response was observed in a patient with metastatic esophageal cancer previously treated by radiochemotherapy. Antitumor activity in previously treated metastatic NSCLC was also seen in two patients who experienced a 21% tumor reduction, including a decrease in pleural effusion during five courses, and a 27% tumor reduction. Metastatic subcutaneous tumor in gastric cancer patient reduced with necrosis on the next day after TZT-1027 administration, with a tumor reduction rate of 29%. Preclinical studies have demonstrated the potent in vitro cytotoxicity of TZT-1027 against several tumor cell lines and its in vivo antivascular effects, e.g., disruption of the tumor vasculature.

In conclusion, the present study showed that TZT-1027, a synthetic analogue of the natural marine product dolastatin 10, is effective for Japanese patients with advanced solid tumors when administered on days 1 and 8 in 3-week courses, possesses an improved safety profile as compared with other dolastatin analogues, and is active at a tolerable dose.

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Phase I Study of Combination Therapy with S-1 and Weekly Docetaxel for Advanced Gastric Cancer

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Abstract. *Background: The primary objective of this study was to determine the maximum tolerated dose (MTD), the toxicity profile and the recommended dose (RD) for phase II of a combination of S-1 and weekly administration of docetaxel. Patients and Methods: Patients with histologically diagnosed recurrent or unresectable locally advanced gastric cancer were enrolled. A fixed oral dose of 80 mg/m^2 S-1 was given for 3 weeks. Docetaxel was infused intravenously on day 1, 8 and 15, repeated every 5 weeks. A pharmacokinetic study was also performed. Results: A total of 14 patients were enrolled. One dose-limiting toxicity (DLT) (grade 3 diarrhea with febrile neutropenia) occurred at level 2. DLTs occurred in 3/5 patients at level 3, (grade 3 stomatitis, with febrile neutropenia or continuous grade 4 neutropenia). The pharmacokinetic study suggested no drug interactions. Overall response and disease control rates were 20% and 80%, respectively. The response rate at the RD (level 2) was 50%. Overall survival was 9.4 months. Conclusion: RD was level 2 (80 mg/m^2 of S-1 for 3 weeks and 20 mg/m^2 of docetaxel on day 1, 8 and 15, every 5 weeks). Dose intensities of S-1 and docetaxel were 48 mg/m^2/week and 12 mg/m^2/week, respectively. This regimen showed promising activity for advanced gastric cancer.*

The incidence and mortality of gastric cancer has been declining, however, it remains one of the most common causes of cancer-related death (1). It is often diagnosed in advanced stage or recurrent disease, both of which are incurable, and carries a dismal prognosis with a short median survival. The one year survival rate is approximately 50% in stage III gastric cancer patients, and 25% in stage IV. Although gastric cancer has been regarded as a resistant tumor, several clinical trials have revealed that some chemotherapeutic agents are effective. 5-Fluorouracil (5-FU)-containing regimens are considered as standard chemotherapy because they provide survival benefit and improvement in quality of life compared with best supportive care (2-4). Hence in the 1980's, many combinations of drugs, 5-FU/doxorubicin/mitomycin (FAM) (5), 5-FU/doxorubicin/methotrexate (FAMTX) (6), etoposide/doxorubicin/cisplatin (EAP) (7), epirubicin/cisplatin/5-FU (ECF) (8), 5-FU/doxorubicin/cisplatin (FAP) (9) and 5-FU/cisplatin (FP) (10, 11) were reported in the treatment of gastric cancer. Although response rates were improved by 40-70%, the survival advantage over single agent 5-FU alone was not significant and severe adverse effects were observed (12). To improve efficacy of chemotherapy against gastric cancer, development of novel agents and combinations which have higher antitumor activity with favorable safety profiles is crucial.

S-1, a fourth-generation oral fluoropyrimidine, is a formulation of tegafur (FT), 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo) at a molar ratio of 1:0.4:1 (13). FT is the prodrug for cytotoxic fluorouracil (FU) and CDHP prevents its degradation. CDHP is a potent and competitive inhibitor of dihydropyrimidine dehydrogenase, which reduces the degradation of FU and allows efficacious concentrations to enter the anabolic pathway. The diarrheagenic property of FU is a result of its phosphorylation in the intestine, primarily by orotate phosphoribosyltransferase (OPRT). Oxo is a competitive inhibitor for OPRT. Thus, the protective effect of Oxo is due to its ability to reduce phosphorylation of FU. Thus, one component of S-1, CDHP, reduces the degradation of cytotoxic FU, and another component, Oxo, potentially reduces its GI toxicity. Phase II studies of S-1 monotherapy in patients with advanced gastric cancer showed an overall

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response rate of 26-49% with the most relevant side-effects being fatigue, diarrhea and neutropenia (14-16). Recently, phase II studies of S-1 plus cisplatin (17), or S-1 plus irinotecan (18) have been evaluated and showed promising response rates.

Docetaxel is a semisynthetic taxoid which enhances microtubule assembly and inhibits the depolymerization of tubulin (19); it has broad antitumor activity against malignancies. It demonstrated promising single-agent efficacy in gastric cancer (20-23) and was therefore investigated in different combination regimens. The combinations of docetaxel with 5-FU (24), capecitabine (25, 26), irinotecan (27) and cisplatin (28) have demonstrated high efficacy. The triplet combination of docetaxel/cisplatin and 5-FU has significantly prolonged overall survival compared to cisplatin plus 5-FU (29). Thus, docetaxel is one of the key drugs playing an integral part in routine combination regimens against gastric cancer.

Based on the clinical activity of both docetaxel and S-1, and the fact that there is no cross resistance or synergistic anti-tumor effect between docetaxel and 5-FU (30) or S-1 (31, 32) *in vitro* or *in vivo*, two Japanese investigators combined docetaxel and S-1 in a clinical trial (33-35). The recommended dose of docetaxel was 40 mg/m^2 on day 1, in combination with S-1 80 mg/m^2 on days 1-14, every 3-4 weeks. The total dose of docetaxel was restricted by neutropenia, with around 70% of patients having grade 3 or 4 neutropenia (33). The real dose intensities of S-1 and docetaxel were around 40 mg/m^2/week and 10 mg/m^2/week, respectively. A weekly administration schedule of docetaxel has been reported as a safe and effective treatment for advanced gastric cancer (26, 36, 37). The aims of the present study were to determine the maximum-tolerated dose (MTD) of docetaxel with weekly administration in combination with S-1 in order to achieve higher dose intensities of both drugs with a feasible toxicity profile and to establish the recommended dose (RD) for Phase II trials.

Patients and Methods

Eligibility criteria. Patients, aged 20 to 75 years, with at least one measurable lesion of pathologically proven inoperable or recurrent gastric cancer were enrolled. Inoperability was determined on the basis of clinical evaluation, radiological imaging, laparoscopy or laparotomy with failed resection. Patients who had no more than two previous treatment regimens not including taxanes (docetaxel or paclitaxel) or S-1 were eligible.

Other eligibility criteria were: Eastern Cooperative Oncology Group performance status 0 or 1; estimated life expectancy of at least 3 months; adequate renal function (serum creatinine <1.5x upper limit of the reference range (ULN)), adequate hepatic function (serum bilirubin <1.5x ULN; transaminases <2.5x ULN) and adequate hematological function (hemoglobin >8 g/dl, leukocytes >4,000/μL and thrombocytes >100,000/μL). No other anti-tumor therapy was allowed 28 days prior to treatment.

Table I. *Patient characteristics.*

Characteristics	Number of patients
Number of patients (evaluable)	14
Age, years; median (range)	61 (31-76)
Gender	
Male	11
Female	3
Performance status (ECOG)	
0	2
1	12
Histology	
Not assessable 2	
Well-differentiated	0
Moderately differentiated	3
Poorly differentiated	9
Extent of disease	
Primary site only	2
Primary and metastatic sites	9
Metastasis only	3
Previous treatment	
None	7
Surgery alone	2
Surgery and adjuvant chemotherapy	2
Surgery and intra-peritoneal chemotherapy	1
Systemic chemotherapy alone	1
Intra-peritoneal chemotherapy alone	1

Eligibility also included the ability to reliably tolerate and comply with oral medication. Patient compliance was recorded using chemotherapy diary cards. Pre-treatment evaluation included a complete medical history and physical examination, basic laboratory evaluation and staging of the underlying malignancy with either ultrasound, chest radiograph or computed tomography (CT) scan.

Main exclusion criteria were follows: pregnancy or breast feeding, symptomatic infectious disease, pulmonary fibrosis or interstitial pneumonia, grade 3 or severe hemorrhage/bleeding, grade 2 or severe peripheral neuropathy, symptomatic peripheral effusion or ascites, past history or allergic reaction to polysorbate 80, obstructive bowel disease or severe diarrhea, congestive heart failure, uncontrolled angina pectoris, or arrhythmia, uncontrolled diabetes or hypertension, symptomatic brain metastasis and active concomitant malignancy.

Patient characteristics are given in Table I. This was a phase I study, conducted at the Department of Medical Oncology, Kinki University, Japan. This study was approved by the institutional review board of Kinki University and all patients provided written informed consent.

