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Once-Weekly Epoetin-Beta Improves Hemoglobin Levels in Cancer Patients with Chemotherapy-Induced Anemia: A Randomized, Double-Blind, Dose-Finding Study

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Objective: To determine a recommended dose of once-weekly epoetin-beta administration for anemic cancer patients receiving myelosuppressive chemotherapy, we conducted a multicenter, randomized, double-blind trial.

Methods: A total of 86 patients with malignant lymphoma or lung cancer who received chemotherapy containing platinum, taxanes or anthracyclines were enrolled in the study. Patients were randomly assigned into groups that received three dose levels of epoetin-beta (9000, 18 000 or 36 000 IU) administered subcutaneously once a week for 12 weeks. The primary endpoint was change in hemoglobin, while the secondary endpoints were quality of life (QOL) assessed by Functional Assessment of Cancer Therapy-Anemia (FACT-An) questionnaire and transfusion requirements.

Results: Among the 69 patients (per protocol set population) assessable for efficacy, hemoglobin level change in the 36 000 IU group was significantly greater than that in the 9000 IU group (1.75 ± 2.15 versus 0.04 ± 1.98 g/dl; $P = 0.009$), and a significant dose–response relationship was observed for the change in hemoglobin level ($P = 0.003$). Although changes in FACT-An Total Fatigue subscale (Fatigue subscale) scores were similar for the three dosage groups, there was a statistically significant correlation ($r = 0.435$, $P < 0.001$) between the change in hemoglobin levels and the change in Fatigue subscale scores. The proportion of transfused patients was significantly smaller in the 36 000 IU group compared with that in the 9000 IU group ($P = 0.022$, not adjusted for pre-study transfusions). The incidence of adverse events was similar in the three dosage groups.

Conclusions: Once-weekly epoetin-beta 36 000 IU for 12 weeks was well tolerated and significantly increased hemoglobin levels in anemic cancer patients receiving chemotherapy.

Key words: chemotherapy-induced anemia – erythropoietin – lung cancer – malignant lymphoma – quality of life

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INTRODUCTION

Erythropoietin (EPO) is a glycoprotein (MW 30 000) which is the hematologic growth factor produced primarily in the kidney. EPO interacts with erythroid progenitor cells in the bone marrow to increase the peripheral red blood cells (1). Epoetin-beta is recombinant human erythropoietin (rhEPO) (2), which was introduced clinically in the 1990s for the treatment of anemia associated with chronic renal failure, especially in patients receiving hemodialysis.

Cancer patients treated with chemotherapy often suffer from anemia, which is a major contributing factor to fatigue leading to compromised quality of life (QOL) (3,4). In addition, the presence of anemia is associated with shorter survival of patients with malignancies (5). Red blood cell transfusion is the traditional and quickest method of alleviating symptoms of cancer-related anemia. However, the side effects of transfusion such as viral infections have not been completely resolved. Patients tend to decline transfusions, and physicians do not prescribe them in most cases until the hemoglobin levels become <8.0 g/dl. The administration of rhEPO is another choice for the treatment of chemotherapy-inducted anemia. Numerous studies on anemic cancer patients receiving chemotherapy have demonstrated that rhEPO increased hemoglobin levels and reduced the need for transfusions, and some studies reported improvements in QOL as well (6–11). The schedule of rhEPO administration in most trials was three-times per week. This schedule is inconvenient for outpatients receiving chemotherapy. Gabrilove et al. (10) studied a weekly fixed-dose schedule using 40 000–60 000 IU of epoetin-alfa in cancer patients with anemia. The efficacy was comparable with data on the historical regimen of 10 000 IU three-times weekly. Cazzola et al. (12) compared the efficacy and tolerability of epoetin-beta 30 000 IU once-weekly with that of a 10 000 IU three-times weekly regimen in patients with lymphoproliferative malignancies. Their study showed that the once-weekly regimen was as effective as the three-times weekly one in increasing hemoglobin levels and reducing transfusion requirements.

We therefore conducted a multicenter, randomized, double-blind, dose-finding trial of once-weekly epoetin-beta treatment of malignant lymphoma and lung cancer patients receiving platinum-, taxane- or anthracycline-containing chemotherapy. These chemotherapy regimens are the most active and frequently used for the treatment of these malignancies and also produce relatively high incidences of anemia (4). According to the results of this trial, a recommended dose of epoetin-beta was determined for the subsequent randomized placebo-controlled phase III trial in Japan.

PATIENTS AND METHODS

Patient Eligibility

Patients with histologically or cytologically confirmed malignant lymphoma or lung cancer fulfilling the following criteria were enrolled in the study. (i) Age 20–79 years; (ii) Either platinum-, taxane- or anthracycline-based chemotherapy was administered, and more than 2 courses of chemotherapy were scheduled during the study (radiotherapy during the study period was permitted); (iii) Hemoglobin $\leq$ 11 g/dl after chemotherapy administered within 6 weeks before the study, without iron-deficiencies; (iv) Adequate hepatic and renal function (serum total bilirubin $\leq$ 2.0 mg/dl; serum AST $\leq$ 80 IU/l; serum ALT $\leq$ 80 IU/l; serum creatinine < 2.0 mg/dl); (v) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; (vi) Life expectancy of at least 12 weeks. Exclusion criteria included uncontrolled hypertension, gastrointestinal bleeding, and a known history of myocardial infarction, cerebral infarction or pulmonary embolism. Patients with known hypersensitivity to rhEPO and previous treatment with rhEPO within 4 weeks before the study were also excluded. Female patients who were pregnant were not eligible. Written informed consent was obtained from all patients before entry into the study.

Study Design and Treatment Schedule

This study was a multicenter, randomized, double-blind, parallel-group comparative trial. The study protocol was approved by the institutional review board for each of the 11 participating centers in Japan. Epoetin-beta was supplied by Chugai Pharmaceutical Co., LTD (Tokyo, Japan).

Enrolled patients were randomly assigned to receive one of the three dose levels of epoetin-beta (9000, 18 000, or 36 000 IU). Randomization was prospectively stratified according to age, PS, disease (lung cancer or malignant lymphoma) and institution. Subcutaneous injection of epoetin-beta was started at the beginning of the subsequent chemotherapy course and continued, thereafter, once a week for 12 weeks. If the hemoglobin level increased to more than 14 g/dl, epoetin-beta was discontinued until the hemoglobin level decreased to <12 g/dl, and then re-administered at the same dose. An oral iron supplementation (200 mg/day) was taken daily during the study period. No specific guidelines for transfusion use were defined.

Assessment of Efficacy and Safety

The primary end point was change in hemoglobin level, and the secondary end points were QOL and red blood cell transfusion requirements. The change in hemoglobin between the baseline and 12 weeks of administration or the last observation was evaluated. If chemotherapy was discontinued within the 12-week period, the change in hemoglobin was evaluated at the last observation; 4 weeks after the beginning of a final-course of chemotherapy. The QOL instrument used in the study was the Functional Assessment of Cancer Therapy-Anemia (FACT-An) questionnaire (13). The Total Fatigue subscale (Fatigue subscale), which consists of 13 items from FACT-An, was mainly analyzed (scores range from 0 to 52). QOL was measured at the baseline, at 7–11 weeks; at the beginning of a chemotherapy course and at 12 weeks after the initiation of epoetin-beta administration.

Adverse events were graded according to the NCI-Common Toxicity Criteria version 2.0 (Japanese edition; Japan Clinical Oncology Group version 1).

Statistical Analysis

Of the enrolled patients, those who received epoetin-beta at least once were included in the safety analysis. For efficacy analysis, the per protocol set (PPS) population was defined as eligible patients who received epoetin-beta without protocol violation. Differences in mean changes in hemoglobin between the groups were assessed by Dunnett's multivariate comparison test (14). Changes in the Fatigue subscale scores were compared by using a *t*-test. Pearson's correlation coefficient was calculated to assess the relationship between change in hemoglobin and change in the Fatigue subscale scores. The potential factors influencing the change in the Fatigue subscale scores were examined by multiple regression analysis.

To determine the required number of patients, Dunnett's multiple comparison test was conducted with the 9000 IU group as the control arm. At 2.0 g/dl of the change in hemoglobin from baseline and with a 1.8 g/dl standard deviation between the 9000 and 36 000 IU groups, the required number of patients was calculated to be 21 per group; this means that 63 in total (two-tailed significance level: 5.0%; power: 90%). In the study, it was planned to use the PPS as the main analysis for efficacy; therefore, the target number of subjects was established as 84 to allow for patient dropout.

RESULTS

Patient Characteristics

A total of 86 patients were enrolled between April 2002 and January 2003, and 83 patients were administered epoetin-beta. All of these 83 patients were eligible for the assessment of safety. For efficacy analysis, 14 patients were then excluded; 13 patients received <7 doses of epoetin-beta with or without <2 courses of chemotherapy mainly due to progression of the disease; and one patient lacked the baseline hemoglobin data. So 69 patients comprised the PPS population evaluated for efficacy. Baseline characteristics of the patients in the PPS population were generally well balanced among the three dosage groups (Table 1), except for transfusion requirements within 4 weeks before the study; in the 9000 IU group, more patients had required transfusions ($P = 0.130$). Table 2 shows the distribution of chemotherapy regimens used during the study.

