Pergamon

European Journal of Cancer Vol. 30A, No. 2, pp. 188–194, 1994

0959-8049/94 $6.00 + 0.00

0959-8049(93)E0030-T

A Study of Dose Escalation of Teniposide (VM-26) Plus Cisplatin (CDDP) with Recombinant Human Granulocyte Colony-Stimulating Factor (rhG-CSF) in Patients with Advanced Small Cell Lung Cancer

Kenji Eguchi, Hisashi Etou, Sumiki Miyachi, Hajime Morinari, Kouichiro Nakada, Kazumasa Noda, Yoshihiro Ohkuni, Koshiro Watanabe, Yuzuru Yamada, Yuichiro Ohe, Tomohide Tamura, Yasutsuna Sasaki, Tetsu Shinkai and Nagahiro Saijo

A dose escalation study of teniposide (VM-26) plus cisplatin (CDDP) was carried out using recombinant human granulocyte colony-stimulating factor (rhG-CSF) in 46 previously untreated patients with advanced small cell lung cancer (SCLC). The dose of CDDP was 80 mg/m²/day intravenously (i.v.) (day 1) and VM-26 was escalated from 60 mg/m²/day to 80, 100 and 120 mg/m²/day i.v. × 5 days for four cycles. The dose of rhG-CSF was 90 μg/m²/day subcutaneously for 13 days. The feasibility of the regimen at the starting dose level of VM-26 with or without rhG-CSF was initially examined in 10 patients chosen through random allocation. WHO grade 4 neutropenia was observed in 17% (three out of 18 courses) of patients in the rhG-CSF group and in 63% (12 out of 19 courses) of the control group ($P < 0.01$). The number of patients with febrile episodes (> 38°C) over the four courses of chemotherapy was 1 in the rhG-CSF group and 4 in the control group. According to these results, all 36 patients received rhG-CSF in the dose escalation stage. The incidence of WHO grade 4 neutropenia at the dose levels of 60, 80, 100 and 120 mg/m²/day of VM-26 was 66, 57, 76 and 85%, respectively ($P > 0.1$). The incidence of grade 4 thrombocytopenia was 19, 31, 18 and 46%, respectively ($P > 0.1$). The overall response rate was 100% in patients with limited stage SCLC and 83% in patients with extensive stage SCLC. The actual administered VM-26 dose per week at the dose level of 100 mg/m²/day was 1.6-fold higher than the planned starting dose (60 mg/m²/day) per week. At the dose level of 120 mg/m²/day, 50% of patients developed WHO grade 4 leucopenia, which lasted longer than 1 week and 67% of the patients had WHO grade 3 or 4 diarrhoea. At this same dose, all patients had at least one febrile episode (> 38°C), and 1 patient died of cerebral bleeding with severe thrombocytopenia. The median survival time of all patients was 451 days (411 days, extensive disease; 497 days, limited disease). VM-26 plus CDDP with rhG-CSF was active in previously untreated patients with SCLC. The recommended dose of VM-26 in combination with CDDP for a phase II study is 100 mg/m²/day for 5 days with rhG-CSF support.

Key words: rhG-CSF, teniposide(VM-26), small cell lung cancer

Eur J Cancer, Vol. 30A, No. 2, pp. 188–194, 1994

INTRODUCTION

SMALL CELL lung cancer (SCLC) accounts for approximately 15% of all lung cancer in Japan. In patients with stage II, III and IV SCLC, intensive systemic chemotherapy is the first choice of treatment. Despite trials with various combinations of cytotoxic agents including non-crossresistant chemotherapy, survival of SCLC patients has not improved for several years [1–3]. An increase in the number of complete responses (CR) during initial treatment is considered to be essential for prolonging the survival of patients with SCLC [4, 5].

Although prior reports on the therapeutic efficacy of teniposide (VM-26) in previously treated patients with SCLC have not been encouraging [6–11], recent clinical trials have shown this agent to be highly active in untreated patients with SCLC [12–15]. Cytotoxicity and DNA damage studies in Chinese hamster ovary (CHO), L1210 and human lung cancer cell lines suggest that VM-26 may be more potent than etoposide [16–18]. Although *in vitro* studies have shown the crossresistance of VM-26 and etoposide in lung cancer cell lines, this has not yet been proven clinically [19, 20]. The efficacy of etoposide plus cisplatin (CDDP) for patients with SCLC has already been demonstrated [1, 3], although there are very few reports on the possibility of

using VM-26 as a combination chemotherapy with CDDP. VM-26 combined with CDDP could achieve a better response than etoposide in previously untreated patients with SCLC. It has not yet been clarified whether the conventional dose of VM-26 was high enough to benefit patients with SCLC. In previous reports, neutropenia has been the dose-limiting toxicity resulting from VM-26 treatment [21–23]. In evaluating recombinant human granulocyte colony-stimulating factor (rhG-CSF) as a means of shortening the duration of cytotoxic drug-induced neutropenia [24, 25], we determined the feasibility of using escalated doses of VM-26 plus CDDP with rhG-CSF for its antineoplastic effect. Our primary objectives were to assess toxicity and the maximum tolerable dose of VM-26 plus CDDP when used with rhG-CSF, and to examine the activity of the escalated dose of VM-26 plus CDDP in previously untreated patients with SCLC.

