Cancer Chemother Pharmacol (2005) 55: 552–558
DOI 10.1007/s00280-004-0921-z

ORIGINAL ARTICLE

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# Sequence effect of docetaxel and carboplatin on toxicity, tumor response and pharmacokinetics in non-small-cell lung cancer patients: a phase I study of two sequences

Received: 9 May 2004 / Accepted: 3 September 2004 / Published online: 15 March 2005


**Abstract** *Purpose*: To investigate sequence effects on toxicity, tumor response and pharmacokinetics of docetaxel and carboplatin, together with a determination of the maximum-tolerated dose (MTD) and recommended dose for each schedule. *Patients and methods*: A total of 46 chemotherapy-naive patients with advanced non-small-cell lung cancer were randomized to receive docetaxel before (schedule A) or after (schedule B) carboplatin. The dose levels studied were [docetaxel (mg/m$^2$)/carboplatin (mg×min/ml)] 50/5, 60/5, 60/6, 60/7, and 70/6. Treatment cycles were repeated every 3 or 4 weeks unless disease progression or undue toxicity occurred. *Results*: Of the 46 patients, 44 were assessable for toxicity and received a total of 84 cycles. The major dose-limiting toxicity was neutropenia. When the docetaxel dose was 60 mg/m$^2$, the carboplatin MTD was deemed to be AUC 7 in both schedules. When the docetaxel dose was escalated to 70 mg/m$^2$, the carboplatin MTD was reached in schedule A, and the dose-limiting toxicity was not observed in schedule B. Tumor response was observed in 4 of 22 patients (18%) with schedule A and 8 of 19 (42%) with schedule B. Clearances of both drugs were not affected by sequence: $111.2 \pm 26.8$ ml/min and $107.8 \pm 29.0$ ml/min for carboplatin ($P = 0.69$), and $26.7 \pm 8.3$ l/h and $22.8 \pm 7.0$ l/h for docetaxel ($P = 0.19$) in schedules A and B, respectively. *Conclusions*: Carboplatin AUC 6 followed by docetaxel 70 mg/m$^2$ was a favorable regimen for phase II study because of likely lower toxicity and a potentially higher response rate than the reverse sequence schedule. The mechanism of the sequence effects on toxicity and tumor response could not be explained by the pharmacokinetic interactions.

**Keywords** Maximum-tolerated dose · Recommended dose · Dose-limiting toxicity · Chemotherapy

Supported by grants from the Ministry of Health, Labor and Welfare, and the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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## Introduction

Docetaxel is a semisynthesized taxoid derived from a noncytotoxic precursor, 10-deacetyl baccatin III, that is extracted from the needles of the European yew, *Taxus baccata*. Docetaxel exhibits antitumor activity through binding to free tubulin and promoting assembly of stable microtubules causing $G_2$-M phase arrest. Docetaxel

shows clinically significant activity against anthracycline-resistant breast cancer, ovarian cancer, head and neck cancers, and non-small-cell lung cancer [5, 6, 8–11, 24]. Phase II studies of docetaxel alone at a dose of 100 mg/m$^2$ have demonstrated significant activity, i.e., response rates of 23–38% and median survivals of 25–47 weeks in chemotherapy-naive patients with non-small-cell lung cancer [6, 8, 9, 11]. The recommended dose of docetaxel is 60 mg/m$^2$ in Japan, which is lower than that in the United States or Europe. However, at a dose of 60 mg/m$^2$ the drug has shown a response rate of 23% with a median survival of 42 weeks in untreated non-small-cell lung cancer patients, effects equivalent to those observed at a dose of 100 mg/m$^2$ [16]. The main dose-limiting toxic effect of docetaxel is neutropenia, and others include paresthesias, infrequent hypersensitivity reactions, nausea, vomiting, and dose-dependent fluid retention.

