Carboplatin-based chemotherapy in patients with gynecological malignancies on long-term hemodialysis

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We report on three cases of long-term dialysis patients with gynecological malignancies who were successfully treated with chemotherapy. Two epithelial ovarian carcinoma patients were treated with a single agent, carboplatin (100–200 mg/m^2). One recurrent endometrial carcinoma patient was treated with carboplatin (200 mg/m^2) and paclitaxel (135 mg/m^2). Hemodialysis was started 2 h after the carboplatin infusion and lasted 4 h in all three cases. All patients tolerated these therapies without significant myelosuppression or severe side-effects. Our findings suggest these regimens are feasible, and the combination of paclitaxel and carboplatin is effective chemotherapy when administered to long-term hemodialysis patients with recurrent endometrial carcinoma. *Anti-Cancer Drugs* 14:735–738 © 2003 Lippincott Williams & Wilkins.

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Introduction

The prognosis of patients with chronic renal failure has been improving following advances in hemodialysis techniques. However, the incidence of malignant tumors in patients on chronic hemodialysis has been increasing, resulting in a greater number of hemodialysis patients with gynecologic malignancies requiring treatment.

Carboplatin-based regimens have played a central role in the treatment of gynecologic malignancies, especially ovarian cancer. Furthermore, the combination of carboplatin and paclitaxel has been reported to be effective in treating recurrent endometrial cancer. However, much is still unknown about the long-term effects of administration of carboplatin and paclitaxel to patients on long-term hemodialysis.

In this study, we report three cases of primary ovarian carcinoma or recurrent endometrial carcinoma in patients who were treated with carboplatin while undergoing hemodialysis.

Case reports

Case 1

The first patient was a 33-year-old woman with chronic renal failure secondary to chronic glomerulonephritis. She also had a history of hypertensive retinopathy and cardiomyopathy. In 1998, endometrial carcinoma was diagnosed and she underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH-BSO). Postsurgically, her cancer was staged as IIIc according to the FIGO classification and a histological diagnosis confirmed endometrioid adenocarcinoma. She received two courses of adjuvant chemotherapy with 150 mg/m^2 carboplatin and 150 mg/m^2 cyclophosphamide followed by radiotherapy consisting of 50 Gy to the pelvic cavity. After therapy was completed in 1999, her chronic renal failure had progressed to the point where she required hemodialysis 3 times a week. Two and a half years after the initial treatment for endometrial carcinoma, she developed ascites, suggestive of recurrence, and was referred to our hospital for further examination and therapy.

Ultrasonography (USG) and magnetic resonance imaging (MRI) revealed a moderate amount of ascites and a small solid mass 1.0 × 1.0 cm in size in the pelvic cavity. Her serum level of carbohydrate antigen (CA) 125 was as high as 120 U/ml and cytology of the ascitic fluid was positive for adenocarcinoma cells. Recurrent endometrial carcinoma was therefore diagnosed. She had the following laboratory values on admission: white blood count (WBC) 4.2×10^9/l, hemoglobin (Hb) 9.0 g/dl, platelet count 130×10^9/l, blood urea nitrogen (BUN) 44 mg/dl, creatinine 8.8 mg/dl and uric acid 5.3 mg/dl. A treatment plan including both carboplatin and paclitaxel was initiated. Correct dosing of the chemotherapy regimen and the timing of administration of chemotherapy with hemodialysis were based on data published by Kurata *et al.* [1]. The calculated area under the curve (AUC) of 4 mg/min/ml for carboplatin required the i.v. administration of

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approximately 200 mg/m^2 of carboplatin if hemodialysis was performed 2 h after administration. Paclitaxel was therefore administered at a dose of 135 mg/m^2 for 3 h and then carboplatin was administered at a dose of 200 mg/m^2 for 2 h. Hemodialysis was started 2 h after the carboplatin infusion using a dialyzer, BK-1.3P (Toray Industries, Japan). Dialysis was continued for 4 h at a blood flow rate during hemodialysis of 200 ml/min. The nadir of WBC was 1.9×10^9/l and the nadir of the absolute neutrophil count was 1.1×10^9/l. Neutropenia was controlled with 100 μg of granulocyte colony stimulating factor (G-CSF) daily as a s.c. injection for 7 days. The other data are summarized in Table 1. The nadir platelet count was 78×10^9/l and did not increase above 100×10^9/l until day 30 after chemotherapy. Consequently the dose of carboplatin was reduced to 100 mg/m^2 for two additional courses of combination chemotherapy, which she tolerated without significant myelosuppression (summarized in Table 1), neurotoxicity or allergic reaction. The main side-effect of chemotherapy was alopecia.

After three courses of chemotherapy, CA125 decreased to within the normal range, at 12 U/ml, and both the ascites and the pelvic mass were no longer visible on MRI. The patient has shown no signs of recurrence up to 1 year after the last treatment.

Case 2

The second patient was a 56-year-old woman with chronic renal failure secondary to glomerulonephritis, requiring hemodialysis 3 times a week for 7 years. She was admitted to our hospital with a complaint of a large lower abdominal mass. USG and MRI revealed a multicystic mass with irregular solid components in the pelvic cavity. Her serum levels of CA 125 and sialyl Lewis-x (SLX) [2] were as high as 3400 and 57 U/ml, respectively. Ovarian carcinoma was diagnosed.

