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.

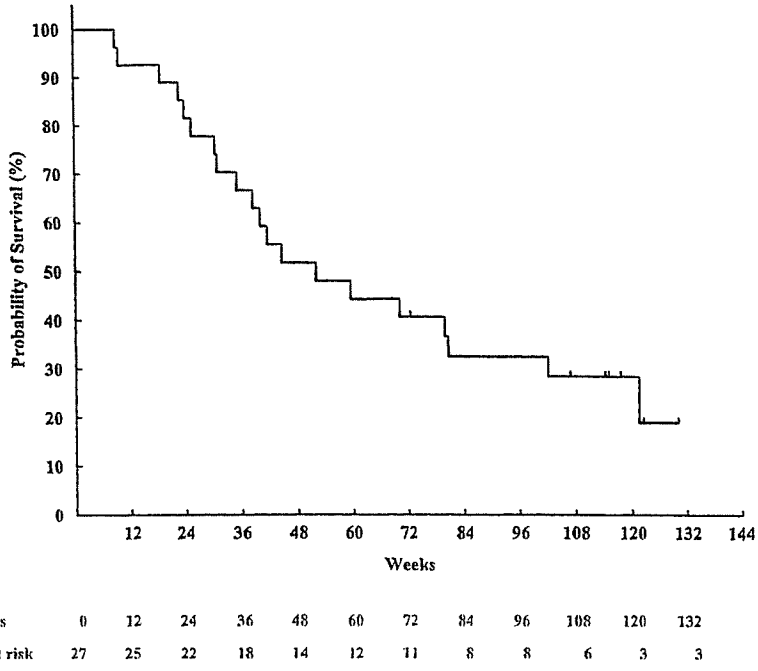

FIGURE 1. Kaplan-Meier survival curve of 27 evaluable patients with advanced nonsmall cell lung cancer.

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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CASE REPORT

Pemetrexed-induced edema of the eyelid

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KEYWORDS
Chemotherapy;
Eyelid edema;
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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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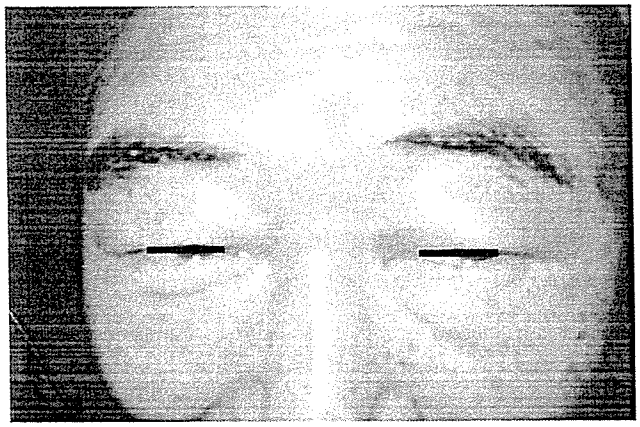

(A)

(B)

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.

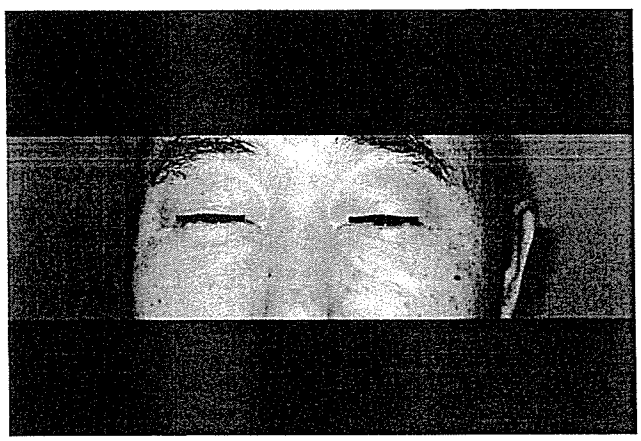

Fig. 2 The edema of the eyelid was improved by the administration of corticosteroid.

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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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

