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ORIGINAL ARTICLE

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Phase I study of second-line chemotherapy with docetaxel and carboplatin in advanced non-small-cell lung cancer

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Abstract *Purpose*: Docetaxel and carboplatin have a broad spectrum of antitumor activity. We conducted a phase I study of docetaxel and carboplatin as second-line chemotherapy in previously treated non-small-cell lung cancer (NSCLC). This study aimed to determine the maximum tolerated dose (MTD) and the dose-limiting toxicities in this second-line combination chemotherapy. *Methods*: Patients with advanced NSCLC were treated with escalating docetaxel doses in combination with a fixed-target area under the concentration-time curve (AUC) of 5 mg·min/ml of carboplatin on day 1 of a 3–4-week cycle. The carboplatin dose was determined by multiplying the AUC by the clearance predicted using the Chatelut formula. The docetaxel dose was escalated from 40 mg/m^2 to the MTD by 10 mg/m^2 increments. *Results*: A total of 16 patients previously treated with anticancer drugs were enrolled through three dose levels (40, 50 and 60 mg/m^2 of docetaxel). All patients were assessable for toxicity and response. The MTD was docetaxel 60 mg/m^2 with a carboplatin target AUC of 5 mg·min/ml, and the dose-limiting toxicities in two of four patients were neutropenia and thrombocytopenia. Overall, neutropenia and thrombocytopenia of grade 3/4 occurred in eight patients (50%) and three patients (19%), respectively. Four patients (25%) and two patients (13%) experienced both grade 1 diarrhea and dermatitis, respectively. Allergic reactions, fluid retention, pneumonitis, neurotoxicity and mucositis were not observed. Of 16 patients, 5 showed an objective response (response rate 31%; 95%CI 14–56%). *Conclusions*: The combination of docetaxel and carboplatin is a feasible and well-tolerated second-line chemotherapy regimen in the treatment of NSCLC. Docetaxel 50 mg/m^2 under the carboplatin target AUC of 5 mg·min/ml using the Chatelut formula was the recommended dose for phase II study.

Keywords Docetaxel · Carboplatin · Non-small-cell lung cancer · Second-line chemotherapy · Phase I study

This work is reported on behalf of the Nagasaki Thoracic Oncology Group.

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Introduction

Most of the recent chemotherapy regimens in non-small-cell lung cancer (NSCLC) include newer agents such as taxanes, vinorelbine, gemcitabine, and irinotecan [20]. Furthermore, regimens with these agents alone have recently been investigated to further improve survival, although platinum-based chemotherapy has been used as a standard [20]. Docetaxel is a semisynthetic taxane with antitumor activity partially through promotion of

microtubule assembly and inhibition of tubulin depolymerization. As a single agent, docetaxel has shown a response rate of approximately 30% in more than 200 chemotherapy-naive NSCLC patients [4]. Docetaxel in combination with cisplatin has manageable toxicities and is active in NSCLC [15]. On the other hand, carboplatin is also an active drug in NSCLC and shows less toxicity than cisplatin. In a five-arm study of cisplatin-containing regimens and single agents, its analogue, carboplatin, showed the best 1-year survival rate with the least toxicity [2]. A number of phase II and III studies have shown that carboplatin as well as cisplatin has a broad spectrum of antitumor activity and that the nonhematological toxicities of carboplatin are clearly less than those of cisplatin [16]. In addition, in recent phase II studies, carboplatin and docetaxel as first-line chemotherapy in NSCLC have yielded promising response rates of approximately 40% with acceptable toxicity [1, 11, 13, 17, 23].

Recent reviews of second-line chemotherapy in NSCLC have found no responses in almost one-third to one-half of studies, and the response rate in most regimens was less than approximately 20% [7, 12]. Among them, docetaxel has been most extensively evaluated in the second-line setting and is the only agent that has been evaluated in phase III trials [8, 12, 21]. Phase II studies of single-agent docetaxel as second-line therapy in platinum-treated NSCLC have shown that the response rate, median survival and 1-year survival are approximately 20%, 7 to 9.7 months, and approximately 25%, respectively [6, 10, 19]. Interestingly, single-agent docetaxel shows similar response rates in platinum-sensitive and -refractory NSCLC [6, 10, 19].

