Results

Patients Characteristics

Between February 2000 and November 2002, 51 patients were enrolled onto this study. Table 1 lists the baseline characteristics of the patients. Two patients were considered to be ineligible because a secondary primary tumor was found after the administration of EP with concurrent TRT. Therefore, 49 patients were assessable for response and toxicity.

Treatment Administration

Seven patients were removed from the study after the administration of EP with concurrent TRT because of treatment delay due to toxicity (six patients) and patient rejection (one patient). Eight patients each discontinued the treatment after each cycle of IP. The major reasons for the discontinuation of IP included treatment delay due to toxicity (three patients), diarrhea (three patients), and ileus (three patients), patient rejection (two patients), and the doctor's judgment (two patients). Overall, 34 patients (69%) received at least two cycles of IP and 26 patients (53%) completed the entire treatment. Irinotecan was omitted in 35 (11%) of 306 cycles. The dose-intensity of irinotecan was 30.5 mg/m^2/wk (68% of the planned dose) and cisplatin 11.6 mg/m^2/wk (77% of the planned dose) in the consolidation chemotherapy.

Response and Survival

On an intention-to-treat basis, the overall response rates and the complete response rates were 88% (95% CI, 78.6% to 96.9%) and 41%, respectively. After a median follow-up of 29.9 months, the median survival time for all patients was 23 months (Fig 1). The 2-year and 3-year survival rates were 49% and 29.7%, respectively. The median progression-free survival was 11.8 months (Fig 2).

Toxicity

Tables 2 and 3 show the major toxicities. Grade 4 neutropenia was observed in 80% of the patients and 10 (20%) patients had febrile neutropenia in concurrent chemoradiotherapy, whereas grade 4 neutropenia was observed in 40% of the patients and seven patients (17%) had febrile neutropenia in consolidation chemotherapy. In contrast, anemia and thrombocytopenia were relatively mild. One patient had grade 4 esophagitis in concurrent chemoradiotherapy. In the consolidation chemotherapy, grade 3 or 4 diarrhea was observed in six patients (14%) and grade 3 or 4 infection was observed in seven patients (17%). Two patients had grade 3 or 4 radiation pneumonitis. Grade 4 adhesive ileus developed in a patient who had a history of abdominal surgery and ileus. The major toxicities observed through the entire course of the treatment were neutropenia (grade 4, 84%), febrile neutropenia (grade 3, 31%), infection (grade 3 to 4, 33%), electrolytes imbalance (grade 3 to 4, 20%) and diarrhea (grade 3 to 4, 14%). There was one treatment-related death caused by radiation pneumonitis.

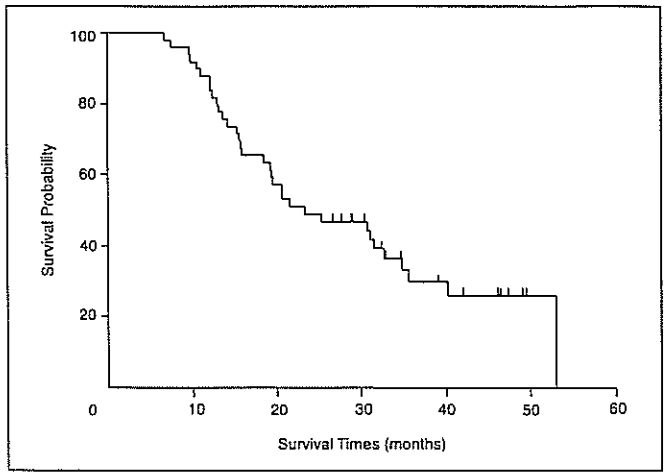

Fig 1. Kaplan-Meier survival curve of 49 eligible patients with limited-disease small-cell lung cancer. The median survival time was 23 months, and the 2-year and 3-year survival rates were 49% and 29.7%, respectively.

Patterns of Relapse

Table 4 lists first sites of relapse. Of 12 patients (24%) with local relapse (defined as relapse within the radiation portal), only one had a relapse solely at locoregional sites and 11 at both local and distant site including three with brain metastasis. Of 27 patients (55%) with distant relapse only, 13 had brain metastasis. Overall, 16 patients (33%) showed brain metastasis as the initial site of relapse, and eight of them had received PCI.

Table 1. Patient Characteristics (N = 51)

Characteristic	No.	%
Age, years		
Median	62	
Range	45-70	
Sex		
Male	42	82
Female	9	18
ECOG performance status		
0	22	43
1	28	55
2	1	2
Stage		
II	2	4
IIIA	35	69
IIIB	14	27

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

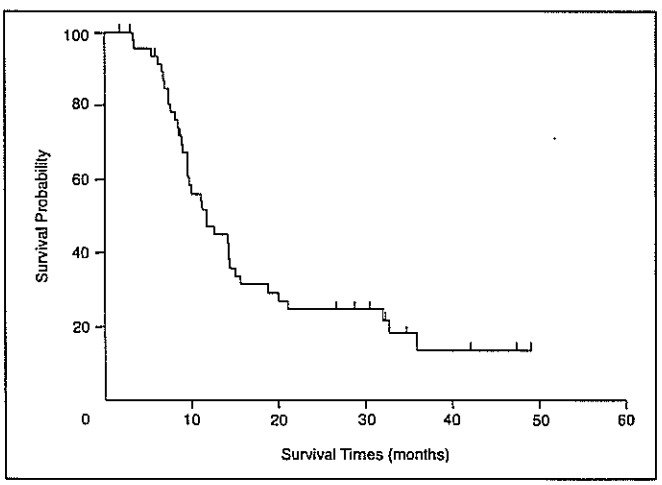

Fig 2. Kaplan-Meier progression-free survival curve of 49 eligible patients with limited-disease small-cell lung cancer. The median progression-free survival time was 11.8 months.

Table 2. Major Toxicities During Concurrent Chemoradiotherapy (n = 49)

Toxicity	Grade 3		Grade 4	
	No.	%	No.	%
Hematologic				
Leukopenia	27	55	19	39
Neutropenia	8	16	39	80
Anemia	2	4	1	2
Thrombocytopenia	10	20	0	0
Febrile neutropenia	10	20	0	0
Nonhematologic				
Nausea/vomiting	7	14	0	0
Diarrhea	0	0	0	0
Constipation	0	0	0	0
Infection	9	18	0	0
Mucositis	0	0	0	0
Esophagitis	0	0	1	2
Dyspnea	1	2	0	0
Pneumonitis	0	0	0	0
Hepatic	0	0	0	0
Electrolytes	2	4	2	4

DISCUSSION

In this phase II study, we evaluated the consolidation of IP after EP with concurrent twice-daily TRT and thus achieved an overall response rate of 88%, a 2-year-survival rate of 49% and a 3-year-survival rate of 29.7%. Although the number of assessable patients was slightly smaller than the planned sample size, this study confirmed 24 2-year survivors, and the power calculation showed a 97% probability to correctly reject inactive treatment, thus yielding only a 35% or less 2-year-survival rate. These results are comparable to those in phase III studies evaluating EP with concurrent twice-daily TRT.[3-6] Jeremic et al[7] reported a better survival outcome by using daily carboplatin and etoposide with concurrent twice-daily TRT followed by EP. However, this result has rarely been confirmed by other groups. The Japanese Clinical Oncology Group (JCOG) conducted a pilot study to evaluate the feasibility of IP after EP with concurrent TRT (JCOG9903).[14] The doses and schedule of cisplatin, etoposide, and irinotecan and dose, fractionation and schedule of TRT were similar to ours. They reported that this regimen was feasible with a response rate of 97%, a 2-year survival rate of 41% and a 3-year survival rate of 38%, which are similar to those in our study. Although a phase III study conducted in Japan showed the superiority of IP over EP in ED-SCLC,[9] another phase III study conducted in North America failed to confirm the superiority of IP over EP.[15] A randomized phase III study to compare IP versus EP after EP with concurrent TRT is currently ongoing in patients with LD-SCLC in Japan.

