TABLE 3. Hazard Ratios According to Quantitative Aspects of Smoking

	Ad			Non-Ad		
	HR	95% CI	*p*	HR	95% CI	*p*
Years after cessation	(*n* = 1731)			(*n* = 740)		
Current	1.492	1.271–1.750	<0.001	1.204	0.849–1.707	0.297
Exsmoker 1–4 yr	1.438	1.114–1.857	0.005	1.101	0.733–1.653	0.643
Exsmoker 5–9 yr	1.549	1.101–2.180	0.012	1.228	0.700–2.155	0.474
Exsmoker 10–14 yr	1.127	0.783–1.621	0.520	1.235	0.680–2.245	0.488
Exsmoker 15–19 yr	1.199	0.761–1.890	0.433	1.410	0.712–2.794	0.325
Exsmoker ≥20 yr	0.873	0.834–1.203	0.407	1.103	0.662–1.837	0.706
Trend *p*	<0.001			0.434		
Pack-yr	(*n* = 1665)			(*n* = 702)		
<10	1.267	0.899–1.785	0.176	1.196	0.535–2.672	0.662
10–19	1.118	0.801–1.561	0.513	0.963	0.512–1.812	0.908
20–29	1.346	1.048–1.729	0.020	1.368	0.887–2.109	0.157
30–39	1.345	1.071–1.689	0.011	0.954	0.624–1.458	0.827
40–49	1.370	1.096–1.712	0.006	1.128	0.763–1.669	0.546
50–59	1.483	1.164–1.890	0.001	1.238	0.828–1.851	0.298
≥60	1.595	1.312–1.939	<0.001	1.135	0.791–1.628	0.491
Trend *p*	<0.001			0.519		

[a] Nonsmokers were set as the reference category.
Ad, adenocarcinoma; HR, hazard ratio; CI, confidence interval.

In agreement with the findings of another study,[15] we also found that a large proportion of Ad patients were nonsmoking. The prognostic difference between Ad in never-smokers and smokers may suggest that both are different disease entities. Of note, tumor-mutational frequencies and spectra suggest differences between smokers and nonsmokers.[16,17] However, significant differences in the frequency of somatic mutations in oncogenes such as *EGFR* and *KRAS* have been observed between smoking and nonsmoking lung cancer patients.[11] *EGFR* mutations, clinical predictors of EGFR-TKI therapeutic benefits, are more frequently found in nonsmoking Ad patients.[11] In another study, *EGFR* mutations were identified in nonsmokers (51%), former smokers (19%), and current smokers (4%).[18] Moreover, the incidence of *EGFR* mutations decreased with increasing number of pack-years of cigarette smoking.[18] However, *KRAS* mutations, predicting poor survival and resistance to EGFR-TKI, are more frequently found in smoking Ad patients. Interestingly, *EGFR* and *KRAS* mutations are mutually exclusive.[11]

Currently, therapeutic options other than EGFR-TKIs (e.g., bevacizumab and pemetrexed) are available in Japan. Still, NSCLC subtypes have been showing variable response rates and adverse events.[2,4,19,20] Non-Sq histology, especially Ad, is currently the NSCLC subtype with broader and more efficacious treatment options. At the time of this study, however, the only approved therapeutic agent for NSCLC in Japan was gefitinib. Unfortunately, we did not investigate *EGFR* mutation status. However, genetic background could possibly predict response to gefitinib. Along with its retrospective nature, this was a limitation of our study. However, we found that the treatment choice was made on the basis of clinical background, and we were unable to conclude whether or not gefitinib contributed to better survival under unknown *EGFR* mutation status. Hence, we suggest that decision-making based on clinical information alone is inappropriate. Both the V15-32 study[21] and the Iressa Survival Evaluation in Lung Cancer (ISEL) study[22], support our observations. Furthermore, the IRESSA Pan-Asia Study (IPASS) study,[23] conducted under the hypothesis that EGFR-TKI would be effective in clinically selected patients, confirmed the strong predictive value of *EGFR* mutations for the response of Ad to gefitinib.

This retrospective study has a few other limitations as well. First, information on smoking was not obtained from the interview or the self-administered questionnaire. Smoking data can be inaccurate, particularly when collected retrospectively. Second, we did not collect data on the procedures for histological diagnosis. The basis for pathological diagnosis is important because cytological assessment alone may lead to underdiagnosis of specific histologic types.

In conclusion, this survey demonstrated that Ad histology is associated with better prognosis, and that smoking status has a prognostic impact only in patients with Ad.

REFERENCES

1. Mitsudomi T, Morita S, Yatabe Y, et al.; West Japan Oncology Group. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. *Lancet Oncol* 2010;11:121–128.
2. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naïve patients with advanced-stage NSCLC. *J Clin Oncol* 2008;26:3543–3551.

3. Maemondo M, Inoue A, Kobayashi K, et al. Gefitinib or chemotherapy for non–small-cell lung cancer with mutated EGFR. *N Engl J Med* 2010;362:2380–2388.
4. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N Engl J Med* 2006;355:2542–2550.
5. Andrea K, Helena F, Sverre S. Prognostic significance of C-reactive protein and smoking in patients with advanced non-small cell lung cancer treated with first-line palliative chemotherapy. *J Thoracic Oncol* 2009;4:326–332.
6. Yelena YJ, Kevin M, Kark GK, et al. Pack-years of cigarette smoking as a prognostic factor in patients with stage IIIB/IV nonsmall cell lung cancer. *Cancer* 2010;116:670–675.
7. Toh CK, Gao F, Lim WT, et al. Never-smokers with lung cancer: epidemiologic evidence of a distinct disease entity. *J Clin Oncol* 2006;24:2245–2251.
8. Kawaguchi T, Takada M, Kubo A, et al. Gender, histology, and time of diagnosis are important factors for prognosis analysis of 1499 never-smokers with advanced non-small cell lung cancer in Japan. *J Thorac Oncol* 2010;5:1011–1017.
9. American Joint Committee on Cancer: *AJCC Cancer Staging Manual*, 6th Ed. New York: Springer, 2002. Pp. 167–181.
10. Feld R, Borges M, Giner V, et al. Prognostic factors in non-small cell lung cancer. *Lung Cancer* 1994;11:S19–S23.
11. Sun S, Schiller JH, Gazdar AF. Lung cancer in never smokers—a different disease. *Nat Rev Cancer* 2007;7:778–790.
12. Nordquist LT, Simon GR, Cantor A, et al. Improved survival in never smokers vs current smokers with primary adenocarcinoma of the lung. *Chest* 2004;126:347–351.
13. Tammemagi CM, Neslund-Dudas C, Simoff M, Kvale P. Smoking and lung cancer survival: the role of comorbidity and treatment. *Chest* 2004;125:27–37.
14. Zell JA, Ou SH, Ziogas A, et al. Epidemiology of bronchioloalveolar carcinoma: improvement in survival after release of the 1999 WHO classification of lung tumors. *J Clin Oncol* 2005;23:8396–8405.
15. Ou SH, Ziogas A, Zell JA. Asian ethnicity is a favorable prognostic factor for overall survival in non-small cell lung cancer (NSCLC) and is independent of smoking status. *J Thorac Oncol* 2009;4:1083–1093.
16. Gealy R, Zhang L, Siegfried JM, Luketich JD, Keohavong P. Comparison of mutations in the p53 and K-ras genes in lung carcinomas from smoking and nonsmoking women. *Cancer Epidemiol Biomarkers Prev* 1999;8 (4 Pt 1):297–302.
17. Hainaut P, Pfeifer GP. Patterns of p53 G–>T transversions in lung cancers reflect the primary mutagenic signature of DNA-damage by tobacco smoke. *Carcinogenesis* 2001;22:367–374.
18. DuyKhanh P, Mark GK, Gregory JR, et al. Use of cigarette-smoking history to estimate the likelihood of mutations in epidermal growth factor receptor gene exons 19 and 21 in lung adenocarcinomas. *J Clin Oncol* 2006;24:1700–1704.
19. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small-cell lung cancer. *J Clin Oncol* 2004;22:2184–2191.
20. Scagliotti G, Hanna N, Fossella F, et al. The differential efficacy of pemetrexed according to NSCLC histology: a review of two Phase III studies. *Oncologist* 2009;14:253–263.
21. Yamamoto N, Nishiwaki Y, Negoro S, et al. Disease control as a predictor of survival with gefitinib and docetaxel in a phase III study (V-15-32) in advanced non-small cell lung cancer patients. *J Thorac Oncol* 2010;5:1042–1047.
22. Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet* 2005;366:1527–1537.
23. Mok TS, Wu YL, Thongprasert S, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947–957.

