Case Report

PD-1 Blockade in Advanced Melanoma in Patients with Hepatitis C and/or HIV

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On the basis of remarkable antitumor activity, programmed death receptor-1 (PD-1) inhibitors pembrolizumab and nivolumab were approved for the treatment of advanced melanoma in the second-line setting following progression on either CTLA-4 inhibitor ipilimumab or BRAF/MEK inhibitors (for BRAF mutated melanoma). Given hypothesized risk of triggering exacerbations of autoimmune diseases and/or chronic viral infections, clinical trials (including regulatory studies) evaluating checkpoint blocking antibodies PD-1 and CTLA-4 have excluded patients with autoimmune diseases, chronic hepatitis B/C virus (HBV/HCV), and/or human immunodeficiency virus (HIV) infections. Herein, we describe two patients with advanced melanoma and concomitant HCV/HIV infections treated with PD-1 inhibitor pembrolizumab. Patient 2 with HIV/HCV coinfection progressed after 2 doses of pembrolizumab. Patient 1 who had HCV alone was treated with pembrolizumab with initial partial response. HCV viral load remained stable after 9 cycles of pembrolizumab following which 12-week course of HCV-directed therapy was commenced, resulting in prompt reduction of HCV viral load below detectable levels. Response is ongoing and HCV viral load remains undetectable. In both patients, no significant toxicities were observed when pembrolizumab was initiated. We argue for the further investigation of checkpoint inhibition in cancer patients with underlying chronic viral infections in the context of carefully designed clinical trials.

1. Background

Pembrolizumab is a programmed death receptor-1 (PD-1) blocking antibody approved for the treatment of metastatic melanoma that has progressed past cytotoxic T-lymphocyte antigen 4 (CTLA-4) inhibitor Ipilimumab and BRAF inhibitors such as vemurafenib or dabrafenib (if BRAF mutated). Pembrolizumab was granted accelerated approval by the Food and Drug Administration (FDA) on the basis of a phase I trial that evaluated two cohorts that received either 2 mg/kg or 10 mg/kg of pembrolizumab every 3 weeks in which investigators reported high response rates (38%–52%) with most of the responders (82%) remaining on treatment [1].

PD-1/PD-L1 and CTLA-4 play important roles in regulating the immune system; hence, patients with autoimmune diseases requiring systemic immunosuppression and/or patients with hepatitis B/C (HBV/HCV) or human immunodeficiency virus (HIV) infection have been excluded from studies evaluating these agents over concerns about inadvertent augmentation of infectious and/or inflammatory activity. Although anti-CTLA-4 treatment has been shown to trigger or worsen severity of autoimmune diseases in experimental models, a similar effect has not been shown for PD-1/PD-L1 abrogation [2–4].

We report on two patients with advanced melanoma and concomitant HCV/HIV infections (patient 1: HCV; patient 2: HCV and HIV) treated with PD-1 inhibition. In both cases, pembrolizumab was well tolerated with no exacerbation of underlying HCV/HIV infection or observed toxicity.

2. Case Presentation 1 (Patient 1)

A 59-year-old Caucasian female presented with a subcutaneous right breast lesion on screening mammography in August 2014. Ultrasound-guided biopsy revealed malignant cells with an immunophenotype consistent with metastatic melanoma. Physical examination was negative for a possible
primary lesion. Molecular testing was negative for either 
BRAF V600 or NRAS codon 61 mutations. Staging positron
emission tomography (PET) and magnetic resonance imag-
ing (MRI) scans confirmed two metabolically active nodules 
in right lower lung with no evidence of metastases in other 
visceral structures, brain, or skeletal system.

Prior history was notable for HCV infection docu-
mented in March 2014 following mildly elevated blood 
alanine transaminase (ALT) and aspartate aminotransferase 
(AST) levels. HCV-specific characteristics included high viral 
load (2,290,867 IU/mL) and 1A genotype. Clinically relevant 
parameters included IL28B polymorphism CC genotype, 
mild-moderate active chronic hepatitis (Ishak index 6/18) 
with moderate portal/perportal hepatic fibrosis (fibrosis 
stages 2-3/6). Her social history was notable for history 
of intranasal cocaine and intravenous drug abuse between 
ages of 20 and 30. She was in a long-term monogamous 
relationship with her husband of 30 years without prior high-
risk sexual partners.