Table 3. Major Toxicities During Consolidation Chemotherapy (n = 42)

Toxicity	Grade 3		Grade 4	
	No.	%	No.	%
Hematologic				
Leukopenia	27	64	8	19
Neutropenia	18	43	17	40
Anemia	17	40	5	12
Thrombocytopenia	8	19	0	0
Febrile neutropenia	7	17	0	0
Nonhematologic				
Nausea/vomiting	9	21	0	0
Diarrhea	5	12	1	2
Constipation	3	7	2	5
Ileus	2	5	1	2
Infection	9	21	1	2
Mucositis	0	0	0	0
Esophagitis	0	0	0	0
Dyspnea	2	5	0	0
Pneumonitis	1	2	1	2
Hepatic	1	2	0	0
Electrolytes	4	10	1	2

Table 4. Site of First Failure (n = 49)

Site	No. of Patients	%
Progression free	10	20
Locoregional	1	2
Locoregional and distant	11	22
Distant	27	55
Brain only	8	16
Brain and others	5	10
Others	14	29

Although a potential approach is to substitute irinotecan for etoposide in the combination of EP with concurrent TRT, we did not combine IP concurrently with TRT because two phase I studies demonstrated that combining IP with concurrent TRT was not feasible when the full dose of irinotecan was administered on days 1, 8, and 15.[16,17] On the basis of these results, we administered IP as consolidation therapy after EP with concurrent twice-daily TRT. After this article was initially submitted, Langer et al[18] reported phase I study of once every 3 weeks scheduling of IP with concurrent twice-daily TRT (45 Gy) or once-daily TRT (70 Gy) in patients with LD-SCLC, thus concluding that IP with concurrent twice-daily TRT was safe and feasible. A further evaluation of this regimen is thus warranted.

One group evaluated IP administered as an induction followed by EP with concurrent twice-daily TRT.[19] Their results are comparable to those of our study and EP with concurrent twice-daily TRT.[3-6] However, this regimen was highly myelotoxic (grade 4 neutropenia, 91%) with febrile neutropenia in 60% of the patients. Furthermore, early TRT is an important issue to obtain the improved outcome in LD-SCLC. Recent meta-analyses revealed that when platinum-based chemotherapy was concurrent with TRT in LD-SCLC, an improved survival was associated with early TRT.[20-22] Another group evaluated the addition of paclitaxel to EP with concurrent TRT.[23] Although their results are comparable to those of our study and EP with concurrent twice-daily TRT,[3-6] they concluded that the triplet regimen would not further improve the survival outcome in patients with LD-SCLC.

Esophagitis is a toxicity of a particular concern in concurrent chemoradiotherapy. We observed grade 3 or 4 esophagitis in one patient (2%), whereas the JCOG9903 trial reported it in 7% of the patients. These figures contrast with those in the studies evaluating etoposide and a platinum with concurrent twice-daily TRT (9% to 32%).[3-7] The substitution of irinotecan for etoposide may reduce the incidence of grade 3 or 4 esophagitis. Furthermore, a lower incidence of esophagitis has been noted in a Japanese trial.[4] A possible explanation for this includes differences in the

chemotherapy interval (once every 4 weeks *v* once every 3 weeks) and in ethnic background. Neutropenia was the most prominent toxicity in this study and its incidence is higher than that in the Turrisi et al study.[3] However, no toxic death resulting from neutropenia was observed. Diarrhea was the most troublesome nonhematologic toxicity of irinotecan and one of the major causes for treatment discontinuation in this study.

Brain metastasis as an initial site of relapse was observed in 33% of our patients. The JCOG9903 trial reported brain metastasis in 37% of their patients. These rates were higher than those in the studies evaluating etoposide and a platinum with concurrent twice-daily TRT.[4,7] The rate of local recurrence solely was observed in only one patient and none in the JCOG9903 trial. This contrasts with the higher rate of distant failure either with or without local failure in these two studies (77% and 67%, respectively). These increased rates of distant failure including brain metastasis may be partly explained by insufficient administration of IP as consolidation.

A limitation of this study is the treatment feasibility. In this study, 53% of the patients completed the entire treatment and 69% received two or more cycles of IP. The respective values were 58% and 73% in the JCOG9903 trial.[14] In contrast, Takada et al reported that 86% of the patients completed the treatment in EP with concurrent twice-daily TRT.[4] Although the optimal duration of consolidation chemotherapy remains unclear, we consider that at least two cycles of IP is clinically meaningful in view of encouraging survival outcomes in these phase II studies. Whether the relatively low completion rate of IP causes increased distant metastasis and detrimentally affects the outcome will be addressed by the ongoing phase III study. To improve the feasibility, certain supportive measures including the prophylactic GCSF and/or antidiarrheal measures[24] and different dose scheduling (eg, 3-weekly scheduling of IP) should be considered in future studies.

In conclusion, EP with concurrent twice-daily TRT followed by the consolidation of IP appears to be active in patients with LD-SCLC, thus supporting the conduct of the currently ongoing phase III study to compare EP with concurrent twice-daily TRT followed by the consolidation of either EP or IP.

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Appendix

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®).

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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CASE REPORT

Pemetrexed-induced edema of the eyelid

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KEYWORDS
Chemotherapy;
Eyelid edema;
Lung cancer;
Supportive care

Summary Pemetrexed is a novel antimetabolite that targets multiple enzymes in the folate pathway, and has exhibited clear antitumor activities in the treatment of malignant pleural mesothelioma and non-small cell lung cancer. Although many adverse events of pemetrexed, such as bone marrow suppression, have been reported, edema of the eyelid has been previously reported in only one case (0.2%, $n = 519$), according to the Pemetrexed Clinical Investigator's Brochure, April 2005 version. We experienced a patient who developed the valuable edema of the eyelid. We believe that medical oncologists should be aware of this rare adverse event, although the mechanism responsible for it is not yet known.

1. Introduction

Pemetrexed is a novel antimetabolite that targets multiple enzymes in the folate pathway, and has exhibited clear antitumor activities in the treatment of malignant pleural mesothelioma and non-small cell lung cancer [1,2]. In early-phase pemetrexed studies, severe unpredictable toxicities were observed. Recently, Niyikiza et al reported that pemetrexed-based toxicities were associated with elevated serum homocysteine levels at baseline [3], and that to avoid pemetrexed-based severe toxicities, patients have received folic acid and vitamin B_{12} supplements. In the Japanese protocol, prophylactic steroids need not be administered, since the incidence of severe rash is very low in Japanese patients [4].

2. Case description

A 56-year-old Japanese man was diagnosed with adenocarcinoma of the lung with brain and pulmonary metastases in April, 2004 (cT4N3M1; stage IV). He received three courses of cisplatin/gemcitabine and subsequently received gefitinib as maintenance therapy from April to August, 2004, with a best response of partial response. After radiation therapy to the brain metastasis, which had exhibited aggravation, he was enrolled in a clinical trial of pemetrexed (Alimta®) in December, 2004 and received 1000 mg/m^2 of pemetrexed on day 1 of a 21-day cycle according to the trial design using randomized assignment (500 or 1000 mg/m^2 arm). He developed edema of the eyelid, which appeared on day 8 of the second course of pemetrexed (cumulative

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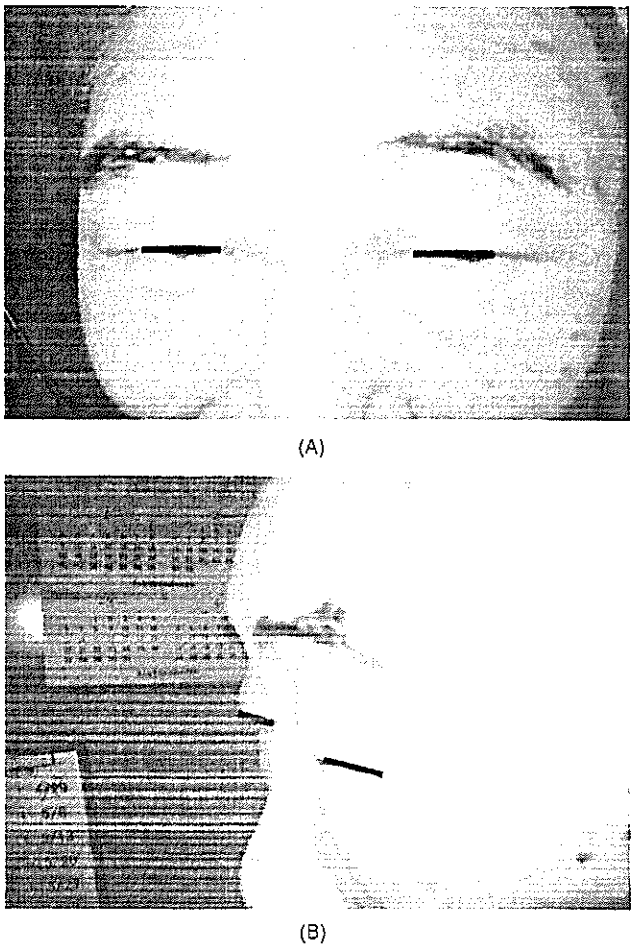

Fig. 1 A 56-year-old man with adenocarcinoma of the lung. Edema of the eyelid appeared on day 8 of the second course of pemetrexed. (A) Photograph taken from the front. (B) Profile.

dose: 3900 mg/body) (Fig. 1). He developed no other type of edema. He had no hypoproteinemia or did not undergo hydration. Initially, cardiac failure and conjunctivitis were considered possible causes. A diuretic was given, but did not improve the edema. The edema was therefore thought to be a side effect of pemetrexed, and 8 mg dexamethasone was administered. The edema was dramatically improved 6 days after administration of steroid (Fig. 2). Since the tumor had decreased in size, administration of pemetrexed was continued. The eyelid edema appeared whenever a course of pemetrexed was repeated. This edema was therefore considered probably related to pemetrexed.