The combination of docetaxel with cisplatin has a significant effect on non-small-cell lung cancer, with response rates ranging from 35% to 45%, and overall median survival reaching 12 months [19]. Despite its significant antitumor activity [4, 13], the clinical use of cisplatin is sometimes hampered by its severe toxicity, e.g., nephrotoxicity, neurotoxicity, and gastrointestinal toxicity including nausea and vomiting. Carboplatin, a second-generation platinum-containing compound, is much less nephrotoxic, neurotoxic and emetogenic than its parent compound cisplatin. Carboplatin as a monotherapy has shown the best 1-year survival rate with the least toxicity in a randomized study conducted by the Eastern Cooperative Oncology Group [3]. In addition, in another randomized study by the European Organization of Research and Treatment of Cancer, a combination chemotherapy of carboplatin plus etoposide was less toxic than cisplatin plus etoposide in advanced non-small-cell lung cancer patients, with no significant difference in survival [15]. Thus, carboplatin is a suitable agent as a substitute for cisplatin, and we considered that a combination regimen with docetaxel and carboplatin should be explored.

In dose-escalating studies with two drugs, the toxicity, antitumor activity and pharmacokinetics often vary with the sequence in which they are administered [14, 22, 23]. For example, Rowinsky et al. found a sequence dependency with the combination of paclitaxel and cisplatin [23]. In this study, we investigated the sequence effect of docetaxel and carboplatin on toxicity, tumor response, and pharmacokinetics, and also sought to determine the maximum-tolerated dose (MTD) and recommended dose for each schedule.

## Patients and methods

### Patient eligibility

Patients were required to have histologically or cytologically proven stage IV or unresectable stage III non-small-cell lung cancer. No prior chemotherapy was permitted. Patients who had been previously treated with radiation therapy were eligible if it had been completed at least 4 weeks before entering the study. Other eligibility criteria were age 20–74 years of age, performance status (World Health Organization) [25] of 2 or better, life expectancy of at least 12 weeks, adequate bone marrow function (leukocyte count ≥4000/μl, absolute neutrophil count ≥2000/μl, and platelet count ≥100,000/μl), aspartate transaminase (AST) not more than twice the upper limit of normal for the institution, alanine transaminase (ALT) not more than twice the upper limit of normal for the institution, serum creatinine level ≤ 1.5 mg/dl (enzymatic methods), and $PaO_2$ ≥60 mmHg or $SaO_2$ (arterial hemoglobin oxygen saturation) ≥90%. Exclusion criteria included: malignant pleural or pericardial effusions that required treatment; uncontrolled serious medical illnesses such as cardiac disease, hypertension, diabetes mellitus and active infection; hypertension being treated with any calcium channel blockers; concurrent malignancy; preexisting malignancy within 5 years; and pregnancy or lactation. All patients gave written informed consent and the ethics committee of the participating medical institutions approved the protocol.

### Regimen

Patients were randomized to receive docetaxel given as a 1-h infusion before (schedule A) or after (schedule B) carboplatin as a 1-h infusion on day 1. Both docetaxel and carboplatin were dissolved in 250 ml 5% dextrose solution just before infusion. The starting doses (level 1) of docetaxel and carboplatin (target area under the time versus concentration curve, AUC, by the Calvert formula with adjusted creatinine clearance) were 50 mg/m$^2$ and AUC 5 (mg×min/ml), respectively (Table 1). Docetaxel was increased to 60 mg/m$^2$ (levels 2, 3, 4), then to 70 mg/m$^2$ (level 5). Carboplatin was increased to AUC 7 (levels 4) then to AUC 6 (level 5). At least six patients were enrolled at each dose level and were subsequently randomized to receive either schedule A or schedule B, i.e., at least three patients were enrolled in each schedule at the same dose level. Serotonin receptor antagonist and corticosteroids were recommended for antiemesis, except for the first course of chemotherapy where corticosteroids were used as premedication.

