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Case report

Pharmacokinetics of paclitaxel and cisplatin in a hemodialysis patient with recurrent ovarian cancer

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This is the first report that the combination of paclitaxel and cisplatin is feasible in a patient with recurrent ovarian cancer undergoing hemodialysis. Paclitaxel at a dose of 150 mg/m^2 was administered as a 3-h continuous i.v. infusion. Thirty minutes after paclitaxel administration, cisplatin was administered at a dose of 30 mg/m^2 for 30 min. Hemodialysis was started 30 min after completion of the cisplatin infusion and performed for 5 h. The maximum plasma concentrations of paclitaxel, total platinum and free platinum were 3.26, 2.44 and 1.84 μg/ml, respectively. The AUC of paclitaxel and free platinum were 15.3 and 1.76 μg·h/ml, respectively. The pelvic tumor size was reduced by 42% on MRI after the second course of this therapy. Grade IV neutropenia and grade III thrombopenia were observed. We conclude that paclitaxel and cisplatin combination chemotherapy is efficacious and feasible for an ovarian cancer patient under hemodialysis.

Key words: Cisplatin, hemodialysis, ovarian cancer, paclitaxel, pharmacokinetics.

Introduction

Patients receiving hemodialysis have been increasing in number while their life span has been growing longer as a result of advances in hemodialysis technology itself and in supporting therapies.

The combination of paclitaxel and cisplatin (TP) has emerged as the 'gold standard' for combination first-line chemotherapy for the treatment of epithelial ovarian cancer.[1] To our knowledge, there is no published report of TP chemotherapy in a patient undergoing hemodialysis. Only two case reports are available on use of paclitaxel as a single agent.[2,3] We report here for the first time the feasibility of TP chemotherapy for recurrent ovarian cancer in a patient undergoing hemodialysis.

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Case report

The patient was a 51-year-old Japanese woman with chronic renal failure who had been undergoing hemodialysis 3 times a week for 16 years and who was found to have a stage IIc serous papillary adenocarcinoma of the ovary in March 1991. She was treated with complete resection surgery followed by three cycles of chemotherapy consisting of 40 mg/m^2 of cisplatin, 25 mg/m^2 of adriamycin and 250 mg/m^2 of cyclophosphamide.[4]

In May 1999, she was found to have recurrence of pelvic tumor, 6×7 cm in diameter, and it was decided to administer a combination chemotherapy of paclitaxel and cisplatin.

Drug administration

Paclitaxel was administered at a dose of 150 mg/m^2 as a 3-h continuous i.v. infusion in 300 ml saline. Granisetron hydrochloride (3 mg) was then given i.v. for 30 min, followed by cisplatin at a dose of 30 mg/m^2 in 100 ml saline for 30 min.

Hemodialysis was started 30 min after completion of the cisplatin infusion and performed for 5 h. Hemodialysis was also performed on days 3 and 6 of chemotherapy, and then 3 times a week.

Pharmacokinetic analysis

At specified times after administration of paclitaxel and cisplatin, blood samples were collected and centrifuged at 3000 r.p.m. for 10 min, and plasma samples

were obtained. Plasma and dialysate paclitaxel concentrations were measured using a high-performance liquid chromatography–UV method.[5] Free platinum was prepared by centrifuging 1 ml of plasma in a Centrifree Micropartition System (Amicom, Beverly, MA) at 3000 r.p.m. for 10 min. Plasma and plasma ultrafiltrates were analyzed for platinum by flameless atomic absorption spectrometry.[6]

Results

The paclitaxel and platinum plasma concentrations during and following i.v. infusions are shown in Figures 1 and 2. The maximum plasma concentrations (C_{max}) of paclitaxel, plasma platinum and free platinum were 3.26, 2.44 and 1.84 μg/ml, respectively. The area under the curve (AUC) of paclitaxel and free platinum was 15.3 and 1.76 μg·h/ml, respectively.

This combination chemotherapy was repeated twice with the same schedule at 26 days interval. The adverse events encountered during this therapy were grade II arthralgia and alopecia. After the first course, nadir counts of WBC, neutrophils, platelets and hemoglobin were 1.1×10^9/l on day 11, 0.33×10^9/l on day 12, 76×10^9/l on day 11, and 6.8 g/dl on days 6 and 8, respectively. Filgrastim [granulocyte colony stimulating factor (G-CSF)] was administered as a s.c. injection at 50 μg/m^2 from day 10 for 3 days. After the second course of treatment, nadir count of WBC was 0.7×10^9/l on day 8 (neutrophil count was not determined at this time). Platelets were 26×10^9/l on day 11. Filgrastim was administered at 50 μg/m^2 from day 6 for 4 days. Platelet concentrate was transfused on days 9, 10 and 11.

After the second cycle, the pelvic tumor size was reduced by 42% in estimated area on pelvic MRI compared with the size before the first chemotherapy. She finally underwent complete resection of the recurrent tumor with colostomy on 15 November 1999. No signs of recurrence have been observed.

Discussion

This is the first report of the feasibility of use of paclitaxel and cisplatin combination chemotherapy in a patient with ovarian cancer on hemodialysis.

