Combination Chemotherapy of Alternating Etoposide and Carboplatin with Weekly Administration of Irinotecan and Cisplatin in Extensive-stage Small-cell Lung Cancer

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Abstract. *Background: A phase II study was conducted to determine the tumor efficacy and tolerance of alternating chemotherapy in extensive-stage small-cell lung cancer (ED-SCLC). Patients and Methods: Thirty-six patients with previously untreated ED-SCLC were enrolled in the study. At least four courses of chemotherapy consisting of alternation of two drug combinations were given: alternating cycles of etoposide and carboplatin (EC) with weekly administration of irinotecan and cisplatin (IP) at 3- or 4-week intervals. Results: The overall response rate was 81.8%. The median duration of survival and progression-free survival were 314 days and 144 days, respectively. Hematological toxicity was the main adverse event. Grade 3 or 4 neutropenia, thrombocytopenia and anemia were observed in 69.2, 25.6 and 23.1% of the patients, respectively. Severe diarrhea (10.8%) was remarkable during the IP regimen. Conclusion: This novel alternating chemotherapy for patients with ED-SCLC showed moderate tumor efficacy and an acceptable safety profile.*

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Lung cancer is the leading cause of cancer-related death and the incidence rate is steadily increasing in Japan. Small-cell lung cancer (SCLC) accounts for 15-20% of all lung cancer cases; it is one of the most chemo-sensitive solid tumors and some active chemotherapeutic agents have facilitated the development of effective combination regimens.

In the early 1990s, commonly used regimens for SCLC consisted of combinations of etoposide plus cisplatin (EP) or cyclophosphamide, doxorubicin and vincrisitine (CAV) (1, 2). Despite the substantial initial sensitivity of SCLC to chemotherapy, a high rate of relapse has been observed. In order to overcome this hurdle for successful treatment, other therapeutic approaches have been investigated, including alternating non-cross-resistant, high-dose and dose-intensive chemotherapies (1-5). However, these new strategies do not appear to have provided any obvious advantage on the survival of patients with extensive- or limited-stage SCLC. With regard to alternating non-cross-resistant chemotherapy, based upon the mathematical model developed by Goldie *et al.* (6), a combination chemotherapy of alternating CAV with EP (CAV/EP) also provided no therapeutic advantage compared with either CAV- or EP-alone in randomized studies (1, 2). It was concluded that these failed attempts could be ascribed to incomplete non-cross-resistance between CAV and EP, thus, further trials in this setting should await for the development of regimens that are more non-cross-resistant (1, 2).

EP is presently accepted as one of the standard regimens for therapy of extensive-stage SCLC. Furthermore, combination of etoposide plus carboplatin (EC) has shown

sufficient efficacy against SCLC, comparable to that of EP (7). Irinotecan hydrochloride (CPT-11), a topoisomerase I inhibitor, is effective as a single-agent against SCLC, and the combination regimen of CPT-11 plus cisplatin (IP) also demonstrates acceptable activity against SCLC (8, 9). Ando *et al*. reported that weekly administration of cisplatin in a single-dose in combination with CPT-11 was also effective (10). Both etoposide, a topoisomerase II inhibitor, and CPT-11 are effective chemotherapeutic agents against SCLC and it is assumed that these drugs are non-cross-resistant with each other due to their different mechanisms of action.

Therefore, we conducted a phase II study in ED-SCLC to determine tumor efficacy and tolerance of a new alternating non-cross-resistant chemotherapy, consisting of the alternation of etoposide and carboplatin with weekly administration of CPT-11 and cisplatin.