On admission, she had the following laboratory values: WBC 4.9×10^9/l, Hb 11.3 g/dl, platelet count 216×10^9/l, BUN 42 mg/dl, creatinine 6.7 mg/dl and uric acid 4.5 mg/dl. The patient underwent TAH-BSO and postoperatively did not have any residual disease. Her postsurgical stage was IIc according to the FIGO classification and histological diagnosis was serous papillary adenocarcinoma.

Carboplatin at a dose of 200 mg/m^2 was administered i.v. for 2 h as adjuvant chemotherapy. Hemodialysis was started 2 h after the carboplatin infusion using a dialyzer, BK-1.3P. Dialysis was continued for 4 h at a blood flow rate during hemodialysis of 200 ml/min. The major side-effect, severe thrombocytopenia, was not unexpected. The nadir of platelet count was 13×10^9/l, which required platelet transfusion. Additional data are summarized in Table 1. The dose of carboplatin was reduced to 100 mg/m^2 for four additional courses of chemotherapy. The lower dose of carboplatin did not produce severe myelosuppression and the patient tolerated the additional four courses without requiring administration of G-CSF (summarized in Table 1).

After treatment, the tumor markers decreased to within the normal ranges and she has had no recurrence for over 1 year.

Case 3

The third patient was a 45-year-old woman with chronic renal failure secondary to nephrotic syndrome, requiring hemodialysis 3 times a week for 23 years. She also had a history of hypertension and hyperparathyroidism. Her main complaint on admission was hypermenorrhea. USG and MRI revealed a cystic mass with irregular solid components in the left ovary, a small cystic mass in the right ovary and a uterine myoma with multiple nodules. Serum levels of tumor markers were all within normal limits. She had the following laboratory values on admission: WBC 4.5×10^9/l, Hb 5.9 g/dl, platelet count 167×10^9/l, BUN 38 mg/dl, creatinine 8.8 mg/dl and uric acid 3.7 mg/dl.

Table 1 Cycles and regimens of chemotherapy [carboplatin (C) or paclitaxel (P)] used to treat three patients with gynecologic malignancies on long-term hemodialysis

Case	Cycle	Regimen dose (mg/mm^2)	Pretreatment (nadir)		
			WBC ($\times 10^9$/l)	Hb (g/dl)	Platelets ($\times 10^9$/l)
1	1	C 200 P 135	4.2 (1.9)	9.0 (8.4)	130 (78)
	2	C 100 P 135	2.9 (2.0)	10.5 (9.8)	105 (96)
	3	C 100 P 135	3.6 (2.2)	11.8 (10.7)	144 (104)
2	1	C 200	4.9 (2.4)	11.3 (7.4)	216 (13)
	2	C 100	3.2 (2.5)	7.8 (7.3)	276 (132)
	3	C 100	4.4 (3.6)	10.1 (8.8)	193 (107)
	4	C 100	5.9 (3.1)	13.1 (12.4)	186 (122)
	5	C 100	4.6 (3.7)	12.6 (12.1)	159 (122)
3	1	C 150	4.2 (3.2)	7.4 (7.4)	207 (171)
	2	C 150	3.6 (2.8)	8.4 (8.4)	128 (107)
	3	C 150	3.5 (3.1)	10.8 (10.6)	199 (173)

The patient underwent TAH-BSO and postoperatively was without residual disease. Her postsurgical stage was Ic according to the FIGO classification, and the histological diagnosis were serous papillary adenocarcinoma of the ovary and leiomyoma of the uterus.

Adjuvant chemotherapy was initiated with carboplatin similar to the previous cases. However, the initial dose of carboplatin was reduced to 150 mg/m^2 to avoid severe bone marrow suppression as seen in Case 2. Three courses of carboplatin were administered i.v. for 2 h and hemodialysis was started 2 h after the carboplatin infusion using a dialyzer, BK-1.3P. Dialysis continued for 4 h with a blood flow rate during hemodialysis of 200 ml/min. Nadir blood counts are summarized in Table 1. Patient 3 tolerated chemotherapy without severe side effects. She has had no recurrence for 1 year after her last chemotherapy cycle.

Discussion

We report here successful treatments with carboplatin-based chemotherapy in three patients who developed endometrial carcinoma or ovarian carcinoma with hemodialysis-dependent renal failure. Only nine cases of patients with gynecologic malignancies undergoing long-term hemodialysis have been reported to be successfully treated with chemotherapy: seven with ovarian carcinoma [1,3–8], one with endometrial carcinoma [9] and one with cervical carcinoma [10]. These cases are summarized in Table 2. Carboplatin is the most widely used chemotherapeutic agent against gynecologic malignancies in patients undergoing hemodialysis. Unlike cisplatin, a high proportion of the carboplatin administered remains free in plasma, and the major route of elimination of carboplatin is through glomerular filtration and tubular secretion. These biological characteristics of carboplatin result in high dialysis efficiency. By contrast, the majority of cisplatin is rapidly protein-bound, and renal excretion accounts for a minority of the elimination of free platinum [11]. Because of its predictable kinetics and limited toxicity, carboplatin is preferable to cisplatin in cases of renal failure.

