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Original Paper

Phase II Study of Infusional Cisplatin in Combination with Etoposide in the Treatment of Small Cell Lung Cancer

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The efficacy of a 5 day continuous infusion of cisplatin, 25 mg/m²/day, in combination with a bolus infusion of etoposide, 100 mg/m²/day over 2 h for 3 days (PiE therapy), was evaluated in a phase II study of previously untreated patients with small cell lung cancer (SCLC). There were 39 evaluable patients, of whom 17 had limited disease (LD) and 22 extensive disease (ED). The overall response rate was 92% (LD, 100%; ED, 86%). The complete response rate was 21% (LD, 41%; ED, 5%). The median survival time was 45.6 weeks (LD, 123.2 weeks; ED, 28.8 weeks). The major side-effects were grade 3 or 4 leucopenia (55%), neutropenia (88%) and thrombocytopenia (20%). There were no episodes of bleeding, severe infection or treatment-related deaths. PiE therapy was associated with significant myelosuppression, but was effective, with an especially encouraging response rate and survival for LD patients.

Key words: small cell lung cancer, cisplatin, etoposide, continuous infusion, phase II study
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INTRODUCTION

In 1985, Evans and associates [1] used combined chemotherapy of cisplatin and etoposide (PVP) as first-line therapy for small cell lung cancer (SCLC), and obtained a response rate of 86%. In 1988, Einhorn and associates [2] evaluated PVP therapy in patients who did not respond to combined chemotherapy with cyclophosphamide (CPA), doxorubicin (ADM), and vincristine (CAV), and reported a response rate of 81%, including 9% complete responses. They suggested that PVP therapy shows non-cross-resistance to CAV therapy. Subsequently, PVP therapy as the first-line therapy has achieved a response rate of 85–100% [3], and has been widely used instead of CAV therapy. At present, PVP therapy, together with CAV therapy alternating with PVP therapy or CAE therapy (CPA + ADM + etoposide) [4] is considered to be a standard therapy for SCLC.

There are various routes of administration for cisplatin and etoposide in PVP therapy. The cisplatin administration methods include intravenous (i.v.) infusion on day 1 [5, 6], bolus infusion in divided doses for 3–5 days [1, 7–9] and continuous i.v. infusion [7, 10]. At our institution, non-SCLC patients have been treated with a 5 day continuous i.v. infusion of cisplatin (25 mg/m²/day), and good results have been obtained [11, 12].

We therefore carried out a phase II study in SCLC patients, using a 5 day continuous i.v. infusion of cisplatin and bolus infusion of etoposide, and evaluated the response and safety of this schedule.

PATIENTS AND METHODS

The subjects of this study were inpatients at the Tochigi Cancer Center Hospital, Japan between October 1987 and March 1993. All patients had histologically or cytologically proven SCLC and satisfied the following criteria: measurable lesion; ≤79 years of age and performance status (PS) of 0–2; no prior therapy; well retained function of the principal organs; normal bone marrow function (WBC ≥4000/mm³, neutrophil ≥2000/mm³, platelet ≥10 × 10⁴/mm³, haemoglobin ≥10 g/dl); and had provided informed consent.

Pretreatment evaluation included a medical history, physical examination, complete blood count (CBC), determination of urinary creatinine clearance, blood chemistry, chest X-ray, an electrocardiogram (ECG), complete urine analysis, and a bone marrow examination. All patients underwent bronchofibroscopy, a radionuclide bone scan, bone marrow aspiration and/or biopsy, computerised tomography (CT) scan of the brain and thorax, and an abdominal ultrasound examination or CT scan. Physical examinations and chest X-rays were obtained weekly. CBC, biochemical tests and serum electrolyte determinations were performed two or three times per week. A chest CT scan and determination of creatinine clearance were carried out before each course of this therapy. Staging was according to the 4th edition of the UICC TNM classification.

