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ORIGINAL ARTICLE

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A phase I trial of carboplatin and etoposide for elderly (≥75 year-old) patients with small-cell lung cancer

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Abstract *Purpose:* The combination of carboplatin and etoposide is currently considered the most appropriate regimen for treating elderly patients with small-cell lung cancer (SCLC). Previous reports on elderly patients, 70 years or older, found that the recommended dose was close to that of younger patients. Then, we conducted a phase I study of carboplatin and etoposide in elderly patients, 75 years or older, with SCLC. This study aimed to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT). *Methods:* Twenty-six patients fulfilling the eligibility criteria, chemotherapy-naive, performance status (PS) of 0–2, age ≥75, and adequate organ functions were enrolled. Patients' characteristics were: male/female = 21/5; PS 0/1/2 = 9/11/6; median age (range) = 78 (75–82); and limited/extensive stage = 16/10. The patients intravenously received carboplatin with a target AUC of 4 or 5 mg min/ml (Chatelut formula) on day 1 and etoposide at 80–120 mg/m^2 on days 1, 2 and 3. Therapy was repeated four times in every 4 weeks. *Results:* The MTD of carboplatin/etoposide was AUC = 5/80, 4/110, and 4/120. The DLTs were thrombocytopenia, neutropenia, leukopenia, and febrile neutropenia. Overall, grade 4 thrombocytopenia, neutropenia (≥4 days), leukopenia (≥4 days), and febrile neutropenia occurred in 27, 20, 7, and 13% of cases at MTD levels, respectively, and 0% at other levels. Twenty of 26 patients showed objective responses (2CR, 18PR; RR = 77%). Conclusion: A dose of carboplatin of AUC = 4 and etoposide of 100 mg/m^2 was recommended in this regimen.

Keywords Small-cell lung cancer · Elderly patients · Carboplatin · Etoposide · Chatelut formula

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Introduction

Lung cancer is the leading cause of cancer-related deaths in many countries [1]. Small-cell lung cancer (SCLC) accounts for approximately 20% of all lung cancers. SCLC differs from other types of lung cancer in its propensity for early systemic spread and its aggressive clinical course if left untreated. At diagnosis, 25% of patients with SCLC are 70 years or older, and the number of patients has increased in recent years with the prolongation of the average life span [2, 3]. However, many elderly patients receive less intensive chemotherapy, with greater dose reductions and fewer cycles, because they may be less able to tolerate these therapies [4, 5]. The age cut-off in recent studies of combination chemotherapy in elderly patients with SCLC was 70 years [6–10]. However, previous trials of chemotherapy for patients with SCLC have been conducted with an age cut-off of 75 years [11–15]. Other trials had no

restriction on age and included 77 and 78 year olds [16, 17]. The median age was 72 to 73 years in reports on elderly patients with SCLC, and the recommended dose was close to that for younger patients. Consequently, many elderly patients have been undertreated because of fear of excessive toxicity.

The combination of carboplatin/etoposide is an active chemotherapy regimen in cases of previously untreated SCLC [11, 17, 18], and equally as effective as cisplatin/etoposide, which is the regimen most commonly used to treat patients with SCLC [19]. To use carboplatin effectively and safely, several formulas, such as the Calvert and the Chatelut formulas, have been proposed for predicting the drug's clearance (CL) in individual patients [20–23]. In a prior study, we prospectively evaluated the Chatelut formula and reported that the predicted CL was closely correlated with the actual CL [24]. Furthermore, the Chatelut formula is considered suitable for elderly patients because it includes age as a parameter [23].

Thus, we designed a phase I dose-escalation trial evaluating the combination of carboplatin and etoposide in the treatment of elderly patients, 75 years or older, with SCLC. The primary objective of this study was to determine the optimal doses of carboplatin/etoposide.

