# TREATMENT OF AN ADVANCED OVARIAN CANCER PATIENT RECEIVING HEMODIALYSIS

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Treatment of patients with advanced ovarian cancer mainly involves aggressive cytoreductive surgery and administering adjuvant chemotherapy with carboplatin and paclitaxel. Carboplatin is metabolized by the kidney, and thus, a diminished dose of carboplatin is considered for patients with chronic renal failure to prevent further renal impairment resulting in secondary complications, such as anemia, hypertension, and thrombocytopenia [1,2]. Paclitaxel is metabolized by the liver, and less than 10% of the metabolite is eliminated renally [3]. So, we are able to administer a full dose of paclitaxel in renal insufficient patients, since its elimination does not depend on renal clearance [2]. Here, we present the course of treatment of a patient with advanced ovarian cancer who was receiving hemodialysis.

A woman aged 69, gravida 2, para 2, had suffered from glaucoma for 12 years and chronic nephritis for 10 years and was receiving hemodialysis three times a week. The patient attended hospital because of the lower abdominal pain she had suffered for 4 months. Pelvic ultrasonography revealed a right adnexal tumor $12 \times 10 \times 9$ cm in size and a left adnexal tumor $5.4 \times 3.2 \times 3$ cm in size, which were partly solid and had an irregular septum. Multiple enlarged right axillary lymph nodes were also found. In addition to the aforementioned findings, pelvic computed tomography scan revealed an omental lesion. Laboratory findings were as follows: 1,603 U/mL CA125, 95 mg/dL blood urea nitrogen (BUN), and 7.7 mg/mL creatinine. Transperitoneal laparotomy confirmed that the bilateral ovarian tumor had invaded the bilateral fallopian tubes and the surface of the uterus and had metastasized to the greater omentum and peritoneum. The patient underwent total hysterectomy, bilateral salpingo-oophorectomy, omentectomy, pelvic lymphadenectomy, and right axillary lymphadenectomy. Pathologic findings indicated undifferentiated papillary serous adenocarcinoma. Pelvic lymph nodes were unaffected, but right axillary lymph nodes were affected by serous adenocarcinoma. The patient was diagnosed with stage IV ovarian cancer, according to the International Federation of Gynecology and Obstetrics (FIGO) staging system.

After surgery, the patient was treated with carboplatin and paclitaxel. The dose (mg) of carboplatin used was AUC × (GFR + 25), according to the Calvert formula [4,5]. The area under the concentration-time curve (AUC) was administered at 5 mg/mL, with a glomerular filtration rate (GFR) of zero. Hence, the dose of carboplatin used was 125 mg ($5 \times 25$), and the dose of paclitaxel used was 135 mg/m$^2$. However, after the first course of chemotherapy, the patient experienced pancytopenia, with white blood count decreasing to 1,300/mm$^3$, hemoglobin to 7.5 g/dL and platelet count to 2,100/mm$^3$. After supportive treatment, the blood count became normal again. In the second course of chemotherapy, the dose of carboplatin was reduced to 80 mg and paclitaxel to 90 mg/m$^2$. Then, the patient followed the reduced dosing schedule for the remaining five courses without occurrence of severe bone marrow suppression. After the fourth course of chemotherapy, the CA125 had decreased to 15 U/mL, and the patient was fine. However, after 3 months of completion of chemotherapy, the patient died of acute myocardial infarction suddenly without any signs of relapse.

Treating ovarian cancer with first-generation platinum, such as cisplatin, is often complicated by renal dysfunction, neurotoxicity, and severe vomiting. These side effects are less common in the second-generation platinum analogue carboplatin, but carboplatin causes bone marrow suppression and particularly decreases platelet count. At present, carboplatin combined with paclitaxel is the most acceptable first-line chemotherapy for ovarian cancer.