Based on these findings, we conducted a phase I trial of docetaxel and carboplatin in previously treated NSCLC. The main objectives of our study were to determine the maximum tolerated dose (MTD) and the clinical toxicities encountered with this regimen.

Patients and methods

Patients

The study protocol was approved by the Ethical Committee of Nagasaki University School of Medicine. Patients with advanced and previously chemotherapy-treated NSCLC were included in this study. Eligibility criteria included the following: (a) a histologically or cytologically confirmed diagnosis of NSCLC; (b) previous treatment with anticancer drugs; (c) age $\leq$ 75 years; (d) Eastern Cooperative Oncology Group (ECOG) performance status (PS) $\leq$ 2; (e) life expectancy greater than 12 weeks; (f) adequate bone marrow function (leukocyte count $\geq$4000/μl, platelet count $\geq$100,000/μl and hemoglobin level $\geq$9 g/dl); (g) serum bilirubin level $\leq$ 1.5 mg/dl; (h) s-AST and s-ALT levels no more than twice the normal upper limit; (i) serum creatinine level $\leq$ 1.2 mg/dl; (j) no medical problems severe enough to prevent compliance with the protocol; and (k) provision of written informed consent.

Table 1 Dose-escalation and extension phase study. Docetaxel and carboplatin were administered on day 1 of each cycle. Carboplatin clearance was predicted by the Chatelut formula

Dose level	No. of patients	Docetaxel (mg/m^2)	Carboplatin target AUC (mg·min/ml)
1	3	40	5
2	3 (6[a])	50	5
3	4	60	5

[a]Number of patients enrolled in the extension phase study

Treatment, dose escalation, and extension phase of the study

Under a fixed-target area under the concentration-time curve (AUC) of 5 mg·min/ml for carboplatin on day 1, the starting dose of docetaxel was 40 mg/m^2 injected intravenously on day 1. The dose of docetaxel was increased by 10 mg/m^2 increments as shown in Table 1. The carboplatin dose was determined by multiplying the target AUC of 5 mg·min/ml by the carboplatin clearance, which was predicted by the Chatelut formula using the Jaffe method for serum creatinine measurement [3]. Carboplatin was administered as a 60-min intravenous infusion with 250 ml 5% dextrose, followed by 500 ml normal saline as a 2-h infusion. This was followed by a 60-min intravenous infusion of docetaxel in 250 ml 5% dextrose. Premedication of docetaxel was not dispensed. The next cycle at each level commenced after leukocyte and platelet counts reached 3000/μl and 100,000/μl, respectively. In patients showing a response, this chemotherapy was repeated every 3–4 weeks.

The dose escalation was evaluated during the first cycle of each dose level, when toxicities were assessed according to the common toxicity criteria of the WHO [24]. Dose-limiting toxicity (DLT) in this study was defined as grade 4 leukopenia or neutropenia lasting 4 days or more, grade 4 thrombocytopenia, and grade 3 or worse nonhematological toxicity, with the exception of nausea and vomiting. For dose escalation, three patients were enrolled at each dose level, and the dose was escalated to the next level when none of the patients experienced DLT. When two or more patients experienced DLT, the dose level was defined as the MTD. When one of three patients experienced DLT, an additional three patients were treated at the same level. When none of the additional patients experienced DLT, the dose was escalated to the next level. When one or more of the additional patients experienced DLT, the dose level was also defined as the MTD. The recommended dose of this regimen for phase II study was defined as the previous level 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.

Patient evaluation and response assessment

Tumor staging was based on a thorough medical history and physical examination, chest radiography, bone scintigraphy, computed tomography of the chest and abdomen, computed tomography or magnetic resonance imaging of the head, and endoscopy. The stage of malignancy was determined according to the tumor-node-metastasis (TNM) system [18]. Before the first cycle, a blood cell count, urinalysis, and biochemistry tests for the assessment of renal and hepatic function and electrolytes were performed. These monitoring tests were repeated during treatment, and other investigations were repeated as necessary to evaluate marker lesions. After the completion of treatment, disease was assessed, and tumors were restaged.

