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Phase II trial of the combination of carboplatin and irinotecan in elderly patients with small-cell lung cancer

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ABSTRACT

Aim: The aim of the present phase II study was to assess the antitumour activity and safety of the combination of irinotecan and carboplatin in elderly patients with small-cell lung cancer (SCLC).

Material and methods: Patients with previously untreated SCLC were eligible if they had a performance status of 0–2, were 70 years or older, and had adequate organ function. Patients were treated with carboplatin at an area under the plasma concentration versus time curve of 5 min/ml on day 1 and with irinotecan at 50 mg/m^2 on days 1 and 8 every 3 weeks.

Results: Thirty patients (26 men and 4 women; median age, 76 years; age range, 70–86 years) were enrolled. Eight patients had limited disease (LD) and 22 patients had extensive disease (ED). The overall response rate was 83.3% (95% confidence interval: 65.3–94.4%). Response rates did not differ significantly between patients with LD (87.5%) and those with ED (81.8%; $p = 0.71$). The median survival time was 14 months overall and was significantly longer in patients with LD (26 months) than in patients with ED (11 months; $p = 0.025$). The median progression free survival time was 6 months overall and was significantly longer in patients with LD (12 months) than in patients with ED (6 months; $p = 0.016$). Grade 3–4 toxicities included neutropenia in 83% of patients, thrombocytopenia in 47%, anaemia in 60%, infection in 23%, and diarrhoea in 20%. There were no treatment-related deaths.

Conclusions: This chemotherapy is safe and effective for elderly patients with SCLC.

1. Introduction

When small-cell lung cancer (SCLC) is diagnosed, more than 50% of patients are older than 65 years, and 30% are older than 70 years; the number of elderly patients with SCLC is expected to increase.[1] However, elderly patients tolerate chemotherapy poorly because of progressive, age-related organ failure. Decreased hepatic, renal, and bone-marrow functions increase the degree of toxicity resulting from chemotherapy.[2] Additionally, elderly patients, particularly those with long smoking histories, are more likely to have comorbid conditions, such as chronic obstructive pulmonary disease (COPD) and cardiovascular and peripheral vascular disease.[1] Comorbidities can also adversely affect patient functional status.[3]

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Chemotherapy is the cornerstone of treatment for SCLC. The combination of concurrent thoracic radiotherapy and chemotherapy, usually consisting of the combination of cisplatin and etoposide, is a standard treatment for limited disease (LD) SCLC,[4,5] whereas the combination of cisplatin and etoposide or irinotecan is the standard treatment for extensive disease (ED) SCLC.[6,7] However, the results of clinical trials cannot be readily extrapolated to elderly patients, because elderly patients are often excluded from clinical trials.[8–10] Additionally, some authors have reported that the elderly patients often receive less than the planned protocol dose and experience greater toxicity, although response rates and overall survival rates in elderly patients receiving combination chemotherapy are similar to those in younger patients.[10–13] On the other hand, single-agent chemotherapy regimens, such as oral etoposide, and attenuated doses of combination chemotherapy have not been recommended for elderly patients with SCLC, because they achieve lower survival rates than do standard treatments in elderly patients or patients with a poor performance status (PS).[14,15] Until now, a standard regimen for elderly patients with SCLC has not been established. Therefore, it is important to establish appropriate chemotherapy for elderly patients with SCLC.

Carboplatin and irinotecan show no cross-resistance.[16] Additionally, the combination of cisplatin and irinotecan has shown synergistic effects against a human SCLC cell line.[17] In a randomiszed phase III trial in patients with ED SCLC among whom 35% of patients were older than 70 years and about 50% had a PS of 2 or lower, survival was longer with the combination of irinotecan and carboplatin than with the combination of oral etoposide and carboplatin.[18] Additionally, in a randomiszed phase II trial in patients with ED SCLC, the combination of irinotecan and carboplatin caused less myelosuppression and achieved longer progression-free survival (PFS) than did the combination of etoposide and carboplatin.[19] We have previously studied the combination of irinotecan of 50 mg/m^2 and carboplatin at an area under the plasma concentration versus time curve (AUC) of 5 mg min/ml in patients with relapsed SCLC.[20] In this previous study, all toxicities were manageable and well tolerated. Both elderly patients and previously treated patients have lower reserves of organ function than do younger patients or previously untreated patients. Although Okamoto et al. have already reported results of the combination of irinotecan and carboplatin with prophylactic granulocyte colony-stimulating factor (G-CSF) in 18 elderly patients with SCLC, three different doses were used according to individual patient characteristics, such as age and PS.[21] Thus, this combination chemotherapy is difficult to assess for safety and efficacy and troublesome to administer to a large population. Therefore, we performed a phase II study to assess the antitumour activity and safety of the combination of irinotecan and carboplatin for elderly patients with SCLC.