**Table 1** Dose levels

| Level | Docetaxel (mg/m$^2$) → carboplatin (mg×min/ml) (schedule A) | Carboplatin (mg×min/ml) → docetaxel (mg/m$^2$) (schedule B) |
|---|---|---|
| 1 | 50 → 5 | 5 → 50 |
| 2 | 60 → 5 | 5 → 60 |
| 3 | 60 → 6 | 6 → 60 |
| 4 | 60 → 7 | 7 → 60 |
| 5 | 70 → 6 | 6 → 70 |

Dose escalation was based on the toxicity observed through cycle 1. If a dose-limiting toxicity (DLT) was detected following the first cycle in one or two of three patients, an additional three patients were studied. If three or more patients experienced DLT, enrollment was stopped and this level was considered as the MTD. Hematological DLT was defined as follows: a leukocyte count less than 1000/μl or a neutrophil count less than 500/μl for more than 3 days, or a neutrophil count less than 500/μl with fever and a platelet count less than 25,000/μl. DLT other than hematological was defined as toxicity of grade 3 or greater, except nausea, vomiting or alopecia, according to NCI-CTC version 2 [20]. When the MTD was reached, three additional patients were enrolled at the dose level just below the MTD to ensure their safety. Intrapatient dose escalation was not allowed. Docetaxel and carboplatin were reduced by 25% when patients experienced DLT.

Treatment cycles were repeated every 3 or 4 weeks provided patients had sufficiently recovered from toxic effects. Treatment was performed for at least two cycles unless an unacceptable level of toxicity or disease progression occurred. Responders were allowed to continue the treatment until the appearance of disease progression or major adverse events.

## Carboplatin dosing

The carboplatin dose was based on a target AUC from 5 to 7 (mg×min/ml) using the Calvert formula with adjustment for creatinine clearance (ml/min) [1], where the creatinine levels were measured by the enzymatic method.

$$\text{Dose (mg/body)} = \text{AUC} \times [\text{adjusted creatinine clearance} + 25]$$

$$\text{Adjusted creatinine clearance} = 24 - \text{h urine volume (dl)} \times \text{urine creatinine (mg/dl)} / (\text{serum creatinine level (mg/dl)} + 0.2) \times 24 \times 60$$

## Pretreatment and follow-up studies

In all patients a full medical history was obtained and physical examination carried out before treatment. The laboratory workup included complete blood cell count with differential, electrolytes, total protein, albumin, total bilirubin, AST, ALT, lactate dehydrogenase (LDH), alkaline phosphatase (ALP), blood urea nitrogen (BUN), sodium, potassium, chloride, serum creatinine, creatinine clearance (24-h urine collection was measured twice), and urinalysis. Electrocardiograms, chest radiographs, computed scans of the chest, head and upper abdomen, and bone scintigrams were also obtained.

Complete blood cell counts and electrolytes were repeated twice weekly. Total protein, albumin, total bilirubin, AST, ALT, LDH, ALP, BUN, sodium, potassium, chloride, creatinine and chest radiography were performed weekly. Toxicity from treatments was graded according to NCI-CTC version 2 [20]. In patients with measurable disease, tumor response was assessed according to the WHO standardized response definitions after two complete cycles and after study discontinuation [25].

## Pharmacological studies

Pharmacological studies of docetaxel and carboplatin were performed in the first cycle. When docetaxel was administered before carboplatin (schedule A), blood samples for the analysis of docetaxel were taken from the arm opposite the infusion site at 0, 0.25, 0.5, 1, 2, 4, 8, and 24 h after the end of the infusion of docetaxel. Another set of samples for the analysis of carboplatin was taken at 0, 0.25, 0.5, 1, 3, 7 and 23 h after the end of infusion of carboplatin. When carboplatin was infused before docetaxel (schedule B), blood samples for carboplatin analysis were taken at 0, 0.25, 0.5, 1, 2, 4, 8 and 24 h after the end of carboplatin infusion. Then, samples for docetaxel analysis were taken at 0, 0.25, 0.5, 1, 3, 7 and 23 h after the end of docetaxel infusion.