Hemoglobin Response

Figure 1 shows the mean weekly hemoglobin levels over the 12 weeks of the study for the patients in the PPS population. In the 36 000 IU group, the mean hemoglobin level increased significantly starting from 6 weeks. In contrast, in the 9000 IU group, the mean hemoglobin levels changed little during the study period, despite a higher transfusion rate. The mean changes in hemoglobin level from baseline to last observation for the three dosage groups were summarized in Fig. 2. In 36 000 IU group, a significantly greater increase in the hemoglobin level was observed compared with that in 9000 IU group ($P = 0.009$); however, there was no significant difference between the 18 000 and 9000 IU groups ($P = 0.154$). A significant dose–response relationship for the change in hemoglobin level was observed ($P = 0.003$). As an additional evaluation of efficacy, the proportion of patients who achieved a $\geq$2 g/dl increase in hemoglobin level during the study was determined. The results were 40.9% (9/22), 66.7% (16/24) and 78.3% (18/23) in the 9000 IU group, 18 000 IU group and 36 000 IU group, respectively. Epoetin-beta was withheld from 16 patients (one patient in 9000 IU, 8 in 18 000 IU and 7 in 36 000 IU) during the study period, whose hemoglobin levels exceeded 14 g/dl.

Red Blood Cell Transfusion Requirements

Five of 22 patients (22.7%) were transfused in the 9000 IU group, 4 of 24 patients (16.7%) in the 18 000 IU group and none of 23 patients in the 36 000 IU group. The proportion of transfused patients was significantly smaller in the 36 000 IU group compared with that in the 9000 IU group ($P = 0.022$). When patients who had received transfusions within 4 weeks before the study were excluded from the analysis; however, there was no significant difference between the three dosage groups.

QOL

Of the PPS population, 69 patients (100%) at baseline, 62 (89.9%) at 7–11 weeks and 61 (88.4%) at 12 weeks were evaluated for QOL scores. No significant mean change in Fatigue subscale scores was observed in any group at 7–11 weeks and 12 weeks. The relationship between change in hemoglobin level and change in the Fatigue subscale score was examined by correlation analysis. There was a statistically significant correlation ($r = 0.435$, $P < 0.001$) between change in hemoglobin levels and change in the Fatigue subscale scores at 7–11 weeks (Fig. 3). Multiple regression analysis was then performed to assess the potential factors contributing to the change in the Fatigue subscale score at 7–11 weeks. The Fatigue subscale score at baseline and change in hemoglobin level were significantly associated with the change in the Fatigue subscale score ($P = 0.001$). Association with other factors such as the weekly dose of epoetin-beta and chemotherapy regimens were not significantly associated. Patients who achieved an increase in hemoglobin of $\geq$2 g/dl at 7–11 weeks had significant improvements in their Fatigue subscale scores ($P = 0.012$) (Fig. 4).

Safety

The incidence of adverse events was generally similar between the three dosage groups (Table 3). As hematological adverse events, most common were leukocytopenia, neutropenia and thrombocytopenia. As non-hematological adverse events, nausea and appetite loss were commonly observed. One patient

Table 1. Patient characteristics by epoetin-beta dosage group

Patent population	Epoetin-beta dosage groups			
	9000 IU	18 000 IU	36 000 IU	
Randomly assigned patients (*n*)	28	29	29	
Patients evaluated for safety (*n*)	28	27	28	
Patients evaluated for efficacy (PPS) (*n*)	22	24	23	
Characteristic	9000 IU (*n* = 22)	18 000 IU (*n* = 24)	36 000 IU (*n* = 23)	*P*
Age (year)				
Mean ± SD	60.5 ± 16.6	63.0 ± 11.9	61.9 ± 11.7	0.828
Min–Max	22–79	31–76	34–77	
Weight (kg)				
Mean ± SD	53.5 ± 8.7	50.9 ± 7.3	55.1 ± 11.5	0.316
Min–Max	36.1–69	38.8–66.9	34.8–87.5	
Sex male/female (*n*)	13/9	13/11	14/9	0.890
Disease				
Lung cancer (*n*)	11	13	11	0.907
Malignant lymphoma (*n*)	11	11	12	
de novo/relapse (*n*)	17/5	19/5	18/5	0.988
Performance Status 0/1/2 (*n*)	10/11/1	11/12/1	10/12/1	1.000
RBC transfusion before the study (*n*)	5	2	1	0.130
Hemoglobin (g/dl)				
Mean ± SD	10.1 ± 1.3	10.0 ± 1.5	10.2 ± 1.0	0.914
Min–Max	7.4–12.2	7.4–13.2	8.1–11.7	
Serum EPO concentration (mIU/ml)				
Mean ± SD	43.3 ± 38.1	46.8 ± 43.9	30.4 ± 18.4	0.259
Min–Max	13.1–173	14.4–170	7.0–103	
Serum transferrin saturation (%)				
Mean ± SD	31.1 ± 15.9	25.4 ± 11.5	25.5 ± 13.8	0.287
Min–Max	9.4–77.8	10.1–48.0	6.9–77.4	

SD, standard deviation; Min, minimum; Max, maximum; RBC, red blood cell; EPO, erythropoietin.

in the 36 000 IU group experienced deep vein thrombosis, which was evaluated as unrelated to epoetin-beta. When the thrombosis was found, anemia had not improved (baseline hemoglobin level was 9.9 g/dl and that at the onset of thrombosis was 9.2 g/dl); therefore, deep vein thrombosis was considered to be due to prolonged immobility brought on by aggravated malignant lymphoma and PS.

Severe adverse events were reported for 12 patients and were judged by the investigators as unrelated to the administration of epoetin-beta. Of the adverse events, 65 events in 23 patients (27.7%) were considered related to epoetin-beta. The incidence of these events was similar between the three dosage groups (Table 3). An increase of serum ALT was observed in one patient (3.6%) in the 9000 IU group, two (7.4%) in the 18 000 IU group and two (7.1%) in the 36 000 IU group. Hypertension or an increase of blood pressure was observed in one patient (3.6%) in the 9000 IU group, three (11.1%) in the 18 000 IU group and one (3.6%) in the 36 000 IU group. Drug administration was discontinued in one of these patients due to hypertension. No tendency was found in the onset time of hypertension, nor in changes of hemoglobin from baseline at the time hypertension occurred.

Anti-erythropoietin antibody was not detected in any patient, but pure red cell aplasia (PRCA) was reported in one malignant lymphoma (Angioimmunoblastic T-cell Lymphoma) patient over a year after this trial. In this patient, neutralizing anti-erythropoietin antibody was not detected even after PRCA was diagnosed.

Table 2. Chemotherapy regimens used by PPS population during the study

Chemotherapy regimens	Epoetin-beta dosage groups		
	9000 IU (n = 22)	18 000 IU (n = 24)	36 000 IU (n = 23)
Malignant lymphoma			
(R)CHOP	5	6	9
(R)EPOCH	2	3	2
ESHAP	0	2	0
Other regimens	4	0	1
Lung cancer			
Platinum + Paclitaxel	4	2	2
Platinum + Irinotecan	1	4	3
Platinum + Etoposide	3	2	1
Platinum + Vinorelbine	1	2	1
Other regimens	2	3	4

PPS, Per Protocol Set; (R)CHOP, (Rituximab) + Cyclophosphamide + Doxorubicin + Vincristine + Prednisolone; (R)EPOCH, (Rituximab) + Etoposide + Doxorubicin + Vincristine + Cyclophosphamide + Prednisolone; ESHAP, Etoposide + Methylprednisolone + High Dose Ara C (Cytarabine) + Cisplatin.

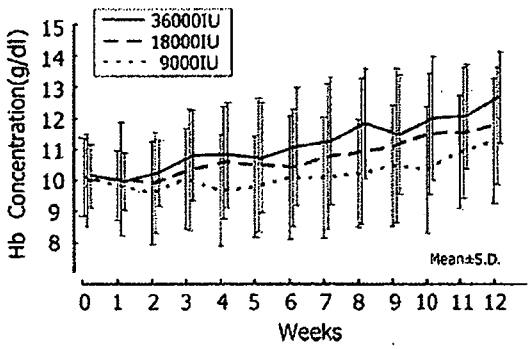

Figure 1. Mean weekly hemoglobin levels for Per Protocol Set population by epoetin-beta dosage Group. Hb, hemoglobin; SD, standard deviation.

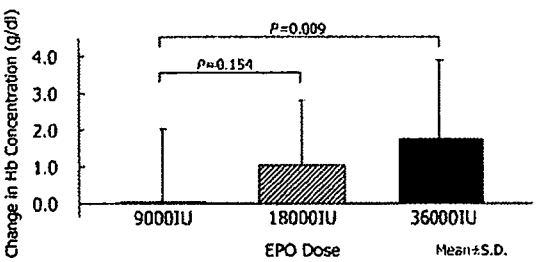

Figure 2. Mean change in hemoglobin level from baseline to last observation (at 12 weeks or 4 weeks after the beginning of a final-course of chemotherapy) by epoetin-beta dosage group (Per Protocol Set population). Hb, hemoglobin; EPO, epoetin-beta; SD, standard deviation.