Patients and Methods

Patients. Eligibility criteria for study entry included histologically- or cytologically-confirmed SCLC; extensive disease (defined as distant metastasis, contralateral hilum node metastasis, or both; those with malignant pleural effusion alone were also included); measurable disease; no prior therapy; age 20 to 75 years; an Eastern Cooperative Oncology Group performance status of 0 to 2; adequate organ function, defined as a white blood cell count of at least 4,000/μl and less than 12,000/μl, a platelet count of at least 100,000/μl, a hemoglobin level of at least 9.5 g/dl, a bilirubin level of less than 1.5 mg/dl, serum transaminase and alkaline phosphatase levels of less than twice the upper limit of normal, a creatinine value of less than 1.5 mg/dl; a 24-h creatinine clearance level of at least 50 ml/min; PaO_2 level of at least 70 Torr; and a life expectancy of at least three months. Written informed consent was obtained from each patient. Patients who were excluded had one or more of the followings: active infection, other active malignant disease, pulmonary fibrosis or interstitial pneumonia, ileus, intractable diarrhea, uncontrolled complications (diabetes mellitus, bronchial asthma, cardiac disease *etc*.), symptomatic brain metastases, massive ascites or pleural effusion, pregnancy, or medical history of drug hypersensitivity.

Pre-registration evaluations consisted of a complete medical history consideration, physical examination, recording of performance status, complete blood cell count with differential serum biochemistry, urine analysis, and electrocardiogram (ECG). Patients were monitored weekly throughout treatment by physical examination, recording of toxicities, complete blood cell count with differential, and serum chemistry determination. Radiographic evaluation included chest X-ray, computed-tomography scans of brain, chest and abdomen, and radionuclide bone scan. This study was approved by the Institutional Review Boards of all participating hospitals.

Treatment. A regimen of etoposide and carboplatin was alternated with weekly irinotecan and cisplatin treatments given at 3- or 4-week intervals. Etoposide was administered at 100 mg/m^2 over 2-h by intravenous (*i.v.*) infusion on days 1 to 3. Carboplatin, dosed to a target (AUC) of 5× (24-h creatinine clearance + 25) according to Calvert's formula, was administered over 2 h by *i.v.* infusion on day 1 before administration of etoposide (11). On days 1, 8 and 15, CPT-11 was administered at 60 mg/m^2 for over 2 h by *i.v.* infusion and cisplatin was sequentially given at 30 mg/m^2 over half an hour by *i.v.* infusion with adequate hydration before and after treatment and with furosemide diuresis. Standard antiemetic medication included serotonin 5-HT3-receptor antagonist and corticosteroids given half an hour before each chemotherapy regimen. Administration of granulocyte colony-stimulating factor (G-CSF) was permitted when grade 4 neutropenia or febrile neutropenia with grade 3 neutropenia were observed and preventive use of G-CSF was allowed when grade 4 neutropenia was detected during the previous chemotherapy.

Dosage modifications of each drug were made based upon hematological, renal, and gastrointestinal toxicity according to the NCI-Common Toxicity Criteria version 2.0 (12). If one of the therapeutic regimens led to no tumor shrinkage, it was discontinued and the effective one was allowed to be continued. The patients underwent at least four cycles of chemotherapy unless disease progression or severe toxicities including renal, gastrointestinal (especially diarrhea) and others were observed. No maintenance treatment was used.

Evaluation. Toxicity was evaluated after each cycle according to NCI-Common Toxicity Criteria version 2.0. Patients were evaluated for response according to the WHO criteria (13). In brief, complete response (CR) was defined as complete disappearance of all tumor lesions for at least four weeks, with documented disappearance of all targeted lesions by physical examination and radiographic imaging and no appearance of new lesions. Partial response (PR) was indicated by a decrease of 50% or greater, compared with initial measurements, in the sum of the products of the two largest perpendicular diameters of all measurable lesions and no concomitant growth of new lesions for at least one month. Stable disease (SD) was indicated by a decrease of less than 50% or an increase in tumor size less than 25% over the initial measurements. Progressive disease (PD) was defined as an increase of 25%, or greater, over the initial measurements in the sum of the products of the two largest perpendicular diameters of any measurable lesions, and relapse was documented if reappearance, enlargement, or novel occurrence of a lesion was confirmed.

A full staging evaluation was performed before treatment initiation, as described above, and a follow-up evaluation was performed after each course of chemotherapy was completed. The response rate was confirmed by objective extramural review.