Table 2 Published cases with gynecological malignancies on long-term hemodialysis

Reference	Disease	Stage	Regimen
1	ovarian cancer	I	carboplatin 240 mg/m^2 cyclophosphamide 300 mg/body
3	ovarian cancer	III	paclitaxel 175 mg/m^2
4	ovarian cancer	IV	carboplatin 160 mg/m^2
5	ovarian cancer	III	paclitaxel 175 mg/m^2 carboplatin 125 mg/body
6	ovarian cancer	II	paclitaxel 150 mg/m^2 cisplatin 30 mg/m^2
7	ovarian cancer	IV	carboplatin 180 mg/m^2
8	ovarian cancer	III	carboplatin 150 mg
9	endometrial cancer	III	cisplatin 40 mg/m^2 cyclophosphamide 250 mg/m^2
10	cervical cancer	I	cisplatin 30 mg
Present study			
Case 1	endometrial cancer	III	paclitaxel 135 mg/m^2 carboplatin 200–100 mg/m^2
Case 2	ovarian cancer	II	carboplatin 200–100 mg/m^2
Case 3	ovarian cancer	I	carboplatin 150 mg/m^2

The AUC of 5–7 mg/min/ml for carboplatin is sufficient to obtain a high likelihood of complete response without prohibitory toxicity [12]. The carboplatin dose for hemodialysis patients is calculated using the Calverts formula, and considering the glomerular filtration rate (GFR) to be equal to zero and the extrarenal clearance, 25 ml/min. However, the AUC clinically observed in a hemodialysis patient is not only dependent on the dose and GFR, but also on the interval between the drug administration and hemodialysis, i.e. a shorter interval decreases the AUC. Kurata *et al.* compared the AUC of carboplatin during hemodialysis (1 h after 240 mg/m^2 of carboplatin administration) with the AUC 2 h after the administration [1]. The predicted AUC was 9.6 mg/min/ml, but the observed AUCs were 3.1 mg/min/ml for the former and 5.1 mg/min/ml for the latter. From these empirical data, we chose the dose of 200 mg/m^2 for the initial administration of carboplatin, which would be expected to result in an AUC of 4 mg/min/ml during hemodialysis 2 h after administration. This dose was also supported by previous reports in which carcinoma patients on long-term hemodialysis were successfully treated with 200–300 mg/m^2 of carboplatin without life-threatening side-effects [11]. However, severe or prolonged thrombocytopenia during chemotherapy for Cases 1 and 2 suggested that this dose was too high for patients on hemodialysis. On the other hand, Patient 1 had been given radiotherapy 2 years before, which may have reduced her bone marrow reserve. Patients on long-term hemodialysis may have abnormal bone marrow function and therefore the dose of carboplatin may need to be reduced in spite of reported pharmacokinetic data. Chatelet *et al.* reported on one case in which 100–150 mg/m^2 of carboplatin administration for six courses produced a complete response against an advanced ovarian carcinoma in a patient undergoing hemodialysis [8]. Clinically complete remission was observed for Patient 1 of the present study even though the carboplatin dose was reduced to 100 mg/m^2 for the second course of chemotherapy. From these data, we recommend 100–150 mg/m^2 of carboplatin as an appropriate dose for patients undergoing hemodialysis in spite of low AUC achieved pharmacokinetically [1], and even though we could not judge the efficacy of the administration of carboplatin because two of the patients (Cases 2 and 3) had no residual disease and chemotherapy was in the adjuvant setting.

In recurrent endometrial carcinoma, trials of the Gynecologic Oncology Group have found that doxorubicin and cisplatin have anti-tumor activity [13,14]. However, since

Patient 1 in this report had a history of cardiomyopathy and chronic heart failure, doxorubicin could not be the drug of choice. Recent reports indicate that combination chemotherapy with carboplatin and paclitaxel is effective for recurrent endometrial carcinoma [15], and therefore this regimen was preferred. To our knowledge, there has been no report on the use of paclitaxel for endometrial carcinoma in a long-term hemodialysis patient, although two papers have reported on the use of paclitaxel for hemodialysis patients with ovarian carcinoma [3,6]. The dose of paclitaxel was 175 mg/m^2 as a single agent in one case [3] and 150 mg/m^2 in combination with 30 mg/m^2 of cisplatin in a second case [6]. As paclitaxel is not eliminated by hemodialysis [16], no dosage alteration for infusion of paclitaxel was required on the basis of renal failure alone. Our administering of 135 mg/m^2 of paclitaxel in combination with carboplatin in Patient 1 resulted in thrombocytopenia and leukopenia; however, side-effects characteristic of paclitaxel, such as allergy and neurotoxicity, were not observed. The result in this patient suggested that the combination of paclitaxel and carboplatin was also an effective and feasible regimen against recurrent endometrial carcinoma in patients undergoing hemodialysis.

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