



A phase I dose escalation study of multicyclic, dose-intensive chemotherapy with peripheral blood stem cell support for small cell lung cancer

M Takahashi¹, H Yoshizawa¹, H Tanaka¹, J Tanaka¹, H Kagamu¹, K Ito¹, T Shimbo¹, D Chou¹, M Wakabayashi¹, E Suzuki¹, K Sakai², M Arakawa¹ and F Gejyo¹

¹Department of Medicine (II) and ²Department of Radiology, Niigata University Medical School, Niigata, Japan

Summary:

A phase I dose-escalation study of multicyclic, ifosfamide, carboplatin, and etoposide (ICE) with sequential reinfusion of peripheral blood stem cells (PBSCs) was conducted to determine the maximum-tolerated dose (MTD) of ICE. Twenty-four patients with SCLC (LD: 6, ED: 18) were treated with ifosfamide (3000–9000 mg/m², 24-h infusion), carboplatin (300–400 mg/m²), and etoposide (300 mg/m²) followed by subcutaneous filgrastim (75 µg/day) from day 4 to the day of PBSC collection. PBSC were harvested when the WBC count reached $\geq 5 \times 10^9/l$. The leukapheresis product was cryopreserved and reinfused on day 4 of the next cycle, which was started 48 h after the last PBSC collection. The ifosfamide dose was escalated as follows: 3000 mg/m² (level 1), 5000 mg/m² (level 2), 7000 mg/m² (level 3), 9000 mg/m² (level 4). Patients with LD were treated with concurrent radiotherapy at 1.5 Gy twice daily for the initial 3 weeks to a total dose of 45 Gy and MTD, defined separately. Patients were evaluated for hematologic and non-hematologic toxicity, actual dose intensities, as well as response to therapy. The maximum-tolerated dose (MTD) was defined as the dose level at which more than 5 days of grade 4 myelosuppression or non-hematologic toxicity greater than grade 3 developed in two thirds of the patients. For ED cases, MTD was level 4 and the recommended dose of ifosfamide was 7000 mg/m². For LD cases, the recommended dose of ifosfamide was 5000 mg/m². The dose limiting toxicity of multicyclic ICE was hematologic toxicity and CNS toxicity which manifested as ataxia. Tumor responses were seen in all patients, with 14 patients showing a complete response. The actual total dose-intensity at the recommended dose level was 2.2 and 1.74, for ED and LD, respectively, compared with previously reported ICE regimens. PBSC support for dose-intensive ICE regimen permitted dose escalation of ifosfamide with a mean interval of 16–17 days. We conclude that this regimen is well tolerated, with

acceptable hematological and non-hematological toxicity. *Bone Marrow Transplantation* (2000) 25, 5–11.

Keywords: small cell lung cancer; dose intensive chemotherapy; granulocyte colony-stimulating factor; hematopoietic stem cell transplantation; leukapheresis

Studies on a variety of tumors indicate that cytotoxic dose intensity is an important determinant of treatment outcome.^{1,2} Models of the development of cytotoxic drug resistance suggest that maximal initial treatment will reduce the risk of relapse.^{3,4} Although small cell lung cancer (SCLC) is the histologic type most sensitive to combination chemotherapy, the majority of SCLC patients relapse with chemoresistant tumors. Circumvention of this secondary chemoresistance has been addressed using different treatment modalities.

In a recent study, patients with limited-disease SCLC were randomly assigned to receive higher- or lower-dose cyclophosphamide and cisplatin during the first course of a cisplatin, etoposide, doxorubicin and cyclophosphamide regimen followed by five additional cycles at standard doses.⁵ A moderate increase in the cisplatin and cyclophosphamide doses during the first course resulted in a 17% increase in 2-year survival. However, myelosuppression is the limiting toxicity for this chemotherapy regimen.

For the majority of drugs, myelosuppression is the initial dose-limiting toxicity. While hematopoietic growth factors have been utilized to reduce the toxicity and improve delivery of the planned dose, only a modest increase in dose intensity can be achieved.

Recently, peripheral blood stem cells (PBSCs) have been used as a source of stem cells and shown to restore hematopoietic functions rapidly after PBSC autografting. High-dose chemotherapy with PBSC rescue has been used for leukemia and lymphoma, but for most chemosensitive solid tumors, a single high-dose chemotherapy as late intensification does not appear to prolong survival.⁶

Since adjustments of the dose of cytotoxic drugs, as well as shortening of the intervals between courses, can increase dose intensity, multicyclic chemotherapy may offer the opportunity to maximize dose intensity of the treatment.^{7–9}

This report describes the results of a phase I dose-escalation study of multicyclic ICE chemotherapy supported by sequential reinfusion of PBSCs for SCLC and defines the

maximum-tolerated dose (MTD) for ICE administered in a multicyclic fashion and the maximum actual dose intensity in this regimen.