Statistical analysis. The primary end-point of this study was the objective response rate (ORR); secondary end-points were determination of overall survival, progression-free survival and evaluation of toxicity. Overall survival was calculated using the Kaplan-Meier method and was calculated from the day of start of treatment until death by any cause; surviving patients were censored at the last date of follow-up. Progression-free survival was calculated from the day of treatment until disease progression or death from any cause. Assuming that an 80% ORR in eligible patients would indicate potential usefulness, whereas a 60% ORR would constitute the lower limit of interest, with α=0.05 and β=0.20, the estimated accrual was 35 patients.

Results

A total of 36 consecutive patients with previously-untreated ED-SCLC were enrolled from four institutions between November 1998 and July 2004. Thirty-three patients were

Table I. *Patients' characterisitics and drug delivery.*

Eligible patients, n	33
Median age (range), years	65 (44-75)
Gender (M/F)	29/4
ECOG PS (0-1/2)	25/8
ED	27
PE	6
Chemotherapy cycles	
1	1
2	5
3	4
4	12
5	6
6	5

ED, Extensive disease, patients with distant metastasis, contralateral hilum node metastasis, or both; PE, patients with malignant pleural effusion alone; M, male; F, female; ECOG, Eastern Cooperative Oncology Group.

Table II. *Tumor response and survival.*

	n	%
Response		
Complete response	3	9.1
Partial response	24	72.7
Stable disease	2	6.1
Progressive disease	4	12.1
Overall response rate	27	81.8 (95% CI=68.6-95)
ED	22/27	81.5
PE	5/6	83.3
Disease control rate	29	87.9
Survival		
Median survival time (days)		314
Median PFS (days)		133
1-year OS (%)		45 (95% CI=30.1-66.7)

ED, extensive disease, patients with distant metastasis, contralateral hilum node metastasis, or both; PE, patients with malignant pleural effusion alone; PFS, progression-free survival; OS, overall survival; 95% CI, 95% confidence interval.

eligible and assessable for efficacy and safety of the treatment; three patients were not assessable because they did not undergo the chemotherapy. Characteristics of these 33 patients are shown in Table I. There were 29 men and four women, with a median age of 65 years, and 76% of them had a good performance status of 0 or 1. There were 27 patients with distant metastasis, contralateral hilum node metastasis, or both, and six patients with malignant pleural effusion-alone. The median number of chemotherapy cycles was four (range 1-6). Twenty-three patients underwent the planned four or more cycles of chemotherapy, although 10 patients underwent three or fewer cycles because of disease progression (six patients), severe adverse events (three patients) or both (one patient).

The ORR and CR were 81.8% [27/33 patients, 95% confidence interval (CI)=68.6-95%] and 9.1% [3/33, 95% CI=0-18.9%], respectively (Table II). The disease control rate was 87.9% [29/33, 95% CI=76.8-99.0%], whereas disease progression was observed in four patients. The response rates in patients with distant metastasis, contralateral hilum node metastasis, or both, and in those with malignant pleural effusion-alone were 81.5% [22/27, 95% CI=66.9-96.1%] and 83.3% [5/6, 95% CI=68.1-98.5%], respectively. At the time of analysis, 27 patients had died, while six patients had been lost to follow-up. The overall median survival time (MST) was 314 days, and one-year overall survival was 45% [95% CI=30.1-66.7%] (Figure 1, Table II). The median progression-free survival time was 144 days (Figure 2).

Overall adverse events are demonstrated in Table III. Hematological toxicity was the main event. Grade 3 or 4 neutropenia, thrombocytopenia and anemia were observed in 69.2, 25.6 and 23.1% of the patients, respectively. With regard to non-hematological adverse events, diarrhea, nausea/vomiting and anorexia were observed in 20.5, 7.7 and 7.7% of the patients, respectively. Adverse events are shown according to the course of each treatment in Table IV. Hematological adverse events were more common during the EC regimen than in the IP one. Grade 3 or 4 neutropenia, thrombocytopenia and anemia were observed in 80.0, 21.7 and 11.7% of the patients during the EC regimen, respectively. By contrast, grade 3 or 4 neutropenia, thrombocytopenia and anemia were observed in 27.7, 4.6 and 15.4% of the patients during the IP regimen, respectively. Non-hematological adverse events frequently occurred during the IP regimen, in particular, severe diarrhea (10.8%) was remarkable. No treatment-related death occurred during either regimen.

