

# Chronic Kidney Failure in a Patient with Stage IV Epithelial Ovarian Cancer After Cytoreductive Surgery Following HIPEC with Cisplatin: A Case Report

## Evre IV Epitelial Over Kanseri Olan Hastada Sitoredüktif Cerrahi ve Sisplatin ile HIPEC Sonrası Kronik Böbrek Yetmezliği: Olgu Sunumu

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### ÖZET

**Giriş:** İleri evre over kanseri tedavisinde maksimal sitoredüksiyon sonrası platin bazlı kemoterapi yaygın olarak kullanılan standart tedavi yaklaşımıdır. Son yıllarda ileri evre epitelial over kanseri (EOK) için hipertermik intraperitoneal kemoterapi (HIPEC) uygulanasıda sık kullanılmaya başlanmıştır. Yakın tarihli yapılan bir çalışmada TSR'yi takip eden HIPEC'in evre III EOK'li hastalarda genel sağkalımı artırdığı gösterilmesine rağmen HIPEC komplikasyonları iyi çalışılmamıştır. Bu çalışmada, neoadjuvan kemoterapi ve ardından TSR'yi takiben sisplatin ile HIPEC alan 45 yaşında ileri evre EOK tanılı hastada gelişen postoperatif kronik böbrek yetmezliği sunulmuştur

**Anahtar Kelimeler:** Yumurtalık kanseri; sitoredüksiyon; HIPEC; sisplatin; akut böbrek hasarı; kronik böbrek yetmezliği; hemodiyaliz

### ABSTRACT

**Acknowledgments:** The authors would like to thank the patient for her cooperation and the midwife Sema Koca for her assistance.

**Abstract:** The mainstay of treatment for advanced-stage ovarian cancer is a maximal surgical effort for complete cytoreduction (CRS) defined as no visible residual disease followed by platinum-based adjuvant chemotherapy. Hyperthermic intraperitoneal chemotherapy (HIPEC) has been started to use for advanced-stage epithelial ovarian cancer (EOC). Although a recent study showed that HIPEC following interval CRS improves the overall survival in patients with stage III EOC, its complications are not well studied. This report aims to present a 45-year-old female with advanced-stage EOC who had neoadjuvant chemotherapy, followed by CRS and HIPEC with cisplatin. Postoperatively, she developed acute kidney injury that was found to be due to HIPEC with cisplatin and complicated by chronic renal failure requiring lifelong hemodialysis.

**Keywords:** ovarian cancer; cytoreductive surgery; HIPEC; cisplatin; acute kidney injury; chronic kidney failure; hemodialysis

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## Introduction

Ovarian cancer is the fifth most common cause of cancer-related death in women [1]. The majority of the patients are diagnosed at an advanced stage (Stage II-IV according to The International Federation of Gynecology and Obstetrics (FIGO) Ovarian Cancer Staging 2014 Guideline). The mainstay of treatment for advanced-stage ovarian cancer is a maximal surgical effort for complete cytoreduction (CRS) defined as no visible residual disease followed by platinum-based adjuvant chemotherapy. In patients where complete CRS is not predicted to be achieved, neoadjuvant chemotherapy (NCT), followed by interval CRS, is the most common treatment modality.

Although hyperthermic intraperitoneal chemotherapy (HIPEC) has been previously reported in the treatment of peritoneal carcinomatosis, it is still not considered to be the standard of care for patients with epithelial ovarian cancer (EOC). It is hypothesized that HIPEC potentiates the antitumoral effect by several mechanisms, including enhancing the effect of a selected chemotherapeutic agent by hyperthermia. There are several chemotherapeutic agents used for HIPEC, such as cisplatin, mitomycin, and carboplatin. Among these agents, cisplatin is well known to be nephrotoxic. A recent study showed that HIPEC following interval CRS improves the overall survival in patients with stage III EOC [2]. However, adding this promising treatment to the standard of care for EOC might increase the risk of acute kidney injury (AKI) and also chronic renal failure (CRF) [3-5].

This report aims to present a 45-year-old female with advanced-stage EOC who had NCT followed by CRS and HIPEC with cisplatin. Postoperatively, she developed AKI that was found to be due to HIPEC with cisplatin and complicated by CRF requiring lifelong hemodialysis.

## Case

A 45-year-old, gravida 2, para 2 woman presented with abnormal uterine bleeding (AUB) and pelvic pain to gynecology outpatient clinic. A left-sided pelvic mass and pelvic free fluid were identified by physical examination and ultrasonography. All of the tumor markers were within normal limits except CA-125 and HE-4, which were 789 U/mL and 145 pmol/L, respectively. The risk of malignancy (ROMA) score was calculated to be 56.5%. Intravenous contrast-enhanced pelvic MRI showed pelvic peritoneal plaques suspicious for metastatic disease. Positron emission tomography (PET) scan revealed implants on pelvic, peri-hepatic, and peri-splenic peritoneum, as well. Gastroscopy,

colonoscopy, and mammography were negative for any malignancy. She did not report any chronic disease. Past surgical history included two cesarean sections. Family history included a maternal chronic kidney disease requiring hemodialysis. This case was approved by Koc University Institutional Review Board (2018. 220. IRB1.025).