Plasma was immediately obtained by centrifugation of the blood samples. Part of the carboplatin-containing plasma was directly transferred to an MPS-1 device equipped with a YMT-30 filter (Grace Japan, Amicon, Tokyo, Japan) and centrifuged to obtain plasma ultrafiltrate. The plasma and plasma ultrafiltrate were stored at −20°C until analysis. The ultrafiltered platinum levels were analyzed by flameless atomic absorption spectrometry [17]. The carboplatin level was calculated based on the molar ratio of platinum to carboplatin, and is expressed in micrograms per milliliter. The AUC of carboplatin was calculated by the trapezoidal method with extrapolation to infinity using WINNONLIN software (Scientific Consulting, Apex, N.C.).

Docetaxel concentrations were measured by reverse-phase high-performance liquid chromatography (HPLC) with UV detection [7]. Docetaxel pharmacokinetic parameters were estimated by non-linear least-squares weighted regression analysis using a three-compartment model.

## Statistical analysis

We assessed the effect of sequence on response rate using Fisher's exact test. The effect of sequence on pharma-

**Table 2** Patient characteristics

| | Docetaxel → carboplatin (schedule A) | Carboplatin → docetaxel (schedule B) |
|---|---|---|
| Gender (male/female) | 18/5 | 15/6 |
| Age (years) | | |
| Median | 65 | 66 |
| Range | 39–74 | 41–74 |
| Performance status | | |
| 0 | 7 | 5 |
| 1 | 12 | 16 |
| 2 | 4 | 0 |
| Histological subtype | | |
| Adenocarcinoma | 13 | 9 |
| Squamous cell carcinoma | 9 | 9 |
| Large cell carcinoma | 1 | 3 |
| Stage | | |
| IIIA | 5 | 4 |
| IIIB | 8 | 13 |
| IV | 10 | 4 |

cokinetics was compared using Wilcoxon's rank-sum test. We used JMP version 4 software (SAS Institute, Cary, N.C.). A difference was considered statistically significant when the two-tailed $P$ value was $< 0.05$.

Hematological toxicity was assessed as the percentage decrease in neutrophil count or platelet count using the following equation

$$\text{Percentage decrease} = (\text{pretreatment value} - \text{value of the nadir})/\text{pretreatment value}$$

Data were fitted to a sigmoid Emax model, which is defined by a formula for the drug effect

$$E = \text{AUC}^{\gamma}/(\text{EC}_{50}^{\gamma} + \text{AUC}^{\gamma}),$$

where E is the drug effect, i.e., the percent decrease in platelet count or neutrophil count, and $EC_{50}$ is the AUC associated with one-half of the maximal drug effect.

## Results

### Patient characteristics

Of the 46 patients, 44 were assessable for toxicity after excluding two patients (Table 2) (dose adjustment of carboplatin was not accurate in one patient, and bone marrow function did not satisfy the eligibility criteria in the other). Most patients (91%) had a performance status of 0 or 1. A total of 84 cycles were given, with a median of 2 (range 1–4). Of the 46 patients, 12 (26%) stopped the therapy after the first course because of disease progression or toxicity. No treatment-related death was reported in this study.

### Toxicity

The major DLT was neutropenia, and others included diarrhea, infection and hepatotoxicity (Table 3). Neutropenia of grade 4 was seen in 19 of 22 cycles (86%) at levels 4 and 5 in schedule A, and in 10 of 10 cycles (100%) in schedule B. When the docetaxel dose was 60 mg/m$^2$, the carboplatin MTD was deemed to be AUC 7 in both schedules (level 4). Neutropenia of grade 4 continued for more than 3 days in two patients and another patient experienced fever associated with neutropenia at level 4 in schedule A. One patent experienced neutropenia of grade 4 for more than 3 days, and two had fever associated with neutropenia at level 4 in schedule B. When docetaxel dose was escalated to 70 mg/m$^2$ (level 5), the carboplatin MTD was reached only in schedule A. Two patients experienced neutropenia of grade 4 for more than 3 days, and a grade 3 infection occurred in one patient. In schedule B, no DLT was observed. The dose escalation of docetaxel was stopped because the use of docetaxel more than at 70 mg/m$^2$ is not approved in Japan.