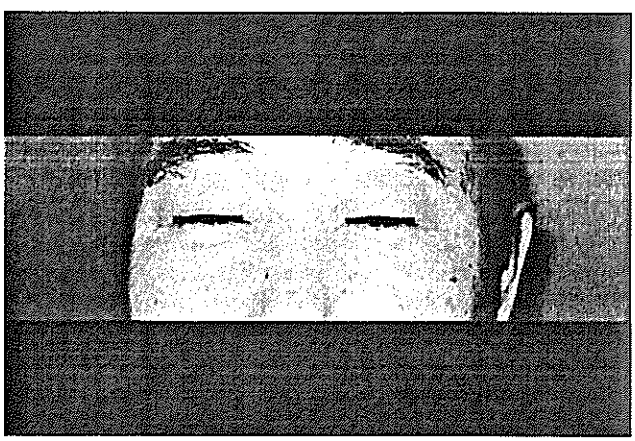

Fig. 2 The edema of the eyelid was improved by the administration of corticosteroid.

3. Discussion

Pemetrexed-associated edema of the eyelid has been previously reported in only one case (0.2%, $n = 519$), according to the Pemetrexed Clinical Investigator's Brochure, April 2005 version. The mechanism responsible for this severe swelling is unknown. Similarly, docetaxel has also been documented to cause peripheral edema. Recently, Semb et al. [5] reported that docetaxel enhances fluid filtration, followed by capillary protein leakage that causes edema and nonmalignant effusion. Prophylactic administration of corticosteroid during docetaxel administration appears to delay and decrease the severity of these adverse events. It may be that pemetrexed-induced eyelid edema is due to the same mechanism as the edema produced by docetaxel.

There are still unanswered questions regarding this drug-induced eyelid edema. Why is it confined to the eyelid? Is it a cumulative adverse event? We believe that medical oncologists should be aware of this rare adverse event and attempt to determine its cause.

Conflict of interest statement

None declared.

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Phase II Study of 3-Week Scheduling of Irinotecan in Combination With Cisplatin in Patients With Advanced Nonsmall-Cell Lung Cancer

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Objectives: The combination of irinotecan and cisplatin given every 4 weeks is one of the standard treatments for advanced nonsmall-cell lung cancer (NSCLC) in Japan. The purpose of this study is to evaluate the efficacy, safety and dose-intensity as a measure of the feasibility of 3-week scheduling of irinotecan and cisplatin in patients with advanced NSCLC in phase II study.

Methods: Previously untreated patients with stage IIIB and IV NSCLC were treated intravenously with irinotecan (60 mg/m^2) on days 1 and 8 and cisplatin (60 mg/m^2) on day 1 of a 3-week cycle.

Results: Of the 28 patients enrolled, 27 were evaluable for response and toxicity. The response rate was 30% (95% confidence interval, 14–50%). The median duration of response was 16 weeks (range, 10–26 weeks). The median survival time for all patients was 52 weeks and the 1-year and 2-year survival rates were 48% and 29%, respectively. The dose-intensity of irinotecan was 34 mg/m^2/wk (range, 19–40). The major toxicities observed were neutropenia (grade 3, 30%; 4, 30%), leukopenia (grade 3, 30%), and diarrhea (grade 3, 22%). Other toxicities were generally mild.

Conclusions: Three-week scheduling of irinotecan and cisplatin is effective and feasible in advanced NSCLC.

Key Words: irinotecan, cisplatin, nonsmall-cell lung cancer

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Lung cancer is the leading cause of cancer mortality. Nonsmall-cell lung cancer (NSCLC) accounts for 80% to 85% of patients with lung cancer and approximately two-thirds of them are inoperable at the time of diagnosis. Therefore, chemotherapy is a mainstay of the treatment of advanced nonsmall-cell lung cancer (NSCLC).[1] Recent meta-analyses have shown that cisplatin-based chemotherapy produces improved survival in advanced NSCLC.[2,3] Several new agents including irinotecan, taxanes, vinorelbine, and gemcitabine are active as single agents against NSCLC with the response rate ranging from 20% to 27%.[4] Among these, irinotecan hydrochloride, a camptothecin derivative, is active against NSCLC with a response rate of 32% as a single agent when given on a weekly basis.[5] The combination of irinotecan and cisplatin is considered to be synergistic and is active against advanced NSCLC.[6,7] A phase III study performed in Japan has revealed that a combination therapy with irinotecan and cisplatin given every 4 weeks produced comparable survival to a combination of cisplatin and vindesine in patients with advanced NSCLC.[8] In the subgroup analysis, the combination of irinotecan and cisplatin was also superior to the combination of cisplatin and vindesine in terms of survival prolongation in patients with stage IV disease.[8] Based on these results, the combination of irinotecan and cisplatin given every 4 weeks is one of the standard treatments for advanced NSCLC in Japan. In that study, there were considerable delays in treatment with or dose omissions of irinotecan, mostly on day 15, because of leukopenia and/or diarrhea, and the dose intensity of irinotecan was only 30 mg/m^2/wk (range, 12–46) in contrast to the planned dose intensity of 45 mg/m^2/wk.[8] Therefore, we conducted this phase II study of irinotecan and cisplatin scheduled every 3 weeks to evaluate response rate, safety and dose intensity as a measure of feasibility in patients with advanced NSCLC.

PATIENTS AND METHODS

Eligibility Criteria

Patients with histologically or cytologically proven diagnosis of NSCLC were eligible for this study. Other eligibility criteria included the following: stage IIIB with malignant pleural or pericardial effusion or contralateral hilar node metastasis that precluded curative radiotherapy or stage IV; measurable disease; no prior therapy including chemotherapy, radiotherapy or surgery to the primary tumor; age ranging from 20 to 74 years; a life expectancy ≥12 weeks; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1; an adequate baseline organ function defined

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as leukocyte count from 4000 to 12,000/mm^3, platelet count ≥ 100,000/mm^3, hemoglobin ≥9.5 g/dL, aspartate aminotransferase and alanine aminotransferase ≤100 IU/L, total bilirubin ≤1.5 mg/dL, serum creatinine ≤ the institutional upper limit of normal or 24-hour creatinine clearance ≥60 mL/min, and PaO_2 at rest ≥60 mm Hg. Patients were ineligible if they had the following criteria: superior vena caval syndrome; history of serious drug allergy; massive pleural or pericardial effusion or ascites that required drainage; active infection; persistent diarrhea (watery stool); paralytic ileus; interstitial pneumonia or pulmonary fibrosis; symptomatic brain metastasis; other concurrent active malignancy; uncontrolled diabetes mellitus; pregnancy or lactation, other concomitant serious medical conditions. The study protocol was approved by each institutional review board for clinical use. All patients gave written informed consent before enrollment.

Study Evaluations

Pretreatment baseline evaluation included a complete medical history and physical examination, complete blood cell count (CBC), blood chemistry studies, chest radiography, computed tomography (CT) of the chest, CT or ultrasound study of the abdomen, CT or magnetic resonance imaging of the brain, bone scintigraphy and electrocardiography. Complete blood cell count and blood chemistry studies were repeated weekly.