Peritoneal carcinomatosis with widespread, numerous implants on intestinal walls was identified during laparoscopy in addition to the imaging findings before the operation. Based on the laboratory and imaging studies, the surgery was started as diagnostic laparoscopy. Due to extensive tumor implantation, she was found to be inoperable, and the tissue samples and cytology were obtained for further evaluation. The final pathology revealed a high-grade serous ovarian adenocarcinoma. She underwent three cycles of platinum-based (paclitaxel 175 mg/m<sup>2</sup> and carboplatin AUC 5 every 21 days) neoadjuvant chemotherapy (NACT). CA 125 level decreased to 70.5 U/mL, and abdominopelvic MRI showed a significant response to NACT after three cycles. Before the definitive cytoreductive surgery (CRS), HIPEC was discussed with the patient, and she received very detailed information regarding the possible benefits and risks of the HIPEC procedure according to the currently available data in the literature. She has been fully informed about the fact that HIPEC was an experimental procedure, and informed consent was obtained. All of the blood tests were in normal limits, including renal function tests and electrolytes pre-operatively.

A complete CRS was performed, including total abdominal hysterectomy, bilateral salpingo-oophorectomy, total infragastric omentectomy, appendectomy, cholecystectomy, low anterior resection and anastomosis, liver metastasectomy, total abdominal peritonectomy including right diaphragmatic stripping, resection and repair, small bowel resection, and bilateral pelvic and paraaortic lymphadenectomy. There was no visible residual disease. The surgery was uneventful. The surgery was uneventful without any hypotensive period, which is a well-known etiology for AKI. CRS was followed by HIPEC using the closed abdomen technique. The desired temperature (42°C) was obtained via three liters of saline, and 75 mg/m<sup>2</sup> cisplatin subsequently applied for 60 minutes. The patient was monitored in the intensive care unit for two days, and she was transferred to the patient-ward uneventfully.

On postoperative day (POD) four, laboratory results showed serum creatinine and blood urea nitrogen (BUN)

levels to be 3.5 mg/dL and 62,6 mg/dL, respectively. The previous early postoperative laboratory tests were in normal limits, including a creatinine level of 0.7 mg/dL.

Renal ultrasonography following nephrology consultation did not reveal any pathology. All of the possible pre-renal and post-renal pathologies were ruled out, and a diagnosis of AKI due to cisplatin was made in collaboration with the nephrology department.

Her fluid volume and electrolytes were then monitored closely. However, the renal functions, as well as the laboratory tests, gradually deteriorated. Hemodialysis was required on POD seven due to acute renal failure, and the patient was discharged on POD 15 without any sign of recovery. She received six cycles of platinum-based adjuvant chemotherapy (paclitaxel, 175 mg/m<sup>2</sup> and carboplatin, AUC=5 every 21 days) for six weeks after CRS. At the end of the adjuvant chemotherapy, the control MRI revealed a recurrence. She underwent six cycles of liposomal doxorubicin (30 mg/m<sup>2</sup>) and bevacizumab (7.5 mg/kg) every 21 days as second-line chemotherapy. She has received 17 cycles of bevacizumab as maintenance therapy so far. The patient is still on hemodialysis for 25 months postoperatively. Currently, the frequency of hemodialysis has decreased to twice from three times per week, and the spontaneous urination volume has increased. Creatinine and estimated glomerular filtration rate ranged between 3.8- 9.19 mg/dL and 5.92-13.48 mL/min/1.73m<sup>2</sup>, respectively. However, she is still being followed by a diagnosis of chronic renal failure requiring hemodialysis. Her Ca 125 was progressively increased, 230 U/mL being the final. Her last thorax computed tomography, and abdominopelvic MRI did not reveal recurrence.

## Discussion

This report aims to present a case of CRF due to HIPEC with cisplatin. It is well known that cisplatin has strong nephrotoxic effects that might lead to AKI. Elevated serum creatinine and BUN levels after several days following the systematic cisplatin administration are the initial signs of AKI. Additionally, it was reported that cisplatin given during HIPEC perfuses into the bloodstream, hence, to the kidneys, as in systemic therapy.[6] This might be the possible reason for AKI in the patient reported here. A retrospective study claimed that HIPEC with cisplatin is an independent risk factor for postoperative AKI. It is reported that the patients in HIPEC with the cisplatin group experienced more frequent AKI than the patients in only the CRS group and only the cisplatin group. [3] Thus, it is reasonable to claim that systemic side effects of cisplatin, including

AKI and CRF, can also be seen after HIPEC with cisplatin. A recent randomized controlled trial showed that the addition of HIPEC with cisplatin to interval CRS resulted in an improvement of overall survival in patients with stage III EOC with similar rates of side effects compared to CRS alone. [2] However, in a retrospective study, including 53 patients who underwent CRS followed by HIPEC with cisplatin and doxorubicin, AKI was reported in two patients (3.7%) and CRF in one patient (1.9%). [4] Another study concluded that of 47 patients with ovarian cancer who received HIPEC with cisplatin, 19 patients (40.4%) developed AKI, and two patients (4.3%) needed long-term dialysis. Nevertheless, NACT with cisplatin was not found to increase the risk of postoperative AKI. [5] This also supports that HIPEC with cisplatin was the most probable etiology of AKI and CRF in our patient who received NACT with the paclitaxel-carboplatin regimen that is reported to be less nephrotoxic than a paclitaxel-cisplatin regimen. [7]

In conclusion, the case presented here highlights the importance of early diagnosis and management of AKI due to HIPEC with cisplatin, even in the absence of other risk factors of AKI. Nevertheless, there is a substantial risk of CRF after HIPEC with cisplatin even in a patient with normal preoperative kidney function tests. Patients with advanced-stage ovarian cancer are experiencing ultra-radical surgical procedures in the experienced hands to achieve complete cytoreduction which also needs a very meticulous pre-, peri-, and post-operative management. Since HIPEC, mainly when performed with cisplatin, increases the risk of AKI, these patients require very well organized and coordinated teamwork and a close postoperative follow-up. Thus, these procedures are best to be performed in centers of expertise of ovarian cancer, and with this report, we aim to alert the physicians to the risk of both AKI and CRF in the patients who received HIPEC with cisplatin.

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