Given the minimal disease burden, we encouraged her 
to pursue initial HCV therapy followed by therapy for 
advanced melanoma given the recent approval of antiviral 
agents with unprecedented levels of antiviral activity in HCV. 
However, she elected against this. In the setting of mild-
moderate hepatitis with moderate fibrosis and mildly elevated 
ALT/AST, we were concerned about a heightened risk of 
ipilimumab-related hepatitis. Following an extensive discus-
sion of the available options and carefully considering the 
respective risks of treatment, she commenced therapy with 
PD-1 inhibitor pembrolizumab at 2 mg/kg every three weeks. 
Restaging scans following 3 cycles showed a mixed response, 
slight increase in size of right breast lesion and new hilar 
and right axillary lymphadenopathy although pulmonary 
lesions were significantly decreased in size with an overall 
reduction in total tumor burden. Restaging scans following 
further 3 cycles of therapy showed significant reduction in 
size of both hilar/axillary lymphadenopathy and pulmonary 
nodules consistent with partial response (see Figure 1). After 
9 cycles of pembrolizumab with ongoing response, she 
commenced a 12-week course of ledipasvir (NS5A inhibitor) 
and sofosbuvir (viral RNA polymerase inhibitor). During 
cycle 1–3 of pembrolizumab, ALT/AST levels and HCV viral 
loads remained stable. Following commencement of ledi-
 pasvir/sofosbuvir (after 9 cycles of pembrolizumab), HCV 
 viral load declined to below detectable levels. At the time 
of reporting, she has an ongoing excellent partial response 
after 15 cycles of therapy with pembrolizumab with normal 
ALT/AST and undetectable HCV viral load.

3. Case Presentation 2 (Patient 2)

A 47-year-old Caucasian male was diagnosed with a left 
axillary lymph node confirmed malignant melanoma and 
subsequently underwent completion lymph node dissection 
which revealed multiple foci of metastatic melanoma in 2 of 
36 lymph nodes removed with no extracapsular extension. 
Molecular testing confirmed BRAF V600E mutation though 
NRAS codon 61 mutation was not identified.

Past medical history was significant for remote diagnosis 
HIV-1 and chronic HCV diagnosed in June 2011. He was 
treated with an antiretroviral therapy (ART) regimen that 
consisted of 2 nucleoside reverse transcriptase inhibitors 
and 1 nonnucleoside reverse transcriptase inhibitor. HIV-
1 viral load was consistently undetectable. HCV-specific 
characteristics included low viral load (863,475 IU/mL) and 
1C genotype. Clinically relevant parameters included IL28B 
polymorphism CT genotype and chronic hepatitis associated 
with mild activity (Ishak index 5/18) and mild-moderate 
portal/perportal fibrosis (fibrosis stage 2/6). His social 
history was notable for homosexual orientation with multiple 
prior high-risk partners though recently monogamous and 
there was no prior history of intravenous drug abuse.

He received adjuvant high-dose interferon (IFN) between 
December 2012 and May 2013, during which time HIV 
and HCV viral loads were unchanged. IFN was stopped 
given development of subcutaneous melanoma metastases. 
Given well-controlled HIV and HCV, he was offered CTLA-
4 inhibitor ipilimumab and received 3 doses (3 mg/kg every 
3 weeks) between October and December 2013, discontinued 
for progression. Subsequent treatments included 2 cycles of 
high-dose IL-2 (4 and 6 doses in cycles 1/2, resp.) from Jan-
uary to March 2014 and dabrafenib/trametinib from March 
August 2014, discontinued for progressive cutaneous and 
pulmonary disease with new hepatic lesions. Given excellent 
performance status despite widely metastatic disease, PD-1 
inhibitor pembrolizumab (2 mg/kg every three weeks) was 
initiated after careful consideration of risks and benefits of 
treatment and he received 2 doses. Throughout treatment, 
despite progressive disease, he experienced no immune-
related adverse events (ir-AEs), substantial increases in 
HIV/hepatitis C viral loads, and/or any abnormalities in 
hepatic function studies. Throughout treatment, he was 
maintained on ART.

Unfortunately, following 2 doses of pembrolizumab, he 
developed brain metastases requiring stereotactic radio-
surgery and declined in performance status. Pembrolizumab 
was stopped and he transitioned to hospice care. He passed 
away shortly thereafter.

