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Case Report

A Patient with Refractory Metastatic Germ Cell Tumor Successful Salvaged after Treatment with Paclitaxel, Ifosfamide, and High-Dose 5-Fluorouracil Infusional Therapy

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Abstract

We report a case of a 24-year-old male with a metastatic extragonadal germ cell tumor (GCT) which was refractory to conventional chemotherapy and progressed after high-dose chemotherapy. The addition of a 24-h infusion of high-dose 5-fluorouracil (5-FU) with leucovorin regimen to a salvage regimen of paclitaxel and ifosfamide provided a durable clinical response. We also discuss the potential of repurposing 5-FU for the treatment of a refractory GCT.

Keywords: 5-fluorouracil, germ cell tumor, high-dose chemotherapy, platinum-refractory

Introduction

The prognosis of a metastatic germ cell tumor (GCT) refractory to conventional chemotherapy and salvage high-dose chemotherapy is poor,[1] and there is currently no standard treatment for these patients.[2] Conventional 5-fluorouracil (5-FU) is rarely used in the treatment of a metastatic GCT. However, in recent decades, the modulation of 5-FU infusion by high-dose continuous infusion has led to better efficacy and broader indications.[3-8] We report the case of a patient who failed platinum-based conventional chemotherapy and experienced disease progression after high-dose chemotherapy with an autologous stem cell transplantation. The level of the tumor marker, beta-human chorionic gonadotropin (beta-hCG) (originally >120,000 mIU/mL), normalized after the addition of a 24-h infusion of high-dose 5-FU and leucovorin (HDFL) to a salvage regimen of paclitaxel and ifosfamide. We also discuss the potential efficacy of HDFL for refractory GCTs.

Case Report

A 24-year-old male complained of intermittent dyspnea for 1 month, and he was referred to our hospital in February

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2017. Multiple pulmonary nodules were detected. A physical examination was unremarkable. Laboratory examinations showed an elevated beta-hCG level of >120,000 mIU/mL (reference range: 0–5 mIU/mL) and an elevated level of lactate dehydrogenase of 930 U/L (reference range: 100–460 U/L). The initial white blood cell count, hemoglobin, serum creatinine, and alfa-fetoprotein were 14.29 K/μL, 12.5 g/dL, 0.7 mg/dL, and 10.88 ng/mL (reference range: <20 ng/mL), respectively. Scrotal ultrasonography revealed no abnormal testicular mass lesions. Contrast-enhanced computerized tomography (CT) showed multiple nodules in the bilateral lungs and hypodense lesions over the liver and para-aortic area [Figure 1a]. An ultrasound-guided liver biopsy disclosed metastatic carcinoma with multinucleated syncytiotrophoblast-like tumor cells. Immunohistochemistry staining revealed that the tumor was reactive to HSD3B1 and CD30 and negative to glypican-3 and c-kit. He was diagnosed with extragonadal GCT, choriocarcinoma, with lung, liver, retroperitoneal, and bone metastases.

He received the first cycle of etoposide (100 mg/m^2 from day 1 to day 5) and cisplatin (20 mg/m^2 from day 1 to day 5) (EP as a tri-weekly protocol) in March 2017. After the first course of chemotherapy, dyspnea worsened with respiratory failure, and he received endotracheal intubation. A superimposed pulmonary infection was suspected. The beta-hCG level increased to a peak of 546,712 mIU/mL in April 2017 [Figure 2]. After recovering from the episode, he received the EP protocol and his condition gradually improved. A CT scan disclosed a marked reduction in the size of the lung metastases and the left para-aortic mass; however, the liver nodules increased in size [Figure 1b]. The serum beta-hCG level plateaued at around 160 mIU/ml. Since the first-line treatment failed to achieve complete remission, he was scheduled for high-dose chemotherapy and peripheral blood stem cell salvage. He received two additional cycles of the EP protocol while waiting to be admitted to the transplantation ward. The beta-hCG level increased to 280 mIU/mL and the serum creatinine level slightly increased to 1.1 mg/dL after six cycles of the EP protocol.

