this study, gefitinib treatment was commonly used for patients with recurrent NSCLC in Japan [29]. Asian ethnicity is a well-known predictive factor for a response for gefitinib [30].

Two randomized phase II trials compared docetaxel alone with docetaxel plus irinotecan in second-line chemotherapy for NSCLC [31, 32]. No significant treatment differences in survival were observed in either trial; however, the trials were phase II study and were not powered or designed to compare survival. This study was not powered to compare survival when it was terminated early due to the unexpected high incidence of ILD in the docetaxel plus gemcitabine arm. However, based on previous studies, as well as the present results, combination chemotherapy with docetaxel and another chemotherapeutic agent has not improved survival in patients with previously treated NSCLC.

In conclusion, docetaxel alone is still the standard second-line treatment for advanced NSCLC. The combination of docetaxel and gemcitabine was too toxic to obtain any survival

Table 4. Reports of interstitial lung disease due to docetaxel plus gemcitabine regimen

Author	Year	Study type	Treatment schedule	*n*	Grades 3–4 ILD (%)	TRD (%)
Rebattu et al. [13]	2001	Phase I/II	Docetaxel (60, 75, 85, 100 mg/m^2) day 8; gemcitabine (1000 mg/m^2), days 1 and 8, every 3 weeks	49	3 (6.1)	0
Kouroussis et al. [25]	2004	Phase I	Docetaxel (30, 35, 40 mg/m^2), days 1, 8 and 15; gemcitabine (700, 800, 900, 1000 mg/m^2), days 1, 8 and 15, every 4 weeks	26	6 (23)	2 (7.7)
Matsui et al. [21]	2005	Phase I/II	Docetaxel (50, 60 mg/m^2) day 1 or 8; gemcitabine (800, 1000 mg/m^2), days 1 and 8, every 3 weeks	59	3 (5.1)	0
Pujor et al. [27]	2005	Phase III	Docetaxel (85 mg/m^2) day 8; gemcitabine (1000 mg/m^2), days 1 and 8, every 3 weeks	155	8 (5.2)	1 (0.6)
			Cisplatin (100 mg/m^2) day 1; vinorelbine (30 mg/m^2), days 1, 8, 15 and 22, every 4 weeks	156	1 (0.6)	0
Takeda (present study)	2008	Phase III	Docetaxel (60 mg/m^2) day 8; gemcitabine (800 mg/m^2), days 1 and 8, every 3 weeks	65	8 (12.3)	3 (4.6)
			Docetaxel (60 mg/m^2) day 1, every 3 weeks	64	0 (0)	0

ILD, interstitial lung disease; TRD, treatment-related death.

benefit in patients with recurrent advanced NSCLC. The development of less toxic and more effective chemotherapeutic agents, including molecular targeted drugs, is warranted for the second-line treatment of NSCLC.

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appendix

The following institutions participated in the study: Hokkaido Cancer Center (Sapporo), Ibaragi Prefectural Central Hospital (Kasama), Tochigi Cancer Center (Utsunomiya), Nishigunma National Hospital (Shibukawa), Gunma Prefectural Cancer Center Hospital (Ohta), Saitama Cancer Center Hospital (Ina), National Cancer Center Hospital East (Kashiwa), National Cancer Center Hospital (Tokyo), International Medical Center of Japan (Tokyo), Cancer Institute Hospital (Tokyo), Toranomon Hospital (Tokyo), Kanagawa Cancer Center Hospital (Yokohama), Yokohama Municipal Hospital (Yokohama), Niigata Cancer Center Niigata Hospital (Niigata), Gifu Municipal Hospital (Gifu), Aichi Cancer Center Hospital (Nagoya), Nagoya National Hospital (Nagoya), Prefectural Aichi Hospital (Okazaki), Osaka City University Medical School (Osaka), Kinki University School of Medicine (Osaka-Sayama), Osaka Medical Center for Cancer and Cardiovascular Disease (Osaka), Osaka Prefectural Medical Center for Respiratory and Allergic disease (Habikino), Kinki-Chuo Chest Medical Center (Sakai), Toneyama National Hospital (Toyonaka), Osaka Prefectural General Hospital (Osaka), Osaka City General Hospital (Osaka), Kobe City General Hospital (Kobe), Hyogo Collage of Medicine (Nishinomiya), Hyogo Cancer Center (Akashi), Shikoku Cancer Center Hospital (Matsuyama), Kyusyu University Hospital (Fukuoka), and Kumamoto Regional Medical Center (Kumamoto).