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ORIGINAL ARTICLE

Phase I and pharmacokinetic study of gefitinib and S-1 combination therapy for advanced adenocarcinoma of the lung

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Abstract
Background A phase I dose-escalation study was performed to investigate the safety and pharmacokinetics of the combination of S-1 and gefitinib in patients with pulmonary adenocarcinoma who had failed previous chemotherapy.
Methods Patients received gefitinib at a fixed daily oral dose of 250 mg, and S-1 was administered on days 1–14 every 21 days at doses starting at 60 mg/m^2 (level 1) and escalating to 80 mg/m^2 (level 2). The primary end point of the study was determination of the recommended dose for S-1 given in combination with a fixed dose of gefitinib.
Results Twenty patients were enrolled in the study. Two of the first six patients at dose level 2 experienced a dose-limiting toxicity (elevation of alkaline phosphatase of grade 3 in one patient; elevations of aspartate and alanine aminotransferases of grade 3 in the other). The recommended dose was thus determined as level 2, and an additional 11 patients were assigned to this level. All observed adverse events were well managed. The response rate was 50 % (10 of 20 patients), and the median progression-free survival (PFS) and overall survival times were 10.5 and 21.2 months, respectively. In *EGFR* mutation–positive patients ($n = 9$), seven patients achieved an objective response and the median PFS was 12.4 months, whereas none with wild-type *EGFR* ($n = 6$) responded. No pharmacokinetic interaction between S-1 and gefitinib was detected.
Conclusions The combination of S-1 and gefitinib is well tolerated and appears to possess activity against *EGFR* mutation–positive NSCLC.

Keywords Gefitinib · S-1 · Non-small-cell lung cancer · Epidermal growth factor receptor · Phase I study

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Introduction

Gefitinib was the first molecularly targeted agent to become clinically available for the treatment of non-small-cell lung cancer (NSCLC). Somatic activating mutations of *EGFR* have been identified as a major determinant of the clinical response to treatment with gefitinib, with achievement of a clinical benefit with this drug in NSCLC patients with wild-type *EGFR* having been problematic [1, 2]. Furthermore, despite the therapeutic efficacy of gefitinib for patients with *EGFR* mutation–positive NSCLC, most such patients ultimately develop resistance to the drug. The development of combination therapy with gefitinib and other chemotherapeutic agents is being pursued in an attempt to improve treatment efficacy.

S-1 is an oral fluorinated pyrimidine formulation that combines tegafur (FT), 5-chloro-2,4-dihydroxypyridine (CDHP), and oxonic acid (Oxo) in a molar ratio of 1:0.4:1 [3]. FT is a prodrug that generates 5-fluorouracil (5-FU) in blood largely as a result of its metabolism by cytochrome

P450 in the liver. CDHP increases the plasma concentration of 5-FU through competitive inhibition of dihydropyrimidine dehydrogenase, which catalyzes 5-FU catabolism. CDHP also attenuates the indirect cardiotoxic and neurotoxic effects of 5-FU by reducing the production of fluoro-β-alanine, the main catabolite of 5-FU. Oxo reduces the gastrointestinal toxicity of 5-FU. After its oral administration, Oxo becomes distributed selectively to the small and large intestine, where it inhibits the phosphorylation of 5-FU to fluoropyrimidine monophosphate catalyzed by orotate phosphoribosyltransferase within gastrointestinal mucosal cells, thereby reducing the incidence of diarrhea [4]. S-1 has shown promising antitumor activity as a single agent for the treatment of advanced NSCLC as well as a good safety profile with manageable toxicities [5]. Furthermore, we recently presented the results of a phase III trial showing that S-1 in combination with carboplatin is not less efficacious and is better tolerated than carboplatin–paclitaxel, a representative platinum-based doublet chemotherapy for first-line treatment of advanced NSCLC [6].

We have previously shown that the combination of S-1 and gefitinib has a synergistic antiproliferative effect on NSCLC cells regardless of the absence or presence of *EGFR* mutations and that this enhanced antitumor effect is mediated by gefitinib-induced down-regulation of thymidylate synthase, a major target of 5-FU [7]. The combination of S-1 and gefitinib also exerted a synergistic antitumor effect in gefitinib-resistant cells with *MET* amplification both in vitro and in vivo, suggesting that such combination therapy is a promising strategy to overcome gefitinib resistance [8]. On the basis of these preclinical data, we have performed a phase I trial to assess the safety–tolerability, pharmacokinetics, and antitumor efficacy of the combination of gefitinib and S-1 in patients with advanced adenocarcinoma of the lung.

Patients and methods

Patient selection

Eligible patients had a confirmed histological or cytological diagnosis of adenocarcinoma of the lung that was either recurrent or stage IIIB or IV; had failed at least one prior systemic anticancer regimen including one platinum-based regimen (up to two regimens allowed); had not previously received therapy with an EGFR-TKI or S-1; and had adequate organ function (hemoglobin level ≥9.0 g/dl, neutrophil count ≥1,500/mm^3, platelet count ≥100,000/mm^3, total bilirubin level ≤1.5 mg/dl, aspartate (AST) and alanine (ALT) aminotransferase levels of ≤100 IU/l, saturation of peripheral O_2 ≥90 %, serum creatinine concentration ≤1.2 mg/dl, and predicted creatinine clearance or 24-h creatinine clearance ≥60 ml/min as estimated by the Cockcroft and Gault formula [9]). The study protocol was approved by the institutional review board at each participating center, and the study was conducted in accordance with the guidelines of the Declaration of Helsinki. All patients provided written informed consent before study-related procedures were performed. This trial was registered at the UMIN Clinical Trials Registry (UMIN 000001594).

Study design

Patients received a fixed daily dose of gefitinib (250 mg) for an initial period of 14 days followed by continuous daily administration of gefitinib and the administration of S-1 for 14 consecutive days every 21 days until disease progression or development of intolerable toxicity. The dose level of S-1 was set at 40 mg/m^2 (level 0), 60 mg/m^2 (level 1), or 80 mg/m^2 (level 2), with the dose escalation following a traditional 3 + 3 phase I trial design. The dose escalation–reduction scheme was based on the occurrence of a drug-related dose-limiting toxicity (DLT) within the first treatment course. A DLT was defined as a toxicity occurring in cycle 1 that met one of the following criteria: neutropenia of grade 4 persisting for ≥7 days, febrile neutropenia, thrombocytopenia of grade 4, or a nonhematologic toxicity (with the exception of nausea, vomiting, or anorexia) of grade 3. A delay of >2 weeks in administering the second treatment cycle was also considered a DLT. The maximum tolerated dose (MTD) was defined as the highest dose level at which ≤33 % of the patients experienced a DLT during the first treatment cycle. After the MTD had been determined, the corresponding cohort was to be expanded to a maximum of 20 patients for a more complete assessment of the safety and tolerability of the dose level. At least 14 patients were to be treated at the recommended dose. The probability of adverse events (AEs) with an incidence of ≥20 % not being detected in any of the 14 patients was 4.4 %.

