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Chemotherapy in patients with testicular germ-cell tumors and end-stage renal disease requiring hemodialysis: two case reports

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Abstract

The number of patients with end-stage renal disease requiring hemodialysis and diagnosed with various types of cancer is constantly growing, but guidelines on systemic treatment in this particular clinical scenario are lacking. Testicular cancer is a highly curable malignancy, but data on post-orchidectomy systemic treatment based on cisplatin in patients requiring hemodialysis are scarce. We present two cases of patients with testicular germ cell tumors (one intermediate-risk seminoma and one low-risk non-seminoma) treated with chemotherapy while on hemodialysis in our center. Furthermore, we discuss the appropriate doses of cytotoxic drugs and the timing of hemodialysis.

Keywords: germ-cell tumor, testicular cancer, end-stage renal disease, hemodialysis

Introduction

The number of patients with end-stage renal disease (ESRD) requiring hemodialysis (HD) is constantly growing and currently affects > 10% of the general population worldwide, amounting to > 800 million individuals [1]. In the last few years, a significant increase in cancer incidence and mortality in dialysis patients has been observed [2]. This may be caused by impaired renal function leading to the blood accumulation of nitrogen transformation products, negatively affecting the immune system [3]. So far only a few guidelines on oncological treatment in chronic kidney disease (CKD) has been published, with the International Consensus Guideline for Anticancer Drug Dosing in Kidney Dysfunction (ADDIK) by Cancer Institute NSW, eviQ, and the ADDIKD Guideline Working Group being the most comprehensive ones [4, 5]. However, there are no specific international guidelines regarding anti-cancer therapy in patients with ESRD requiring HD.

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Testicular cancer is the most common type of neoplasm among young men (aged 15–40 years) worldwide. It represents 1% of adult neoplasms and 5% of urological tumors, with incidence ranging from 3 to 11 new cases per 100 000 males/per year with 74 458 new cases in 2020 worldwide [6]. Patients who require post-orchidectomy systemic treatment are usually managed with cisplatin-based chemotherapy that has a well-known risk of nephrotoxicity. This article will present the first two cases of patients with testicular germ cell tumors treated with chemotherapy while on HD in our center.

Descriptions of the clinical cases

Patient 1

A 37-year-old man undergoing HD due to ESRD associated with glomerulonephritis and suffering from hypertension, atrial fibrillation, and metabolic syndrome was admitted to the Department of Oncology because of the left testicular cancer. The patient underwent a left orchidectomy in October 2020 due to the tumor diagnosis a month earlier. Histopathology report described mixed germ cell tumor. On the computed tomography (CT) scan of the chest, abdomen, and pelvis, we observed extensive lymph node invasion: the lower right paratracheal lymph node was

Table 1. Changes in neoplastic marker levels before and during chemotherapy in patient 1

Time Point	LDH 135–225 [U/L]	*B*-HCG Male < 2.0 [mIU/mL]	AFP < 7 [ng/mL]
Before 1st cycle of EP	201	1.2	98.8
Before 2nd cycle of EP	231	3519.4	22.8
Before 3rd cycle of EP	205	40.93	7.9
Before 4th cycle of EP	205	10.6	5
Before 5th cycle of EP	208	1.48	5
Before 1st cycle of TIP	186	< 1.2	91.5
Before 2nd cycle of TIP	192	1.2	5.9
Before 3rd cycle of TIP	201	6.2	4.9
After chemotherapy	158	0.9	5.6

AFP — alpha fetoprotein; B-HCG — beta human chorionic gonadotropin; EP — etoposide and cisplatin; LDH — lactate dehydrogenase; TIP — paclitaxel, ifosfamide, cisplatin

