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ORIGINAL ARTICLE

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Clinical trial and pharmacokinetic study of combination paclitaxel and carboplatin in patients with epithelial ovarian cancer

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Abstract *Purpose:* To determine the recommended dose of paclitaxel in chemotherapy used in combination with carboplatin, and to examine the pharmacokinetic parameters of paclitaxel and carboplatin in Japanese patients with epithelial ovarian cancer. *Methods:* The study group comprised 18 patients (median age 53 years, range 30–67 years) who received a total of 28 courses of first-line chemotherapy. The paclitaxel levels were set at 150 mg/m^2 ($n=5$), 175 mg/m^2 ($n=6$) and 200 mg/m^2 ($n=7$), with the fixed dose of carboplatin at AUC 5. The plasma concentrations of paclitaxel in 28 courses and platinum in 23 courses were measured to determine the in vivo pharmacokinetics parameters. *Results:* The nadir of neutrophils in the paclitaxel 200 mg/m^2 group was significantly lower ($P<0.05$) than in the 150 and 175 mg/m^2 groups. Of seven patients in the paclitaxel 200 mg/m^2 group, one had grade 3 myalgia, another grade 3 neuropathy, and two grade 4 neutropenia. Paclitaxel AUC and the peak level tended to be dose-dependent, clearly indicating a two-phase disappearance. Further, the paclitaxel dosage and paclitaxel AUC were also dose-dependent. Using a limited sampling protocol for carboplatin, the carboplatin AUC was found to change little in relation to the paclitaxel dosage. *Conclusions:* Based on the results of this clinical trial and pharmacokinetic study, 175 mg/m^2 of paclitaxel as a 3-h infusion in combination with carboplatin AUC 5 can be considered as the recommended dose for Japanese ovarian cancer patients.

Keywords Carboplatin · Ovarian cancer · Paclitaxel · Pharmacokinetics

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Introduction

Since the clinical use of paclitaxel as an anticancer agent was approved, various infusion protocols of paclitaxel/carboplatin combination chemotherapy have been tried in the treatment of malignant tumors including ovarian, breast, and lung cancers.

In a 1994 study by the European and Canadian Multicenter Joint Research Group [11] it was found that progression-free survival was significantly longer with paclitaxel/carboplatin chemotherapy and than with cyclophosphamide/cisplatin chemotherapy, and these results were verified in study no. 111 of the Gynecologic Oncology Group [14]. Since then, a number of reports have been published in Western countries regarding the safety and recommended dosage of carboplatin/paclitaxel combination chemotherapy for ovarian cancer [3, 4, 17]. However, pharmacokinetic studies of this chemotherapy are scarce. Moreover, in Japan, due to the long delay in approval of paclitaxel as an antiovarian cancer agent, similar comprehensive studies have not been carried out.

Recently, Adachi et al. [1] have reported a pilot study of Japanese patients undergoing carboplatin/paclitaxel combination chemotherapy. In their regimen, 135 mg/m^2 of paclitaxel and AUC 4–5 of carboplatin were used, and the side effects were easily managed. However, the dose of paclitaxel was relatively low (135 mg/m^2), and the safety and recommended dose were not adequately examined. In addition, a pharmacokinetic study of these chemotherapeutic agents was not carried out in that study. In 2001, Fujiwara et al. [12] reported the platelet-sparing effect of paclitaxel, and concluded that it is not related to changes in the pharmacokinetics of

carboplatin. On ethical grounds, a randomized trial could not be performed.

In the present study, we determined the recommended dose of paclitaxel for use in chemotherapy in combination with carboplatin AUC 5 and examined the pharmacokinetic parameters of paclitaxel and carboplatin as a first-line chemotherapy in Japanese patients with epithelial ovarian cancer.

Patients and methods

Our study subjects were 18 patients (median age 53 years, range 30–67 years) undergoing first-line chemotherapy after having been diagnosed histologically with epithelial ovarian cancer. The patients met the following selection criteria: a performance status (ECOG) of 0–2, an age between 15 and 75 years, leukocytes $>4.0\times10^9$/l and $<12.0\times10^9$/l, platelet count $>100\times10^9$/l, hemoglobin >9.0 g/dl, total bilirubin <1.5 mg/dl, serum creatinine <1.5 mg/dl, serum GOT/GPT less than twice the upper limit of normal, 24-h creatinine clearance >60 ml/min, absence of cardiovascular disease, life expectancy of at least 3 months, and absence of any past or current history of other neoplasms.