2. Patients and methods

2.1. Eligibility criteria

The subjects of this study were elderly patients with previously untreated SCLC. The criteria for study entry were as follows: (1) histologically or cytologically confirmed SCLC; (2) age 70 years or older; (3) Eastern Cooperative Oncology Group PS of 2 or less; (4) measurable or assessable lesions; (5) life expectancy of at least 2 months; and (6) adequate bone marrow function (white blood cell [WBC] count from 4000/ul or more, neutrophil count of 2000/ul or more, platelet count of 100,000/ul or more, and haemoglobin level of 9 g/dl or more), hepatic function (total serum bilirubin level less than the upper limit of the normal range, levels of aspartate aminotransferase and alanine aminotransferase less than or equal to twice the upper limits of the normal ranges), and renal function (serum creatinine level less than 1.5 mg/dl, creatinine clearance rate of 40 ml/min or more) and arterial oxygen pressure of 60 mmHg or more. Patients were excluded if they had massive pleural effusion, pericardial effusion and ascites, pulmonary fibrosis, uncontrolled diabetes mellitus, severe heart disease, active infection, symptomatic brain metastasis, superior vena cava syndrome that required radiotherapy, or active second malignancy. The study protocol was approved by the Institutional Review Board of Showa Medical University, and all patients provided written informed consent.

2.2. Treatment schedule

Carboplatin (target AUC, 5 mg min/ml) was diluted in 500 ml of normal saline and given over 60 min as an intravenous drip infusion after irinotecan had been infusion on day 1. The carboplatin dose was calculated with Calvert's formula and the 24-h creatinine clearance rate. Irinotecan (50 mg/m^2) was diluted in 500 ml of normal saline and given as an intravenous drip infusion in 90 min on days 1 and 8. This chemotherapy regimen was repeated every 3 weeks for a maximum of four courses. Palliative radiotherapy was permitted to control persistent pain associated with bone metastasis during chemotherapy. Patients with LD received thoracic irradiation after chemotherapy. Prophylactic cranial irradiation was an option for patients who had achieved a complete response.

Chemotherapy was discontinued for grade 3 or higher nonhaematologoic toxicity, except for nausea/vomiting, anorexia, constipation, diarrhoea, alopecia, and fatigue, at any time, or if the treatment outcome was progressive disease at any time. If 2 or more weeks passed after the scheduled start of the next course until these criteria were satisfied, the patient left the study at that time but was still included in the analysis.

Irinotecan were not given on day 8 of treatment if the neutrophil count was less than 1000/ul, if the platelet count was less than 75,000/ul, or if the patient had diarrhoea of grade 2 or higher. Full doses of irinotecan were then given on day 15 of treatment. The next course of treatment was started when the neutrophil count increased to 1500/μl, the platelet count increased to 100,000/μl, the creatinine decreased to 1.5 mg/dl or less, and the nonhaematologoic toxicity decreased to grade 2 or less. The irinotecan dosage was reduced by 10 mg/m^2 if the patient had grade 4 leukopenia or neutropenia lasting 3 d or longer, grade 3 or 4 neutropenia associated with a fever higher than 38 °C, grade 4 thrombocytopenia, diarrhoea of grade 3 or higher, or if doses had been skipped on both days 8 and 15. The carboplatin dosage was reduced by 1 mg min/ml if the patient had grade 4 thrombocytopenia. Prophylactic antiemetic treatment with ondansetron and

dexamethasone were routinely given before carboplatin in all patients. If the leukopenia or neutropenia had decreased to grade 3 after chemotherapy, G-CSF was administered, according to the guideline of the Japanese Ministry of Health, Labour and Welfare, until the WBC and neutrophil counts recovered.

