CASE REPORT

A case of cisplatin-refractory advanced pure seminoma showing complete remission after treatment with high-dose carboplatin plus etoposide as fourth-line salvage chemotherapy

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Abstract We report the case of a patient who achieved complete remission (CR) of cisplatin-refractory metastatic pure seminoma after treatment with high-dose carboplatin and etoposide (CE) with peripheral blood stem cell transplantation as fourth-line chemotherapy. A 38-year-old man was diagnosed with advanced pure seminoma (pT3N3M1aS3). In the international germ cell consensus classification, his prognosis was classified as intermediate. He was treated with high-dose CE as fourth-line chemotherapy after treatment with BEP, VeIP, and TIN. After two cycles of high-dose CE, the concentrations of T-HCG and other tumor markers showed normal levels. A CT scan and PET-CT showed that the lymph node swelling had disappeared and there was no uptake. The CR has continued for 27 months after the treatment. High-dose CE might be less toxic and have a better prognostic outcome than other treatments as salvage chemotherapy for patients with cisplatin-refractory advanced testicular cancer.

Keywords Relapsed pure seminoma · High-dose carboplatin plus etoposide · Fourth-line salvage chemotherapy

Introduction

Metastatic testicular cancers are cured by cisplatin-based chemotherapy in 70% or more of cases [1, 2]. However, some patients who relapse after initial chemotherapy need salvage chemotherapy. For this purpose, treatment using high-dose carboplatin plus etoposide (CE) with peripheral blood stem cell transplantation was established by Einhorn et al. in the hematology/oncology division of Indiana University [3]. In their report, 184 patients whose cancer had progressed after one or more regimens of cisplatin-based chemotherapy received CE. After this, 63% of the 184 patients were continuously disease-free during a median follow-up of 48 months. Agarwala et al. reported that, in patients with relapsed pure seminoma, CE resulted in high rates of complete remission (CR) [4]. On the basis of these results, CE is recommended as a second-line treatment for patients having metastatic testicular cancers by the National Comprehensive Cancer Network [5]. However, the rate of CR was inferior to that of CE as third-line or subsequent chemotherapy compared to second-line chemotherapy [3, 4]. Here, we report the case of a patient who achieved CR after treatment with CE with peripheral blood stem cell transplantation after third-line chemotherapy for relapsed metastatic pure seminoma.

Case report

A 38-year-old man had noted swelling of his right testis from 2012. He came to our department for treatment of the swelling in December 2013. He had no personal or family history of malignant diseases. Contrast-enhanced computed tomography (CT) showed a 12 cm × 9 cm right testis tumor, paraaortic lymphadenopathy (Fig. 1a), right

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Fig. 1 Computed tomography (CT) and positron emission tomography–computed tomography (PET–CT). Paraaortic lymphadenopathy swelling at the initial examination (**a**), persisted after three lines of chemotherapy (**b**), residual paraaortic lymphadenopathy on CT and

uptake on PET–CT after one course of high-dose carboplatin plus etoposide (**c–d**), residual uptake on PET–CT after radiation therapy (**e**), no uptake on PET–CT after treatment with two courses of high-dose CE (**f**), no residual lymphadenopathy on the latest CT (**g**)

inguinal lymphadenopathy and left pelvic lymphadenopathy. The concentrations of total human chorionic gonadotropin (T-HCG), lactate dehydrogenase (LDH), and alpha-

fetoprotein (AFP) were 157.8 mIU/ml, 3287 U/l, and 11.4 ng/ml, respectively. He was referred to our department and underwent right radical orchiectomy. The

pathological diagnosis was confirmed to be pure seminoma, pT3. We finally diagnosed advanced pure seminoma, pT3N3M1aS3. In the international germ cell consensus classification, his prognosis was classified as intermediate.

Although we treated him with bleomycin, etoposide, cisplatin (BEP) followed by vinblastine, ifosfamide, cisplatin (VeIP), and paclitaxel, ifosfamide, nedaplatin (TIN), T-HCG was 88.3 mIU/ml and paraaortic lymphadenopathy swelling persisted after these three lines of chemotherapy (Figs. 1b, 2). At that time, the Eastern Cooperative Oncology Group (ECOG) performance status score was 0. The white blood cell count was 3600/L and the concentrations of hemoglobin, serum iron, and ferritin were 11.8 g/dL, 36 µg/dL, and 403.7 ng/mL, respectively. Other blood cell counts and biochemical parameters were within normal ranges. We therefore decided to treat him with high-dose CE after TIN. The high-dose CE consisted of 700 mg of carboplatin per square meter of body-surface area and 750 mg of etoposide per square meter for 3 consecutive days, and an infusion of autologous peripheral blood hematopoietic stem cells. During the high-dose CE treatment, palonosetron hydrochloride, dexamethasone, metoclopramide, and prochlorperazine were administered as supportive drugs. In August 2014, high-dose CE and autologous peripheral blood stem cell transplantation (PBSCT) were performed by the Department of Medical Oncology in our university. After one cycle of high-dose CE treatment, the concentration of T-HCG was normal (>1 mIU/ml). However, a CT scan showed residual paraaortic lymphadenopathy with uptake on positron emission tomography–computed tomography (PET–CT) (Fig. 1c, d). We then decided to conduct radiation therapy for the residual paraaortic lymphadenopathy (total 36 gray, 20

fractions). After the radiation therapy, a CT scan showed residual paraaortic lymphadenopathy with uptake on PET–CT (Fig. 1e). Therefore, one additional course of high-dose CE was given in November 2014. As defined by the Common Terminology Criteria for Adverse Events v4.0, the toxic effects with two courses of high-dose CE were neutropenia (Grade 4), thrombopenia (Grade 4), anemia (Grade 2), and fever (Grade 1). Although he needed treatment for the toxic effects with granulocyte-colony stimulating factor, an antibacterial drug and platelet transfusion during high-dose CE, he could complete the two courses of high-dose CE without residual symptoms of the toxic effects.