If a DLT was not observed in any of the first three patients in the first cohort (level 1), an escalated dose of S-1 (80 mg/m^2) was administered to the first three patients at level 2. If a DLT was observed in one or two of the first three patients, an additional three patients were enrolled to assess the tolerability of this dose level. If a DLT occurred in one or two of the six patients at level 1, the dose of S-1 was escalated (to 80 mg/m^2). If three or more of the six patients at level 1 experienced a DLT, additional patients were recruited at level 0. In addition to this dose escalation–reduction scheme, if the investigators and an independent data-monitoring committee agreed that additional patients were necessary to confirm the dose escalation–

reduction decision in cases in which two or more patients experienced DLTs that were not life-threatening and were reversible and manageable with or without medication, then the entry of additional patients at that dose level was allowed.

Pharmacokinetics

The plasma pharmacokinetics of single-agent and combination treatments were investigated in the dose-escalation phase of the study in order to assess the potential for interaction between gefitinib and S-1. The pharmacokinetics of gefitinib were evaluated for 2 days (day 14 of the run-in period of administration of gefitinib alone and day 1 of combination therapy with gefitinib and S-1), and those of S-1 were examined on the first day of combination therapy with gefitinib and S-1. The plasma concentration of gefitinib was measured by Shin Nippon Biomedical Laboratories (Wakayama, Japan). The plasma concentrations of S-1 components (FT, CDHP, and Oxo) and 5-FU were measured by FALCO Biosystems (Kyoto, Japan). All concentrations were determined with the use of liquid chromatography and tandem mass spectrometry [10].

Efficacy measures

All patients underwent a comprehensive baseline assessment including clinical laboratory tests and imaging studies. Toxicity evaluations were based on the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0. Computed tomography scans were obtained every 6 weeks for the first 3 months and every 2 months thereafter. Response was evaluated according to RECIST 1.0. Progression-free survival (PFS) was calculated from the first day of combination therapy with gefitinib and S-1 until the first occurrence of progression, death from any cause, or last follow-up. Overall survival (OS) was calculated from the first day of the combination therapy until death from any cause or the date of last contact. The probability of survival as a function of time was estimated with the Kaplan–Meier method.

Results

Patient characteristics

Between July 2008 and April 2010, twenty patients with advanced adenocarcinoma of the lung were enrolled in the study at the three participating centers. The characteristics of the 20 study patients are summarized in Table 1. The patients included 12 (60 %) women and 10 (50 %) never-smokers. All had adenocarcinoma, and 8 (40 %) had disease of stage IV. The median age was 61 years, with a range of 51–70 years. Thirteen (65 %) of the 20 patients had received one prior chemotherapy regimen, whereas 7 individuals (35 %) had been treated with two prior regimens. Samples from 15 patients were available for *EGFR* mutational analysis, with such mutations being detected in 9 patients [the L858R point mutation in 5 patients (56 %) and exon-19 deletions in 4 patients (44 %)].

Determination of recommended dose

No DLTs were apparent for the first three patients treated at dose level 1, and so three patients were entered at dose level 2 (Table 2). Two of these latter three patients experienced a DLT [alkaline phosphatase (ALP) increase in grade 3 in one patient; AST and ALT increases in grade 3 in the other] in the first cycle, and an additional three patients were therefore treated at dose level 2. None of these three additional patients experienced a DLT. According to the protocol definition, dose level 2 was determined as the recommended dose, and an additional 11 patients were assigned to this level. A total of 17 patients were therefore treated at dose level 2.

Table 1 Characteristics of the study patients ($n = 20$), the median age of whom was 61 years (range 51–70 years)

Characteristics	No. of patients
Sex	
Male	8 (40 %)
Female	12 (60 %)
Performance status (ECOG)	
0	4 (20 %)
1	16 (80 %)
Disease stage	
IIIB	8 (40 %)
IV	8 (40 %)
Postoperative recurrence	4 (20 %)
No. of previous chemotherapies	
1	13 (65 %)
2	7 (35 %)
EGFR mutation	
Positive (L858R, exon-19 deletion)	9 (45 %)
Negative	6 (30 %)
Unknown (not examined)	5 (25 %)
Smoking history (pack-years)	
0	10 (50 %)
1–19	4 (20 %)
≥20	6 (30 %)

ECOG Eastern Cooperative Oncology Group

Table 2 Dose-escalation scheme and dose-limiting toxicities (DLTs)

Level	Gefitinib (mg/body)	S-1 (mg/m^2)	No. of patients		Type of DLT
			Total	DLT in first course	
1	250	60	3	0	
2	250	80	6	2	ALP increase; AST/ALT increases

Safety

A total of 144 cycles of chemotherapy was administered, with a median of 6 treatment cycles per patient (range 1–19). The major AEs during the entire treatment period are shown in Table 3. The most frequent (≥50 %) AEs were anemia, rash, hyperpigmentation, nausea, anorexia, fatigue, diarrhea, stomatitis, AST elevation, ALT elevation, and hyperbilirubinemia, all of which were clinically manageable. At dose level 2 ($n = 17$), hematologic AEs of grade ≥3 were not observed, and nonhematologic toxicities of grade 3 included stomatitis, increased ALP, increased AST, and increased ALT (6 % each). Nonhematologic AEs of grade 4 were not apparent. Interstitial lung disease was not manifest in any patient, and there were no treatment-related deaths.

Pharmacokinetics

Eight patients (three at dose level 1 and five at dose level 2) in the dose-escalation phase of the study were evaluable for pharmacokinetics. The mean steady-state pharmacokinetic parameters for gefitinib (250 mg daily) administered alone or with S-1 are summarized in Table 4. There were no substantial differences in the mean values of the area under the plasma concentration–time curve over 24 h (AUC_{0-24}) or the maximal concentration (C_{max}) for gefitinib when this drug was administered with or without S-1, suggesting that S-1 at either dose did not affect the trough levels of gefitinib.

Pharmacokinetic analysis was also performed for the plasma concentrations of S-1 components (FT, CDHP, and Oxo) and the FT metabolite 5-FU on the first day of gefitinib and S-1 combination therapy. The increases in the mean values of AUC_{0-8} and C_{max} for FT, 5-FU, and CDHP at dose level 2 compared with those at dose level 1 were consistent with the increase in S-1 dose (Table 5), and the pharmacokinetic parameters obtained for S-1 at dose level 2 administered together with gefitinib in the present study did not appear to differ substantially from those obtained previously for S-1 administered alone at 80 mg/m^2 [4].

Efficacy

All 20 patients were evaluable for antitumor response. Three individuals showed a complete response and seven patients showed a partial response, yielding an overall response rate of 50 %. Five patients had stable disease, giving an overall disease control rate of 75 %. In *EGFR* mutation–positive patients ($n = 9$), seven patients achieved an objective response, whereas none with wild-type *EGFR* ($n = 6$) responded. The median PFS and OS for all treated patients were 10.5 months (95 % confidence interval 2.5–12.9 months) and 21.2 months (95 % confidence interval 13.1–26.0 months), respectively. The median PFS was 12.4 and 3.3 months for the *EGFR* mutation–positive patients ($n = 9$) and the patients with wild-type *EGFR* ($n = 6$), respectively.

Discussion

We have previously shown that combined treatment with S-1 and gefitinib has a synergistic antiproliferative effect on NSCLC cells [7]. On the basis of this finding and additional preclinical data, we undertook the present phase I trial to assess the safety–tolerability, pharmacokinetics, and antitumor efficacy of the combination of gefitinib and S-1 in previously treated patients with advanced adenocarcinoma of the lung. Our study has demonstrated that once-daily gefitinib (250 mg) combined with administration of S-1 (80 mg/m^2) for 14 consecutive days every 21 days has an acceptable tolerability profile in such patients, indicating that full single-agent doses of both drugs can be used in combination. Most toxicities were mild or moderate in extent and were similar in type to those observed in monotherapy studies of gefitinib or S-1 [5, 11]. AEs of grade 3 included stomatitis and etlevation of AST, ALT, and ALP levels. All toxicities of grade 3 were reversible and were manageable with symptomatic treatment and dose reduction or interruption. AEs of grade 4 were not observed. The incidence of AEs during combination therapy with gefitinib and S-1 was not higher than that previously determined for either single-agent therapy.