Drug administration. Patients received a dose of intravenous docetaxel administered as a 60 min infusion on day 1, 8 and 15, and oral S-1 administered at a fixed dose of 80 mg/m^2/day on days 1-21, every 5 weeks (Figure 1). Patients were treated for at least two cycles unless disease progression or unacceptable toxicity was observed. The initial starting dose of docetaxel was 15 mg/m^2 (level 1) (Table II). Dose

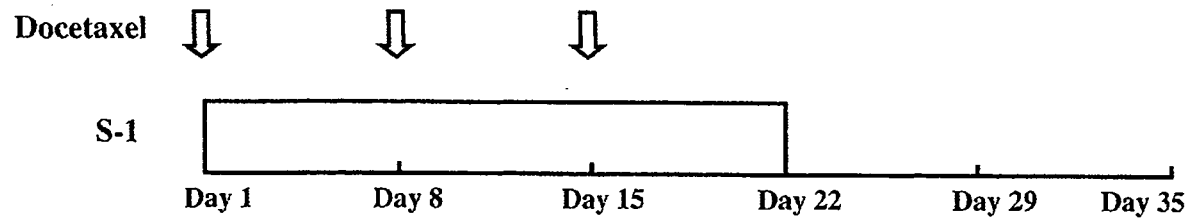

Figure 1. *Treatment schedule of combination therapy with S-1 and docetaxel. Administration of S-1 80 mg/m²/day orally from day 1-21. Administration of docetaxel was given by drip infusion within 60 min. on day 1, 8 and 15. At all dose levels, the administration cycle was repeated every 5 weeks.*

escalation was conducted in increments of 5 mg/m² up to 25 mg/m² (level 3). No intra-individual dose escalation was performed. Docetaxel was only administered on day 8 and 15 if WBC and platelets were >2,000/μl and >75,000/μl, respectively, with non-hematological toxicity <grade 3 and allergic reaction/ AST/ALT/pneumonitis <grade 2. In case of grade 3 neutropenia or thrombocytopenia, or grade 2 diarrhea or mucositis, S-1 administration was interrupted until recovery. Patients were not allowed to escalate or reduce the dose of S-1. If any DLTs were observed, docetaxel was reduced once by one dose level for subsequent courses.

DLTs and MTD. Toxicities were evaluated according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 2 (38). DLTs were defined as follows: (a) grade 4 neutropenia lasting 5 days or longer; (b) febrile neutropenia (grade 3 or 4 neutropenia with fever (≥38.5°C)); (c) grade 4 thrombocytopenia; (d) grade 3 or 4 non-hematological toxicity except for nausea, vomiting, anorexia and general fatigue; (e) failure to administer docetaxel on day 8; (f) failure to administer docetaxel on day 15, even if postponed for one week; and (g) failure to administer S-1 for 14 days continuously during treatment.

Assessment of DLTs was conducted only in the first treatment cycle. Three patients per dose level were planned to be included. In case of one DLT, three further patients were treated at that level. MTD was defined as at least two out of three or three out of six patients with DLT at a given dose level. Throughout this study, the prophylactic administration of granulocyte colony-stimulating factor (G-CSF) was not allowed.

Evaluation during therapy. Hematological and biochemical tests, performance status and clinical assessment of symptoms were monitored at least every week. Tumor response was assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) (39). All partial or complete responses were confirmed for a minimum of 4 weeks. Patients were considered evaluable for response if they received at least one complete cycle of therapy, unless treatment was stopped due to early toxicity. Time to progression and overall survival were estimated using the Kaplan-Meier method.

Pharmacokinetics. The pharmacokinetics of docetaxel and S-1 were studied during the first cycle of therapy. For docetaxel, 5 ml blood samples were taken from each patient at the following time-points: prior to treatment, 30 min into the drug infusion, at the end of docetaxel infusion, and 30 min, 1 h 2 h, 3 h, 4 h, 7 h and 24 h after the end of the infusion. For S-1, 5 ml blood samples were taken from each patient at the following time-points: prior to dose, and 1 h, 2 h, 4 h, 8 h and 24 h after dose. Initial administration of S-1 was started at 8 h after the end of docetaxel infusion on day 1. To evaluate drug-drug interactions between docetaxel and S-1, the pharmacokinetic analysis of docetaxel was conducted on day 1 and day 8, and that of S-1 was conducted on day 7 and day 8. On day1 only, S-1 was administered in the evening, after the blood correction for pharmacokinetic analysis of docetaxel at 7 h after infusion. All blood samples were centrifuged immediately and the separated plasma samples were frozen at –20°C until analysis. The plasma samples were thawed at ambient temperature, then vortexed and centrifuged for 5 min at 3,000 rpm to remove fibrous materials. Pharmacokinetic analysis for docetaxel was performed according to Yoshida *et al.* (34). Pharmacokinetic analysis for S-1 was carried out as described elsewhere (17).

Table II. *Dose escalation scheme and DLTs in course 1.*

Level	1	2	3
Dose of docetaxel (mg/m²)	15	20	25
Dose of S-1 (mg/m²)	80	80	80
Number of patients	3	6	5
Median number of courses (range)	2 (2-9)	2 (2-5)	1 (1-2)
Number of patients with any DLT/Number of patients	0/3	1/6	3/5
ANC: <500/mm³ for >5 days	0	0	2
Febrile neutropenia	0	1[a]	2
Other grade 3-4 non-hematological toxicity	0	1[a]	3[b]
Inability to receive docetaxel on day 8 or day 15	0	0	1[c]
Inability to receive S-1 more than 14 days	0	0	0

ANC: absolute neutrophil count; [a]Same patient with grade 3 diarrhea with febrile neutropenia; [b]All patients with grade 3 stomatitis; [c]Due to neutropenia.

Table III. *Hematological and non-hematological adverse events.*

Adverse events	Level 1 (n=3)				Level 2 (n=6)				Level 3 (n=5)			
NCI-CTC grade	1	2	3	4	1	2	3	4	1	2	3	4
Hematological												
Leukocytopenia	1	0	0	0	0	0	1	0	0	0	1	1
Neutropenia	1	0	0	0	0	0	1	0	0	0	0	2
Anemia	0	0	0	0	1	0	1	0	1	0	3	0
Thrombocytopenia	2	0	0	0	2	0	0	0	0	0	0	0
Non-hematological												
Nausea/vomiting	2	0	0	0	2	0	0	0	0	0	0	0
Anorexia	0	1	0	0	1	3	0	0	1	1	0	0
Fatigue	2	0	1	0	5	0	0	0	1	3	0	0
Stomatitis	2	0	0	0	0	0	0	0	0	0	3	0
Constipation	1	1	0	0	1	1	0	0	1	1	0	0
Diarrhea	1	1	0	0	0	1	1	0	2	1	0	0
AST/ALT	0	1	0	0	0	0	0	0	0	0	0	0
Skin rash	1	0	0	0	0	0	0	0	0	0	0	0
Pneumonia	0	0	0	0	0	0	0	0	0	0	0	0
Infection	1	1	0	0	0	1	0	0	0	0	0	0
Febrile neutropenia	0	0	0	0	0	0	1	0	0	0	2	0

AST: aspartate aminotransferase; ALT: alanine aminotransferase.

Results

Patient characteristics. A total of 14 patients with a median age of sixty-one years (range 31-76 years) were recruited for this study. Patient characteristics are listed in Table I. One patient was clinically diagnosed with primary ovarian cancer and following oophorectomy, a Krukenberg tumor with primary gastric cancer was diagnosed. Five patients received prior chemotherapy. Two patients had uracil-tegafur (UFT) and carboplatin/paclitaxel as adjuvant therapy, respectively. Two patients had received chemotherapy only, of systemic administration with cisplatin/5-FU and irinotecan, or of intra-peritoneal infusion with paclitaxel. Seven patients had not received any prior treatment.

Sequence of dose levels studied and DLTs. Three patients started on level 1 (S-1 80 mg/m^2/day with docetaxel 15 mg/m^2) and no DLTs were observed (Table II). The next cohort of three patients received dose level 2 (S-1 80 mg/m^2/day with docetaxel 20 mg/m^2) and as one patient experienced grade 3 diarrhea and febrile neutropenia (DLT), this group was expanded to six patients. None of the three additional patients experienced DLT. The next cohort of three patients received dose level 3 (S-1 80 mg/m^2/day with docetaxel 25 mg/m^2) and one patient experienced grade 3 stomatitis and grade 2 diarrhea (DLT), so this group was expanded to six patients. Two additional patients experienced DLT (grade 3 stomatitis, febrile neutropenia and continuous grade 4 neutropenia). One of these patients could not be treated with docetaxel on day 8 in the 1st cycle because of neutropenia. Thus, three of five patients had DLTs at level 3. In these five patients, the most frequent DLTs were stomatitis, febrile neutropenia and continuous neutropenia. Therefore, level 2 was considered as the recommend dose for the phase II study. The median number of cycles received per patient was two (range one to nine). Dose intensities of S-1 and docetaxel were 48 mg/m^2/week and 12 mg/m^2/week, respectively.

Adverse effects. All the patients were evaluated for adverse effects which are summarized in Table III. No grade 3 adverse effects were observed at level 1 except for fatigue in one patient. One patient at level 2 had grade 3 diarrhea with febrile neutropenia as DLT, however, no other grade 3 or non-hematological adverse effect was observed at the level in the repeated cycle. No grade 4 hematological adverse effects were observed at level 1 or 2. At level 3, 3 out of 5 patients had grade 3 stomatitis and 2 of them also had febrile neutropenia; furthermore, 3 out of 5 patients had grade 3 anemia while two out of 5 patients had grade 4 neutropenia.

Pharmacokinetics (PK) analyses. Blood samples for PK analyses were available for 13 out of the 14 patients, including all 5 patients at the optimal dose level (20 mg/m^2).

Table IV. *Plasma concentrations of docetaxel.*

	Level 1 (n=3)			Level 2 (n=5)			Level 3 (n=5)		
	C_{max} (ng/mL)	AUC_{0-t} (ng•h/mL)	AUC_{0-A} (ng•h/mL)	C_{max} (ng/mL)	AUC_{0-t} (ng•h/mL)	AUC_{0-A} (ng•h/mL)	C_{max} (ng/mL)	AUC_{0-t} (ng•h/mL)	AUC_{0-A} (ng•h/mL)
Day 1 (-S-1)	205	238	-	521	522	616	591	835	1547
Day 8 (+S-1)	240	308	-	597	547	581	379	555	1028

C_{max}: maximum observed concentration; AUC: area under the concentration-time curve.

