Pharmacokinetic analysis of paclitaxel and carboplatin in a patient with advanced ovarian cancer during hemodialysis - case report

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Summary

We examined pharmacokinetics of paclitaxel and carboplatin in a FIGO Stage IIIb ovarian cancer patient with hemodialysis-dependent chronic renal failure. The patient suffered from recurrence of the disease after treatment with optimal debulking surgery and postoperative chemotherapy consisting of cisplatin, epirubicin and cyclophosphamide, and she was treated with combined paclitaxel and carboplatin as second-line chemotherapy. The carboplatin dose was chosen to produce a target area under the concetration/time curve (AUC) of 5.0 μg-min/ml according to a published formula. Four-hour hemodialysis was started 24 hours and 16 hours after the end of carboplatin administration in the first and second courses of the chemotherapy, respectively. Pharmacokinetic studies showed that the AUCs of free platinum were 8.03 and 5.69 μg-min/ml in the first and second courses of the chemotherapy, respectively, suggesting that the AUC of carboplatin is affected by hemodialysis. However, an attenuation pattern of paclitaxel was almost similar between the first and the second courses, indicating that the change in blood concentration of paclitaxel was similar to that of patients with normal renal function. Hematological and nonhematological adverse effects were at an acceptable degree. The evidence suggests that even patients with chronic renal failure can undergo combination chemotherapy of paclitaxel and carboplatin without suffering any severe adverse effects by determining the time to start hemodialysis.

Key word: Pharmacokinetics; Paclitaxel; Carboplatin; Hemodialysis; Ovarian cancer.

Introduction

The prognosis of patients with chronic renal failure has been improving due to the progress in hemodialysis therapy. Accordingly, the opportunities to treat malignant tumors that develop in hemodialysis patients are increasing. The combination chemotherapy of paclitaxel and carboplatin is considered to be a standard therapy for ovarian cancer, but there have been few reports on the use of this chemotherapy in hemodialysis patients and little is understood about the pharmacokinetics of paclitaxel and carboplatin. In the present study, we implemented combination chemotherapy of paclitaxel and carboplatin in a hemodialysis patient with chronic renal failure who also had Stage III ovarian cancer and measured the blood concentrations of paclitaxel and carboplatin.

Case Report

A 57-year-old Japanese woman with hemodialysis-dependent chronic renal failure secondary to diabetes suffered from abdominal distension. Magnetic resonance imaging revealed a right ovarian tumor measuring 17 cm in diameter with massive ascites. The patient's serum CA125 level was elevated to 5,365 U/ml. She underwent debulking surgery (optimal) on 29 September, 2004. Histopathologic analysis showed serous papillary adenocarcinoma involving the ovaries with metastasis to the omentum (FIGO Stage IIIb). She received three courses of postoperative chemotherapy consisting of 35 mg/m^2 of cisplatin, 35 mg/m^2 of epirubicin and 150 mg/m^2 of cyclophosphamide, one cycle every three weeks. Hemodialysis was started 30 minutes after completion of the cisplatin infusion and performed for 4 hours [1]. Although the serum CA125 level regressed to 33 U/ml, a computed tomography scan revealed a recurrent mass 7 cm in diameter in the pelvic cavity and metastases to the paraaortic lymph nodes. Thereafter, the chemotherapy combining paclitaxel and carboplatin was used as a second line.

For pharmacokinetic analysis, serial blood samples were collected at specified times over 24 hours and analyzed for total platinum, free platinum and paclitaxel. The specimens were centrifuged at 3,000 rpm for ten minutes and plasma samples were obtained for measurement of total platinum and paclitaxel. Aliquots of the plasma were recentrifuged at 3,000 rpm for 20 minutes in an Amicon Centrifree device (Millipore, Bedford, MA, USA) for preparation of free platinum. Plasma and plasma ultrafiltrates were analyzed for platinum by flameless atomic absorption spectrometry according to the method of LeRoy *et al.* [2] and plasma paclitaxel was measured by a high-performance liquid chromatography UV method [3].

In the first course of the chemotherapy, paclitaxel was administered at 150 mg/m^2 as a 3-hour intravenous infusion followed by a 30-minute infusion of carboplatin. The carboplatin dose was chosen to produce a target AUC of 5.0 μg-min/ml according to a previously published formula [4] and was calculated to be 200 mg. Hemodialysis was started 24 hours after the end of carboplatin administration and carried out for four hours [5]. The maximum plasma concentration (C_{max}) of free platinum and paclitaxel was 6.48 μg/ml and 870 ng/ml, respectively. The AUCs of free platinum and paclitaxel were 8.03 μg-min/ml and 7.17 μg-h/ml, respectively. Free platinum and paclitaxel concentrations in the first course of the chemotherapy are demonstrated in Figure 1. Nadir white blood cell and platelet counts were 2,880/mm^3 and 13.9 x 10^4/μl, respectively.