DISCUSSION

Recently, results of several clinical studies have demonstrated the efficacy and safety of weekly rhEPO for the treatment of cancer-related anemia (10,12,15,16). In a large,

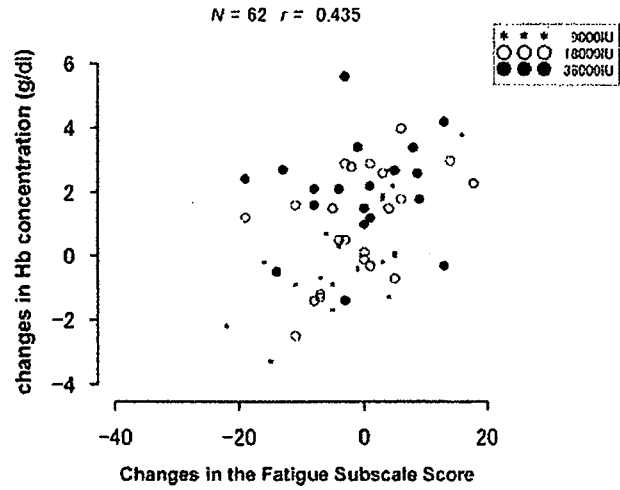

Figure 3. Correlation between change in hemoglobin levels and change in the Functional Assessment of Cancer Therapy—Anemia total Fatigue subscale scores at 7–11 weeks (Per Protocol Set population). Hb, hemoglobin.

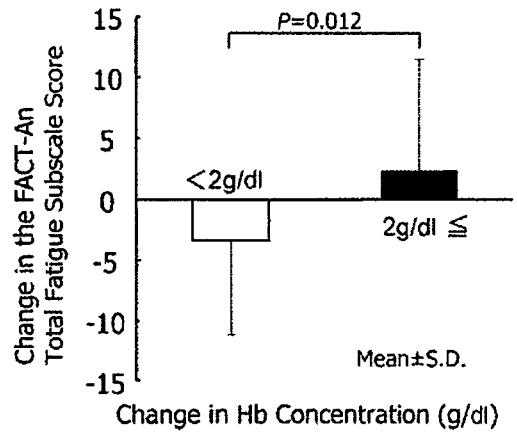

Figure 4. Change in mean Functional Assessment of Cancer Therapy—Anemia total Fatigue subscale score between baseline and 7–11 weeks by change in hemoglobin level (change in hemoglobin of ≥2 g/dl or <2 g/dl from baseline). FACT-An, Functional Assessment of Cancer Therapy–Anemia; Hb, hemoglobin; SD, standard deviation.

nonrandomized, community-based study reported by Gabrilove et al. (10), once-weekly dosing of epoetin-alfa was as effective as three-times weekly dosing in increasing hemoglobin levels and improving QOL. Cazzola et al. (12) reported a randomized study of epoetin-beta that compared the efficacy and tolerability of 30 000 IU once-weekly with the conventional 10 000 IU three-times weekly regimen in patients with lymphoproliferative malignancies. Between these two dosing regimens, there was no significant difference in time-adjusted area under the hemoglobin curve and increase in hemoglobin. Two randomized phase III studies using 40 000 IU once-weekly epoetin-alfa also support the use of epoetin-alfa as an ameliorative agent for cancer-related anemia (15,16).

Table 3. Incidence of most common adverse events by epoetin-beta dosage group (safety population)

	Epoetin-beta dosage groups							
	9000 IU (n = 28)		18 000 IU (n = 27)		36 000 IU (n = 28)		All patients (n = 83)	
	No.	%	No.	%	No.	%	No.	%
Adverse events (incidence > 20%, any grade)								
Leukopenia	23	82.1	24	88.9	23	82.1	70	84.3
Neutropenia	20	71.4	19	70.4	15	53.6	54	65.1
Nausea	15	53.6	19	70.4	16	57.1	50	60.2
Thrombocytopenia	17	60.7	13	48.1	15	53.6	45	54.2
Anorexia	18	64.3	17	63.0	8	28.6	43	51.8
Fever	10	35.7	6	22.2	12	42.9	28	33.7
Vomiting	8	28.6	9	33.3	11	39.3	28	33.7
Malaise	9	32.1	10	37.0	7	25.0	26	31.3
Increased ALT	7	25.0	8	29.6	10	35.7	25	30.1
Diarrhea	8	28.6	10	37.0	6	21.4	24	28.9
Lymphopenia	13	46.4	6	22.2	5	17.9	24	28.9
Fatigue	8	28.6	7	25.9	8	28.6	23	27.7
Increased AST	5	17.9	6	22.2	9	32.1	20	24.1
Increased LDH	3	10.7	11	40.7	6	21.4	20	24.1
Constipation	5	17.9	6	22.2	6	21.4	17	20.5
Adverse events related to epoetin beta (incidence > 3%, any grade)								
Total number of patients	9	32.1	8	29.6	6	21.4	23	27.7
Total number of events	16		32		17		65	
Hypertension/increased blood pressure	1	3.6	3	11.1	1	3.6	5	6.0
Increased ALT	1	3.6	2	7.4	2	7.1	5	6.0

ALT, alanine aminotransferase.

This is the first prospective randomized dose-finding study of once-weekly epoetin-beta in anemic cancer patients treated with chemotherapy. The study demonstrated that the mean increase in hemoglobin level in the 36 000 IU group was significantly higher than that in the 9000 IU group, while the mean increase in hemoglobin level in the 18 000 IU group was not significantly higher than that in the 9000 IU group. In the present study, epoetin-beta 36 000 IU once-weekly administration showed the same efficacy (an increase in hemoglobin level) as a 200 IU/kg thrice-weekly regimen studied in lung cancer patients receiving chemotherapy (6). It is noteworthy to point out that once-weekly epoetin-beta can be conveniently used in an outpatient-based chemotherapy regimen.

FACT-An is one of the widely used QOL assessment tools, which comprises the FACT-General and a 20-item Anemia subscale, 13 items of which make up a Fatigue subscale. Many reports indicated that chemotherapy-induced anemia increased the case of a patient becoming fatigued and resulted in decreased patient QOL (17–19). The administration of 36 000 IU epoetin-beta did not significantly improve the patients' Fatigue subscale score in spite of increased hemoglobin levels. As a primary goal of the study was to determine a recommended dose of epoetin-beta, the study design was not planned and did not have adequate statistical power to determine whether epoetin-beta would improve the Fatigue subscale scores. According to the results of the study by Hedenus et al. (20), patients with the lowest baseline Fatigue subscale scores (baseline scores of <24) reported the largest improvement in Fatigue subscale scores after the treatment with darbepoetin alfa. In contrast, patients with baseline Fatigue subscale scores of >36 did not show any improvement. In the subset analysis of our study, among the patients with baseline Fatigue subscale scores of ≤36, a mean improvement in the Fatigue subscale scores at 7–11 weeks were −1.8 for the 9000 IU group, +1.9 for the 18 000 IU group and +4.3 for the 36 000 IU group (36 000 IU versus 9000 IU P = 0.183). Our data also demonstrated a significant correlation between change in Fatigue subscale score and change in hemoglobin level and showed that the patients who responded

with a hemoglobin increase of ≥2 g/dl showed significant improvements in the Fatigue subscale scores. In conjunction with these findings, the administration of epoetin-beta may not be beneficial for the patients with relatively high hemoglobin levels and/or less symptomatic even in an anemic state. Thus, the actual hemoglobin level for initiation of epotein beta will be critical for its optimal use. The ASCO/ASH clinical practice guideline in 2002 recommends the use of rhEPO for chemotherapy-associated anemia patients with the hemoglobin level of ≤10 g/dl and that the use of rhEPO for patients with the hemoglobin level of 10–12 g/dl should be determined by clinical circumstances (21).

Most of the adverse events in the present study were considered to be related to concomitant chemotherapy, and the incidence of side effects was similar among the three dosage groups. Two large randomized studies (22,23) targeting higher hemoglobin levels raised concerns about the safety of rhEPO, because of the increased thrombovascular events and worsening survival of cancer patients. In our study, one patient in the 36000 IU group experienced deep vein thrombosis, which was evaluated as unrelated to epoetin-beta. Stimulated tumor growth is another possible mechanism for worsened survival in the rhEPO studies. A meta-analysis of 27 randomized trials of rhEPO showed suggestive but inconclusive evidence for improved overall survival in patients who received rhEPO (8). Further large scale randomized studies are necessary to confirm the effect of rhEPO on tumor outcome and overall survival.

In conclusion, once-weekly epoetin-beta 36000 IU for 12 weeks was well tolerated and significantly increased hemoglobin levels in anemic cancer patients receiving chemotherapy. Therefore, the weekly dose of 36000 IU epoetin-beta was determined as a recommended dose for a subsequent randomized, placebo-controlled, phase III study in Japan.