Table V. *Plasma concentrations of FT, 5-FU, CDHP and Oxo.*

	FT		5-FU		CDHP		Oxo	
	C_{max} (ng/mL)	AUC_{0-A} (ng•h/mL)	C_{max} (ng/mL)	AUC_{0-A} (ng•h/mL)	C_{max} (ng/mL)	AUC_{0-A} (ng•h/mL)	C_{max} (ng/mL)	AUC_{0-A} (ng•h/mL)
Day 7 (n=8)	2526±615	15189±3184	151.3±70.6	810.5±349.3	299.8±175.8	1342.4±624.3	76.1±21.1	414.2±118.8
Day 8 (n=8)	2509±380	14882±2219	156.4±62.7	765.0±304.4	307.5±149.5	1368.8±537.2	93.8±46.4	491.0±216.3

FT: tegafur; 5-FU: fluorouracil; CDHP: 5-chloro-2,4-dihydroxypyridine; Oxo: potassium oxonate; C_{max}: maximum observed concentration; AUC: area under the concentration-time curve; Values are expressed as mean ± standard deviation (SD).

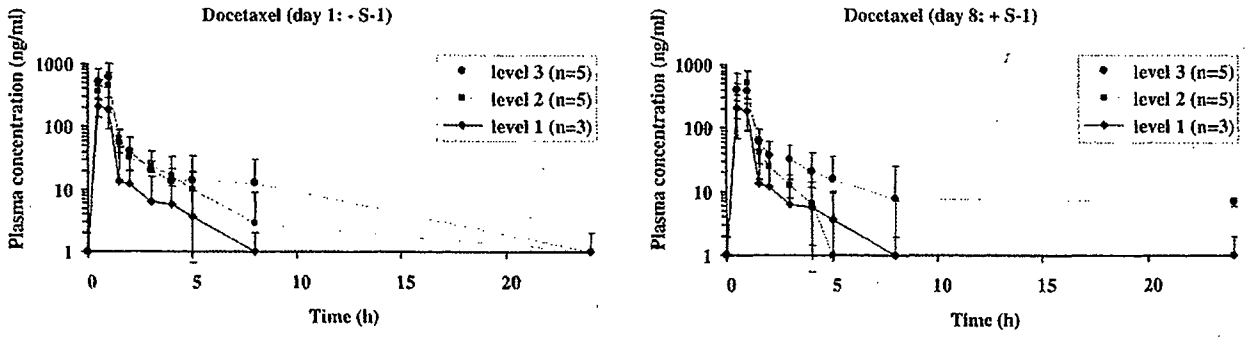

Figure 2. *Plasma concentrations of docetaxel with and without administration of S-1 (day 1 vs. day 8).*

The PK parameters for docetaxel are shown in Table IV. The plasma concentration of docetaxel with or without S-1 (day 1 *vs.* day 8) are shown in Figure 2. Although C_{max}, AUC_{0-t}, AUC_{0-A} of docetaxel on day 8 were slightly lower than those of day 1, PK parameters for docetaxel were equivalent between day 1 and day 8. The PK parameters for FT, 5-FU, CDHP and Oxo are shown in Table V. The plasma concentration of FT, 5-FU, CDHP and Oxo with administration or not of docetaxel (day 7 *vs.* day 8) are shown in Figure 3. PK parameters of S-1 were equivalent on day 7 and on day 8. Thus, no drug interactions between S-1 and docetaxel were observed.

Efficacy. Response and survival data were updated in October 2006. Ten patients were assessable for tumor response (Table VI). Four patients were considered not evaluable for response, because of early drop-out due to early toxicity. Two patients were also considered not evaluable for RECIST criteria, because there were only primary tumors and no metastatic site (Table I). One patient was considered not evaluable for response after entry because there was only peritoneal dissemination and no target lesion (Table VI). There were 2 partial responses at level 2 and no complete response. The overall response rate was 20% (2 out of 10). The response rate at the

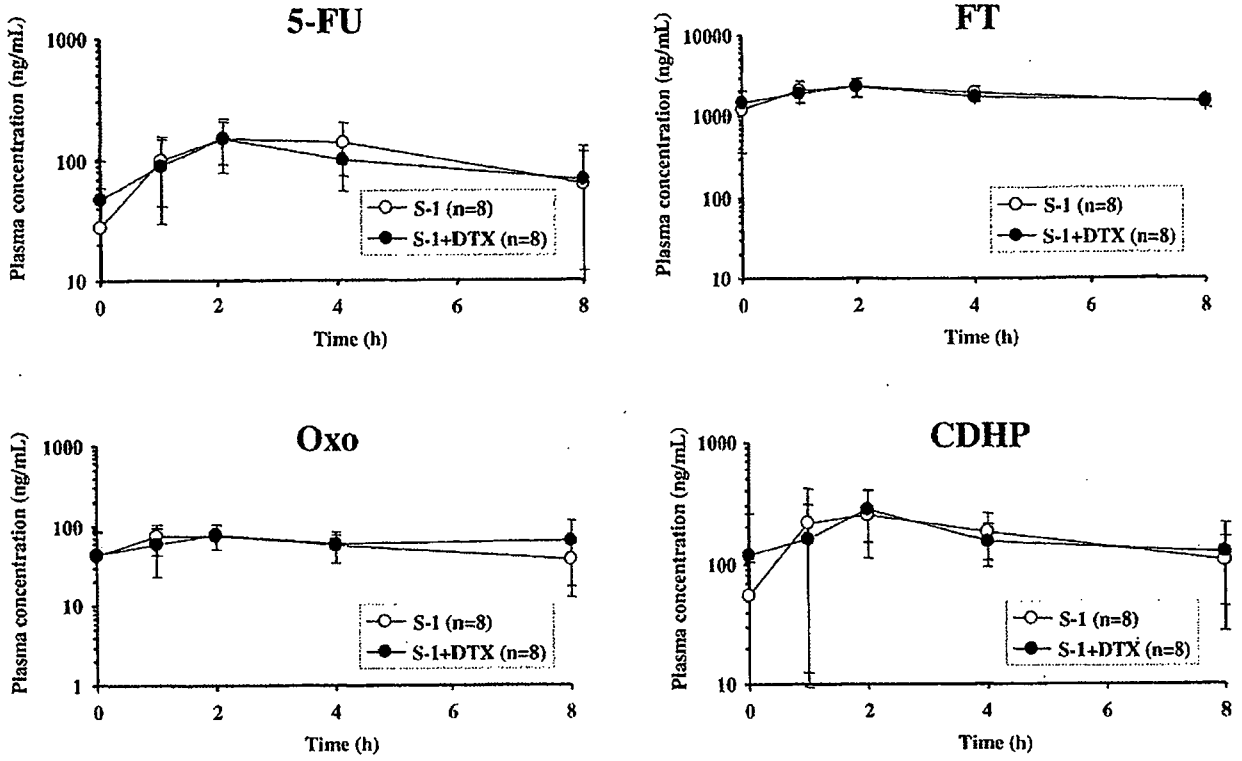

Figure 3. *Plasma concentrations of 5-fluorouracil (5-FU), tegafur (FT), potassium oxonate (Oxo), and 5-chloro-2,4-dihydroxypyridine (CDHP) with and without administration of docetaxel (day 7 vs. day 8).*

recommended dose (level 2) was 50% (2 out of 4). The disease control rate was 80% (8 out of 10). All fourteen patients were assessable for survival (Figure 4). The median survival time was 9.4 months and the median time to progression was 2.4 months. The median survival time at the recommended dose (level 2) was 10.0 months.

Discussion

Current key drugs for the treatment of gastric cancer are cisplatin, taxoids (paclitaxel and docetaxel), irinotecan and 5-fluorouracil (5-FU) or its derivative drugs (such as doxifluridine, capecitabine, tegafur and UFT). 5-FU-based combinations are considered as a standard chemotherapy for first-line treatment of advanced gastric cancer because they provide survival benefit compared with best supportive care (2-4) In western countries, triplet combinations such as epirubicin/cisplatin/5-FU (ECF) or docetaxel/cisplatin/5-FU (DCF) (29) regimens are the current standard, however, they are sometimes not recommended practically because of their severe hematological toxicity. S-1 is a novel oral fluoropyrimidine derivative. Single use of S-1 has revealed promising response in advanced gastric cancer with acceptable side-effects being stomatitis, fatigue, diarrhea and neutropenia (14-16), but no hand-foot syndrome which is frequently caused by capecitabine. Based on the clinical activity of S-1 monotherapy, phase II studies of S-1 plus cisplatin (17), S-1 plus irinotecan (18) and S-1 plus docetaxel have been evaluated. Several reports suggested that there is synergistic anti-tumor effect between docetaxel and both 5-FU (30) and S-1 (31, 32).

This phase I study showed that combination therapy with S-1 and weekly docetaxel is active in advanced and recurrent gastric cancer and has an acceptable and manageable toxicity

Table VI. *Tumor response.*

Level	Number of patients	CR	PR	SD	PD	RR (%)
1	2	0	0	2	0	0
2	4	0	2	1	1	50
3	4	0	0	3	1	0
Total	10	0	2	6	2	20

CR: complete response; PR: partial response; SD: stable disease, PD: progressive disease; RR: response rate; Tumor responses were evaluated using RECIST criteria.