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Twenty-five mg/m² of cisplatin were given daily for 5 days by continuous i.v. infusion. One-third of the daily dose was administered every 8 h dissolved in 800 ml of physiological saline [11]. On days 1–3, 100 mg/m² of etoposide was administered i.v. (PiE therapy).

The anti-emetic drugs used were metoclopramide (3 mg/kg/day, continuous infusion for 5 days), methylprednisolone (125 mg bolus infusion every 8 h days 1–5), diphenhydramine (30 mg orally, days 1–7) and alprazolam (1.2 mg orally, days 1–7) [13]. We did not use serotonin antagonists. From the second cycle, we allowed the use of recombinant human granulocyte colony-stimulating factor (G-CSF) (subcutaneous at 2 μg/kg daily) until the neutrophil count recovered in patients who developed leucopenia (WHO grade ≥3). Chemotherapy was repeated every 4 weeks.

Patients were evaluated for response after completion of two cycles. Complete response (CR) was defined as the complete disappearance of all known disease, as indicated by examinations performed at least 4 weeks apart. Partial response (PR) was defined as a reduction of >50% in the tumour area (determined from the product of the two longest perpendicular tumour diameters, summed over all measurable lesions) over >4 weeks, without the appearance of new lesions. Stable disease (SD) was defined as either a reduction of <50% or an increase of <25% in the tumour area, without the occurrence of new lesion, over >4 weeks. Progressive disease (PD) was defined as an increase of >25% in the tumour area or the appearance of new lesions.

Therapy was discontinued if disease progression occurred after the first course of treatment or if SD was observed after the second course. In patients with a CR or PR, treatment was continued for a total of four courses. All patients achieving a CR received chest radiation therapy (50–60 Gy) after this chemotherapy. Patients achieving a CR were allowed prophylactic whole brain irradiation (30–40 Gy). Patients who were resistant to chemotherapy or who experienced a relapse were given cyclophosphamide 800 mg/m², doxorubicin 50 mg/m², and vincristine 1 mg/m² (CAV) i.v. every 4 weeks as second-line chemotherapy, depending on their clinical condition.

The toxicity criteria recommended by the World Health Organization (WHO) were used. The responses and drug toxicities were evaluated during regular meetings of the group, which consisted of members and extramural observers. Survival curves from day 1 of treatment until death were generated by the method of Kaplan and Meier, and statistical differences between survival curves were computed by the log-rank test. To assess differences between proportions, P values were calculated by the χ^2 test.

RESULTS

Of the 40 patients entered into this study, 39 were considered evaluable for response; 1 patient refused further therapy after the first cycle and thus the response and survival time could not be assessed. Safety was evaluated in all 40 patients. The pretreatment characteristics of the evaluable patients and their therapeutic responses are summarised in Table 1.

Most of the patients were male. 17 had limited disease (LD) and 22 had extensive disease (ED). Those with LD tended to have lower PS than those with ED. One hundred and thirty treatment cycles were completed (median, 3.3 cycles).

The response rate in the LD group was 100%; a CR was observed in 7 patients (41%) and PR in the other 10. The response rate in the ED group was 86%; a CR was observed in 1 patient (5%) and PR in 18. The overall CR rate in the 39 patients was 21% (8/39), and the overall response rate was 92% (36/39). The median duration of response was 53.8 weeks in all patients, 94.6 weeks (range 6–371 weeks) in the LD group and 25.8 weeks (range 7–92 weeks) in the ED group.

Table 1. Patient characteristics

	Limited disease	Extensive disease
Eligible patients	17	23
Evaluable patients	17	22
Age		
Median	61.2	63.5
Range	50–79	43–75
Sex		
Male	16	19
Female	1	3
Performance status		
0	9	6
1	4	6
2	4	10
Response		
CR	7 (41%)	1 (5%)
PR	10	18
SD	–	2
PD	–	1

