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ORIGINAL ARTICLE

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The platelet-sparing effect of paclitaxel is not related to changes in the pharmacokinetics of carboplatin

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Abstract *Purpose*: To determine whether the platelet-sparing effect of paclitaxel is related to changes in pharmacology of carboplatin. *Methods*: A group of 32 patients with epithelial ovarian cancer were treated with intraperitoneal (i.p.) carboplatin-based chemotherapy with carboplatin alone or in combination with cyclophosphamide or paclitaxel, and the relationship between the pharmacology of serum platinum and thrombocytopenia was examined. The target AUC of i.p. carboplatin was 6.5 mg · min/ml. Cyclophosphamide was administered intravenously at 400 mg/m^2 after i.p. carboplatin and paclitaxel at 175 mg/m^2 was given before i.p. carboplatin. *Results*: Ten patients received i.p. carboplatin alone, 10 received cyclophosphamide and 12 received paclitaxel. The ages of the patients, body surface area, serum creatinine, platelet count before chemotherapy, and the total dose of carboplatin in each patient were similar in all groups. The measured AUC, C_{max}, $T_{1/2}$, and MRT were similar in these groups. The nadir platelet counts were significantly higher ($P = 0.0018$) in patients treated with i.p. carboplatin with paclitaxel ($12.1 \pm 4.3 \times 10^4$/mm^3) compared with carboplatin alone ($5.2 \pm 3.3 \times 10^4$/mm^3) or with cyclophosphamide ($5.2 \pm 4.8 \times 10^4$/mm^3). The percentage decrease in platelet counts was significantly lower ($62.5 \pm 18.2\%$) in patients treated with paclitaxel than in the other two groups ($81.5 \pm 12.6\%$ carboplatin alone, $88.7 \pm 7.9\%$ with cyclophosphamide). *Conclusion*: The addition of paclitaxel or cyclophosphamide to i.p. carboplatin did not alter the pharmacology of serum platinum. Thrombocytopenia was significantly less in patients treated with carboplatin in combination with paclitaxel. The platelet-sparing effect of paclitaxel is not related to changes in the pharmacology of carboplatin.

Key words Carboplatin · Thrombocytopenia · Paclitaxel · Platelet-sparing effect · Pharmacology

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Introduction

Standard chemotherapy for advanced epithelial ovarian cancer is now a combination of paclitaxel and a platinum compound. Recent randomized studies have demonstrated that carboplatin has a better therapeutic index than cisplatin [6, 12]. Thrombocytopenia, which is a dose-limiting toxicity of carboplatin, is a major concern when it is used as a single agent or in combination with other antineoplastic drugs. Indeed, Reyno et al. have demonstrated that combining carboplatin with cyclophosphamide results in a greater than expected reduction in platelets than would be expected from single-agent carboplatin [15]. On the other hand, a phase I trial performed at Fox Chase Cancer Center of the combination of paclitaxel and carboplatin has shown that the target carboplatin AUC of 7.5 mg · min/ml, a relatively high dose compared with AUCs of 4–5 mg · min/ml for other combinations, was well tolerated [2]. Belani et al. have also demonstrated that carboplatin induces the same degree of thrombocytopenia at a higher dose when combined with paclitaxel than when used alone [1]. These studies indicate that paclitaxel has a platelet-sparing effect, but no clear explanation of the mechanism has been demonstrated.

One possible mechanism of this effect is an alteration in the pharmacology of serum platinum by the addition of paclitaxel. In this study, we examined the association between the thrombocytopenia induced by carboplatin and the pharmacology of serum platinum following treatment with carboplatin with or without paclitaxel or cyclophosphamide.

