**Novel therapies in platinum-refractory metastatic germ cell tumor: a case report with a focus on a PD-1 inhibitor**

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**Abstract**

Testicular germ cell tumor (GCT) is the most common malignancy in young males between the ages of 15 to 35 years. Although the overall cure rate of GCTs approaches 95%, almost 25% of patients with distant metastases die from the cancer. Active investigations on novel treatment options for platinum-refractory GCTs include immunotherapies such as program-death 1 (PD-1)/program death-ligand 1 (PD-L1) inhibitors. In this case, we report a patient with metastatic GCTs who was treated with pembrolizumab, a PD-L1 inhibitor, in a phase II study after failing several lines of chemotherapy. We highlighted the rationale for the use of PD-L1 inhibitor in this population.

**Introduction**

Testicular germ cell tumor (GCT) is the most common malignancy in males between the ages of 15 and 35 years. Approximately 12% of patients with testicular GCTs present with distant metastases, and the 5-year survival rate in these patients is approximately 75%. In recent years, studies have demonstrated the efficacy of immunotherapy that targets the program-death 1 (PD-1)/program death-ligand 1 (PD-L1) pathways in various cancer types. Antitumor activity of PD-L1 inhibitors correlates with PD-L1 expression. In testicular GCTs, Cierna et al. showed that testicular cancer cells expressed higher levels of PD-L1 than normal testicular tissue. Therefore, the use of PD-1 and PD-L1 inhibitors in testicular GCTs is an active area of investigation. We report a patient with metastatic SCT of choriocarcinoma subtype, who was refractory to several lines of platinum-based chemotherapy and eventually underwent immunotherapy with pembrolizumab, a PD-1 inhibitor.

**Case Report**

A healthy 27-year-old male initially presented to his primary care physician with left-sided abdominal pain. Few days later, he was admitted admitted to the hospital with new onset headache and left-sided tingling and numbness. His work-up included an abdominal ultrasound and computed tomography (CT) scans of the chest, abdomen and pelvis that demonstrated a 7.8 cm left pelvic mass, bilateral pulmonary lesions, and prominent mediastinal and hilar lymphadenopathy. A testicular ultrasound revealed a 0.8 cm hypoechoic lesion in the inferior left testicle, and magnetic resonance imaging (MRI) of his brain and spine revealed two hemorrhagic masses located in the right parietal and left occipital lobes and a non-hemorrhagic enhancing lesion in the right occipital lobe. A biopsy of the left pelvic mass showed choriocarcinoma, and his levels of beta-human chorionic gonadotropin (b-HCG), alpha-fetoprotein (AFP) and lactate dehydrogenase (LDH) at the time of diagnosis were 462,748 mIU/mL, <1 IU/mL, and 1108 U/L, respectively (see Table 1 for his tumor marker levels during treatment). Initially, he received stereotactic radiation therapy to the brain lesions and subsequently was started on four cycles of systemic chemotherapy with cisplatin, etoposide, and ifosfamide (VIP), standard chemotherapy for poor-risk GCT. At completion of VIP, his b-HCG decreased to 5 mIU/mL and his AFP and LDH levels normalized. Subsequently, he underwent left radical orchiectomy and retroperitoneal lymph node dissection (RPLND); pathologic showed no residual tumor in the retroperitoneal nodes. One month after RPLND, his b-HCG increased to 4143 mIU/mL and LDH to 350 U/L. Repeat imaging studies showed persistent bilateral pulmonary nodules.

Because of the development of platinum-refractory disease, he underwent two courses of high-dose chemotherapy with carboplatin and etoposide followed by autologous peripheral-blood hematopoietic stem cell transplant (PBSCT). He initially responded with declining levels of b-HCG and LDH, but his b-HCG began to rise one month after completion of autologous PBSCT. At that time, his CT chest documented new pulmonary nodules. For third-line treatment, he was started on gemcitabine and oxaliplatin, but his disease continued to progress. He was then enrolled on a phase II clinical trial that evaluated the use of pembrolizumab 200 mg IV every 3 weeks for patients with platinum-refractory GCTs. He received one cycle of pembrolizumab, but three weeks later his b-HCG rose to 45,397 mIU/L. Given the rapid progression of his disease, treatment with pembrolizumab was terminated. He was subsequently given two cycles of paclitaxel, which were complicated by neutropenic fever requiring hospitalization, before he elected to focus on comfort care. He passed away approximately a month later.