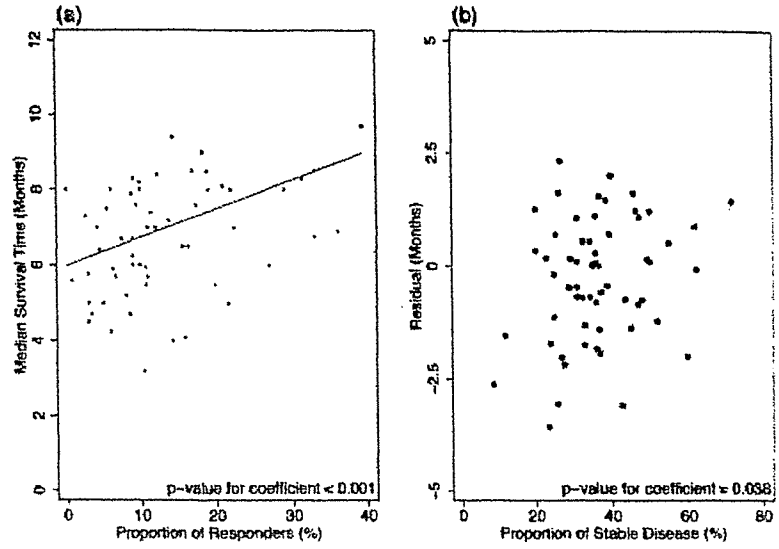

FIGURE 1. Scatterplot for MST and response/stable disease rates. (*A*) The observed MST corresponding to the percentage of responders. (*B*) The residuals (observed MST minus fitted MST in the model for *A*). The figure indicates that both response rate and stable disease rate significantly influence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

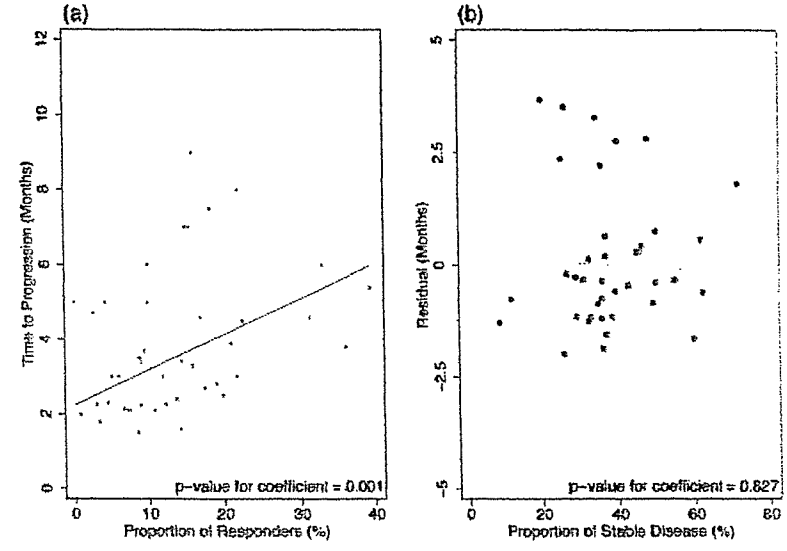

FIGURE 2. Scatterplot for TTP and response/stable disease rates. (*A*) The observed median TTP corresponding to the percentage of responders. (*B*) The residuals (observed TTP minus fitted TTP in the model for *A*). The figure indicates that the response rate but not the stable disease rate significantly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

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Irinotecan in the treatment of small cell lung cancer: a review of patient safety considerations

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A water soluble derivative of camptothecin, irinotecan (CPT-11) is effective against small-cell lung cancer (SCLC), as well as non-SCLC and gastrointestinal cancers. This extended review of recently concluded and ongoing studies focuses on irinotecan in the treatment of limited (LD) and extensive (ED) SCLC specifically considering the safety of patients. Irinotecan-induced diarrhoea is pervasive, and can be severe and life-threatening especially in combination with neutropenia. It can have a significant impact on patient quality of life, negatively influencing compliance with therapy and dose-intensity. For LD SCLC, irinotecan can be administered with radiotherapy concurrently or sequentially. In a Phase III study for ED SCLC comparing etoposide and cisplatin (EP) and irinotecan and cisplatin (IP) regimens, severe myelosuppression was more frequent in the EP arm than in the IP arm, and conversely severe or life-threatening diarrhoea was more frequent in the IP arm than in the EP arm. IP resulted in significantly higher response rates and overall survival in Japan, and confirmatory Phase III studies are ongoing. Irinotecan should not be administered to patients with any degree of ongoing diarrhoea above their baseline. Irinotecan can be administered with relative safety for patients with SCLC only through careful patient monitoring, especially regarding diarrhoea and myelosuppression.

Keywords: chemotherapy, irinotecan (CPT-11), radiotherapy, small-cell lung cancer (SCLC), toxicity

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1. Introduction

Lung cancer is the leading cause of cancer deaths worldwide, with > 900,000 deaths per year attributed to the disease [1]. About 15 – 20% of lung cancers are small-cell lung cancer (SCLC), although the frequency has been decreasing relative to other lung cancer over the last two decades [2]. SCLC is considered distinct from other non-small cell lung cancers (NSCLC) because of its clinical and biological characteristics [3]. The clinical characteristics of SCLC tend to be aggressive behaviour with rapid growth, early spread to distant sites, but more sensitive to chemotherapy and radiation. SCLC is usually staged as either limited disease (LD), in which the tumour is confined to the hemithorax of origin, the mediastinum, or the supraclavicular lymph nodes, or extensive disease (ED), in which tumours have spread beyond the supraclavicular areas. About 30% of patients with SCLC have LD. Management of most cases of LD SCLC involves combination chemotherapy, usually with a platinum-containing regimen, and thoracic radiation therapy (TRT). If a complete response is obtained, the patient may be offered prophylactic cranial irradiation. The median survival time (MST) of LD SCLC is 16 – 24 months with current forms of treatment, such as chemoradiotherapy with or without surgery. ED SCLC patients are treated with combination

chemotherapy, but the disease remains incurable. Usually a platinum-containing regimen is chosen. For ED SCLC, the MST is less than one year with currently available chemotherapy, and long-term survivors are still rare [4,5].