The eligibility, assessability, and response of each patient were determined by independent reviewers. Tumor response was classified as complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD), according to the WHO criteria [24].

Results

A total of 16 patients were enrolled in this trial between November 1997 and March 2000, and all received chemotherapy. Ten and six patients were enrolled in the

dose escalation and the extension phases of the study, respectively. Patient characteristics were male/female 11/5, median age 61 years (range 33–74 years), and PS 0, 1 and 2 in 1, 12 and 3 patients, respectively. Of the 16 patients, 14 (88%) had received prior platinum-containing chemotherapy (10 cisplatin and 4 carboplatin) without taxanes, and 2 had received oral tegafur/uracil (UFT). There had been one chemotherapy regimen in 14 patients, two regimens in 1, and three in 1. No patients had received prior paclitaxel or more than four cycles of first-line chemotherapy. Five patients had had prior radiotherapy.

A total of 31 cycles of this regimen were administered through three dose levels, and all were assessable for toxicity. One cycle was administered to ten patients (63%), two cycles to one (6%), three cycles to four (25%), and seven cycles to one (6%).

Recommended dose level and extension phase

None of three patients at level 1 or 2 experienced DLTs. At level 3, one of three original patients experienced DLT (neutropenia), and the first additional patient experienced DLT (thrombocytopenia). At that time, level 3 was defined as the MTD, and level 2 was the recommended dose. The study was extended to enroll additional patients at the dose level recommended above, that is level 2. One of the additional six patients experienced DLT (thrombocytopenia). Therefore, we concluded that level 2 was the recommended dose in this regimen.

Toxicity

Hematological toxicity

Leukoneutropenia and thrombocytopenia were the principal toxicities, as shown in Table 2. Of the 16 patients, 5 (31%) experienced grade 4 hematological toxicities, and three (19%) experienced hematological DLTs. At dose level 3, three patients (75%) experienced grade 4 hematological toxicities including two (50%) hematological DLTs, and one patient required platelet transfusion. At dose level 2, two patients (22%) experienced grade 4 hematological toxicities including one (11%) hematological DLT, and one patient required platelet transfusion. At dose level 1, no patients experienced grade 4 hematological toxicities in any treatment cycle. Anemia requiring blood transfusion was not observed in any treatment cycle at any level.

Nonhematological toxicity

Nonhematological toxicities were mild as shown in Table 3. Gastrointestinal toxicities were prominent, and included nausea/vomiting, diarrhea, and liver dysfunction. No patient experienced nonhematological DLTs. Five patients (31%) had grade 2 or worse nausea/vomiting in the first cycle. Four patients (25%) had diarrhea: one patient (6%) grade 2, but none grade 3 or worse in any treatment cycle. Two patients (13%) showed liver dysfunction with a transient increase in serum transaminases, and transient dermatitis was also observed in two patients (13%). None showed allergic reactions, fluid retention, pneumonitis, neurotoxicity or mucositis.

Response

All of the 16 patients were assessable for response. PRs were observed in five patients (one patient at dose level 1, two at level 2, and two at level 3). Eight patients (50%) had SD and three (19%) PD. Prior chemotherapy regimens of the five PR patients were two UFT, and one each of irinotecan/cisplatin, carboplatin/vindesine, and mitomycin/cisplatin/vinorelbine. The overall response rate was 31%.

Table 2 Hematological toxicities (WHO grade). The numbers in parentheses are the number of patients in the extension phase study

Dose Level	No. of patients	Anemia		Leukopenia			Neutropenia			Thrombocytopenia		
		2	3	2	3	4	2	3	4	2	3	4
1	3	0	0	0	0	0	1	0	0	0	0	0
2	3 (6)	0 (2)	0 (1)	1 (4)	0 (1)	0	2 (1)	0 (3)	0 (1)[a]	0	0	0 (1)
3	4	0	01	3	0	0	2	2[b]	1	1	1	1

[a]Grade 4 neutropenia lasting 2 days, which was not a DLT
[b]Grade 4 neutropenia lasting 4 days (DLT) and 2 days (not DLT)