After obtaining written informed consent from the patients, we conducted a dose escalation study, setting the three paclitaxel levels at 150 mg/m^2 ($n=5$), 175 mg/m^2 ($n=6$) and 200 mg/m^2 ($n=7$), and the carboplatin dose at AUC 5. Paclitaxel diluted in 500 ml physiological saline was administered as a 3-h intravenous infusion followed by a 30-min intravenous infusion of carboplatin (diluted in 250 ml physiological saline). All patients were premedicated with intravenous dexamethasone (20 mg) at 12 to 14 h and 6 to 7 hours before paclitaxel administration, and intravenous ranitidine hydrochloride (50 mg) and oral diphenhydramine (50 mg) were administered 30 min before paclitaxel. Granisetron hydrochloride (3 mg in 100 ml physiological saline) was administered as a 30-min intravenous infusion 30 min after paclitaxel.

We calculated the carboplatin dose from Calvert's formula [6], assuming that the mean of the 24-h creatinine clearance with two measurements or more was the glomerular filtration rate. To ensure the safety of this clinical trial, we set the maximum dose of carboplatin at 800 mg/patient; however, no patient needed this limit. No significant differences in age, performance status, body weight, histological type, or clinical stage were observed among the three groups (Table 1).

To determine the in vivo pharmacokinetic parameters of paclitaxel and carboplatin, we measured the concentrations of paclitaxel in the plasma of 18 patients during a total of 28 courses, and measured the concentration of platinum in the plasma of 18 patients during a total of 23 courses. Being a subject in a pharmacokinetic study is a burden to the patient. Therefore, blood sampling was limited to seven sampling points, giving a priority to measurement of the pharmacokinetic parameters of carboplatin. The measurement was limited to registered patients in the first and second courses of chemotherapy. We collected a total of 8 ml of blood at seven time-points: 0.5, 1.0, 1.5, 2.5, 4.5, 6.5 and 24.5 h after carboplatin administration; in other words, at 1.5, 2.0, 2.5, 3.5, 5.5, 7.5 and 25.5 h after paclitaxel administration. To measure paclitaxel concentrations, plasma was separated by centrifugation at 3000 rpm for 5 min, then immediately stored at –20°C until analysis. To measure platinum concentrations, after storing the total blood for 10 min in ice water, the blood was centrifuged for 5 min at 3000 rpm. The plasma obtained was filtered using Amicon Centri Filters (Danvers, Mass.). After ultrafiltration by centrifugation for 20 min at 3000 rpm, the filtered fluid was stored at –20°C until analysis.

Paclitaxel concentrations in plasma were measured using the method of Huizing et al. [16], and the platinum concentrations in

Table 1. Patient characteristics

Parameter	Paclitaxel dosage group (mg/m^2)			Total
	150	175	200	
Number of patients	5	6	7	18
Age (years)				
Median	52	53.5	54	53
Range	50–67	30–66	52–63	30–67
Performance status (ECOG)				
Median	0	0	0	0
Range	0–1	0–2	0–1	0–2
Body weight (kg)				
Median	49.5	43.5	57.0	48.0
Range	34.2–52.0	38.0–50.0	45.5–73.0	34.2–73.0
FIGO stage				
Ia	1	0	1	2
Ib	0	1	0	1
Ic	0	2	1	3
IIb	0	1	0	1
IIIc	3	2	5	10
IV	1	0	0	1
Histological type				
Serous	3	1	5	0
Mucinous	0	1	0	1
Clear cell	0	1	2	3
Endometrioid	1	2	0	3
Mixed epithelial	0	1	0	1
Unclassified	1	0	0	1
Residual disease				
<0.5 cm	1	4	4	9
≥ 0.5 cm	4	2	3	9

plasma were measured using the flameless atomic absorption spectrophotometry method of Harland et al. [15]. The free platinum AUC was calculated by a previously published method [13]. The HPLC system consisted of an LC-9A chromatograph system (Shimadzu, Kyoto, Japan), an SIL-6B autoinjector, an SPD-6AV UV detector at 227 nm, and a Chromatopac C-R4A data processor. We measured the concentrations of paclitaxel and platinum in plasma diachronically, and calculated the pharmacokinetic parameters including the area under the plasma concentration curve (AUC), half-life, volume of distribution (Vdss), and clearance (Cl) based on the moment analysis described by Yamaoka et al. [22] and Cutler [8].

The significance of differences were determined by the Mann-Whitney *U*-test in this exploratory study.