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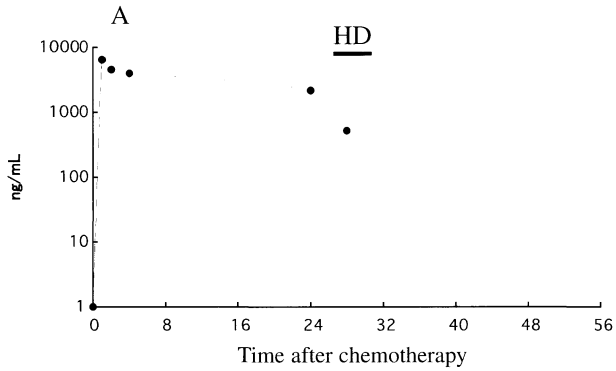


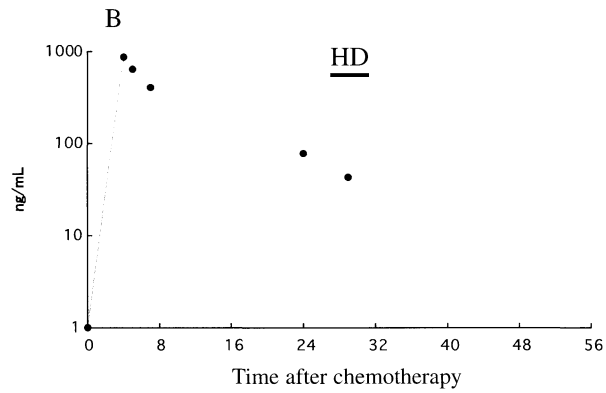
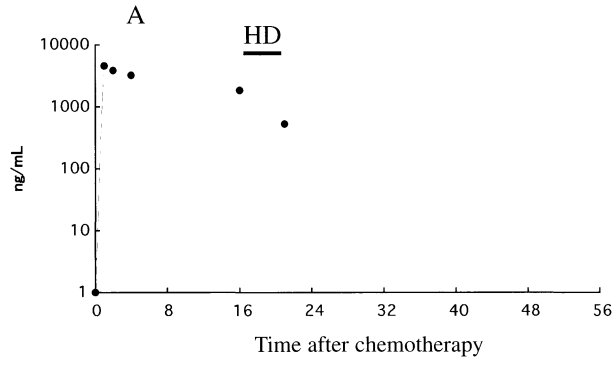


Figure 1. — Concentrations of free platinum and paclitaxel after the first course of chemotherapy. Hemodialysis (HD) was performed for four hours starting 24 hours after the completion of carboplatin administration. A) Free platinum, B) Paclitaxel.



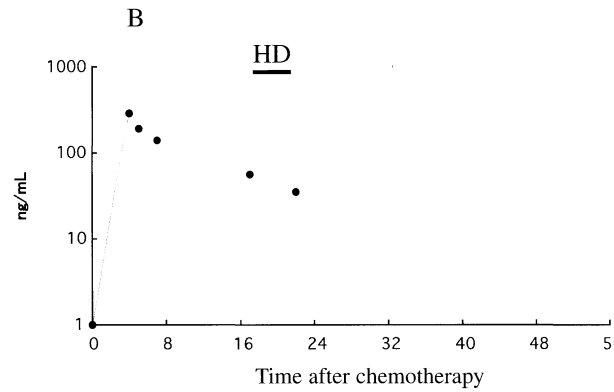


Figure 2. — Concentrations of free platinum and paclitaxel after the second course of chemotherapy. Hemodialysis (HD) was performed for four hours starting 16 hours after the completion of carboplatin administration. A) Free platinum, B) Paclitaxel.

In the second course of the chemotherapy, because the AUC of free platinum was higher than that expected in the first course of the chemotherapy, the same dose of carboplatin was administered and hemodialysis was started 16 hours after the completion of carboplatin administration [6]. Also since the patient complained of palpitations and suffered from sinus tachycardia during paclitaxel administration at the first course of the chemotherapy, the dose of paclitaxel was reduced to 110 mg/m^2. The Cmax of free platinum and paclitaxel was 4.56 μg/ml and 288 ng/ml, respectively. The AUCs of free platinum and paclitaxel were 5.69 μg-min/ml and 2.55 μg-h/ml, respectively. Free platinum and paclitaxel concentrations in the second course of the chemotherapy are demonstrated in Figure 2. Nadir white blood cell and platelet counts were 1.750/mm^3 and 8.3 x 10^4/μl, respectively. The level of the peripheral neurological disorder, arthralgia and myalgia as nonhematological adverse effects were all grade 1, apart from palpitations and sinus tachycardia. However, after the third course of chemotherapy, the tumors became progressive and the patient died of disease on 4 April, 2005.