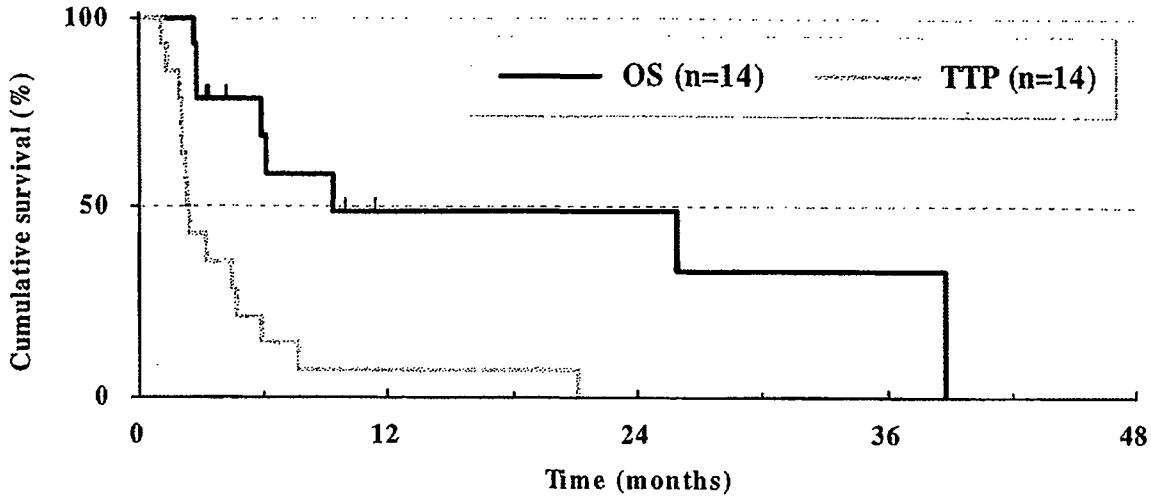

Figure 4. *Kaplan-Meier plot of log-rank analysis for overall survival (OS) and time to progression (TTP). Median overall survival time was 9.4 months. Median time to progression was 2.4 months.*

profile. The recommended dose of docetaxel was 20 mg/m^2 administered weekly (treatment on days 1, 8 and 15) in combination with 80 mg/m^2/day of S-1 for 3 weeks, repeated every 5 weeks. Two investigations (33, 35) previously reported a combination S-1 and once infusional docetaxel. In both studies, the recommended dose of docetaxel was 40 mg/m^2 on day 1 combined with full dose S-1 (80 mg/m^2) on days 1-14. Although Tomiak *et al.* (36) reported that such a regimen could be repeated every 3 weeks, treatment administration of the next cycle was delayed for a median 7 days because of neutropenia. Yamaguchi *et al.* (33) have described a similar regimen which should be repeated every 4 weeks. Thus, the real dose intensities of S-1 and docetaxel of the previous regimen were 40 mg/m^2/week and 10 mg/m^2/week, respectively. In the present study, expected dose intensities of S-1 and docetaxel were 48 mg/m^2/week and 12 mg/m^2/week, respectively, and were equivalent or higher than those of the previous regimen. Moreover, the presented weekly docetaxel based regimen is convenient and can be applied on an outpatient basis. In a previous study, docetaxel was found to modulate the level of metabolic enzymes of 5-FU and produced a synergistic effect in a gastric cancer cell line (32), however, in the present study, there were no drug-drug interactions between S-1 and docetaxel.

DLTs with the presented combination were stomatitis and febrile neutropenia. DLTs at the MTD dose level were severe stomatitis. Diarrhea and stomatitis are similar DLT profiles to that found with single use of S-1 and the addition of docetaxel renders this combination more serious. Phase II studies of S-1 monotherapy in patients with advanced gastric cancer showed an overall response rate of 26-49%. In combination S-1 with once infusional docetaxel, response rates were 46-56%. In our study, the overall response rate was 20%, however, the response rate was 50% at the recommend dose level. The disease control rate of 80% was also promising. With a median survival time of 9.4 months, a median time to progression of 2.4 months, and a median survival time at the recommended dose of 10.0 months, the survival benefit was considered favorable in comparison with median survival times of other regimens, such as docetaxel (6-8 months), S-1 (7-8 months), ECF (10 months) and DCF (10 months).

Conclusion

The combination of S-1 and weekly docetaxel is an active and well-tolerated regimen in patients with advanced gastric cancer. This regimen can be applied on an outpatient basis, maintaining the dose intensity of both drugs and reducing neutropenia-based side-effects. A phase II trial of the regimen in patients with advanced and recurrent gastric cancer is ongoing.

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CLINICAL INVESTIGATION **Lung**

PHASE I/II TRIAL OF SEQUENTIAL CHEMORADIOTHERAPY USING A NOVEL HYPOXIC CELL RADIOSENSITIZER, DORANIDAZOLE (PR-350), IN PATIENTS WITH LOCALLY ADVANCED NON–SMALL-CELL LUNG CANCER (WJTOG-0002)

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Purpose: This Phase I/II trial was conducted to assess the efficacy and safety of PR-350, a novel hypoxic cell radiosensitizer, when administered with thoracic radiation therapy (RT) after induction chemotherapy (CT) for locally advanced non–small-cell lung cancer (NSCLC).

Methods and Materials: Two cycles of cisplatin (80 mg/m^2) and paclitaxel (180 mg/m^2), or carboplatin (AUC = 6) and paclitaxel (200 mg/m^2) were given before RT of 60 Gy in 30 fractions. In the Phase I portion, the starting dosage of PR-350 was 10 daily administrations (2000 mg/m^2) in combination with RT, and this number was increased in increments of 10 for successive groups to 30 doses.

Results: In total, 37 patients were enrolled. In Phase I (n = 20), PR-350 could be administered 30 times with concurrent thoracic RT. Thus, in Phase II (n = 17), PR-350 was administered 30 times. The major toxicity was radiation pneumonitis, with Grade 3 or more pneumonitis noted in 6 patients (16%) including 2 with treatment-related deaths. However, no Grade 3 or more esophageal toxicity was noted, and only Grade 1 peripheral neuropathy was noted in 9 patients (24%). For all 37 patients, the median survival time (MST) and the 2-year survival rate were 15.9 months and 24%, respectively. For 18 patients receiving 21 to 30 doses of PR-350, the MST and 2-year survival rate were 20.9 months and 33%, respectively.

Conclusions: Thoracic RT combined with 30 daily administrations of PR-350 after induction CT was well tolerated and promising for locally advanced NSCLC. © **2007 Elsevier Inc.**

Hypoxic cell radiosensitizer, Doranidazole, Non–small-cell lung cancer, Clinical trial, Chemoradiation.

INTRODUCTION

The standard treatment for patients with locally advanced non–small-cell lung cancer (NSCLC) has become combined chemotherapy (CT) and radiotherapy (RT). Induction CT before thoracic RT is effective for patients with locally advanced NSCLC, as many such patients have micrometastatic disease at presentation and ultimately develop metastatic disease (1–4). However, induction CT did not improve the local control rate by thoracic RT (3, 4). To obtain long-term survival for the patients, adequate loco-regional control by thoracic RT is essential. Improved loco-regional control and survival rates have been achieved clinically with the concurrent use of CT and RT for locally

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advanced NSCLC (4–7). At present, concurrent chemoradiotherapy (CRT) is the standard treatment for locally advanced NSCLC. However, acute toxicities are inevitably increased during concurrent CRT (4–7). Because hematologic and gastrointestinal toxicities are significantly more common during concurrent CRT than for RT alone or sequential CRT, concurrent CRT is not recommended for elderly patients or patients with a poor performance status.

Hypoxic cells are 2.5 to 3.0 times less sensitive to radiation than well-oxygenated cells (4, 8, 9). Tumors often include hypoxic areas, which are a cause of radioresistance. One approach to conquering hypoxic cells is the use of hypoxic cell radiosensitizers. These drugs mimic the effect of oxygen by increasing radiation damage. Nitroimidazoles such as misonidazole and ethanidazole are highly effective at enhancing the radioresponsiveness of tumors in rodents (4, 8–12). A meta-analysis of 50 randomized clinical trials showed that modifications of tumor hypoxia significantly improve the loco-regional tumor control and overall survival achieved with RT (11). Depending on the site of the tumor, treatment benefits can be observed for head and neck tumors as well as bladder tumors (11–13). A randomized clinical trial performed by the Danish Head and Neck Cancer Study group showed that a hypoxic radiosensitizer, nimorazole, improved loco-regional control in head-and-neck cancer as well as a reduction of cancer-related deaths significantly (13). Based on this positive result, the use of nimorazole becomes standard practice for head and neck cancer in Denmark (12). However, no significant improvement by a hypoxic cell sensitizer has been found for lung cancer.

PR-350, a 2-nitroimidazole nucleoside analog doranidazole, is characterized by a very low level of toxicity, with the 50% lethal dose in mice exceeding 5 g/kg, but an efficiency similar to that of ethanidazole (14–17). In a Phase I trial, no neurotoxicity was observed when PR-350 was administered for 5 consecutive days at a daily dose of 800–2000 mg/m^2 in combination with external RT for various cancers (18). Thereafter, the efficacy of PR-350 combined with intraoperative RT for locally advanced pancreatic cancer was tested in a randomized trial (19). PR-350 (2000 mg/m^2) or placebo was infused immediately before intraoperative RT (25 Gy) in a total of 47 patients. Both groups received postoperative external RT (40 Gy/20 fractions) without CT. No significant difference in the overall survival rate was found between the two groups. However, the 2-year survival rate was 18% for the PR-350 group and 4% for the control group, suggesting that PR-350 improves the long-term local control rate.

Because local control remains a problem for patients with locally advanced NSCLC, PR-350 was added to a sequential CRT regimen in an attempt to improve local control, while maintaining the lower toxicity rate compared with concurrent CRT. This Phase I/II trial was conducted to assess the efficacy, safety, and pharmacokinetics (PK) of PR-350 when administered for 10 to 30 days at a daily dose of 2000 mg/m^2 combined with conventional thoracic RT after induction CT for treatment of locally advanced NSCLC.

METHODS AND MATERIALS

Investigational design

This was a Phase I/II, nonrandomized, multicenter study conducted by the West Japan Thoracic Oncology Group (WJTOG) in compliance with Good Clinical Practice guidelines. The protocol was approved by the institutional review boards or ethics committees of all participating institutions, and written informed consent was obtained twice, before induction CT at the first entry and before thoracic RT combined with PR-350 at the second entry.

Patient eligibility

The pretreatment staging work-up included medical history, physical examination, complete blood count, biochemical screening tests, chest radiography, bronchoscopy, computed tomography of the thorax and upper abdomen. Brain CT or MRI, as well as bone scans were performed whenever possible. Positron emission tomography (PET) was not performed because health insurance did not cover PET at that time. Mediastinal lymph nodes of more than 10 mm in the shortest diameter were regarded as malignant nodes, and histologic proof of N2 or N3 status was not required.

Major eligibility criteria at the first entry included 20–74 years old, histologically, or cytologically proven NSCLC, surgically unresectable stage IIIA and IIIB, no prior therapy, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, and adequate organ functions. Patients with severe emphysema, chronic bronchitis, or apparent findings of pulmonary fibrosis or interstitial pneumonitis on chest radiography were excluded.