Patients and methods

In a previous retrospective study [7], we demonstrated that a target AUC of 6.5 mg · min/ml might be optimal for intraperitoneal (i.p.) carboplatin alone or in combination with intravenous cyclophosphamide at 400 mg/m^2. Following this trial, we started a prospective trial to verify this dose, evaluating thrombocytopenia and the pharmacology of serum platinum [Kawasaki Medical School Gynecologic Oncology Protocol (KMSGOP) 1995-1]. The design of a confirmatory study indicated sample sizes of ten for both for the i.p. carboplatin group and the cyclophosphamide combined group. When paclitaxel became commercially available in Japan in December 1997, ten patients had already been enrolled for the combination group, while the i.p. carboplatin group only had six patients enrolled. Because of the clear evidence from the GOG 111 study [11] and the OV-10 study [14] that the combination of paclitaxel and cisplatin produced better survival than the combination of cyclophosphamide and cisplatin, we decided that cyclophosphamide should be completely replaced by paclitaxel, and the study was continued with this additional group to evaluate the effects of paclitaxel in combination with i.p. carboplatin. Therefore, it became possible prospectively, although not in a randomized fashion, to compare the effects of paclitaxel and cyclophosphamide on carboplatin-induced thrombocytopenia.

For the KMSGOP 1995-1, informed consent was obtained from each patient. Informed consent for the pharmacological study was obtained separately, and blood was taken only from those patients who had signed both consents. This study was approved by the department internal review committee.

Patients

All consecutive patients who met the inclusion criteria were enrolled into the KMSGOP 1995-1 trial. To be eligible for this study, patients had to have been diagnosed with stages IC-IV epithelial ovarian cancer, to have undergone initial laparotomy and to have a histological confirmation of the epithelial ovarian cancer. At the time of laparotomy, an implantable port system (IPS) had to have been placed for future i.p. chemotherapy. Patients had to have a WBC $>3000/mm^3$, neutrophils $>1500/mm^3$, a platelet count $>150{,}000/mm^3$, and normal liver, pulmonary and cardiac functions, before chemotherapy. Those who had had prior chemotherapy or radiotherapy for any reason were ineligible.

Chemotherapy

Following the initial laparotomy, patients who had no residual disease or microscopic residual disease were treated by i.p. carboplatin alone. In patients with macroscopic residual disease who were treated before December 1997, when paclitaxel was not commercially available in Japan, i.p. carboplatin was followed by cyclophosphamide. Patients with macroscopic residual disease entered into this study after January 1998 were treated with i.p. carboplatin after paclitaxel administration. All patients were hospitalized and treatment and follow-up were performed on an inpatient basis.

Carboplatin

The dose of carboplatin was calculated using the Calvert formula [3]. The target AUC was 6.5 mg · min/ml for all patients based on the results of our previous study [7]. Glomerular filtration rate (GFR) was substituted by creatinine clearance calculated by the Cockcroft formula [5] as we have reported previously [7]. The designated amount of carboplatin was administered as a bolus through the IPS following 500 ml 5% glucose.

Cyclophosphamide

Cyclophosphamide at 400 mg/m^2 was dissolved in 500 ml saline and administered intravenously for 3 h immediately after i.p. carboplatin infusion.

Paclitaxel

As premedication 20 mg dexamethasone was injected intravenously 12 h and 6 h prior to paclitaxel administration, followed by 50 mg oral ranitidine and 50 mg intravenous diphenhydramine 30 min before paclitaxel. Paclitaxel at 175 mg/m^2 was diluted in 500 ml saline and administered intravenously over 3 h immediately before i.p. carboplatin treatment.

Pharmacokinetic analysis

Venous blood (5 ml) was drawn from patients for determination of platinum concentration before and 1, 2, 4, and 8 h after carboplatin infusion. To prepare samples suitable for the determination of the protein-free platinum concentration, the serum obtained by centrifugation of the blood samples was ultrafiltered using a 330,000 nominal molecular weight limit centrifugal filter unit (Ultrafree-MC; Millipore, Bedford, Mass.) at 15,000 rpm for 30 min. The ultrafiltered serum samples were immediately frozen at –20 °C and sent to the Sumikin Bio-Science (Kanagawa, Japan). The platinum concentrations were determined using a furnace atomic absorption procedure as described previously [10]. Briefly, the ultrafiltered samples were diluted in 0.2% Triton X-100 and injected onto Spectr AA-880 Zeeman atomic absorption spectrometer (Varian, Walton-on-Thames, UK) equipped with a graphite furnace atomizer, using a nine-step temperature program from 85 °C to 2700 °C.