S-1 is an oral fluorinated pyrimidine formulation that combines FT, CDHP, and Oxo. Oxidation of FT (prodrug of 5-FU) is largely dependent on CYP2A6 [12], and 5-FU showed no inhibitory effect on CYP activity in human liver microsomes [13]. Urinary excretion is the primary elimination pathway for CDHP. Non-CYP enzymes, including xanthine oxidase, contribute to the degradation of Oxo. On the other hand, elimination of gefitinib is dependent largely on CYP3A4 and to a lesser extent on CYP2D6 [14, 15]. Given the differences in metabolism and elimination between gefitinib and S-1, no pharmacokinetic interaction

Table 3 Treatment-related adverse events according to treatment cohort and grade

	Level 1 (n = 3)			Level 2 (n = 17)		
	All grades (%)	Grade 3 (%)	Grade 4 (%)	All grades (%)	Grade 3 (%)	Grade 4 (%)
Hematologic						
Anemia	1 (33)	0	0	12 (71)	0	0
Thrombocytopenia	1 (33)	0	0	4 (24)	0	0
Leukopenia	0	0	0	0	0	0
Neutropenia	1 (33)	1 (33)	0	1 (6)	0	0
Nonhematologic						
Rash	3 (100)	0	0	13 (76)	0	0
Hyperpigmentation	1 (33)			10 (59)		
Vomiting	1 (33)	0	0	2 (12)	0	0
Nausea	2 (67)	0	0	4 (24)	0	0
Anorexia	1 (33)	0	0	11 (65)	0	0
Fatigue	2 (67)	0	0	8 (47)	0	0
Diarrhea	2 (67)	0	0	9 (53)	0	0
Stomatitis	2 (67)	0	0	8 (47)	1 (6)	0
ALP increase	1 (33)	0	0	3 (18)	1 (6)	0
AST increase	2 (67)	0	0	8 (47)	1 (6)	0
ALT increase	2 (67)	0	0	8 (47)	1 (6)	0
Hyperbilirubinemia	2 (67)	0	0	7 (41)	0	0

Table 4 Effect of S-1 on the pharmacokinetics of gefitinib

Parameter	Dose level 1 (n = 3)		Dose level 2 (n = 5)	
	Monotherapy	Combination	Monotherapy	Combination
C_{max} (ng/ml)	516.0 ± 100.5	524.1 ± 96.1	684.8 ± 246.9	741.0 ± 208.3
T_{max} (h)	4.8 ± 2.5	5.0 ± 2.0	4.8 ± 2.5	3.8 ± 1.1
$t_{1/2}$ (h)	20.2 ± 2.4	21.3 ± 6.5	21.5 ± 3.8	29.4 ± 9.3
AUC_{0-24} (ng h/ml)	8,567.2 ± 2,131.0	8,849.3 ± 822.8	12,612.7 ± 4,908.2	12,880.9 ± 4,108.6

Data are mean ± SEM

C_{max} maximal plasma concentration of gefitinib, T_{max} time to achieve C_{max}, $t_{1/2}$ plasma half-life of gefitinib, AUC_{0-24} area under the plasma gefitinib concentration–time curve for 0–24 h

between these two agents would be expected. We evaluated the pharmacokinetics of combination therapy with gefitinib and S-1 in the present study. The C_{max} and AUC values of gefitinib obtained here were similar to those determined in phase I trials in patients with solid malignant tumors who received continuous single-agent treatment with gefitinib [16, 17]. To investigate directly the possible effect of S-1 on the pharmacokinetics of gefitinib, we collected blood samples on day 14 during the run-in period of administration of gefitinib alone as well as on the first day of combination therapy with gefitinib and S-1. The plasma concentration profiles and pharmacokinetic parameters for gefitinib were not altered by coadministration of S-1. The pharmacokinetic parameters obtained for S-1 (80 mg/m^2) during gefitinib dosing did not appear to differ substantially from those previously obtained for S-1 administered as a single agent [4], suggesting that gefitinib affects neither the conversion of FT to 5-FU nor the biological behavior of CDHP or Oxo. Together, these data thus indicate that there was no substantial pharmacokinetic interaction between gefitinib and S-1.

Given that single-agent treatment with EGFR-TKIs is now an established first-line therapeutic option for *EGFR* mutation–positive NSCLC, on the basis of recent phase III trials comparing EGFR-TKIs with platinum-based chemotherapy [18–21], it seems reasonable to test EGFR-TKIs in combination with other chemotherapeutic agents in such patients. The promising safety profile and apparent lack of pharmacokinetic interaction observed for the combination of S-1 and gefitinib in our phase I study suggest that this drug combination is a new treatment option for *EGFR* mutation–positive patients with advanced NSCLC.

Table 5 Pharmacokinetic parameters for S-1 components and 5-FU at the two dose levels

Parameter	Dose level 1 ($n = 3$)				Dose level 2 ($n = 5$)			
	FT	5-FU	CDHP	Oxo	FT	5-FU	CDHP	Oxo
C_{max} (ng/ml)	1,445.0 ± 228.0	101.9 ± 42.9	130.7 ± 72.3	54.5 ± 49.8	1,798.0 ± 138.0	182.1 ± 63.8	251.8 ± 56.5	44.2 ± 21.5
T_{max} (h)	2.0 ± 1.0	4.0 ± 1.0	3.0 ± 0.0	3.0 ± 0.0	2.0 ± 1.0	3.0 ± 0.0	3.0 ± 1.0	3.0 ± 0.0
$t_{1/2}$ (h)	6.13 ± 0.96	1.73 ± 0.30	2.64 ± 0.54	2.95 ± 0.97	6.55 ± 1.37	1.56 ± 0.34	2.41 ± 0.40	2.57 ± 0.96
AUC_{0-8} (ng h/ml)	7,446.0 ± 1,546.0	454.0 ± 193.4	532.1 ± 242.2	208.9 ± 145.9	9,752.0 ± 956.0	794.6 ± 280.1	1,000.6 ± 246.9	190.7 ± 85.0

Data are mean ± SEM

A further clinical concern is that *EGFR* mutation–positive patients who initially respond to EGFR-TKIs eventually develop resistance to these agents. At present, no drug that is able to overcome such acquired resistance is available in clinical practice. We have previously shown that the combination of gefitinib and S-1 has a synergistic antiproliferative effect on EGFR mutation–positive NSCLC cells that have developed resistance to EGFR-TKIs [8]. The addition of S-1 to gefitinib may thus prove effective for the treatment of *EGFR* mutation–positive patients with acquired resistance to EGFR-TKIs.

In conclusion, combination therapy with gefitinib (250 mg/day) and S-1 (80 mg/m^2 for 14 days every 21 days) was well tolerated in previously treated patients with advanced pulmonary adenocarcinoma. Further studies are thus warranted to confirm the efficacy and safety of combination therapy with S-1 and gefitinib in comparison with gefitinib monotherapy.

Conflict of interest The authors declare no conflict of interest.