Results

The nadir, the number of days to reach the nadir, and the toxicity grade (National Cancer Institute Common Toxicity Criteria version 2, 30 January 1998) of the leukocyte, neutrophil, and platelet counts are shown in Table 2. The nadir of the absolute neutrophil count in the paclitaxel 200 mg/m^2 group (median 0.7×10^9/l, range $0.1–1.7\times10^9$/l) was significantly lower ($P<0.05$) than in the paclitaxel 150 mg/m^2 group (2.0×10^9/l, $1.4–2.5\times10^9$/l) and the 175 mg/m^2 group (2.4×10^9/l, $2.3–2.5\times10^9$/l). The toxicity grade of the absolute neutrophil count in the paclitaxel 200 mg/m^2 group (median 3, range 1–4) was significantly higher ($P<0.05$) than in the paclitaxel 150 mg/m^2 group (1, 0–2) and the 175 mg/m^2 group (0, 0–0). However, there were no significant differences in the platelet count values among the groups. Median (range) platelet values for the three groups, respectively, were: nadir 170×10^9/l ($120–240\times10^9$/l), 150×10^9/l ($100–330\times10^9$/l) and 175×10^9/l ($130–300\times10^9$/l); time required to reach the nadir 12 days (5–31 days), 16 days (3–35 days) and 8 days (3–29 days); and toxicity grade all groups 0 (0–0).

Hematological toxicities of grade 4 for 4 days or longer and nonhematological toxicities of grade 3 or higher were not observed in any of the five patients in the paclitaxel 150 mg/m^2 group. In the six patients in the paclitaxel 175 mg/m^2 group, grade 3 febrile neutropenia was observed in one patient. However, of the seven patients in the paclitaxel 200 mg/m^2 group, one had grade 3 myalgia, another grade 3 neuropathy, and two grade 4 neutropenia. Moreover, grade 4 neutropenia lasted 4 days or more in four of seven patients. Thus, we determined that 200 mg/m^2 is the maximum tolerated dose and 175 mg/m^2 is the recommended dose of paclitaxel in carboplatin/paclitaxel combination chemotherapy.

Table 3 shows the paclitaxel pharmacokinetic parameters of a total of 28 courses in 18 patients undergoing carboplatin/paclitaxel combination chemotherapy. The peak level of paclitaxel in a 3-h infusion was 1.49–12.2 μg/ml, and it was still possible to detect paclitaxel in the plasma 25.5 h after infusion. The greater the paclitaxel dosage, the smaller the clearance value. Furthermore, the Vdss decreased dose-dependently. Meanwhile, as the dose increased from 150 mg/m^2 to 200 mg/m^2, the AUC of paclitaxel increased by approximately 1.6 times, from 752 to 1228 μg/ml per min. The terminal half-life (T1/2) was approximately 300 min, and dose-dependency was not found.

Figure 1 shows the paclitaxel concentration-time curves of three patients receiving different doses corresponding to patients 5 (150 mg/m^2), 14 (175 mg/m^2), and 24 (200 mg/m^2) in Table 3. The paclitaxel AUC and the peak level tended to be dose-dependent, clearly indicating a two-phase disappearance. Furthermore, the paclitaxel dosage and paclitaxel AUC were also dose-dependent. However, it was not clear whether the response was linear (Fig. 2). Using a limited sampling protocol for carboplatin, the carboplatin AUC was found to change little with the paclitaxel dosage. However, when the paclitaxel dose was 200 mg/m^2, the carboplatin AUC was widely distributed (Fig. 3).

Discussion

It is well known that thrombocytopenia is a dose-limiting toxicity of carboplatin used as a single agent, although carboplatin induces the same degree of thrombocytopenia at higher doses when used in combination with paclitaxel. Obasaju et al. [20] reported an evaluation of carboplatin pharmacokinetics in the absence and presence of paclitaxel. They concluded that the pharmacokinetics of carboplatin are not altered by

Table 2. Hematologic toxicities observed in patients. Values are medians (range)

Paclitaxel dosage group (mg/m^2)	Hematologic toxicity	Nadir ($\times10^9$/l)	Time to nadir (days)	Grade[a]
150	Leukocytes	2.4 (1.8–4.0)	12 (6–36)	2 (0–3)
	Neutrophils	2.0 (1.4–2.5)	10 (4–16)	1 (0–2)
	Platelets	170 (120–240)	12 (5–31)	0 (0–0)
175	Leukocytes	2.7 (2.1–7.1)	8.5 (3–13)	2 (0–2)
	Neutrophils	2.4 (2.3–2.5)	11 (4–18)	0 (0–0)
	Platelets	150 (100–330)	16 (3–35)	0 (0–0)
200	Leukocytes	2.3 (1.4–3.6)	11 (6–20)	2 (1–3)
	Neutrophils	0.7 (0.1–1.7)*	14 (7–16)	3 (1–4)*
	Platelets	175 (130–300)	8 (3–29)	0 (0–0)