He underwent one cycle of high-dose chemotherapy with carboplatin (700 mg/m^2) and etoposide (750 mg/m^2) for 3 days, followed by autologous peripheral blood stem cell infusion in September 2017. The stem cells were collected by granulocyte-colony-stimulating factor (G-CSF) mobilization. Raised levels of beta-hCG (16,502 mIU/mL) and serum creatinine (1.4 mg/dL) were recorded after high-dose chemotherapy. He also complained of mild high-frequency hearing impairment. Due to concerns of the nephrotoxicity and ototoxicity of platinum, he received salvage chemotherapy of paclitaxel (250 mg/m^2, 3-h infusion on day 1) combined with ifosfamide (1.5 g/m^2 from day 2 to day 5) tri-weekly as the TI protocol from October 2017. He needed G-SCF supplement in each TI protocol because of neutropenia. After three cycles of the TI protocol, the beta-hCG level fluctuated at around 100 mIU/mL, but never became normal.

He was scheduled to receive the fourth cycle of the TI protocol in January 2018. However, as the beta-hCG level increased to 156 mIU/mL, we decided to add a 24-h continuous infusion of high-dose 5-FU (2000 mg/m^2 on day 1 and day 8) with leucovorin (200 mg/m^2) (HDFL) to the original TI protocol. After the addition of HDFL, the beta-hCG level dropped to 2.68 mIU/mL, and then normalized after four cycles of TI-HDFL. No additional toxicities were noted after adding HDFL. The follow-up CT scan in April 2018 showed smaller liver lesions and para-aortic masses [Figure 1c]. He has received maintenance HDFL since April 2018. The tumor

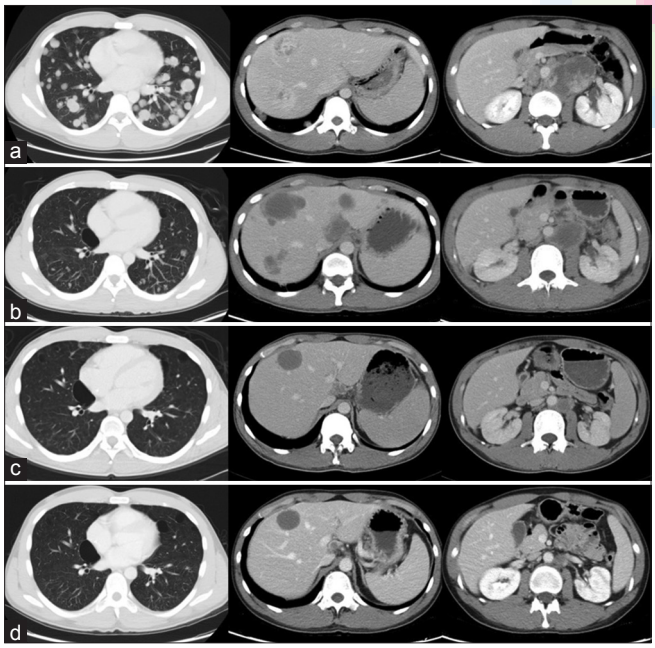

Figure 1: Computed tomography scans showed (a) multiple pulmonary nodules, hepatic nodules, and para-aortic masses in February, 2017. (b) Larger hepatic nodules, lesser pulmonary nodules, and smaller para-aortic masses after four cycles of EP. (c) Pulmonary nodules subsided, and cystic hepatic lesions remained after four cycles of TI- high-dose 5-fluorouracil and leucovorin. (d) Stationary cystic hepatic nodules and para-aortic masses after four cycles of maintenance high-dose 5-fluorouracil and leucovorin

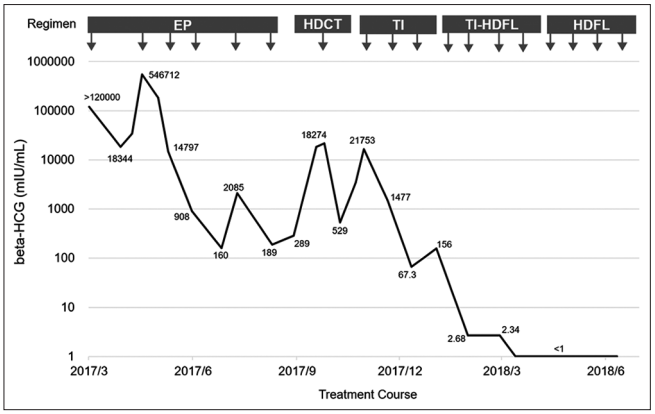

Figure 2: Graphic illustration of the time course of beta-human chorionic gonadotropin level in relation to the treatment

markers have remained normal, although some low-density cyst-like hepatic nodules have remained [Figure 1d].