References

1. Kosaka T, Yatabe Y, Endoh H et al (2004) Mutations of the epidermal growth factor receptor gene in lung cancer: biological and clinical implications. Cancer Res 64:8919–8923
2. Shigematsu H, Lin L, Takahashi T et al (2005) Clinical and biological features associated with epidermal growth factor receptor gene mutations in lung cancers. J Natl Cancer Inst 97:339–346
3. Okamoto I, Fukuoka M (2009) S-1: a new oral fluoropyrimidine in the treatment of patients with advanced non-small-cell lung cancer. Clin Lung Cancer 10:290–294
4. Hirata K, Horikoshi N, Aiba K et al (1999) Pharmacokinetic study of S-1, a novel oral fluorouracil antitumor drug. Clin Cancer Res 5:2000–2005
5. Kawahara M, Furuse K, Segawa Y et al (2001) Phase II study of S-1, a novel oral fluorouracil, in advanced non-small-cell lung cancer. Br J Cancer 85:939–943
6. Okamoto I, Yoshioka H, Morita S et al (2010) Phase III trial comparing oral S-1 plus carboplatin with paclitaxel plus carboplatin in chemotherapy-naive patients with advanced non-small-cell lung cancer: results of a west Japan oncology group study. J Clin Oncol 28:5240–5246
7. Okabe T, Okamoto I, Tsukioka S et al (2008) Synergistic antitumor effect of S-1 and the epidermal growth factor receptor inhibitor gefitinib in non-small cell lung cancer cell lines: role of gefitinib-induced down-regulation of thymidylate synthase. Mol Cancer Ther 7:599–606
8. Okabe T, Okamoto I, Tsukioka S et al (2009) Addition of S-1 to the epidermal growth factor receptor inhibitor gefitinib overcomes gefitinib resistance in non-small cell lung cancer cell lines with MET amplification. Clin Cancer Res 15:907–913
9. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16:31–41
10. Matsushima E, Yoshida K, Kitamura R (1997) Determination of S-1 (combined drug of tegafur, 5-chloro-2,4-dihydroxypyridine and potassium oxonate) and 5-fluorouracil in human plasma and urine using high-performance liquid chromatography and gas

chromatography-negative ion chemical ionization mass spectrometry. J Chromatogr B Biomed Sci Appl 691:95–104
11. Maruyama R, Nishiwaki Y, Tamura T et al (2008) Phase III study, V-15-32, of gefitinib versus docetaxel in previously treated Japanese patients with non-small-cell lung cancer. J Clin Oncol 26:4244–4252
12. Ikeda K, Yoshisue K, Matsushima E et al (2000) Bioactivation of tegafur to 5-fluorouracil is catalyzed by cytochrome P-450 2A6 in human liver microsomes in vitro. Clin Cancer Res 6:4409–4415
13. Park JY, Kim KA (2003) Inhibitory effect of 5-fluorouracil on human cytochrome P(450) isoforms in human liver microsomes. Eur J Clin Pharmacol 59:407–409
14. McKillop D, McCormick AD, Miles GS et al (2004) In vitro metabolism of gefitinib in human liver microsomes. Xenobiotica 34:983–1000
15. McKillop D, McCormick AD, Millar A et al (2005) Cytochrome P450-dependent metabolism of gefitinib. Xenobiotica 35:39–50
16. Nakagawa K, Tamura T, Negoro S et al (2003) Phase I pharmacokinetic trial of the selective oral epidermal growth factor receptor tyrosine kinase inhibitor gefitinib ('Iressa', ZD1839) in Japanese patients with solid malignant tumors. Ann Oncol 14:922–930
17. Ranson M, Hammond LA, Ferry D et al (2002) ZD1839, a selective oral epidermal growth factor receptor-tyrosine kinase inhibitor, is well tolerated and active in patients with solid, malignant tumors: results of a phase I trial. J Clin Oncol 20:2240–2250
18. Mitsudomi T, Morita S, Yatabe Y et al (2010) Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): an open label, randomised phase 3 trial. Lancet Oncol 11:121–128
19. Maemondo M, Inoue A, Kobayashi K et al (2010) Gefitinib or chemotherapy for non-small-cell lung cancer with mutated EGFR. N Engl J Med 362:2380–2388
20. Zhou C, Wu YL, Chen G et al (2011) Erlotinib versus chemotherapy as first-line treatment for patients with advanced EGFR mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): a multicentre, open-label, randomised, phase 3 study. Lancet Oncol 12:735–742
21. Rosell R, Carcereny E, Gervais R et al (2012) Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. Lancet Oncol 13:239–246

Original Study

Postprogression Survival in Patients With Advanced Non–Small-Cell Lung Cancer Who Receive Second-Line or Third-Line Chemotherapy

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Abstract

The effect of subsequent chemotherapy on overall survival (OS) has the potential to result in underestimation of the efficacy of an experimental treatment in clinical trials for advanced non–small-cell lung cancer (NSCLC). In this study, we investigated postprogression survival (PPS), defined as overall survival (OS) minus progression-free survival (PFS), in the second-line setting. PPS was highly associated with OS, and the induction rate for subsequent chemotherapy was associated with the duration of PPS. Our findings indicate that a beneficial effect of treatment on OS in patients with advanced NSCLC can be skewed by the effects of subsequent therapies in the second-line or third-line setting.

Background: The increased availability of active agents has improved overall survival (OS) in patients with advanced non–small-cell lung cancer (NSCLC). We previously showed that postprogression survival (PPS) is highly associated with OS in the first-line setting, but little is known about PPS in the salvage setting. In this study, we analyzed PPS in phase III trials in the second-line or third-line setting. **Patients and Methods:** A literature search identified 18 trials for previously treated patients with advanced NSCLC. We partitioned OS into progression-free survival (PFS) and PPS and evaluated the association between OS and either PFS or PPS. Correlation analysis to examine whether a treatment benefit for PFS carried over to OS was performed by calculation of incremental gains in OS and PFS at the trial level. **Results:** The average median PPS was longer than the average median PFS (5.4 and 2.6 months, respectively). The induction rate for subsequent chemotherapy after second-line or third-line treatment was related to the duration of PPS in linear regression analysis (r^2 = 0.4813). Median OS was highly associated with median PPS but not with PFS (r = 0.94 and 0.51, respectively), and only a weak association between the treatment benefits for PFS and OS was detected (r = 0.29). **Conclusions:** Treatment benefit for OS in patients with advanced NSCLC can be skewed by the effects of subsequent therapies in the second-line or third-line setting. Whether PFS or OS is the more appropriate endpoint for trials in the salvage setting should be considered.

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Keywords: Overall survival, Phase III trial, Progression-free survival, Subsequent chemotherapy

Introduction

Lung cancer remains the leading cause of cancer death worldwide,[1,2] with non–small-cell lung cancer (NSCLC) accounting for approximately 85% of lung cancer cases. Most individuals with NSCLC have metastatic disease at the time of diagnosis and therefore have a poor prognosis. The standard treatment for advanced NSCLC over the past decade has been platinum-based chemotherapy because of the moderate improvement in survival it confers.[3-6] Although many patients initially achieve clinical remission or disease stabilization with first-line chemotherapy, nearly all subsequently experience disease progression.

For advanced NSCLC, overall survival (OS) has been the most commonly used endpoint in phase III trials. However in view of the growing number of drugs and combinations thereof that are available for the treatment of such patients, the effect of subsequent chemotherapy on OS has the potential to result in underestimation of the

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efficacy of an experimental treatment in clinical trials when such treatment is compared with a control arm.[7] Indeed, an improvement in progression-free survival (PFS) has not necessarily resulted in an improved OS in recent randomized trials for patients with advanced NSCLC. The effect of therapies instituted after disease progression on survival is thus of interest. We have recently shown that survival after progression (postprogression survival [PPS]) is highly associated with OS in the first-line treatment setting for advanced NSCLC.[8]

In patients who have experienced disease progression either during or after first-line chemotherapy for advanced NSCLC, second-line chemotherapy has become established over the past decade as a standard option.[9-12] Although many phase III trials have been reported for previously treated patients with advanced NSCLC, little is known about PPS in this group of patients. We partitioned OS into PFS and PPS and then assessed the association of each with OS in phase III trials for previously treated patients with advanced NSCLC. Analysis of PPS has the potential to provide valuable insight for selecting the appropriate method for evaluation of chemotherapy in the second-line setting.