Furthermore, the prognosis is exceedingly poor for patients who receive second-line therapy after relapse. Response is influenced by the time to progression after cessation of first-line therapy. Patients who relapse less than three months after the completion of first-line therapy are termed refractory; they have response rates that are lower than for those patients who relapse more than three months after therapy, who are termed sensitive. The objective for these patients is palliation and increased quality of life, and therefore salvage therapy should be limited to patients with a good performance status (PS) and without significant comorbidities [3].

A water soluble derivative of camptothecin, irinotecan hydrochloride (CPT-11), a topoisomerase I inhibitor, has been synthesised for use in chemotherapy. The chemical structures of irinotecan and its major metabolites found in plasma are shown in **Figure 1**. Irinotecan is converted by hepatic and peripheral carboxylesterase to its active metabolite 7-ethyl-10-hydroxycamptothecin (SN38). This is subsequently glucuronidated by hepatic uridine diphosphate glucuronosyl transferase-1A1 (UGT 1A1), the enzyme responsible for bilirubin glucuronidation with multi-genetic variants, to SN38-glucuronide (SN38G) [6]. The patient with UGT1A1*28 has an impaired capacity for glucuronidation of SN-38, increased exposure to SN-38, and there is increased clinical toxicity when treated with irinotecan. To measure UGT1A1*28, in August 2005, FDA in the US cleared the Invader Molecular Assay for irinotecan dosing. However, irinotecan activity is not determined by the product of one gene [7]. Irinotecan, SN-38 and SN-38 glucuronide (SN-38G) may be shunted out of the cell via members of the ATP-binding cassette transporters [8]. The metabolism and pharmacogenetics of irinotecan is beyond the scope of this review, but there are some excellent reviews on this subject [9-11].

It should be cautioned that there are drug–drug interactions [12] with irinotecan. Exposure to irinotecan and its active metabolite SN-38 is substantially reduced in patients receiving the CYP3A4 enzyme-inducing anticonvulsants phenyntoin, phenobarbital or carbamazepine [13]. Rifampin, rifabutin and St. John's Wort are also CYP 3A4 inducers [14,15]. St. John's Wort is contraindicated during irinotecan therapy. Ketoconazole, a strong inhibitor of CYP3A4 [16], and contraindicated during irinotecan therapy, should be discontinued in patients at least one week prior to starting irinotecan therapy.

In Japan, 1245 cancer patients received irinotecan as a single agent in Phase I or Phase II trials that were conducted to obtain approval for commercial use from the Ministry of Health, Labour and Welfare. Of the 1245 patients, 55 (4.4%) died from toxicities of irinotecan, mainly myelosuppression and/or diarrhoea [17].

The onset of diarrhoea can occur early or be delayed beyond 24 h after injection of irinotecan. Early-onset diarrhoea is a cholinergic effect. Anticholinergic drugs, such as atropine, seem to easily reverse this side effect. Late-onset diarrhoea represents the dose-limiting toxicity (DLT) of irinotecan; it can be severe and life-threatening, especially in combination with neutropenia. Late-onset diarrhoea is treated with loperamide, and identification of high-dose loperamide as an effective remedy for this toxic effect greatly facilitated development of irinotecan [18,19]. These studies established the usefulness of high-dose loperamide. Patients should be instructed to take high-dose loperamide at the first onset of any irinotecan-associated late-onset diarrhoea that has occurred at least 12 h after drug administration. This therapy has been widely used for the management of diarrhoea caused by irinotecan.

For the treatment of SCLC, initial irinotecan is usually administered on days 1 and 8 every 3 weeks or on days 1, 8 and 15 every 4 weeks. The dose ranges from 50 to 70 mg/m^2 when administered weekly. As an example of the dose modification of irinotecan, Kudoh *et al.* [20] used the following dose modification: irinotecan is not given on days 8 or 15 if the leukocyte or platelet counts were < 3000/μl or < 75,000/μl, respectively. It is also withheld if the patient develops diarrhoea of grade 2 (increase of 4 – 6 stools/day, or nocturnal stools) or worse (grade 3: increase of > 6 stools/day or incontinence; grade 4: physiological consequences requiring intensive care). The next course of treatment can only be initiated if the leukocyte count is ≥ 4000/μl, the platelet count is ≥ 10,000/μl, serum creatinine is less than the upper limit of normal, and diarrhoea has been resolved. There is no dose modification for the leukocyte count, platelet count or diarrhoea during the same course. The dose of irinotecan in the next course was reduced by 10 mg/m^2 if the leukocyte count was < 2000/μl, the platelet count was < 50,000/μl, or diarrhoea was grade 3 to 4. This dose modification was applied in most studies with minor variation. For example, in some studies, the delay in the irinotecan doses was applied when the leukocyte count was < 2000/μl [21] instead of 3000/μl.

