CASE REPORT

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High-grade serous ovarian carcinoma in a patient with end-stage renal disease

Serozni karcinom jajnika visokog gradusa kod bolesnice u terminalnom stadijumu bubrežne bolesti

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Abstract

Introduction. Ovarian carcinoma, being one of the most common gynecologic cancers, has the highest mortality rate. The gold standard for the treatment of patients with advanced ovarian carcinoma, along with angiogenesis inhibitors applied in certain advanced stages, is cytoreductive surgery, followed by chemotherapy (CHT). The use of chemotherapeutic agents in hemodialysis (HD) patients has some specificities and limitations, and no CHT guidelines exist for treating those patients. **Case report.** We present a 45-year-old female patient with end-stage renal disease undergoing HD treatment. Abdominal and pelvic magnetic resonance imaging showed a multicystic mass with a total diameter of 93 × 115 × 168 mm in the right ovary and two subcapsular lesions in the VI segment of the liver with a diameter of 22 × 14 mm and 9 mm (stage IVb ovarian cancer). The serum level of the tumor marker cancer antigen 125 (CA-125) was 93 U/mL. A total hysterectomy with bilateral salpingo-oophorectomy and infracolic omentectomy was performed. Histopathological analysis of the surgical specimen confirmed high-grade serous ovarian adenocarcinoma, FIGO stage IVb. After surgery, she was treated with carboplatin and paclitaxel combination CHT, determining the dose of carboplatin according to the Calvert formula and initiating HD within 20 hrs of infusion. Two years after the diagnosis was made, the presented patient is in good condition. **Conclusion.** HD patients can be treated with a combination CHT regimen of carboplatin and paclitaxel, determining the dose of carboplatin according to the Calvert formula and initiating HD within 20 hrs from the end of the chemotherapeutic infusion.

Key words:
antineoplastic agents; antineoplastic combined chemotherapy protocols; diagnosis; kidney failure, chronic; magnetic resonance imaging; ovarian neoplasms; renal dialysis.

Apstrakt

Uvod. Karcinom jajnika, jedan od najčešćih ginekoloških kancera, ima najveću stopu smrtnosti. Zlatni standard lečenja bolesnica sa uznapredovalim karcinomom jajnika, uz inhibitore angiogeneze koji se primenjuju u određenim uznapredovalim stadijumima, jeste citoreduktivna hirurgija, praćena primenom hemioterapije (HT). Primena HT kod bolesnika na hemodijalizi (HD) ima neke specifičnosti i ograničenja, a uz to ne postoje smernice HT za lečenje tih bolesnika. **Prikaz bolesnika.** Prikazujemo 45-godišnju bolesnicu sa terminalnim stadijumom bubrežne bolesti, na programu HD. Magnetska rezonanca abdomena i male karlice pokazala je multicističnu masu ukupnog prečnika 93 × 115 × 168 mm u desnom jajniku i dve subkapsularne lezije u VI segmentu jetre prečnika 22 × 14 mm i 9 mm (stadijum IVb karcinoma jajnika). Nivo tumor markera *cancer antigen* 125 (CA-125) u serumu iznosio je 93 U/mL. Učinjena je totalna histerektomija sa bilateralnom salpingo-ooforektomijom i infrakoličnom omentektomijom. Histopatološkom analizom hirurškog uzorka potvrđen je serozni adenokarcinom jajnika visokog gradusa, FIGO stadijuma IVb. Posle operacije, bolesnica je lečena kombinovanom HT karboplatinom i paklitakselom, uz određivanje doze karboplatina prema Kalvertovoj formuli i započinjanjem HD u roku od 20 sati od završetka HT infuzije. Dve godine posle postavljanja dijagnoze, bolesnica je u dobrom opštem stanju. **Zaključak.** Bolesnici na HD mogu biti lečeni kombinovanim režimom HT karboplatinom i paklitakselom, određivanjem doze karboplatina prema Kalvertovoj formuli i započinjanjem HD u roku od 20 sati od završetka infuzije hemioterapeutika.

Ključne reči:
antineoplastici; lečenje kombinovanjem antineoplastika, protokoli; dijagnoza; bubreg, hronična insuficijencija; magnetska rezonanca, snimanje; jajnik, neoplazme; hemodijaliza.

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Introduction

Patients with a long history of hemodialysis (HD) treatment are more likely to develop malignant illnesses [1, 2]. Chemotherapeutic drugs have some specific characteristics and limits when used in HD patients. There are no chemotherapeutic recommendations for cancer patients undergoing HD treatment due to a paucity of data on actual clinical practice and evidence [3].