2.3. Evaluation

Evaluation before treatment included a baseline history and physical examination, complete blood count with differential, routine chemistry profiles, chest radiography, computed tomography (CT) of the chest and abdomen, magnetic resonance (MR) or CT of the brain, and radionucleotide bone scan. Complete blood counts with differential and routine chemistry profiles were determined at least once a week during chemotherapy. Chest radiography was performed once per week during chemotherapy. Electrocardiograms were obtained before and after chemotherapy.

Tumour response was classified according to the Response Evaluation Criteria in Solid Tumours criteria version 1.0. Toxicities were assessed and graded according to the National Cancer Institute Common Terminology Criteria for adverse events version 3.0. All patients who received at least two cycles of chemotherapy were assessable for response, and all patients who received at least one cycle of chemotherapy were assessable for toxicity and survival.

2.4. Statistical methods

The PFS was defined as the period from the start of this treatment to the identifiable time of the first progression or death from any cause. Survival time was measured from the start of the present treatment until death or last follow-up. The Kaplan–Meier method was used to calculate survival curves. Survival differences between subgroups were compared by means of the log-rank test. The chi-square test was used to determine the significance of differences between means. Differences with a p value <0.05 were considered statistically significant.

The trial was designed as a phase II study, with response rate as the main endpoint. According to the Simons minimax design, our study, with a sample size of 26, had 90% power to accept the hypothesis that the true response rate was greater than 85% and 5% significance to reject the hypothesis that the true response rate was less than 60%.

3. Results

3.1. Patients characteristics

From October 2005 through August 2009, 30 patients were enrolled (Table 1). Fifteen patients (50.0%) were 75 years or older, and 8 patients (26.7%) were 80 years or older. Of the 30 patients, 25 (83.3%) had a comorbid condition, 10 patients (33.3%) had COPD and 8 patients (26.7%) had cardiovascular disease. No patients were homozygous for uridine diphosphate glucuronosyltransferase *(UGT)1A1*28*.

At the time of analysis, 29 patients had recurrence, and 21 (72%) of these 29 patients had received second-line chemotherapy. Regimens used in second-line chemotherapy were as follows: carboplatin plus amrubicin (11 patients), carboplatin plus etoposide (4 patients), etoposide alone (2 patients), cisplatin plus etoposide (2 patients), and amrubicin alone (2 patients).

Toxicity and survival could be assessed in all 30 eligible patients, and response could be assessed in 28 patients. Two patients could not be evaluated for response because they had not received two courses of chemotherapy owing to unacceptable toxicity. These 2 patients were considered nonresponders.

3.2. Treatment response and survival

The overall response rate was 83.3% (95% confidence interval, 65.3–94.4%; Table 2). Response rates did not differ significantly between patients with LD (response rate, 87.5%; 95% confidence interval, 47.3–99.7%) and those with ED (response rate, 81.8%; 95% confidence interval, 59.7–94.8%; $p = 0.71$).

Survival analysis was performed when the median follow-up time of all evaluable patients was 15 months. At the time of analysis, 6 patients (20%) were alive and no patient has been lost to follow-up. The MST was 14 months overall (range, 4–46 months), and the 1-year survival rate was 58% (Fig. 1A). The MST of patients with LD (26 months; range: 11–46 months) was significantly longer than that of patients with ED (11 months; range: 4–28 months; $p = 0.025$; Fig. 1B). The median PFS time was 6 months overall (range: 1–27 months, Fig. 2A), and that in patients with LD (12 months; range: 5–27 months) was significantly longer than that in patients with ED (6 months; range: 1–13 months; $p = 0.016$; Fig. 2B).