Table III. *Adverse events (n=33) experienced due to combination chemotherapy.*

	Grade 3	Grade 4	≥Grade 3 (%)
Hematological			
Neutropeia	8	19	69.2
Thrombocytopenia	6	4	25.6
Anemia	7	2	23.1
Non-hematological			
Diarrhea	7	1	24.2
Nausea/vomiting	3	0	7.7
Anorexia	2	1	7.7

Discussion

CPT-11 is a camptothecin analog with strong antitumor activity and is a strong inhibitor of topoisomerase I, thereby of nucleic acid synthesis, in mammalian cells (14). On the other hand, epipodophyllotoxins such as etoposide are

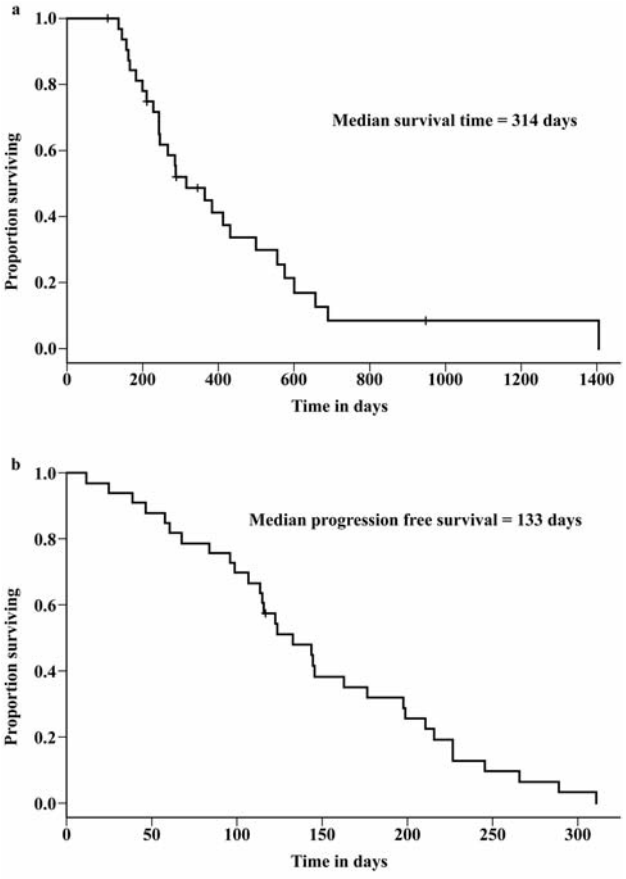

Figure 1. *Overall survival (a) and progression-free survival (b), Kaplan-Meier curves.*

anticancer agents which promote cytotoxicity by inhibiting topoisomerase II, resulting in an accumulation of DNA breaks (15). Both agents are effective against SCLC, and it is assumed that these drugs are potentially non-cross-resistant with each other because they have different mechanisms of action. It is generally thought that resistance to topoisomerase I inhibitors is caused by the following mechanisms: inadequate accumulation of drug in the tumor, resistance-conferring alterations in topoisomerase I, or alterations in the cellular response to topoisomerase I-CPT interaction (16, 17). Furthermore, it is believed that resistance to topoisomerase II inhibitors is associated with active efflux of drug from tumor cells through P-glycoprotein, reduction of the activity of topoisomerase II and reduction of the expression of mismatch repair genes (18, 19).