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CASE REPORT

Pemetrexed-induced edema of the eyelid

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KEYWORDS
Chemotherapy;
Eyelid edema;
Lung cancer;
Supportive care

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

1. Introduction

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

2. Case description

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

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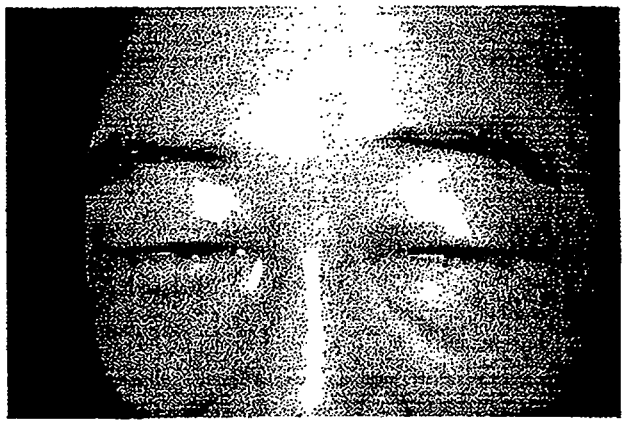

(A)

(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.

Acknowledgment

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Original Articles

Pharmacokinetics and Pharmacodynamics of Weekly Epoetin Beta in Lung Cancer Patients

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Background: To assess the pharmacokinetic profile and time-course of trough concentrations and hemoglobin levels associated with subcutaneous weekly administration of epoetin beta in lung cancer patients with chemotherapy-induced anemia.
Methods: Epoetin beta was subcutaneously administered to 15 anemic lung cancer patients once weekly for 8 weeks at doses of 9000, 18 000 and 36 000 IU. Pharmacokinetic parameters (C_{max}, AUC_{inf} and $T_{1/2}$) were determined after the first single dose administration on a model-independent basis, and the relationship between the dose and these parameters was examined for linearity.
Results: Weekly administration of epoetin beta at 9000, 18 000 and 36 000 IU produced C_{max} values of 308 ± 117 (mean ± standard deviation), 678 ± 86.7 and 1316 ± 766 mIU/ml, and AUC_{inf} values of 15 300 ± 9524, 54 574 ± 16 265 and 88 501 ± 55 687 hr mIU/ml, respectively, showing dose-proportional increases. Trough concentrations tended to increase in the presence of severe bone marrow suppression induced by chemotherapy or other factors. Extremely high values were seen in three patients, but there was no apparent trend toward an increase with repeated doses. After 8 weeks' administration at 9000, 18 000 and 36 000 IU, hemoglobin levels were changed by −0.37 ± 1.26, 2.15 ± 1.36 and 2.82 ± 2.17 g/dl, respectively.
Conclusions: Epoetin beta exhibited linear pharmacokinetics when administered to anemic cancer patients at weekly doses of 9000–36 000 IU and did not cause drug accumulation. Hemoglobin levels increased with weekly doses of 18 000 or 36 000 IU.

Key words: anemia – epoetin beta – pharmacokinetics

INTRODUCTION

Cancer patients receiving multicycle chemotherapy and radiotherapy frequently develop anemia, with one clinical study reporting that hemoglobin levels fell to 8–12 g/dl in 75% of patients undergoing these therapies (1). Among patients undergoing chemotherapy, anemia with hemoglobin levels of <8.0 g/dl reportedly occurs in 50–60% of ovarian cancer, lung cancer, non-Hodgkin's malignant lymphoma or multiple myeloma patients (2).

The etiology of chemotherapy-induced anemia includes the following: myelosuppression of chemotherapy or radiotherapy, reduced production of the bone-marrow-stimulating hormone erythropoietin (EPO), diminished bone marrow response to EPO and cancer cell-induced immune system activation resulting in reduced iron availability (3).

EPO, a hematopoietic hormone mainly produced in the kidneys, acts on erythroblastic precursor cells to promote differentiation and proliferation of erythrocytes and disappears in the bone marrow and spleen. Epoetin beta is a human EPO preparation that is mass-produced by recombinant gene technology and is commonly used in treatment of patients with renal failure-induced anemia. In Europe and the United States, it has already been approved and has also been administered to cancer patients with anemia with demonstrated effects in reducing required blood transfusion volumes, elevating hemoglobin concentrations and improving quality of life (QOL) (4,5). Furthermore, in the US, the American Society of

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Hematology and the American Society of Clinical Oncology jointly issued clinical practice guidelines in 2002 for the use of EPO preparations (6). Thus, the general use of epoetin in anemic cancer patients has been advocated. Meanwhile, in Japan, EPO preparation has not been approved for cancer patients with anemia, but clinical trials are now in progress.

Despite the increasing usage of epoetin, its pharmacokinetics have not been adequately investigated at high, once-weekly doses of 30 000 or 40 000 IU that are typically administered subcutaneously to cancer patients with anemia (7). To the best of our knowledge, the literature contains no pharmacokinetic data for epoetin beta in patients with cancer-related or chemotherapy-induced anemia, and the effect of the chemotherapy on serum EPO concentrations was not clear. We therefore studied the pharmacokinetic profile and time-course of trough concentrations and hemoglobin levels associated with subcutaneous weekly administration of epoetin beta in lung cancer patients with chemotherapy-induced anemia.

PATIENTS AND METHODS

PATIENTS

Inclusion criteria were as follows: (i) histological or cytological confirmation of lung cancer diagnosis; (ii) treated with cyclic chemotherapy; (iii) aged between 20 and 79 years; (iv) life expectancy of at least 2 months; (v) anemia (hemoglobin level of $\leq$11.0 g/dl) considered to be primarily chemotherapy-induced; and (vi) adequate renal and hepatic function.

Exclusion criteria included (i) iron deficiency (Mean corpuscular volume $\leq 80\mu m^3$ or iron saturation [{Fe/(Fe+ Unsaturated iron-binding capacity)} $\times$ 100] $\leq$ 15.0%); (ii) blood cell transfusion in the 4 weeks prior to the study; (iii) rHuEPO therapy in the 4 weeks prior to the study; (iv) documented hemorrhagic lesion; (v) pregnancy, breastfeeding or not using adequate birth control measures; (vi) history of myocardial, pulmonary or cerebral infarction, serious drug allergy, uncontrolled hypertension, hypersensitivity to any EPO preparation, any serious complication; and (vii) a primary hematologic disorder as the cause of the present anemia.

The protocol was approved by the institutional review board of the National Cancer Center Hospital, and written informed consent was obtained from all patients who participated in the study.

STUDY DESIGN

This was an open-label, single-arm, dose-escalation study. Patients were assigned sequentially to one of three groups, receiving epoetin beta at either 9000, 18 000 or 36 000 IU per patient. This was administered by weekly subcutaneous injection for 8 weeks. If the patient's hemoglobin level recovered to 14 g/dl or higher, the treatment was stopped. Chemotherapy and radiotherapy were not performed from 7 days prior to until 4 days following the initial dose, and blood transfusion was not performed until 4 days after the initial dose. Oral iron supplementation (200 mg of ferrous sulfate) was administered daily. Blood samples for detection of epoetin beta antibody were collected before the first administration and 7 days after the last administration. Patients were followed for 1 week after the end of drug administration. Granulocyte colony-stimulating factor administration was allowed to the patients whose neutrophils count was <500 per cubic millimeter or those with neutropenic fever whose neutrophils count was <1000 per cubic millimeter.

SERUM ASSAY

To determine the pharmacokinetic parameters, blood samples were collected immediately prior to and 6, 10, 24, 34, 48, 72, 96 and 168 h after the initial dose of epoetin beta. To investigate the time-course of trough concentrations, samples were also collected immediately prior to the administration of each dose.

Blood samples were allowed to stand at room temperature for ~30 min and then centrifuged at 4°C and 3000 rpm for ~10 min to separate the serum. The resulting serum was stored frozen at below −20°C until used for measurement of serum EPO concentrations.

Serum EPO concentrations were measured by the RIA method developed and validated by Chugai Pharmaceutical Co., Ltd., Tokyo, Japan. Validation of this assay revealed the following: quantification range, 6–384 mIU/ml; intra-assay precision (repeatability) and accuracy of 2.7–6.3% and −22.1 to −5.5%, respectively; and inter-assay precision (reproducibility) and accuracy of 2.4–7.6% and −18.1–3.0%, respectively. If the assayed value exceeded the upper limit of the quantification range (378 mIU/ml), the sample was diluted for re-measurement.

PHARMACOKINETIC ANALYSIS

Since EPO is an endogenous substance, measurements of serum EPO concentration following the first administration were baseline corrected to account for the presence of endogenous EPO. The corrected values were then used to determine descriptive statistics for drug concentration at each blood sampling time-point and the pharmacokinetic parameters.

The following pharmacokinetic parameters were determined after the initial dose by using WinNonlin Pro v.3.3 (Pharsight Corporation, Mountain View, CA) in a model-independent manner: C_{max}, AUC_{inf} and $T_{1/2}$.