Patients and methods

Patients selection

Patients with histologically or cytologically documented, SCLC without prior therapy were eligible for the study. Each patient was required to meet the following criteria: World Health Organization (WHO) performance status (PS) of 0, 1, or 2; <70 years of age; the presence of measurable disease; adequate renal function (creatinine clearance ≥ 60 ml/min); adequate hepatic reserve (total bilirubin, serum AST and ALT <2.5 times normal), normal bone marrow function (WBC count $\geq 3.5 \times 10^9/l$, platelet count $\geq 100 \times 10^9/l$, hemoglobin level ≥ 10 g/dl).

Patients with active concomitant malignancy, liver cirrhosis, active infection and severe heart disease were excluded. Written informed consent was obtained from each patient. Bone marrow aspirates were obtained before beginning the therapy and patients with bone marrow involvement were excluded.

Patient evaluation

Before beginning chemotherapy, patients were staged with physical examinations, computed tomographic (CT) scans of the brain, chest, and abdomen as appropriate for the assessment of measurable disease, radionuclide bone scans and other radiographic examinations as necessary to document measurable disease.

Treatment regimens

The chemotherapy regimen consisted of an escalating dose of ICE (Table 1).

Patients were treated with four to six cycles of ICE followed by subcutaneous injection of filgrastim (Kirin Brewery, Tokyo, Japan) 75 μ g/day from day 4 to the day of PBSC collection. This dose of G-CSF has been shown to induce accelerating neutrophil recovery and effective mobilization of PBSC.^{10,11} Ifosfamide was administered intravenously (i.v.) for 24 h on day 1, carboplatin i.v. on day

Table 1 Dose escalation schedule

Level	Carboplatin ($\times 1$ day)	Etoposide ($\times 3$ days)	Ifosfamide ($\times 1$ day)
1	300	100	3000
2	400	100	5000
3	400	100	7000
4	400	100	9000

Values are mg/m².

1, and etoposide i.v. on days 1, 2 and 3 (Table 2). PBSCs were harvested when the WBC count reached $\geq 5 \times 10^9/l$. The leukapheresis product was cryopreserved and reinfused on day 5 of the next cycle, which was started 48 h after the last PBSC collection. The ifosfamide dose was escalated from 3 g/m² to 9 g/m² along with the dosage of carboplatin and etoposide (Table 1). Mesna was used as a uroprotectant at 1.5 times the dose of ifosfamide and was administered continuously over 36 h. LD patients were treated with concurrent chest radiotherapy at 1.5 Gy twice daily for 3 weeks to a total dose of 45 Gy, starting on day 1 of the initial chemotherapy.

Supportive care

Patients prophylactically received irradiated leukocyte-filtered, single donor platelet concentrate transfusions if the platelet count was less than $2 \times 10^9/l$, and 2 U of packed RBC cells if the hemoglobin level was less than 7.0 g/dl.

PBSC collection and processing techniques

Leukapheresis was performed with a Fresenius AS 104 blood cell separator (Fresenius, Bad Homburg, Germany). Ten liters of blood were processed daily at a flow rate of 70 ml/min on 2 consecutive days. After collection, each leukapheresis product was suspended in 50% CP-1 (5% dimethylsulfoxide (DMSO), 6% hydroxy ethyl starch; Kyokuto, Nihonbashi, Tokyo, Japan), and 50% human serum albumin and cryopreserved by simple immersion in a -80°C freezer until the day of transplantation. An aliquot of these cryopreserved samples was thawed and assayed for the number of CD34⁺ cells, as well as granulocyte colony-forming units.²⁰ The number of CD34⁺ cells present in the harvest product was assayed by direct immunofluorescence (PE-8G12; Becton Dickinson, San Jose, CA, USA). For assay of CFU-GM, the cells obtained (5 ml, $5 \times 10^4/ml$) were plated in MEM Alpha Medium (Life Technologies, Gaithersburg, MD, USA) containing 30% fetal bovine serum, 1% bovine serum albumin, 0.9% methylcellulose, 0.1 mM 2-mercaptoethanol, 2 mM L-glutamine, recombinant