**Table 3** Toxicities (NCI-CTC version 2)

| | Level | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Docetaxel → carboplatin (schedule A) | | | | | Carboplatin → docetaxel (schedule B) | | | | |
| | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| No. of courses | 10 | 5 | 9 | 12 | 10 | 11 | 11 | 6 | 5 | 5 |
| Total WBC grade 3 | 3 | 3 | 4 | 8 | 7 | 4 | 3 | 2 | 5 | 2 |
| Total WBC grade 4 | – | – | – | 1 | 2 | – | – | – | – | – |
| Neutrophils grade 3 | 3 | 4 | 2 | 1 | – | 6 | 3 | 1 | 1 | – |
| Neutrophils grade 4 | 3 | 1 | 6 | 10 | 9 | 2 | 2 | 5 | 5 | 5 |
| Platelets grade 3 | – | 1 | – | – | – | – | – | 2 | 2 | – |
| Nausea/vomiting grade 3 | – | – | – | – | – | – | 2 | – | – | 1 |
| Diarrhea grade 3 | – | – | – | 1 | – | – | 1 | – | – | – |
| Skin grade 2 | – | – | – | – | 2 | 1 | 1 | – | 1 | – |
| Neuropathy grade 2 | – | – | – | – | – | – | 1 | – | – | – |
| Abdominal pain G3 | – | – | – | 1 | – | – | – | – | – | – |
| Pleural effusion grade 4 | – | – | – | – | – | 1 | – | – | – | – |
| Elevated AST/ALT grade 3 | – | – | 1 | – | – | 1 | – | – | – | – |

**Table 4** Pharmacokinetics of carboplatin (C) and docetaxel (D) (*Cl* clearance, *Vss* volume of distribution steady-state, *D* docetaxel, *C* carboplatin, *ND* not done)

| Level | Sequence | Carboplatin | | | | Docetaxel | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | No. | AUC (mg×min/ml) | Cl (l/h) | Vss (l) | No. | AUC (mg×min/ml) | Cl (l/h) | Vss (l) |
| 1 | D → C | 3 | 4.5 ± 0.7 | 104.5 ± 23.5 | 22,712 ± 2,040 | ND | ND | ND | ND |
| | C → D | 6 | 5.2 ± 1.0 | 120.3 ± 33.7 | 19,231 ± 3,246 | ND | ND | ND | ND |
| 2 | D → C | 3 | 5.8 ± 1.0 | 101.3 ± 26.0 | 17,675 ± 2,048 | ND | ND | ND | ND |
| | C → D | 5 | 4.5 ± 0.9 | 105.9 ± 22.3 | 19,052 ± 1,156 | ND | ND | ND | ND |
| 3 | D → C | 6 | 6.2 ± 1.7 | 112.3 ± 30.3 | 17,927 ± 3,866 | 3 | 5.7 ± 2.5 | 13.9 ± 0.8 | 538.1 ± 8.2 |
| | C → D | 3 | 6.5 ± 1.4 | 90.5 ± 35.6 | 19,348 ± 703 | 3 | 4.6 ± 1.7 | 23.6 ± 9.4 | 569.1 ± 111.6 |
| 4 | D → C | 6 | 6.3 ± 1.1 | 117.8 ± 35.4 | 20,600 ± 4,219 | 6 | 3.6 ± 0.7 | 28.1 ± 5.1 | 610.4 ± 29.1 |
| | C → D | 3 | 6.9 ± 1.4 | 88.9 ± 10.7 | 19,134 ± 756 | 3 | 3.6 ± 0.7 | 25.6 ± 4.2 | 518.1 ± 239.0 |
| 5 | D → C | 6 | 5.5 ± 1.0 | 111.7 ± 22.2 | 23,988 ± 8,709 | 6 | 4.1 ± 1.5 | 29.3 ± 9.4 | 611.7 ± 37.2 |
| | C → D | 3 | 5.3 ± 0.6 | 122.0 ± 32.0 | 21,683 ± 2,529 | 3 | 4.1 ± 0.4 | 26.0 ± 3.4 | 618.1 ± 12.0 |