Patients and methods

Patients and evaluation

Patients, 75 years or older, with any stage of SCLC were enrolled. Tumor staging was performed on the basis of a complete medical history and physical examination, routine chest radiography, bone scintiscanning, computed tomography (CT) of the chest and abdomen, magnetic resonance imaging or CT of the head, and bronchoscopy. Staging was performed according to the tumor node metastasis system [25]. Eligibility criteria included the following: histologically or cytologically confirmed SCLC; no previous chemotherapy; measurable or assessable disease; age ≥75 years with a performance status (PS) of the Eastern Cooperative Oncology Group (ECOG) of 0–2; adequate hematologic function (leukocyte ≥3,500/μl, hemoglobin ≥9.0 g/dl, platelet count ≥100,000/μl), hepatic function (total bilirubin ≤ 1.5 mg/dl, ALT, and AST levels ≤ double the normal upper limit) and renal function (serum creatinine ≤ 1.5 mg/dl); no serious cardiac or pulmonary dysfunction (PaO2 ≥70 torr); no other serious illness; no concomitant malignancies; and the ability to provide informed consent. Limited disease (LD) was defined as disease limited to hemithorax, mediastinal lymph nodes, and ipsilateral and/or contralateral supraclavicular lymph nodes, excluding malignant pleural effusion. Extensive disease (ED) was defined as disease beyond that included above. Written informed consent was obtained from all patients. The institutional review board of each institute reviewed and approved the protocol before commencement of the study.

Prior to the first course of therapy, a complete blood cell count including a differential white blood cell count and platelet count, biochemistry tests (renal and hepatic function and electrolytes), and urinalysis were performed. The complete blood cell count and biochemistry were repeated at least once weekly after treatment, while other investigations were repeated as necessary to evaluate various markers. After completion of chemotherapy, each patient was restaged with all tests used during the initial work-up.

Treatment, dose escalation, and extension phase of the study

Treatment commenced within 1 week of enrollment, and four cycles of carboplatin/etoposide therapy were repeated after a 28-day interval. The patients intravenously received 80–120 mg/m^2 of etoposide with a target area under the concentration-time curve (AUC) of 4–5 mg min/ml carboplatin. The dose of carboplatin was determined by multiplying the target AUC by carboplatin CL, which was predicted with the Chatelut formula using the Jaffe method for measuring the serum creatinine concentration [23]. At the institutions where an enzymatic method was used to measure the serum creatinine concentration, the serum creatinine value of enzymatic (X) was converted using the Jaffe (Y) method with the formula: $Y = 0.97X + 0.27$. Then, the estimated carboplatin clearance (CL) (ml/min) was calculated as follows: $CL = 0.134 \times \text{weight} + [218 \times \text{weight} \times (1 - 0.00457 \times \text{age}) \times (1 - 0.314 \times \text{sex})] \times 113 \times 1.03 \times 10^{-4} / (\text{s-Cr} + 0.276)$ (with weight in kg, age in years, and sex = 0 if male and sex = 1 if female). Carboplatin was administered during a 1-h intravenous infusion with 250 ml of 5% dextrose on day 1. Etoposide was administered during 1-h intravenous infusion with 250 ml of 5% dextrose on days 1, 2, and 3. The starting doses of carboplatin and etoposide were an AUC of 5 mg min/ml and 80 mg/m^2, respectively, and these were increased as shown in Table 1. After completion of the chemotherapy, standard thoracic irradiation (60 Gy) was administered to patients with LD. Patients received antiemetics as required and palliative and supportive treatment for tumor-related symptoms were available for all patients. The granulocyte colony-stimulating factor (G-CSF) was injected s.c. when the neutrophil count became < 1,000/μl and was discontinued when the count recovered to > 5,000/μl.

The dose escalation was evaluated during the first cycle of each dose level, and toxicity was assessed according to the common criteria of the World Health Organization [26]. Three patients were enrolled for each dose level. The dose was escalated to the next level if none of the three patients experienced DLT. If two of the three patients experienced DLT, the dose level was defined as the maximum tolerated dose (MTD). If one of

Table 1 Dose escalation and extension phase study

Dose level	No. of patients	Etoposide	Carboplatin target AUC
1	5	80	5
2	3	80	4
3	3	90	4
4	3 (2)	100	4
5	3 (3)	110	4
6	4	120	4

Etoposide on days 1, 2, and 3; carboplatin on day 1
The number in parentheses represents the number of patients enrolled in the extension phase study
Etoposide mg/m^2, AUC mg·min/ml

the three patients experienced DLT, three more patients were treated at that level. If none of the additional three patients experienced DLT, the dose was escalated to the next level. If one or more of the additional three patients experienced DLT, the dose level was then defined as the MTD. The recommended dose of this regimen for phase II study was defined as the level prior to the MTD. To evaluate toxicities and safety at the recommended dose level more accurately, additional patients were enrolled into the extension phase of the study. Blood transfusion was performed only in cases where hemoglobin <7.5 g/dl or platelet count $<20{,}000/\mu l$.