Major eligibility criteria at the second entry included an ECOG performance status of 0 to 2, a white blood cell (WBC) count of $\geq$3,000/μL, a platelet count of $\geq$75,000/μL, a creatinine level of $<$1.5 mg/dL, a PaO_2 level of $\geq$70 mm Hg, a percent diffusion lung carbon monoxide ($\%D_{LCO}$) level of $\geq$60, and neuropathy of Grade 0 or Grade 1. In addition, patients whose RT field exceeded one half of the involved lung were excluded. Although this eligibility criterion on the RT field was relatively subjective and obscure, it was commonly used in Japanese clinical trials for NSCLC to exclude large thoracic RT fields (6).

Treatment plan

Figure 1 provides the design of the Phase I and Phase II portions. In the Phase I trial, patients received two cycles of induction CT consisting of cisplatin at 80 mg/m^2 and paclitaxel at 180 mg/m^2. Induction CT was repeated 3 weeks later. Induction CT with carboplatin (AUC = 6) and paclitaxel (200 mg/m^2) and a 3-week interval was also permitted in the Phase II portion. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria version 2.0. Treatment could be delayed no more than 2 weeks to allow recovery from toxicity. Dose adjustments of CT for toxicity were made according to guidelines stipulated in the protocol.

Thoracic RT combined with PR-350 was begun 3 to 5 weeks after completion of the induction CT when patients agreed to the protocol and fulfilled the second entry criteria. All patients were treated with a linear accelerator photon beam of 4 MV or more. The primary tumor and involved nodal disease received 60 Gy in 2-Gy fractions over 6 weeks.

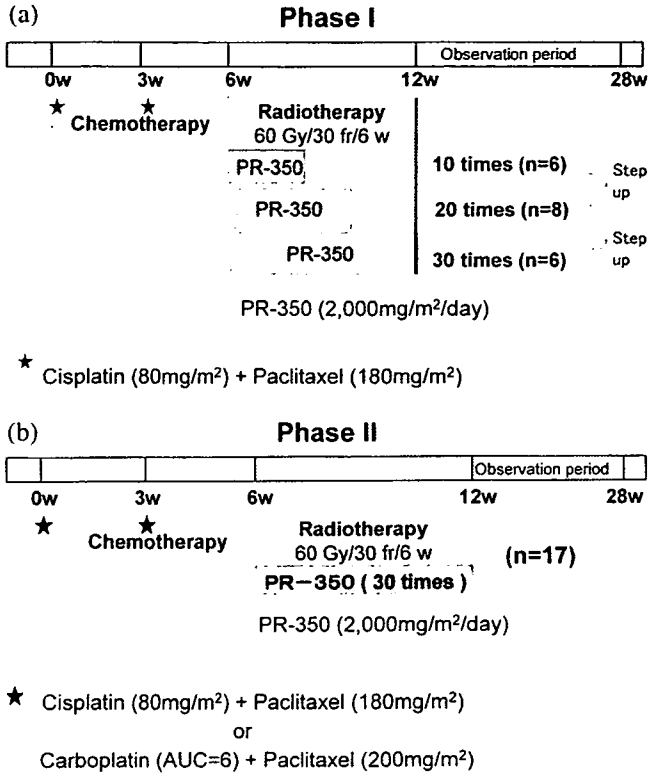

Fig. 1. (a, b) Design of the trial: (a) Phase I portion; (b) Phase II portion.

At the start of this multi-institutional study, three-dimensional treatment planning system using computed tomography was not available at many institutions. Therefore, the protocol for RT was prescribed by a two-dimensional treatment planning techniques, and three-dimensional dose constraints for both planning target volume (PTV) and normal risk organs were not defined in the protocol. The RT doses were specified in the center of the target volume, and calculated assuming tissue homogeneity without correction for lung tissues after the example of Radiation Therapy Oncology Group (RTOG) at that time. No immobilization devices were used, and the position of patients was verified by portal films.

The initial 40 Gy was delivered to clinical target volume 1 (CTV1), and the final 20 Gy was delivered to a reduced volume defined as clinical target volume 2 (CTV2). CTV1 included the primary tumor, ipsilateral hilum, and mediastinal nodal areas from the paratracheal (#2) to subcarinal lymph nodes (#7). The contralateral hilum was not included in CTV1. The supraclavicular areas were not to be treated routinely, but could be treated when supraclavicular nodes were involved. CTV1 included a margin of 1 cm for gross tumor volume (GTV) consisting of the primary tumors and the involved lymph nodes $\geq$1 cm in the shortest diameter, although no margin was added for lymph node areas without involved nodes. CTV2 included only the primary tumor and the involved lymph nodes with a margin of 0.5 to 1 cm. The PTV margins for CTV were 0.5 to 1 cm. Although field margins for PTV were not determined in the protocol, appropriate field margins were added at each institution. The spinal cord was excluded from the fields for CTV2 by appropriate methods such as the oblique opposing method. Portal films were obtained at the first time of each treatment plan, but weekly verification was not mandatory.

Quality assurance of thoracic RT including review of simulation films, portal films, and RT dose data was conducted throughout the trial by one of the authors (Y.N.). Approximately 90% (33/37) of the patients received thoracic RT consistent with the protocol guidelines. For 2 patients, the RT field was larger than the guidelines allowed, whereas for 2 other patients, margins for target volume were insufficient.

A novel hypoxic cell radiosensitizer, PR-350, developed by POLA Chemical Industries Inc. (Yokohama, Japan), was used. PR-350 (1000 mg) was dissolved in a solution of 50 ml. PR-350 at 2000 mg/m^2 was infused intravenously over 20 to 30 min before thoracic RT daily. Thoracic RT was given within 10 to 40 min of the end of infusion. Among the 770 sessions, violation rates for the duration of infusion and time interval were 5.8% (45/770) and 3.0% (23/770), respectively.

In Phase I, the starting dosage of PR-350 was 10 daily doses in combination with thoracic RT for the first 2 weeks, and the number of administrations of PR-350 was escalated in increments of 10 for successive groups of 6 to 8 new patients to 30 doses over 6 weeks. Dose-limiting toxicities (DLTs) were defined as Grade 4 leucopenia or neutropenia, thrombopenia of <20,000/μL, esophagitis of Grade 4 or more, or other nonhematologic toxicities of Grade 3 or more. When one third or less of 6 to 8 patients showed DLTs, the dosage of PR-350 was raised to the next level.

Venous blood samples were collected before, immediately after, and 1.5, 3, 5, 7, and 24 h after the infusion of PR-350 on the first day and the last day of administration for 4 or 5 patients at each dose level of the Phase I trial and 3 patients in the Phase II trial. PR-350 levels in urine were also measured for 24 h before and after the first infusion, 24 h after the last infusion, and 24–48 h after the last infusion. The concentration of PR-350 in serum and urine samples was analyzed by high-performance liquid chromatography.

Efficacy evaluation

The objectives of this trial were to evaluate a recommended dose of PR-350 in the Phase I portion, and to evaluate the local tumor response rate in the chest (radiation portal), overall survival, and toxicities associated with thoracic RT and PR-350 after induction CT in the Phase I/II portion.

Local tumor response in the radiation portal was evaluated using CT scans obtained at baseline, after each induction CT, at 32 to 40 Gy of thoracic RT, every 4 weeks after the completion of thoracic RT to the 20th week of the RT. Tumor response was determined using World Health Organization Criteria for Reporting Cancer Treatment by extramural evaluation. In this analysis, responses of the two target lesions of primary tumors and mediastinal nodes were evaluated separately. When both target lesions showed a complete response (CR; complete disappearance of all known disease) for more than 4 weeks, local tumor response was scored as CR. On the other hand, when one of the two target lesions showed a partial response (PR; 50% or more decrease in tumor size) for more than 4 weeks and the other target lesion showed CR, PR, or no change (NC; less than 50% decrease, or less than 25% increase in tumor size), local tumor response was scored as PR. When both target lesions showed NC, local tumor response was scored as NC. When one or more target lesions showed progressive disease (PD; a 25% or greater increase in tumor size, or the appearance of new lesions in the radiation portal), local tumor response was scored as PD.

Survival time was defined as the period from the first day of induction CT to death. All patients were followed for a minimum of 24 months. The final date for inclusion of survival data in the analysis was December 1, 2006. Overall survival rates were calculated using the Kaplan-Meier estimates.

RESULTS

Patient characteristics and compliance

A diagram explaining the number of patients enrolled and analyzed is provided in Figure 2. A total of 41 patients with unresectable stage IIIA or IIIB NSCLC from 19 institutions in Japan were enrolled in the first entry from August 2000 to November 2004. During the study period, accrual of patients was stopped several times because of observation period of toxicities for the level I (3 months) and level II (7 months), and revision of the protocol for the Phase II portion (18 months).

Of the 41 patients, 2 patients in the Phase I portion could not enter into the second entry because of bleeding from gastric ulcers during induction CT or withdrawal of consent. In the Phase II portion, 1 patient died of tumor bleeding during induction CT, and induction CT was not indicated for another patient because of glaucoma. Thus, the remaining 37 patients (full analysis set [FAS]) were enrolled into the second entry. Pretreatment characteristics of the FAS are presented in Table 1.

In the first level of the Phase I portion (10 doses of PR-350), DLTs (Grade 3 skin rash and Grade 5 radiation pneumonitis) were noted for 2 patients. In the second level (20 doses), DLT (Grade 5 radiation pneumonitis) was noted for 1 patient. In the third level (30 doses), DLT (Grade 3 skin rash) was noted for 1 patient. Thus, in the Phase II portion (n = 17), PR-350 was administered 30 times.

Thoracic RT was terminated before 60 Gy for 4 of the 37 patients because of progressive disease (n = 2) and pneumonia (n = 2). For 5 patients, full-dose RT of 60 Gy and <70% of the planned PR-350 doses were combined because of acute toxicities (n = 3) or patient refusal of PR-350 (n = 2). For the remaining 28 patients, PR-350 at 70% or more of the planned dose could be combined with thoracic RT of 60 Gy.