### Responses

Among 22 patients with measurable disease, tumor responses were observed in 4 of 22 (18%) in schedule A and 8 of 19 (42%) in schedule B. There was no significant difference in response rates between the schedules ($P = 0.17$).

### Pharmacology

Pharmacokinetic studies for docetaxel and carboplatin were carried out during the first cycle in 28 and 44 patients, respectively. The clearances of neither drug was affected by the sequence: 111.2 ± 26.8 l/h and 107.8 ± 29.0 l/h for carboplatin ($P = 0.69$), and 26.7 ± 8.3 l/h and 22.8 ± 7.0 l/h for docetaxel ($P = 0.19$) in schedules A and B, respectively (Table 4).

The pharmacodynamic relationship between the percentage decrease in neutrophil count or platelet count and carboplatin AUC were best described using the following sigmoid Emax models:

$$E_p = \text{Carboplatin AUC}^{1.17} / \left(6.20^{1.17} + \text{carboplatin AUC}^{1.17}\right),$$

$$E_n = \text{Carboplatin AUC}^{1.08} / \left(1.02^{1.08} + \text{carboplatin AUC}^{1.08}\right),$$

where $E_p$ is the percent decrease in platelet count (Fig. 1), and $E_n$ is the percent decrease in neutrophil count (Fig. 2).

No correlation was observed between the percentage decrease in neutrophil or platelet count and docetaxel AUC.

## Discussion

The regimen of carboplatin AUC 6 followed by docetaxel 70 mg/m$^2$ (level 5, schedule B) proved suitable for a subsequent phase II study because of its lower toxicity and potentially higher response rate compared with the reverse sequence. The response rate seems to be better with schedule B, although the difference was not statistically significant.

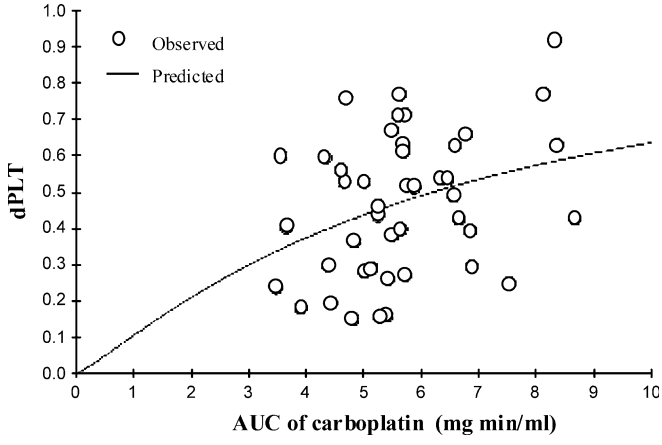


**Fig. 1** Pharmacodynamic correlation between carboplatin AUC and percentage decrease in platelet count. *dPLT* (pretreatment platelet value−platelet value of the nadir)/pretreatment platelet value

