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Phase II trial of combination chemotherapy with cisplatin, carboplatin and etoposide in stage IIIB and IV small-cell lung cancer

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Abstract *Purpose*: A phase II trial combining cisplatin, carboplatin and etoposide was conducted in previously untreated patients with stage IIIB and IV small-cell lung cancer, in an attempt to increase response rates and prolong survival. *Methods*: Previously untreated patients with small-cell lung cancer, with measurable disease, aged ≤ 72 years, performance status ≤ 2, and adequate hematologic, hepatic and renal function were enrolled in the study. They were treated with 80 mg/m^2 cisplatin on day 1, 100 mg/m^2 carboplatin on days 2, 3 and 8, and 50 mg/m^2 etoposide on days 1, 2, 3 and 8. *Results*: A total of 46 patients (20 with stage IIIB and 26 with stage IV disease) were enrolled in the study. A total of 186 courses of chemotherapy were given, and the dose was reduced in 27 courses (15%). The chemotherapy was repeated for four or more courses in 30 patients. There were 10 complete responses and 32 partial responses, for a total response rate of 91% (95% confidence interval, 79% to 98%). The median survival time and 2-year survival rates were 18 months and 22% for stage IIIB disease, and 14 months and 15% for stage IV disease. Major side effects were hematologic: leukopenia, anemia, and thrombocytopenia of grade 3 or more occurred in 48%, 46%, and 43% of patients, respectively. *Conclusions*: The three-drug regimen of cisplatin, carboplatin and etoposide is feasible and active against small-cell lung cancer.

Key words Small-cell lung cancer · Chemotherapy · Cisplatin · Carboplatin · etoposide

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Introduction

Small-cell lung cancer (SCLC) represents 15% to 25% of all lung cancers, and is distinguished from non-small-cell lung cancer (NSCLC) by its high responsiveness to chemotherapy and radiotherapy, as well as its aggressive clinical features. Conventional-dose chemotherapy results in high response rates, but rarely in cure [1]. Although dose escalation of chemotherapy can produce enhanced response rates, toxic effects and treatment-related deaths cancel out any advantage of intensive therapy [2]. There are discrepancies in the survival time of patients in randomized trials comparing high-dose with standard-dose regimens [3–6]. However, an increase in survival time could be expected if the adverse effects of dose-intensified chemotherapy were overcome. Fukuoka et al. reported that the CODE regimen, which

includes the use of granulocyte-colony stimulating factor (G-CSF), produces an increase in median survival time (MST) (7).

The combination of chemotherapeutic agents with different toxicities may allow for the safe administration of higher doses of the drugs. Cisplatin (CDDP) and carboplatin (CBDCA) have distinct pharmacodynamics and additive cytotoxicity in lung cancer cell lines, while sharing a common mechanism of antitumor action [8]. In an effort to overcome the various toxicities induced by high-dose CDDP, combination chemotherapy with CDDP and CBDCA has been performed in patients with advanced NSCLC, and has demonstrated tolerable toxicity [9, 10].

With this background, we conducted a phase II trial combining CDDP, CBDCA, and etoposide (VP-16) in patients with previously untreated SCLC to evaluate the activity and feasibility of the regimen.

Patients and methods

The eligibility criteria for this study were as follows: cytologically or histologically confirmed SCLC; stage IIIB or IV disease according to the new international staging system [11]; no previous treatment; measurable disease; age 72 years or less; World Health Organization (WHO) performance status of 0, 1 or 2; leukocyte count 4000/μl or more; platelet count 100 000/μl or more; hemoglobin 11 g/dl or more; serum bilirubin 1.5 mg/dl or less; serum AST/ALT 50 IU/l or less; serum creatinine 1.5 mg/dl or less; creatinine clearance (CCr) 70 mL/min or more; no uncontrolled infection; no evidence of any severe heart disease; and no concomitant malignant disease.

All patients underwent the following investigations: complete clinical examination, complete blood cell count, chemistries including CCr, ECG, chest roentgenogram, fiberoptic bronchoscopy, computed tomography scans of the thorax, upper abdomen, and brain, and isotope bone scan. Informed consent was obtained from all patients.

CDDP (80 mg/m^2) diluted with 500 ml normal saline was administrated as a 90-min infusion, followed by an infusion of 500 ml 10% mannitol on day 1, when the patients received hydration of at least 2700 ml CBDCA (100 mg/m^2) on days 2, 3 and 8, and VP-16 (50 mg/m^2) on days 1, 2, 3 and 8, were administered with hydration of at least 1500 ml.