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Twenty-Seven Years of Phase III Trials for Patients with Extensive Disease Small-Cell Lung Cancer: Disappointing Results

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Abstract

Background: Few studies have formally assessed whether treatment outcomes have improved substantially over the years for patients with extensive disease small-cell lung cancer (ED-SCLC) enrolled in phase III trials. The objective of the current investigation was to determine the time trends in outcomes for the patients in those trials.

Methods and Findings: We searched for trials that were reported between January 1981 and August 2008. Phase III randomized controlled trials were eligible if they compared first-line, systemic chemotherapy for ED-SCLC. Data were evaluated by using a linear regression analysis. Results: In total, 52 trials were identified that had been initiated between 1980 and 2006; these studies involved 10,262 patients with 110 chemotherapy arms. The number of randomized patients and the proportion of patients with good performance status (PS) increased over time. Cisplatin-based regimens, especially cisplatin and etoposide (PE) regimen, have increasingly been studied, whereas cyclophosphamide, doxorubicin, and vincristine–based regimens have been less investigated. Multiple regression analysis showed no significant improvement in survival over the years. Additionally, the use of a PE regimen did not affect survival, whereas the proportion of patients with good PS and the trial design of assigning prophylactic cranial irradiation were significantly associated with favorable outcome.

Conclusions and Significance: The survival of patients with ED-SCLC enrolled in phase III trials did not improve significantly over the years, suggesting the need for further development of novel targets, newer agents, and comprehensive patient care.

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Introduction

Lung cancer is a leading cause of cancer-related mortality in many industrialized countries. Small-cell lung cancer (SCLC), which accounts for about 15% of all lung cancer cases, is categorized into two clinical stages: limited disease (LD) and extensive disease (ED). For patients with ED-SCLC, combination chemotherapy is the mainstay of treatment.

In the 1980s, the most widely used combination of drugs for initial treatment of ED-SCLC was cyclophosphamide, doxorubicin, and vincristine (CAV), which produced a median survival time of 9 to 11 months [1]. In the late 1980s, a combination regimen of cisplatin and etoposide (PE) was introduced, and an alternating regimen of PE and CAV has been widely investigated in randomized controlled trials [2].

In 1999, the results of a systemic review indicated a modest improvement over the years in the survival time of patients with ED-SCLC treated with chemotherapy between 1972 and 1994 [3]. This improvement was potentially attributable to (i) introduction of the PE regimen in the late 1980s and (ii) improvements in the supportive care and general management of the patients. However, this included just North American trials and would provide some justification for looking at the world-wide result.

A decade has passed since that systemic review, and recent clinical trials have investigated newer antineoplastic agents such as irinotecan and topotecan. Thus, we performed a literature search to determine whether patient outcomes have improved in the treatment of ED-SCLC.

Materials and Methods

Searching

We searched for trials that were reported between January 1981 and August 2008. To avoid publication bias, we identified both published and unpublished trials through a computer-based search of the PubMed database and abstracts from past conferences of the American Society of Clinical Oncology (1998–2008). We used the following search terms: *lung neoplasm*, *carcinoma*, *small-cell*, *chemotherapy*, and *randomized controlled trial*. The search was guided by a

thorough examination of reference lists from original articles, review articles, relevant books, and the Physician Data Query registry of clinical trials.