Table 1. — *The maximum plasma concentration (C_{max}) and the area under the concentration/time curve (AUC).*

	Carboplatin		Paclitaxel	
Course	C_{max} (μg/ml)	AUC (μ-min/ml)	C_{max} (ng/ml)	AUC (μ-h/ml)
1	6.48	8.03	870	7.17
2	4.56	5.69	288	2.55

Discussion

Carboplatin is mainly removed through the kidney and 60-80% of the agent is excreted into the urine as an unaltered substance within 24 hours after its administration. Therefore, the excretion of carboplatin is delayed in patients with renal disorders, resulting in more severe adverse effects [7]. Carboplatin is easily dialyzed in hemodialysis patients because of its low binding rate with plasma proteins that leads to the presence of many unbound forms [8]. Therefore, the removal of the agent by hemodialysis should also be taken into account. Chatelut *et al.* reported that they were able to obtain the targeted AUC by determining the dose of carboplatin according to the method of Calvert and by performing four hours of hemodialysis that started 24 hours after the end of agent administration [5]. Meanwhile, Watanabe et al. reported that they were able to obtain an AUC close to 5.0 μg-min/ml by giving a dose of carboplatin with a predicted AUC of 5.0 μg-min/ml according to the method of Calvert and by performing hemodialysis 16 hours after administration [6]. In the present case, the carboplatin was calculated to have an AUC of 5.0 μg-min/ml and was given by intravenous drip infusion over 30 minutes. For the first course, a four-hour hemodialysis was performed

starting 24 hours after administration resulting in an AUC of 8.03 μg-min/ml, which was higher than expected. For the second course, a four-hour hemodialysis was performed starting 16 hours after administration, resulting in an AUC of 5.69 μg-min/ml, which was almost the targeted value. Meanwhile, there have been conflicting reports on the timing when hemodialysis is started after carboplatin administration. Kurata *et al.* reported that an effective platinum concentration was obtained by performing hemodialysis two hours after carboplatin administration [9], while Watanabe *et al.* reported that the targeted AUC was obtained by performing a four-hour hemodialysis 30 minutes after carboplatin administration [10]. Because the kinetics of carboplatin in the blood of a hemodialysis patient would vary depending on the period between chemotherapy and hemodialysis, and individual differences such as age and general condition play a role in the kinetics of carboplatin, the optimal time to start hemodialysis should be determined by measuring platinum concentrations along with time.

Paclitaxel is metabolized in the liver and excreted via bile into the digestive tract, which is thought to be the main metabolic pathway of the agent [11]. In a phase I study in Japan, the excretion of unaltered paclitaxel into the urine was confirmed to be only 5-12%, and it was reported that the dose does not need to be reduced even in patients with renal disorders [12]. Furthermore, Dreicer *et al.* administered paclitaxel 175-250 mg/m^2 for 24 hours in six cases with renal dysfunction (median serum creatinine level: 2.25 mg/dl) and reported that the toxicities were permissible and there were no apparent associations between toxicity, renal function, and paclitaxel dose [13]. It was also reported that paclitaxel was administered to a child without kidneys who was undergoing artificial hemodialysis [14]. For this patient the kinetics of paclitaxel in the blood showed the same clearance pattern as those in normal healthy subjects [14]. On this occasion, paclitaxel was not detected in the dialyzate and was not removed from the blood in association with hemodialysis. Therefore, it is suggested that paclitaxel can be safely administered in patients with decreased renal function as long as their liver functions are intact. In the present case, the dose of the agent had to be reduced to about 70% for the second therapy mainly due to palpitations and tachycardia that were thought to be caused by paclitaxel. Therefore, the C_{max} and AUC of paclitaxel were slightly lower than those reported in previous cases [6]. However, an attenuation pattern was obtained that was similar to the change in blood concentrations of patients with normal renal function [15], suggesting that the attenuation pattern of paclitaxel was not affected by hemodialysis. Other adverse effects were also within the permissible range, and it was confirmed that the agent could be used even in cases with renal dysfunction. It was also necessary to consider measures such as dividing treatments into small doses or weekly administrations to reduce adverse effects, assuming the possible development of dose-dependent adverse effects of paclitaxel.

The evidence suggests that even patients with chronic renal failure can undergo combination chemotherapy of paclitaxel and carboplatin without suffering any severe adverse effects by determining the time to start hemodialysis.

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