PATIENTS AND METHODS

Patients

The eligibility criteria was as follows: histologically or cytologically proven SCLC, age less than 76 years, no prior therapy, life expectancy longer than 6 weeks and measurable or evaluable lesions. Patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–3 and satisfactory organ function: white blood cell count $> 4 \times 10^3/mm^3$, haemoglobin > 10 g/dl, platelet $> 10 \times 10^4/mm^3$, total serum bilirubin < 3 mg/dl, serum glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) $< 2 \times$ normal, serum creatinine < 1.2 mg/dl. Patients with carcinomatous meningitis, life-threatening infections and concurrent radiotherapy, other than a single involved field, were excluded from this study. Patients with uncontrolled hypertension, evidence of clinically significant multifocal uncontrolled arrhythmia, unstable angina, congestive heart failure (New York Heart Association grade III–IV) or a previous cancer within 5 years were also ineligible, as were patients enrolled in any other investigational drug study.

Informed consent was obtained from all patients. The study was approved by the Institutional Review Board of the National Cancer Centre of Japan, and by those of each participating institute. Eligible patients were registered at the central office of the National Cancer Centre, Tokyo, and the clinical laboratory data of the individual patients were collected weekly by facsimile. The group held a regular monthly meeting at the National Cancer Centre, Tokyo.

Patients were enrolled in this study after routine staging including chest X-ray, bronchoscopy, computed tomography (CT) of the chest, brain CT, abdominal ultrasonography or CT, bone scintigram, bone marrow aspiration examination and other clinical laboratory examinations. Disease extent was defined as follows: a lesion confined to the ipsilateral lung field, including ipsilateral supraclavicular lymph nodes, was defined as a limited disease (LD); disease beyond these limitations was defined as extensive disease (ED). Ipsilateral lung metastasis and cytologically positive pleural effusions were also classified as ED.

Correspondence to K. Eguchi.
K. Eguchi, M. Etou, S. Miyachi, M. Morinari, K. Nakada, K. Noda, Y. Ohkuni, K. Watanabe, Y. Yamada and N. Saijo are at the Kantou Lung Cancer Chemotherapy Group; Y. Ohe, T. Tamara, Y. Sasaki and T. Shinkai are at the Department of Internal Medicine and Thoracic Oncology; and N. Saijo is also at the Division of Pharmacology, National Cancer Center 5-1-1 Tsukiji, Chuo-ku, Tokyo 104, Japan.
Revised and accepted 3 Nov. 1993.

Drug schedule and dosage

VM-26 (Vumon) was supplied by Bristol-Meyers Co. (Troisdorf, Germany). The chemotherapy regimen consisted of CDDP 80 mg/m^2 intravenously (i.v.) on day 1 and VM-26 on 60 mg/m^2/day i.v. on days 1–5 as a starting dose level every 4 weeks for four cycles. The starting dose and the schedule of VM-26 were determined from previous studies [10, 15, 21]. This study consisted of two parts. In the initial stage, the feasibility of the regimen with or without rhG-CSF (KRN8601, Kirin and Sankyo Co., Tokyo, Japan) was examined. 10 patients were randomised to receive the starting dose level of VM-26 (60 mg/m^2/day) plus CDDP with or without rhG-CSF. The second stage of this study consisted of treating 36 patients with escalating doses of VM-26 plus CDDP and rhG-CSF. The dose level of VM-26 was escalated to 80, 100 and 120 mg/m^2/day. rhG-CSF was given at a dose of 90 μg/m^2/day subcutaneously on days 6–18. The dose of rhG-CSF used in this study was determined from a previous dose-escalation study of rhG-CSF in patients with advanced lung tumours [25]. If white blood cell counts increased over $3 \times 10^4/mm^3$ after the nadir, the administration of rhG-CSF was stopped.

If patients showed any abnormal laboratory findings, beyond the initial eligibility criteria after chemotherapy, the next cycle of chemotherapy was postponed until recovery of these laboratory parameters. No dose modification rule relating to haematological toxicity was scheduled, and no dose escalation was performed within the same patient.

Ancillary therapy was as follows: after i.v. prehydration with 1 l of 5% glucose in a 0.45% sodium chloride solution, CDDP was given i.v. over 30 min. Following the administration of CDDP, patients received 20% mannitol i.v. at a rate of 50 ml/h over 6 h and 2000 ml of 5% glucose in a 0.45% sodium chloride solution, with 20 mEq of potassium per litre at a rate of 250 ml/h. Metoclopramide (2 mg/kg) diluted in 100 ml of saline was given i.v. over 30 min, 0.5 h before and 1.5, 3.5 and 5.5 h after CDDP treatment. Dexamethasone at a dose of 20 mg diluted in 100 ml of saline was given i.v. over 30 min 1 h before CDDP. Two doses of 25 mg of promethazine in 100 ml of saline were given i.v. over 30 min, the first dose concomitantly with the dexamethasone and the second dose just after the third dose of metoclopramide. VM-26 was administered i.v. over 1 h in 250 ml of 5% glucose solution. Platelets were transfused when the platelet count fell below $3 \times 10^4/mm^3$ or when any bleeding became prominent. Packed red blood cells were transfused when the haemoglobin count fell below 8 g/dl or the anaemia became symptomatic. Antibiotics were administered to febrile neutropenic patients as indicated.

Evaluation criteria for response

According to the WHO criteria, CR was defined as the disappearance of all evidence of tumour for at least 4 weeks. Partial response (PR) was defined as a > 50% reduction of the sum of the products of the two greatest perpendicular diameters of each indicator lesion for at least 4 weeks, without progressive disease at other sites. Disease progression (PD) was defined as the appearance of new lesions or an increase in indicator lesions by > 25%. No change (NC) was any state of the disease between the PR and PD requirements. In patients with pleural effusion or atelectasis on chest X-ray films, after recovery from atelectasis or the disappearance of pleural effusion, when the lesion became measurable on chest CT or plain X-ray film, we evaluated the response according to WHO criteria. The CR indicators were the same as those for measurable disease. The response was

assessed after two cycles of chemotherapy; assessable patients had to have completed at least two courses of the regimen. The relative dose intensity for VM-26 was calculated as the dose actually administered per week divided by the planned starting dose per week over the scheduled four cycles of chemotherapy.