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

The median survival time was 45.6 weeks in all 39 patients (Figure 1), 123.2 weeks (22–372+ weeks) in the LD group, and 28.8 weeks (12–97 weeks) in the ED group. 7 LD patients are still alive and disease-free (92+, 96+, 99+, 108+, 193+, 324+ and 372+ weeks). The median survival time was compared between PS 0–1 and PS 2. The median survival time was 68.5 weeks in 25 patients with PS 0–1 and 27 weeks in 14 patients with PS 2, being significantly longer in the PS 0–1 group ($P < 0.01$). In the LD group, the median survival time was 130.8 weeks in 13 patients with PS 0–1 and 26.5 weeks in 4 patients with PS 2. In the ED group, the median survival time was 42.6 weeks in 12 patients with PS 0–1 and 24.7 weeks in 10 patients with PS 2 ($P = 0.09$). The 2-year survival rate in all patients was 14.3% (5/35), 38.5% (5/13) in the LD group, and 0% (0/22) in the ED group.

The types and WHO grades of toxicities resulting from the treatment are shown in Table 2 for all 40 patients. The most common toxicity was myelosuppression. Leucopenia <2000/mm³ (grade 3 or 4) was observed in 22 patients (55%), 6 of whom

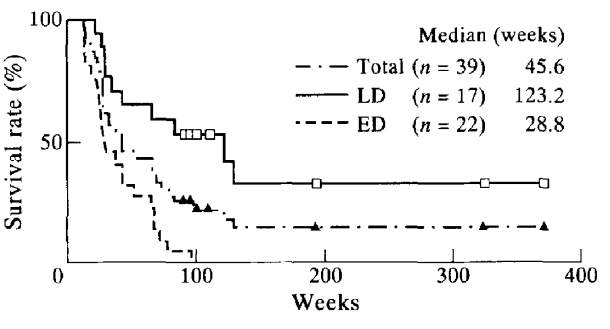

Figure 1. Survival curves of LD and ED patients.

Table 2. Side effects (n = 40)

	Maximum toxicity in terms of WHO grade: no. of patients				
	0	1	2	3	4
Leucopenia	2	1	15	16	6
Thrombocytopenia	20	9	3	6	2
Anaemia	14	10	12	3	1
Nausea, vomiting	19	10	9	2	0
Diarrhoea	34	4	1	1	0
Alopecia	11	0	15	12	2
Neurotoxicity (peripheral)	30	10	0	0	0
Elevated SGOT/SGPT	33	4	3	0	0
Elevated serum creatinine	38	2	0	0	0

(15%) showed grade 4. Neutropenia $<1000/mm^3$ (grade 3 or 4) was observed in 35 patients (87.5%), 28 of whom (70%) showed grade 4. The nadir of the leucocyte count and neutrophil count were recorded after approximately 16 days (range 12–24 days) of treatment. The time required for the neutrophil count to recover to $2000/mm^3$ or more was 24 days (range 16–31 days) after the treatment. 12 patients developed neutropenic pyrexias. The mean duration of the febrile illness was 1.9 days (range 1–5 days). 1 patient had pneumonia. Thrombocytopenia $<5 \times 10^4/mm^3$ (grade 3 or 4) was observed in 8 patients (20%), and anaemia (grade 3 or 4) in 4 patients (10%). There were no episodes of bleeding and fluid overload. No emesis developed in 19 patients (47%), and alopecia was observed in 29 patients (73%). SGOT and/or SGPT (SGOT/SGPT) was transiently increased in 7 patients (18%) as was the serum creatinine in 2 patients (5%). There were no treatment-related deaths.

DISCUSSION

Combined chemotherapy with cisplatin and etoposide has been reported to be effective in previously treated [14] and untreated patients with SCLC [1]. The administration methods of these drugs vary. Cisplatin has been administered by bolus infusion (80–100 mg/m²) on day 1 [5, 6], bolus infusion in divided doses (20–30 mg/m²/day) for 3–5 days [1, 7–9], or continuous i.v. infusion (25–45 mg/m²/day) over 24–120 h [7, 10]. Etoposide has been administered by bolus infusion (80–130 mg/m²/day) for 3 days [1, 5, 7–9], continuous i.v. infusion (130 mg/m²/day) over 72 h [7] or orally (50 mg/m²/day) for 21 days [6].