Another available topoisomerase-I inhibitor, topotecan, has achieved response rates of up to 22% in previously treated patients with SCLC and survival almost double that achieved with other single agents. Compared with cyclophosphamide/doxorubicin/vincristine (CAV), single-agent topotecan achieved a higher response rate, longer survival and statistically significant improvements in dyspnoea, hoarseness, fatigue, anorexia and interference with daily activities [22,23]. The incidence of grade 3 – 4 diarrhoea was extremely low (1%). The clinical comparison of these two topoisomerase-I inhibitors has not been tried. This review focuses mainly on the recent results of irinotecan in the treatment of SCLC in connection with patient safety considerations.

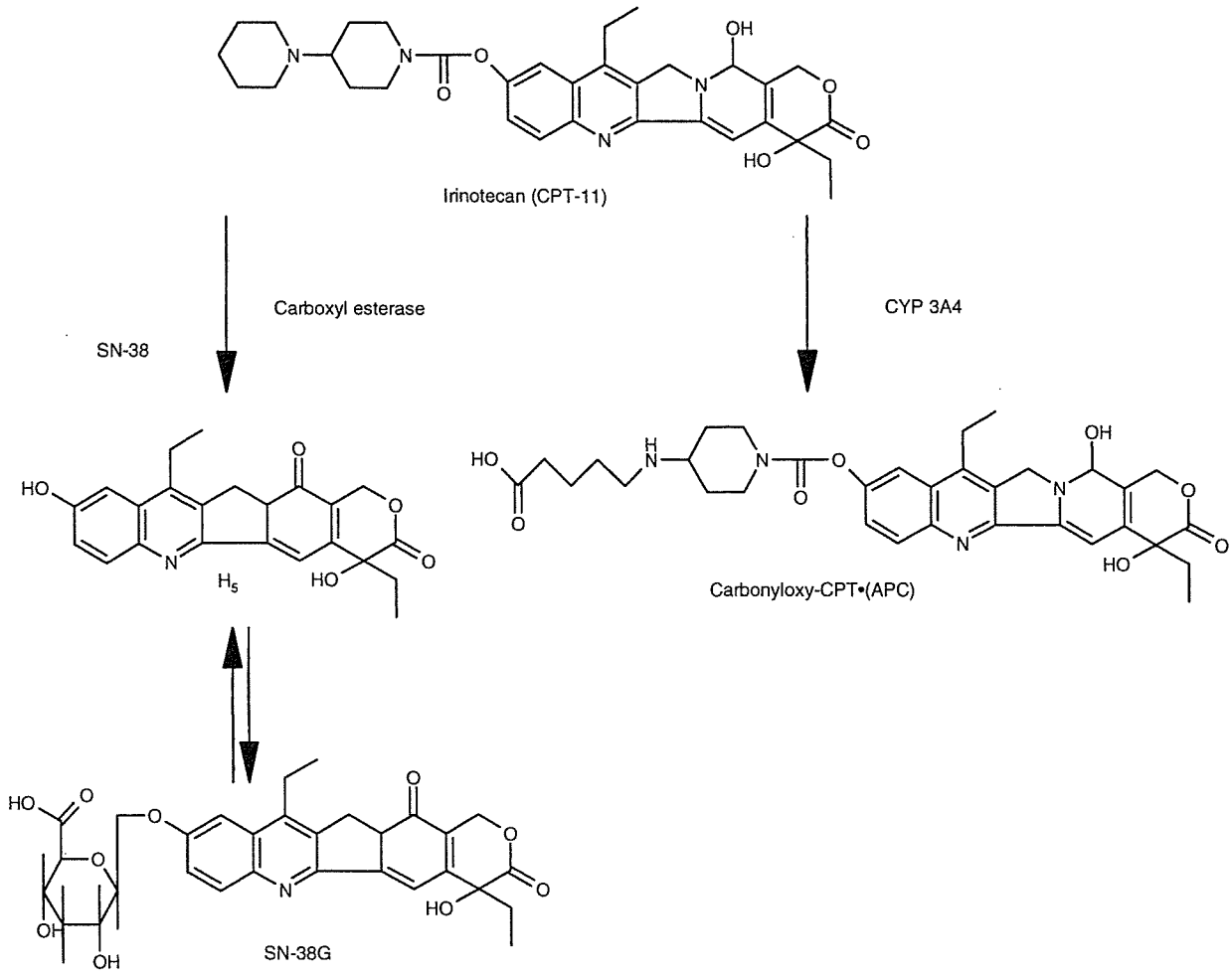

Figure 1. Metabolism of irinotecan. Chemical structures of CPT-11 and its major metabolites.