C_{max} was observed values. AUC_{inf} was calculated by the trapezoidal method with infinite extrapolation by dividing the last plasma concentration by the elimination rate constant (K_{el}). $T_{1/2}$ was calculated as $0.693/K_{el}$.

Trough concentrations were not baseline corrected.

PHARMACODYNAMIC ANALYSIS

Hemoglobin levels and platelet counts were assessed weekly.

STATISTICAL ANALYSIS

All statistical analyses were performed using SAS v. 8.2 (SAS Institute, Cary, NC). Descriptive statistics were not calculated if they were to be based on available data from less than half the subjects.

Analyses of dose linearity were performed for C_{max} and AUC_{inf}. Each analysis used the power model: log $y = \alpha + \beta \cdot$ log dose, where β is the slope and y represents the pharmacokinetic parameter. Fitting a linear relationship between log y and log dose is an extension of the analysis of variance model. The key feature of the power model is the assumption of linearity between the log-transformed values of parameters and doses. The 95% confidential interval (CI) of the slope of the log-transformed parameters plotted against log dose was estimated, and dose-proportionality was concluded to be present if the 95% CI contained a slope with a value of 1.

RESULTS

PATIENTS' CHARACTERISTICS

Fifteen patients were enrolled in the study. Their characteristics are shown in Table 1. Participants were 8 men and 7 women, aged 30–78 years (median age, 69.0 years), who were being treated with chemotherapy (containing platinum in 12 cases). Four patients received prior radiation therapy (brain radiation in four cases and thoracic radiation in three cases). Ten patients had small cell carcinoma, four had adenocarcinoma and one had large cell carcinoma. Doses of 9000, 18 000 and 36 000 IU were administered to 3, 6 and 6 patients, respectively. Data from all 15 patients were included for evaluation of pharmacokinetic analysis and hemoglobin response. In all patients, the hemoglobin levels at the time of registration were <11.0 g/dl. Five patients discontinued this study for the following reasons: recovery of hemoglobin level to 14 g/dl or higher, $n = 1$ (36 000 IU); adverse effects (rotary vertigo), $n = 1$ (36 000 IU); withdrawal of consent, $n = 1$ (9000 IU); and disease progression, $n = 2$ (18 000 IU, 36 000 IU).

PHARMACOKINETICS ANALYSIS

The mean baseline serum EPO concentration across all patients was 77.3 mIU/ml, with a median value of 59.9 mIU/ml, a minimum of 23.6 mIU/ml and a maximum of 301 mIU/ml. The 9000 IU group showed the highest mean, attributable to an extremely high value of 301 mIU/ml in one patient (Table 1).

The time-courses of the mean serum drug concentrations by dose group are shown in Fig. 1, and a summary of the pharmacokinetic parameters are given in Table 2.

The power model gave 95% CI of the slope (β) of the C_{max}-dose and AUC_{inf}-dose curves of 0.551–1.388 and 0.532–1.753, respectively, both including '1'.

Table 1. Patients' characteristics

Characteristic	Item	Total	9000 IU	18 000 IU	36 000 IU
Sex	Male	8	1	3	4
	Female	7	2	3	2
Histology	Small cell	10	3	4	3
	Large cell	1	0	1	0
	Adenocarcinoma	4	0	1	3
ECOG* performance status	0	3	1	1	1
	1	12	2	5	5
Prior chemotherapy	None	2	0	1	1
	Non plantinum based	1	0	0	1
	Plantinum based	12	3	5	4
Age (years)	Median	69.0	78.0	69.5	68.0
	Range	30–78	53–78	54–75	30–71
Hemoglobin** (g/dl)	Mean	9.4	9.1	9.2	9.8
	Range	6.8–11.4	6.8–11	7.5–10.3	7.1–11.4
Serum Fe (μg/dl)	Mean	76.8	111.3	69.5	66.8
	Range	17–154	45–154	37–148	17–106
Serum ferritin (ng/ml)	Mean	371.9	533.8	254.8	408.0
	Range	68.3–786	68.3–786	99.7–509.7	79.6–608.8
Serum endogenous erythropoietin (mIU/ml)	Mean	77.3	122.7	70.9	60.1
	Range	23.6–301	26.9–301	23.6–158	41.5–74.1

*Eastern Cooperative Oncology Group.
**The hemoglobin levels show the values just before the first administration of erythropoietin.

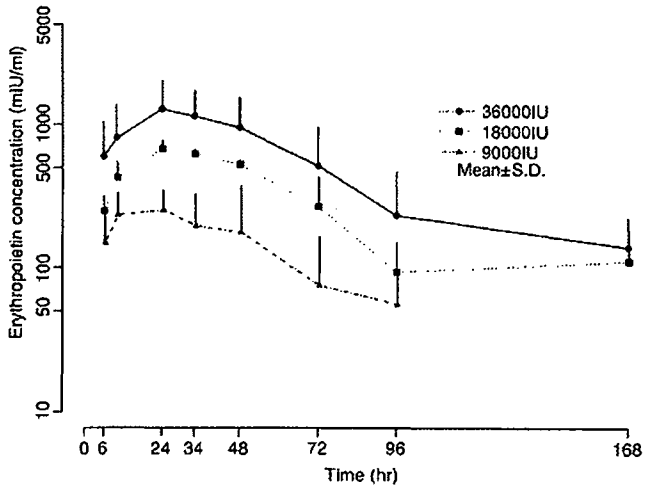

Figure 1. Time-course of mean serum drug concentrations of erythropoietin in each dose group following first dose. The mean drug concentrations for each group changed in a parallel manner up to 96 h.

Table 2. Summary of descriptive statistics for pharmacokinetic parameters of erythropoietin following the first dose

PK parameter	Unit	9000 IU	18 000 IU	36 000 IU
		$n = 3$ (Mean ± SD)	$n = 6$ (Mean ± SD)	$n = 6$ (Mean ± SD)
C_{max}	mIU/ml	308 ± 117	678 ± 86.7	1316 ± 766
AUC_{inf}	hr·mIU/ml	15 300 ± 9524	54 574 ± 16 265	88 501 ± 55 687
$T_{1/2}$	hr	24.5 ± 18.1	43.6 ± 22.0	30.4 ± 22.1

C_{max} and AUC_{inf} increased in an almost dose-proportional manner, whereas $T_{1/2}$ was constant.

Trough Concentrations

Time-courses of trough concentrations are shown by dose group in Fig. 2. Considerable variations in trough concentration occurred over the 8 week period. EPO concentration did not increase with repeated doses of epoetin beta, suggesting that drug accumulation did not occur. In some patients, trough concentrations were extremely high after chemotherapy (Fig. 3).

Relationship of Trough Concentration with Bone Marrow Suppression

Time-courses of trough concentrations, hemoglobin levels and platelet counts in the three patients with markedly elevated trough concentrations are shown in Fig. 3. In these patients, hemoglobin level and platelet count fell during the period in which trough concentration increased rapidly.

Pharmacodynamics Results

The time-course of mean hemoglobin levels is shown in Fig. 4. Hemoglobin levels were unchanged at a dose of 9000 IU, but tended to increase at doses of 18 000 and 36 000 IU. At 8 weeks, the change of hemoglobin levels from baseline was −0.37 ± 1.26 g/dl in the 9000 IU group, 2.15 ± 1.36 g/dl in the 18 000 IU group and 2.82 ± 2.17 g/dl in the 36 000 IU group. One patient receiving 9000 IU and two patients receiving 18 000 IU underwent blood cell transfusion. Only one patient (who received 36 000 IU weekly) exceeded predetermined threshold levels of hemoglobin for discontinuation of the study.

Safety

Once-weekly dosing of epoetin beta was well tolerated in all study patients, with no life-threatening toxic effects occurring during the trial. Leucopenia was the most frequent adverse event (13 of 15), followed by nausea (9 of 15). Other frequent adverse events were anorexia (7 of 15), diarrhea (7 of 15), thrombocytopenia (6 of 15), alopecia (5 of 15), fatigue (5 of 15), constipation (4 of 15), elevated serum lactate dehydrogenase (4 of 15), insomnia (3 of 15), dizziness (3 of 15), vomiting (3 of 15), back pain (3 of 15) and elevated aspartate aminotransferase (3 of 15). These adverse events are typical for this patient population receiving chemotherapy, and none occurred in an epoetin dose-dependent manner. Adverse events possibly associated with epoetin beta occurred in six patients, and these events were manageable. These adverse events consisted of grade 3 hypertension and vertigo, grade 2 increased bilirubin, constipation and hyperkalemia and grade 1 headache, nausea, vomiting, insomnia, diarrhea, mouth dryness, fatigue, neck pain, rash, hyperventilation, cardiomegaly, hyperkalemia, hyponatremia, increased phosphorus and increased asparatate aminotransferase. Only one patient in the 9000 IU cohort showed grade 3 hypertension from the 7th day of the first administration to the 65th day. One serious adverse event (rotary vertigo) occurred in a patient (a 31-year-old woman); it remitted after around 2 weeks and resolved after 5 weeks. This event was considered by the investigator to be related to epoetin beta, and the patient therefore discontinued the study. No antibodies to epoetin beta were detected.