Table 2 Chemotherapy schedule

1st course										
Day	1	2	3	4	5	6	7			
Carboplatin (div)		●								
Etoposide (div)		●	●	●						
Ifosfamide (div)		●								
G-CSF 75 μ g/day (sc)					●	●	●			
2nd-6th course										
Day	-4	-3	-2	-1	1	2	3	4	5	6
Carboplatin (div)						●				
Etoposide (div)						●	●	●		
Ifosfamide (div)						●				
G-CSF 75 μ g/day (sc)	●	●	●						●	●
PBSCC			●	●						
PBSCT									●	

PBSCC = peripheral blood stem cell collection; PBSCT = peripheral blood stem cell transplantation; G-CSF = recombinant human granulocyte colony-stimulating factor.

human (rh)-erythropoietin (3 IU/ml), rh-interleukin-3 (10 ng/ml), rh-granulocyte-macrophage colony-stimulating factor (GM-CSF) (10 ng/ml), and rh-granulocyte colony-stimulating factor (G-CSF) (10 ng/ml). The cells were incubated in a CO₂ incubator for 14 days and counted under phase microscopy.

On the day of PBSC collection, peripheral blood was obtained from some patients and analyzed for positive IMI (immature myeloid information) using SE 9000 (Sysmex, Hyogo, Japan).

Toxicity and response evaluation

Toxicity was graded using the WHO scale for acute and subacute toxicity. A minimum of three patients was evaluated per dose level. The maximum-tolerated dose (MTD) was defined as the dose level that produced grade 4 myelosuppression (≥ 5 days) or grade 3 to 4 non-hematologic toxicity (excluding alopecia) in two thirds of patients. MTD was evaluated on the first course of the regimen and on the rest of the regimen separately. If none of the three patients experienced dose-limiting toxicity (DLT), subsequent patients were treated at the next dose level. If one of the three patients experienced DLT, then more patients were entered at the same dose level. In this study, patients were only treated at higher dose-intensity levels when sustained treatment at the previous level was shown to be tolerable.

Complete blood counts were performed at least twice weekly, while routine chemistry, urine analysis and chest X-rays were performed once a week during chemotherapy.

The standard response criteria used were as follows: complete response (CR) was defined as the disappearance of all measurable disease and complete disappearance of all signs, symptoms, and biochemical evidence of tumor activity for at least 4 weeks; partial response (PR) was defined as a 50% or greater decrease in the product of the perpendicular measurements of disease with no progression in any lesion and no new lesions identified; no change (NC) was defined as no evidence of progressive disease or any measurable response less than a PR; progressive disease (PD) was defined as a greater than 25% increase in the product of the longest perpendicular diameters of any measurable lesion or the appearance of new lesions.

Dose intensity

The actual dose intensity for each drug in the carboplatin, ifosfamide, and etoposide regimen was calculated according to the method of Hryniuk and Bush.¹² Relative dose intensity for each drug was defined as the ratio between the actual dose intensity delivered for each drug and the dose intensity previously reported for ICE chemotherapy.¹³ The averaged relative dose intensity (ARDI) for each level was obtained by calculating the mean of the relative dose intensities for the three drugs.

Table 3 Patient characteristics

<i>Characteristic</i>	<i>No. of patients</i>
Age, years	
Median	61
Range	43–69
Sex	
Male	24
Female	0
Performance status (WHO)	
0	2
1	16
2	6
Disease extent	
LD	6
ED	18
Site of metastasis	
Lung	6
Liver	4
Bone	4
Extrathoracic lymph nodes	4
Brain	3
Adrenal gland	2

LD = limited disease; ED = extensive disease.

Results

Patient characteristics

Patient characteristics are listed in Table 3. Twenty-four patients (six with LD, 18 with ED) were entered into the study between May 1995 and March 1997: three in level 1, 12 in level 2, six in level 3, and three in level 4. All patients were male; the median age was 61 years (range, 43–69). WHO PS was as follows: two patients PS0, 16 patients PS1, and six patients PS2).