Table 3 Nonhematological toxicities (WHO grade). The numbers in parentheses are the number of patients in the extension phase study. Allergic reactions, fluid retention, pneumonitis, neurotoxicity and mucositis were not observed (*s-AST* aspartate aminotransferase, *s-ALT* alanine aminotransferase)

Dose level	No. of patients	Nausea/vomiting			Diarrhea			s-AST		s-ALT		Dermatitis	
		1	2	≥3	1	2	≥3	1	≥2	1	≥2	1	≥2
1	3	1	0	0	0	0	0	0	0	0	0	1	0
2	3 (6)	0 (2)	0 (1)	0 (2)	0 (1)	0	0	0	0	0	0	1	0
3	4	2	2	0	3	0	0	2	0	2	0	0	0

Discussion

The present phase I study of docetaxel (day 1) and carboplatin (day 1) as second-line chemotherapy in NSCLC showed that the recommended docetaxel dose was 50 mg/m^2 under a carboplatin target AUC 5 mg·min/ml using the Chatelut formula for carboplatin clearance. There have been no reports of the use of this regimen in the second-line setting. The main DLTs were neutropenia and thrombocytopenia, as expected, while severe nonhematological toxicities were not observed. This second-line regimen may be useful, especially when various nonplatinum regimens have been extensively investigated as first-line chemotherapy in NSCLC.

In prior phase II studies of first-line docetaxel and carboplatin in NSCLC, the recommended dose of docetaxel has been 65 to 100 mg/m^2 under a carboplatin target AUC 6 mg·min/ml using the Calvert formula [1, 11, 13, 17, 23]. These studies yielded a good response rate of approximately 40%, but grade 3/4 neutropenia and febrile neutropenia have frequently been observed [1, 11, 13, 17]. In addition, severe nonhematological toxicities such as diarrhea, asthenia and myalgia were observed in these studies [1, 13, 17], but not in the present study. Two recent randomized-trials in NSCLC patients previously treated with platinum-based regimens have shown significant prolongation of survival in the single-agent docetaxel arm compared with best supportive care or vinorelbine/ifosfamide therapy [8, 21]. Interestingly, both trials showed benefits in survival and toxicity with docetaxel 75 mg/m^2 rather than 100 mg/m^2, and prior exposure to paclitaxel did not decrease the likelihood of response to docetaxel [8, 21]. Nakamura et al. have also reported results comparable to those of the above-mentioned phase III trials in a phase II trial of 60 mg/m^2 docetaxel as second-line therapy in NSCLC, and this dose is recommended for first-line therapy using the single agent in Japan [19]. Thus, our recommended dose of docetaxel 50 mg/m^2 with carboplatin AUC 5 mg·min/ml as second-line chemotherapy seems appropriate.

Only in one study has carboplatin been incorporated into a second-line chemotherapy regimen in NSCLC, where the target carboplatin AUC was 5 mg·min/ml using the Calvert formula for predicting carboplatin clearance [14]. We consider that AUC 5 mg·min/ml using the Chatelut formula is adequate for a target carboplatin AUC in the present study, while target carboplatin AUCs of 5 to 7 mg·min/ml have been used for combinations with other agents [5]. In our phase I study of carboplatin and irinotecan, we prospectively evaluated the Chatelut formula for predicting carboplatin clearance [9]. 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 [9], and a retrospective study has shown that the predictions are similar between methods for predicting carboplatin clearance [22].

On the other hand, the exact role of platinum-containing regimens still remains undetermined in second-line chemotherapy of NSCLC [12]. In respect of toxicity, the present regimen including carboplatin at least did not increase the risk of cumulative toxicity after prior cisplatin-containing chemotherapy, although cisplatin as second-line therapy seems to increase the risk [12]. Accordingly, carboplatin rather than cisplatin may be useful when platinum agents are used in second-line chemotherapy. To confirm this advantage of carboplatin, further clinical trials are needed. Interestingly, the response rate of 31% in the present study is encouraging as second-line chemotherapy. However, this was not the principal aim of the study. Currently, we are conducting a phase II trial of this regimen as second-line therapy in NSCLC.

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