*$P<0.05$ vs 150 and 175 mg/m^2 groups, Mann-Whitney *U*-test
[a]National Cancer Institute Common Toxicity Criteria, 1998

Table 3. Pharmacokinetic parameters of paclitaxel when administered in combination with carboplatin

Patient	Surface area (m^2)	Paclitaxel dose (mg/m^2)	Peak level ($\mu g/ml$)	AUC ($\mu g/ml/min$)	Half-life (min)	Vdss (l/m^2)	CI ($ml/min/m^2$)
1	1.410	150	3.77	856	134	40	174
2	1.436	150	2.78	669	342	75	231
3	1.436	150	3.71	998	308	47	155
4	1.148	150	2.11	510	357	98	290
5	1.460	150	1.65	531	320	99	284
6	1.460	150	1.49	382	337	146	395
7	1.436	150	7.11	1312	277	30	118
8	1.436	150	5.02	755	309	52	205
Mean	1.403		3.46	752	298	73	232
9	1.560	175	3.19	866	356	64	200
10	1.263	175	3.76	709	240	66	246
11	1.335	175	5.00	1288	388	45	140
12	1.421	175	1.88	639	412	108	264
13	1.421	175	4.59	1027	380	50	164
14	1.350	175	4.35	943	303	57	186
15	1.241	175	2.05	752	220	79	235
Mean	1.370		3.55	889	328	67	205
16	1.790	200	11.30	1970	360	24	85
17	1.790	200	4.55	1061	464	61	158
18	1.670	200	3.93	785	119	61	242
19	1.670	200	2.68	686	299	87	277
20	1.360	200	3.48	723	276	79	265
21	1.360	200	5.51	1065	278	56	186
22	1.615	200	10.30	1880	389	31	105
23	1.615	200	7.17	1935	346	32	102
24	1.329	200	4.72	1308	307	54	155
25	1.329	200	12.20	1432	249	35	142
26	1.417	200	5.36	828	359	75	239
27	1.417	200	7.43	1135	212	44	174
28	1.411	200	5.70	1156	328	58	175
Mean	1.521		6.49	1228	307	54	177

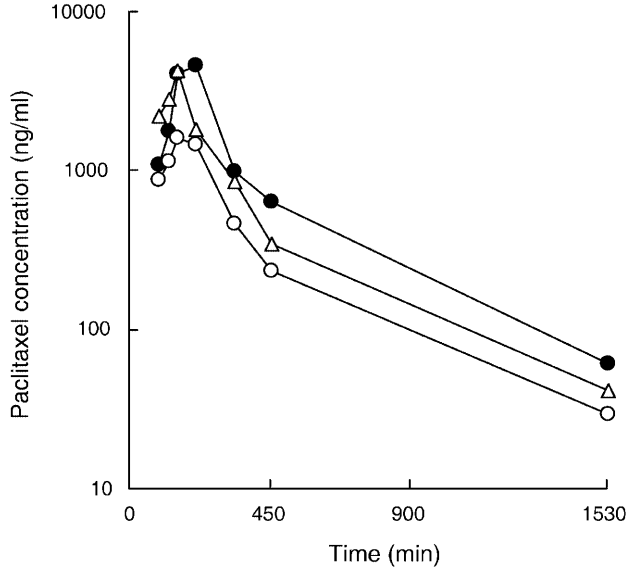

Fig. 1. Paclitaxel concentration-time curves for three patients treated at three different dose levels. Paclitaxel doses: *open circles* 150 mg/m^2, *open triangles* 175 mg/m^2, closed circles 200 mg/m^2

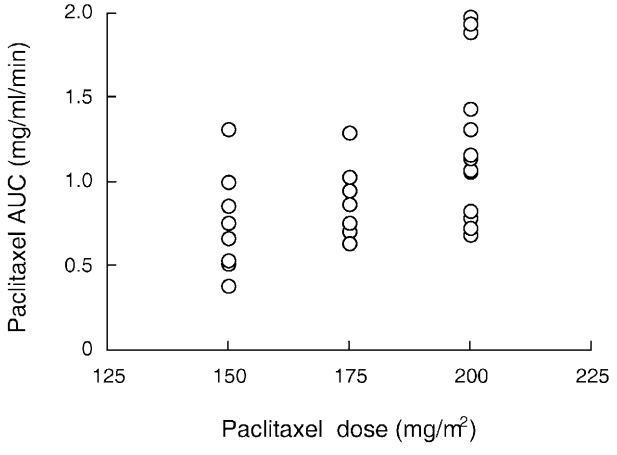

Fig. 2. Relationship between paclitaxel dose and the calculated AUC of paclitaxel