Each drug was administered at the full calculated dose when the leukocyte count was ≥4000/μl and the platelet count ≥100 000/μl. If either the leukocyte count or the platelet count was below these levels, chemotherapy was withheld until the counts recovered. If grade 4 nonhematologic toxicities occurred, treatment was discontinued. If nephrotoxicity was observed after the chemotherapy, the doses of the platinum agents were reduced as follows: Ccr 60–70 ml/min, CDDP 40 mg/m^2 and CBDCA 300 mg/m^2; Ccr 50–60 ml/min, CDDP 20 mg/m^2 and CBDCA 240 mg/m^2. If severe nephrotoxicity was observed (Ccr < 50 mg/m^2 or serum creatinine ≥1.5 mg/dl) the study was discontinued.

This treatment was repeated every 4 weeks. All patients had to be given at least two courses of chemotherapy unless progression of disease, excessive toxicity, or rapid clinical deterioration occurred. Treatment was continued for a maximum of six cycles, provided progression did not occur.

Response was evaluated according to the WHO criteria [12]. The response rate was defined as the total number of patients having a complete response (CR) or a partial response (PR). Toxicities were graded according to the WHO criteria [12].

The binomial exact method (STATA) was used for the calculation of the confidence intervals of the chemotherapy responses. The Kaplan-Meier method was used for the estimation of patient survival, which was defined as the time from the day of the first cycle of chemotherapy through the day of death.

Results

A total of 46 patients were entered into the study from April 1992 to August 1995 (Table 1). All the patients were eligible. The median follow-up period was 17 months (range 4 to 35+ months). Among the 46 patients, 26 had metastatic lesions to distant organs (one metastatic site, 22 patients; two sites, 3 patients; three sites, 1 patient).

One to six cycles of chemotherapy were given (median, four cycles; one cycle, 1 patient; two cycles, 9 patients; three cycles, 6 patients; four cycles, 13 patients; five cycles, 5 patients; six cycles, 12 patients). Of all 186 cycles, the full calculated dose was administered in 159 cycles (85%), and dose reduction was performed in 27 cycles in 16 patients (25% dose reduction of each drug as a result of hematologic toxicity, 24 cycles; reduction of platinum agents as a result of nephrotoxicity, 3 cycles). The response to therapy was as follows: CR, 10; PR, 32; no change (NC), 2; progressive disease (PD), 2. The overall response rate was 91% (95% confidence interval, 79% to 98%). The median duration of response was 6 months (range, 1 to 32 months). After the combination chemotherapy, 19 (41%) patients including the 4 with NC or PD received thoracic irradiation, and 5 (11%) patients received cranial irradiation.

Hematologic toxicity was the major toxicity of this regimen (Table 2). Leukopenia, anemia, and thrombocytopenia of WHO grade 3 or more were observed in

Table 1 Clinical characteristics of patients with small-cell lung cancer enrolled in the study

Characteristic	Number of patients	Percentage
Number of patients	46	
Gender		
Male	41	89
Female	5	11
Age (years)		
Median	66	
Range	46–72	
Performance status		
0	3	7
1	36	78
2	7	15
Weight loss		
+	11	24
−	35	76
Distant metastases		
0[a]	20	43
1	22	48
2 or more	4	9

[a] Of the 20 patients without a distant metastasis, 15 had a malignant effusion

Table 2 Toxicities according to the World Health Organization criteria

Toxicity	Grade					Toxicity grade 3 or more (%)
	0	1	2	3	4	
Leukopenia	3	7	14	18	4	22 (48)
Anemia	2	6	17	14	7	21 (46)
Thrombocytopenia	11	8	7	5	15	20 (43)
Nausea/vomiting	8	14	13	11	–	11 (24)
Alopecia	4	6	26	10	–	10 (22)
Elevation of BUN	31	11	3	1	0	1 (2)
Elevation of serum creatinine	38	6	2	0	0	0
Elevation of alkaline phosphatase	38	6	2	0	0	0
Elevation of transaminase	36	10	0	0	0	0

48%, 46% and 43% of the patients, respectively. Thrombocytopenia of WHO grade 4 was seen in 15 patients (33%), although no obvious bleeding tendency was observed. Nonhematologic toxicities of WHO grade 3 consisted mainly of nausea/vomiting (24%) and alopecia (22%). Elevation of the BUN (WHO grade 3) was seen in only one patient, which was not associated with an elevation of the serum creatinine, and which was transient. There were no deaths related to the treatment.