2. Irinotecan containing regimens as front-line treatment

2.1 Irinotecan plus cisplatin for ED SCLC

Clinically, irinotecan was proved to be effective against SCLC [24]. Negoro *et al.* have demonstrated that 13 (37%) out of 35 patients responded, including 33% of previously treated patients and 50% of chemotherapy-naive patients. In a Phase II trial of irinotecan for previously treated SCLC, the response rate was 47% out of 16 patients [25].

IP was tested in a Phase II trial for patients with previously untreated SCLC [20]. A total of 40 patients (53%) had LD and 35 patients (47%) had ED. Initially, irinotecan 80 mg/m^2 over 90-minutes infusion was given on days 1, 8 and 15, and cisplatin 60 mg/m^2 was given every 4 weeks. After 3 of the initial 10 patients experienced severe haematological toxicity, diarrhoea and hepatic toxicity, and one patient died of diarrhoea and neutropenia, the irinotecan dose was reduced to 60 mg/m^2. The response rate was 84%, with a complete response rate of 29%. The MST was 14.3 months for LD patients and 13.0 months for ED patients, an encouraging result. Although the survival of LD was not increased significantly, this may be due to the small number of LD SCLC patients accrued. This study prompted a Phase III study of the Japan Clinical Oncology Group (JCOG 9511).

The JCOG conducted a multi-centre, randomised, Phase III study which compared irinotecan plus cisplatin with etoposide plus cisplatin (EP) in patients with ED SCLC (JCOG 9511) (**Figure 2**) [26]. IP consisted of four 4-week cycles of 60 mg/m^2 of irinotecan on days 1, 8 and 15, and 60 mg/m^2 of cisplatin on day 1. The regimen of etoposide and cisplatin consisted of four 3-week cycles of 100 mg/m^2 of etoposide on days 1, 2 and 3, and 80 mg/m^2 of cisplatin on day 1. The delivered dose intensity for irinotecan was 80%. The results are listed in **Table 1**. This study was terminated early because an interim analysis found a statistically significant difference in survival between the two arms. The MST was 12.8 months in the IP arm and 9.4 months in the EP arm ($p = 0.002$). At two years, the proportion of patients surviving was 19.5% in the IP group and 5.2% in the EP

Table 1. IP versus EP in phase III studies.

	IP	EP	p-value	IP	EP	p-value
	JCOG9511 study [26]			*Hanna's study* [27]		
	(n = 75)	(n = 77)		(n = 210)	(n = 104)	
Irinotecan: delivered dose intensity	80%			90%		
Survival						
Median survival time (months)	12.8	9.4	0.002	9.3	10.2	0.6226
1-year survival (%)	58.4	37.7		35.4	36.7	
2-year survival (%)	19.5	5.2		8.0	7.9	
Haematological						
Neutropenia	65.3	92.2	< 0.001	36.2	86.5	< 0.0001
Anaemia	26.7	29.9	0.72	4.8	11.5	< 0.0268
Thrombocytopenia	5.3	18.2	0.002	4.3	19.2	< 0.0001
Nonhaematological				(n = 216)	(n = 106)	
Diarrhoea	16	0	< 0.001	21.3	0	0.0001
Response				(n = 221)	(n = 110)	
Complete response	2.6	9.1		3.6	2.7	
Partial response	81.8	58.4		44.3	40.9	
Overall response	84.4	67.5	0.02	48.0	43.6	
Stable disease	2.6	20.8		4.1	7.3	
Progressive disease	3.9	11.7		20.0	20.0	
Not evaluable	6.5	0		28.1	29.1	

EP: Etoposide and cisplatin; IP: Irinotecan and cisplatin.