Dose modification

Leukocytes $\geq 3{,}000/\mu l$ and platelets $\geq 75{,}000/\mu l$ were mandatory to commence the next cycle of treatment, and if the levels fell below these limits, the next cycle was postponed until the counts recovered. Doses of carboplatin and etoposide were reduced to 80% when DLT occurred during the previous treatment cycle.

Toxicity and response evaluation

Eligibility, assessability, and tumor responses were determined by external reviewers. Tumor response and drug toxicity were classified according to the criteria of the WHO [26]. DLT was defined as grade 4 leukopenia or neutropenia lasting 4 days or more, grade 4 thrombocytopenia (less than $25{,}000/\mu l$), and grade 3 or greater nonhematologic toxicities with the exception of nausea and vomiting. A complete response (CR) was defined as the disappearance of any evidence of tumors for at least 4 weeks. A partial response (PR) was defined as $\geq 50\%$ reduction in the sum of the products of the greatest perpendicular diameters of all lesions for at least 4 weeks. No change (NC) was defined as $<50\%$ reduction or $<25\%$ increase in the products of the greatest perpendicular diameters of all lesions without any evidence of new lesions. Progressive disease (PD) was defined as an increase of $\geq 25\%$ or the appearance of new lesions. Response duration was measured from the start of the treatment to disease progression.

Results

A total of 26 patients were enrolled in this trial between February 1998 and May 2003, and all received chemotherapy. Twenty-one and five patients were enrolled in the dose escalation and the extension phases of the study, respectively. Patient characteristics were median age 78 years (range 75–82 years), male/female 21/5, and LD/ED 16/10 patients, respectively (Table 2). A total of 88 cycles of this regimen were administered through six dose levels. One cycle was administered to 4 patients (15%), two cycles to 2 (8%), three cycles to 3 (12%), four cycles to 17 (65%), and five cycles to 1 (4%).

Dose escalation and extension phase study

First, one of the three original and one of the two additional patients at level 1 experienced DLTs (neutropenia and thrombocytopenia, and thrombocytopenia). Level 1 was defined as the MTD. The dose of carboplatin was reduced for the next level. None of the three patients at level 2 or 3 and the original level 4 or 5 experienced DLTs. At level 6, one of the three original and one of the one additional patients experienced DLTs (thromobocytopenia and febrile neutropenia). Level 6 was defined as the MTD. To evaluate toxicities and safety at the recommended dose level more accurately, the study was extended as an extension phase study. At extension level 5, two of the three patients experienced DLTs (neutropenia and leucopenia, neutropenia, thrombocytopenia, and febrile neutropenia). At that time, two of the six patients in total experienced DLTs at level 5 and this level were also defined as MTD. Finally, none of the additional two patients in the extension phase and none of the five patients in total experienced DLT at level 4. Therefore, we concluded that level 4 was the recommended dose in this regimen.

Table 2 Baseline patient characteristics

Characteristics	No	Percentage (%)
Total no. of patients	26	
Age, years		
Median	78	
Range	75–82	
Sex		
Male	21	81
Female	5	19
ECOG performance status		
0	9	35
1	11	42
2	6	23
Creatinine		
Mean	0.85	
Range	0.54–1.16	
c-Stage		
LD	16	62
ED	10	38

ECOG Eastern Cooperative Oncology Group, *LD* limited disease, *ED* extensive disease

Table 3 Hematological toxicities ($n = 26$)

Dose level	No. of patients	RBC		WBC		Neutro		Plt		NF
		Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	0
1	5	1	0	2	0	1	3[a]	0	2	0
2	3	1	0	1	0	0	2	0	0	0
3	3	0	0	3	0	1 (1)	1	0	0	0
4	3 (2)	1	0 (1)	3 (1)	0 (1)	1	2 (1)	1	0	0
5	3 (3)	0	0	0 (2)	0 (1)[a]	0	1 (3)[b]	0 (1)	0 (1)	1
6	4	1	0	0	2	3[c]	1	0	1	1