Patients and Methods

Search Strategy and Selection of Trials

An independent review of PubMed citations from January 1, 2000 to April 31, 2011 was performed to identify trials. Key words included in the search were *non–small-cell lung cancer, clinical trial, advanced*, and *chemotherapy*. The search was limited to randomized controlled phase III trials and articles published in English. We reviewed each publication, and phase III studies that compared 2 or more systemic chemotherapies (including treatment with molecularly targeted agents) in patients with disease recurrence after chemotherapy for advanced or metastatic NSCLC were selected. To find any additional trials, we searched the reference lists of included trials as well as those of large systematic reviews. We also checked articles that were in press at leading journals and searched websites that list abstracts from conferences (organized by the American Society of Clinical Oncology or the Federation of European Cancer Societies). We included trials that provided data for both OS and either PFS or time to progression (TTP), whether or not these parameters were explicitly defined. Trials were excluded if they investigated only immunotherapy regimens or hormonal therapies. Trials that were designed to assess combined-modality treatments, including radiation therapy and surgery, were also excluded. To avoid bias, 2 observers (H.H. and I.O.) independently abstracted the data from the trials.

Data Abstraction

We analyzed in detail the primary and secondary efficacy endpoints, following the definitions of the authors of each trial. When not specifically stated by the authors, we considered the primary endpoint to be that used for calculation of sample size. For the sake of simplicity, 2 endpoints (PFS and TTP) based on tumor assessment are collectively referred to as PFS in the present study, similar to the approach adopted in a recent report.[13] Median OS and median PFS were extracted from all trials that provided data for each treatment group. Median PPS was defined as median OS minus median PFS for each trial. When available, the proportion of patients who received chemotherapy after the study conclusion was recorded for each treatment arm. We also obtained the following information from each report: year of completion of trial enrollment, number of patients randomized, number of patients in each treatment arm, number of treatment arms in each trial, proportion of patients who were men or had adenocarcinoma, and median age of the patients.

Data Analysis

We summarized the survival data (median OS, median PFS, median PPS, and median PFS/median OS) as the average and standard error for trial arms. Standard error was calculated on the basis of previously described models.[14] We investigated the percentage of OS accounted for by PPS for each trial arm as 100 – (100 × median PFS/median OS). To assess the association between median OS and either median PFS or median PPS, we used the Spearman rank correlation coefficient. In addition, linear regression analysis was performed to evaluate the relation between PPS and the induction rate for subsequent chemotherapy after study treatment. We also calculated the incremental gains in median OS and median PFS from the difference between the experimental and control arms as previously described,[15] and we performed correlation analysis to examine whether a treatment benefit for PFS carried over to OS.

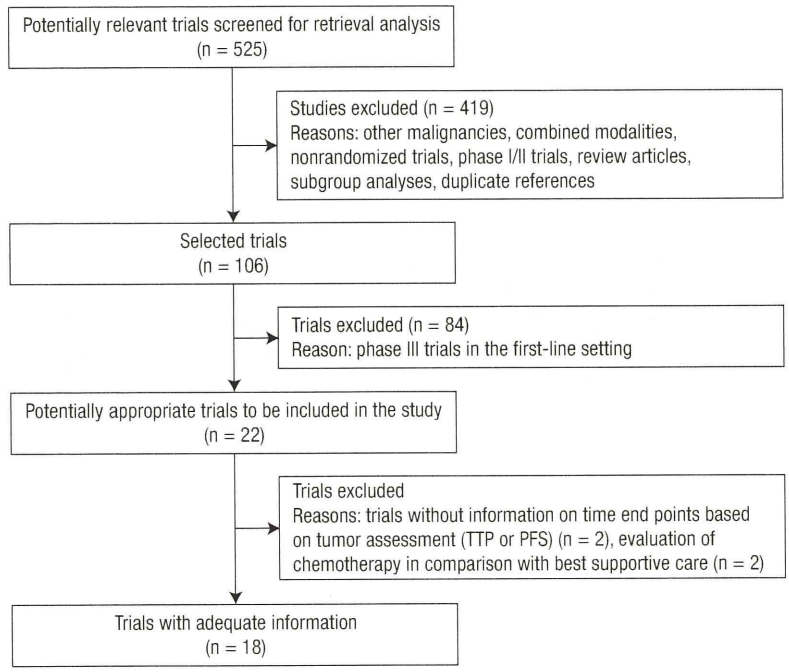
To account for differences in sample size among trial arms, we weighted analyses that treated each trial arm as a unit by the number of patients in each arm. In addition, all trials were divided into 2 groups on the basis of the year in which trial enrollment was completed. Given that the median year for completion of enrollment in the 18 analyzed trials was 2005, we dichotomized at year 2005 (older trials, up to and including 2005; recent trials, 2006 and later) to evaluate a possible change in PPS, and we assessed whether the evaluated relations might be dependent on the year of completion of trial enrollment. All reported P values correspond to 2-sided tests, and those of $< .05$ were considered statistically significant. Analyses were performed with SAS for Windows, version 9.2 (SAS Institute, Cary, NC).

Results

Characteristics of the Trials

Our search yielded a total of 525 potentially relevant publications. The selection process for the randomized controlled trials is shown in Figure 1. Initially, 419 studies were excluded for at least 1 of the following reasons: they examined other malignancies or combined-modality treatments, they were not randomized, they were phase I or II trials, they were review articles, they represented subgroup analyses, or they were duplicates. Review of the remaining 106 publications yielded 18 trials that were considered to be highly relevant for the present study (Supplementary Table 1). Thirty-seven treatment arms in second-line or third-line settings were detected. The main characteristics of the 18 phase III trials included in the analysis are listed in Table 1. A total of 11,310 patients with advanced NSCLC were enrolled, with a median number of patients per study of 561 (range, 130-1466). Most of the trials had a high proportion of male patients and of patients with adenocarcinoma. The average median age of the patients was 61.0 years. Five trials used a primary endpoint based on tumor assessment (PFS or TTP), whereas OS was assessed as the primary endpoint in 12 trials.

Figure 1 Flow Chart Showing the Progress of Trials Through the Selection Process



Abbreviations: PFS = progression-free survival; TTP = time to progression.

Table 1 Characteristics of 18 Phase III Trials for Advanced NSCLC Included in Present Analysis

	No. of Trials
Trial Characteristics	
Median no. of patients per trial (range)	561 (130–1466)
Percentage of male patients (median)	67.30%
Percentage of adenocarcinoma patients[a]	54.40%
Average of median age (y)[b]	61
Primary Endpoint	
OS	12
PFS or TTP	5
1-y survival rate	1
Endpoint Based on Tumor Assessment	
TTP	14
PFS	4
Number of Treatment Arms	
2	17
3	1

Abbreviations: OS = overall survival; PFS = progression-free survival; TTP = time to progression.
[a] Two trials were excluded (data were not shown).
[b] One trial was excluded (data were not shown).

Association Between Median OS and Either Median PFS Or Median PPS

The average median OS, median PFS, and median PPS in the present analysis are shown in Table 2. The average median PPS was longer than the average median PFS (5.4 vs. 2.6 months). The average proportion of median OS accounted for by median PPS was 66.6%. The relation between median OS and either median PFS or median PPS is shown in Figure 2. We found that median PPS was highly associated with median OS ($r = 0.94$; $P < .0001$) on the basis of the Spearman correlation coefficient, whereas median PFS was moderately associated with median OS ($r = 0.51$; $P = .001$). Furthermore, analysis performed according to the year in which trial enrollment was completed revealed that the average median PFS in older (up to and including 2005) trials was similar to that in recent (2006 and later) trials (2.5 and 2.7 months, respectively; $P = .357$) and that the average median PPS was significantly longer in recent trials than in older trials (6.2 and 4.4 months, respectively; $P < .0001$). The average proportion of median OS accounted for by median PPS was also significantly increased from 63.6% in older trials to 68.8% in recent trials ($P = .014$).