Platelet count

Complete blood cell count was determined at least once a week and more frequently (every day if necessary) around the nadir period. The percentage decrease in platelet count was calculated as follows:

Percent decrease in platelet counts
$= 1 -$ (nadir platelet count/platelet count immediately before treatment) $\times 100$

Both nadir platelet counts and the percentage decrease were compared across the groups.

Statistical analysis

One-way analysis of variance (ANOVA) was applied to test the differences in the parameters shown in Tables 1 and 2 among the three groups (i.p. carboplatin alone, i.p. carboplatin plus cyclophosphamide, and i.p. carboplatin plus paclitaxel). The differences in the nadir platelet counts and the percentage decreases in platelet counts among the three groups were also tested using ANOVA. For ANOVA P-values less than 0.05, the Bonferroni multiple comparisons test was performed to test the differences among the groups. All statistical analyses were performed using InStat version 3.01 for Windows (GraphPad Software, San Diego, Calif.).

Results

This study was started in October 1995 and closed in May 1999. Entered into the study were 32 consecutive patients, and informed consent for the pharmacological analysis was obtained from 27 patients. Ten patients

Table 1 Characteristics of patients treated with i.p. infusion of carboplatin alone or in combination with cyclophosphamide or paclitaxel. Values are means ± SD (range)

	Carboplatin alone ($n=10$)	Plus cyclophosphamide ($n=10$)	Plus paclitaxel ($n=12$)	P-value[a]
Age	60.0 ± 12.0 (40–83)	59.0 ± 10.6 (41–72)	56.3 ± 14.4 (30–77)	0.7693
Body surface area (m^2)	1.46 ± 0.13 (1.25–1.62)	1.37 ± 0.13 (1.13–1.60)	1.43 ± 0.12 (1.26–1.68)	0.7693
Serum creatinine before chemotherapy	0.60 ± 0.12 (0.5–0.8)	0.61 ± 0.11 (0.5–0.8)	0.73 ± 0.53 (0.5–2.4)	0.5872
Platelet count before chemotherapy ($\times 10^4$)	29.4 ± 10.5 (14.9–46.6)	37.7 ± 6.5 (28.6–49.8)	33.3 ± 9.2 (14.1–48.4)	0.1316
Carboplatin dose				
mg/patient	717.0 ± 170.3 (463–967)	656.2 ± 116.4 (531–859)	675.1 ± 189.7 (395–1160)	0.6989
mg/m^2	493.5 ± 104.8 (307–624)	470.5 ± 84.4 (355–590)	474.8 ± 122.6 (230–706)	0.8753

[a] Calculated by one-way analysis of variance

Table 2 Pharmacokinetic parameters of ultrafiltered platinum in serum after i.p. carboplatin infusion alone or with cyclophosphamide or paclitaxel. Values are means ± SD (range)

	Carboplatin alone ($n=8$)	Plus cyclophosphamide ($n=10$)	Plus paclitaxel ($n=9$)	P-value[a]
Measured AUC (mg · min/ml)	4.54 ± 0.46 (3.859–5.271)	4.65 ± 0.93 (2.563–5.605)	4.04 ± 0.81 (2.790–5.161)	0.2186
C_{max} (mg/ml)	0.012 ± 0.003 (0.006–0.017)	0.012 ± 0.003 (0.007–0.018)	0.011 ± 0.003 (0.006–0.016)	0.7898
$T_{1/2}$ (min)	124.0 ± 3.4 (120.4–130.1)	126.3 ± 8.1 (120.0–142.1)	127.5 ± 4.9 (120.8–134.5)	0.482
MRT (min)	270.3 ± 40.5 (207.8–320.0)	269.1 ± 36.6 (225.4–328.9)	255.7 ± 29.0 (208.9–290.7)	0.6363

[a] Calculated by one-way analysis of variance

received i.p. carboplatin alone during the study period. Ten patients entered into the study before December 1997 were treated with i.p. carboplatin and cyclophosphamide, and 12 patients were entered into the i.p. carboplatin plus paclitaxel group because the last three patients were enrolled at the same time. The patient characteristics are summarized in Table 1. Mean age, body surface area, serum creatinine concentration and platelet counts before chemotherapy were not significantly different among the three groups.