The 1-year and 2-year overall survival rates of patients were 70% and 18%, respectively (Fig. 1). The MST was 17 months (range, 4 to 35+ months). For the 20 patients with stage IIIB disease, the 1-year and 2-year survival rates, and MST were 75%, 22%, and 18 months (range, 4 to 26+ months), respectively. For the 26 patients with stage IV disease, the 1-year and 2-year survival rates, and MST were 65%, 15%, and 14 months (range, 4 to 35+ months), respectively.

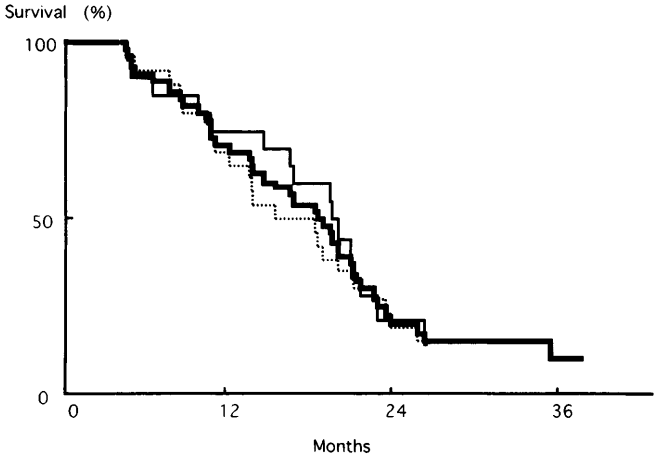

Fig. 1 In terms of overall survival for the 46 patients (—), the median survival, and 1-year and 2-year survival rates were 17 months, 70% and 18%, respectively. Of the 46 patients, 6 were alive at the time of writing. The median survival times of the 20 patients with stage IIIB disease (—) and of the 26 patients with stage IV disease (···) were 18 months and 14 months, respectively

Discussion

The combination of CDDP and VP-16 is a standard regimen for the treatment of SCLC [4]. However, the administration of CDDP is often associated with nausea, vomiting, and other adverse effects, such as renal and neurologic toxicity, hindering the administration of high doses of CDDP. The combination of CBDCA and VP-16 is estimated to have similar activity to CDDP and VP-16 [13]. Because CDDP and CBDCA have distinct pharmacodynamics and additive cytotoxicity in lung cancer cell lines, and different dose-limiting toxicities, high doses of platinum compounds can be administered in this combination. Dose-intense CDDP and CBDCA and vindesine has been reported in patients with NSCLC [14, 15]. Dose intensification of the three-drug regimen, CDDP, CBDCA and VP-16, with or without hematopoietic growth factors has also been reported in patients with NSCLC [16, 17] and SCLC [18]. Sakurai et al. conducted a phase I/II trial of CDDP, CBDCA and VP-16 in 25 patients with SCLC (9 limited disease [LD] and 16 extensive disease [ED]), and recommended a dose of 60 mg/m^2 CDDP, 200 mg/m^2 CBDCA and 300 mg/m^2 VP-16 [18]. They reported that the overall response rate is 91%, with a median survival of 16.6 months.

We administered 80 mg/m^2 CDDP, 300 mg/m^2 CBDCA, and 200 mg/m^2 VP-16. Hematologic toxicity, particularly thrombocytopenia and leukopenia, was the major toxicity of this regimen. However, it was acceptable. Nephrotoxicity and neurotoxicity were minimal. The combination of CDDP and CBDCA is reported to be less toxic than high-dose CDDP [10]. In terms of overall response rate and survival, our results are in general agreement with those of Sakurai et al. As shown in Fig. 1, we achieved an encouraging survival not only in patients with stage IIIB disease, but also in those with stage IV disease. This may, in part, have resulted from patient selection since 22 of 26 patients with stage IV disease had only one metastatic site, or from improved diagnostic procedures [19]. In addition, the encouraging survival in the present study may have been a result of the relatively high dose of platinum agents, as ED-SCLC is more heterogeneous than LD-SCLC, and may contain more resistant components [20], for example NSCLC.

SCLC is known to contain NSCLC components [21], and chemotherapy to SCLC often brings about morphological changes such as partial or complete conversion to NSCLC [22]. It has been reported that the addition of CDDP to the basic regimen improves the survival of patients with NSCLC [23, 24], and that high-dose CDDP is associated with response and survival advantages [25, 26]. Regimens containing high doses of platinum compounds such as CDDP may therefore be effective in more advanced SCLC, which may contain more chemoresistant components.

In conclusion, the combination of CDDP, CBDCA and VP-16 is feasible and active against ED-SCLC. Further evaluation of this three-drug combination at the doses and schedule used in this study is warranted.

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