Toxicity and MTD determination

Toxicity was evaluated for all eligible patients. Since LD patients were treated with concurrent radiotherapy, MTD was defined separately. A total of 132 courses of ICE chemotherapy were administered; all patients tolerated from four (LD) to six (ED) courses of chemotherapy. For the patients that experienced DLT, subsequent courses were given at the dose level below that at which the DLT was noted. The recommended dose of ifosfamide was deemed to be 7000 mg/m² because at 9000 mg/m², all of the three patients experienced DLT as defined by the protocol; in two patients grade 3 CNS toxicity and in one patient grade 4 leukopenia persisted for over 5 days (Table 4). Dose-

Table 4 WHO grade 3 and 4 toxicity

<i>Dose level</i> (<i>No. of patients</i>)	<i>Stage</i>	<i>No. of patients</i>								
		<i>WBC</i>		<i>Platelets</i>		<i>Hemoglobin</i>		<i>CNS</i>		
		<i>Grade</i>	<i>3</i>	<i>4</i>	<i>3</i>	<i>4</i>	<i>3</i>	<i>4</i>	<i>3</i>	<i>4</i>
Level 1 (3)	ED	1	0	0	1	1	0	0	0	0
Level 2 (6)	LD	3	3	2	4	4	2	0	0	0
(6)	ED	2	3	0	4	1	3	0	0	0
Level 3 (6)	ED	2	1	4	1	4	2	0	0	0
Level 4 (3)	ED	0	2	0	3	3	0	2	0	0

Table 5 Toxicity: support requirements

Parameter	Level 1	Level 2	Level 3	Level 4
	(n = 3) ED	(n = 6) LD	(n = 6) ED	(n = 3) ED
Platelets transfused				
Mean (unit/cycle)	0.6	4.4	3.3	3.5
Range (unit/cycle)	0–10	0–40	0–40	0–30
Blood transfused				
Mean (unit/cycle)	0.3	1.7	1.2	0.6
Range (unit/cycle)	0–6	0–4	0–4	0–4

limiting CNS toxicity, manifested as ataxia, was seen in two out of three patients treated at dose level 4. CNS toxicity subsided upon fluid injection, steroid administration, and discontinuation of ifosfamide.

Although ICE chemotherapy is a severely myelosuppressive treatment and the nadirs of WBC were frequently less than $1 \times 10^9/l$, recovery was rapid with the exception of only one patient who experienced hematologic DLT.

Although blood or platelet transfusions were required in most patients, the mean units transfused per cycle were 0.9 and 3.7, respectively (Table 5).

No other clinically significant (grade 3 or 4) toxicity, including nausea and vomiting, hemorrhagic cystitis, renal toxicity, cardiac arrhythmia or hepatic toxicity, was observed in the remaining patients. Moreover, no grade 3 or 4 infections occurred during leukopenia.

Level 4 was therefore defined as the MTD of ICE given in this way: ifosfamide 9000 mg/m², carboplatin 400 mg/m², and etoposide in a total dose of 300 mg/m².

Since dose level 3 was the recommended dose for ED cases, dose escalation for LD cases was started from level 2. None of the six patients treated with dose level 2 and concurrent radiotherapy experienced hematological toxicity as defined by MTD criteria. Since three of six patients experienced RTOG/EORTC grade 2 pulmonary toxicity (severe coughing that required use of narcotic drugs and mild respiratory distress), further dose escalation was discontinued. These respiratory symptoms disappeared 2 to 3 months after completion of the treatment.

Response

Response was assessable in all 24 eligible patients and 100% received an overall objective response, with a 58% CR rate (Table 6). The tendency towards a higher CR rate in level 3 and 4 compared with lower levels was noted.

Table 6 Response to cyclic ICE chemotherapy

Dose level	Stage	No. of Patients	CR (%)	PR	Overall response (%)
Level 1	ED	3	0 (0)	3	3 (100)
	LD	6	5 (83)	1	6 (100)
Level 2	ED	6	3 (50)	3	6 (100)
	LD	6	4 (67)	2	6 (100)
Level 3	ED	3	2 (67)	1	3 (100)

Hematopoietic progenitors

Numbers of CFU-GM collected for reinfusion at each chemotherapy cycle are shown in Figure 1. During cycles 1 to 3, more CFU-GM were collected by leukapheresis in level 2 to 4 than in level 1. Although PBSCs were efficiently mobilized in level 4 at cycle 1 to 3, the numbers of CFU-GM collected at each cycle were decreased in subsequent cycles. The optimal dose of ICE chemotherapy for mobilization of PBSCs appeared to be levels 2 and 3, which effectively mobilized hematopoietic progenitors into the peripheral blood.

The positive IMI rate of peripheral blood on the day of PBSC collection highly correlated with the CFU-GM ($r = 0.805$) as well as with the CD34-positive count ($r = 0.825$) of PBSC collected (Figure 2).

Dose intensity

The cytotoxic dose intensities for each drug are shown in Table 7.