Relation of the Induction Rate of Subsequent Chemotherapy To Duration of PPS

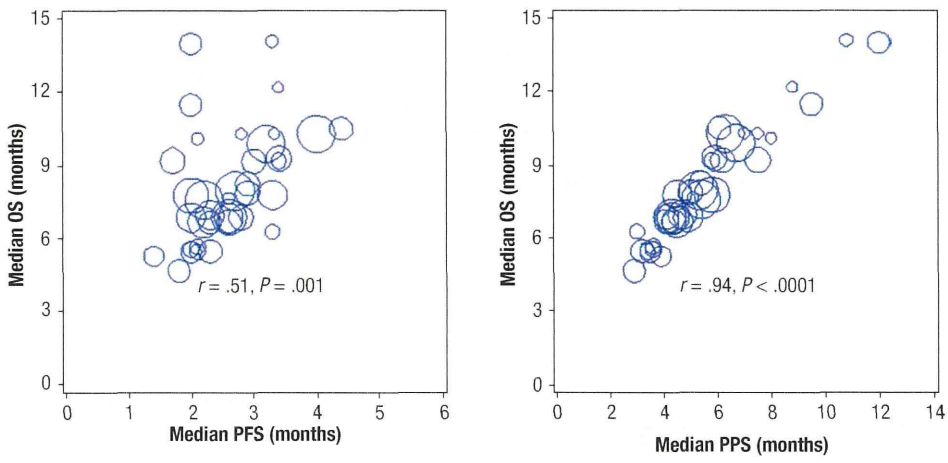
Given the relatively long duration of PPS detected for clinical trials in the second-line or third-line setting, we performed an ex-

Table 2 Average Values of Median PFS, OS and PPS for Trial Arms According to Year of Completion of Trial Enrollment*

Trials	No. of Arms	No. of Patients	Average Median (Mo)			Average PPS/OS (%)
			PFS	OS	PPS	
All	37	11,310	2.6 [0.13]	8.0 [0.32]	5.4 [0.26]	66.6 [1.16]
Recent (2006 and later)	18	6473	2.7 [0.22]	8.9 [0.46]*	6.2 [0.38]*	68.8 [1.77]**
Older (up to and including 2005)	19	4837	2.5 [0.12]	6.2 × [0.22]	4.4 × [0.16]	63.6 [1.20]

Values in brackets are standard errors.
Abbreviations: OS = overall survival; PFS = progression-free survival; PPS = postprogression survival.
* $P < .0001$ (Both of OS and PPS in recent trials were significantly longer than older trials). ** $P = .014$ vs. the corresponding value for older trials (z test).

Figure 2 Association Between Median Overall Survival (OS) and Either Median Progression-Free Survival (PFS) or Median Postprogression Survival (PPS) For 37 Arms of 18 Phase III Trials for Patients With Advanced NSCLC in the Second-Line or Third-Line Setting. The Area of Each Circle is Proportional to the Number of Patients in Each Trial Arm. The r Values Represent Spearman Rank Correlation Coefficient



ploratory analysis to identify whether the induction rate of subsequent chemotherapy was related to PPS duration. The percentage of patients who received subsequent chemotherapy was available for 24 of the 37 treatment arms. The characteristics of the patients in this subgroup of treatment arms were similar to those of all patients in the primary analysis (data not shown). Linear regression analysis revealed that the duration of PPS was indeed related to the induction rate of subsequent chemotherapy ($r^2 = 0.4813$; $P = .025$) (Figure 3).

Correlation Between the Incremental Gains In Median OS and Median PFS

To investigate further the relation between OS and PFS, we analyzed the incremental gains in median OS and median PFS for each trial (Figure 4). There was only a weak correlation between the gain in median PFS and that in median OS ($r = 0.29$; $P < .0001$).

Discussion

In the present study, we defined median PPS as median OS minus median PFS for each treatment arm of phase III trials for patients with advanced NSCLC in the second-line or third-line setting, as previously described.[8,13] We found that the average median PPS accounted for more than half of the average median OS derived from second-line or third-line chemotherapy (5.4 and 8.0 months, respectively).

As far as we are aware, the current analysis is the first to determine the duration of PPS for previously treated patients with advanced NSCLC. The relatively long duration of PPS (5.4 months) observed in the present study is similar to that for our previous study in the first-line setting,[8] although there is no further line of chemotherapy (fourth line or later) proved to provide a survival benefit in comparison with best supportive care. Several potential factors might explain such results. Performance status (PS) has traditionally been identified as a strong prognostic factor in terms of OS for patients with advanced NSCLC.[16,17] Patients with a good PS are usually enrolled in clinical trials as a result of the inclusion criteria. Although information on changes in PS during disease progression was not available for the selected clinical trials, maintenance of a good PS may allow a patient to receive a further line of chemotherapy and thereby contribute to prolongation of PPS. Furthermore, the current study

Figure 3 Linear Regression Analysis of the Relation Between the Induction Rate of Subsequent Chemotherapy and the Duration of Postprogression Survival (PPS). The Area of Each Circle is Proportional to the Number of Patients in Each Trial Arm

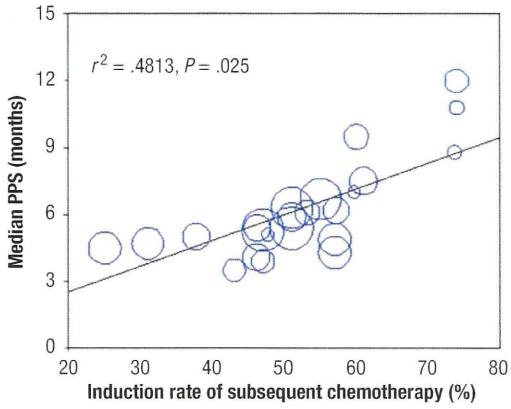
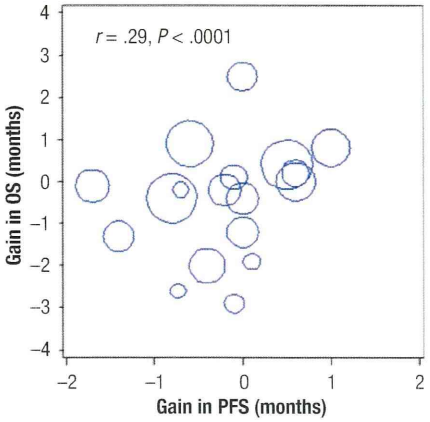


Figure 4 Relation Between the Incremental Gain in Median Progression-Free Survival (PFS) and That in Median Overall Survival (OS) for Paired Arms of All 18 Trials Weighted by the Number of Randomized Patients. The Area of Each Circle is Proportional to the Number of Patients in Each Trial Arm. The *r* Value Represents Spearman Rank Correlation Coefficient



showed that median PPS was significantly longer in recent trials than in older trials. The recent increase in the number of available active compounds may thus have contributed to more widespread clinical use of chemotherapy in the fourth-line or later-line setting, resulting in prolongation of PPS even in the second-line or third-line setting.

Indeed, we found that the induction rate of subsequent chemotherapy after second-line or third-line chemotherapy is related to the duration of PPS. These data suggest that the efficacy of the late-line therapies contributes, at least in part, to the prolongation of PPS. Such factors may thus explain the relatively long duration of PPS in the second-line or third-line setting and its similarity to that in the first-line setting. Precise assessment of clinical course, including changes in PS during disease progression and subsequent chemotherapy after such progression, is warranted in future clinical trials.