Treatment Schedule

Patients were treated intravenously with irinotecan 60 mg/m^2 on days 1 and 8 and cisplatin 60 mg/m^2 on day 1. Irinotecan was reconstituted in 250 mL of normal saline or 5% dextrose in water and infused over 60 minutes. Cisplatin was administered over 60 minutes with adequate hydration, usually ≥2500 mL infusion. Diuretics and antiemetics were given at the discretion of each treating physician. Therapy was repeated every 3 weeks for at least 4 cycles unless there was evidence of disease progression, unacceptable toxicity or withdrawal of consent.

Dose Modification

Dose modifications were made in response to any myelosuppression and nonhematologic toxicity that occurred. If a leukocyte count of less than 3000/mm^3 or a platelet count of less than 100,000/mm^3 was determined or if the patient had fever (≥38.0°C) or grade ≥1 diarrhea, or other grade ≥3 toxicity on days 8 through 15, irinotecan was withheld. Irinotecan was decreased by 10 mg/m^2 in the subsequent cycle if a leukocyte nadir count of less than 1000/mm^3 or a platelet nadir count less than 50,000/mm^3 or grade ≥2 diarrhea, or other grade ≥3 nonhematologic toxicity (excluding electrolytes imbalance, nausea, appetite loss, fatigue, and hair loss) was observed during the previous course of treatment. Cisplatin was decreased by 10 mg/m^2 in the subsequent cycle if grade ≥2 creatinine or other grade ≥3 nonhematologic toxicity (excluding electrolyte imbalance, nausea, appetite loss, fatigue, and hair loss) was observed during the previous course of treatment.

Evaluation

The Response Evaluation Criteria in Solid Tumors (RECIST) were used for response assessment.[9] Toxicity was evaluated according to National Cancer Institute-Common Toxicity Criteria (version 2.0). An independent review was conducted to validate the eligibility of the patients, staging, response, and toxicity.

Statistical Analysis

The primary end point of this study was the estimate of the response rate. We assumed that the response rate was 45% from a prior trial reported by Negoro et al[8] and the distance from the point estimate to the 95% confidence interval (CI) was 20%. Thus, 24 evaluable patients were required. If 11 out of 24 evaluable patients have response, the response rate is 46% with the exact 95% CI of 26% to 67%. Durations of response and survival were measured from the first day of the treatment, and the overall survival curve and progression-free survival curve were calculated by the method of Kaplan and Meier.[10]

RESULTS

Patient Characteristics

Between January and June 2003, 28 patients were entered in this study. Baseline characteristics of the evaluable patients were listed in Table 1. Twenty patients (74%) had stage IV disease and 11 patients (41%) had ECOG performance status of 0. Adenocarcinoma was the dominant histology (74%).

Treatment Administration

Patients received a median of 4 treatment cycles (range, 1–6 cycles). Seven patients received only 1 cycle of treatment because of adverse events (4 patients) and progressive disease (3 patients). A total of 92 cycles were given. Irinotecan administration on day 8 was withheld in 9 cycles (10%)

TABLE 1. Patients Characteristics

No. patients	27
Age (years)	
Median	63
Range	38–72
Gender (% of patients)	
Male	19 (70)
Female	8 (30)
Performance status (ECOG) (% of patients)	
0	11 (41)
1	16 (59)
Stage (% of patients)	
IIIB	7 (26)
IV	20 (74)
Histology (% of patients)	
Adenocarcinoma	20 (74)
Squamous cell carcinoma	7 (26)

ECOG, Eastern Cooperative Oncology Group.

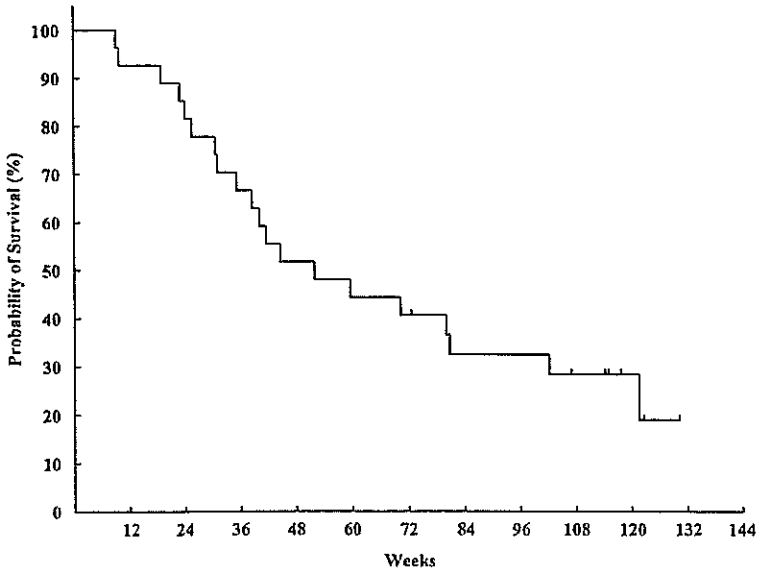

FIGURE 1. Kaplan-Meier survival curve of 27 evaluable patients with advanced nonsmall cell lung cancer.

and dose reduction was made in 41 cycles (45%). The dose of cisplatin was reduced in 18 cycles (20%). The dose-intensity of irinotecan was 34 mg/m^2/wk (85% of the planned dose) and cisplatin 19 mg/m^2/wk (95% of the planned dose).

Response and Survival

Three of 7 patients (43%) with stage IIIB disease achieved partial response while 5 of 20 patients (25%) with stage IV disease showed partial response, with an overall response rate of 30% (95% CI, 14–50%). The response rate for adenocarcinoma and squamous cell carcinoma were 20% and 57%, respectively. Thirteen patients showed stable disease and 6 had progressive disease. No complete response was seen. The median duration of response was 16 weeks (range, 10–26 weeks). The median survival time for all patients was 52 weeks and a 1-year and 2-year survival rate was 48% (95% CI, 29–67%) and 29% (95% CI, 11–46%), respectively (Fig. 1).

Toxicity

The major adverse events were shown in Table 2. Hematologic toxicity was the principal toxicity of this regimen. Grade 4 neutropenia and anemia was observed in 8 patients (30%) and 1 patient (4%), respectively. There was no grade 4 leukopenia. Thrombocytopenia was predominantly mild (grade 1–2) and only 1 patient had grade 3 toxicity. Nonhematologic toxicities mainly consisted of diarrhea, nausea and vomiting, and anorexia. Grade 3 diarrhea was observed in 6 patients (22%) but no patient had grade 4 diarrhea. Grade 3 infection was observed in 4 patients (15%) and 1 patient had febrile neutropenia. There were no treatment-related deaths.

TABLE 2. Major Toxicities by Patient and Cycle

	Grade 3/4	
	Patients (%), n = 27	Cycles (%), n = 92
Neutropenia	8/8 (59)	27/8 (38)
Leukopenia	8/0 (30)	10/0 (11)
Anemia	5/1 (22)	7/1 (9)
Thrombocytopenia	1/0 (4)	1/0 (1)
Diarrhea	6/0 (22)	9/0 (10)
Nausea	8/0 (30)	9/0 (10)
Vomiting	2/0 (7)	2/0 (2)
Infection	4/0 (15)	4/0 (4)
Anorexia	9/0 (33)	13/0 (14)

DISCUSSION

In this phase II study, we have explored the potential advantages of 3-week schedule of irinotecan and cisplatin in patients with advanced NSCLC and have achieved a 30% response rate. In the chemotherapy of advanced lung cancer, irinotecan is usually given weekly on days 1, 8, and 15 in a combination with cisplatin and the treatment cycle is repeated every 4 weeks. Masuda et al reported a 48% response rate in 4-week scheduled therapy for irinotecan and cisplatin in a phase II study.[7] Based on this result, 2 randomized phase III studies have been conducted in Japan. Negoro et al[8] compared a combination of irinotecan and cisplatin with a combination of cisplatin and vindesine and irinotecan alone while Niho et al[11] compared a combination of irinotecan and cisplatin with a combination of cisplatin and vindesine. The response rates of irinotecan and cisplatin were 44% and 29%,

respectively. Despite the difference of the response rates between the 2 phase III studies, the median survival times (50 versus 45 weeks) and the 1-year survival rates (47 versus 43%) were comparable between the 2 studies. These 2 studies have revealed that a combination therapy with irinotecan and cisplatin given every 4 weeks produced comparable survival to a combination of cisplatin and vindesine in patients with advanced NSCLC.[8,11] Furthermore, Negoro et al reported that in the subgroup analysis, the combination of irinotecan and cisplatin was superior to the combination of cisplatin and vindesine in survival prolongation in patients with stage IV disease.[8] The response rate of 30% in our study is between those of the 2 phase III studies evaluating 4-week scheduled therapy for irinotecan and cisplatin. This, plus the median survival time of 52 weeks and the 1-year survival of 48% in our study are encouraging.