Selection

Phase III randomized controlled trials were eligible for inclusion in this study if they compared first-line, systemic chemotherapy for ED-SCLC that contained cytotoxic agents, providing the year of trial initiation. Trials were excluded if they only investigated immunotherapy regimens, or if they enrolled only responders to the initial chemotherapy. Trials initially designed to assess combined-modality treatment, including radiotherapy and surgery concurrently undergone with the initial chemotherapy, were also ineligible, but those optionally designed to conduct these therapies or prophylactic cranial irradiation (PCI) sequentially after the induction chemotherapy were allowed. Some phase III trials incorporated patients with both LD-SCLC and ED-SCLC. These were considered eligible only if survival data for patients with ED-SCLC could be solely obtained. We acknowledge that the definitions for LD-SCLC and ED-SCLC vary somewhat in the different groups compared, and we could not strictly reallocate each patient because we were unable to access the individual patient databases. Instead, we applied the definition described in each original report to this study. If no relevant descriptions were documented, we considered that the definition in that trial would have been based on the guidelines in existence at the time of that trial initiation [4,5]. The control arms in each of the phase III trials were identified based on statements in each trial.

Validity Assessment

To avoid bias in the data abstraction process, four medical oncologists (I.O., N.O., Y.F., and K.H.), one of whom (K.H.) holds a board certificate for medical oncology, independently abstracted the data from the trials and subsequently compared the results. All data were checked for internal consistency, and disagreements were resolved by discussion among the investigators.

Data Abstraction

The following information was obtained from each report: year of trial initiation (i.e., year when the first patient was accrued); number of patients enrolled and randomized; median age of patients; proportion of patients with good performance status (PS); proportion of patients who were male and who had brain metastasis; chemotherapy regimen; definition of ED; description of the administration of sequential thoracic irradiation, surgery, or PCI as one of the trial designs; and median survival time (per treatment arm).

Study Characteristics

All studies included were phase III randomized controlled trials of first-line systemic chemotherapy for ED-SCLC. The study outcomes were median survival time. Variation in study characteristics and clinical heterogeneity between studies were adjusted statistically (see below).

Quantitative Data Synthesis

Data from phase III trials were evaluated by using multiple, stepwise regression analysis (with the following stepping method criteria: probability of F to enter the model, <0.05; to remove from the model, >0.10). The data analyzed included year of trial initiation, use of PE regimen, maximal age of patients, proportion of patients with good PS, proportion of male patients, and definition of PCI settings. These data were used to determine whether each factor had an independent impact on the survival of patients with ED-SCLC who were treated in the phase III studies over time. All P values corresponded to 2-sided tests, and significance was set at $P<0.05$.

Results

Trial Flow/Flow of Included Studies

Figure 1 shows a flow chart of this study. In total, 52 trials for ED-SCLC were identified as a result of the computer-based and manual searches for relevant articles, abstracts, and references

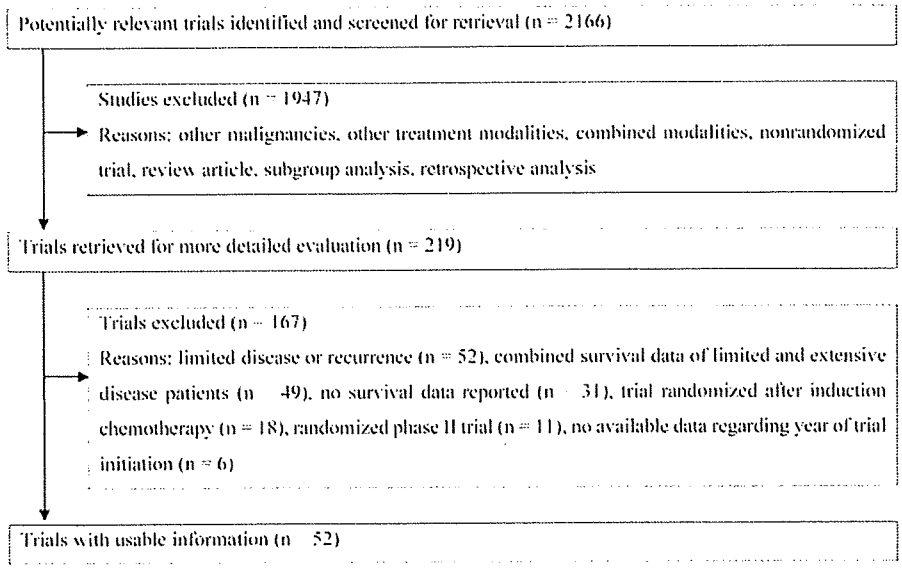

Figure 1. Flow chart showing the progress of trials through the review.
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