The mean chemotherapy interval at each level was 15 to 17 days and escalation of the dose of ifosfamide per cycle

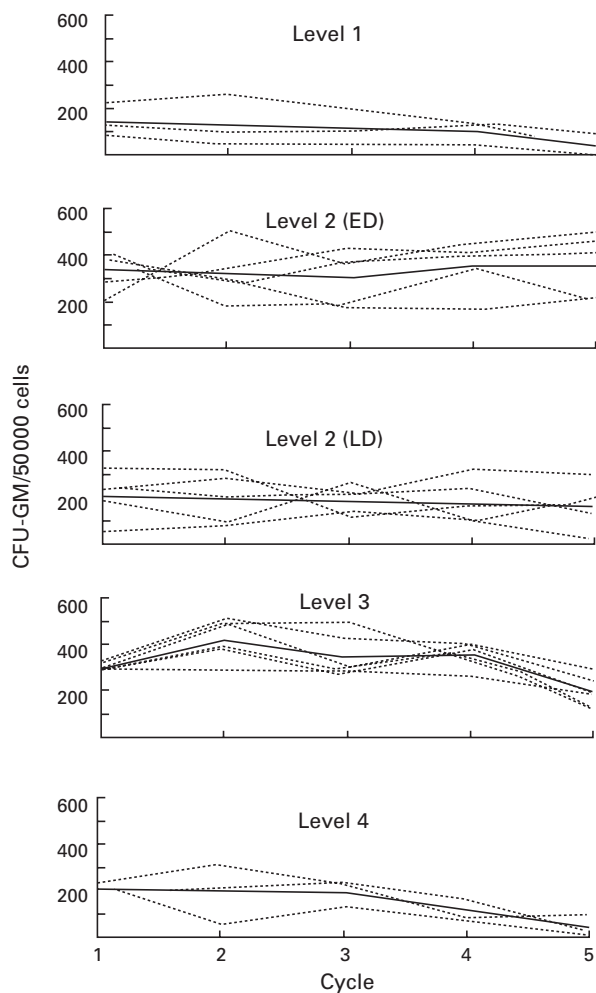


Figure 1 Numbers of CFU-GM/5000 cells in collected peripheral stem cells for each chemotherapy cycle. Data are shown as the number per 5000 collected cells for individual patients (---) with means (—).

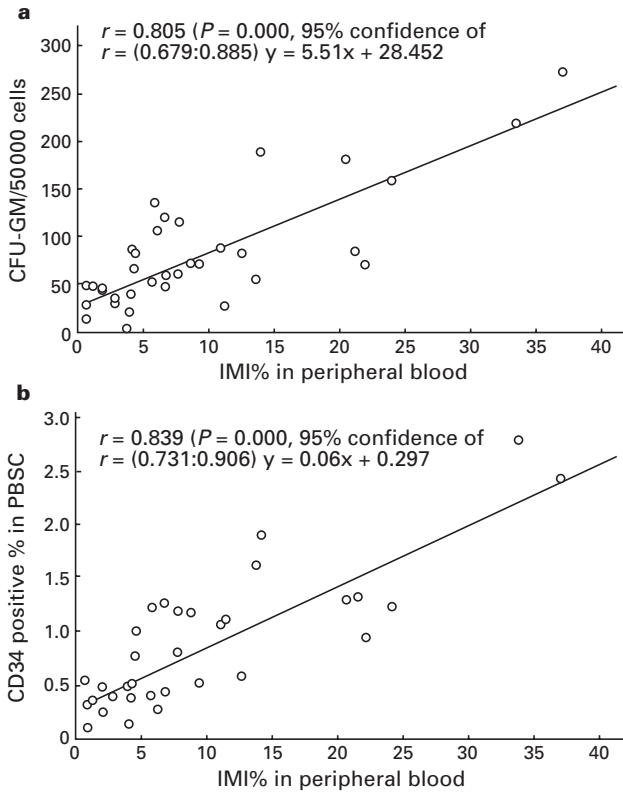


Figure 2 Correlation between the IMI positive % in peripheral blood on the day of PBSC collection and the CFU-GM count or CD34 positive % in PBSCs. (a) Correlation between the IMI positive % on the day of PBSC collection and the CFU-GM count/50000 PBSCs. (b) Correlation between the IMI positive % on the day of PBSC collection and the CD34 positive % of PBSCs.