DISCUSSION

Serum EPO levels are reported to be higher in cancer patients than in healthy adults (8). The results of this study were in accordance with this, showing higher baseline serum EPO concentrations in patients than in healthy adults (8.40 ± 3.82, 8.62 ± 5.83 mIU/ml) (9) or renal anemia patients (23.05 ± 16.63 mIU/ml) (10). In addition, serum EPO concentrations in cancer patients exhibited wide variation, from typical levels in healthy adults to extremely high levels. Overall, this suggests that the predose endogenous EPO exhibited high mean serum levels and wide individual differences in cancer patients with anemia.

In the present study, we have investigated the pharmacokinetic characteristics of epoetin beta after the initial dose of 9000, 18 000 and 36 000 IU and have studied the time-course

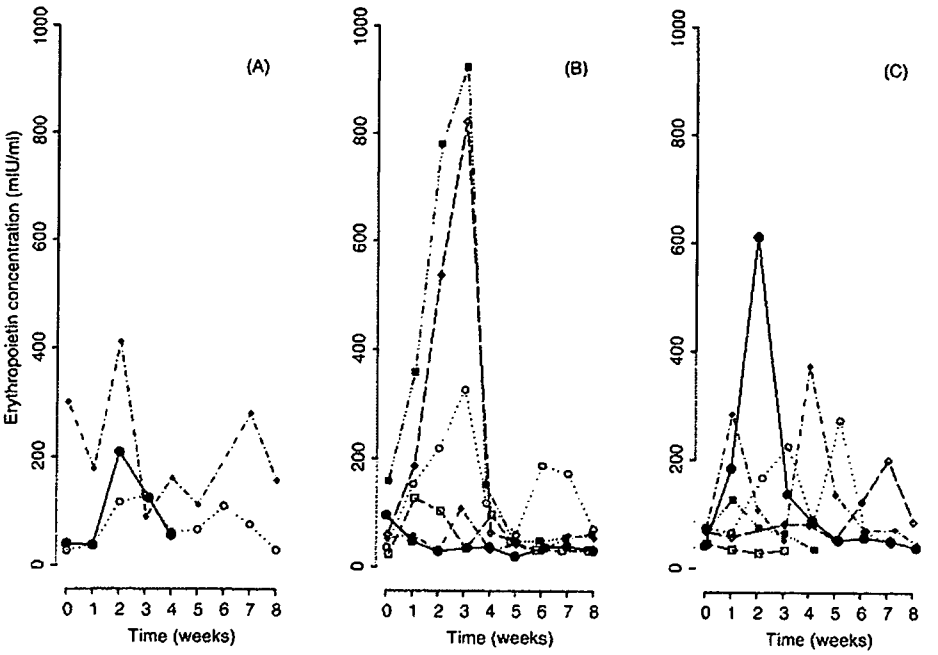

Figure 2. Time-course of trough concentrations of erythropoietin in each dose group. (A) 9000 IU, (B) 18 000 IU, (C) 36 000 IU. Trough concentrations of erythropoietin did not increase with repeated doses of epoetin beta, suggesting that drug accumulation did not occur.

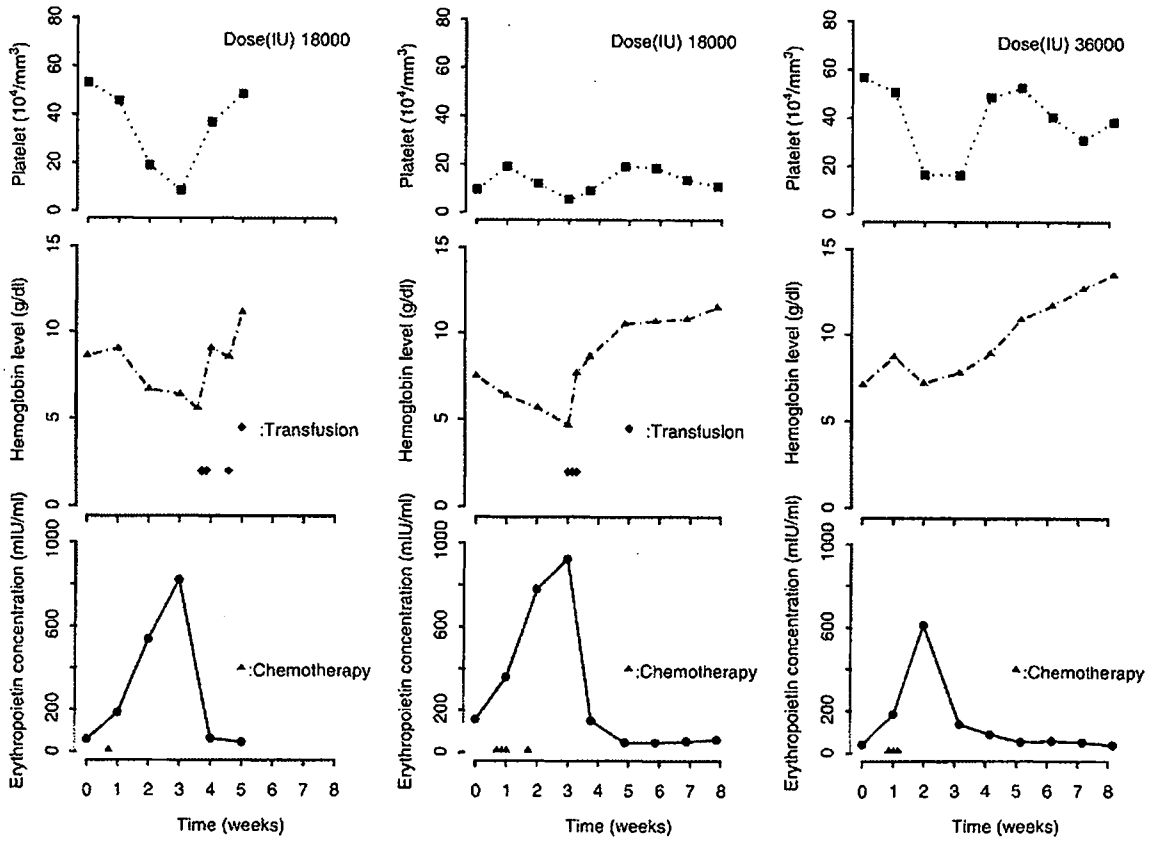

Figure 3. Time-course of trough concentrations of erythropoietin, hemoglobin levels and platelet counts in three patients with extremely high trough concentrations. The elevation of trough concentration is correlated with decrease of platelet counts and Hb levels, which may be associated with bone marrow suppression.

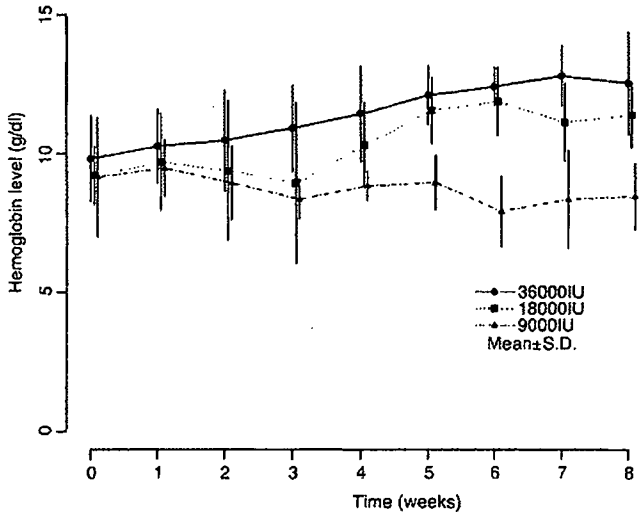

Figure 4. Time-course of mean hemoglobin levels in each dose group. Hemoglobin levels were unchanged at a dose of 9000 IU, but tended to increase at doses of 18 000 and 36 000 IU.

of trough concentrations after once-weekly repeated dose subcutaneous administration in anemic lung cancer patients. The study provides evidence that epoetin beta has almost linear, dose-dependent pharmacokinetics following subcutaneous administration at doses of 9000–36 000 IU in cancer patients.

During the period of once-weekly administrations of epoetin beta, trough concentrations transiently increased after cancer chemotherapy in many patients, but did not appear to continue to increase with repeated administration of epoetin beta. Some patients showed extremely high trough concentrations that were correlated with periods of marked thrombocytopenia. Increases in trough concentrations may be associated with bone marrow suppression, and this finding is in agreement with reports showing that busulfan-induced bone marrow ablation increases serum EPO concentrations (11) and that chemotherapy increases EPO concentrations in patients with leukemia (12,13). Jelkmann reported that elimination of EPO occurs mainly in bone marrow (14). It is conceivable that the function of bone marrow could be damaged by chemotherapeutic agents after chemotherapy. Elimination of EPO could decrease in the damaged bone marrow, thereby the trough levels of EPO could increase.