After four cycles of initial chemotherapy, the response was evaluated by repeating the initial staging tests including bronchoscopy. LD patients who showed a response received thoracic irradiation (TRT) with a total dose of 50–60 Gy, 2 Gy/fraction/5 days per week. If patients achieved CR or PR, no additional treatment was scheduled until there was evidence of relapse or disease progression. ED patients received two additional courses of chemotherapy for a total of six courses. If CR or PR was achieved, patients were followed until disease progression. TRT was a symptom relief modality for ED patients. If patients had brain metastasis but no clinical symptoms, they received chemotherapy instead of cranial irradiation. The second-line chemotherapy regimen after relapse was decided by the lead doctor at each institution. Duration of response and survival were recorded from the first day of treatment.

Criteria for removal from study and the stopping rule

Toxicity was evaluated using WHO toxicity criteria. Removal from the study was allowed if the patient experienced: objective PD after one course of therapy, unacceptable toxicity of any kind, WHO grade 4 haematological toxicity lasting longer than 7 days, prolonged increased serum creatinine level (> 2.0 mg/dl) after chemotherapy or patient's refusal to continue therapy.

If one third of the patients experienced WHO grade 4 haematological toxicity lasting more than 1 week, or if two-thirds of the patients showed WHO grade 3 non-haematological toxicity or any severe, uncontrollable side-effect, the study was to be closed.

Statistical analysis

The P value of the difference in the incidence of side-effects, such as neutropenia and febrile episode, was calculated using the χ^2 test. The P value of the difference of the mean blood cell counts from the base-line values was calculated using the paired Student's t-test. Survival was analysed using the Kaplan–Meier method [26].

RESULTS

From October 1988 until June 1990, a total of 46 patients were enrolled in this study. As an initial step, 10 patients were randomised to receive the starting dose level of VM-26 (60 mg/m^2/day) plus CDDP, with or without rhG-CSF. There were 2 female patients in the rhG-CSF group, but no female patients in the group that did not receive rhG-CSF. There was no significant difference in distribution of patient characteristics such as age, PS and stage. There was no dose adjustment during this protocol study. 2 of the 5 patients receiving rhG-CSF experienced WHO grade 4 neutropenia in three of the 18 courses (17%). 4 of the 5 patients not receiving rhG-CSF experienced WHO grade 4 neutropenia in 12 of the 19 courses (63%) ($P < 0.01$). In patients receiving rhG-CSF, the mean neutrophil nadirs were significantly higher than in patients without rhG-CSF after the third and fourth cycle of chemotherapy ($P = 0.01$, $P = 0.02$, respectively, Fig. 1a). The duration of grade 3–4 neutropenia in the two patients groups, with or without rhG-CSF, was 4 ± 3 versus 8 ± 4 days (mean ± S.D.) in the first cycle, and 0 versus 7 ± 3, 0 versus 14 ± 7 and 2 versus 6 ± 2 days following the second, third and fourth cycles, respectively. The duration of

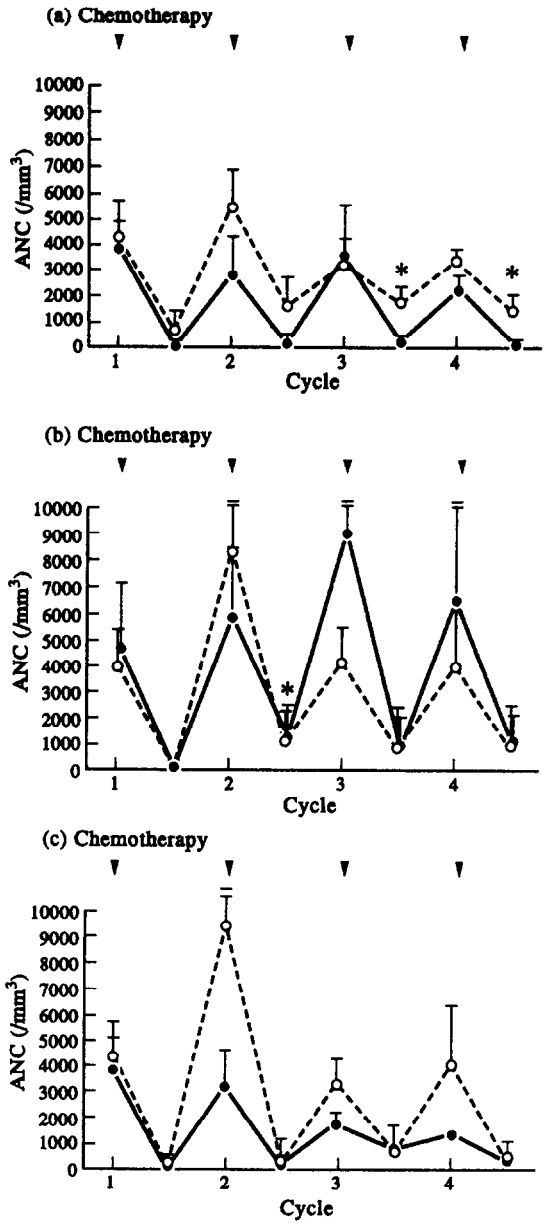

Fig. 1. Comparison of mean pretreatment and nadir values of absolute neutrophil count (ANC) in successive cycles. (a) VM-26 60 mg/m^2/day with rhG-CSF --○--, without rhG-CSF --●--. * Significant increment of the nadirs in patients receiving VM-26 with compared to those without rhG-CSF ($P = 0.04$, $P = 0.02$). (b) VM-26 60 mg/m^2/day + rhG-CSF --○--, 80 mg/m^2/day + rhG-CSF --●--. * Significant increment of the nadirs in the second cycle compared to those of first cycle at the both dose levels ($P = 0.005$, $P = 0.01$). (c) VM-26 100 mg/m^2/day +rhG-CSF --○--, 120 mg/m^2/day + rhG-CSF --●--.