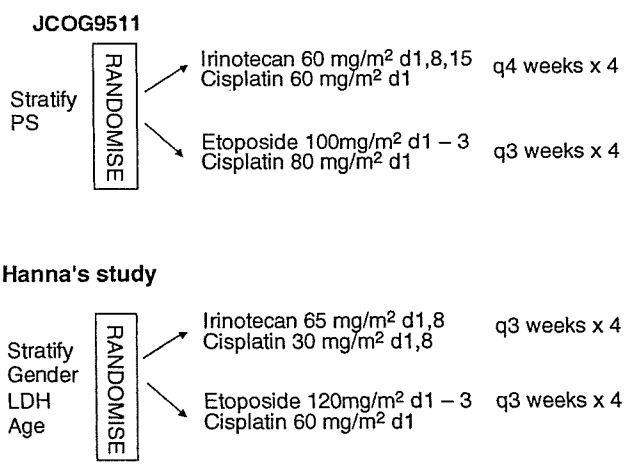

Figure 2. Two Phase III randomised trials.
LDH: Lactate dehydrogenase.

group. This was the first study to show the superiority of any one regimen over etoposide plus cisplatin for the front-line treatment of ED SCLC, and IP has become one of the standard regimens for ED SCLC in Japan. Severe myelosuppression was more frequent in the EP group than in the IP group. On the other hand, severe diarrhoea was more frequent in the IP arm than in the EP arm. Despite the dose modifications, major deviations from the protocol resulted in failure to reduce the dose of chemotherapy (in 6 patients); administration of irinotecan despite the presence of grade 1 (increase of < 4 stools/day) or 2 diarrhoea (in 9 patients); continuation of the study treatment despite grade 2 to 3 pulmonary toxicity (in 3 patients); and continuation of the treatment despite grade 3 hepatic toxicity (in 1 patient). There were 3 treatment-related deaths in the IP arm; one patient died of bleeding from a metastatic site in the lung, another patient died of sepsis associated with neutropenia and diarrhoea, and the third patient died of pneumonia associated with neutropenia. These three treatment-related deaths in the IP arm occurred during the first or second cycle of treatment and were attributed to haematological toxicities of the first cycle. This may indicate that severe haematological toxicities, as well as diarrhoea, during the first cycles of chemotherapy should be managed carefully. All cases of grade 1 to 4 diarrhoea occurred during the first and second cycles of the IP arm but early suspension of treatment may have prevented death associated with diarrhoea in all but one patient, which

involved a protocol violation because the patient was given irinotecan on day 8 of the first cycle despite the presence of grade 1 diarrhoea. This suggests that irinotecan should not be administered to patients with any degree of ongoing diarrhoea above their baseline.

Confirmatory studies are underway; currently, there is only one concluded study showing IP superiority, but it had a small sample size. Additionally, pharmacogenomic differences may exist between Japanese and Western populations.

Hanna *et al.* presented a Phase III trial comparing IP with EP in patients with previously untreated ED SCLC at the ASCO meeting in 2005 (**Figure 2, Table 1**) [27]. This was designed to confirm the JCOG9511 trial. However, the dose and schedule were modified to increase dose intensity.

The IP arm consisted of cisplatin 30 mg/m^2 and irinotecan 65 mg/m^2 on days 1 and 8 every 3 weeks. The EP arm was cisplatin 60 mg/m^2 on day 1, and etoposide 120 mg/m^2 on days 1 – 3 every 3 weeks for 4 cycles, or disease progression, or intolerable toxicity. This was planned to improve tolerability, achieve greater dose intensity and maintain or improve efficacy. The 336 patients were stratified by gender, lactate dehydrogenase level and age, and were randomised in a 2:1 fashion, with 221 treated with IP (median age, 63 years; range, 37 – 82 years; male, 57.5%) and 109 to EP (median age, 62 years; range, 38 – 83 years; male, 57.3%). Baseline characteristics were well balanced across the 2 arms, with a high representation of PS of 0 or 1 (IP, 92.3%; EP, 88.2%). After 30 patients with PS 2 were enrolled, study amendment excluded PS 2 patients. Delivered dose intensity of irinotecan was 39 mg (94%), higher than that of the JCOG9511 trial (80%). In both arms, 65% of patients received 4 or more cycles. Selected grade 3 or 4 toxicities in IP versus EP arm were: diarrhoea (21 versus 0%), neutropenia (35 versus 84%), febrile neutropenia (4 versus 11%). Grade 3 or 4 haematological toxicities were significantly more common with EP than IP. There was a trend towards more febrile neutropenia in the EP arm (10 versus 4%), and significant differences were seen in rates of dehydration (13 versus 3%; $p = 0.15$), vomiting (13 versus 4%; $p = 0.0445$), and diarrhoea (21 versus 0%; $p < 0.0001$). The survival of EP in both trials was similar (MST: 10.2 months in this study and 9.4 months in the JCOG9511 trial). However, the MST of IP was 9.3 months in this trial and 12.8 months in the JCOG9511 trial. Differences in outcome of this study from the JCOG trial may be due to pharmacogenomic or patient characteristic differences, or a change in the dose/schedule of IP. Pharmacogenomic studies among ethnic populations are needed to address this issue. It is likely that IP will prove to be at least as effective as other treatments for patients with ED SCLC.