4. Conclusions

We describe two patients with active HCV/HIV infec-
tions and advanced melanoma treated with pembrolizumab 
in the setting of limited alternative treatments. To our 
knowledge, this is the first report of advanced melanoma 
patients with active HCV or HIV infection to be treated 
with pembrolizumab. The PD-1/PD-L1 pathway is known 
to be upregulated in chronic viral (HBV, HCV, and HIV) 
infections where it may attenuate T-cell or NK-cell mediated 
antiviral host immune responses, thereby sustaining chronic 
infection [5]. Abrogation of PD-1/PD-L1 signaling may have
Figure 1: Changes in tumor size and correlation with laboratory results in patient 1. After 3 cycles, index right breast lesion (A-B, lower panel) increased in size while index right pulmonary lesion decreased in size consistent with immune-related response pattern (A-B, upper panel). After 6 cycles, both lesions had decreased in size significantly (C, upper and lower panels). Although pembrolizumab treatment was associated with grade 1 leucopenia and grade 1 ALT/AST elevations initially, total white count and ALT/AST levels subsequently stabilized (graph). HCV viral load fluctuated between 3.36 IU/mL (6.53 log IU/mL) and 5.17 IU/mL (6.71 log IU/mL) before initiation of ledipasvir and sofosbuvir in April 2015. After 12-week course, HCV viral load became undetectable and remains so. To date, she has completed 15 cycles to date with ongoing excellent partial response.

Benefit in chronic viral diseases and this strategy is being explored in both HIV-1 infection (NCT02028403) and HCC associated with HBV/HCV related hepatitis (NCT01658878) with anti-PD L1 BMS-936559 and anti-PD-1 BMS-936558, respectively. However, HIV/HCV patients have hitherto been systematically excluded from clinical trials of pembrolizumab in advanced melanoma and whether pembrolizumab truly exacerbates HCV/HIV infection remains unknown. Prior phase I studies of PD-1 inhibitor BMS-936558 and PD-L1 inhibitor BMS-936559 had similarly excluded patients with HCV/HIV infection [6, 7].

Although patient 2 did not demonstrate antitumor benefit from pembrolizumab (or any other prior treatment including the combination of dabrafenib/trametinib), HIV viral
load remained undetectable likely secondary to continued compliance with ART therapy while on therapy. Previously received treatments including HD IL-2, CTLA-4 inhibitor ipilimumab, and PD-1 inhibitor pembrolizumab were discontinued secondary to clinical and/or radiologic progression rather than development of ir-AEs. Throughout treatment, HCV viral loads were variable though HIV viral load was undetectable. ALT/AST elevations were of no more than Common Terminology Criteria for Adverse Events (CTCAE) grade 1 severity.

Remarkably, patient 1 has demonstrated an ongoing sustained response to therapy following a mixed response at first staging evaluation. The clinical development of ipilimumab was notable for the heterogeneity of responses observed which led several authors to propose “immune-related response criteria” (irRC) to specifically evaluate responses to immunotherapeutic agents [8]. Using these criteria, physicians are permitted to continue therapy in the face of new lesions (measurable or nonmeasurable) as long as the overall tumor burden is stable or is declining. Ongoing PD-1/PD-L1 trials are evaluating response using RECIST v1.1 though response by irRC is often a secondary endpoint on these studies. Treatment with pembrolizumab was notable for variable pancytopenia and ALT/AST elevations of no more than CTCAE grade 1 severity. HCV viral load remained stable throughout therapy and became undetectable following initiation of anti-HCV therapy.

Given the incidence of chronic viral hepatitis (hepatitis B 0.4%; hepatitis C 1.0%) and HIV infection (0.4%) separately and HIV/HCV coinfection (up to 80% in intravenous drug abusers) and the rising incidence of melanoma, evaluating the safety of immunotherapies for the treatment of melanoma in these cohorts is of pressing importance. Additionally, viral hepatitis and HIV are global health scourges which have an outsized impact on patients in developing countries. Demographic and lifestyle changes in developing countries will likely result in cancer incidences that approach those of developed countries such as the United States, Australia, and the European Union. These trends coupled with the availability of highly active treatments that turn HCV and HIV into chronic illnesses make these diseases important considerations as we develop and evaluate effective antitumor immunotherapy.

Anecdotal reports are not substitutes for well-conducted clinical trials to evaluate the safety and efficacy of agents in specific settings. Moreover, our experience with these two patients is in no way generalizable to other patients. However, this experience argues for the systematic evaluation of PD-1/PD-L1 immunotherapy in patients with chronic HBV/HCV and/or HIV infection and potentially other entities including autoimmune illnesses requiring systemic immunosuppression, either as extensions of existing studies or within the confines of an organ dysfunction trial.

Abbreviations

ALT: Alanine transaminase  
ART: Antiretroviral therapy  
AST: Aspartate aminotransferase  
CTLA-4: Cytotoxic T-lymphocyte-associated protein 4

References