At 8 weeks, mean changes in hemoglobin levels from baseline were -0.37 ± 1.26, 2.15 ± 1.36 and 2.82 ± 2.17 g/dl for 9000, 18 000 and 36 000 IU, respectively. Hemoglobin levels increased with repeated doses of 18 000 IU or more. A dose-finding study conducted by Sakai et al. (15) in Japanese patients with lung cancer or malignant lymphoma revealed a similar pattern of hemoglobin change (0.04 ± 1.98, 1.04 ± 1.75 and 1.75 ± 2.15 g/dl for 9000, 18 000 and 36 000 IU doses of epoetin beta) and concluded that the recommended dose was 36 000 IU in chemotherapy-induced anemic patients. Taken together, these results suggest that epoetin beta is sufficiently effective for cancer patients with anemia.

In conclusion, subcutaneous administration of epoetin beta at doses of 9000–36 000 IU in cancer patients with anemia yielded pharmacokinetic linearity, with no drug accumulation caused by repeated doses. Epoetin beta administration at 18 000 IU or higher is therefore anticipated to raise hemoglobin levels without compromising safety.

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Phase I and Pharmacokinetic Study of Combination Chemotherapy Using Irinotecan and Paclitaxel in Patients with Lung Cancer

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The purpose of this study was to investigate the maximum tolerated doses, dose-limiting toxicities, efficacy, and pharmacokinetic profiles in the combination of irinotecan and paclitaxel. Eligibility criteria included age 75 years or younger, good performance status, adequate organ function, and unresectable non–small cell or extensive disease of small cell lung cancer. Irinotecan was administered on days 1 and 8 over 90 minutes, and paclitaxel was administered on day 8 over 3 hours after 90 minutes from the end of the irinotecan infusion. Irinotecan and paclitaxel were dose-escalated from 40 and 135 mg/m^2 and repeated every 4 weeks. The authors also administered a higher dosage with preventive granulocyte colony-stimulating factor support from day 9. Thirty-one patients were assessed for toxicities and responses. Dose-limiting toxicities were neutropenia and febrile neutropenia. The dose of irinotecan 60 mg/m^2 and paclitaxel 200 mg/m^2 with preventive granulocyte colony-stimulating factor support was tolerable and suitable for a phase II trial. Nine of 25 (36%) patients with non–small cell and all six patients with small cell carcinoma achieved partial response. The areas under the concentration versus time curves of irinotecan and its metabolites on day 8 were significantly higher than on day 1. This combination therapy must be planned only after careful consideration of the drug–drug interaction.

Key Words: Lung cancer, Irinotecan, Paclitaxel, Phase I, Pharmacokinetics.

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Chemotherapy for non–small cell lung cancer (NSCLC) has recently improved survival by using platinum compounds and new drugs (e.g., vinorelbine, gemcitabine, taxanes, and irinotecan).[1] Chemotherapy for extensive disease of small cell carcinoma (ED-SCLC) has also improved survival using cisplatin and irinotecan.[2] Although these regimens statistically improved survival, the benefits are far from satisfactory. There are comparatively few reports of nonplatinum regimens, and we do not have sufficient knowledge about these regimens regarding maximum tolerated doses (MTD), toxicities, responses, and pharmacokinetic profiles. However, irinotecan and paclitaxel have shown antitumor activity for both non–small cell and small cell carcinoma as a single agent.[3–6] This combination is also reported to have additive or supra-additive antitumor effects for lung cancer cells in vitro by using an isobologram.[7,8] Therefore, we conducted this combination phase I study to evaluate MTD, dose-limiting toxicities (DLTs), and pharmacokinetics in this combination therapy. We also evaluated the response rate and pharmacokinetic profiles.

Before planning this study, we performed this combination trial by another administration schedule.[9] In the prior trial, irinotecan was administered over 90 minutes on days 1, 8, and 15 and paclitaxel was given by infusion over 3 hours on day 2. Starting doses of irinotecan and paclitaxel were 50 and 135 mg/m^2, respectively. DLTs were neutropenia and febrile neutropenia, and MTD was the starting dose. Furthermore, most of the patients could not receive irinotecan on days 8 and 15 because of neutropenia. Although the neutropenia from this combination regimen was intolerable, an antitumor response was seen in the majority of the patients, suggesting that this combination might provide good antitumor activity and that an alternative administration schedule was needed to use these drugs. In this new trial, we therefore modified the administration schedule to escalate dose intensity while avoiding severe toxicities.

PATIENTS AND METHODS

Patient Selection

Patients with unresectable NSCLC or ED-SCLC were eligible for the trial. Pathologic confirmation and assessable lesions were necessary before study entry. Previous chemotherapy or radiotherapy, if given, must have been completed at least 4 weeks before entry. Other eligibility criteria included age 20 to 75 years, Eastern Cooperative Oncology Group performance status of 0 to 1, estimated life expectancy of at least 3 months, and adequate organ function defined as follows: white blood cell count greater than or equal to 4000 cells/μl, absolute neutrophil count greater than or equal to

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2000 cells/μl, platelet count greater than or equal to 100,000 cells/μl, serum creatinine less than or equal to 1.2 mg/dL, bilirubin less than or equal to 1.5 mg/dL, serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) less than twice the upper limit of normal, and PaO_2 greater than or equal to 60 mmHg. Patients with interstitial pneumonia, active infection, unstable cardiac disease, uncontrolled diabetes mellitus, pleural or cardiac effusion that required drainage, or symptomatic brain metastasis were ineligible. Our hospital institutional review committee approved this study, and all patients provided written informed consent.

Treatment

Irinotecan was administered on days 1 and 8 over 90 minutes, and paclitaxel was administered on day 8 over 3 hours after 90 minutes from the end of irinotecan infusion (Figure 1). All patients received premedication for paclitaxel and vomiting. The treatment was repeated every 4 weeks. The latter therapy was permitted using preventive granulocyte colony-stimulating factor (G-CSF) support from day 9 if patients experienced DLT of leukopenia or neutropenia and achieved partial response or stable disease on the previous course. The criteria for administration on day 8 were white blood cell count greater than or equal to 3000 cells/μl and other eligibility criteria before study entry. If patients did not clear this criteria for day 8, their treatment was cancelled and they were excluded from the evaluation of toxicities and responses.

Dose Escalation

The dose escalation schedule is shown in Table 1. Evaluation of DLTs for dose escalation was performed for the first course of chemotherapy. DLTs were defined using National Cancer Institute Common Toxicity Criteria (version 2.0)[10] as grade 4 neutropenia lasting 5 days or more, other grade 4 hematologic toxicities, neutropenic fever, or grades 3 and 4 toxicities in other organ systems except for nausea and vomiting. Three patients were assigned to each dose level. When all three patients did not experience DLT, we shifted to the next dose level. If one or two patients experienced DLT, an additional three patients were entered at the dose level before dose escalation. When at least three patients were found to have DLT, the dose was defined as the MTD. After the MTD was determined without preventive G-CSF support, we continued this study with preventive G-CSF support from day 9 until the recovery of neutropenia. We permitted the latter therapy by using preventive G-CSF support if patients who experienced DLT achieved stability or a partial response. Intrapatient dose escalation was not permitted. World Health Organization tumor evaluation criteria were used for tumor response evaluation.[11,12]

TABLE 1. Dose Escalation Schedule

Dose Level	CPT-11 (mg/m²)	Paclitaxel (mg/m²)
1	40	135
2	50	135
3	60	135
4	60	150
5	60	175
6	60	200

CPT-11, irinotecan.

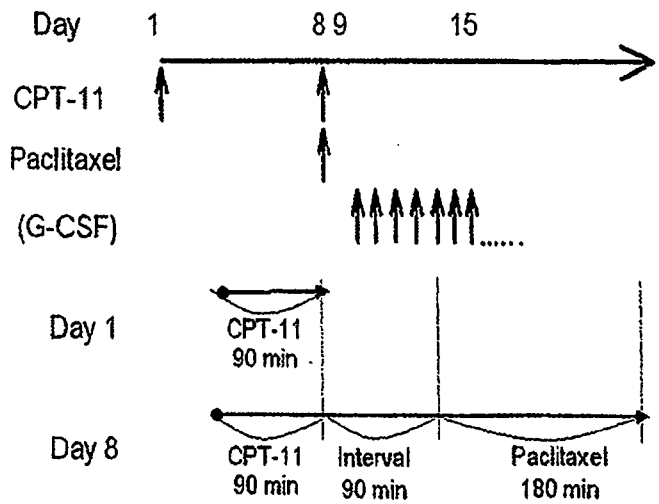

FIGURE 1. Treatment schedule of irinotecan and paclitaxel.

Pharmacokinetic Analysis

Blood samples for pharmacokinetic analysis were obtained on days 1 and 8 in the first course. We collected samples by means of a peripheral venous catheter at the following times from the end of irinotecan infusion: 0, 15, 30, 90, 180, 240, 300, 420, 540, and 1410 minutes on day 1; and 0, 15, 30, 90, 180, 240, 270, 285, 300, 360, 420, 540, 630, and 1410 minutes on day 8, respectively. To analyze the pharmacokinetics of paclitaxel and the influence on the pharmacokinetics of irinotecan by paclitaxel, several processes were

TABLE 2. Patient Characteristics

Characteristic	Value
No. of patients enrolled	31
Median age (range) (yr)	62 (36–75)
Sex	
Male	23
Female	8
PS	
0	4
1	27
Prior chemotherapy	
Yes	2
No	29
Type of lung cancer	18
Adenocarcinoma	6
Squamous cell carcinoma	1
Large cell carcinoma	6
Small cell carcinoma	
Median no. of courses (range)	2 (1–5)

PS, performance status.

