Annals of Hematology & Oncology

Open Access

Austin Publishing Group

Case Report

Pembrolizumab Plus Brentuximab-Vedotin in a Patient with Pretreated Metastatic Germ Cell Tumor

Mayrhofer K*, Strasser-Weippl K and Niedersüß-Beke D

Department of Medical Oncology, Wilhelminenspital Vienna, Austria

***Corresponding author:** Mayrhofer K, Department of Medical Oncology, Wilhelminenspital Vienna, Austria

Received: March 15, 2018; **Accepted:** April 17, 2018; **Published:** May 04, 2018

Abstract

We hereby report the outcome of using a combination of brentuximab-vedotin with immunotherapy (pembrolizumab) in a patient with a metastatic extragonadal embryonal carcinoma after multiple lines of chemotherapy. Based on the tumor's expression of CD30 we first initiated therapy with brentuximab-vedotin and later added pembrolizumab because of PD-L1 positive immune-cell infiltration. This treatment resulted in a notable and durable response, calling for further investigation of combined immunotherapy in germ cell cancers.

Keywords: Pembrolizumab, Brentuximab-vedotin, Embryonal carcinoma, Immunotherapy

Case Presentation

In April 2015, a 31-year old patient was diagnosed with embryonal carcinoma metastasizing to the duodenum. Histologic diagnosis was obtained via gastroscopy. In addition, a CT (computed tomography scan) revealed a pulmonary lesion of 4 mm in diameter of unknown dignity, and pulmonary embolism. An ultrasound of the testes showed inhomogeneous testicular parenchyma on the right side. Orchiectomy was declined by the patient. The resulting stage was Tx N1 M1a S0 stage IIIa International Germ Cell Cancer Collaborative Group poor risk.

The patient initially received three cycles of chemotherapy with bleomycin, etoposide and cisplatin according to the BEP-protocol from April to July 2015, resulting in complete remission of the pulmonary lesion and partial response of the duodenal metastasis shown by CT. Unfortunately, the attending clinic omitted performing a gastroscopy or metastasis resection, respectively. A follow-up CT in September 2015 still showed residual duodenal disease which again did not prompt further diagnostic or therapeutic procedures.

At the end of October 2015, the patient presented with symptoms suggestive of gastric outlet obstruction. Gastroscopy confirmed duodenal obstruction due to tumor masses. In addition, a CT showed pathologic retroperitoneal lymphadenopathy. The patient received two cycles of ifosfamid/paclitaxel in November 2015 and was then referred to our clinic for high-dose chemotherapy. At our department, he received carboplatin/etoposid with autologous stem cell support in December 2015 and January 2016. Complete remission was confirmed by CT and gastroscopy. Inguinal right-sided orchiectomy was performed in March 2017 without evidence of disease.

In May 2016, recurrent disease was evident in an abdominal magnetic resonance imaging showing two liver metastases, so that combination chemotherapy with gemcitabine, oxaliplatin and docetaxel was initiated. Because of a severe allergic reaction, docetaxel had to be discontinued immediately. Therapy was continued with gemcitabine and oxaliplatin resulting in a partial remission in August 2016. In September 2016, splenectomy, retroperitoneal lymph node dissection, segmental resection of the duodenum and segmental liver resection were performed. Histology revealed necrotic tumor tissue in the liver with negative margins (R0 resection) and tumor-free tissue of the spleen and the lymph nodes. The patient went on to receive a second course of high-dose chemotherapy as consolidation treatment, consisting of gemcitabine, nab-paclitaxel and carboplatin with autologous stem cell support in November 2016.

Unfortunately, recurrent disease was evident again in March 2017 with hepatic lesions and paraaortal lymphadenopathy. With no further established palliative chemotherapies available, a literature search was performed to identify novel treatment options for our patient. We found reports describing the antibody-drug conjugate brentuximab-vedotin as salvage therapy in men with relapsed germ cell tumors [1-3]. This agent selectively binds to the cell membrane protein cluster of differentiation 30 (CD30), which is commonly expressed in embryonal carcinoma, and this was also the case in our patient. Therapy was initiated in March 2017 and early staging in May 2017 showed a partial remission. A short follow-up staging due to thoraco-abdominal pain in June 2017 revealed a mixed response of the liver metastases. At this time, the programmed death ligand 1 (PD-L1) status of the previously resected liver metastases was analyzed and found to be negative, but there was evidence of PD-L1 positive immune-cell infiltration covering approximately 15% of the tumor surface. We therefore added pembrolizumab to brentuximab-vedotin at cycle 4, starting in June 2017. Staging in August 2017 showed a very good partial remission. After receiving four cycles of pembrolizumab, the patient however developed grade 3 immune-mediated hepatitis in September 2017 requiring corticosteroids and discontinuation of the drug. During prednisolone tapering he subsequently developed grade 2 pneumonitis, which regressed after re-elevating the dosage of prednisolone. Monotherapy with brentuximab-vedotin was continued, stabilizing the disease until November 2017. When new pulmonary lesions were described in a CT scan at that time, pembrolizumab was added to brentuximab-vedotin again in December 2017. In Jaunary 2018, brentuximab-vedotin was paused because of grade 3 polyneuropathy. Treatment with pembrolizumab is ongoing, leading to a further regression of all lesions in a CT scan in January of 2018.

Citation: Mayrhofer K, Strasser-Weippl K and Niedersüß-Beke D. Pembrolizumab Plus Brentuximab-Vedotin in a Patient with Pretreated Metastatic Germ Cell Tumor. Ann Hematol Oncol. 2018; 5(3): 1196.