Two groups evaluated 3-week scheduled therapy for irinotecan and cisplatin in patients with advanced NSCLC in the phase II studies.[12,13] Takeda et al administered irinotecan (75 mg/m^2) and cisplatin with antilate-diarrheal program and reported the response rate of 63%.[12] Han et al evaluated 2 sequences of 3-week scheduled therapy for irinotecan (80 mg/m^2) and cisplatin without any antidiarrheal measures and reported the overall response rate of 47%.[13] These studies including our own suggest that 3-week cycle of irinotecan and cisplatin is effective in patients with advanced NSCLC. Recently, another randomized phase III study conducted in Japan has compared the 4-week scheduled therapy for irinotecan and cisplatin as the control arm with 3 platinum-based doublets with new agents (carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine).[14] This study has shown that 4-week scheduled therapy for irinotecan and cisplatin was comparable to other platinum doublet therapy with new agents in terms of response rate and survival with different toxic profiles. Further evaluation will be necessary to clarify whether 3-week scheduled therapy for irinotecan and cisplatin is superior in terms of survival and toxicity to 4-week scheduled therapy as well as other platinum doublet therapy with new agents in the treatment of advanced NSCLC.

Neutropenia was the most prominent toxicity in this study and grade 4 neutropenia was observed in 8 patients (30%). This incidence was lower than in other studies evaluating the 4-week scheduled therapy for irinotecan and cisplatin, in which the incidence of grade 4 neutropenia was 37% to 38%.[7,8] The incidence of grade 4 neutropenia in the 4-week scheduled therapy for irinotecan and cisplatin was lower than in the platinum-based doublet in a combination with a new agent such as paclitaxel, gemcitabine, vinorelbine, and docetaxel.[15–18] In 3-week scheduled therapy, the incidence of grade 4 neutropenia is further reduced. Leukopenia was usually less severe than neutropenia. In our study, grade 3 leukopenia was observed in 30% of the patients and there was no grade 4 leukopenia observed. Anemia and thrombocytopenia were relatively mild with this regimen. Diarrhea was the most troublesome nonhematologic toxicity in irinotecan-containing regimens.[5,19] We observed grade 3 diarrhea in 22% of our patients and no patient experienced grade 4 diarrhea. Antilate-diarrheal program may be beneficial to further reduce moderate to severe diarrhea.[12]

Another aim of this study was to evaluate dose-intensity as a measure of the feasibility of a 3-week schedule of irinotecan and cisplatin. In the previous phase III study, the dose intensity of irinotecan was only 30 mg/m^2/wk (67% of the planned dose).[8] We planned to administer irinotecan at a dose of 60 mg/m^2 on days 1 and 8, giving the planned dose-intensity of irinotecan of 40 mg/m^2/wk. The actual dose-intensity of irinotecan administered was 34 mg/m^2/wk (85% of the planned dose). In contrast, the actual dose intensities of irinotecan in the studies of Takeda et al and Han et al were 48.5 mg/m^2/wk and 44 mg/m^2/wk, respectively.[12,13] One explanation for this difference is that we reduced the dose of irinotecan based on the toxicity in the previous cycle while they did not reduce the dose of irinotecan based on the toxicity in the previous cycle. Despite this difference, these data suggest that 3-week cycle of irinotecan and cisplatin is better tolerated than the 4-week scheduling of irinotecan and cisplatin with greater irinotecan dose-intensity.

In summary, this study suggests that therapy with a 3-week cycle of irinotecan and cisplatin is effective and feasible in the treatment of advanced NSCLC. Further evaluation of the combination of irinotecan and cisplatin, at the doses and schedule used in this study, is warranted in advanced NSCLC.

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Is the Importance of Achieving Stable Disease Different between Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors and Cytotoxic Agents in the Second-Line Setting for Advanced Non-small Cell Lung Cancer?

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Background: It is controversial whether achieving stable disease leads to a survival benefit and whether the importance of achieving stable disease differs between cytotoxic agents and molecular targeted agents. To examine these questions, the authors retrospectively reviewed phase II and III studies in the second-line setting for advanced non-small cell lung cancer using epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) and cytotoxic agents separately.

Methods: The authors chose 45 trials for the chemotherapy group and nine for the EGFR TKI group by searching the PubMed database. All nine trials in the EGFR TKI group concern gefitinib and erlotinib.

Results: The median survival time increased 0.0375 month with each 1% increase in stable disease rate ($p = 0.039$), and each 1% increase in response rate resulted in 0.0744 ($p < 0.001$) month of median survival time in the analysis combined with both cytotoxic agents and EGFR TKIs. Main and interaction terms for EGFR TKI treatment were not statistically significant. With respect to time to progression, only response rate showed a statistically significant relationship with survival.

Conclusions: To obtain response seems to be more important than to achieve stable disease for both cytotoxic agents and EGFR TKIs, although achieving stable disease is still valuable. The relationship between survival and response or stable disease appears similar for cytotoxic agents and EGFR TKIs.

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In 1995, a meta-analysis demonstrated a modest survival benefit for cisplatin-based chemotherapy compared with best supportive care as first-line therapy in patients with locally advanced or metastatic non-small cell lung cancer (NSCLC).[1] Equal survival improvement is provided by introducing several new agents with novel mechanisms and significant activity against NSCLC such as taxanes, gemcitabine, and vinorelbine, when used in combination with a platinum agent.[2–4] However, most patients relapse following platinum-based chemotherapy, leading to poor survival. Until recently, the role of second-line chemotherapy was not well defined because most patients had a poor performance status by the time of relapse. However, as newer agents in combination with platinum agents have increased, the number of patients with durable antitumor effects and the number of patients for second-line chemotherapy have increased. Therefore, second-line chemotherapy for advanced NSCLC is becoming increasingly important. Several chemotherapy agents have been evaluated in the second-line setting. Among them, docetaxel was the first agent to show a survival benefit and an improvement in quality of life in two large phase III studies[5,6] and has been approved as a second-line agent. A recent randomized phase III study reported that pemetrexed (a multitargeted antifolate, Alimta; Eli Lilly & Co., Indianapolis, IN) had comparable activity and better symptom relief than docetaxel.[7] Both of these cytotoxic agents demonstrated response rates of less than 10%, but both agents have demonstrated survival benefits and an improvement in quality of life. This indicates that it is important to achieve stable disease and objective response for second-line cytotoxic agents.

The molecular targeted agents are attractive because they promise to produce specific cytostatic action with a resultant mild toxicity profile. In many tumors, overexpression of the epidermal growth factor receptor (EGFR) is associated with a poor prognosis and chemoresistance,[8,9] and it is common in NSCLC.[10–12] The low-molecular-weight EGFR tyrosine kinase inhibitors (TKIs) gefitinib and erlotinib are the most advanced agents in clinical trials. The results of a recent phase III study in the second-line setting showed that erlotinib significantly improved survival compared with best supportive care,[13] although the overall response rate was only 9% on the erlotinib arm.

Because of their mechanism of action, it might be more important to achieve stable disease for most molecular targeted agents than for their cytotoxic counterparts. However, evaluating stable disease in clinical trials is very difficult, as patients with stable disease are not a homogeneous population.

Based on this background, we hypothesized that not only objective response but also stable disease could lead to survival benefit, in particular, with molecular targeted agents. Therefore, we retrospectively reviewed phase II and randomized phase III studies in the second-line setting using EGFR TKIs and cytotoxic agents separately to evaluate our hypothesis and ascertain whether the importance of achieving stable disease was different between EGFR TKIs and cytotoxic agents.