Ovarian cancer (OC) is the seventh most frequent cancer diagnosis worldwide, the second leading cause of gynecologic cancer mortality, and the eighth leading cause of cancer mortality [4, 5]. The average relative 5-year survival rate for patients with spread OC stage IVb is about 31%. In advanced epithelial ovarian cancer (EOC), the standard of treatment is surgical staging and resection followed by paclitaxel (PTX)/platinum-based chemotherapy (CHT) and in some cases, angiogenesis inhibitors are used, such as monoclonal antibody bevacizumab that binds vascular endothelial growth factor [6].

We present an International Federation of Gynecology and Obstetrics (FIGO) stage IVb OC patient with chronic renal failure undergoing HD treatment, treated with surgery and PTX/carboplatin (CBDCA) combination CHT.

Case report

A 45-year-old Caucasian woman with a 2-year history of chronic kidney disease and hypothyreosis was hospitalized at the Clinic for Nephrology at the University Clinical Center of Serbia to begin peritoneal dialysis treatment for end-stage renal disease. She denied having any symptoms. The patient was a non-smoker. She denied previous use of contraceptives. She did not give birth and had no miscarriages. Her mother died of breast cancer. On physical examination, she was afebrile, with a blood pressure of 125/70 mmHg, a heart rate of 82 beats *per* minute, a respiratory rate of 16 breaths *per* minute, oxygen saturation of 99%, no masses or organomegaly on abdominal palpation, and no peripheral edema.

Her electrocardiogram and chest X-ray results were both without pathological findings. The laboratory results obtained at the time of admission are shown in Table 1. Ultrasonography of the abdomen and pelvis showed a right ovarian mass. We performed abdominal and pelvic magnetic resonance imaging (MRI) to evaluate the pelvic mass, which revealed a multicystic mass in the right ovary with an overall diameter of 93 × 115 × 168 mm (Figure 1), as well as two subcapsular lesions in the VI segment of the liver with

Table 1

Laboratory values on admission of a patient with ovarian carcinoma and end-stage renal disease

Test	Result	Normal range
WBC count, $\times 10^9$/L	6.9	3.4–9.7
Hb, g/L	88	122–157
PLT, $\times 10^9$ /L	196	150–450
Ur, mmol/L	21	2.5–7.5
Cr, µmol/L	619	45–84
Na, mmol/L	138	135–148
K, mmol/L	4.5	3.5–5.1
CA-125, U/mL	93	0–35
HE4, pmol/L	1,023	< 140
[1]ROMA index, %	99	

WBC – white blood cell; Hb – hemoglobin; PLT – platelets; Ur – urea; Cr – creatinine; Na – sodium; K – potassium; CA-125 – cancer antigen 125; HE4 – human epididymis protein 4; ROMA – Risk of Ovarian Malignancy Algorithm.
Note: [1]Reference range is considered as high-risk for premenopausal women.

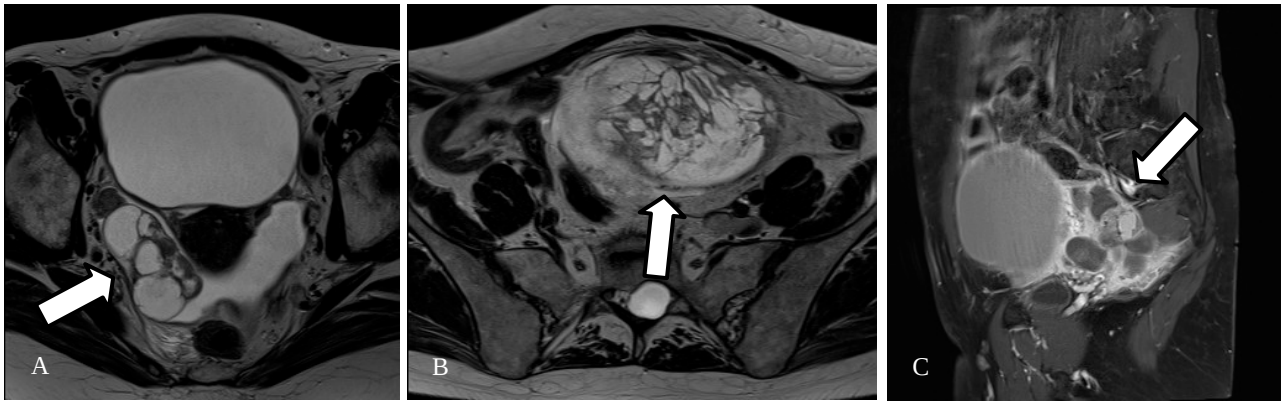

Fig. 1 – Preoperative abdominal and pelvic magnetic resonance imaging in axial (A and B) and sagittal (C) view in a patient admitted to begin peritoneal dialysis showing a multicystic mass in the right ovary (white arrows).

diameters of 22 × 14 mm and 9 mm (Figure 2). Neither ascites nor peritoneal metastatic deposits were noticed.