neutropenia in patients not receiving rhG-CSF was prolonged significantly after each cycle ($P < 0.04$). The nadir of the platelet count after the fourth cycle of chemotherapy was significantly lower in patients without rhG-CSF ($P = 0.02$), but no difference was observed after the other cycles. There was no significant difference during any cycle in the haemoglobin nadirs of the two groups. The number of febrile episodes (> 38°C) during all chemotherapy cycles was one out of 18 cycles (5%) in the rhG-CSF group and five out of 19 cycles (26%) in the control group ($P = 0.2$). 1 patient in the rhG-CSF group and 4 in the control group experienced a febrile episode. The mean duration of febrile days (> 38°C) was 1 ± 2 days in patients supported

with rhG-CSF and 5 ± 5 days in patients without rhG-CSF treatment. Patients not treated with rhG-CSF received 3 ± 3 units of red blood cells compared to none for patients receiving rhG-CSF. The mean duration of treatment for four cycles was 88 ± 4 days in patients with rhG-CSF support and 90 ± 6 days without. However, these parameters were not statistically significant. Considering these results, we felt that the use of rhG-CSF support for the bone marrow was necessary for the safe administration of higher doses of VM-26.

The second stage of this study consisted of treating 36 patients with escalating doses of VM-26 plus CDDP and rhG-CSF. 10 patients were enrolled at each dose level except the highest (120 mg/m^2/day) (Table 1). After two cycles of chemotherapy, 1 patient at the 60 mg/m^2/day level was chosen to have surgery. Another patient had a transient stroke and an arrhythmia during the neutropenic period of the initial cycle of chemotherapy. After a similar episode in the third week, after the second cycle, the patient was removed from the protocol. 1 patient at the 80 mg/m^2/day dose level was removed from protocol because of non-cancerous pericarditis and enteritis before the fourth cycle. At the dose level of 100 mg/m^2/day, 1 patient was removed from the protocol prior to the third cycle of chemotherapy because of progressive disease.

Haematological toxicity

Incidence of neutropenia. Haematological toxicity is summarised in Table 2 and Fig. 1. The incidence of WHO grade 4 neutropenia in this regimen was 21/32 courses (66%), 20/35 courses (57%), 26/34 courses (76%) and 11/13 courses (85%) at the dose levels of 60, 80, 100 and 120 mg/m^2/day, respectively. There were no significant differences in the incidence of grade 4 neutropenia between the dose levels ($P > 0.1$). The duration of neutropenia (days of grades 3 and 4) at the dose levels of 60, 80, 100 and 120 mg/m^2/day was 4 ± 2, 5 ± 2, 5 ± 3 and 6 ± 3 days, respectively, in the first cycle, and 1 ± 2, 4 ± 2, 3 ± 2 and 5 ± 3 days, respectively, following the second cycle. At the dose levels of 60, 80 and 100 mg/m^2/day of VM-26 there was no significant prolongation of the duration of neutropenia during the third and fourth cycles of chemotherapy. At the dose level of 120 mg/m^2/day, 1 patient developed grade 4 neutropenia which lasted for 10 days; this patient was removed from the study after the initial cycle. The number of febrile episodes (> 38°C) during all chemotherapy cycles was 15/32 (47%), 11/35 (31%), 13/34 (38%), and nine out of 13 (69%) at the dose levels of 60, 80, 100 and 120 mg/m^2/day, respectively. The total numbers of days with fever (> 38°C) were 2 ± 3, 3 ± 3, 4 ± 6 and 5 ± 4 days at each dose level of VM-26, respectively. There was no clear dose-dependency. 1 patient at the 100 mg/m^2/day dose level was removed from the study because of a lung abscess during neutropenia which occurred in the initial cycle of chemotherapy; this complication was not fatal.

Table 1. Patients' characteristics

	VM-26 dose (mg/m^2/day)			
	60	80	100	120
Sex				
Male	8	7	7	4
Female	2	3	3	2
Age (years)				
Median (range)	68(62–75)	65(40–75)	64(39–74)	59(46–67)
PS(ECOG)				
0–1	7	8	9	6
2–3	3	2	1	0
Stage				
LD	7	2	3	1
ED	3	8	7	5
Sites of metastasis				
Lung	1	3	2	2
Brain	0	3	3	0
Liver	1	2	1	3
Bone	0	2	0	0
Others	4	3	2	1

PS, performance status; LD, limited disease; ED, extensive disease.

Table 2. Incidence of haematological toxicity with VM-26 + CDDP + rhG-CSF regimen

	VM-26 (mg/m^2/day)			
	60	80	100	120
Neutrophil count				
1st cycle	9/10	10/10	8/10	6/6
2nd cycle	3/9	4/9	8/9	3/4
3rd cycle	5/7	4/9	6/8	1/2
4th cycle	4/6	2/7	4/7	1/1
Total (%)	21/32(66)	20/35(57)	26/34(76)	11/13(85)
Haemoglobin				
1st cycle	0/10	0/10	0/10	0/6
2nd cycle	0/9	0/9	1/9	0/4
3rd cycle	2/7	2/9	1/8	0/2
4th cycle	1/6	2/7	1/7	0/1
Platelet count	3/32(9)	4/35(11)	3/34(9)	0/13(0)
1st cycle	3/10	3/10	1/10	3/6
2nd cycle	0/9	1/9	2/9	2/4
3rd cycle	2/7	4/9	1/8	1/2
4th cycle	1/6	3/7	2/7	0/1
Total (%)	6/32(19)	11/35(31)	6/34(18)	6/13(46)

Neutrophil count (< 500/mm^3); haemoglobin (< 6.5 g/dl); platelet count (< 2.5 × 10^4/mm^3).