enlarged to 21 × 15 mm, the left paraaortic lymph node below the renal vessels was enlarged to 27 × 23 × 40 mm, the right external iliac lymph node was enlarged to 17 × 13 mm, and the left external iliac lymph node was enlarged to 15 × 13 mm. Marker levels before and during chemotherapy are shown in Table 1. The patient was diagnosed with IIIA (pT2cN2M1aS1) non-seminoma categorized as a favorable-risk group according to the International Germ Cell Cancer Collaborative Group (IGCCCG). According to the European Society for Medical Oncology (ESMO) guidelines, patients should receive three cycles of bleomycin, etoposide, and cisplatin (BEP) or four cycles of etoposide and cisplatin (EP) chemotherapy. Due to ESRD, our patient was considered to be at very high risk of any complications of the chemotherapy, especially due to pnemotoxicity of bleomycin. The first cycle of chemotherapy according to the EP regimen was administered at doses reduced by 50% (cisplatin 10 mg/m^2 and etoposide 50 mg/m^2) only on days 1, 3, and 5. He was maintained with HD three times a week, on the days of chemotherapy. Hemodialysis was started within 1 hour after completion of cisplatin administration and was performed according to the standard protocol (FX10 Dialyzer, with 380 mL/min blood flow, dialysate flow 50 mL/min). Unfortunately, after the first cycle, the patient was diagnosed with a central venous catheter-related bloodstream infection, and the second cycle was substantially delayed. Even so, because of the radical intent of the treatment, doses of cytotoxic drugs were escalated to 75% from cycle 3 on days 1, 3, and 5 and to 100% on days 1, 3, and 5 in cycle 4, and the additional 5th cycle according to the PE protocol (cisplatin 20 mg/m^2 and etoposide 100 mg/m^2 on days 1, 3, and 5) was administered. On the control CT, we observed partial response to the treatment — the left paraaortic lymph nodes below the renal vessels had a size of 17 × 13 mm, and other lymph nodes were not enlarged. The patient was scheduled for an ambulatory visit to consider further treatment but did not show up. When he contacted our center five months after the end of the last PE cycle, we saw a rise in the alpha fetoprotein (AFP) level and progression in lymph node size on the CT. The patient was scheduled for second-line chemotherapy using the paclitaxel, ifosfamide, cisplatin (TIP) protocol. The 1st cycle was administered in modified doses — paclitaxel 175 mg/m^2 on day 1, ifosfamide 900 mg/m^2 (75%), and cisplatin 20 mg/m^2 were administered on days 1, 3, and 5. Chemotherapy was followed, as previously, with standard 4-hour HD. In the second and third cycles, doses of ifosfamide were escalated to 1200 mg/m^2. After the third cycle, anemia G3 according to Common Terminology Criteria for Adverse Events (CTCAE) was observed, which was managed with blood transfusion. Because of hematological toxicity and bacterial conjunctivitis, the 4th cycle was omitted, and control CT was performed that showed a remaining enlarged right external iliac lymph node with a short axis dimension of 14 mm. The patient underwent retroperitoneal lymph node dissection 8 weeks after the 3rd TIP course. In the histopathology examination non-seminomatous germ cell tumor containing 20% necrosis was observed. On the control CT performed 3 months later after surgery, there were no visible metastatic lesions. The patient remains under close observation and has been free of disease for 6 months.

Patient 2

A 39-year-old man with stage 4 chronic kidney disease of a transplanted kidney according to the Kidney Disease Improving Global Outcomes (KIDGO), caused by vesicoureteral reflux diagnosed in childhood, with a history of peritoneal dialysis and kidney transplantation performed in 2005 was admitted to the Department of Oncology due to the diagnosis of left testicular cancer. In March 2022, the patient underwent a left-sided orchidectomy. The histopathology report described seminoma, beta-hCG positive, with angioinvasion and neuroinvasion. On the CT scan, we observed an extensive (152 × 127 × 167 mm)

Table 2. Changes in neoplastic marker levels before and during chemotherapy in patient 2

Time Point	LDH 135–225 [U/L]	*B*-HCG Male < 2.0 [mIU/mL]	AFP < 7 [ng/mL]
Before 1st cycle of EP	944	0.63	1.2
Before 2nd cycle of EP	438	< 0.5	5.8
Before 3rd cycle of EP	244	< 0.5	3.3
Before 4th cycle of EP	188	< 0.5	5.5
After chemotherapy	137	< 0.5	3.1

AFP — alpha fetoprotein; B-HCG — beta human chorionic gonadotropin; EP — etoposide and cisplatin; LDH — lactate dehydrogenase

nodular mass in the retroperitoneal space, enlarged retroperitoneal lymph nodes up to 24 mm, and an enlarged lymph node of 19 × 12 mm in the hilum of the liver. Marker levels before chemotherapy are shown in Table 2. The patient was diagnosed with IIIC (pT3cN3M1b S2) seminoma categorized as an intermediate-risk group according to IGCCCG. According to the ESMO guidelines, 4 cycles of BEP are the preferred chemotherapy regimen. Due to stage 4 CKD (eGFR = 15 mL/min/1.73m^2), cisplatin and bleomycin were contraindicated, etoposide and ifosfamide were relatively contraindicated. Carboplatin could be used with caution instead of cisplatin, but such an approach would not be equally effective. After consultation within the nephron-oncology team, we decided to start the patient on HD after placement of a tunneled cuffed catheter to deliver the most appropriate renal replacement therapy together with anticancer treatment. At the same time, immunosuppressive therapy was withdrawn, leaving only 5 mg of prednisone. The patient received 4 courses of chemotherapy according to the EP scheme, with the following doses: cisplatin 30 mg/m^2 and etoposide 100 mg/m^2, respectively, on days 1, 3, and 5. Bleomycin was omitted due to the high risk of pulmonary complications. Hemodialysis was performed on the days of chemotherapy, starting 1 hour after completion of cisplatin administration. After the second course of EP chemotherapy, the patient reported visual field disturbances in the right eye. For this reason, head CT and magnetic resonance imaging (MRI) were performed but did not reveal any potential cause of his symptoms i.e. metastases or vascular events. The patient was consulted with an ophthalmologist who diagnosed, in the right eye, papilledema with still relatively good visual acuity. The patient was treated with 1g intravenous methylprednisolone for 5 days with a good response. On the control CT after chemotherapy completion, a nodular mass in the retroperitoneal space 50 × 27 × 87 mm was observed. During 10 months of follow-up, two control 18F-FDG PET-CT scans were performed that revealed stable disease without high 18F-FDG uptake. Because of the high risk of complications after the retroperitoneal dissection in this patient, further observation was scheduled.