TABLE 3. Major Toxicities

	Level 1	Level 2	Level 3	Level 3' (G-CSF)	Level 4 (G-CSF)	Level 5 (G-CSF)	Level 6 (G-CSF)
No. of patients	3	6	3	2* + 1	6	6	6
Neutropenia							
G3	1	0	0	1	2	0	1
G4 (<5 days)	1	4	3	1	2	2	1
G4 (≥5 days)	0	0	0	0	0	0	0
Neutropenic fever	0	1	2*	0	1	1	1
AST or ALT							
G2	0	0	0	0	0	0	0
G3	0	1	0	0	0	0	0
Diarrhea							
G2	0	1	1	0	1	0	1
G3	0	0	0	0	0	1	0
DLT patients	0	2	2*	0	1	2	1

*Two patients who had neutropenic fever in level 3 were treated with preventive G-CSF support in second courses as level 3'. Level 3' was tolerable for them. G, National Cancer Institute Common Toxicity Criteria grade; DLT, dose-limiting toxicity.

added on day 8. Heparinized tubes were used, and the plasma was immediately separated by centrifugation and stored at −20°C until analysis. Plasma concentrations of irinotecan, its metabolites (SN-38 and SN-38G), and paclitaxel were measured using high-performance liquid chromatography on the reported conditions.[13,14]

The area under the plasma concentration-time curve (AUC) of irinotecan, its metabolites, and paclitaxel were calculated by the trapezoidal method with extrapolation to infinity using WinNonlin (version 1.1; Scientific Consulting, Inc., Apex, NC).

The AUC of irinotecan, SN38, and SN-38G on day 1 were compared with those on day 8 using paired *t* test and Wilcoxon matched-pairs signed ranks test. Clearance of paclitaxel was compared with reported data in monotherapy.

RESULTS

Patient Characteristics

Twenty-six men and eight women were enrolled in the study and were treated between March of 1999 and November of 2002 at Kinki University Hospital in Osaka, Japan. Two men in level 3 and one man in level 4 were excused because of the criteria for administration of day 8. One showed grade 3 elevation of ALT and ileus, another showed grade 2 elevation of ALT, and the other exhibited grade 2 rash. These patients were excluded from evaluation of toxicities and responses at each dose escalation. Finally, 31 patients were evaluated for their toxicities and responses, and blood samples were drawn on both day 1 and day 8 from 31 patients. The characteristics of the 31 patients are listed in Table 2.

Toxicities and Dose Escalation

Major toxicities are hematologic toxicities, diarrhea, and elevation of AST and ALT. Other nonhematologic toxicities are mild. Details are listed in Table 3. In level 2, one patient developed grade 3 liver dysfunction and the other developed neutropenic fever. In level 3, all patients developed grade 4 neutropenia and two of three patients developed neutropenic fever. Although level 3 had not reached the definition of MTD at this point, we judged that the dose of level 3 was probably MTD, and that further continuation of level 3 was dangerous. However, two patients who had neutropenic fever did not develop DLT in the second course of level 3 with preventive G-CSF support. We decided, therefore, to continue this study with preventive G-CSF support from level 3. One patient added to level 3 with preventive G-CSF support did not develop DLT. Most patients received second or later courses on schedule in each level. Although the schedules were delayed in a few patients, the reasons were not toxicities. This study was subsequently continued until level 6, and the dose did not reach the MTD with preventive G-CSF support. Although level 6 with G-CSF support was tolerable, this phase I study was discontinued because each dose was close to the recommended dose for monotherapy in Japan. We estimated that the recommended dose for phase II study was irinotecan 60 mg/m^2 (days 1 and 8) and paclitaxel 200 mg/m^2 (day 8) with preventive G-CSF support from day 9.

TABLE 4. Tumor Responses

Level	Patients	PR	SD	PD
1	3		3	
2	6	2 + 1*	2	1
3	4	1	1	2
4	6	0 + 3*	2	1
5	6	4 + 2*		
6	6	2	2	2

*Patients with ED-SCLC. †NSCLC (25 patients): PR, 9 (36%; 95% CI, 18–57%). ED-SCLC (6 patients): PR, 6 (100%; 95% CI, 61–100%). PR, partial response; SD, stable disease; PD, progressive disease; CI, confidence interval.

TABLE 5. Comparison of AUCs of Day 1 and Day 8

	CPT-11	SN-38	SN-38G
Average (μg/min/ml) ± SD			
Day 1	223.3 ± 73.6	5.92 ± 5.30	70.24 ± 70.40
Day 8 (with paclitaxel)	296.3 ± 92.0	8.31 ± 7.13	102.71 ± 123.14
Paired *t* test (*p* value)	<0.0001	0.0271	0.0136
Wilcoxon matched-pairs signed ranks test (*p* value)	<0.0001	0.0044	0.0001

SD, standard deviation; CPT-11, irinotecan.

Tumor Responses

Nine of 25 (36%) patients with NSCLC achieved partial response, and all six patients with ED-SCLC achieved partial response (Table 4).

Pharmacokinetics

Pharmacokinetic analyses were conducted on 31 patient blood samples. AUCs of irinotecan and its metabolites on day 8 were significantly higher than on day 1 (Table 5). Clearance of paclitaxel (day 8) was 14.3 ± 5.3 liters/hr/m^2.

DISCUSSION

Several other studies of this combination were reported.[15–17] Both paclitaxel and irinotecan were administered weekly in some studies, and patients were given paclitaxel on day 1 and irinotecan on days 1, 8, and 15 in some studies. DLTs and other major toxicities were hematotoxicities and diarrhea. These toxicities were similar to those in this study. Administration of irinotecan on day 8 or 15 was generally skipped in the weekly schedule, or administration of paclitaxel on day 1, because of hematotoxicities. This study schedule was designed to avoid skipping administration on day 8 and to elevate dose intensity and its efficacy by using G-CSF without any risky administration on day 15. Other studies did not increase the dosage with G-CSF and did not treat patients with ED-SCLC. This combination showed comparatively stronger hematologic toxicity than the other platinum combination regimens or nonplatinum regimens as indicated from our results and the other reports on this combination.

Platinum-based combinations with third-generation drugs are standard regimens in the treatment of advanced NSCLC.[1,18,19] However, a recent meta-analysis has reported that 1-year survival was not significantly prolonged when platinum-based therapies were compared with third-generation–based combination regimens.[20] Platinum-free doublet regimens are expected to offer improved survival without decreasing quality of life. Although this trial showed a response rate similar to other nonplatinum regimens, hematotoxicities were stronger than those of the other regimens. Therefore, this combination therapy might not be suitable for the treatment of NSCLC.

In the treatment of small cell lung cancer, the regimen of cisplatin and irinotecan ensures better survival than the regimen of cisplatin and etopside.[2] There have been very few reports of platinum-free doublet regimens based on third-generation drugs in small cell lung cancer. The response rate of this study regimen was noteworthy. Although the number of patients with small cell carcinoma was limited, all patients achieved partial response (95% confidence interval, 61–100%). This combination showed similar or better response than the combination of cisplatin and etoposide, and this regimen might be as effective as the combination of cisplatin and irinotecan. Therefore, this combination is proposed as an attractive regimen for small cell lung cancer chemotherapy.

In this trial, three persons were withdrawn from treatment by the criteria of day 8 and thus excluded from evaluation. We know from our previous study that this combination may cause severe neutropenia and that some patients occasionally show stronger toxicities for irinotecan than most. For example, it has been suggested that the polymorphism of UDP-glucuronosyltransferase might raise severe toxicities.[21,22] If only single administration of low-dose irinotecan produced toxicities that conflicted with the criteria of day 8, we can regard that patient as an anomaly regarding irinotecan. At this point, our administration schedule seems to be safe for this combination.

In the pharmacokinetic study, AUCs of irinotecan and its metabolites on day 8 were significantly higher than those of day 1. Clearance of paclitaxel was similar to that in many previously reported studies. We observed a 90-minute interval between irinotecan infusion and paclitaxel infusion to avoid severe drug interactions. We concluded that the mechanism of drug elimination is competitive because we had found indications of interaction from the pharmacokinetic investigation in our previous study. Irinotecan and its metabolite are mainly excreted by P-glycoprotein and cMORT in the liver, and paclitaxel or its vehicle (Cremophor EL) will compete in some stage of excretion. Noninterval administration of paclitaxel and irinotecan would heighten the AUC and the risk of toxicities. It has been advised in phase II trials that the administration time schedule of a phase I study be retained because it is very likely that the MTDs are different in each administration schedule. If the interval between irinotecan and paclitaxel administration is shorter or the order of administration is reversed, the possible pharmacokinetic interaction and toxicities might be much stronger. This combination therapy must be planned carefully with due consideration of the drug–drug interaction.

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