After the 2 cycles of high-dose CE, the concentrations of T-HCG and other tumor markers were within the normal ranges. A CT scan and PET–CT showed that the lymph node swelling had disappeared and there was no uptake (Fig. 1f). In March 2017, the patient was still free from new metastatic lesions or progression two years after the treatment, and blood cell counts and biochemical parameters were within normal ranges (Fig. 1g).

Discussion

50–70% of patients with metastatic testicular tumors treated with cisplatin-based chemotherapy and second-line chemotherapy achieve CR [1, 2]. However, this does not occur for some patients treated with cisplatin-based chemotherapy and VeIP. Nakamura et al. reported the results of salvage chemotherapy for advanced testicular cancer. Of 253 patients, 111 needed third-or-later-line chemotherapy. The five-year overall survival rates stratified by chemotherapy line were 45.1% in the fourth-line

Fig. 2 The concentration of total human chorionic gonadotropin (T-HCG) before and after high-dose carboplatin plus etoposide (CE). EP (bleomycin, etoposide, cisplatin), VeIP (vinblastine, ifosfamide, cisplatin), and TIN (paclitaxel, ifosfamide, nedaplatin), peripheral blood hematopoietic stem cell harvest (PBSCH)

and 58.9% in the fifth- or later-line. There were significantly different prognoses for patients [6], with the prognosis being poorer for fourth-or-later-line therapies than for first- to third-line therapies.

High-dose CE was established by Einhorn et al. in the hematology/oncology division of Indiana University. Of all patients with metastatic testicular cancer that had progressed after cisplatin-based chemotherapy, 63% achieved disease-free status at 48 weeks after high-dose CE treatment [3]. On the basis of these results, the National Comprehensive Cancer Network guidelines recommend high-dose CE for patients who cannot achieve CR after conventional-dose chemotherapy [5]. Agarwala et al. reported on 48 patients with relapsed, pure seminoma who were treated with high-dose CE. Twenty-four patients underwent this treatment as third- or fourth-line chemotherapy. Of these, 67% achieved CR, and 64% were alive after a median follow-up of 61.3 months [4]. However, in this study, only 2 of the 24 patients were treated with high-dose CE as fourth-line chemotherapy and the survivals of these two patients were not reported. Notably, our patient had CR following two courses of CE as fourth-line chemotherapy. Furthermore, the complete response was still maintained 2 years after this treatment.

From the 1980s to the early 1990s, high-dose chemotherapy that consisted of ifosfamide, carboplatin, etoposide (ICE) and etoposide, carboplatin, cyclophosphamide was tried to treat the advanced testicular cancer with cisplatin resistance. However, these regimens had CR rates of 13–40%, with treatment-related death rates of 3–13% [2, 7]. In Japan, Miki et al. investigated the long-term results of high-dose ICE in patients with advanced testicular cancer. In their study, 25 patients whose tumor markers were still elevated following three cycles of induction BEP therapy were included. No patients achieved CR after one cycle of high-dose ICE. Nine patients achieved PR. Marker-negative PR was achieved in only three patients. All patients experienced WHO grades 2–4 thrombocytopenia and all but one had grade 4 neutropenia. One (4%) patient died of rhabdomyolysis due to the high-dose ICE [8]. One randomized trial compared conventional cisplatin-based salvage to high-dose intensification chemotherapy. The death rate due to toxicity was 7% for high-dose chemotherapy and there were no significant improvements with such treatment in either the 3-year event-free survival or overall survival. There were four (2.9%) toxic deaths and 67 cases of febrile neutropenia among 136 patients treated with conventional cisplatin-based salvage chemotherapy [9]. Some reports analyzed the differences of the outcomes in patients with advanced metastatic seminoma treated with either single-agent carboplatin and those treated with cisplatin-based combination therapy as first-line chemotherapy [10, 11]. Bakemeyer

et al. reported prospective randomized trials comparing single-agent carboplatin at a dose of 400 mg/m² with the combination of etoposide and cisplatin (EP) or etoposide, ifosfamide, and cisplatin (VIP) for advanced metastatic seminoma. Hematological as well as non-hematological side effects were significantly more frequent with EP or VIP than in the carboplatin-treated patients. But patients treated with single-agent carboplatin had inferior 5-year overall survival (89% and 94%; $p = 0.09$) and progression-free survival rates (72 and 92%; $p < 0.0001$) compared with patients receiving EP or VIP [11]. These results showed that standard-dose carboplatin was inferior to cisplatin-based combination therapy. However, Einhorn et al. reported three (2.2%) drug-related deaths and three (2.2%) cases of acute leukemia among 184 patients treated with high-dose CE. There were 57 episodes of neutropenic fever in 112 cycles of high-dose CE. There were grade 3 or higher hematologic, renal, hepatic, neurogenic, and pulmonary toxic effects in 3, 4, 6, 9, and 3 patients, respectively [3, 9]. This indicated that high-dose CE might be less toxic and have a better prognostic outcome than other high-dose regimens and conventional cisplatin-based salvage chemotherapy. In our patient, neutropenia (Grade 4), thrombopenia (Grade 4), anemia (Grade 2), and fever (Grade 1) were observed during the treatment with high-dose CE. However, he could complete two courses of this treatment safely without residual symptoms of toxic effects. At present, though, there is limited evidence regarding the effect of high-dose CE for testicular tumors, so further trials and reports are needed.

Herein we reported a patient with relapsed pure seminoma who achieved long-term CR following high-dose CE treatment as fourth-line chemotherapy and the CR has continued for 27 months after the treatment.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

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