Incidence of thrombocytopenia and anaemia. The incidences of WHO grade 4 thrombocytopenia in the dose escalation study were six out of 32 (19%), 11 out of 35 (31%), six out of 34 (18%) and six out of 13 courses (46%) at the dose levels of 60, 80, 100 and 120 mg/m^2/day, respectively. There was a significant difference between the platelet nadir at the 100 mg/m^2/day dose level and that at the 120 mg/m^2/day dose level. At the dose level of 120 mg/m^2/day, 1 patient died of a cerebral haemorrhage which was associated with severe thromobocytopenia. This study was closed at the 120 mg/m^2/day dose level.

The incidences of WHO grade 4 anaemia were three out of 32 (9%), four out of 35 (11%), three out of 34 (9%) and none out of 13 courses at the dose levels of 60, 80, 100 and 120 mg/m^2/day, respectively. The mean numbers of transfused packed red blood cells were 2 ± 2, 7 ± 7, 6 ± 6 and 4 ± 4 units per patient and the mean number of platelet units transfused was 11 ± 24, 23 ± 33 and 9 ± 10 units per patient at the respective dose levels. These differences were not statistically significant.

Non-haematological toxicity

Incidence of non-haematological toxicity is summarised in Table 3. The renal toxicity of this regimen was transient and tolerable. The incidence of the elevation of serum transaminases

Table 3. Non-haematological toxicity of VM-26 + CDDP + rhG-CSF regimen

	Grade*	VM-26 (mg/m²/day) 60	80	100	120
No. of patients		10	10	10	6
Serum creatinine	1*	2	2	2	1
	2		1	1	
Serum GOT, GPT	1		2		
	2	1	2	1	1
	3			1	
	4		1		
Nausea and vomiting	1	4	1	3	4
	2	5	3	3	2
	3	1	6	4	
Mucositis	1	3	1	4	1
	2		2	1	
Diarrhoea	1	1		1	
	2		2	2	
	3	1	1	2	2
	4				2

*Grading by WHO toxicity criteria. GOT, glutamic oxaloacetic transaminase; GPT, glutamic pyruvic transaminase.

Table 4. Response to VM-26 + CDDP + rhG-CSF regimen

VM-26 (mg/m²/day)	Stage	CR	PR	NC	PD	NE*	RR (%)
60	LD	1	6	0	0	0	100
	ED	0	1	1	0	1	50
80	LD	1	1	0	0	0	100
	ED	0	6	1	0	1	86
100	LD	1	2	0	0	0	100
	ED	2	3	1	0	1	83
120	LD	0	1	0	0	0	100
	ED	1	2	0	0	2	100

*NE, chemotherapy was administered for only one cycle. LD, limited disease; ED, extensive disease; CR, complete response; PR, partial response; NC, no change; PD, progressive disease; RR, response rate.

was 25% (9/36 patients) but was not VM-26 dose dependent. At doses of 60 and 80 mg/m²/day, 2 patients were removed from the study because of an elevation of the serum transaminases. However, in these patients, serum hepatitis was strongly suggested. At the dose level of 100 mg/m²/day, 1 patient was removed from the protocol because of prolonged enteritis with dehydration occurring after the first cycle of chemotherapy. At the 120 mg/m²/day dose level, 67% of the patients experienced abdominal colicky pain and bloody diarrhoea. 1 patient experienced severe melaena after the first cycle of chemotherapy, and another patient experienced severe colitis after the second cycle of chemotherapy at this dose level. Diarrhoea with abdominal pain occurred in 39% of the patients and was thought to be dose dependent. The difference in the incidence of WHO grades 3 and 4 diarrhoea between the dose level of 60 and 120 mg/m²/day was marginal ($P = 0.07$, Fisher's probability test). At the dose level of 60 mg/m²/day, 1 patient developed urticaria immediately after the infusion of VM-26 at the beginning of the second course, the treatment was discontinued in this patient.

Response

In the first stage of the study 1/10 patients had NC, while the other 9 patients achieved PR, 4 in the group without rhG-CSF and 5 in the group receiving rhG-CSF. There was no significant difference in the response between the treatments with or without rhG-CSF.

In the second stage, the dose escalation study with rhG-CSF, 25 patients were evaluable for response (Table 4). Response rates were not clearly dose dependent in the dose range of VM-26 used, with one CR observed at each of the doses of 60, 80 and 120 mg/m²/day, and three CRs at the 100 mg/m²/day dose. In LD patients, the overall response rate was 100%; in evaluable ED patients, the overall response rate was 83%. The median response duration was 164 days (range 42–336).

Relative dose intensity and survival

The actual interval periods of the four cycles of treatment were 98 ± 7, 87 ± 6 and 95 ± 9 days (mean ± S.D.) at the dose levels of 60, 80 and 100 mg/m²/day, respectively, versus the planned 89-day schedule. The relative dose intensity actually administered was 0.9, 1.4 and 1.6 at the dose levels of 60, 80 and 100 mg/m²/day compared to 1.0 of the planned initial dose (60 mg/m²/day).

There are four disease-free survivors (median observation period 689 days, range 575–953). The median survival time of all patients enrolled in this study was 451 days. The median survival times were 411 days and 497 days in patients with ED and LD, respectively.