Local response and survival

According to the extramural assessments, CR and PR were achieved by 8% (3/37) and 68% (25/37) of patients, respectively. Thus, the overall response rate (CR+PR) was 76% (28/37). The response rate for patients who received PR-350 21 to 30 doses was 89%, whereas that for those who received 2 to 20 doses was 63%. The difference in tumor response was not significant.

Table 1. Patient and tumor characteristics (full analysis set; n = 37)

Gender (men/women)	30/7
Age, y (mean and range)	61.8 (46–74)
PS (0/1)	12/25
Stage (IIIA/IIIB)	8/29
Histology:	
Adenocarcinoma	17
Squamous cell carcinoma	16
Large-cell carcinoma	1
Unclassified carcinoma	3

Figure 3 shows the Kaplan-Meier survival curve for the 37 patients. The median survival time (MST) was 15.9 months, and overall survival rates at 2 and 3 years were 24% and 18%, respectively. The MSTs and survival rates were also analyzed according to clinical stage and actual doses of PR-350. There was no significant difference in the survival rate between stage IIIA (n = 8) and stage IIIB (n = 29). The MST and 2-year survival rate for 18 patients receiving 21 to 30 doses of PR-350 were 20.9 months and 33%, respectively, whereas those for 19 patients who received 2 to 20 doses were 13.7 months and 16%, respectively (Fig. 4a). However, this trend was not observed when compared with their intended prescribed dose (10 and 20 doses vs. 30 doses) of PR-350 (Fig. 4b). The MST and 2-year survival rate for 14 patients enrolled in the 10 and 20 doses levels were 15.9 months and 21%, respectively, whereas those for 19 patients in the 30 doses level were 14.9 months and 26%, respectively.

Toxicities

Tables 2 and 3 show hematologic and nonhematologic toxicities after the second entry, respectively. A major hematologic toxicity for most patients was lymphopenia.

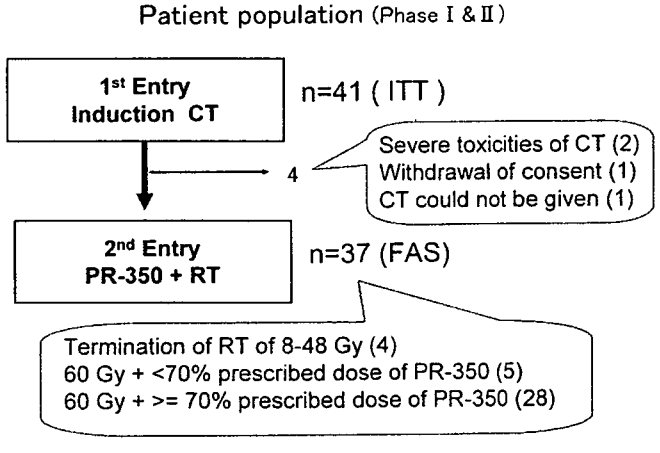

Fig. 2. Patient population in this trial. Of the 41 patients enrolled in the first entry (intention to treat [ITT]), 37 patients were included in the second entry (full analysis set [FAS]).

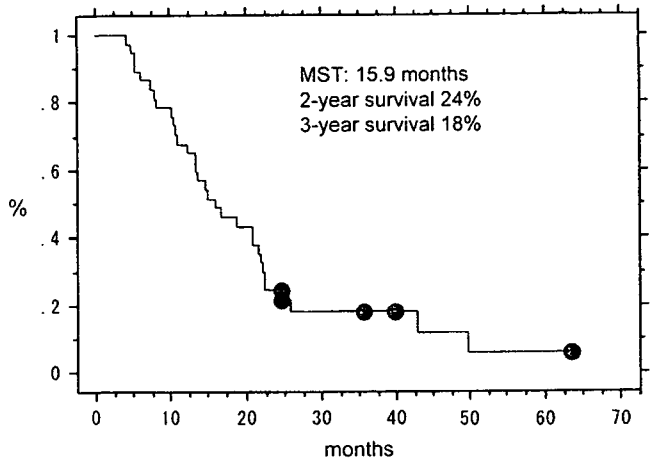

Fig. 3. Overall survival rate for the 37 patients (full analysis set [FAS]). MST = median survival time.

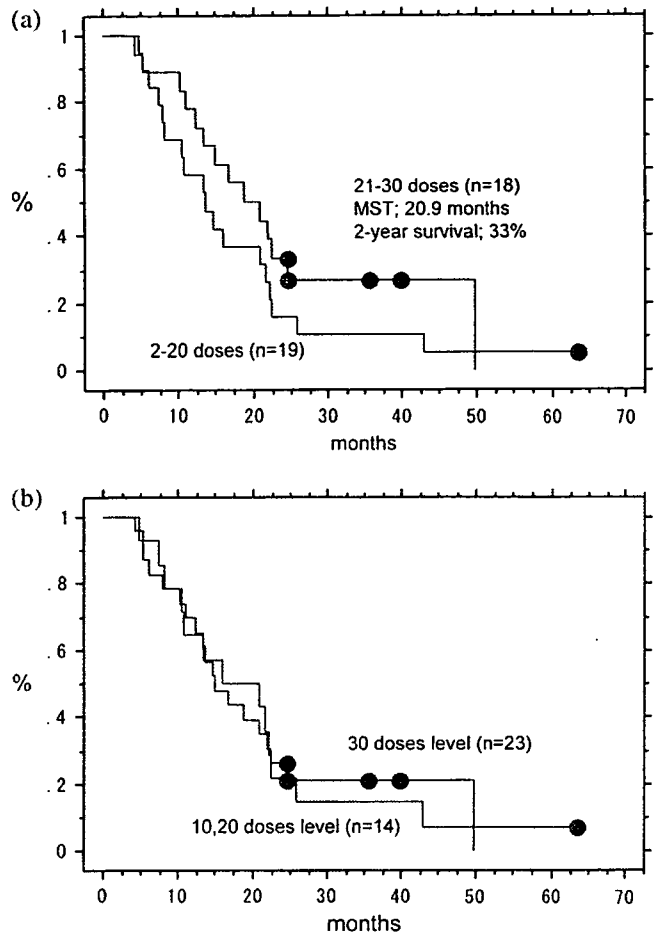

Fig. 4. (a, b) Overall survival rates according to the actual doses of PR-350. No significant difference between the two groups. (b) Overall survival rates according to the intended prescribed doses of PR-350. MST = median survival time.

The incidence of Grade 3 or more lymphopenia was 78%. However, only a few patients showed Grade 3 or more leucopenia or anemia. A major nonhematologic toxicity was radiation pneumonitis, and Grade 3 or more pneumonitis was noted in 6 patients (16%) including the 2 with treatment-related deaths. For 1 of the 2 patients with treatment-related deaths, the initial RT field exceeded one half of the involved lung, which violated the guidelines for RT fields. For the other patient with treatment-related death, extramural review revealed apparent pulmonary fibrosis on his chest radiography before treatment, which was a violation of the eligibility criteria.

Table 2. Hematologic toxicities after the second entry (full analysis set; $n = 37$)

Grade of toxicities	G1	G2	G3 or more
Leukocytes	12 (32%)	9 (24%)	2 (5%)
Lymphopenia	0 (0%)	6 (16%)	29 (78%)
Neutrophils	6 (16%)	9 (24%)	1 (3%)
Hemoglobin	2 (5%)	12 (32%)	3 (8%)
Platelets	11 (30%)	0 (0%)	1 (3%)
AST	9 (24%)	1 (3%)	1 (3%)
ALT	9 (24%)	3 (8%)	2 (5%)
Creatinine	1 (3%)	0 (0%)	0 (0%)

Table 3. Nonhematologic toxicities after the second entry (full analysis set; $n = 37$)

Grade of toxicities	G1	G2	G3 or more
Radiation pneumonitis	7 (19%)	5 (14%)	6* (16%)
Skin rash	5 (14%)	3 (8%)	3 (8%)
Peripheral neuropathy	9 (24%)	0 (0%)	0 (0%)
Radiation dermatitis	18 (49%)	4 (11%)	0 (0%)
Dysphagia/esophagitis	25 (68%)	6 (16%)	0 (0%)
Febrile neutropenia	0 (0%)	0 (0%)	1 (3%)
Edema	3 (8%)	1 (3%)	1 (3%)

* Two patients with treatment-related deaths were included.

During induction CT, Grade 1 or 2 peripheral neuropathy was observed in 26 patients, and at the start of second entry 17 patients (46%) had only Grade 1 peripheral neuropathy. After the second entry, Grade 1 peripheral neuropathy was prolonged for 3 of the 17 patients. Newly developed peripheral neuropathy of Grade 1 was noted in 6 patients. In total, peripheral neuropathy of Grade 1 was noted in 9 patients (24%). Allergic skin rash of Grade 3 or less was observed in 11 patients (30%). Skin rash was seen out of RT field, and scored differently from radiation dermatitis. Notably, no Grade 3 or more esophageal toxicity was noted.

Pharmacokinetic study

Figure 5 shows changes in the serum concentration of PR-350 in the first and the last sessions. After both sessions, PR-350 was rapidly cleared by the kidney, and no accumulation was observed even after the 30th session. Similarly, no cumulative effect was demonstrated after the 10th and 20th sessions (data not shown).