Table 7 Comparison of actual dose intensity

	Stage	Carboplatin	Etoposide	Ifosfamide	ARDI
Level 1	ED	118	118	1181	1.46
Level 2	LD	150	112	1876	1.74
	ED	171	128	2139	1.98
Level 3	ED	168	126	2786	2.12
Level 4	ED	154	116	2556	1.96
Smith IE <i>et al</i> ¹³	LD, ED	79	59	1311	1.0
Pettengel R <i>et al</i> ⁹ (planned DI)	ED	150	180	2500	—

DI = dose intensity (mg/m²/week); ARDI = averaged relative dose intensity.

resulted in prolongation of the treatment interval at dose level 4. Since all of the three patients treated with level 4 experienced DLT as defined by the protocol, subsequent courses were performed at dose level 3.

ARDI were 1.46, 1.98, 2.13, and 1.90 for level 1, 2, 3, and 4, respectively. Treatment at level 3, defined as the recommended dose, achieved the highest dose intensity.

Discussion

Combination chemotherapy is the accepted first-line therapy for SCLC. Although no optimal regimen has been

identified, combinations of cisplatin, carboplatin, etoposide, ifosfamide or doxorubicin have been demonstrated to be active.^{14–18} The combination of carboplatin-etoposide-ifosfamide (ICE), used in the current study, has been accepted world-wide as one of the standard chemotherapy regimens in the treatment of SCLC.^{13,18}

Despite these active regimens, curative therapy is only available to a small minority of patients with limited disease SCLC, while treatment of extensive disease is virtually always palliative. To overcome this situation, various strategies have been explored in an attempt to further improve the efficacy of available regimens. These include strategies to increase dose intensity by either dose escalation with or without hematopoietic growth factors or late intensification chemotherapy.^{19,21,22}

High-dose chemotherapy with PBSC rescue has been used for leukemias and lymphoma but for most chemosensitive solid tumors, a single high-dose chemotherapy as late intensification does not appear to prolong survival.

Some experimental models suggest that initial doses of chemotherapy are disproportionately important in reducing the probability of developing drug-resistant clones due to subsequent dosing.^{3,4} Regular doses administered during induction chemotherapy may allow the propagation and/or emergence of chemo-resistant population of tumor cells. Thus when high-dose chemotherapy is administered at the end of the treatment, it is ineffective. If this is the case, it would be reasonable to administer chemotherapy at the highest dose for the shortest interval from the onset of treatment.

Arriagada *et al*⁵ reported that higher initial doses of cyclophosphamide and cisplatin improved disease-free and overall survival in patients with limited small-cell lung cancer. In another randomized study, G-CSF was used with VICE (ICE plus midcourse vincristine).²¹ Results of the study demonstrated that a significantly higher dose intensity was achieved in the G-CSF group over the control group. Although the respective median survivals did not differ, the proportion of patients alive at 2 years was 32% for those who received the higher dose-intensity regimen with G-CSF vs 15% for the controls. A similarly designed recent randomized study also demonstrated that there was a survival advantage for the groups who received G-CSF.²² In contrast, other investigators did not observe a difference in clinical outcome.

Increased dose intensity can be effected by delivery of a larger amount of drug, increasing the cumulative dose while keeping the interval of the chemotherapy or shortening treatment intervals.

Since the primary objective of the current study was to achieve maximum dose intensity, the treatment was repeated after the shortest interval. As expected, the mean treatment interval for the highest level (level 4) was longer than for the lower levels. This prolongation was reflected in dose intensity and level 3 achieved a higher dose intensity than level 4. From the stand-point of both toxicity and dose-intensity, dose level 3 was deemed to be the recommended dose. As shown in Table 7, the averaged relative dose intensity (ARDI) for level 3 was 2.12 when compared with the dose intensity of a previously reported ICE chemotherapy.¹³ In that trial, the response rate was

more than 90%, while 6% of patients died of septicemia secondary to severe myelosuppression.

Recently, peripheral blood stem cells (PBSCs) have been used as a source of stem cells and have been shown to restore hematopoietic functions rapidly after PBSC autograft. Pettengell *et al*⁹ attempted to overcome the toxicity using autologous stem cell transplantation and actual dose intensity was doubled when compared with the ICE chemotherapy at 4-week intervals. The actual dose intensity of level 2 and 3 of our study, calculated according to their method, was 207% and 219%, respectively. Their actual dose intensity was comparable to that of level 2 in our study and level 3 achieved an even higher dose intensity with less toxicity. The higher dose intensity in our study could be explained in part by the difference of the schedule for the peripheral blood stem cell collection. In our study, PBSCs were not collected on a fixed schedule but rather the timing was decided according to the peripheral blood WBC count.

