Case Study

Immunotherapy to Address Unmet Needs in Oncology; Two Clinical Vignettes of Response in Metastatic Malignant Melanoma and Non-Small Cell Lung Cancer

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Abstract

The management of unresectable advanced, metastatic malignant melanoma (MM) and chemotherapy-resistant or refractory non-small cell lung cancer (NSCLC) has been an uphill challenge in clinical oncology. The advent of immunotherapy in cancer has put forward some new hopes to cover unmet needs in treating such cases. Immune-checkpoint inhibitors are among the well-supported options in the same vein. Alongside other cancer immunotherapy class-molecules, pembrolizumab (PZB), a programmed cell death protein 1 (PD-1) blocking antibody, has recently been approved both for MM and NSCLC. This report presents an overview of the clinical benefits of PZB in MM and NSCLC and highlights the clinical features of two eligible cases who have undergone immunotherapy using PZB.

Keywords: Malignant melanoma, NSCLC, Immunotherapy, Pembrolizumab, Clinical response

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Introduction

An extensive line of research has recently been pursued in the development of immunotherapy for the treatment of cancer(1). For the most part, checkpoint blockade using antibodies impeding immune pathways, such as programmed cell death protein 1 (PD-1)/PD-1 ligand 1 (PD-L1), embodies an innovative strategy (2-4).
Herein, we report two cases of metastatic malignant melanoma (MM) and non-small cell lung cancer (NSCLC) responding to an immunotherapeutic agent, pembrolizumab (PZB), a PD-1 inhibitor. PZB is the first-in class drug approved by the US Food and Drug Administration (FDA) for unresectable melanoma(5, 6) as well as non-small cell lung cancer (NSCLC)(6, 7). Preclinical studies have shown that transgenic mice overexpressing PD-L1 demonstrate accelerated cancer cell formation(8). Hence, blockade of the PD-1/PD-L1 pathway is expected to help controlling the progress of various types of solid tumors (9-13) .

The presented cases highlight the potential for immunotherapy in the form of PD-1/PD-L1 inhibition to address challenges i.e. low overall survival (OS) rate and underprivileged quality of life upon the treatment of MM and NSCLC(14, 15). Pembrolizumab (PZB) is a human PD-1-blocking antibody indicated for the treatment of platinum-based chemotherapy-resistant NSCLC as well as for patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF (a human gene that makes the protein B-Raf) V^{600} mutation is positive, a BRAF inhibitor (16). PZB tends to harvest the natural ability of the patient's own immune system to eliminate cancer cells.

The molecule, MK-3475, received FDA's "Breakthrough Therapy "designation for advanced melanoma, based on the significance of early study findings and the unmet medical need. It demonstrated superior efficacy and safety and durable clinical benefits, advancing a therapeutic goal which could potentially induce long-term cancer remission. The clinical results were capitalized through the KEYNOTE studies which showed superiority over ipilimumab. Applying the regimen resulted in reduced risk of death by 31.5 to 37%, increased progression-free survival (PFS) by 1.8 fold in 6 months rate and increased overall response rate (ORR) by 2.8 fold (5, 17).

Quite recently, FDA granted the second "Breakthrough Therapy" designation to PZB in NSCLC cases whose disease has progressed on or following platinum-based chemotherapy. This designation has been supported by data from the Phase 1b KEYNOTE-001 study on 495 cases. Results from this elegant trial indicated the ORR of 19.4%, PFS of 3.7 months and the OS of 12 months (7).

New data has been cumulating in 10 different cancer types from the fast-growing immuno-oncology research program for PZB. So far findings have corroborated the anti-tumor activity of PZB in five additional malignancies including colorectal, esophageal, ovarian, renal cell carcinoma and small-cell lung cancer(18).

A rapidly-expanding clinical development program comprises over 85 clinical trials on more than 30 tumor types and over 14,000 patients both as a monotherapy and in combination with other therapies (18, 19).

Such robust clinical data prompted us to administer this novel treatment to a handful number of cases of which the clinical vignettes of two cases are highlighted herewith.

Clinical vignette 1

TD, a 64 year-old male presented in January 2014 with persistent cough and progressive dyspnea on exertion over a 3 month period. Initial chest X-ray and CT scan revealed evidence of large right-upper lobe (RUL) lung mass lesion with hilar and mediastinal nodes involvement. In addition, multiple liver lesions, a left adrenal and bone metastases were detected.

Biopsy of the lung mass revealed evidence of a poorly-differentiated adenocarcinoma. Epidermal growth factor receptor (EGFR) mutation and anaplastic lymphoma kinase (ALK) translocation testing revealed the tumor to be wild type for both. The patient was active with an ECOG (Eastern Cooperative Oncology Group) performance status of 1. No significant comorbidities and no hemoptysis was recorded. The patient was started on cisplatin/pemetrexed and zoledronic acid every 3 weeks. Reassessment after 3 cycle of therapy revealed a partial response and he completed 3 additional cycles of chemotherapy. The course of therapy was completed in June 2014.

