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ORIGINAL ARTICLE

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Phase II study of irinotecan combined with carboplatin in previously untreated non-small-cell lung cancer

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Abstract *Purpose*: Irinotecan, a topoisomerase I inhibitor, is an effective agent for non-small-cell lung cancer (NSCLC). To determine the efficacy and toxicity of irinotecan and carboplatin, we conducted a phase II study in 61 patients with advanced NSCLC. *Methods*: Every 4 weeks, the patients received irinotecan 50 mg/m^2 (days 1, 8 and 15) and carboplatin (day 1) with a target AUC of 5 mg min/ml using the Chatelut formula. *Results*: All patients were evaluable for toxicity, and of 59 patients evaluable for response, 20 achieved a partial response and 26 showed no change. The overall response rate was 34% (95% confidence interval 23–48%). Grade 3 or 4 anemia, leukopenia, neutropenia, thrombocytopenia and diarrhea occurred in 32%, 32%, 60%, 25%, and 7%, respectively. The median survival time and 1-year, and 2-year survival rates were 10.0 months, 37.6%, and 15.2%, respectively. *Conclusions*: Irinotecan with carboplatin is effective for advanced NSCLC and safe.

Keywords Lung cancer · Chemotherapy · Clinical trial · Topoisomerase I inhibitor · Irinotecan · Carboplatin

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Introduction

Irinotecan hydrochloride is a water-soluble prodrug that is metabolized to the active metabolite SN-38, which inhibits the function of DNA topoisomerase I in cancer cells [1, 2]. Irinotecan displays antitumor activity in various cancer cells in vitro, and it has been used in the treatment of human cancers, including lung cancer [3]. Preclinical studies have demonstrated synergism and non-cross-resistance between platinum agents and irinotecan or SN-38 [4–6]. In advanced non-small-cell lung cancer (NSCLC), clinical trials with cisplatin and weekly irinotecan (irinotecan/cisplatin therapy) have shown relatively high response rates of 29–52% and better overall survival with a median survival time of 43–52 weeks, and a 1-year survival rate of 33–49% [7–10].

Carboplatin is a platinum derivative with less renal toxicity, nausea and vomiting than cisplatin [11, 12], and it has been combined with other newer agents in chemotherapy of NSCLC [13]. Accordingly, we conducted a phase I trial with carboplatin and weekly irinotecan (irinotecan/carboplatin therapy), which resulted in a relatively good response rate: 36% (4 of 11 patients) for NSCLC and 85% (11 of 13 patients) for SCLC [14].

On the other hand, pharmacodynamic studies of carboplatin have shown that thrombocytopenia, its major toxicity at maximal doses, strongly depends on the area under the concentration–time curve (AUC) of the ultrafilterable plasma concentration [15–17]. To use carboplatin effectively and safely, several formulas, such as the Calvert and the Chatelut formulas, have been proposed for predicting carboplatin clearance (CL) in individual patients [15–18]. In a prior phase I study, we prospectively evaluated the Chatelut formula, and reported that the predicted carboplatin CL was closely correlated with the actual CL [14]. Indeed, the actual AUCs of carboplatin nearly reached the target AUC of 5 mg min/ml [14]. Of 11 NSCLC patients in the phase I study, 4 had a partial response, for a response rate of 36% [14].

Based on these findings, we conducted a phase II study of irinotecan/carboplatin therapy for advanced NSCLC. The main objectives of the study were to determine the efficacy and safety of this regimen in previously untreated patients with advanced NSCLC.

Patients and methods

The study protocol was approved by the Ethical Committee of Nagasaki University School of Medicine. This study was an independent collaborative (non-sponsored) group study.

Patients

Eligibility criteria for patients in this study included the following: a histologically confirmed diagnosis of NSCLC; stage IIIB or IV; no prior chemotherapy or radiotherapy; age ≤ 75 years; Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 2; life expectancy greater than 12 weeks; adequate bone marrow function (leukocyte count $\geq 4\times10^9\ l^{-1}$, platelet count $\geq 100\times10^9\ l^{-1}$, and hemoglobin ≥ 100 g/l); serum bilirubin ≤ 25 μmol/l; ALT and AST levels not more than twice the normal upper limit; serum creatinine $\leq 10^5$ μmol/l and $PaO_2 \geq 70$ Torr; no medical problems severe enough to prevent compliance with the protocol; and written informed consent.