Discussion

The antibody-drug conjugate brentuximab-vedotin consists of a chimeric antibody binding to the cell surface antigen CD30 conjugated to the cytotoxic antitubulin agent monomethyl auristatin E. As CD30 is commonly expressed in embryonal carcinoma and the agent has shown signs of preclinical activity in this disease [4], ongoing clinical trials evaluate the efficacy of brentuximab-vedotin in patients with germ cell tumors. In 2016, Necchi, et al. reported initial results of an ongoing phase 2 trial using brentuximab-vedotin as salvage treatment for males with chemotherapy-refractory germell tumors [1]. Two out of nine patients achieved an objective response (one partial remission, one complete remission); more mature results are eagerly awaited. More recently, a case series of seven patients with relapsed or refractory CD30 expressing testicular cancer treated with brentuximab-vedotin resulted in one durable complete remission and one partial response [3]. Even as a monotherapy, the agent therefore seems to exhibit significant clinical activity in a subset of patients.

Immune checkpoint inhibition has likewise shown some antitumor activity in several patients with germ cell tumors in various case reports [5-7]. The known positive correlation between PD-L1 expression on tumor or infiltrating immune cells and therapy response in various solid tumor types, has not been confirmed for germ cell tumors. Recently, the results of a phase 2 trial evaluating pembrolizumab independent of PD-L1 expression in patients with platinum refractory germ cell tumors showed disappointing results [8]. No partial or complete remissions were observed; 2 out of 12 patients (both had negative PD-L1 staining) achieved radiographic stable disease for 19 and 28 weeks, respectively, despite continuously rising alpha-fetoprotein levels.

Despite these discouraging results, combining immunotherapies with other targeted agents could possibly be effective. This has been shown using a combination of brentuximab-vedotin and nivolumab in patients with treatment refractory Hodgkin's lymphoma. In an interim analysis of an ongoing phase I/II trial, an objective response rate of 82%, with 61% of patients achieving a complete remission, was reported in 61 patients evaluable for response [9].

To our knowledge, this is the first case report combining brentuximab-vedotin with the immunotherapeutic agent pembrolizumab in a patient with a germ cell tumor. Based on the pronounced and durable response achieved in this patient, we conclude that this combination needs further evaluation in patients with treatment refractory germ cell tumors.

References

1. Necchi A, Magazzu D, Anichini A, Raggi D, Giannatempo P, Nicolai N, et al. An open-label, single-group, phase 2 study of brentuximab vedotin as salvage therapy for males with relapsed germ cell tumors (GCT): Results at the end of first stage (FM12GCT01). J Clin Oncol. 2016; 34: 480-480.

2. Necchi A, Anichini A, Raggi D, Giannatempo P, Magazzù D, Nicolai N, et al. Brentuximab Vedotin in CD30-Expressing Germ Cell Tumors After Chemotherapy Failure. Clin Genitourin Cancer. 2016; 14: 261-264.e4.

3. Albany C, Einhorn L, Garbo L, Boyd T, Josephson N, Feldman DR. Treatment of CD30-Expressing Germ Cell Tumors and Sex Cord Stromal Tumors with Brentuximab Vedotin: Identification and Report of Seven Cases. Oncologist. 2017; Oncologist. 2017-0544.

4. Schönberger S, van Beekum C, Götz B, Nettersheim D, Schorle H, Schneider DT, et al. Brentuximab vedotin exerts profound antiproliferative and pro-apoptotic efficacy in CD30-positive as well as cocultured CD30-negative germ cell tumour cell lines. J Cell Mol Med. 2018; 22: 568-575.

5. Zschäbitz S, Lasitschka F, Jäger D, Grüllich C. Activity of immune checkpoint inhibition in platinum refractory germ cell tumors. Ann Oncol. 2016; 27: 1356-1360.

6. Shah S, Ward JE, Bao R, Hall CR, Brockstein BE, Luke JJ. Clinical Response of a Patient to Anti-PD-1 Immunotherapy and the Immune Landscape of Testicular Germ Cell Tumors. Cancer Immunol Res. 2016; 4: 903-909.

7. Zschäbitz S, Lasitschka F, Hadaschik B, Hofheinz RD, Jentsch-Ullrich K, Grüner M, et al. Response to anti-programmed cell death protein-1 antibodies in men treated for platinum refractory germ cell cancer relapsed after high-dose chemotherapy and stem cell transplantation. Eur J Cancer. 2017; 76: 1-7.

8. Adra N, Einhorn LH, Althouse SK, Ammakkanavar NR, Musapatika D, Albany C, et al. Phase II trial of pembrolizumab in patients with platinum refractory germ cell tumors: a Hoosier Cancer Research Network Study GU14-206. Ann Oncol. 2018; 29: 209-214.

9. Herrera AF, Moskowitz AJ, Bartlett NL, Vose JM, Ramchandren R, Feldman TA, et al. Interim results of brentuximab vedotin in combination with nivolumab in patients with relapsed or refractory Hodgkin lymphoma. Blood. 2017; 10-811224.

Ann Hematol Oncol - Volume 5 Issue 3 - 2018
ISSN : 2375-7965 | www.austinpublishinggroup.com

Citation: Mayrhofer K, Strasser-Weippl K and Niedersüß-Beke D. Pembrolizumab Plus Brentuximab-Vedotin in a Patient with Pretreated Metastatic Germ Cell Tumor. Ann Hematol Oncol. 2018; 5(3): 1196.