The gynecologist performed a total hysterectomy with bilateral salpingo-oophorectomy and infracolic omentectomy. The surgical specimen's histopathology revealed high-grade serous OC, FIGO stage IVb, pathological tumor-nodus-metastasis (pTNM): T2b, Nx, M1. Postoperatively, the serum level of CA-125 dropped to 6 U/mL. Because she was on dialysis, oncologists at the Clinic for Gynecology and Obstetrics of the University Clinical Center of Serbia were hesitant to begin CHT due to the significant risk of side effects. Nonetheless, following the meeting of nephrologists and oncologists from the Institute of Oncology and Radiology of Serbia, it was decided that the patient would be treated with CHT, with CBDCA dosage adjusted to the renal function and dialysis term adjusted with the CHT infusions. The patient received five cycles of combination CHT with CBDCA and PTX, one cycle every three weeks. PTX was administered as a 3-hour intravenous (iv) infusion of 175 mg/m^2, followed by a 1-hour CBDCA infusion at 125 mg. HD sessions were performed three times a week for 4 hrs. On the day of CHT administration, HD was started within 20 hrs of the end of the CHT infusion.

After the fifth treatment of CHT, the patient had thrombocytopenia grade 2, which did not improve for a lengthy period of time. Therefore, she did not have a sixth course. The serum CA-125 level was 5 U/mL after the fifth cycle of CHT, and the control MRI of the abdomen and pelvis revealed no evidence of local disease relapse.

The patient had regular check-ups, and a lesion in the liver was noticed on the positron emission tomography/computed tomography (PET/CT) scan ten months after the last cycle of CHT. Due to severe myelosuppression, with thrombocytopenia and neutropenia grade 3, she got four cycles of mono CBDCA CHT in a single dose of 125 mg in an extended schedule, one cycle every month. Anemia was treated with red blood cell transfusions and recombinant human erythropoietin. During the oncologic treatment, genetic analyses revealed a *BRCA1* gene mutation. The Oncology Council advised the application of poly ADP ribose polymerase (PARP) inhibitor olaparib as a maintenance therapy, but the special board of the Republic Fund of Health Insurance did not approve olaparib use.

Thrombocytopenia did not improve for an extended period of time, so treatment was continued with a single 125 mg CBDCA CHT regimen for an extended period of four months.

Table 2 displays the laboratory results obtained two years after surgery and CHT. The control MRI of the abdomen and pelvis revealed one lesion in the VI segment of the liver and one in the VII segment, with diameters of 22 × 10 mm and 17 × 12 mm, respectively. For the described liver lesions, X-knife radiation therapy was performed with 40 Gy in five fractions for the lesion located near the right kidney and 25 Gy in one fraction for the subcapsular lesion.

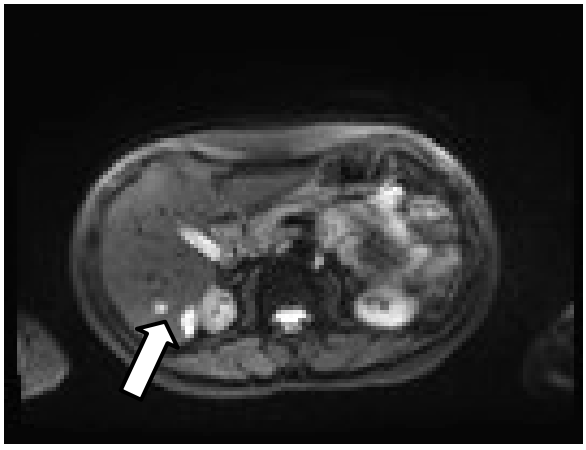

Fig. 2 – Abdominal and pelvic magnetic resonance imaging showing lesions in the liver (white arrow).

Table 2

Laboratory values two years after surgery and chemotherapy

Test	Result	Normal range
WBC count, ×10^9/L	4.2	3.4–9.7
Hb, g/L	97	122–157
PLT, ×10^9/L	123	150–450
Ur, mmol/L	21	2.5–7.5
Cr, μmol/L	619	45–84
Na, mmol/L	138	135–148
K, mmol/L	4.5	3.5–5.1
CA-125, U/mL	9.44	0–35

For abbreviations, see Table 1.