**Discussion**

The International Germ Cell Cancer Collaborative Group (IGCCCG) risk classification system was created in 1997 to stratify patients with metastatic testicular cancer into favorable-risk (91% 5-year survival rate), intermediate-risk (79% 5-year survival rate), and poor-risk (48% 5-year survival rate) groups based on the primary tumor site (testis versus mediastinum), metastatic sites, and absolute serum tumor marker levels. Patients with poor-risk metastatic non-seminoma are usually treated with three-drug regimens consisting of bleomycin, etoposide and cisplatin (BEP) or VIP, as in our patient. In relapsed GCTs, the role of salvage therapies in platinum-refractory disease is an active area of investigation. pembrolizumab, a PD-1 inhibitor, in a phase II study after failing several lines of chemotherapy. We highlighted the rationale for the use of PD-L1 inhibitor in this population.

**Key words:** Metastatic germ cell tumor; immunotherapy; pembrolizumab; PD-L1 expression.

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chemotherapy with standard-dose versus high-dose chemotherapy (HDCT) is not clearly defined. Results from two prospective trials were mixed. A recent retrospective study using a large international database showed superior 2-year progression-free survival (PFS) (49.6% vs. 27.8%; P<0.001) and 5-year overall survival (OS) (53.2% vs. 40.8%; P<0.001) for the high-dose group compared to the standard-dose group, respectively (Table 2). However, these results need to be confirmed in a randomized trial. Two HDCT regimens are commonly used. At Indiana University, HDCT consists of high-dose carboplatin and etoposide followed by PBSCT for two courses. Disease-free survivals among patients who received this treatment as second- and third-line regimens were 70% and 45%, respectively. Patients in the high-risk group had a 2-year PFS of 45%. At Memorial Sloan Kettering Cancer Center (MSKCC), investigators treat with ifosfamide and paclitaxel followed by three cycles of high-dose carboplatin and etoposide with PBSCT. The 5-year OS for this regimen was reported to be 52%. Currently, no curative treatment options are available for patients with relapsed/refractory GCTs following HDCT. In selected cases with limited disease burden, salvage surgery may be considered, though this is rarely used. Other chemotherapy regimens in use include gemcitabine and oxaliplatin, or paclitaxel as a single agent or in combination therapies, and responses range between 21 and 38%. Given the relatively low response rates of these salvage therapies, investigations are ongoing to explore novel therapies, including immunotherapy that targets the PD-1/PD-L1 pathways.

Tumor cells can down-regulate immune responses by inhibiting T-cells via the PD-1 and PD-L1 interactions. Pembrolizumab is an IgG4 humanized monoclonal antibody that targets the PD-1 receptors present on T cells, thereby restoring the ability of activated T-cells to exert their immune response. In other cancer subtypes such as melanoma and non-small cell lung carcinoma, pembrolizumab has been shown to be effective, with better responses seen in tumors with higher levels of PD-L1 expression. Fankhauser et al. showed that testicular GCTs expressed higher levels of PD-L1 than normal testicular tissues (73% of all seminomas and 64% of all non-seminomas, compared to no expression in normal testicular tissues). This finding was consistent with a study by Cierna et al., who reported that PD-L1 expression was detected in 76% of seminomas and 99% of nonseminomas. Additionally, patients with more advanced disease and poor prognostic features such as three or more metastatic sites, increased serum tumor markers, and/or non-pulmonary visceral metastases as well as choriocarcinoma histology had higher levels of PD-L1 expression. High levels of PD-L1 expression also correlated with diminished PFS and OS. This study suggested that PD-1/PD-L1 inhibitors may benefit patients with poor risk metastatic GCTs with high tumor burdens. A phase 2 trial was therefore designed to evaluate pembrolizumab (NCT02499952) in patients with platinum-refractory GCTs. Results are not yet avail-

### Table 1. The time course of alpha-fetoprotein, beta-human choric gonadotropin, and lactate dehydrogenase levels.

| Date       | Events                                                                 | B-HCG (mIU/mL) | LDH (U/L) | AFP (IU/mL) |
|------------|------------------------------------------------------------------------|----------------|-----------|-------------|
| Dec 2014   | Initial presentation                                                   | 462,748        | 1108      | <1          |
| Jan 2015   | Received stereotactic radiation to the brain metastases. Initiation of VIP | 480            | 205       | 1           |
| Mar 2015   | Completed 4 cycles of VIP chemotherapy                                 | 295            | 213       | 1           |
| Mar-June 2015 | Left radical orchiectomy and RPLND                                  | 5              | 188       | <1          |
| Jul 2015   | One month after surgery                                                | 125            | 131       | <1          |
| Sep-Nov 2015 | High dose carboplatin/etoposide and autologous PBSCT                | 4143           | 350       | <1          |
| Dec 2015   | One month after completion of PBSCT                                   | 85             | 207       | 1           |
| Jan 2016   | Initiation of gemcitabine/oxaliplatin                                  | 624            | 223       | 1           |
| Jan 2016   | Admitted to hospital due to intractable nausea, vomiting and fever     | 11,519         | 207       | 3           |
| Mar 2016   | Initiation of pembrolizumab                                            | 14,677         | -         | -           |
| Mar 2016   | Three weeks after first cycle of pembrolizumab                         | 45,397         | 1249      | 1           |
| Apr 2016   | Initiation of paclitaxel                                               | 98,648         | -         | -           |