3.3. Toxicity

The most frequent toxicity was myelosuppression (Table 3). Grade 3–4 haematologic toxicities occurred frequently: leukopenia developed in 43% of patients, neutropenia in 83%, thrombocytopenia in 46%, and anaemia in 60%. G-CSF was given during 49% of courses (52 of 109 courses; median duration of administration, 3 d; range, 1–9 d). Twelve patients received transfusions of erythrocytes, and 1 patient received platelet transfusions. However, there were no severe episodes related to myelosuppression.

Almost all nonhaematologic toxicities were mild to moderate and temporary. Grade 3 to 4 nonhaematologic toxicities included diarrhoea in 20.0% of patients and nausea in 3.3%. Grade 3 to 4 infection occurred in 23.3% of patients. One

Table 1 – Patient characteristics.

Total number of patients	30
Sex (M/F)	26/4
Age, years (range)	76 (70–86)
Performance status (0/1/2)	2/25/3
Stage	
Limited disease	8
Extensive disease	22
UGT1A1 genotype	
Wild-type	25
Heterozygous	4
Unknown	1
Comorbidity (yes/no)	25/5

Table 2 – Response rate.

	Limited disease (*n* = 8)		Extensive disease (*n* = 22)		Total (*n* = 30)	
	Number	%	Number	%	Number	%
Complete response	3	37.5	3	13.7	6	20.0
Partial response	4	50.0	15	68.2	19	63.3
Stable disease	0	0.0	0	0.0	0	0.0
Progressive disease	0	0.0	3	13.7	3	10.0
Not evaluable	1	12.5	1	4.5	2	6.7

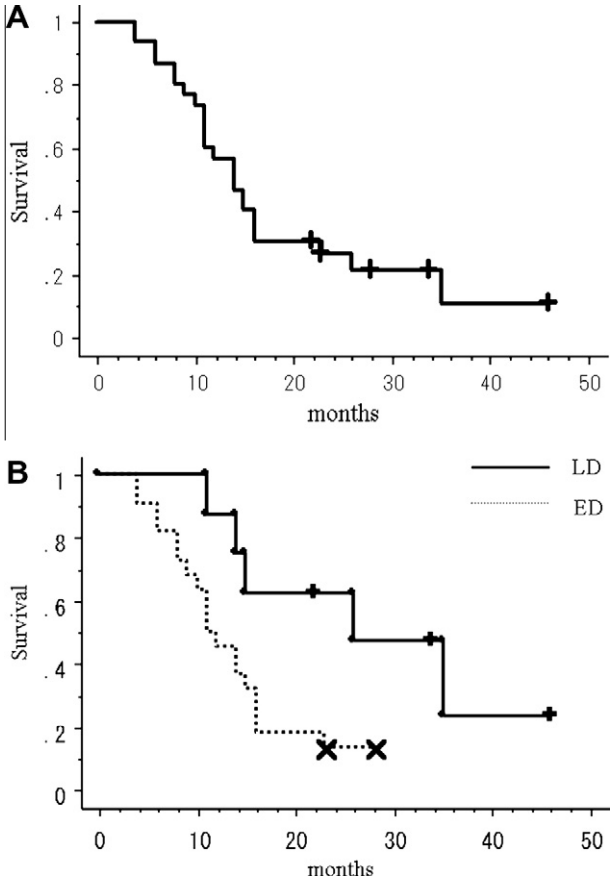

Fig. 1 – (A) Overall survival estimated with the Kaplan–Meier method. The median survival time (MST) was 14 months (range, 4–46 months). (B) Overall survival estimated with the Kaplan–Meier method according to stage. The MST of patients with limited disease (26 months; range: 11–46 months) was significantly longer than that of patients with extensive disease (11 months; range: 4–28 months; $p = 0.025$).