DISCUSSION

In this study, the activity of VM-26 in untreated SCLC patients was confirmed. Recently, Tummarello and coworkers [23] reported the efficacy of VM-26 in elderly patients with SCLC. They concluded that VM-26 at 60 mg/m²/day for 5 consecutive days every 3 weeks was safe and effective with a low CR rate. Sorensen and coworkers [27] reported the results of a combination chemotherapy of carboplatin plus VM-26 for untreated ED SCLC patients. The dose of VM-26 was 60 mg/m²/day, days 1–5, and the dose of carboplatin was 200 mg/m². The overall response rate was 51% with 9% CR. Although the sample size was small, the overall response rate of our study is comparable to that reported by other investigators using high dose regimens. It is of note that the median survival was 411 days in ED patients which compares favorably to other reports. The concept of enhancing dose intensity in order to improve treatment of SCLC patients has been studied intensely [1–3]. Using meta-analysis, Klasa and coworkers [28] showed that the dose intensity and the outcome for patients do not correlate with conventional regimens such as etoposide plus CDDP (EP). Miles and coworkers [29] demonstrated the increase of CR rate using EP alternating with ifosphamide plus doxorubicin on a weekly schedule; however, the median survival was 54 weeks (LD, 58 weeks; ED, 42 weeks), which is similar to standard therapy results. Ihde and coworkers [30] demonstrated no superiority in the efficacy of increased drug doses during the first 6 weeks of treatment in patients with ED SCLC, using high dose EP versus standard dose EP regimen. The haematological toxicity was significantly higher in the high dose EP regimen. Thus, the improvement of measurable outcome endpoints, such as pro-

longation of survival, in patients with high dose chemotherapy has not been confirmed yet [1–3, 5].

Using CSFs that allow high dose chemotherapy regimens to be used safely is a very attractive idea [27, 31]. However, Gurney and coworkers [32] were unable to show a significant difference in the occurrence of febrile episodes with moderately intensive chemotherapy with or without granulocyte–macrophage colony-stimulating factor (GM-CSF) support in patients with SCLC. Furthermore, actual dose escalation of cytotoxic agents was about 0.8–1.5 times the starting dose with CSF support [33–35]. Our data support the use of rhG-CSF to reduce the depth of neutrophil nadir and duration of neutropenia. However, the benefit of using rhG-CSF decreased with the dose escalation of the chemotherapeutic agent. In recent studies thrombocytopenia has interfered with further dose escalation [33, 36]. This study was performed to assess the feasibility of the dose escalating regimen with rhG-CSF support and, therefore, we could not evaluate the real clinical benefits of rhG-CSF, such as reducing antibiotics use or duration of hospitalisation. Other studies have shown the enhanced, ameliorative effect of rhG- or rhGM-CSF in the second cycle of chemotherapy compared to the first cycle, when combined with intensive chemotherapy [24, 37]. Kaplan and coworkers [38] stated that the myelosupportive effect of GM-CSF after intensive chemotherapy was more notable during cycles two to six than after cycle one. Crawford and coworkers [24] also showed that neutrophil nadirs were higher in cycles two to six than in cycle one. In our study, similar results were seen at the dose levels of 60 and 80 mg/m^2/day of VM-26 (Fig. 1). In future studies, the optimal dose and schedule of rhG- or rhGM-CSF need to be determined in order to clarify if "priming" with pre- or concurrent administration of rhG- or rhGM-CSF may be effective for ameliorating chemotherapy-induced neutropenia. The combination use of CSFs and circulating progenitor cells may be promising [39, 40].

A few clinical studies have commented on the hepatotoxicity of VM-26 [41–43]. Approximately 1% of patients (11/1069) experienced liver dysfunction, although it was mild and transient [42]. We carefully reviewed the clinical data of patients who showed abnormal liver function, and they all received blood transfusions before there was an elevation of serum transaminases, which suggests the possibility of serum hepatitis. Iberti and coworkers [44] reported no hepatotoxicity in 30 non-SCLC patients treated at a VM-26 dose level of 100 or 120 mg/m^2/day for 3 days plus CDDP 80 mg/m^2, although 1/14 and 3/15 patients experienced grade 2 or 3 diarrhoea. In our study, 67% of all patients showed grade 3 or 4 diarrhoea at the dose of 120 mg/m^2/day for 5 days. The VM-26 dose-limiting factor was myelotoxicity, especially neutropenia and thrombocytopenia, but diarrhoea was also an intolerable side-effect at the higher dose levels.

In conclusion, the VM-26 plus CDDP regimen with rhG-CSF was active in previously untreated patients with SCLC. The recommended dose of VM-26 for a phase II study in previously untreated patients is 100 mg/m^2/day for 5 days in combination with cisplatin and rhG-CSF. The exact role of dose intensity chemotherapy for SCLC needs to be addressed in appropriately designed, randomised phase III trials.