Discussion

5-FU has never been studied in a systematic fashion for metastatic GCTs. Lapis *et al*. reported that a bolus of 5-FU led to a 47% reduction in tumor growth of GCTs in a mice model.[9] Some retrospective studies have reported that tumor cells expressing high levels of thymidine phosphorylase were more sensitive to 5-FU.[10,11] The overexpression of thymidine phosphorylase has also been detected in GCT compared with normal testis tissue.[12] In addition, a few anecdotal reports in the 1960s revealed a modest activity of bolus 5-FU to GCT, in which three of the ten patients obtained a partial response, and the cumulative response rate of 5-FU monotherapy was 30%.[13-15]

A phase I trial of bi-weekly flavopiridol (a pan-cyclin-dependent kinase inhibitor) plus FOLFOX (5-FU 1800 mg/m^2 over 48 h, oxaliplatin 85 mg/m^2 and leucovorin 400 mg/m^2) showed clinical activity in platinum-refractory GCTs. Three of nine (33%) evaluable patients showed a partial response on imaging[16] compared with a 19% response rate to oxaliplatin monotherapy.[17] The increased response rate after flavopiridol therapy led to a phase II trial conducted to evaluate the efficacy of flavopiridol plus oxaliplatin or FOLFOX and the necessity of including 5-FU/LV. Importantly, there were no responders in the arm of flavopiridol combined with oxaliplatin, whereas a 50% response rate was found in flavopiridol plus FOLFOX arm.[18] HDFL may increase the response rate in platinum-refractory GCTs. However, whether increased survival benefits or synergic effects can be achieved with HDFL is not clear yet.

The paclitaxel, ifosfamide, and cisplatin (TIP) regimen is a salvage chemotherapy regimen for GCTs. In our case, the patient received paclitaxel and ifosfamide without cisplatin or carboplatin due to concerns of nephrotoxicity and myelosuppression. However, there was an increase in serum beta-hCG level from 67.4 mIU/mL to 156 mIU/mL on day 22 of the third cycle of paclitaxel and ifosfamide (TI), probably due to tumor progression since the median time to peak beta-hCG level was 5 days (range of 1–12 days). Serum beta-hCG usually decreases if the regimen is responsive.[19,20] HDFL has already been used for many other cancer types, and it has been associated with less myelosuppression and nephrotoxicity.[3-8] In our patient, the addition of HDFL to the TI regimen, which appeared effective but failed to eradicate the tumors, resulted in a dramatic normalization of the beta-hCG level.

We hypothesize that some residual tumors which are refractory to conventional and high-dose chemotherapies might be sensitive to HDFL. Although the level of beta-hCG was normalized in our patient, some low-density cystic hepatic lesions remained. The nature of these tumors was not clear. Several studies have reported that nearly 50% of residual masses contained necrotic tissue after successful chemotherapy, 30%–40% contained mature teratoma, and only 15%–20% contained residual GCT.[21,22] A single-center study reported that progression-free survival and overall survival were similar comparing surgery to observation after achieving a serological complete remission.[23] Surgical resection of residual hepatic metastases may be associated with a complication rate of 27%–30%.[24,25] Therefore, considering the cost–benefit balance, we decided to perform conservative treatment with regular follow-up assessments of CT scans and tumor markers.

HDFL-containing protocols have already been expanded to cover many other types of gastrointestinal and nongastrointestinal cancers. Based on our case, we suggest that a 24-h infusion of HDFL combined with paclitaxel and ifosfamide for platinum-refractory GCT s can provide a durable clinical response. HDFL deserves to be further investigated as a component of salvage treatment for refractory GCTs.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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