Other Phase III trials will clarify these issues, including a SWOG S0124-randomised Phase III trial with the dose and schedule of each arm the same as the JCOG9511 trial, and a Phase III study started in June 2002 – (NCT00143455) sponsored by Pfizer. In this second study, IP consists of irinotecan 65 mg/m^2 on days 1 and 8 and cisplatin 80 mg/m^2 on day 1. EP consists of etoposide 100 mg/m^2 on days 1 – 3 and cisplatin 80 mg/m^2 on day 1 every 3 weeks. The results of these studies are awaited.

The debate continues regarding the optimal dose of combination chemotherapy as related to improvement of the outcome of SCLC. However, the author can state that too low a dose intensity may lead to poor results. Takigawa *et al.* used fractionated administration of IP in 15 patients with ED SCLC [28]. Both irinotecan at a dose of 50 mg/m^2 and cisplatin at a dose of 60 mg/m^2 were given on days 1 and 8, and repeated every 4 weeks up to 4 cycles. Although objective response rates were 80%, no complete response (CR) were obtained. The MST was 9.4 months and one-year survival was 40.0%. They stopped enrollment because of no CR and poor survival compared to Kudoh's data [20]. The dose intensity may be low because this regimen had a lower dose of irinotecan (50 mg/m^2) and a two-week rest period.

Han *et al.* reported a Phase II study of dose-intensified weekly IP in chemo-naive patients with ED SCLC [29]. The initial six patients received cisplatin 50 mg/m^2 followed by irinotecan 90 mg/m^2 on day 1 and 8 of a 21-day cycle (level I), with one treatment death and three febrile neutropenias. The doses of cisplatin and irinotecan were then reduced to 40 mg/m^2 and 80 mg/m^2, respectively (level II). The overall response rate was 97%, with a complete response rate of 26%. The MST was 11.1 months and 1- and 2-year survival rates were 44.1% and 11.8%, respectively. Major grade 3 or 4 toxicities included neutropenia (89%), anaemia (59%) and diarrhoea (27%). There were three treatment-related deaths, occurring in elderly patients aged > 60 years and/or relative poor baseline PS 2 or 3. Although they adopted the oral alkalisation and control of defecation to prevent irinotecan-induced side effects, especially delayed diarrhoea, they are uncertain whether or not this preventive treatment reduced the observed incidence of severe delayed diarrhoea.

2.2 Irinotecan plus carboplatin for ED SCLC

Schmittel *et al.* studied the DLT and maximum tolerated dose (MTD) of a dose escalation of carboplatin to a fixed dose of irinotecan (IC) in Caucasian patients [30]. They demonstrated that the maximum tolerated dose is irinotecan 50 mg/m^2 administered on day 1, 8 and 15, and carboplatin at an area under the concentration–time curve (AUC) of 5 mg/ml x min, on day 1 of a 4-week cycle. DLT (neutropenia, thrombocytopenia and diarrhoea) was comparable to the results of the Japanese trial at a dose of 60 mg/m^2 of irinotecan and AUC = 5 of carboplatin [31].

Subsequently, Schmittel *et al.* presented a randomised Phase II trial comparing IC and etoposide plus carboplatin (EC) in ED SCLC [32]. Chemotherapy-naive ED SCLC patients were randomly assigned to receive carboplatin AUC = 5 either in combination with 50 mg/m^2 of irinotecan on days 1, 8 and 15 or with etoposide 140 mg/m^2 on days 1 – 3. In the IC arm, treatment was repeated every four weeks; in the EC arm, every

three weeks. IC improved response rate (10% CR and 61% partial response (PR) in IC, 0% CR and 50% PR in EC) and progression free survival (9 months, $p = 0.03$) over standard EC (6 months). The MST was 12 months in the IC arm and 10 months in the EC arm, but with no significant difference. Patients with EC had significantly higher incidence of grade 3 to 4 leucopenia, neutropenia and thrombocytopenia. Grade 3 – 4 diarrhoea developed more frequently in the IC arm (11 versus 6%), but with no significant difference. Haematotoxicity was favourable in the IC arm. They extended into a randomised Phase III trial to assess impact on overall survival, and concluded this study showed that even when carboplatin is used instead of cisplatin, the survival of IC and EC was not significantly different, and that myelosuppression was more frequent in EC than IC.

2.3 Irinotecan plus etoposide for ED SCLC

A Phase II study of irinotecan and etoposide (IE) for chemotherapy-naive ED SCLC was recently conducted without platinum by the West Japan Thoracic Oncology Group (WJTOG) [33]. A total of 50 patients were enrolled. This regimen consisted of irinotecan 60 mg/m^2 on days 1, 8 and 15, and etoposide 80 mg/m^2 on days 2 – 4. The overall response rate was 66% with a complete response rate of 10%. The MST was 11.5 months and the 1-year survival rate was 43.2%. Grade 3 – 4 neutropenia, thrombocytopenia and diarrhoea were 62.9, 4 and 2%, respectively. There was no treatment-related death. This regimen seems to be equal to the EP regimen. The dose intensity of irinotecan and etoposide achieved with this regimen was not adequate. This may be the reason for the low incidence of diarrhoea (2%). A schedule of irinotecan administered on days 1 and 8 at 3-week intervals may be preferred.