METHODS

Search and Selection for Trials

Data concerning response rates, rates of stable disease, time to progression, and survival from all published studies including phase II and randomized phase III studies assessing the activity of EGFR TKIs and cytotoxic agents in the second-line setting were identified electronically. We performed the search for trials through a computer-based search of the PubMed database using the following terms: "NSCLC," "chemotherapy (second or pretreated)," "advanced," "not radiation," "not adjuvant," "randomized controlled trial," "human," and "English," in the chemotherapy group. In the EGFR TKI group, we used the following terms: "NSCLC," "clinical trial," "human," "English," and the name of the EGFR TKI (e.g., gefitinib, referred from the review of Wendy et al.[14]). All trials that had been reported by September 30, 2004, were targeted. However, because there was no phase III study in the EGFR TKI group, only one abstract from the *Proceedings of the American Society of Clinical Oncology*, by Shepherd et al., was added. Among the retrieved studies, we excluded the trials that had missing outcomes data. We also excluded phase I/II studies. When we examined randomized phase III and randomized phase II studies, if both arms (experimental and reference arms) included cytotoxic agents or EGFR TKIs, both were included in our analysis.

Statistical Analysis

All the analyses were performed with Stata version 8 (Stata Corp., College Station, TX). Multiple linear regression analysis was applied to examine impacts on the proportion of subjects who responded and achieved stable disease on survival (median survival time [MST] and time to progression [TTP]). Scales in the models were percentages and months for proportion of subjects and survival, respectively. Two models were examined: model 1, including response rate and stable disease rate or disease control rate (response rate plus stable disease rate) as explanatory variables; and model 2, including EGFR TKI usage (yes/no) and interaction terms between EGFR TKI usage and response/stable disease rate or disease control rate in addition to model 1. In the models, each study was weighted by the number of subjects in an intent-to-treat analysis setting in each study. Thereafter, we chose model 1 based on the significance of interaction terms. To further evaluate the impact of stable disease rate considering response rate, we chose a linear regression model for residual (the observed median survival minus fitted median survival in the response rate only model) as a dependent variable with stable disease rate as a responsible variable. This approach was applied to MST and TTP separately (Figures 1 and 2). The statistical significance was defined as a value of $p < 0.05$, and adjustment for multiple comparison was not considered because of the exploratory setting of this study.

RESULTS

Study Characteristics

As a result of our search, we identified 219 references and chose 45 trials for the chemotherapy group and nine trials for the EGFR TKI group. The baseline characteristics of the 45 trials and nine trials are shown in Tables 1 and 2, respectively. There are four randomized phase II and three phase III studies for cytotoxic agents, and two randomized phase II studies and one phase III study for EGFR TKIs. In the analysis of cytotoxic agents, docetaxel, pemetrexed, other agents, and many types of combination regimens are included. In the analysis of EGFR TKIs, only monotherapies of gefitinib and erlotinib were detected. The median number of enrolled patients per study was 40 (range, 17–288) for the cytotoxic agents and 103 (range, 31–488) for the analysis of EGFR TKIs.

Median Survival Time

As shown in Table 3, both rate of stable disease and response rate were statistically significanty associated with MST in model 1 in the analysis that combined both cytotoxic agents and EGFR TKIs. The coefficient 0.0375 ($p = 0.039$) for stable disease in model 1 indicates that MST increases by 0.0375 month for each 1% increase in stable disease rate. Similarly, each 1% increase in response rate is associated with an increase of 0.0744 month in MST ($p < 0.001$). This trend was similarly observed in model 2, which considered the interaction between EGFR TKI treatment and two response parameters. As interaction terms for EGFR TKI treatment were not statistically significant, one may interpret that the relationship between survival and response rate or stable disease rate is not different between EGFR TKI and cytotoxic chemotherapy. We therefore took model 1 as the model

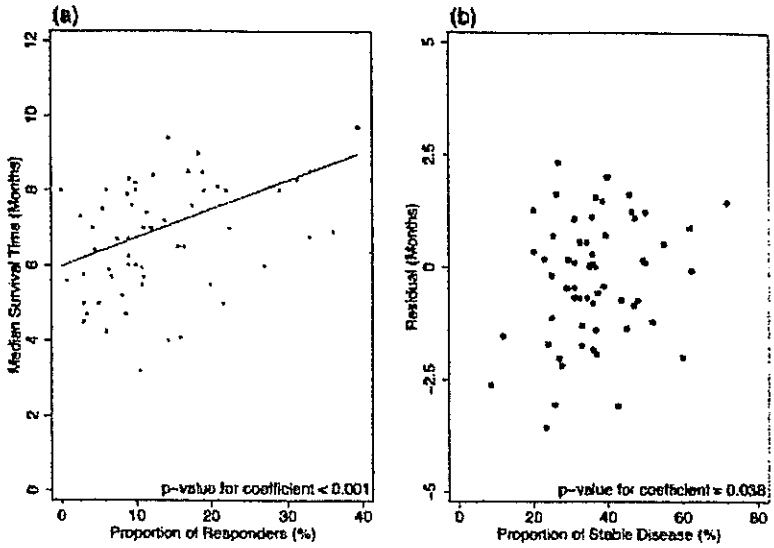

FIGURE 1. Scatterplot for MST and response/stable disease rates. (*A*) The observed MST corresponding to the percentage of responders. (*B*) The residuals (observed MST minus fitted MST in the model for *A*). The figure indicates that both response rate and stable disease rate significantly influence the prolongation of MST.

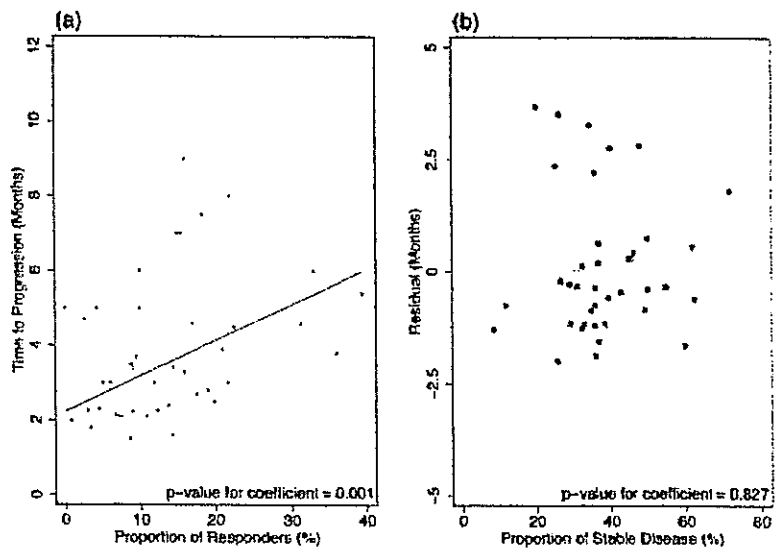

FIGURE 2. Scatterplot for TTP and response/stable disease rates. (*A*) The observed median TTP corresponding to the percentage of responders. (*B*) The residuals (observed TTP minus fitted TTP in the model for *A*). The figure indicates that the response rate but not the stable disease rate significantly influences the prolongation of TTPs.

explaining associations between MST and response variables. Figure 1A is a graphic presentation of observed MSTs corresponding to response rates with the fitted line. Figure 1B presents how well the stable disease rate explains the residual by the response rate only model. Both figures indicate that the response rate and the stable disease rate significantly contribute to MST prolongation. The coefficient for the disease control rate in model 1 was 0.05, indicating that a 1% increase in the disease control rate prolongs MST by 0.05 month ($p < 0.001$). Similar results regarding EGFR TKI terms are listed in Table 3.

Time to Progression

Table 4 shows similar analyses as MST for TTP considering stable disease rate and response rate. Contrary to MST analyses, only response rate showed a statistically significant association with TTP. The coefficient 0.0954 ($p = 0.001$) for response rate in model 1 indicates that TTP increases 0.0954 month with each 1% increase in response rates. Nonsignificant coefficient for stable disease rates indicates lack of impact of this factor on TTP after response rate has been accounted for. As interaction terms for EGFR TKI treatment were not statistically significant, we took model 1 as the model explaining associations between TTP and response variables. Figure 2 is a similar graphic presentation of observed TTPs. Although Figure 2A shows that response rate significantly influences the TTPs, there is no apparent association between TTPs and stable disease rate (Figure 2B). As shown in Table 4, disease control rate was not significantly associated with prolongation of TTP in model 1 and model 2. EGFR TKI interaction terms were not statistically significant.