The number in parentheses represents the number of patients enrolled in the extension phase study
RBC anemia, *WBC* leukocytopenia, *Neutro* neutropenia, *Plt* thrombocytopenia, *NF* neutropenic fever
[a]Grade 4 includes one DLT
[b]Grade 4 includes two DLTs
[c]Grade 3 includes one DLT

Toxicity

Leukocytopenia, neutropenia, and thrombocytopenia were the principal hematological toxicities, as shown in Table 3. Of 26 patients, 16 (62%) experienced grade 4 hematological toxicities, and 6 (23%) experienced hematological DLTs. At dose level 1, two patients (40%) experienced hematological DLTs and one patient required platelet transfusion. At dose levels 5 and 6, six patients (60%) experienced grade 4 hematological toxicities and four patients (40%) experienced DLTs. At dose levels 2–4, although six patients (55%) experienced grade 4 hematological toxicities, no patient experienced DLT. Seven patients (27%) required a blood transfusion in all treatment cycles because of anemia (15%), thrombocytopenia (8%), or both (4%).

Nonhematological toxicities were mild as shown in Table 4. Gastrointestinal toxicities were prominent, and included nausea/vomiting and liver dysfunction. No patient experienced nonhematological DLT. Four patients (15%) had grade 2 or worse nausea/vomiting in all the cycles. Two (8%) and one (4%) patient had dermatitis (grade 1) and an elevated serum creatinine level in all the cycles, respectively. There were no allergic reactions, pneumonitis, neurotoxicity, and fluid retention.

Response and survival

All of the 26 patients were assessable for response and survival. CRs and PRs were observed in 2 (8%) and 18 (69%) patients, respectively. These response cases numbered 4 (80%) at level 1, 2 (67%) at level 2, 2 (67%) at level 3, 3 (60%) at level 4, 5 (83%) at level 5, and 4 (100%) at level 6. Three patients (12%) had SDs and three (12%) had PDs. The overall response rate was 77% (LD 81%, ED 70%). The median survival time, and 1 and 2-year survival rates were 16.4 (LD 34.9, ED 8.3) months, 68.7 and 29.6%, respectively.

Discussion

The present phase I study of carboplatin (day 1) and etoposide (days 1, 2, 3) as first line chemotherapy in elderly patients, 75 years or older, with SCLC demonstrated that the recommended carboplatin target AUC was 4 mg·min/ml and etoposide dose was 100 mg/m^2. Carboplatin and etoposide seem currently the most appropriate two-drug combination in elderly patients [5], but there has been no report of a prospective chemotherapy trial in the elderly patients, 75 years or older. The main DLTs were as anticipated, thrombocytopenia, neutropenia, and febrile neutropenia, while severe nonhematological toxicity was not observed. The MTD levels were 1, 5, and 6. Although the appearance rates of DLTs were the same (40%, 2/5 vs. 4/10), comparing level 1 and levels 5 and 6, the toxicity profiles were different. In patients with DLTs, two of two (100%) experienced thrombocytopenia as DLT at level 1, and two of four (50%) at levels 5 and 6, respectively.

Table 4 Nonhematological toxicities ($n = 26$)

Dose level	No. of patients	N/V		s-AST		s-ALT		Diarrhea
		Grade 1	Grade 2 ≤	Grade 1	Grade 2 ≤	Grade 1	Grade 2 ≤	Grade 1 ≤
1	5	1	0	0	0	0	0	0
2	3	0	0	0	0	0	0	0
3	3	1	1	0 (1)	0	1	0 (1)	0 (1)
4	3 (2)	1	0 (1)	1 (1)	0	0 (1)	0	0
5	3 (3)	1 (1)	0	0	0	0	0	0
6	4	2	0	0	0	0	0	0

The number in parentheses represents the number of patients enrolled in the extension phase study
N/V nausea and vomiting, *s-AST* aspartate aminotransferase, *s-ALT* alanine aminotransferase

Neutropenia and febrile neutropenia as DLTs were observed in one patient (50%) and no patients at levels 1 and 2 (0%) and two (50%) patients at levels 5 and 6, respectively. Thrombocytopenia, which is a major toxicity of carboplatin at maximal dose, strongly depends on the AUC of the ultrafilterable plasma concentration [20–22]. Eventually, the excessive toxicities of this regimen were amended by reduction of the carboplatin dose at level 1, and etoposide dose at levels 5 and 6, respectively.