DISCUSSION

In the Phase I portion of this trial, thoracic RT combined with 30 daily administrations of PR-350 at 2000 mg/m^2 after induction CT was well tolerated. As a single dose or five daily doses of PR-350 at 2000 mg/m^2 has been shown to be safe in previous clinical trials (18, 19), dose escalation

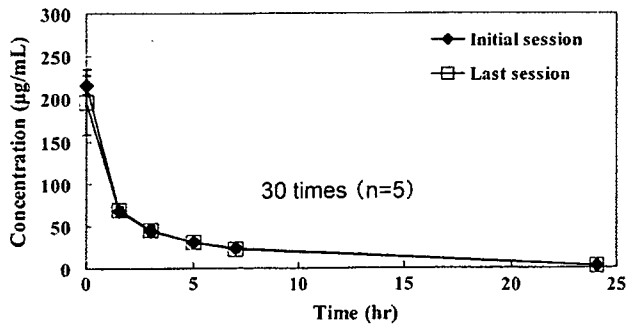

Fig. 5. Changes in serum concentration of PR-350 in the first and the last (30th) session. Means and standard errors are shown. PR-350 was rapidly cleared in both sessions, and no accumulation of PR-350 was observed in the 30th session.

was started from 10 doses of PR-350 in this study. As DLTs, radiation pneumonitis or skin rash of Grade 3 or more was noted in one third or less of 6 to 8 patients at each level, and so 30 daily administrations of PR-350 at 2000 mg/m^2 was determined as the recommended dosage in the Phase II portion of the trial.

A major hematologic toxicity was lymphopenia, although other hematologic toxicities were mild (Table 3). A major nonhematologic toxicity was radiation pneumonitis including two patients with TRD. Grade 3 or higher radiation pneumonitis was observed in 6 patients (16%). A similar rate of radiation pneumonitis is reported by a retrospective study at the National Cancer Center Hospital in Japan (20). In that analysis, severe radiation pneumonitis of Grade 3 or more was noted in 13% of 191 patients with lung cancer treated by CRT or RT alone between 1988 and 1998 (20). On the other hand, a less than 2% incidence of Grade 3 or higher pulmonary toxicity was reported for both sequential and concurrent CRT groups in a Japanese Phase III trial for locally advanced NSCLC using the same eligibility criterion on RT fields (6). It is unclear why pulmonary toxicity in the trial was so low. However the low total RT dose of 56 Gy may have contributed to that.

Because 3D RT planning was not available, it was impossible to correlate toxicity parameters with dose–volume histogram (DVH) information in this study. Although it can not be excluded that PR-350 enhances the effects of radiation on normal lung tissues, we consider that the relatively high incidence of radiation pneumonitis is attributable to our former two-dimensional RT technique. Extramural review of RT films revealed that two TRDs might have been attributable to a violation of protocol guidelines for RT fields or a violation of eligibility criteria on pulmonary disease. To evaluate the effect of PR-350 on radiation pneumonitis, an additional Phase II trial with a three-dimensional RT method may be required.

Neither Grade 3 or more esophageal toxicity, nor Grade 2 or more peripheral neuropathy, was noted. In the PK study, no accumulative effect was observed even after the 30th dose (Fig. 5). The major limitation of 2-nitroimidazoles including misonidazole and ethanidazole is neuropathy (10–12, 21, 22). For head-and-neck cancer, randomized clinical trials comparing RT plus ethanidazole and RT alone have been reported (21, 22). In these trials, ethanidazole at 2000 mg/m^2 given three times weekly for 17 doses was combined with RT, and peripheral neuropathy of Grade 1 to 3 was noted in 24% to 28% of patients. In the present trial, PR-350 at 2000 mg/m^2 was given five times weekly for 10 to 30 doses, and only peripheral neuropathy of Grade 1 was noted in 24% of patients. Thus, PR-350 is apparently less neurotoxic than ethanidazole.

The overall response rate in the RT field was 76% (28/37). For patients who received 21 to 30 doses of PR-350, the overall response rate was as high as 89%. The MST and 2-year survival rate for FAS were 15.9 months and 24%, respectively. This result is well in the range of values for sequential CRT for locally advanced NSCLC (3, 6, 7). In the FAS, patients treated with suboptimal doses of PR-350 (10 or 20 doses) were included in the Phase I portion. Although the analysis according to the intended prescribed doses of PR-350 did not show the difference in survival rate (Fig. 4b), the MST and 2-year survival rate for 18 patients actually receiving 21 to 30 doses of PR-350 were 20.9 months and 33%, respectively (Fig. 4a). These values are well compatible with those for concurrent CRT (6, 7). This Phase II result is promising because a survival rate similar to that for concurrent CRT was obtained by daily administration of PR-350 with an incidence of acute toxicities as low as that for sequential CRT.

At present, concurrent CRT is the standard treatment for locally advanced NSCLC. However, acute toxicities are inevitably more common during concurrent CRT (4–7). So, concurrent CRT is not recommended for elderly patients or patients with a poor performance status. The low incidence of hematologic toxicities and radiation esophagitis in this study has special significance for these patients. The results of this Phase I/II study support the hypothesis that adding PR-350 to sequential CRT may decrease the rate of local recurrence without a significant increase in toxicity. Similarly, a promising clinical result obtained by adding a radiosensitizer, efaproxiral, to sequential CRT has been reported (23). Therefore, the present strategy of sequential CRT combined with PR-350 is a promising approach for locally advanced NSCLC, and a randomized study should be pursued. Furthermore, PR-350 may also be an ideal candidate for incorporation into concurrent CRT, as it could potentially increase the efficacy of concurrent CRT without increasing the toxicities.

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Short Communication

Randomised phase II trial of irinotecan plus cisplatin *vs* irinotecan, cisplatin plus etoposide repeated every 3 weeks in patients with extensive-disease small-cell lung cancer

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Patients with previously untreated extensive-disease small-cell lung cancer were treated with irinotecan 60 mg m^{-2} on days 1 and 8 and cisplatin 60 mg m^{-2} on day 1 with ($n=55$) or without ($n=54$) etoposide 50 mg m^{-2} on days 1–3 with granulocyte colony-stimulating factor support repeated every 3 weeks for four cycles. The triplet regimen was too toxic to be considered for further studies.

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Keywords: small-cell lung cancer; chemotherapy; irinotecan; etoposide; three drug combination

Small-cell lung cancer (SCLC), which accounts for approximately 14% of all malignant pulmonary tumours, is an aggressive malignancy with a propensity for rapid growth and early widespread metastases (Jackman and Johnson, 2005). A combination of cisplatin and etoposide (PE) has been the standard treatment, with response rates ranging from 60 to 90% and median survival times (MSTs) from 8 to 11 months in patients with extensive disease (ED)-SCLC (Fukuoka *et al*, 1991; Roth *et al*, 1992). A combination of irinotecan and cisplatin (IP) showed a significant survival benefit over the PE regimen (MST: 12.8 *vs* 9.4 months, $P=0.002$) in a Japanese phase III trial for ED-SCLC (Noda *et al*, 2002), although another phase III trial comparing these regimens failed to show such a benefit (Hanna *et al*, 2006). Thus, irinotecan, cisplatin and etoposide are the current key agents in the treatment of SCLC. A phase II trial of the three agents, IPE combination, in patients with ED-SCLC showed a promising antitumour activity with a response rate of 77%, complete response (CR) rate of 17% and MST of 12.9 months (Sekine *et al*, 2003).

We have developed these IP and IPE regimens in a 4-week schedule where irinotecan was given on days 1, 8 and 15. The dose of irinotecan on day 15, however, was frequently omitted because of toxicity in both regimens (Noda *et al*, 2002; Sekine *et al*, 2003).

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The objectives of this study were to evaluate the toxicities and antitumour effects of IP and IPE regimens in the 3-week schedule in patients with ED-SCLC and to select the right arm for subsequent phase III trials.

PATIENTS AND METHODS

Patient selection

Patients were enrolled in this study if they met the following criteria: (1) a histological or cytological diagnosis of SCLC; (2) no prior treatment; (3) measurable disease; (4) ED, defined as having distant metastasis or contralateral hilar lymph node metastasis; (5) performance status of 0–2 on the Eastern Cooperative Oncology Group (ECOG) scale; (6) predicted life expectancy of 3 months or longer; (7) age between 20 and 70 years; (8) adequate organ function as documented by a white blood cell (WBC) count $\geqslant 4.0\times10^3\,\mu l^{-1}$, neutrophil count $\geqslant 2.0\times10^3\,\mu l^{-1}$, haemoglobin $\geqslant 9.5\,g\,dl^{-1}$, platelet count $\geqslant 100\times10^3\,\mu l^{-1}$, total serum bilirubin $\leqslant 1.5\,mg\,dl^{-1}$, hepatic transaminases $\leqslant 100\,IU\,l^{-1}$, serum creatinine $\leqslant 1.2\,mg\,dl^{-1}$, creatinine clearance $\geqslant 60\,ml\,min^{-1}$, and $PaO_2\geqslant 60$ torr; and (9) providing written informed consent.

Patients were not eligible for the study if they had any of the following: (1) uncontrollable pleural, pericardial effusion or ascites; (2) symptomatic brain metastasis; (3) active infection; (4) contraindications for the use of irinotecan, including diarrhoea, ileus, interstitial pneumonitis and lung fibrosis; (5) synchronous active malignancies; (6) serious concomitant medical

illness, including severe heart disease, uncontrollable diabetes mellitus or hypertension; or (7) pregnancy or breast feeding.

Treatment schedule

In the IP arm, cisplatin, 60 mg m^{-2}, was administered intravenously over 60 min on day 1 and irinotecan, 60 mg m^{-2}, was administered intravenously over 90 min on days 1 and 8. Prophylactic granulocyte colony-stimulating factor (G-CSF) was not administered in this arm. In the IPE arm, cisplatin and irinotecan were administered at the same dose and schedule as the IP arm. In addition, etoposide, 50 mg m^{-2}, was administered intravenously over 60 min on days 1–3. Filgrastim 50 μg m^{-2} or lenograstim 2 μg kg^{-1} was subcutaneously injected prophylactically from day 5 to the day when the WBC count exceeded 10.0×10^3 μl^{-1}. Hydration (2500 ml) and a $5HT_3$ antagonist were given on day 1, followed by an additional infusion if indicated in both arms. These treatments were repeated every 3 weeks for a total of four cycles.

Toxicity assessment, treatment modification and response evaluation

Toxicity was graded according to the NCI Common Toxicity Criteria version 2.0.

Doses of anticancer agents in the following cycles were modified according to toxicity in the same manner in both arms. Objective tumour response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) (Therasse *et al*, 2000).