Discussion

OC incidence and mortality rise with age, but it can be diagnosed at any age [7]. The most prevalent histologic subtype is High-Grade Serous OC [3]. The majority of instances of EOC are identified at an advanced stage when the tumor has migrated to the peritoneal cavity and higher abdominal organs, limiting the possibility of curing this cancer [8]. PTX 175 mg/m^2 in combination with CBDCA area under the curve (AUC) 5–7.5 every three weeks for six cycles, given iv, was accepted as first-line CHT for EOC [6]. Women with a family history of OC are at a higher risk of developing the disease. Mutations in the *BRCA* gene cause a significant percentage of hereditary malignancies [9]. Our 45-year-old patient had a *BRCA1* mutation and a positive family history of breast cancer. In these patients with *BRCA*-mutated advanced OC, a PARP inhibitor, olaparib, may be used for maintenance therapy alone or in combination with bevacizumab. Unfortunately, our patient was treated only by the application of PTX in combination with CBDCA.

Many people undergoing HD therapy have malignancies of various forms. However, only a few cases have been published on the pharmacokinetics of PTX and CBDCA combination treatment in HD patients with EOC [10]. PTX is primarily metabolized and eliminated in the liver. The kidneys eliminate only 5–10% of PTX unaltered [11]. PTX at standard doses and infusion durations, alone or in combination with platinum, can be utilized in HD patients without necessitating dose adjustments due to renal failure. Furthermore, it has been demonstrated that HD does not alter the pharmacokinetics of PTX [12].

Within the first 24 hrs, 55–70% of CBDCA is eliminated renally. The AUC of CBDCA has been demonstrated to correspond with its therapeutic efficacy [13]. According to the manufacturer's guidelines, CBDCA is not indicated for individuals with creatinine clearances less than 16 mL/min. Fortunately, CBDCA is not as tightly linked to proteins almost 24 hrs after infusion, making it more dialysis-resistant if dialysis is performed 24 hrs after CBDCA infusion [14, 15]. The dialysis elimination half-life was substantially shorter than the pre-dialysis value, indicating that some CBDCA (mainly free) was dialyzed [16]. The appropriate CBDCA dose and time for HD are still unknown. Its AUC is affected by the CBDCA dose, the timing of HD treatment, and the length of HD sessions [17]. Some reports refer to pharmacokinetic studies in HD patients receiving CBDCA infusions [18–21]. AUC values vary, but the calculation of AUC plays an important role in CBDCA dose determination, not just for the optimal anticancer effect but also for avoiding adverse reactions. However, in controlled prospective investigations, the safety and therapeutic advantages of CBDCA alone or combined with other medicines in patients with renal failure have yet to be adequately studied [22]. To calculate the CBDCA dose for a fixed AUC and glomerular filtration rate (GFR) [14], the Calvert formula dose (mg) = target AUC × (GFR + 25) [20] is often used. GFR was set to 0 mL/min in individuals receiving chronic HD therapy using the Calvert formula [10].

Our patient received a combination CHT of CBDCA and PTX every three weeks for five cycles. PTX was administered as a 3-hour iv infusion of 175 mg/m^2, and CBDCA as a 1-hour infusion of 125 mg. The Calvert formula [22] was used to calculate the CBDCA dose. The GFR was set to zero, the desired AUC was 5.0 mg/mL/min, and the HD was done around 20 hrs after the CHT course. Unfortunately, we were unable to measure free platinum and, therefore, determine AUC. However, even without measuring free platinum, determining the CBDCA dose using the Calvert formula and initiating HD within 24 hrs of infusion delivery offers beneficial therapeutic results without significant side effects [10].

The major toxicity of CBDCA is hematological, frequently appearing as myelosuppression [13]. AUC has been observed to correlate not only with ovarian malignancy response but also with myelotoxicity [23]. The optimal AUC is yet to be determined in prospective studies in order to reduce the risk of bone marrow suppression. It was reported that even a CBDCA AUC value of 3.5 mg/mL/min was associated with grade 4 thrombocytopenia [21]. We might infer that our patient was not underdosed in terms of cancer treatment because she developed grade 2 thrombocytopenia after the fifth course of the first CHT regimen. Since thrombocytopenia did not improve, a single 125 mg CBDCA CHT regimen was continued for four months.

Conclusion

Our patient is in good condition two years after the diagnosis was made. We can conclude that HD patients can be treated with CBDCA and PTX combined CHD regimen, with the CBDCA dose determined using the Calvert formula and HD initiated within 20 hrs of CBDCA infusion. If blood platinum levels cannot be monitored, blood cell counts and dialysis timing must be carefully monitored to avoid hematotoxicity. In order to design an adequate chemotherapeutic CBDCA regimen for HD patients with ovarian cancer, prospective studies involving a more significant number of such patients investigating the pharmacokinetic characteristics of CBDCA are needed.

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