Paclitaxel is extensively metabolized by the liver and secreted in bile, with less than 10% extracted by the kidneys.[5,7] We therefore administered 150 mg/m^2 of paclitaxel, which was 20% less than the ordinary dose as a 3-h infusion. Ohtsu *et al.*[8] reported the mean C_{max} and AUC for a dose of 180 mg/m^2 delivered as a 3-h infusion to be 5.232 μg/ml and 19.28 μg·h/ml, respectively, the corresponding values for 135 mg/m^2 were 3.944 μg/ml and 13.14 μg·h/ml. Huizing *et al.*[9] reported the mean C_{max} and AUC for a dose of 175 mg/m^2 delivered as a 3-h infusion to be 4.27 μg/ml and 16.81 μg·h/ml, the corresponding values for 135 mg/m^2 were 2.54 μg/ml and 9.37 μg·h/ml. Our AUC and C_{max} values were similar to those of patients treated by these two previous authors.

We collected dialysate samples 30 min after the start of hemodialysis for measurement of paclitaxel concentration, but no paclitaxel was identified. The rate of

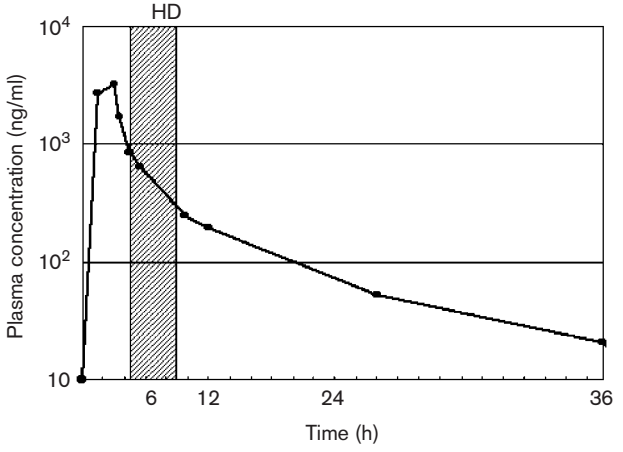

Figure 1. Plasma concentration of paclitaxel (ng/ml) after 3-h administration of 150 mg/m^2 in 300 ml saline. Hemodialysis (HD) was started 4.5 h after beginning the paclitaxel infusion and performed for 5 h. The C_{max} and AUC were 3.26 μg/ml and 15.3 μg·h/ml, respectively.

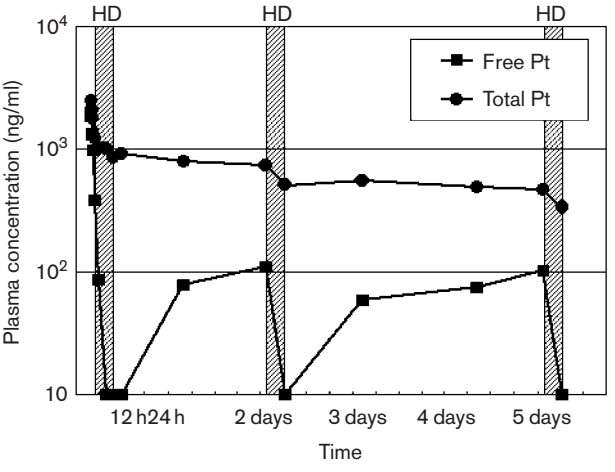

Figure 2. Plasma concentration of total (●) and ultrafiltrate (free) platinum (■) (ng/ml). The C_{max} of total platinum and free platinum was 2.44 and 1.84 μg/ml, respectively. The AUC of free platinum was 1.76 μg·h/ml.

elimination of paclitaxel was not affected by hemodialysis. The report by Woo *et al.*[3] and our data suggest that the phamacokinetics of paclitaxel are not altered in patients with renal failure.

We normally administer 60 mg/m^2 of cisplatin in combination with paclitaxel for ovarian cancer to patients with normal renal function. In the present case, we injected a half dosage of cisplatin, 30 mg/m^2. This dosage was used in her previous treatment in 1991, which included cisplatin, adriamycin and cyclophosphamide.[4] Tanabe *et al.*[10] reported the pharmacokinetics of cisplatin in a hemodialysis patient. According to their report, peak ultrafiltrate platinum at the end of infusion was 1.43 μg/ml and peak total platinum level was 1.86 μg/ml. The patterns of disposition of ultrafiltrate platinum and total platinum were nearly identical to our results.

In our case, grade III leukopenia and grade IV neutropenia were observed in the first course of treatment. Just before this course, her leukocyte and neutrophil counts were, respectively, 2.5×10^9/l and 1.1×10^9/l, and platelet count was 121×10^9/l. Since her baseline leukocyte counts were less than 3.0×10^9/l, we obtained informed consent for possibility of severe leukopenia in advance of the first course of treatment. Severe neutropenia was noted and G-CSF was administered for 3 days. In the second course, grade IV leukopenia and grade III thrombopenia were observed, but earlier than after the first course. G-CSF was administered for 4 days and platelet concentrate was transfused for 3 days.

We conclude that paclitaxel and cisplatin combination chemotherapy was efficacious for our patient. It is important to carefully determine the dosage of cisplatin and a time of hemodialysis start after the cisplatin infusion. Severe neutropenia must also be monitored for and treated.

Acknowledgments

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