Study design, data management and statistical considerations

This study was designed as a multi-institutional, prospective randomised phase II trial. This study was registered on 6 September 2005 in the University hospital Medical Information Network (UMIN) Clinical Trials Registry in Japan (http://www.umin.ac.jp/ctr/index.htm), which is acceptable to the International Committee of Medical Journal Editors (ICMJE) (http://www.icmje.org/faq.pdf). The protocol and consent form were approved by the Institutional Review Board of each institution. Patient registration and randomisation were conducted at the Registration Center. No stratification for randomisation was performed in this study. The sample size was calculated according to the selection design for pilot studies based on survival (Liu *et al*, 1993). Assuming that (1) the survival curve was exponential for survivals; (2) the MST of the worse arm was 12 months and that of the better arm was 12 months × 1.4; (3) the correct selection probability was 90%; and (4) additional follow-up in years after the end of accrual was 1 year, the estimated required number of patients was 51 for each arm. Accordingly, 55 patients for each arm and their accrual period of 24 months were planned for this study.

The dose intensity of each drug was calculated for each patient using the following formula as previously described:

$$\text{The dose intensity (mg m}^{-2}\text{ week}^{-1}\text{)} = \frac{\text{Total milligrams of a drug in all cycles per body surface area}}{\text{Total days of therapy}/7}$$

where total days of therapy is the number of days from day 1 of cycle 1 to day 1 of the last cycle plus 21 days for both arms (Hryniuk and Goodyear, 1990).

Differences in the reason for termination of the treatment and the frequencies of grade 3–4 toxicities were assessed by χ tests. Survival was measured as the date of randomisation to the date of death from any cause or the date of the most recent follow-up for overall survival and to the date of disease progression or the date of death for progression-free survival (PFS). The survival of the arms was estimated by the Kaplan–Meier method and compared in an exploratory manner with log-rank tests (Armitage *et al*, 2002).

RESULTS

Patient characteristics

From March 2003 to May 2005, 55 patients were randomised to IP and 55 patients to IPE. One patient in the IP arm was excluded because the patient was ineligible and did not receive the study treatment. The remaining 109 patients were included in the analyses of toxicity, tumour response and patient survival. There were no differences between the two arms in any demographic characteristics listed (Table 1).

Treatment delivery

Treatment was well tolerated with respect to the number of cycles delivered in both arms (Table 2). Among reasons for termination of the treatment, disease progression was noted in nine (17%)

Table 1 Patient characteristics

	IP ($n=54$)	IPE ($n=55$)
Sex		
Female	11	8
Male	43	47
Age (years)		
Median (range)	63 (42–70)	62 (48–70)
PS		
0	11	12
1	42	41
2	1	2
Weight loss		
0–4%	38	43
5–9%	10	10
⩾10%	6	2

Table 2 Treatment delivery

	IP ($n=54$) No. (%)	IPE ($n=55$) No. (%)
Number of cycles delivered		
6[a]	—	1 (2)
4	41 (76)	36 (65)
3	6 (11)	6 (11)
2	3 (6)	6 (11)
1	4 (7)	6 (11)
Reasons for termination of the treatment[†]		
Completion	40 (74)	35 (64)
Disease progression	9 (17)	2 (4)
Toxicity	3 (6)	13 (24)
Patient refusal	2 (4)	4 (7)
Others	0 (0)	1 (2)
Total number of cycles delivered	192 (100)	186 (100)
Total number of omission on day 8	35 (18)	37 (17)
Total number of cycles with dose reduction	28 (15)	31 (17)

[†]$P=0.013$ by χ^2 test. [a]Protocol violation.

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patients in the IP arm and in two (4%) patients in the IPE arm, whereas toxicity was noted in three (6%) patients in the IP arm and 13 (24%) patients in the IPE arm ($P=0.013$) (Table 2). The dose of irinotecan on day 8 was omitted in 35 (18%) cycles in the IP arm and 37 (17%) cycles in the IPE arm (Table 2). The total dose and dose intensity of cisplatin and etoposide were similar between the IP and IPE arms in the present study (Table 3).

Toxicity

The myelotoxicity was more severe in the IPE arm (Table 4). Grade 3 febrile neutropaenia was noted in 5 (9%) patients in the IP arm and 17 (31%) patients in the IPE arm ($P=0.005$). Packed red blood cells were transfused in 4 (7%) patients in the IP regimen and 14 (26%) patients in the IPE regimen ($P=0.011$). Platelet concentrates were needed in none in the IP regimen and 2 (4%) patients in the IPE regimen ($P=0.16$). Grade 3–4 diarrhoea was observed in 8 (15%) patients in the IP arm and 13 (24%) patients in the IPE arm ($P=0.262$). Grade 3–4 fatigue was more common in the IPE arm with marginal significance (2 *vs* 11%, $P=0.054$). The severity of other non-haematological toxicities did not differ significantly between the arms. No treatment-related death was observed in this study.

Table 3 Total dose and dose intensity

	3-week regimens in this study		4-week regimen[a]
	IP ($n=54$) Median (range)	**IPE ($n=55$) Median (range)**	**IPE ($n=30$) Median (range)**
Total dose ($mg\,m^{-2}$)			
Cisplatin	240 (60–240)	240 (60–360)	240 (60–240)
Irinotecan	420 (60–480)	390 (60–720)	563 (60–720)
Etoposide	0	600 (150–900)	600 (150–600)
Dose intensity ($mg\,m^{-2}\,week^{-1}$)			
Cisplatin	19 (14–25)	20 (16–34)	15 (12–15)
Irinotecan	33 (14–40)	35 (15–55)	35 (19–45)
Etoposide	0	48 (34–68)	37 (28–38)

[a]From our previous study (Sekine *et al*, 2003).

Table 4 Grade 3–4 toxicities

	IP ($n=54$)			IPE ($n=55$)		
	Grade 3	**4**	**3+4 (%)**	**Grade 3**	**4**	**3+4 (%)**
Leukocytopaenia	9	1	10 (19)	18	11	29 (53)*
Neutropaenia	17	11	28 (52)	24	28	52 (95)*
Anaemia	18	0	18 (25)	16	9	25 (45)
Thrombocytopaenia	2	0	2 (4)	13	0	13 (13)†
Febrile neutropaenia	5	0	5 (9)	17	0	7 (13)
Diarrhoea	8	0	8 (15)	11	2	13 (24)
Vomiting	4	0	4 (7)	3	0	3 (5)
Fatigue	1	0	1 (2)	5	1	6 (11)‡
Hyponatraemia	9	3	12 (22)	11	2	13 (24)
AST elevation	0	0	0 (0)	3	0	3 (5)
CRN elevation	1	0	1 (2)	0	0	0 (0)

*$P<0.001$; †$P<0.01$; and ‡$P=0.054$ by χ^2 test.

Response, treatment after recurrence and survival

Four CRs and 37 partial responses (PRs) were obtained in the IP arm, resulting in the overall response rate of 76 with 95% confidence interval (CI) of 65–87%, whereas six CRs and 42 PRs were obtained in the IPE arm, and the overall response rate was 87% with a 95% CI of 79–96% ($P=0.126$). Median PFS was 4.8 months (95% CI, 4.0–5.6) in the IP and 5.4 months (95% CI, 4.8–6.0) in the IPE arm ($P=0.049$) (Figure 1A). After recurrence, 22 (44%) patients in the IP arm and 8 (16%) patients in the IPE arm received etoposide-containing chemotherapy. The MST and 1-year survival rate were 12.4 months (95% CI, 9.7–15.1) and 54.8% (95% CI, 41.4–68.2%) in the IP and 13.7 months (95% CI, 11.9–15.5) and 61.5% (95% CI, 48.6–74.4%) in the IPE arm ($P=0.52$), respectively (Figure 1B).

DISCUSSION

This study showed that the IPE regimen in a 3-week schedule with CSF support produced a promising response rate, PFS and overall survival. Haematological toxicity in the IPE arm, however, was very severe in spite of the G-CSF support with the grade 3 febrile neutropaenia noted in 31% of patients.

In comparison between the 3-week IPE regimen in this study and the 4-week IPE regimen in the previous study, the delivery of cisplatin and etoposide was improved in the 3-week IPE regimen when compared with the 4-week IPE regimen at the cost of the irinotecan total dose. The response rate and MST were 87% and 13.7 months, respectively, in the 3-week IPE regimen and 77% and 12.9 months in the previous 4-week schedule, and toxicity profiles were comparable to each other (Sekine *et al*, 2003).

The MST of 12.4 months in the IP arm in this study was comparable to that of the previous phase III study, with an MST of 12.8 months (Noda *et al*, 2002). Thus, this study showed the reproducible excellent survival outcome of patients with ED-SCLC who were treated with the IP combination. In contrast, a recent American phase III study of the PE regimen *vs* IP regimen failed to show the superiority of the IP regimen to the PE regimen; the MST

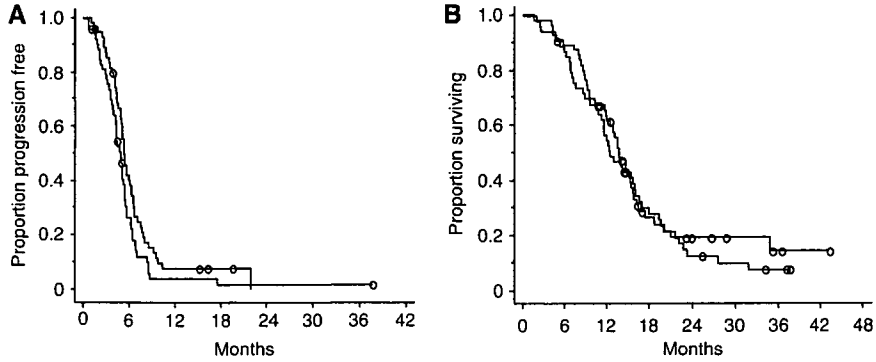

Figure 1 Progression-free survival (**A**) and overall survival (**B**). Thick line indicates the IPE regimen and thin line indicates the IP regimen.

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