DISCUSSION

Since the introduction of molecular targeted agents (especially epidermal growth factor receptor inhibitors) in clinical trials in recent years, the importance of achieving stable disease has become an important issue. For these

TABLE 1. Characteristics of the Trials with Cytotoxic Agents in the Second-Line Setting for NSCLC

Author	Phase	Regimen	No. (ITT)	RR (%)	SD (%)	DCR (%)	TTP (mo)	MST (mo)
Stewart et al., 1996[15]	II	Paclitaxel + hydroxyurea	30	3	52	55	—	5
Georgoulias et al., 1997[16]	II	Paclitaxel + gemcitabine	26	29	25	54	—	8
Gridelli et al., 1999[17]	II	Gemcitabine	30	20	60	80	2.5	5.5
Crino et al., 1999[18]	II	Gemcitabine	83	19	31	50	—	8.5
Stathopoulos et al., 1999[19]	II	Paclitaxel + cisplatin	36	38.9	58.3	97.2	—	—
Perng et al., 2000[20]	II	Docetaxel	14	28.6	—	—	4.75	11.7
Mattson et al., 2000[21]	II	Docetaxel	72	13.8	29.3	43.1	2.4	7.2
Rosati et al., 2000[22]	II	Paclitaxel + cisplatin + gemcitabine	26	27	27	54	—	6
Sculier et al., 2000[23]	II	Gemcitabine	77	6	27.7	33.7	—	4.25
Gridelli et al., 2000[24]	II	Docetaxel	23	21.7	8.7	30.4	3	5
Hainsworth et al., 2000[25]	II	Gemcitabine + vinorelbine	55	16.4	43.6	60	—	6.5
Shepherd et al., 2000[5]	III	Docetaxel	55	5.5	47.3	52.8	—	7.5
		Docetaxel	49	6.3	37.5	43.8	—	5.9
Fossellá et al., 2000[6]	III	Docetaxel	125	10.8	33	43.8	2.1	5.5
		Docetaxel	125	6.7	36	42.7	2.13	5.7
		Vinorelbine/ifosfamide	123	0.8	31	31.8	1.98	5.6
Kosmas et al., 2001[26]	II	Gemcitabine + vinorelbine	43	33	37	70	6	8.5
Hainsworth et al., 2001[27]	II	Docetaxel + gemcitabine	40	10	48	58	6	6
		Docetaxel + vinorelbine	23	0	40	40	5	8
Agelaki et al., 2001[28]	II	Vinorelbine + carboplatin	37	16	30	46	9	—
Kakolyris et al., 2001[29]	II	Cisplatin + irinotecan	44	22	20	42	8	8
Huisman et al., 2001[30]	II	Cisplatin + epirubicin	27	33	33	66	—	6.75
Pectasides et al., 2001[31]	II	Gemcitabine + vinorelbine	39	2.6	35.9	38.5	4.7	7.3
Lilenbaum et al., 2001[32]	II	Docetaxel	30	10	20	30	—	8
Kosmas et al., 2001[33]	II	Gemcitabine + docetaxel	40	22.5	32.5	55	4.5	7
Kakolyris et al., 2001[34]	II	Docetaxel + gemcitabine	32	15.6	34.4	50	7	6.5
Spiridonidis et al., 2001[35]	II	Docetaxel + gemcitabine	40	32.5	—	—	—	8.1
Juan et al., 2001[36]	II	Paclitaxel	40	39.47	39.47	78.94	5.4	9.7
Chen et al., 2002[37]	II	Docetaxel + gemcitabine	36	36.1	36.11	72.21	3.8	6.9
Gonzalez et al., 2002[38]	II	Irinotecan + vinorelbine	35	9	39	48	—	6.25
Rinaldi et al., 2002[39]	II	Topotecan + gemcitabine	35	11	23	34	—	7
Socinski et al., 2002[40]	II	Paclitaxel	62	8.1	37	45.1	—	5.2
Herbst et al., 2002[41]	II	Gemcitabine + vinorelbine	36	17	50	67	4.6	8.5
Sculier et al., 2002[42]	II	Paclitaxel	67	3	24	27	—	4.5
Thongprasert et al., 2002[43]	II	Docetaxel	34	10.7	47	57.2	—	5.95
Han et al., 2003[44]	II	Irinotecan + capecitabine	37	11.4	34.3	45.7	—	7.4
Chen et al., 2003[45]	II	Docetaxel + ifosfamide	17	31.3	62.5	93.8	4.6	8.3
Font et al., 2003[46]	II	Irinotecan + docetaxel	51	6	37	43	3	8
Chen et al., 2003[47]	II	Vinorelbine + cisplatin	22	9.5	61.9	71.4	3.7	7.6
Smit et al., 2003[48]	II	Pemetrexed	45	4.5	36	40.5	2.3	6.4
		Pemetrexed	36	14.3	26	40.3	1.6	4
Chen et al., 2003[49]	II	Gemcitabine + vinorelbine	50	10	72	82	5	8.2
Dongiovanni et al., 2004[50]	II	Paclitaxel + gemcitabine	34	12	50	62	3	7
Georgoulias et al., 2003[51]	II	Irinotecan + gemcitabine	76	18.4	26.3	44.7	7.5	9
		Irinotecan	71	4.2	25.3	29.5	5	7
Park et al., 2003[52]	II	Gemcitabine + vinorelbine	38	21	55	76	3.9	8.1
Serke et al., 2003[53]	II	Docetaxel	36	11	25	36	—	5.7
Hanna et al., 2003[7]	III	Pemetrexed	283	9.1	45.8	54.9	3.4	8.3
		Docetaxel	288	8.8	46.4	55.2	3.5	7.9
Ceresoli et al., 2003[54]	II	Paclitaxel	53	15	21	36	7	—
Ardizzoia et al., 2003[55]	II	Docetaxel	42	10.5	23.5	34	—	3.2
Quoix et al., 2003[56]	II	Docetaxel	93	8.6	37.1	45.7	1.5	4.7
		Docetaxel	89	7.4	49.4	56.8	2.1	6.7

ITT, intention to treat; RR, response rate; SD, stable disease; DCR, disease control rate; TTP, time to progression; MST, median survival time.

TABLE 2. Characteristics of the Trials with EGFR TKIs in the Second-Line Setting for NSCLC

Author	Phase	Regimen	No. (ITT)	RR (%)	SD (%)	DCR (%)	MST (mo)
Gridelli et al., 2000[57]	II	Gefitinib	59	3.4	11.8	15.2	4.7
Cappuzzo et al., 2003[58]	II	Gefitinib	63	15.9	42.8	58.7	4.1
Pallis et al., 2003[59]	II	Gefitinib	31	3	29	32	5.75
Fukuoka et al., 2003[60]	II	Gefitinib	103	17.5	35.9	53.4	7.6
		Gefitinib	109	19.1	32.4	51.5	8
Kris et al., 2003[61]	II	Gefitinib	106	12	31	43	7
		Gefitinib	115	9	31	40	6
Shepherd et al., 2004[62]	III	Erlotinib	488	9	35	44	6.7
Pérez-Soler et al., 2004[63]	II	Erlotinib	57	12.3	38.6	50.9	8.4
Cappuzzo et al., 2004[64]	II	Gefitinib	106	14.4	26.8	41.2	9.4
Cappuzzo et al., 2000[65]	II	Gefitinib	40	5	45	50	5

ITT, intention to treat; RR, response rate; SD, stable disease; DCR, disease control rate; TTP, time to progression; MST, median survival time.