2.4 Triplets including irinotecan for ED SCLC

JCOG9902-DI was a randomised Phase II trial to compare two kinds of three-drug combinations of cisplatin, etoposide and irinotecan (PEI regimens) for the treatment of ED SCLC [34]. A total of 60 patients were randomised to receive either arm A (cisplatin 25 mg/m^2 on day 1, on weeks 1, 3, 5, 7 and 9 and etoposide 60 mg/m^2 on days 1 – 3, on weeks 2, 4, 6, 8), or arm B (cisplatin 60 mg/m^2 on day1, irinotecan 60 mg/m^2 on days 1, 8, 15 and etoposide 50 mg/m^2 on days 1 – 3, every week for 4 cycles). Prophylactic G-CSF support was provided in both arms. This study suggested that the PEI combinations in both schedules have significant activity against ED SCLC with acceptable toxicity. The CR rate of 17% and MST of 12.9 months in arm B were much more promising compared with the CR rate of 7% and MST of 8.9 months in arm A. They concluded that arm B should be selected for future Phase III studies. However, because irinotecan administration often needed to be skipped, especially on day 15, they suggested a 3-week schedule in which irinotecan is administered only on days 1 and 8.

Briasoulis *et al.* showed that irinotecan can be safely combined with cisplatin and etoposide in a convenient and simple schedule of administration over three days [35]. They treated 36 patients with irinotecan on day 1 in combination with fixed doses of cisplatin (20 mg/m^2) and etoposide (75 mg/m^2), both for 3 consecutive days. Irinotecan dose was escalated from 60 mg/m^2 by increments of 40 mg/m^2 in this Phase I trial. The MTD of irinotecan was 140 mg/m^2 and the recommended optimal dose 120 mg/m^2. DLTs were febrile neutropenia and grade 3 diarrhoea. This same regimen is being studied with concurrent TRT in a total dose of 54 Gy in 30 fractions (1.8 Gy once daily) [36].

Thompson *et al.* reported a Phase II trial of the Minnie Pearl Cancer Research Network at the 2005 ASCO meeting [37]. They added a molecular targeted agent, imatinib (60 mg/day, per os) to chemotherapy of irinotecan (60 mg/m^2 on days 1, 8 and 15) and carboplatin (AUC = 4) every 4 weeks. Imatinib targets c-kit expression. Grade 3/4 haematological toxicity included: neutropenia (29%/16%), anaemia (13%/1%) and thrombocytopenia (7%/0%). The response rate was 66% with 10% CR. Grade 3 diarrhoea was observed in 21%. There were no treatment-related deaths. The MST was 8.5 months. This suggests that C-kit expression did not correlate with survival and that imatinib offers no efficacy at a cost of increased toxicity when combined with irinotecan and carboplatin in the treatment of ED SCLC.

3. Irinotecan-containing regimens for relapsed or refractory SCLC

Huisman *et al.* have summarised 21 Phase II studies and 3 randomised trials of second-line chemotherapy in patients with SCLC reported from 1989 to 1999 [38]. They found a cumulative response rate of 21% for multi-drug regimens and 19% for single agents. As yet there is no standard second-line treatment established for patients with SCLC who fail or relapse after front-line treatment.

Irinotecan was combined with various anticancer drugs in doublet or triplet. As doublets, these include cisplatin [39], weekly or every three weeks carboplatin [40,41], etoposide [42], gemcitabine [43,44], ifosfamide [45] and paclitaxel [46]. The responses vary from 10 to 94%, and the MST ranges from 5.8 to 8.9 months. As described earlier on triplet including irinotecan [34,47], a three-drug combination Phase II study of irinotecan, cisplatin and etoposide (PEI regimen) was conducted only for sensitive relapsed SCLC (40 patients) [48]. This Phase II regimen consisted of cisplatin 25 mg/m^2 weekly for 9 weeks, etoposide 60 mg/m^2 for 3 days on weeks 1, 3, 5, 7 and 9, and irinotecan 90 mg/m^2 on weeks 2, 4, 6 and 8 with G-CSF support after day 1 on week 2. The results showed a response rate of 78% (CR rate of 13%) and the MST of 11.8 months. A total of 39 patients (98%) had a good PS of 0 or 1. Grade 3 – 4 neutropenia, thrombocytopenia, and diarrhoea were observed in 73, 33, and 8%, respectively. Nonhaematological toxicities were mild and transient.

Another three-drug combination of cisplatin, ifosfamide and irinotecan with G-CSF was conducted by Fujita *et al.* [49].