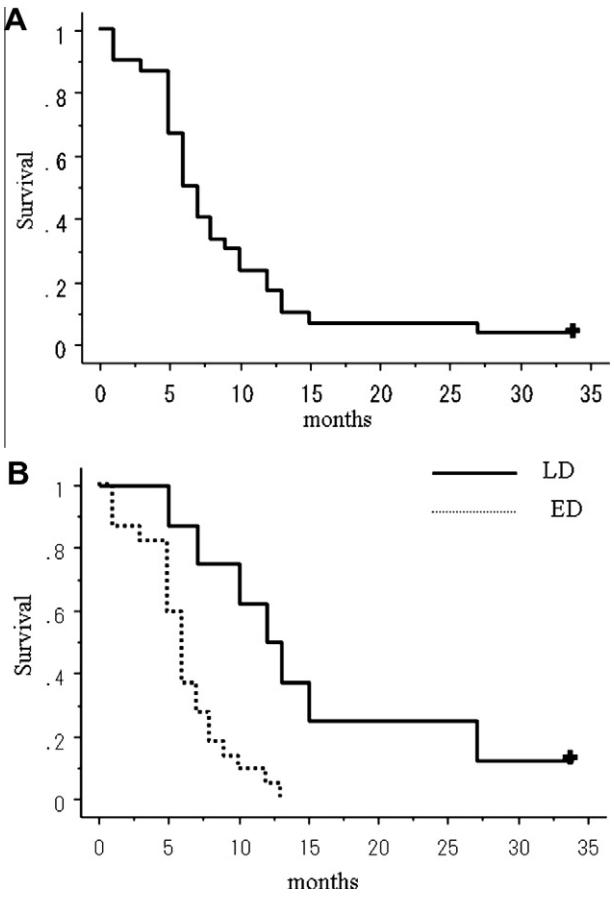

Fig. 2 – (A) Progression-free survival (PFS) time estimated with the Kaplan–Meier method. The median PFS time was 6 months (range, 1–27 months). The median PFS time of patients with limited disease (12 months; range: 5–27 months) was significantly longer than that of patients with extensive disease (6 months; range: 1–13 months; $p = 0.016$).

patient had sepsis, but recovered by antibiotic therapy. There were no treatment-related deaths.

3.4. *Dose intensity*

A total of 109 courses of chemotherapy were given. The median number of courses given per patients was 4 (range, 1–4). Owing to toxicity, doses of carboplatin were reduced in 1 (3%) patient because of grade 4 thrombocytopenia. Doses of irinotecan were reduced in 9 (30%) patients: the causes were grade 4 neutropenia lasting 3 d in 4 patients, grade 4 thrombocytopenia in 1 patient, and grade 3 diarrhoea in 4 patients. During the 109 courses of chemotherapy, 12 (11%) doses of irinotecan were cancelled on day 8, mostly because of neutropenia. Of the 109 courses of chemotherapy, 38 (35%) courses

Table 3 – Toxicity.

Toxicity	National Cancer Institute-Common Terminology Criteria grade				
	1	2	3	4	3/4 (%)
Leukopenia	5	12	9	4	43
Neutropenia	1	4	11	14	83
Thrombocytopenia	10	5	10	4	46
Anaemia	4	8	13	5	60
Nausea	10	7	1	0	3
Vomiting	5	3	0	0	0
Diarrhoea	8	6	6	0	20
Infection	6	6	6	1	23
Elevation of serum creatinine	0	0	1	0	3
Elevation of aminotransferases	2	0	1	0	3
Abnormality of potassium	5	0	1	1	7
Hyponatremia	6	0	1	0	3
Fatigue or asthenia	1	1	2	0	7

were delayed, usually because of prolonged neutropenia or thrombocytopenia. However, 33 (86.8%) of these 38 courses were delayed less than 1 week. The actual delivered mean individual doses of irinotecan and carboplatin were 40.6 mg/m^2 (81.2% of planned) and 4.5 mg min/ml (90.0% of planned), respectively.

4. Discussion

The combination of etoposide and cisplatin and of irinotecan and cisplatin are standard treatments for SCLC.[4–7] However, results from clinical trials cannot be readily extrapolated to elderly patients, because elderly patients have often been excluded from clinical trials.[8–10] Previous studies have found that the percentages of patients 70 years or older enrolled in clinical trial were significantly less (20% and 13%) than their percentages in the general cancer population (46% and 47%).[8,9] In particular, most patients 80 year or older have been excluded in clinical trials. Chrischilles et al.[22] have reported that elderly patients with non-small cell lung cancer were much less likely to have received chemotherapy or platinum-based chemotherapy, particularly cisplatin-based chemotherapy, and that those who had received chemotherapy had significantly lower baseline comorbidity rates, a finding that suggests that only the fittest elderly patients were selected to receive treatment. Nevertheless, elderly patients had more adverse events during chemotherapy. Therefore, it is important to establish appropriate chemotherapy regimens for elderly patients with SCLC.