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For patients diagnosed with ovarian cancer and receiving hemodialysis, a lower dose of carboplatin is still effective, because carboplatin is metabolized to a lesser extent in this situation. Approximately 65% to 75% of carboplatin is excreted in the urine. In the human body, carboplatin has a half-life of 2 to 6 hours in normal kidney function, but carboplatin has a half-life of 13–16 hours in renal failure [6]. Approximately 25% of carboplatin is removed by irreversible protein binding and hepatic metabolism [2]. Only 15% to 20% of carboplatin is removed by hemodialysis. Accordingly, carboplatin administered to patients with chronic renal failure must be low-dose; otherwise, carboplatin would cause enhanced toxicity and side effects to the patients.

The dosage of most anticancer drugs is calculated by body surface area (BSA). An average person has a BSA of 1.5, as indicated by the point of intersection between the linear functions of body height (cm) and body weight (kg). For instance, a patient receiving carboplatin for 3 weeks at a rate of 300–400 mg/m$^2$ has to be administered with approximate 450–600 mg dose of carboplatin ($1.5 \times 300–400 = 450–600$ mg). The aforementioned dosage is too high for patients with renal failure and causes severe side effects in the patients, because carboplatin is mostly metabolized by the kidneys. The suggested dose (mg) is AUC (mg/mL) × (GFR + 25), according to the Calvert formula, where AUC denotes the area under the concentration-time curve and GFR denotes glomerular filtration rate [5]. Carboplatin is usually administered to previously treated patients at AUC of 4–6 mg/mL and chemotherapy-naïve patients at AUC of 5–7.5 mg/mL.

In our case, the GFR was zero, and thus, the carboplatin clearance was 25 mL/min ($GFR + 25 = 0 + 25 = 25$). With an AUC of 5 mg/mL, the dosage of carboplatin used was $5 \times 25$ mg = 125 mg. After receiving the aforementioned dose for one course of chemotherapy, the patient experienced severe pancytopenia and, therefore, needed a rest and transfusion. Then, the dose of carboplatin was reduced to 80 mg, and the dose of paclitaxel was decreased from 135 mg/m$^2$ to 90 mg/m$^2$, in order to proceed with chemotherapy without pancytopenia.

Jeyabalan et al [7] reported administering 125 mg of carboplatin and 175 mg/m$^2$ (total of 298 mg) of paclitaxel for six courses after surgery to a patient diagnosed with staged III ovarian cancer complicated by renal failure. The chemotherapy caused numbness to the patient's fingers but did not decrease the platelet count, and the patient was fine at 11 months after commencement of chemotherapy. Hence, the required dosage adjustment of carboplatin for patients diagnosed with ovarian cancer complicated by renal failure seems to differ from person to person; hopefully, more upcoming cases can give us an insight into the issue. Our case had CA125 returning to a normal level, and the patient had complete response by the time the fourth course of chemotherapy ended. Unfortunately, the patient suddenly died of heart disease after 3 months of chemotherapy, thus raising questions about the course of chemotherapy. The possibility of paclitaxel inducing cardiomyopathy was less likely, because myocardial infarction is seen only during and not over 14 days following paclitaxel therapy [8].

Watanabe et al [3] reported of a woman with ovarian cancer and chronic renal failure on hemodialysis who was treated with carboplatin/paclitaxel combination chemotherapy after surgery. Paclitaxel was administered at 150 mg/m$^2$, and carboplatin was chosen to produce a target AUC of 5 mg/mL. Hemodialysis was started 1.5 and 16 hours after the end of carboplatin administration in the first and second course of chemotherapy, respectively. The pharmacokinetic studies showed that the AUCs of free platinum and paclitaxel were 2.21 μg-min/mL and 16.3 μg-h/mL, respectively, in the first course, and 4.43 μg-min/mL and 15.9 μg-h/mL, respectively, in the second course. These values were comparable to those analyzed by pharmacokinetic studies in patients with normal renal function previously [9–11]. Therefore, when carboplatin was administered with AUC of 5 mg/mL, as well as a similar dose of paclitaxel on hemodialysis, they were able to produce good tumor response.

In summary, it is feasible to administer carboplatin and paclitaxel concurrently to patients with ovarian cancer who are receiving hemodialysis, though a lower-dose chemotherapy is recommended, especially a lower dose of carboplatin. The chemotherapy can start with 125 mg of carboplatin, and the carboplatin dose should be reduced in the case of severe bone marrow suppression.

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