Complete Response to Pembrolizumab in a Patient with Malignant Peripheral Nerve Sheath Tumor: The First Case Reported

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ABSTRACT
Pembrolizumab and procarbazine have been developed as anticancer agents. This study aimed to evaluate the efficacy of the combination of pembrolizumab plus procarbazine in a case with malignant peripheral nerve sheath tumor (MPNST) for the first time. A 48-year-old man referred to the Clinic of Oncology with complaints of constant abdominal pain for a week that the pathology diagnosis showed MPNST. The pathologist reported spindle cell sarcoma (probably dedifferentiated liposarcoma) with a significant PD-L1 expression-tumor proportion score (TPS): 90%. The patient was treated with six courses bi-weekly pembrolizumab combined with procarbazine that after this treatment, abdominopelvic CT scan showed that his lesions completely were resolved. In conclusion, the combination of pembrolizumab with procarbazine can be a new treatment in the patients with MPNST that in the future studies, the clinicians can check PD-L1 in these patients for better therapeutic aims.

INTRODUCTION
Malignant peripheral nerve sheath tumors (MPNSTs) are aggressive sarcomas of soft tissue distinguished with high risk of local recurrence and distant metastasis (Bradford and Kim, 2015; Farid et al., 2014) that pose tremendous challenges to effective (Farid et al., 2014). Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks interaction with its ligands (PD-L1 and PD-L2). This binding activates T-cell-mediated immune responses against cancer cells (Raedler, 2015). Procarbazine hydrochloride (HCl) is an oral alkylating agent similar to dacarbazine and hexamethylamine. This drug was synthesized for the first time in the late 1950s during a search for a new monoamine oxidase inhibitor, but was soon developed as an antitumor agent (Friedman, 2001). The present study evaluated the efficacy of combination of pembrolizumab plus procarbazine HCl in a case with MPNST for the first time.

Case Report
On January 2016, a 48-year-old man referred to the Clinic of Oncology with complaints of constant abdominal pain for a week. The abdominopelvic CT scan showed retroperitoneal masses that the pathology diagnosis showed MPNST and he referred again to the clinic (Figure 1). Microscopically, a specimen of the patient contained infiltrates of a mesenchymal proliferation composed of spindled tumor cells.

In immunohistochemistry (IHC) evaluation, MDM2 protein (scattered), CD54, CD56, S100, SMA were positive, whereas desmin, B-catenin, synaptophysin, CD34, and DOG1 were negative. Also, Ki67 was positive in 1% of tumoral cells and CD117 (c-Kit) was weakly positive (1-2% of tumoral cells).
By surgery a limited debulking was done, and he treated with six courses combination of doxorubicin (100 mg/m² per day) and ifosfamide (3 g/m² for 3 days). In follow-up, there were the bulk of mass lesions in the CT scan (Figure 2).

Therefore, the patient was treated with imatinib 400 mg per day. After 3 months from this process, he referred again with generalized abdominal pain. On September 2016, the CT scan showed a mesenteric solid mass in the dimensions of 30 x 44 mm in a position inferior of the stomach with an adhesion to the stomach wall and was suggestive of previous tumor recurrence in this location (Figure 3).

The patient was admitted for three surgical consults and abdominal mass debulking resection. In this line, he was treated with eribulin (1.4mg/m² IV infused for 2-5 min on days 1 and 8) for six cycles. The new specimen was contained from more than 100 viable tumor cells and was suitable for PD-L1 test. The IHC was carried out by using the DAKO 22C3 pharm DX kit on an Autostainer Link 48 platform for a PD-L1 test that suitable negative controls were included. The pathologist reported spindle cell sarcoma (probably dedifferentiated liposarcoma) with
significant PD-L1 expression-tumor proportion score (TPS): 90%. The patient was treated with six courses biweekly Keytruda (pembrolizumab) (200mg every 3 weeks) combined with procarbazine hydrochloride (HCl) (50 mg/m2 twice a day). In new abdominopelvic CT scan, lesions completely were resolved (Figure 4) and he was followed during last 3 months. The patient is alive on Jun 2017.

DISCUSSION

This study showed that for the first time, pembrolizumab combined with procarbazine therapy had a complete response in MPNST patient.

Pembrolizumab was approved by the Unites States Food and Drug Administration (FDA) as the first anti-PD-1 antibody in the treatment of unresectable or metastatic melanoma patients with disease progression following ipilimumab that if mutant BRAF as a BRAF inhibitor (Khoja et al., 2015). This drug is a high-affinity, highly selective monoclonal antibody against PD-L1 that has shown important clinical activity in multiple tumor types (Khoja et al., 2015). A phase II clinical trial (SARC028) is doing on the efficacy of pembrolizumab in patients with MPNST (Guren TK, 2016) that these patients will receive pembrolizumab therapy for up to 10 courses. A few trials are doing to evaluate the best use of pembrolizumab alone in melanoma, non-small cell lung cancer, and other tumor types (Khoja et al., 2015), as low-dose pembrolizumab (cumulatively only 6 mg/kg at interim assessment) was used to treat Hodgkin’s lymphoma that resulted in an excellent response with the lowest adverse events and cost (Kwong et al., 2017).

Procarbazine HCl has been introduced as an oral alkylating agent with activity against lymphoma (Chaar et al., 2006). Insufficient results with standard agents have caused an interesting on developed targeted therapeutics of MPNST that this interest and desire build a large number of molecular data surrounding MPNST pathogenesis (Farid et al., 2014). Response rate in combination of doxorubicin plus ifosfamide (the most active agents) in unselected soft tissue sarcomas was approximately 25% that this response in MPNST was 21% (Kroep et al., 2011). The present study reported that the combination of these two drugs didn’t have good response in MPNST patient. Recently, there are renew interests in procarbazine combinations with other chemotherapeutic factors, specifically in the treatment of Hodgkin’s lymphoma, gliomas and with a less extent in non-Hodgkin’s lymphoma and primary central nervous system lymphoma (Armand et al., 2007). A case reported (Payandeh et al., 2015) showed maintenance therapy with procarbazine and chlorambucil is a new option for the patient with Hodgkin’s lymphoma that reduced lesions of liver and lung and had a complete response in the patient. To conclude, the combination of pembrolizumab with procarbazine can be a new treatment in the patients with MPNST that in the future studies, the clinicians can checkPD-L1 in these patients for better therapeutic aims.

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INFORMED CONSENT

The informed consent was signed by the patient for reporting this case.

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