Carboplatin causes less renal, neurologic, and gastrointestinal toxicity and is easier to administer than cisplatin.[23] Additionally, carboplatin does not require hydration and can be given in an outpatient setting. In a phase III study in patients with previously untreated SCLC, the combination of carboplatin plus etoposide achieved response and survival rates similar to those of cisplatin plus etoposide but was significantly less toxic.[24] Thus, we believe carboplatin is more appropriate than cisplatin for elderly patients who had several organs with lower functional reserve.

A meta-analysis of chemotherapy alone versus chemotherapy plus radiotherapy in patient with LD SCLC demonstrated that the addition of radiotherapy confers a survival benefit for patients younger than 70 years but not for older patients.[25] Moreover, Yuen et al. have reported that elderly patients receiving 4 cycles of the combination of cisplatin and etoposide with concurrent thoracic radiotherapy show increased rates of grade 3–4 haematologic toxicity and a fatal toxicity rate of 10%.[12] Furthermore, patients enrolled in phase III trials for LD SCLC were generally younger, with median ages of 61–65 years, than the general population of patients with SCLC, and only 5% of patients had a PS of 2.[4,5] Therefore, we believe the combination of full-dose chemotherapy and concurrent radiotherapy could be too toxic for most elderly patients with LD SCLC. Therefore, in the present study, patients with LD SCLC received thoracic radiotherapy after they had received chemotherapy.

In the present study, the overall response rate was 83.3% (LD patients, 87.5%; ED patients, 81.8%), and the overall MST was 14 months (LD patients, 26 months; ED patients, 11 months). Our results compare favourably with those of most published trials in elderly patients with SCLC. Several prospective trials have been performed in elderly patients with SCLC[15,21,26–32]; in these trials, the overall response rates have ranged from 39% to 89%, and the MSTs have ranged from 5.9 to 13 months.

In the present study the most frequent toxicity was myelosuppression. Grade 3–4 haematologic toxicities included neutropenia in 83% of patients, thrombocytopenia in 38%, and anaemia in 58%. However, all side-effects were manageable, despite 50% of patients being 75 years or older, and 26.7% being 80 years or older. Additionally, these rates of toxicity compare favourably with those in most recently published trials in elderly patients with SCLC: in these trials, rates of grade 3–4 neutropenia, thrombocytopenia, and anaemia were 10–95%, 12–56%, and 0–50%, respectively.[15,21,26–32] Diarrhoea is another common dose-limiting toxicity of irinotecan treatment. However, in the present study, only 20% of patients had grade 3 diarrhoea and no patient had grade 4 diarrhoea. Additionally, in our study, there were no treatment-related deaths, although several previous studies in elderly patients with SCLC have reported treatment-related death rates of about 10%.[27,30,31]

Some previous studies have found that homozygosity for *UGT1A1*28* predicts severe neutropenia or diarrhoea.[33,34]

However, the frequency of homozygosity for *UGT1A1*28* in Japanese (3–6%) is less than that in the white population (10–15%).[35] In our study, because no patients were homozygous for *UGT1A1*28*, we cannot draw definitive conclusions about the rate of toxicity in such patients.

Approximately 80% of elderly patients have one or more chronic medical conditions, and such comorbidities can adversely affect the functional status of patients.[3] In our study, 83.3% of patients had a comorbid condition such as COPD or cardiovascular diseases. However, there were no treatment-related deaths. In addition, the actual delivered dose intensities of irinotecan and carboplatin were 81.2% and 90.0%, respectively. Given the lower bone marrow reserves and poorer organ function in elderly patients, the dose intensities in our study can be considered to be quite high.

In conclusion, the combination of irinotecan and carboplatin is safe and effective for elderly patients with SCLC, including patients 80 years or older. Therefore, this treatment is an acceptable option for elderly patients with SCLC.

Conflict of interest statement

None declared.

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