TABLE 3. Multiple Regression Models for Predicting MST by Study Parameters

	Model 1			Model 2		
	Coefficient	SE	*p* Value	Coefficient	SE	*p* Value
Models evaluating SD/RR and interactions with EGFR TKIs use No. 1*						
SD (%)	0.0375	0.0178	0.039	0.0500	0.0188	0.01
RR (%)	0.0744	0.0181	<0.001	0.0669	0.0190	0.001
SD_EGFR interaction	—	—	—	−0.0967	0.0703	0.175
RR_EGFR_interaction	—	—	—	0.1082	0.0591	0.073
EGFR TKI	—	—	—	2.2773	2.5364	0.373
_cons	4.6156	0.6532	<0.001	4.1579	0.7617	<0.001
			$R^2 = 0.214$			$R^2 = 0.284$
Models evaluating DCR and an interaction with EGFR TKIs use No. 2†						
DCR (%)	0.0501	0.0119	<0.001	0.0559	0.0132	<0.001
DCR_EGFR_interaction	—	—	—	−0.0226	0.0466	0.629
EGFR TKI	—	—	—	1.3146	2.0593	0.526
_cons	4.4323	0.6003	<0.001	4.0573	0.7019	<0.001
			$R^2 = 0.19$			$R^2 = 0.204$

*Coefficients for SD and RR denote increase of MST in months for 1% increase in SD/RR (model 1).
†Coefficients for DCR denote increase of MST in months for 1% increase in DCR (model 1).
SD, stable disease; RR, response rate; DCR, disease control rate.

agents, stabilization of disease without tumor shrinkage may represent a meaningful benefit. This phenomenon has been derived from two randomized phase II studies (Iressa Dose Evaluation in Advanced Lung Cancer [IDEAL]-1 and IDEAL-2).[60,61] In IDEAL-2, the median survival time of patients achieving stable disease was 9.4 months versus 5.2 months for those with progressive disease.[61] Moreover, when survival and symptom improvement were analyzed together, the median survival time for patients achieving stable disease with symptom improvement was 12.8 months versus 4.8 months for those without symptom improvement.

In contrast, the importance of achieving stable disease has been evaluated for cytotoxic agents. Docetaxel significantly improved overall survival compared with best supportive care as second-line therapy despite the overall response rate of only 6%.[5] In this study, 42.7% of patients achieved stable disease, which suggests that docetaxel also confers clinical benefit by producing stable disease.

In this retrospective review, we investigated the relationship between response rates and survival benefit and between the rates of stable disease and survival benefit in second-line treatment of NSCLC using both cytotoxic agents and EGFR TKIs. The more the rates of response and stable disease increase, the more the improvement of overall survival is obtained in the analysis that combined both cytotoxic agents and EGFR TKIs. However, as shown in Table 3, for both cytotoxic agents and EGFR TKIs, the survival improvement for a 1% increase in response rate is higher than for a 1% increase in stable disease rate. Moreover, for time to progression, only response rate showed a statistically significant association with TTP. These results indicate that it is more important to increase response rates than to achieve

TABLE 4. Multiple Regression Models for Predicting TTP by Study Parameters

	Model 1			Model 2		
	Coefficient	SE	*p* Value	Coefficient	SE	*p* Value
Models evaluating SD/RR and interactions with EGFR TKIs use No. 1*						
SD (%)	−0.0050	0.0229	0.828	−0.0248	0.0292	0.402
RR (%)	0.0954	0.0265	0.001	0.0963	0.0291	0.002
SD_EGRF_interaction	—	—	—	0.0297	0.0353	0.406
RR_EGFR_interaction	—	—	—	−0.0344	0.0391	0.385
EGFR TKIs	—	—	—	−1.9322	1.3858	0.172
_cons	2.4205	0.9348	0.014	3.5861	1.2925	0.009
			$R^2 = 0.183$			$R^2 = 0.325$
Models evaluating DCR and an interaction with EGFR TKIs use No. 2†						
DCR (%)	0.0281	0.1430	0.057	0.0166	0.0197	0.405
DCR_EGFR_interaction	—	—	—	0.0088	0.0210	0.677
EGFR TKIs	—	—	—	−1.5120	1.3021	0.253
_cons	1.9636	0.8734	0.03	2.8927	1.2334	0.024
			$R^2 = 0.047$			$R^2 = 0.148$

*Coefficients for SD and RR denote increase of TTP in months for 1% increase in SD/RR (model 1).
†Coefficients for DCR denote increase of TTP in months for 1% increase in DCR (model 1).
SD, stable disease; RR, response rate; DCR, disease control rate.

stable disease to improve overall survival for both cytotoxic agents and EGFR TKIs in the second-line setting, although increasing stable disease rates is still valuable.

In our analysis, we could not find a significant difference between cytotoxic agents and EGFR TKIs in terms of the relationship between survival and response and stable disease rate, as interaction terms for EGFR TKI treatment were not statistically significant. As a result, one may infer that the effect on survival of increasing response rates and stable disease rates is similar for cytotoxic agents and EGFR TKIs. However, this interpretation requires cautions on two points. First, our review contains many heterogeneous phase II studies with greatly different registered numbers of cases, and many heterogeneous patient characteristics with a greatly different administered number of regimens before these studies. The method of evaluating response is also different. These may possibly lead to a false conclusion. Moreover, the main effect of EGFR TKI was large but not statistically significant, indicating no evidence of a difference between EGFR TKIs and cytotoxic agents in terms of survival. However, there are very few EGFR TKI studies included in this review, and therefore the ability to detect such an effect may be low. Second, evaluating stable disease in clinical trials is very difficult, as patients with stable disease are not a homogeneous population. The Response Evaluation Criteria in Solid Tumors study defined stable disease as the longest diameter of tumor size from a less than 30% decrease to a less than 20% increase.[65] True disease stabilization inhibits tumor growth and metastasis and may be associated with improvement of survival, symptoms, and quality of life. However, it is difficult to distinguish true stable disease from nonstable disease. Therefore, it is crucial to classify a category of stable disease in the future.

CONCLUSIONS

In conclusion, our review indicated that although it is appropriate to adapt disease control rates to assess the effect of agents in the second-line setting, which is a new concept often used by clinical trials for molecular targeted agents, to obtain response seems to be more important than to achieve stable disease when new agents are developed, although achieving stable disease is still valuable. The relationship between survival and response and stable disease appears similar for cytotoxic agents and EGFR TKIs.

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ORIGINAL ARTICLE

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Phase I/II study of weekly docetaxel dose escalation in combination with fixed weekly cisplatin and concurrent thoracic radiotherapy in locally advanced non-small cell lung cancer

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Abstract *Purpose*: We conducted a phase I study to determine the maximum-tolerated dose (MTD) and dose-limiting toxicities (DLT) of weekly docetaxel and cisplatin (DOC/CDDP) with concurrent thoracic radiotherapy (TRT) in patients with unresectable stage III non-small-cell lung cancer (NSCLC). *Materials and methods*: The DOC/CDDP administration schedules consisted of a split schedule (SS) with administration in 3 out of every 4 weeks, and a continuous schedule (CS) with administration every week. TRT was given to a total dose of 60 Gy at 2 Gy per fraction over 6 weeks. *Results*: Twenty-one patients entered the study. The patient characteristics were: PS 0/1/2, 6/13/2; Sq/Ad, 16/5; stage IIIA/IIIB, 4/17. The principal DLT was grade3 esophagitis. The MTD of DOC on the SS and CS in combination with CDDP (25 mg/m2/week) was 25 and 20 mg/m^2/week, respectively. We determined the RD and schedule of DOC/CDDP on the SS to be 20/25 mg/m^2/week. The serum α-1-acid glycoprotein (AAG) concentration values were found to be negatively correlated with the grade of esophagitis. The median survival time was 23.1 months. *Conclusion*: The chemoradiation regimen tested in this study has promising activity and manageable toxicity. The continuous schedule could not be recommended due to excessive toxicity. The main DLT was esophagitis, and it significantly correlated with the plasma AAG concentration.

Keywords Docetaxel · Cisplatin · Chemoradiation · AAG

Conflicts of interest: The authors indicated no potential conflicts of interest

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Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers, and although surgery offers the best chance of cure and long-term survival, only a small percentage of patients present with resectable disease. In fact, 25–30% of patients with NSCLC present with locally or regionally advanced unresectable tumors. Chest irradiation with modern megavoltage equipment plays a critical role in the treatment of these patients, since it assures good local control of the tumor in most patients. However, the development of distant metastases also affects their prognosis, and the addition of chemotherapy to thoracic radiation therapy (TRT) has been proposed in an attempt to reduce the risk of distant metastases.

Recent studies support the benefit of combined modality therapy in stage III NSCLC. The results of randomized studies that used sequential or concomitant chemotherapy for unresectable non-small cell lung cancer have shown significant differences in survival, local control rates, and distant metastasis rates for chemoradiotherapy over radiotherapy alone [1–5], and a recent meta-analysis of all randomized trials that compared TRT alone with the combined approach showed an unequivocal, although modest, survival advantage when cisplatin-based chemotherapy was added to TRT [6]. Concomitant chemoradiotherapy offers the potential advantage of synergistic interactions for local control