Discussion

The number of patients requiring HD and diagnosed with various types of cancer is constantly growing. In two studies looking at cancer treatment in patients undergoing HD, only 28% and 41% of HD patients diagnosed with cancer received chemotherapy, and the authors concluded that therapy is often withheld, prematurely stopped or insufficiently dosed [7, 8]. Standard treatment for patients with metastatic germ cell tumors is 3–4 cycles of the BEP chemotherapy regimen according to the risk group. Patients with CKD or ESRD in need of HD pose a great challenge in qualification for chemotherapy because of the lack of specific guidelines for this rare clinical scenario. The BEP regimen is fairly toxic with a high risk of neutropenia, nausea and vomiting, nephrotoxicity, pneumotoxicity, and peripheral neuropathy [9]. The main concern during this treatment in HD patients is, on the one hand, a higher risk for those toxicities (except renal toxicity which is no longer a problem) and the possibility of lower efficacy due to premature drug elimination during dialysis on the other. Hence, one problem is dose adjustment, and the other is dialysis timing.

At our institution, we have decided to omit the bleomycin due to the high risk of toxicity, but it is disputable if the second patient who was categorized as having intermediate-risk seminoma should rather receive 4 cycles of etoposide, ifosfamide and cisplatin (VIP) or TIP instead of 4 cycles of EP as such management can be seen as undertreatment. Another problem was an appropriate dosing. At our institution, we performed a literature search, and our approach has been based on cases reporting successful treatment in similar settings [9–12]. Because of the lack of high-quality evidence, we decided to start with caution with reduced dosage, and even so, the first cycle in the first patient was complicated by a life-threatening bloodstream infection. That is why we decided to administer cytotoxic drugs only on HD days but a different approach with daily chemotherapy and daily HD on days 1–5 for every cycle could be considered to deliver more appropriate doses. Our second patient received a full dose of cisplatin (90 mg/m^2 per every cycle) with fairly good tolerance, but we observed transient

ocular complications that could be attributed to cisplatin toxicity.

Another problem is the timing of hemodialysis. Cisplatin is eliminated through the kidneys in about 90%. Its plasma concentration decays with a typical biphasic pattern characterized by a rapid initial clearance (half-life < 1 hour) followed by a slower drop (half-life between 58 and 73 hours). In addition, cisplatin rapidly forms a strong and irreversible bond with plasma proteins [4]. Consequently, ESRD patients are exposed to potential dose-dependent side effects so hemodialysis should be started after cisplatin administration [10–12] although other authors recommend administration of reduced cisplatin dose after HD as free cisplatin is dialyzable and the loss of free cisplatin during HD could not be compensated by bound cisplatin [13]. A summary of the Associazione Italiana di Oncologia Medica and the Società Italiana di Nefrologia recommendation published in 2017 [4] includes dose adjustment and timing of HD after chemotherapy administration. It also includes possible regimens for HD patients with germ cell tumors, i.e. cisplatin (14–20 mg/m^2) and etoposide (50–100 mg/m^2) on days 1-4 with daily HD or only on days 2 and 4; or carboplatin (100 mg/m^2) on day 1 and etoposide (50–100 mg/m^2) on days 1–4, combined with HD on days 2 and 4. Data on the optimal use of chemotherapeutic agents in the HD population are sparse and mainly derived from case reports or small case series; data on kidney transplant recipients are even more limited. Therefore, treatment by a multidisciplinary team of oncologists, nephrologists, and transplant physicians in a center with round-the-clock access to HD is essential.

Conclusions

In conclusion, guidelines on chemotherapy dosing and timing in HD patients are still lacking, but data from clinical cases series, including our two patients, suggest that chemotherapy in HD patients is feasible and should be administered in possibly maximal doses. Close cooperation between oncologists, nephrologists, or even a multidisciplinary team including transplant physicians is needed to maximize the effectiveness of treatment.

Article Information and Declarations

Ethics statement

Verbal informed consent was obtained from the patients for their anonymized information to be published in this article.

Author contributions

M.T.: conceptualization, methodology, writing — original draft preparation; L.R.: methodology, writing — original draft preparation, visualization; J.M.: conceptualization, writing — review and editing; R.S.: conceptualization, writing — review and editing

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Conflict of interest

All authors declare no conflict of interest

Supplementary material

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