In this study, continuous i.v. infusion of cisplatin (25 mg/m²/day) for 5 days was combined with bolus infusion of etoposide (100 mg/m²/day) for 3 days. An interval of 4 weeks between chemotherapy courses was used in this regimen because in a preliminary study, it took 3–4 weeks for the neutrophil count to recover to above $2000/mm^3$ from the nadir. In the present study, the neutrophil count recovered to above $2000/mm^3$ on the 24th day (16–31 days) after therapy. Therefore, the interval of 4 weeks between administrations was considered appropriate in this regimen. Compared with the state of the art treatment of SCLC [15], the response rate in our study was higher but the CR rate lower, and the median survival time in all patients and ED patients was similar, although longer in LD patients.

These results are compared in Table 3 with the clinical results reported by Fukuoka and associates [5] and Maksymiuk and associates [7]. The dose intensity of cisplatin in our study was 1.56 times higher than that in Fukuoka and colleagues' study,

Table 3. A comparison of trials using cisplatin and etoposide in SCLC

	Current study	Fukuoka *et al.* [5]	Maksymiuk *et al.* [7]
Treatment schedule*	CI 25 mg/m² CDDP d1–5 BI 100 mg/m² VP16 d1–3	BI 80 mg/m² CDDP d1 BI 100 mg/m² VP16 d1–3	BI 30 mg/m² CDDP d1–3 BI 130 mg/m² VP16 d1–3
Dose intensity			
CDDP	31.3 mg/m²/week	20 mg/m²/week	22.5 mg/m²/week
Etoposide	75 mg/m²/week	75 mg/m²/week	97.5 mg/m²/week
Response			
Overall	92%	78%	87%
ED	86%	78%	82%
LD	100%	77%	92%
Median survival			
Overall	11.4 months	9.9 months	14.6 months
ED	7.2 months	8.3 months	10.5 months
LD	30.8 months	11.7 months	20 months
2 year survival rate			
Overall	14.3%	11.5%	26%
ED	0%	–	9%
LD	38.5%	–	42%
Toxicity			
Leucopenia ≥ grade 3	55%	46%	75%
Thrombocytopenia ≥ grade 3	20%	21%	?
Emesis/nausea ≥ grade 3	5%	?	29%
≥ grade 2	28%	68%	?

* Treatment course was repeated every 4 weeks.

CI, continuous infusion; BI, bolus infusion; CDDP, cisplatin; VP16, etoposide; d, day; ED, extensive disease; LD, limited disease.

and 1.39 times higher than that in Maksymiuk and colleagues' study. The dose intensity of etoposide in our study was similar to Fukuoka's and 0.77 times as high as Maksymiuk's. Our response rate was slightly higher. In our study, the median survival time was longer in the LD patients, but slightly lower in the ED patients, compared with the other studies. The poor results of median survival in our study may be associated with the high percentage of patients with PS 2 compared with Fukuoka's and Maksymiuk's studies. The main side-effect was haemotoxicity, the incidence of which did not markedly differ among the three studies, although the incidence of nausea and vomiting was lower in our study than in the other studies. There were no treatment-related deaths in our study, but in the study by Fukuoka and colleagues 3 patients (3%) died, and in that conducted by Maksymiuk and colleagues 2 patients (1.5%) died.

In conclusion, the dose intensity of cisplatin in this study is 1.39–1.56 times higher than that obtained with a bolus infusion of cisplatin and etoposide, and a response rate of 92% (LD, 100%; ED 86%) was obtained. The principle side-effects were haematological, the incidence of leucopenia and thrombocytopenia being similar to that seen in comparable studies, and nausea and vomiting being less frequently encountered. There were no treatment-related deaths. As neutropenia is a side-effect that can be treated with G-CSF, PiE therapy appears to be a safe and effective regimen for the treatment of SCLC.