Treatment

Based on our phase I study [14], patients received 50 mg/m^2 irinotecan on days 1, 8, and 15, and carboplatin with a target AUC of 5 mg min/ml on day 1. The carboplatin dose was determined by multiplying the target AUC of 5 mg min/ml by carboplatin CL, which was predicted with the Chatelut formula using the Jaffé method for serum creatinine measurement [18]. Carboplatin was administered during a 60-min intravenous infusion of 250 ml 5% dextrose followed by 500 ml normal saline as a 2-h infusion. This was followed by a 90-min intravenous infusion of irinotecan in 250 ml 5% dextrose. Irinotecan was not administered on days 8 or 15 in the cycle if the leukocyte count was $< 3\times10^9\ l^{-1}$, the platelet count was $< 100\times10^9\ l^{-1}$, or the patient had diarrhea on those days. The next cycle commenced after the leukocyte and platelet counts reached at least $3\times10^9\ l^{-1}$ and $100\times10^9\ l^{-1}$, respectively. In patients showing a response, this chemotherapy was repeated every 4 weeks.

Patient evaluation

Tumor staging was performed as described previously [14]. The tumor stage was determined according to the tumor-node-metastasis system [19]. Before the first cycle, a blood cell count, urinalysis, and biochemistry tests were performed to assess renal and hepatic function, and electrolytes. This monitoring was repeated during treatment, while other investigations were repeated, as necessary, to evaluate marker lesions. After the completion of treatment, each disease was assessed and tumors restaged. The eligibility, assessability, and response of each patient were determined by extramural reviewers.

Tumor response and toxicities were classified according to World Health Organization criteria [20]. 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 a 50% or more reduction in the sum of the product of the greatest perpendicular diameter of all lesions for at least 4 weeks. No change (NC) was defined as $< 50\%$ reduction or $\leq 25\%$ increase in the products of the greatest perpendicular diameters of all the lesions, but without any evidence of new lesions. Progressive disease (PD) was defined as an increase of $> 25\%$ or the appearance of new lesions. Radiological studies included chest radiography once per week and chest CT scan once per chemotherapy cycle to assess response to therapy.

Statistical methods

The primary endpoint of this study was the estimation of the objective response rate. The two-stage accrual design described by Simon was used [21]. Assuming an overall response rate of 20% for standard therapy, a target response rate of 35% was established. $\alpha = 0.05$, $\beta = 0.20$, and the estimated required number of patients was more than 53. Overall survival was calculated by the Kaplan–Meier method [22].

Results

A total of 61 patients from eight institutions were enrolled in the trial between February 1998 and December

Table 1 Patient characteristics ($n = 61$)

Age (years)	
Median (range)	68 (33–75)
Sex (*n*)	
Male	46
Female	15
ECOG performance status (*n*)	
0	15
1	45
2	1
Stage (*n*)	
IIIB	15
IV	46
Histology (*n*)	
Adenocarcinoma	39
Squamous cell carcinoma	17
Large cell carcinoma	3
Adenosquamous cell carcinoma	2

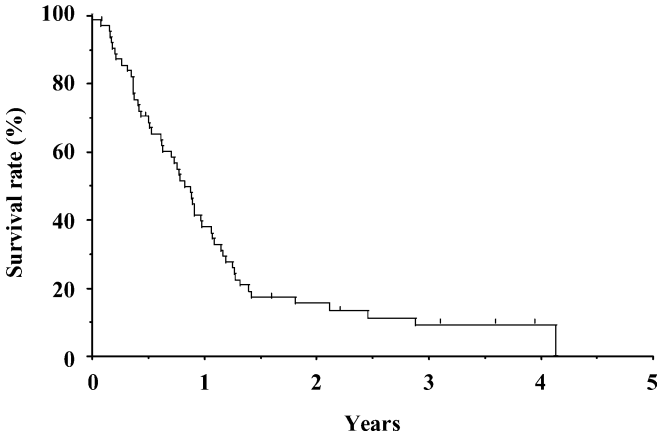

Fig. 1 Overall survival curve for the 61 patients enrolled in the study

2000. All patients received irinotecan/carboplatin therapy and were evaluable for toxicity. The patient characteristics are shown in Table 1.