To determine the optimal timing for PBSC collection, peripheral blood from some patients was obtained and analyzed for positive IMI on the day of collection. IMI has been shown to be useful in the diagnosis of hematopoietic malignancies as well as for evaluating the number of hematopoietic stem cells in peripheral stem cell collections. The positive IMI index of peripheral blood on the day of PBSC collection correlated highly with the CFU-GM ($r = 0.805$), as well as with the CD34-positive count ($r = 0.839$) of PBSCs collected. This result shows that the positive IMI rate is useful for predicting the optimal timing for the collection (Figure 2).

These favorable factors for collection allowed efficient harvesting of stem cells, which would contribute to the rapid recovery of myelosuppression in subsequent cycles of the treatment. In fact, the treatment intervals between cycles were not prolonged for later cycles at level 2 and 3. In contrast, the intervals for level 4 were prolonged for the latter half of the cycles. Level 2 (ifosfamide 5000 mg/m²) and level 3 (ifosfamide 7000 mg/m²) doses of ICE chemotherapy induced stable mobilization of PBSCs, while level 1 (ifosfamide 3000 mg/m²), and level 4 (ifosfamide 9000 mg/m²) did not, indicating that there is a dose range of ifosfamide for optimal mobilization of PBSCs (Figure 1). The reduced number of CFU-GM found in the later cycles for level 4 may have resulted from cumulative chemotherapy damage to the stem cell or marrow stroma.

Thoracic radiotherapy administered in combination with chemotherapy has been used in numerous trials and is considered standard treatment for limited stage SCLC.^{23–26} In the current study, LD patients received thoracic radiotherapy in combination with ICE chemotherapy. Although the hematological toxicity of dose level 2 with concurrent thoracic radiotherapy was tolerable, three out of six patients experienced grade 2 pulmonary toxicity and further dose escalation was not undertaken. Respiratory symptoms recovered after completion of the treatment. Dose level 2 appeared to be the recommended dose for ICE concurrently administered with radiotherapy.

Although the primary objective of the current study was to define the MTD of ICE chemotherapy, survival of patients was followed and the median survival of patients

with ED was 16 months. All of the LD patients are still alive at a median follow-up period of 22 months.

In summary, the addition of peripheral blood stem cell transplantation to ICE chemotherapy permitted dose escalation with a median interval of 16 days. The maximum-tolerated dose of ifosfamide was 9000 mg/m² and the recommended dose was 7000 mg/m². The dose-limiting toxicities were CNS toxicity and cumulative leukocytopenia. Future studies that examine the survival benefit of multicyclic ICE at the recommended dose will be important in defining clinical usefulness.

Acknowledgements

We are grateful to Satomi Takeuchi for technical assistance.

References

- 1 Gurney H, Dodwell D, Thatcher N, Tattersall MH. Escalating drug delivery in cancer chemotherapy: a review of concepts and practice – part 1. *Ann Oncol* 1993; **4**: 23–34.
- 2 Gurney H, Dodwell D, Thatcher N, Tattersall MH. Escalating drug delivery in cancer chemotherapy: a review of concepts and practice – part 2. *Ann Oncol* 1993; **4**: 103–115.
- 3 Coldman AJ, Goldie JH. Impact of dose-intense chemotherapy on the development of permanent drug resistance. *Semin Oncol* 1987; **14** (Suppl. 4): 29–33.
- 4 DeVita VT Jr. The influence of information on drug resistance on protocol design. *Ann Oncol* 1991; **2**: 93–106.
- 5 Arriagada R, Le Chevalier T, Pignon JP *et al*. Initial chemotherapeutic doses and survival in patients with limited small-cell lung cancer. *New Engl J Med* 1993; **329**: 1848–1852.
- 6 Humblet Y, Symann M, Bosly A *et al*. Late intensification chemotherapy with autologous bone marrow transplantation in selected small-cell carcinoma of the lung: a randomized study. *J Clin Oncol* 1987; **5**: 1864–1873.
- 7 Shea TC, Mason JR, Storniolo AM *et al*. Sequential cycles of high-dose carboplatin administered with recombinant human granulocyte-macrophage colony-stimulating factor and repeated infusions of autologous peripheral blood progenitor cells: a novel and effective method for delivering multiple courses of dose-intensive therapy. *J Clin Oncol* 1992; **10**: 464–473.
- 8 Tepler I, Cannistra SA, Frei E *et al*. Use of peripheral blood progenitor cells abrogates the myelotoxicity of repetitive outpatient high-dose carboplatin and cyclophosphamide chemotherapy. *J Clin Oncol* 1993; **11**: 1583–1591.
- 9 Pettengell R, Woll PJ, Thatcher N *et al*. Multicyclic, dose-intensive chemotherapy supported by sequential reinfusion of hematopoietic progenitors in whole blood. *J Clin Oncol* 1995; **13**: 148–156.
- 10 Kohno A, Takeyama K, Narabayashi M *et al*. Low-dose granulocyte colony-stimulating factor enables the efficient collection of peripheral blood stem cells after disease-oriented, conventional-dose chemotherapy for breast cancer, malignant lymphoma and germ cell tumor. *Bone Marrow Transplant* 1995; **15**: 49–54.
- 11 Martinez C, Sureda A, Martino R *et al*. Efficient peripheral blood stem cell mobilization with low-dose G-CSF (50 µg/m²) after salvage chemotherapy for lymphoma. *Bone Marrow Transplant* 1997; **20**: 855–858.
- 12 Hryniuk W, Bush H. The importance of dose intensity in