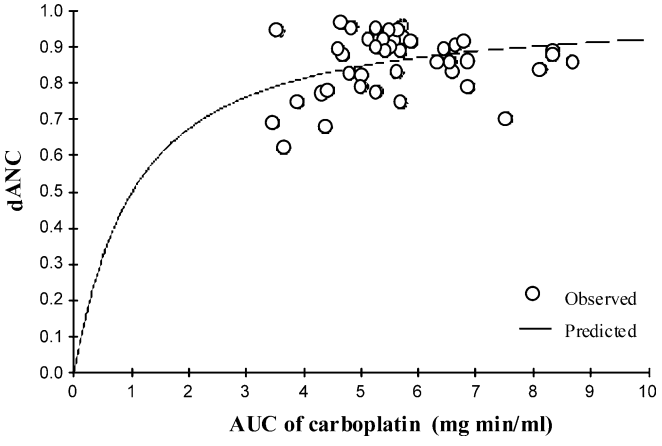


**Fig. 2** Pharmacodynamic correlation between carboplatin AUC and percentage decrease in neutrophil count. *dANC* (pretreatment neutrophil value−neutrophil value of the nadir)/pretreatment neutrophil value

The phase I study reported here was performed to assess the feasibility of the combination and to determine the MTD and its side effects with an emphasis on sequence-dependent effects [14, 22, 23]. To our best knowledge, our study was the first to assess the sequence of carboplatin with docetaxel. The sequence of carboplatin followed by docetaxel seemed to show lower toxicity and potentially higher response rate than the reverse sequence. The mechanism of the sequence effects on toxicity and tumor response could not be explained by pharmacokinetic interactions because there was no significant difference in the pharmacokinetic parameters between the two schedules. In a phase I study that combined paclitaxel and cisplatin, concurrent pharmacological studies have demonstrated that the treatment sequence of cisplatin followed by paclitaxel is associated with a 25% lower clearance rate of paclitaxel, and that body exposure to paclitaxel is 33% higher [23]. Pronk et al. have reported that there are no significant differences between the sequence effects on pharmacokinetic parameters or on the occurrence of hematological and non-hematological toxicities with the combination of docetaxel with cisplatin [22]. According to a phase I study of the combination of paclitaxel and carboplatin reported by Huizing et al., there are no pharmacokinetic-sequence interactions [14].

According to a recent phase I trial of docetaxel and carboplatin as a first-line therapy, the MTDs have been reported as docetaxel 80 mg/m$^2$ followed by carboplatin AUC 7 or docetaxel 100 mg/m$^2$ followed by carboplatin AUC 6 [12]. The main DLTs in that study were grade 4 neutropenia, neutropenic fever, and diarrhea. Another phase I trial indicated that the MTD is docetaxel 90 mg/m$^2$ followed by carboplatin AUC 6 (mg×min/ml) [2]. Despite the use of a lower dose of docetaxel 70 mg/m$^2$, the carboplatin dose could not be escalated more than AUC 6 when docetaxel preceded carboplatin in the present study. Although the reason for this discrepancy is not clear, there might be ethnic differences in susceptibility to docetaxel. Based on a phase I trial of docetaxel conducted in Japan, the recommended dose was 60 mg/m$^2$ [9], which is lower than that in the United States [6, 8, 9, 11]. In another phase I trial of docetaxel and carboplatin in Japan, the recommended dose was docetaxel 50 mg/m$^2$ with carboplatin AUC 5 for previously treated patients. Although their prior chemotherapy might have affected the result, the recommended dose was again lower than in either the United States or Europe [21]. A previous study has demonstrated that African-American patients with colon cancer appear to experience less treatment-related toxicity from 5-fluorouracil-based chemotherapy. One possible explanation is the inter-ethnic differences in genetic polymorphisms of drug-metabolizing enzymes related to 5-fluorouracil [18]. Similarly, although there was no consistent inter-ethnic difference in the CYP3A4 activity that metabolizes docetaxel, further investigation may elucidate the mechanisms underlying the potential difference in susceptibility to docetaxel among ethnic groups.

In conclusion, carboplatin AUC 6 followed by docetaxel 70 mg/m$^2$ is a favorable regimen for the subsequent phase II study because it seems to show lower toxicity and a potentially higher response rate than the reverse sequence. The mechanism of the sequence effects on toxicity and tumor response could not be explained by pharmacokinetic interactions.

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