Treatment administration

A total of 137 cycles of this therapy were administered: one cycle in 20 patients, two cycles in 19, three in 9, and four in 13. The numbers of irinotecan administrations skipped were 26 on day 8, 42 on day 15, and 10 on both days. The major reasons for omissions were 12 patients with leukopenia and 10 with diarrhea on day 8, and 14 patients with leukopenia, 10 with thrombocytopenia, 8 with diarrhea, and 5 with leukopenia and thrombocytopenia on day 15. The administration rate of irinotecan on days 8 and 15 were 81% and 70%, respectively. The dose intensity of irinotecan was 30.9 mg/m^2 per week, which was 82.5% of the projected dose intensity. The dose intensity of carboplatin was 99.2% of the projected dose intensity.

Efficacy

Of 61 patients, 59 were evaluable for response. An objective tumor response was observed in 20 patients with a partial response, for an overall response rate of 34% (95% confidence interval, CI, 22–47%). No change was observed in 26 patients (44%), and the remaining 13 patients (22%) had progressive disease.

The overall survival of all 61 patients is shown in Fig. 1. The median potential follow-up time was 43.3 months (range 1.0–54.9 months). The median follow-up for five patients who survived the longest was 37.2 months (range 19.4–47.7 months). Two patients were lost to follow-up at 1.0 months and 6.0 months after the beginning of treatment, and the other 54 patients died during the follow-up period. Median time to tumor progression was 4.0 months (range 0.3–17.0 months). Median survival time was 10.0 months (range, 0.1–49.7 months), and the 1-year, 2-year, and 3-year survival rates were 37.6%, 15.2%, and 8.9%, respectively. Median survival times, and the 1-year and 2-year survival rates for stage IIIB/IV were 8.9/10.6 months, 40.0/37.3% and 20.0/17.8%, respectively.

Toxicity

The toxicities noted during the treatment are listed in Table 2. Of the 61 patients enrolled, 60 were assessable for toxicity. There was one treatment-related death, as mentioned below. Among the patients assessable for toxicity, 44 (73%) experienced grade 3 or 4 hematological toxicity, and 15 (25%) had grade 4. The principal grade 3/4 hematological toxicity was neutropenia in 36 patients (60%), and the principal grade 4 toxicities were neutropenia and thrombocytopenia in 9 (15%) and 8 (13%), respectively. Febrile neutropenia occurred in 2 patients (3%). Concerning nonhematological toxicity, 4 patients (7%) experienced grade 3/4 diarrhea, one of

Table 2 Toxicities ($n = 61$)[a]

Adverse event	WHO grade (*n*)			Grade 3/4 (%)
	2	3	4	
Hematological				
Anemia	21	17	2	32
Leukopenia	25	19	0	32
Neutropenia	12	27	9	60
Thrombocytopenia	16	7	8	25
Nonhematological				
Diarrhea	12	3	1	7
Elevated transaminases	2	1	0	5
Nausea/vomiting	15	6	–	10
Fever	12	0	0	0
Alopecia	9	0	0	0
Pneumonitis	0	1	0	2

[a]There was one treatment-related death due to anaphylactic shock after intravenous administration of carboplatin

whom had grade 4 with fever and ileus on day 15 of the first cycle. Interstitial pneumonitis occurred in 1 patient (2%), who had a high fever for 2 days. The patient had hypoxemia with ground-glass opacity on the chest CT image on day 27 of the second cycle. The patient improved with corticosteroid therapy. There was one treatment-related death due to anaphylactic shock followed by hypotension, serious sweating, and dyspnea with wheezing after the administration of carboplatin on day 1. Despite intensive care, the patient died on day 3. No other severe toxicities were observed in the liver, kidney, nervous system, urinary bladder, skin or mucous membrane.

Discussion

The present irinotecan/carboplatin therapy for advanced NSCLC yielded an overall response rate of 34% and a 1-year survival rate of 37.6%, results comparable with those of standard chemotherapy regimens [13, 23]. Moreover, this irinotecan/carboplatin therapy, using the Chatelut formula to predict carboplatin CL, was well-tolerated in terms of toxicities and convenient.

In the past 10 years, newer drugs such as taxanes (paclitaxel and docetaxel), gemcitabine, vinorelbine, and irinotecan have been used for chemotherapy of NSCLC chemotherapy [13]. Recent large randomized trials of newer drugs with a platinum agent have demonstrated no difference in response or survival rates for advanced NSCLC [23, 24], suggesting that chemotherapy for NSCLC has reached a therapeutic plateau. These trials had response rates of 17–33%, median survival times of 7.4–8.1 months, and 1-year survival rates of 31–36% [23, 24]. Irinotecan/cisplatin therapy for NSCLC has been extensively evaluated in clinical trials including phase III studies, and results in response rates of 30–40%, 1-year survival rates of 30–40%, and a median survival time of 10 months [7–10, 24]. Thus, the efficacy of our irinotecan/carboplatin therapy for NSCLC is comparable with the above-mentioned data.