1. Seifter EJ, Ihde DC. Therapy of small cell lung cancer: a perspective on two decades of clinical research. *Semin Oncol* 1988, **15**, 278–299.
2. Klastersky JA, Sculier JP. Intensive chemotherapy of small cell lung cancer. *Lung Cancer* 1989, 5, 196–206.
3. Ihde DC. Chemotherapy of lung cancer. *N Engl J Med* 1992, 327, 1434–1441.
4. Smith IE, Perren TJ, Ashley SA, *et al.* Carboplatin, etoposide, and ifosphamide as intensive chemotherapy for small-cell lung cancer. *J Clin Oncol* 1990, **8**, 899–905.
5. Johnson DH, Deleo M, Hande K, Wolff ST, Hainthworth JD, Greco FA. High-dose induction chemotherapy with cyclophosphamide, etoposide, and cisplatin for extensive-stage small-cell lung cancer. *J Clin Oncol* 1987, 5, 703–709.
6. Issell BF. The podophyllotoxin derivatives VP16-213 and VM26. *Cancer Chemother Pharmacol* 1982, **7**, 73–80.
7. Samson MK, Baker LH, Talley RW, Fraile RJ. VM26(NSC-122819): a clinical study in advanced cancer of the lung and ovary. *Eur J Cancer* 1978, **14**, 1395–1399.
8. Woods RL, Fox RM, Tattersall MHN. Treatment of small cell bronchogenic carcinoma with VM26. *Cancer Treat Rep* 1979, **63**, 2011–2013.
9. Creech RH, Tritchler D, Ettinger DS, *et al.* Phase II study of PALA, amsacrine, teniposide and zinostatin in small cell lung carcinoma (EST 2579). *Cancer Treat Rep* 1984, **68**, 1183–1184.
10. Pedersen AG, Bork E, Osterlind K, Dombernowsky P, Hansen HH. Phase II study of teniposide in small cell carcinoma of the lung. *Cancer Treat Rep* 1984, **68**, 1289–1291.
11. Johnson DH. New drugs in the management of small cell lung cancer. *Lung Cancer* 1989, 5, 221–231.
12. O'Dwyer PJ, King SA, Fortner CL, Leyland-Jones B. Hypersensitivity reactions to teniposide (VM-26): an analysis. *J Clin Oncol* 1986, **14**, 1262–1269.
13. Joss RA, Cavalli F, Goldhirsch A, Brunner KW. New drugs in small-cell lung cancer. *Cancer Treat Rev* 1986, **13**, 157–176.
14. Suga J, Saijo N, Eguchi K, *et al.* A case of small cell lung cancer successfully treated with VM26. *Jpn J Clin Oncol* 1986, **16**, 123–128.
15. Bork E, Hansen M, Dombernowsky P, Hansen SW, Pedersen AG. Teniposide(VM-26), an overlooked highly active agent in small-cell lung cancer. Results of a phase II trial in untreated patients. *J Clin Oncol* 1986, **4**, 524–527.
16. Long BH, Musial ST, Brattain MG. DNA breakage in human lung carcinoma cells and nuclei that are naturally sensitive or resistant to etoposide and teniposide. *Cancer Res* 1986, **46**, 3809–3816.
17. Ross W, Rowe T, Glisson B, Yalowich J, Liu L. Role of topoisomerase II in mediating epipodophyllotoxin-induced DNA cleavage. *Cancer Res* 1984, **44**, 5857–5860.
18. Van Maanen JMS, Akker EVD, de Vries J, *et al.* Structure-biactivation relationship of a series of podophyllotoxin derivatives. *Eur J Cancer Clin Oncol* 1988, **24**, 1415–1419.
19. Roed H, Vindelov LL, Christensen IJ, *et al.* The effect of the two epipodophyllotoxin derivatives etoposide (VP-16) and teniposide (VM-26) on cell lines established from patients with small cell carcinoma of the lung. *Cancer Chemother Pharmacol* 1987, **19**, 16–20.
20. Hill BT, Bellamy AS. Establishment of etoposide-resistant human epithelial tumour cell line *in vitro*: characterization of patterns of cross-resistance and drug sensitivites. *Int J Cancer* 1984, **33**, 599–608.
21. Giaccone G, Donadlo M, Ferrati P, *et al.* Teniposide in the treatment of non-small cell lung cancer. *Cancer Treat Rep* 1987, **71**, 83–85.
22. Cerny T, Pedrazzini A, Joss RA, Brunner KW. Unexpected high toxicity in a phase II study of teniposide (VM-26) in elderly patients with untreated small cell lung cancer (SCLC). *Eur J Cancer Clin Oncol* 1988, **24**, 1791–1794.
23. Tummarello D, Isidori P, Pasini F, Cetto G, Cellerino R. Teniposide as single drug therapy for elderly patients affected by small cell lung cancer. *Eur J Cancer* 1992, **28A**, 1081–1084.
24. Crawford JC, Ozer H, Stoller R, *et al.* Reduction by granulocyte colony-stimulating factor of fever and neutropenia induced by chemotherapy in patients with small-cell lung cancer. *N Engl J Med* 1991, **325**, 164–170.
25. Eguchi K, Shinkai T, Sasaki Y, *et al.* Subcutaneous administration of recombinant human granulocyte colony-stimulating factor (KRN8601) in intensive chemotherapy for patients with advanced lung cancer. *Jpn J Cancer Res* 1990, **81**, 1168–1174.
26. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1981, **53**, 457–481.
27. Sorensen BT, Nielsen K, Steenholdt S, Schultz H, Jakobsen A. Treatment of extensive small cell lung cancer with carboplatin and teniposide. *Eur J Cancer* 1991, **27**, 1109–1112.
28. Klasa RJ, Murray N, Coldman AJ. Dose-intensity meta-analysis of chemotherapy regimens in small-cell carcinoma of the lung. *J Clin Oncol* 1991, **9**, 499–508.