The total dose of carboplatin administered per patient and the calculated dose per body surface area were also similar in the three groups. Figure 1 demonstrates the free platinum concentration as a function of time after i.p. carboplatin administration; the time-concentration curves of the three groups were virtually identical. Table 2 summarizes the pharmacological parameters, i.e. measured serum AUC, maximum concentration (C_{max}), half life ($T_{1/2}$), and mean residual time (MRT), of protein-free platinum after i.p. carboplatin treatment alone or with cyclophosphamide or paclitaxel. These parameters were not significantly different among the three groups. These results show that the addition of systemic cyclophosphamide or paclitaxel to an i.p. carboplatin infusion did not change the pharmacology of serum protein-free platinum.

Thrombocytopenia was significantly less severe when i.p. carboplatin was administered following paclitaxel treatment (Table 3). Nadir platelet counts of patients receiving the paclitaxel combination were significantly higher than those receiving i.p. carboplatin alone ($P<0.01$) or in combination with cyclophosphamide ($P<0.01$). There was no difference in nadir platelet counts between patients receiving i.p. carboplatin alone

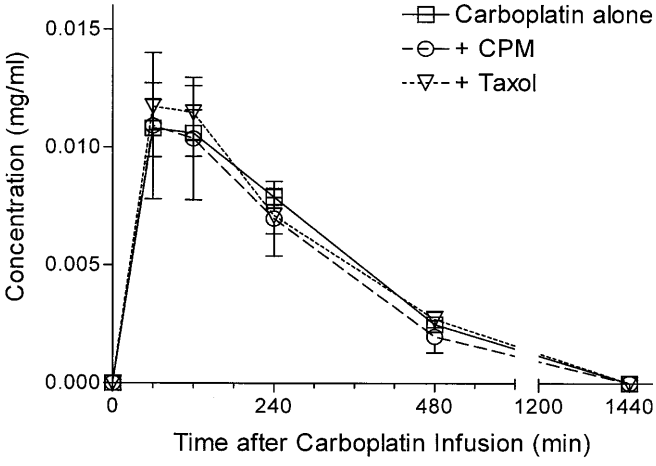

Fig. 1 Serum concentration of free platinum after i.p. infusion of carboplatin alone or with cyclophosphamide or paclitaxel. Pharmacokinetic parameters are shown in Table 2

and those receiving the combination of i.p. carboplatin plus cyclophosphamide. The percentage decrease in platelet count was significantly smaller in the i.p. carboplatin plus paclitaxel group than in the i.p. carboplatin alone group ($P<0.05$) or the i.p. carboplatin plus cyclophosphamide group ($P<0.001$). No significant difference was observed between the i.p. carboplatin alone and the i.p. carboplatin plus cyclophosphamide groups.

These results suggest that the combination of paclitaxel and carboplatin resulted in significantly less carboplatin-induced thrombocytopenia. Since the pharmacokinetics of serum platinum were not changed by the addition of paclitaxel, the mechanism by which

Table 3 Thrombocytopenia after intraperitoneal carboplatin infusion alone or with cyclophosphamide or paclitaxel. Values are means ± SD (range)

	Carboplatin alone ($n = 10$)	Plus cyclophosphamide ($n = 10$)	Plus paclitaxel ($n = 12$)	P-value[a]
Mean nadir platelet count ($\times 10^4/mm^3$)	5.2 ± 3.3 (1.2–12.4)	5.2 ± 4.8 (1.6–16.2)[*1]	12.1 ± 4.3 (4.8–16.3)[*3,*4]	0.0018
Decrease in platelet count (%)	81.5 ± 12.6 (53.0–92.2)	88.7 ± 7.9 (70.9–95.8)[*1]	62.5 ± 18.2 (34.1–87.0)[*2,*5]	0.0004

[*1] $P > 0.05$, [*2] $P < 0.05$, [*3] $P < 0.01$, vs alone; [*4] $P < 0.01$, [*5] $P < 0.001$, vs cyclophosphamide; Bonferroni multiple comparisons test
[a] Calculated by one-way analysis of variance

paclitaxel protects against carboplatin-induced thrombocytopenia is independent of the pharmacokinetics of carboplatin.