- chemotherapy of metastatic breast cancer. *J Clin Oncol* 1984; **2**: 1281–1288.
- 13 Smith IE, Perren TJ, Ashley SA *et al*. Carboplatin, etoposide, and ifosfamide as intensive chemotherapy for small-cell lung cancer. *J Clin Oncol* 1990; **8**: 899–905.
 - 14 Gatzemeier U, Hossfeld DK, Neuhaus R *et al*. Combination chemotherapy with carboplatin, etoposide, and vincristine as first-line treatment in small-cell lung cancer. *J Clin Oncol* 1992; **10**: 818–823.
 - 15 Loehrer PJ Sr, Rynard S, Ansari R *et al*. Etoposide, ifosfamide, and cisplatin in extensive small cell lung cancer. *Cancer* 1992; **69**: 669–673.
 - 16 Seifter EJ, Ihde DC. Therapy of small cell lung cancer: a perspective on two decades of clinical research. *Semin Oncol* 1988; **15**: 278–299.
 - 17 Skarlos DV, Samantas E, Kosmidis P *et al*. Randomized comparison of etoposide-cisplatin vs etoposide-carboplatin and irradiation in small-cell lung cancer. A Hellenic Co-operative Oncology Group study. *Ann Oncol* 1994; **5**: 601–607.
 - 18 Thatcher N. Ifosfamide/carboplatin/etoposide (ICE) regimen in small cell lung cancer. *Lung Cancer* 1993; **9**: S51–S67.
 - 19 Blackstein ME. Advances in chemotherapy for small cell lung cancer. *Semin Oncol* 1994; **21** (Suppl. 1): 38–42.
 - 20 Van der Wall E, Richel DJ, Holtkamp MJ *et al*. Bone marrow reconstitution after high-dose chemotherapy and autologous peripheral blood progenitor cell transplantation: effect of graft size. *Ann Oncol* 1994; **5**: 795–802.
 - 21 Woll PJ, Hodgetts J, Lomax L *et al*. Can cytotoxic dose intensity be increased by using granulocyte colony-stimulating factor? A randomized controlled trial of lenograstim in small-cell lung cancer. *J Clin Oncol* 1995; **13**: 652–659.
 - 22 Thatcher N, Sambrook RJ, Stephens RJ *et al*. Dose intensification (DI) with G-CSF improves survival in small cell lung cancer (SCLC): results of a randomized trial. *Proc Am Soc Clin Oncol* 1998; **18**: (Abstr. 1754) 17456a.
 - 23 Pignon JP, Arriagada R, Ihde DC *et al*. A meta-analysis of thoracic radiotherapy for small-cell lung cancer (see comments). *New Engl J Med* 1992; **327**: 1618–1624.
 - 24 Murray N, Coy P, Pater JL *et al*. Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group. *J Clin Oncol* 1993; **11**: 336–344.
 - 25 Perry MC, Herndon JE, Eaton WL, Green MR. Thoracic radiation therapy added to chemotherapy for small-cell lung cancer: an update of Cancer and Leukemia Group B Study 8083. *J Clin Oncol* 1998; **16**: 2466–2467.
 - 26 Turrisi AT, Kim K, Blum R *et al*. Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide. *New Engl J Med* 1999; **340**: 265–271.