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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/m² after i.p. carboplatin and paclitaxel at 175 mg/m² 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, Cₘₐₓ, T₁/₂, 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 ± 4.3 × 10⁹/mm³) compared with carboplatin alone (5.2 ± 3.3 × 10⁹/mm³) or with cyclophosphamide (5.2 ± 4.8 × 10⁹/mm³). The percentage decrease in platelet counts was significantly lower (62.5 ± 18.2%) in patients treated with paclitaxel than in the other two groups (81.5 ± 12.6% carboplatin alone, 88.7 ± 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

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/m². 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/mm³, neutrophils > 1500/mm³, a platelet count > 150,000/mm³, 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/m² 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/m² 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 a 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

\[ = 1 - \left( \frac{\text{nadir platelet count}}{\text{platelet count immediately before treatment}} \right) \times 100 \]

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