The proportion of elderly people is increasing in industrialized countries. Age is the most important risk factor for most types of cancer. The decreases in lean body mass, hepatic blood flow, and renal function that accompany aging affect drug distribution, metabolism, and excretion. Myelotoxicity is also sometimes severer in this population than in younger populations because the absolute amount of hematopoietic marrow decreases with age. Although the combination of cisplatin and etoposide is a popular chemotherapy regimen for first line treatment of SCLC, cisplatin can be associated with toxicity including severe vomiting and nephrotoxicity, and carboplatin could be substituted for cisplatin without apparent loss of therapeutic efficacy [11, 17–19]. The age cut-off in recent studies of combination chemotherapy in elderly patients with SCLC was 70 years [6–10], but previous trials for younger patients have been conducted up to the age of 75 years [11–15]. Then the recommended dose for elderly patients comes close to that for younger ones, and we sometimes hesitate to use. The present study is the first prospective report for patients aged 75 years or older with SCLC, and we consider it to be valuable for treatment in this field.

Carboplatin and oral etoposide have been used in elderly patients with SCLC [6, 9, 27]. However, two randomized studies in elderly or poor-prognosis SCLC patients demonstrated the superiority of intravenous combination chemotherapy over single-drug oral etoposide [28, 29]. There are two studies of AUC-based carboplatin and etoposide for elderly patients with SCLC. Okamoto et al. [7] reported a phase II study of 36 patients with SCLC, which yielded a response rate of 75% and median survival time of 10.8 months (LD 11.6, ED 10.1), and concluded that this regimen was active and relatively nontoxic in elderly patients with SCLC. Matsui et al. [30] also reported an AUC-based carboplatin and etoposide study as a phase I study. Although their schedule of drugs and etoposide at 100 mg/m^2 were the same as in the present study, the carboplatin target AUC of 5 [7] and 4.5 [30] were higher than the recommended target AUC of 4 in the present study. The lower age cut-off of 70 years and the difference in median age of 73 [7] and 77 years [30] are considered to have produced the difference in recommended dose in their studies. Thus, our recommended dose of carboplatin (AUC of 4 mg·min/ml) with etoposide (100 mg/m^2) for the elderly patients, 75 years or older, with SCLC as first line chemotherapy seems appropriate. We considered that an AUC of 5 mg·min/ml using the Chatelut formula is adequate for a target carboplatin AUC with irinotecan in younger patients [31, 32], while target carboplatin AUCs of 5–7 mg·min/ml have been used for combinations with other agents [22]. In our phase I study of carboplatin and irinotecan, we prospectively evaluated the Chatelut formula for predicting carboplatin clearance [24]. The pharmacokinetic analysis of carboplatin using three dose levels of irinotecan showed that the actual AUCs were close to the target AUC of 5 mg·min/ml [24], and a retrospective study has shown that the predictions are similar between methods for predicting carboplatin clearance [33]. In the present study, the recommended AUC was reduced by myelosuppression especially thrombocytopenia. In addition, the Chatelut-based estimation of carboplatin clearance [23] is considered favorable for elderly patients because it includes age as a parameter like the Calvert-Cockcroft, and unlike the Calvert-24h CrCl formula (which may be suitable for elderly patients because it involves creatinine clearance). The Cockroft-Gault, Jelliffe and Wright formulas were already evaluated [34], and it is required to validate the Chatelut formula in elderly cancer patients.

In conclusion, combination chemotherapy with carboplatin (day 1) using the Chatelut formula to estimate carboplatin clearance and etoposide (days 1, 2, and 3) for elderly patients, 75 years or older, with SCLC was well tolerated and the recommended dose of carboplatin was an AUC of 4 mg·min/ml and of etoposide was 100 mg/m^2.

Appendix

Principal Investigators in this trial: Tetsuya Iida, Mikio Oka, Takashi Kasai, Shigeru Kawabata, Tetsuro Kanda, Shigeru Kohno, Ken Kitazaki, Akitoshi Kinoshita, Yoshifumi Soejima, Hiroshi Soda, Hiroshi Takatani, Junji Tsurutani, Seiji Doi, Seiji Nagashima, Katsumi Nakatomi, Hirofumi Nakano, Reiji Nakano, Yoichi Nakamura, Masaaki Fukuda, Minoru Fukuda, Satoru Fujino, and Hiroyuki Yamaguchi.

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