pretreatment with paclitaxel at a standard dose. Belani et al. [2] found that there is no pharmacokinetic interaction between paclitaxel and carboplatin, but there is a pharmacodynamic, platelet-sparing effect on this dose-limiting toxicity of carboplatin. In the present study, less severe thrombocytopenia was observed, which is in accordance with the previous reports [7]. However, the nadir of the absolute neutrophil count was significantly lower in the paclitaxel 200 mg/m^2 group than in the other groups and 57.1% of patients (four of seven) showed a grade 4 neutropenia in this dose escalation study.

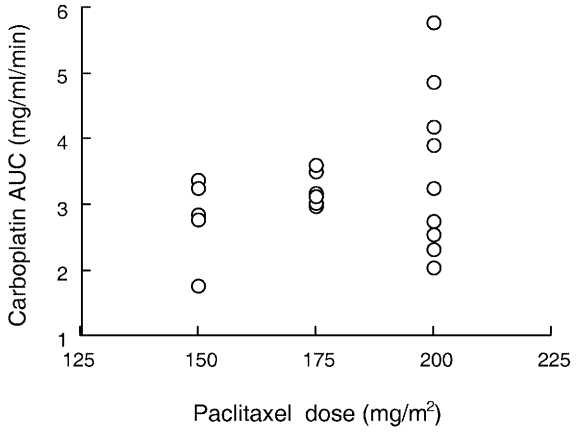

Fig. 3. Calculated AUC of carboplatin at different dose levels of paclitaxel

Regarding nonhematological toxicities, with the combination of carboplatin AUC 5 plus paclitaxel 175 mg/m^2 as a 3-h infusion, all patients but one had grade 2 or lower toxicity. In the one patient with grade 3 febrile neutropenia, remission was achieved following intravenous administration of antibiotics as an inpatient. However, of the seven patients in the paclitaxel 200 mg/m^2 group, one had grade 3 myalgia and another grade 3 neuropathy.

The results of this clinical trial indicate 175 mg/m^2 of paclitaxel as a 3-h infusion to be the recommended dose for Japanese ovarian cancer patients undergoing this chemotherapy in combination with carboplatin AUC 5. This dose is similar to or slightly lower than the dosage recommended in previous reports [3, 11, 14, 18] of combination chemotherapy with carboplatin AUC 5.

The pharmacokinetic parameters of paclitaxel are similar to those reported previously [21]. There were consistent relationships between paclitaxel dosage and (1) clearance, (2) volume of distribution and (3) AUC. Regarding the relationship between paclitaxel dosage and carboplatin AUC, our result was very similar to that reported previously [17]. Thus, we consider that the maximum tolerated dose and the recommended dose of paclitaxel used in this combination chemotherapy, as clarified in this study, are very significant and can be used as the standard in Japan.

Fujiwara et al. [12] set the target carboplatin AUC at 6.5, and demonstrated that paclitaxel has a platelet-sparing effect that alleviates thrombocytopenia induced by carboplatin, but does not affect the pharmacokinetics of carboplatin. Thus, further study regarding the standard carboplatin dosage is essential. For example, determination of the dosage of carboplatin using the Bayesian algorithm could contribute to the development of a better dosage plan [10]. Nannan Panday et al. [19] have demonstrated that the carboplatin AUC decreases during paclitaxel/carboplatin combination chemotherapy, and built various limited-sampling models.

We should be cautious in recommending a dose as the treatment dose for all future patients. Both safety and efficacy should be considered in making such a recommendation. Unfortunately, the present study was not randomized and increasing carboplatin doses was not studied. Therefore, the results obtained from this study only suggest that 175 mg/m^2 of paclitaxel is better tolerated than 200 mg/m^2 of paclitaxel when given in combination with carboplatin AUC 5 for Japanese ovarian cancer patients. We used the Calvert formula in the present study to set the carboplatin dose. Many other dose optimization procedures have been proposed in other countries [5, 9]. Without examining the optimal doses of both paclitaxel and carboplatin in a randomized study, a conclusion regarding recommended doses for treatment cannot be made. However, we believe that the recommended dose indicated in this study could be the recommended dose for further investigation in a randomized study.

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