1. Evans WK, Shepherd FA, Feld R, Osoba D, Dang P, Deboer G. VP-16 and cisplatin as first-line therapy for small-cell lung cancer. *J Clin Oncol* 1985, **3**, 1471–1477.
2. Einhorn LH, Crawford J, Birch R, Omura G, Johnson DH, Greco FA. Cisplatin plus etoposide consolidation following cyclophosphamide, doxorubicin, and vincristine in limited small-cell lung cancer. *J Clin Oncol* 1988, **6**, 451–456.
3. Seifter EJ, Ihde DC. Therapy of small cell lung cancer: a prospective on two decades of clinical research. *Semin Oncol* 1988, **15**, 278–299.
4. Bunn PA, Greco FA, Einhorn L. Cyclophosphamide, doxorubicin, and etoposide as first-line therapy in the treatment of small-cell lung cancer. *Semin Oncol* 1986, **13**, 45–53.
5. Fukuoka M, Furuse K, Saijo N, *et al.* Randomized trial of cyclophosphamide, doxorubicin, and vincristine versus cisplatin and etoposide versus alternation of these regimens in small-cell lung cancer. *J Natl Cancer Inst* 1991, **83**, 855–861.
6. Schiller JH, Ettinger DS, Larson MM, Gradishar W, Merkel D, Johnson DH. Phase II trial of oral etoposide plus cisplatin in extensive stage small cell carcinoma of the lung: an Eastern Cooperative Oncology Group Study. *Eur J Cancer* 1994, **30A**, 158–161.
7. Maksymiuk AW, Jett JR, Earle JD, *et al.* Sequencing and schedule effects of cisplatin plus etoposide in small-cell lung cancer: results of a North Central Cancer Treatment Group Randomized Clinical trial. *J Clin Oncol* 1994, **12**, 70–76.
8. Feld R, Evans WK, Coy P, *et al.* Canadian multicenter randomized trial comparing sequential and alternating administration of two non-cross resistant chemotherapy combinations in patients with limited small cell-carcinoma of the lung. *J Clin Oncol* 1987, **5**, 1401–1409.
9. Roth BJ, Johnson DH, Einhorn LH, *et al.* Randomized study of cyclophosphamide, doxorubicin, and vincristine versus etoposide and cisplatin versus alternation of these two regimens in extensive small-cell lung cancer: a phase III trial of the Southeastern Cancer Study Group. *J Clin Oncol* 1992, **10**, 282–291.
10. Frytak S, Eagan RT, Richardson RL, *et al.* Cyclophosphamide, etoposide and infusion cisplatin in refractory small cell lung cancer. *Am J Clin Oncol* 1987, **10**, 33–35.
11. Saito Y, Mori K, Tominaga K, Yokoi K, Miyazawa N. Phase II study of 5 day continuous infusion of cis-diamminedichloroplatinum (II) in the treatment of non-small-cell lung cancer. *Cancer Chemother Pharmacol* 1990, **26**, 389–392.
12. Mori K, Saitoh Y, Tominaga K. Recombinant human granulocyte colony-stimulating factor in patients receiving intensive chemotherapy for non-small cell lung cancer. *Eur J Cancer* 1993, **29A**, 677–680.
13. Mori K, Saitoh Y, Tominaga K. Antiemetic efficacy of alprazolam in the combination of metoclopramide plus methylprednisolone. *Am J Clin Oncol* 1993, **16**, 338–341.
14. Evans WK, Osoba D, Feld R, Shepherd FA, Bazos MJ, DeBoer G. Etoposide (VP-16) and cisplatin: an effective treatment for relapse in small-cell lung cancer. *J Clin Oncol* 1985, **3**, 65–71.
15. Aisner J, Alberto P, Bitran J, *et al.* Role of chemotherapy in small cell lung cancer: a consensus report of the International Association for the Study of Lung Cancer Workshop. *Cancer Treat Res* 1983, **67**, 37–43.

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