VIP, cisplatin, etoposide, and ifosfamide; RPLND, retroperitoneal lymph node dissection; PBSCT, peripheral blood hematopoietic stem cell transplant; HCG, human chorionic gonadotropin; LDH, lactate dehydrogenase; AFP, alpha fetoprotein.

### Table 2. Studies evaluating high-dose chemotherapy versus standard dose chemotherapy in relapsed germ cell tumor after first line chemotherapy.

| Study         | Design        | Treatment regimens                  | N.  | Results                                                                 |
|---------------|---------------|-------------------------------------|-----|-------------------------------------------------------------------------|
| Pico et al.²  | Phase III     | VIP×6IP × 4 cycles; High-dose CEC   | 280 | CR and PR similar in both arms: 50%; 3-year EFS: 35% vs. 53% (P=0.16); 3-year DFS 55% vs. 57% (P<0.04); 5-year OS similar in both arms: 53% |
| Lorch et al.³ | Phase III     | VIP×1 cycle followed by high dose CEC×3 cycles (longer course of HDCT); VIP×3 cycles followed by high dose CEC×1 cycle (shorter course of HDCT) | 216 | 5-year OS: 49% vs. 39% (P=0.057); 5-year PFS: 47% vs. 45% (P=0.454) |
| Lorch et al.³ | Retrospective | Cisplatin-based; HDCT: High dose CEC×1 cycle with or without additional agents | 1984 | OR for PFS: 0.44 (95% CI, 0.39 to 0.51), favoring HDCT; OR for OS: 0.65 (95% CI, 0.56 to 0.75), favoring HDCT |

VIP, vinblastine, ifosfamide, and cisplatin; VIP, vinblastine, etoposide and cisplatin; CEC, carboplatin, etoposide and cyclophosphamide; CR, complete response; PR, partial response; EFS, event-free survival; OS, overall survival; DFS, progression-free survival; CDT, conventional dose chemotherapy; HDCT, high dose chemotherapy; OR, odds ratio
able. Targeted therapy based on actionable mutations may also be considered for refractory disease after HDCT. A group of investigators at MSKCC evaluated actionable mutations in 120 patients with advanced GCTs using whole-exome sequencing in a study known as the Memorial Sloan Kettering Integrated Mutation Profiling of Actionable Cancer Targets (MSK IMPACT). In the study, TP53/MDM2 alterations were found exclusively in patients with resistant disease.17 Other genetic alterations included MDM2 gene amplification, MYCN gene amplifications, and mutations in the KRAS, NRAS, and BRAF genes. Multiple studies also demonstrated up-regulation of cyclin D2 in testicular GCTs.8,19 Cyclin D2 together with cyclin-dependent kinase 4 and 6 (CDK4/6) promotes cell cycle progression.20 In a phase I study and a case series involving 4 patients with GCTs, 2 had stable disease and 2 had a partial response to PD 0332991, a cyclin-dependent kinase inhibitor.21,22 A phase II trial (NCT01037790) is currently ongoing to evaluate the use of PD 0332991, a cyclin-dependent kinase inhibitor, in cisplatin-refractory, unresectable GCTs. Further studies are needed to analyze the efficacies of targeted therapies based on these actionable mutations. In our patient, next generation sequencing was not performed given his rapid disease progression. Other novel treatments that are being evaluated in clinical trials include chemotherapeutic agents such as carbazitaxel (NCT02115165) and immunotherapy using a combination of ipilimumab and nivolumab (NCT02834013).

Conclusions

In summary, we highlight the treatment challenges in a case of platinum-refractory metastatic GCT. Despite an overall high cure rate in testicular cancer, some patients with metastatic GCTs who failed first and second regimens have limited treatment options and high mortality rates. This case illustrates the need to examine novel agents in metastatic platinum-refractory GCT. Although our patient did not benefit from pembrolizumab, this is a single case. We await the results of the phase II trial evaluating the use pembrolizumab in incurable platinum refractory GCTs.

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