Regarding cross-resistance between topoisomerase I and II inhibitors, Chauvier *et al*. showed that MCF7/VP and MCF7/DOX breast carcinoma cells, which are resistant to both etoposide and daunorubicin and express multidrug resistance-associated protein (MRP-1), were resistant to CPT-11 (20). However, Schneider *et al*. reported that MCF7/VP, which was selected for resistance to etoposide by stepwise exposure to two-fold increasing concentrations of this agent, exhibited no cross-resistance to camptothecin (21). Furthermore, it has been demonstrated that sequential and simultaneous association of camptothecin and daunorubicin provides complete reversal of resistance, showing a synergistic effect in daunorubicin-resistant cells, and camptothecin has been suggested as a potential candidate for the reversal of the MRP1 phenotype at clinically achievable concentrations (20). No conclusive evidence has shown cross-resistance between topoisomerase I and II inhibitors.

In this study, we have demonstrated the efficacy of a novel alternating non-cross-resistant chemotherapy of etoposide and carboplatin with weekly administration of CPT-11 and cisplatin for patients with previously untreated ED-SCLC, as shown by a response rate of 81.8%, overall MST of 314 days, and one-year overall survival rate of 45%.

In previous phase II and III studies involving patients with previously untreated ED-SCLC, combination chemotherapy of EP and IP had shown response rates of 57 to 78% and 60 to 87%, respectively, while that of CAV/EP combination chemotherapy was reported to be 59-76% (1, 2, 9, 22, 23). The MST of patients after EP, IP and CAV/EP were shown to be 8.6 to 9.9 months, 9.9 to 13.0 months, and 8.1 to 11.8 months, respectively (1, 2, 9, 22, 23).

A phase III study in Japan revealed that combination chemotherapy using IP is more effective against extensive-stage SCLC compared with EP, although the benefit of the IP regimen has not yet been confirmed (22). The Southwest Oncology Group 0124 trial, however, failed to show a survival benefit of IP over EP in patients with previously untreated ED-SCLC (23). Lara *et al*. reported significant differences between the 9511 and 0124 populations in patient demographics, toxicity, and efficacy and concluded that these results warrant: consideration of differential patient characteristics and outcomes among populations receiving identical therapy; utilization of the common arm model in prospective trials; and inclusion of pharmacogenomic correlates in cancer trials where ethnic/racial differences in drug disposition are expected (24).

Hematological toxicities were the common adverse events in this study; toxicities of grade 3 or 4 including neutropenia (69.2%), thrombocytopenia (25.6%) and anemia (23.1%) were observed. Non-hematological adverse events such as diarrhea (24.2%), nausea/vomiting (7.7%) and anorexia (7.7%) also occurred. According to the course of each treatment, the incidence of hematological toxicities on EC was similar to that observed in earlier phase III trials for previously untreated SCLC (22, 23). On the other hand, the incidence of hematological toxicities on IP was different to the one observed previously in the phase III trials because of weekly administration of cisplatin. The incidence of severe

Table IV. *Adverse events according to treatment course for each regimen.*

	Etoposide/carboplatin (60 courses)			Irinotecan/cisplatin (65 courses)		
	Grade 3	Grade 4	≥Grade 3 (%)	Grade 3	Grade 4	≥Grade 3 (%)
Hematological						
Neutropeia	21	27	80.0	15	3	27.7
Thrombocytopenia	8	5	21.7	2	1	4.6
Anemia	7	0	11.7	8	2	15.4
Non-hematological						
Diarrhea	1	0	1.7	6	1	10.8
Nausea/vomiting	0	0	0.0	3	0	4.6
Anorexia	0	1	1.7	2	1	4.6

neutropenia (27.7%) was lower and that of severe thrombocytopenia (15.4%) was higher than previously (1, 23). Non-hematological adverse events occurred frequently during the IP regimen, in particular, severe diarrhea (10.8%) was remarkable, although the incidence rate was lower than in previous phase III trials (22, 23). Treatment was discontinued in two patients because of severe diarrhea. However, no treatment-related death occurred during either regimen.

In conclusion, this phase II study of a novel alternating non-cross-resistant chemotherapy in patients with ED-SCLC, consisting of an alternation of etoposide and carboplatin with weekly administration of CPT-11 and cisplatin, revealed moderate tumor efficacy and acceptable toxicities. Further evaluation of this treatment for ED-SCLC in randomized phase III trials is warranted.

Conflicts of Interest

None declared.

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