Patient did fine until January 2015, when he was noticed to have progressive disease on follow-up CT scan. He was then started on docetaxel/zoledronic acid. Repeated imaging following 3 cycles revealed further progression in his disease. Patient was subsequently started on PBZ at 2 mg/kg, intravenous (IV) infusion every 3 weeks with no significant side effects. A follow-up CT scan after 3 cycles demonstrated a partial response. Patient has received a total of 6 cycles of the drug and continued to do extremely well to date.

Clinical vignette 2

AS, a 24 year-old male who presented in January 2014 with an enlarged left axillary lymph node. Excisional biopsy revealed evidence of MM. Our systemic work-up including a positron emission tomography (PET) scan, brain magnetic resonance imaging (MRI), dermatologic and ophthalmologic exams turned out to be negative. Patient had left axillary dissection in March 2014 and the pathology report confirmed the presence of melanoma in 3 out 24 excised lymph nodes.

The patient was started on adjuvant pegylated interferon alpha-2b (PegIFNa-2b) which was well-

tolerated with minimal side effects. He did fine until January 2015 when the repeated PET scan revealed evidence of metastatic disease in both axillae, bone, lymph nodes as well as some subcutaneous nodules. Biopsy confirmed a recurrent disease. The proto-oncogene B-Raf (BRAF)-mutation testing was found to be negative.

Patient then received ipilimumab at 3 mg/kg, IV infusion, every 3 weeks for 3 cycles. In March 2015, he developed severe bone pain and hypercalcemia. A follow-up PET image in March 2015 showed bone involvement (Figure 1).

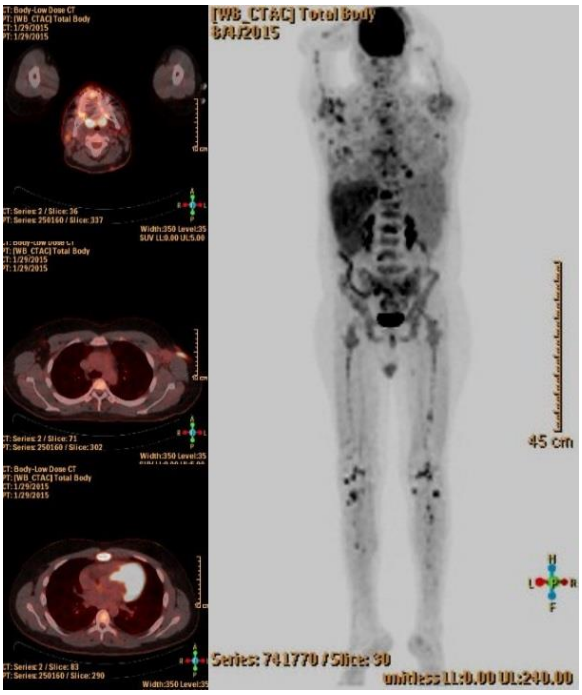

Figure 1. Chest and whole-body Positron-Emission Tomography scan revealing lung and bone metastasis in the present case of advanced metastatic malignant melanoma.

Upon the completion of ipilimumab therapy, the patient's ECOG performance status was 3. He continued to have severe pain requiring high doses of opiates. He has also become dependent to red-blood cell (RBC) and platelet transfusion. He also developed lung involvement with recurrent pleural effusions requiring frequent drainage (Figure 1).

The patient was subsequently shifted to PZB at 2 mg/kg, IV infusion, every 3 weeks starting from April 2015 and continued to receive supportive care. PZB was continued as it caused minimal side effects (grade 1 skin rash).

Patient has had 6 cycles of PZB with relatively stable disease. His pain has completely resolved, he is ambulatory and able to maintain his weight at this time. His RBC and platelet transfusion requirements have significantly diminished.

Pembrolizumab and nivolumab are among the foremost anti-PD-1 antibodies which are being/have been tested in different cancers including but not restricted to melanoma, non-small cell lung cancer, renal cell carcinoma as well as head and neck cancers and lymphoma (20, 21). This case discussion was as attempt to discuss the evidence supporting the efficacy of anti-PD-1 antibodies in cancers, namely MM and NSCLC, and the possibility for their combination with other anti-cancer agents in future directions of clinical trials to help increasing the number of long-term survivors.

Concluding remark

Although significant progress has been made in the area of oncology, effective treatment options for patients with advanced or metastatic disease remain limited, toxic and sometimes ineffective in this patient population. PZB appears to provide a real chance for those patients with advanced malignant stages to extend their overall survival while notably improving their quality of life.

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