We found that PPS, but not PFS, was highly associated with OS for patients with advanced NSCLC in the second-line or third-line setting. Our examination of the association between median PFS and median OS was not an exercise in surrogate validation, however, because of the lack of investigation into the relation between the effects of chemotherapy on these endpoints. Although hazard ratios are often analyzed for such examination of surrogacy, only a limited number of the trials included in the current analysis provided hazard ratios for both PFS and OS. Given that median PFS and median OS were available for all trials, we investigated the relation between the incremental gains in median OS and median PFS, as previously described,[15] to examine how a treatment benefit for PFS might carry over to OS. To the best of our knowledge, the current analysis is the first to investigate the surrogacy of PFS for OS in previously treated patients with advanced NSCLC, and we found a weak relation between the gain in median OS and that in median PFS. A previous study showed that the probability of detecting a statistically significant difference in OS decreases substantially as the median PPS increases.[18] From this standpoint, it is reasonable to conclude that the high proportion of median OS accounted for by median PPS in the present study contributed to the weakness of the association between the treatment benefit for PFS and that for OS. Indeed, an improvement in PFS has not necessarily resulted in an improved OS in several phase III trials for previously treated patients with NSCLC.[19-23] These findings suggest that OS in the second-line setting is heavily skewed by the effects of subsequent therapies.

The present study has several limitations. First, our analysis was based on abstracted data. The use of individual patient data might be expected to allow a better characterization of the relation between OS and other endpoints based on tumor assessment, including PFS and TTP. However, such an approach would restrict the analysis to a small number of trials and would hinder its replication by independent researchers. Second, the results of our study potentially have several confounders due to selection of many heterogeneous trials for analysis. The results are generally unaccountable without appropriate adjustment for patient characteristics dependent on differences in predefined eligibility criteria for enrollment in the clinical trials. Finally, 2 endpoints (PFS and TTP) based on tumor assessment are considered as the same parameter, following the example of previous studies.[8,13] PFS is defined as the time from randomization to tumor progression or death, whereas TTP is defined similarly but considers death as the time point when censoring occurs. TTP is the same as PFS if death does not occur during treatment. Given that death rarely occurs before disease progression in patients with advanced NSCLC, we reasonably considered PFS to be the same as TTP for our analysis.

Conclusion

As far as we are aware, our study is the first to analyze PPS in clinical trials for patients with advanced NSCLC who receive second-line or third-line chemotherapy. Our findings indicate that median PPS is highly associated with median OS even in the salvage setting. Moreover, only a weak correlation between the treatment-associated gain in OS and that in PFS was detected. Given the recent increase in the opportunity for administration of subsequent chemotherapy, PFS should not be considered a surrogate endpoint for OS in the second-line or third-line setting for patients with advanced NSCLC.

Clinical Practice Points

- An improvement in PFS has not necessarily resulted in an improved OS in recent randomized trials for patients with advanced NSCLC.
- Given the growing number of drugs and combinations thereof available for the treatment of such patients, the effect of subsequent chemotherapy on OS has the potential to result in underestimation of the efficacy of an experimental treatment in clinical trials in which such treatment is compared with a control arm.
- The average median PPS in phase III trials of second-line or third-line chemotherapy in patients with advanced NSCLC was 5.4 months in the present study.
- Median PPS was highly associated with median OS for patients with advanced NSCLC who receive second-line or third-line chemotherapy ($r = 0.94$; $P < .0001$).
- The duration of PPS was related to the induction rate of subsequent chemotherapy in linear regression analysis ($r^2 = 0.4813$; $P = .025$).
- The treatment benefit in terms of OS for patients with advanced NSCLC in the second-line or third-line setting can be skewed by the effects of subsequent therapies.

Supplementary Data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cllc.2012.09.006.

Disclosures

The authors have stated that they have no conflicts of interest.

References

1. Breathnach OS, Freidlin B, Conley B, et al. Twenty-two years of phase III trials for patients with advanced non-small-cell lung cancer: sobering results. *J Clin Oncol* 2001; 19:1734-42.
2. Carney DN. Lung cancer—time to move on from chemotherapy. *N Engl J Med* 2002; 346:126-8.
3. Hotta K, Matsuo K. Long-standing debate on cisplatin- versus carboplatin-based chemotherapy in the treatment of advanced non-small cell lung cancer. *J Thorac Oncol* 2007; 2:96.
4. Hotta K, Matsuo K, Ueoka H, et al. Meta-analysis of randomized clinical trials comparing cisplatin to carboplatin in patients with advanced non-small-cell lung cancer. *J Clin Oncol* 2004; 22:3852-9.
5. Azzoli CG, Baker S, Jr, Temin S, et al. American Society of Clinical Oncology Clinical Practice guideline update on chemotherapy for stage IV non-small-cell lung cancer. *J Clin Oncol* 2009; 27:6251-66.
6. Wakelee HA, Bernardo P, Johnson DH, et al. Changes in the natural history of nonsmall cell lung cancer (NSCLC)—comparison of outcomes and characteristics in patients with advanced NSCLC entered in Eastern Cooperative Oncology Group trials before and after 1990. *Cancer* 2006; 106:2208-17.
7. Soria JC, Massard C, Le Chevalier T. Should progression-free survival be the primary measure of efficacy for advanced NSCLC therapy? *Ann Oncol* 2010; 21:2324-32.
8. Hayashi H, Okamoto I, Morita S, et al. Postprogression survival for first-line chemotherapy of patients with advanced non-small-cell lung cancer. *Ann Oncol* 2012; 23:1537-41.
9. Fossella FV, DeVore R, Kerr RN, et al. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. *J Clin Oncol* 2000; 18:2354-62.
10. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004; 22:1589-97.
11. Kim ES, Hirsh V, Mok T, et al. Gefitinib versus docetaxel in previously treated non-small-cell lung cancer (INTEREST): a randomised phase III trial. *Lancet* 2008; 372:1809-18.
12. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med* 2005; 353:123-32.
13. Saad ED, Katz A, Buyse M. Overall survival and post-progression survival in advanced breast cancer: a review of recent randomized clinical trials. *J Clin Oncol* 2010; 28:1958-62.
14. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; 7:177-88.
15. Johnson KR, Ringland C, Stokes BJ, et al. Response rate or time to progression as predictors of survival in trials of metastatic colorectal cancer or non-small-cell lung cancer: a meta-analysis. *Lancet Oncol* 2006; 7:741-6.
16. Sculier JP, Chansky K, Crowley JJ, et al. The impact of additional prognostic factors on survival and their relationship with the anatomical extent of disease expressed by the 6th edition of the TNM classification of malignant tumors and the proposals for the 7th edition. *J Thorac Oncol* 2008; 3:457-66.
17. Brundage MD, Davies D, Mackillop WJ. Prognostic factors in non-small cell lung cancer: a decade of progress. *Chest* 2002; 122:1037-57.
18. Broglio KR, Berry DA. Detecting an overall survival benefit that is derived from progression-free survival. *J Natl Cancer Inst* 2009; 101:1642-9.
19. Ramlau R, Gervais R, Krzakowski M, et al. Phase III study comparing oral topotecan to intravenous docetaxel in patients with pretreated advanced non-small-cell lung cancer. *J Clin Oncol* 2006; 24:2800-7.
20. Herbst RS, Sun Y, Eberhardt WE, et al. Vandetanib plus docetaxel versus docetaxel as second-line treatment for patients with advanced non-small-cell lung cancer (ZODIAC): a double-blind, randomised, phase 3 trial. *Lancet Oncol* 2010; 11:619-26.
21. Lee DH, Park K, Kim JH, et al. Randomized phase III trial of gefitinib versus docetaxel in non-small cell lung cancer patients who have previously received platinum-based chemotherapy. *Clin Cancer Res* 2010; 16:1307-14.
22. Pallis AG, Agelaki S, Agelidou A, et al. A randomized phase III study of the docetaxel/carboplatin combination versus docetaxel single-agent as second line treatment for patients with advanced/metastatic non-small cell lung cancer. *BMC Cancer* 2010; 10:633.
23. Takeda K, Negoro S, Tamura T, et al. 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). *Ann Oncol* 2009; 20:835-41.