Discussion

Protection against carboplatin-induced thrombocytopenia by paclitaxel is an interesting and clinically advantageous finding, particularly as this combination therapy is now becoming the standard chemotherapy for epithelial ovarian cancer [6, 12, 13].

This study, although indirectly, provided evidence that paclitaxel has a so-called platelet-sparing effect. To our knowledge there is only one previous study that has shown that protection from carboplatin-induced thrombocytopenia by paclitaxel is not related to a pharmacokinetic interaction, but this conclusion was based on a historical control. Belani et al. have reported that there is no pharmacokinetic interaction between paclitaxel and carboplatin, but there is a pharmacodynamic, platelet-sparing effect on the dose-limiting toxicity of carboplatin [1]. In their study, a significant shift occurred in the relationship between the free platinum AUC and relative thrombocytopenia when paclitaxel was administered with carboplatin. More carboplatin was required to produce the same degree of thrombocytopenia than was required when carboplatin was administered alone. In other clinical studies less severe thrombocytopenia has been found than expected [4]. These results support our findings. However, since the mechanism by which paclitaxel protects against carboplatin-induced damage to platelets still needs to be elucidated.

Our study compared thrombocytopenia after i.p. administration of carboplatin alone and after administration in combination with paclitaxel or cyclophosphamide. The dose of carboplatin was fixed at a target AUC of 6.5 mg · min/ml. This dose was based on our previous retrospective study, which indicated that the target i.p. carboplatin AUC of 6.5 mg · min/ml would induce a 67% reduction in platelet count when combined with intravenous cyclophosphamide at 500 mg/m^2 or less [7]. The observed percentage decreases in platelet count were more than expected: 81.5 ± 12.6% and 88.7 ± 7.9%, respectively, for the administration of carboplatin alone and with cyclophosphamide. However, when compared with the administration of paclitaxel, the percentage decreases in platelet count and the nadir platelet count were significantly improved.

The weakness of this study was the fact that the patients were not randomly allocated to the cyclophosphamide and paclitaxel groups, although consecutive patients were enrolled. It was, however, ethically difficult to perform a randomized trial to examine only toxicity because there is clear evidence that the combination of a platinum compound with paclitaxel is more efficacious than its combination with cyclophosphamide [11, 13]. Under these circumstances, we believe this prospective case-controlled study using consecutively entered patients as a historical control is feasible to evaluate the association between thrombocytopenia and the pharmacology of carboplatin.

The measured AUCs of serum free platinum after i.p. carboplatin administration were between 4.0 and 4.7 mg · min/ml when the total dose of carboplatin was calculated using a combination of the Cockcroft and the Calvert formulas using a target AUC of 6.5 mg · min/ml. It has been reported that carboplatin AUC is systematically underestimated by approximately 10% when the GFR in the Calvert formula is substituted by the Cockcroft formula or the 24-h urine creatinine collection value. We now know that the actual AUC of the platinum is between 61% and 72% of the target AUC after bolus i.p. carboplatin administration if the GFR in the Calvert formula is substituted by creatinine clearance calculated by the Cockcroft formula. However, this measured AUC was less than the target AUC of 5 mg · min/ml in the European trials [6, 9] and that of 7.5 mg · min/ml in the GOG carboplatin and paclitaxel phase III study [12]. A dose escalation study is now ongoing to optimize the target AUC for i.p. carboplatin as a function of thrombocytopenia.

In addition to elucidating the platelet-sparing effect of paclitaxel, we believe that this study provides important information to determine the i.p. dose of carboplatin. One of our major concerns is to determine clinical efficacy of i.p. carboplatin-based therapy. A retrospective analysis of i.p. carboplatin-based combination chemotherapy showed the expected 5-year survival of patients with stage III epithelial ovarian cancer to be approximately 45%, even though the majority of patients did not receive paclitaxel [8]. Based on this result we suggest that i.p. carboplatin-based chemotherapy with paclitaxel should be evaluated further.

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