29. Miles DW, Earl HM, Harper PG, *et al.* Intensive weekly chemotherapy for good-prognosis patients with small-cell lung cancer. *J Clin Oncol* 1991, **9**, 280–285.
30. Ihde DC, Johnson BE, Mulshine JL, *et al.* Randomised trial of high dose versus standard dose etoposide and cisplatin (VP16/Plat) in extensive stage small cell lung cancer (SCLC). *Proc ASCO* 1991, **10**, 240.
31. Crawford J, Green MR. The role of colony stimulating factors as an adjunct to lung cancer chemotherapy: a commentary. *Lung Cancer* 1992, **8**, 153–158.
32. Gurney H, Anderson H, Radford J, *et al.* Infection risk in patients with small cell lung cancer receiving intensive chemotherapy and recombinant human granulocyte–macrophage colony-stimulating factor. *Eur J Cancer* 1992, **28A**, 105–112.
33. Rasthoven J, Levin L, Eisenhauer E, *et al.* Two phase I studies of carboplatin dose escalation in chemotherapy-naive ovarian cancer patients supported with granulocyte–macrophage colony-stimulating factor. *J Natl Cancer Inst* 1991, **83**, 1748–1753.
34. Hoekman K, Wagstaff J, van Groeningen CJ, Vermorken JB, Boven E, Pinedo HM. Effects of recombinant human granulocyte–macrophage colony-stimulating factor on myelosuppression induced by multiple cycles of high-dose chemotherapy in patients with advanced breast cancer. *J Natl Cancer Inst* 1991, **83**, 1546–1553.
35. Walsh C, Blum RH, Oratz R, Goldenberg A, Downey A, Speyer JL. Phase I study of doxorubicin, ICRF-187 and granulocyte-macrophage colony-stimulating factor. *J Cancer Res Clin Oncol* 1992, **118**, 61–66.
36. O'Dwyer PJ, LaCreta FP, Schilder R, *et al.* Phase I trial of thiotepa in combination with recombinant human granulocyte–macrophage colony-stimulating factor. *J Clin Oncol* 1992, **10**, 1352–1358.
37. Neidhart J, Mangalik A, Kohler W, *et al.* Granulocyte colony-stimulating factor stimulates recovery of granulocytes in patients receiving dose-intensive chemotherapy without bone marrow transplantation. *J Clin Oncol* 1989, **7**, 1685–1692.
38. Kaplan LD, Kahn JO, Crowe S, *et al.* Clinical and virologic effects of recombinant human granulocyte–macrophage colony-stimulating factor in patients receiving chemotherapy for human immunodeficiency virus-associated non-Hodgkin's lymphoma: results of a randomized trial. *J Clin Oncol* 1991, **9**, 929–940.
39. Vadhan-Raj S, Broxmeyer HE, Hittelman WN, *et al.* Abrogating chemotherapy-induced myelosuppresion by recombinant granulocyte–macrophage colony-stimulating factor in patients with sarcoma: protection at the progenitor cell level. *J Clin Oncol* 1992, **10**, 1266–1277.
40. Lowry PA, Tabbara IA. Peripheral haematopoietic stem cell transplantation: current concepts. *Exp Haematol* 1992, **20**, 937–942.
41. Macbeth FR. VM26: phase I and II studies. *Cancer Chemother Pharmacol* 1982, **7**, 87–91.
42. O'Dwyer PJ, Alonso MT, Leyland-Jones B, Marsoni S. Teniposide: a review of 12 years of experience. *Cancer Treat Rep* 1984, **68**, 1455–1466.
43. Hayes FA, Green AA, Casper J, Cornet J, Evans WE. Clinical evaluation of sequentially scheduled cisplatin and VM26 in neuroblastoma: response and toxicity. *Cancer* 1981, **48**, 1715–1718.
44. Iberti V, Donadio M, Giaccone G. Cisplatin and teniposide chemotherapy for advanced non-small cell lung cancer. *Eur J Cancer* 1991, **27**, 1104–1106.

Acknowledgements—This study was carried out with the cooperation of the following doctors: Akira Kojima, Fumihiro Oshita, Kazuhiko Nakagawa (National Cancer Center, Tokyo), Ikuo Nomura, Tamotsu Kaneko (Kanagawa Cancer Center), Masaru Suzuki, Junichi Nakano (Kantou Central Hospital), Akio Onaka (The Second Tokyo National Hospital), Tsutomu Fukuda (Shizuoka General Hospital), Kazuo Fujieda (Tokyo Teishin Hospital), Yoshio Murayama (Tokyo University Branch Hospital), Masayuki Noguchi, Kouji Narui (Toranomon Hospital), Akira Nagatomo, Susumu Arai, Kouzou Yamada, Hideo Kunitou (Yokohama Municipal Citizen's Hospital). We thank Dr Dean Brenner (Associate Professor of Internal Medicine, University of Michigan) for his valuable advice on this manuscript. Dr Brenner's activities were supported by the Foundation for Promotion of Cancer Research's Visiting Scientist Program, based on the Comprehensive 10-Year Strategy for Cancer Control. We also thank Dr James R. Jett (Professor of Internal Medicine, Mayo Medical School and Staff Consultant, Mayo Clinic) for his thoughtful suggestions. The secretarial assistance of Ms Sachiyo Asanuma and Yukako Sato is gratefully acknowledged. We also thank Ms Jennifer M. Jett for the English editing of this manuscript.
This study was supported in part by Grant for Aid 10 Year Comprehensive Strategy for Cancer Research, Ministry of Health and Welfare, Japan.

Pergamon

European Journal of Cancer Vol. 30A, No. 2, pp. 194–201, 1994

0959–8049/94 $6.00 + 0.00

0959-8049(93)E0045-R

Feature Articles

What is the Place of Carboplatin in Paediatric Oncology?

François Doz and Ross Pinkerton

INTRODUCTION

THE FIRST experimental evidence of the cytotoxic effect of cisplatin was reported in 1965 [1]. The use of this drug in paediatric oncology practice dates from the end of 1970s [2]. Its use is limited by cumulative toxicity (hearing and renal impairment) [3]. However, the high activity of this drug in numerous childhood tumours has made this drug an essential component of paediatric oncology practice. In an attempt to improve the therapeutic index, a number of platinum analogues have been synthesised. The main analogue used at present is cis-diaminodicarboxylato-cyclobutane-platin (carboplatin), whose indications in solid tumours of childhood are becoming more and more numerous. In this review we consider the pharmacodynamic characteristics and the pharmacokinetics of carboplatin compared to cisplatin, its current indications, toxicity and possible future use in children.