In the present study, we used irinotecan 50 mg/m^2 (days 1, 8 and 15) and carboplatin (day 1) with a target AUC of 5 mg min/ml using the Chatelut formula. Although irinotecan 60 mg/m^2 is recommended in irinotecan/cisplatin therapy, the dose was toxic in irinotecan/carboplatin therapy without the use of prophylactic granulocyte-colony stimulating factor [14]. The carboplatin dose for AUC 5 mg min/ml was well tolerated and adequate in combination with irinotecan 50 mg/m^2, as reported previously [14, 25]. The main toxicity of our irinotecan/carboplatin therapy was hematological. Comparing grade 3 or higher toxicities in irinotecan/carboplatin with those in irinotecan/cisplatin therapy [7, 8, 10], neutropenia was comparable (60% vs 46–80%), but thrombocytopenia was higher (25% vs 9–12%) with irinotecan/carboplatin. Platelet transfusion was performed only twice in 136 cycles of irinotecan/carboplatin therapy. In addition, nonhematological toxicities of grade 3 or higher were generally infrequent in irinotecan/carboplatin therapy: 10% vs 33–35% for nausea/vomiting, 7% vs 13–17% for diarrhea and 0% vs 0–4% for elevation of serum creatinine [7, 8, 10]. Thus, the nonhematological toxicities in our irinotecan/carboplatin therapy seem milder than those in irinotecan/cisplatin therapy.

In irinotecan-containing regimens, most life-threatening or lethal cases include severe diarrhea with neutropenia [3]. However, only four patients (7%) in our study experienced grade 3 or 4 diarrhea. This irinotecan-induced diarrhea led to omission of irinotecan administration on days 8 and/or 15, resulting in a low dose intensity of irinotecan [8]. The dosage was 30 mg/m^2 per week in irinotecan (60 mg)/cisplatin therapy [8], which is comparable to that in the irinotecan (50 mg)/carboplatin therapy. Thus, a low frequency of severe diarrhea in irinotecan/carboplatin therapy is beneficial to patients.

Takeda et al. also conducted the phase II study of irinotecan/carboplatin [25] and reported that this regimen is disappointing for two reasons: one the overall response rate and two myelosuppression. The response rate of 25% (9/36) in their study appears to be not as high as that with irinotecan/cisplatin and irinotecan monotherapy. However, considering that the response rates were 17–28% with recent standard regimens of ECOG [23] and SWOG [26], the regimen is not disappointing. The response rates in their phase I study, our phase I study and the phase II study were 35% (6/17), 36% (4/11) and 34% (20/59), respectively. Interestingly, these data are very close and reliable. The overall response rate of these four irinotecan/carboplatin studies is 32% (39/123).

With regard to myelosuppression, grade 3/4 thrombocytopenia/neutropenia was 47/77% in their phase II study and 25/60% in our phase II study. The incidence of febrile neutropenia were also lower in our study (11%, 4 of 36, vs 3%, 2 of 60). In two studies an irinotecan dose of 50 mg/m^2 and a carboplatin target AUC of 5 mg min/ml were adopted, so we presume the difference was caused by carboplatin clearance estimation. Furthermore, because the measurement of GFR using injection of ^{51}Cr-EDTA, as used in the study by Calvert et al. [15], employs an isotope, the 24-h creatinine clearance was substituted for GFR in the study by Takeda et al. Consequently, the myelosuppression seen in our study was not as severe as that found with irinotecan/cisplatin. Grade 3/4 thrombocytopenia and neutropenia were reported as 9% and 80% in phase II study of irinotecan/cisplatin [7].

The present study population included nearly 25% stage III patients. This rate was higher than in the ECOG [23] and SWOG [26] trials, which included only 10–15%. The median survival in these two trials were 7.4–8.1 months. Although the higher proportion of stage III patients seems to have had a greater influence on the survival data of the trial, the survival of stage IIIB patients was not superior to that of stage IV patients in the present study.

In conclusion, our multicenter phase II trial demonstrated the usefulness of irinotecan (50 mg/m^2 on days 1, 8, and 15) and carboplatin (target AUC 5 mg min/ml on day 1) in the chemotherapy of advanced NSCLC. This regimen was well tolerated and comparable in terms of both response and survival rates when compared with other regimens for NSCLC.

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