BRIEF REPORT

Safety and Efficacy of PD-1 Inhibitors Among HIV-Positive Patients With Non–Small Cell Lung Cancer

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ABSTRACT

Introduction: Despite widespread administration of programmed death receptor 1 (PD-1) pathway inhibitors among individuals with NSCLC, little is known about the safety and activity of these agents among human immunodeficiency virus (HIV) – infected patients since this population has largely been excluded from immunotherapy clinical trials.

Methods: Here, we describe seven patients with metastatic NSCLC and HIV infection who were treated with PD-1 inhibitors nivolumab (two cases) or pembrolizumab (five cases with three in the first-line setting).

Results: Partial responses to immune checkpoint inhibitors were observed in three of seven cases. Among four patients with a programmed death ligand-1 tumor proportion score $\geq$50%, three partial responses were observed. All patients received antiretroviral therapy while on anti–PD-1 treatment. None of the patients experienced grade 3 or 4 immune-related adverse events or immune reconstitution inflammatory syndrome, and none required PD-1 inhibitor dose interruption or discontinuation due to toxicity.

Conclusions: Nivolumab and pembrolizumab can be safe and effective among patients with NSCLC and HIV. Larger studies will be needed to determine the overall safety and efficacy of immune checkpoint inhibitors among cancer patients with HIV.

Keywords: Lung cancer; HIV; Pembrolizumab; Nivolumab; PD-1; PD-L1; Immunotherapy

Introduction

Several programmed death 1 (PD-1) pathway inhibitors have been approved for the treatment of advanced NSCLC in recent years. In previously treated NSCLC, nivolumab, pembrolizumab, and atezolizumab have each shown an overall survival benefit compared to docetaxel, and pembrolizumab has been approved for the first-line treatment of NSCLCs with a programmed death-ligand 1 (PD-L1) tumor proportion score (TPS) $\geq$ 50% on the basis of superior efficacy and safety over platinum doublet chemotherapy.[1–5] In addition, the PD-L1 inhibitor durvalumab is approved in locally advanced, unresectable NSCLC whose disease has not progressed following concurrent chemoradiation therapy.[6]

Patients with human immunodeficiency virus (HIV) have been excluded from nearly all clinical trials of immune checkpoint inhibitors in lung cancer, resulting in a

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Table 1. Characteristics of Patients With HIV and NSCLC Treated With PD-1 Inhibitors

Case	Age	Sex	History of Tobacco Use	Histology	Driver Mutation	PD-L1 TPS	Line/ Drug	BOR[a]	Length of Time on PD-1 Therapy	Toxicities[b]	On ART Before PD-1	ART Regimen	Baseline[e]		Last Known Values		Concurrent Illnesses
													CD4	HIV VL[f]	CD4	HIV VL	
1	53	M	30 pk-yr	Adeno	*KRAS* G12C	90%	1st Pembro	SD	3 Months, ongoing	None	No[c]	Abacavir, dolutegravir and lamivudine	423/μL	12,589	307/μL	<20	Kaposi sarcoma, latent syphilis
2	52	M	45 pk-yr	Adeno	None detected	N/A	2nd Nivo	PD	2 Months, discontinued due to PD	Grade 1 arthralgia, headache, chest pain	Yes	Abacavir/ lamivudine, dolutegravir and tenofovir disoproxil fumarate	N/A	<20	N/A	<20	None
3	59	M	7.5 pk-yr	Adeno	*KRAS* G12C	90%	1st Pembro	PR	3 Months, ongoing	Grade 2 arthralgia	Yes[d]	Emtricitabine/ tenofovir disoproxil fumarate, ritonavir and atazanavir	57/μL	<20	140/μL	42	Chronic HCV genotype 1a
4	52	M	23 pk-yr	Adeno	None detected	90%	2nd Pembro	PR	10 Months, discontinued due to unrelated death	Grade 1 fatigue	Yes	Raltegravir, etravirine and darunavir	1147/μL	<20	1229/μL	<20	None
5	43	M	30 pk-yr	Adeno	None detected	N/A	3rd Nivo	SD	5 Months, discontinued due to PD	None	Yes	Emtricitabine/ tenofovir disoproxil fumarate and dolutegravir	435/μL	<20	440/μL	<20	None
6	51	M	30 pk-yr	Adeno	None detected	90%	1st Pembro	PR	8 Months, ongoing	Grade 2 arthralgia	Yes	Elvitegravir/ cobicistat/ emtricitabine/ tenofovir alafenamide fumarate	223/μL	<20	233/μL	<20	None

(continued)

Table 1. Continued

Case	Age	Sex	History of Tobacco Use	Histology	Driver Mutation	PD-L1 TPS	Line/ Drug	BOR[a]	Length of Time on PD-1 Therapy	Toxicities[b]	On ART Before PD-1	ART Regimen	Baseline[e] CD4	Baseline[e] HIV VL[f]	Last Known Values CD4	Last Known Values HIV VL	Concurrent Illnesses
7	47	F	30 pk-yr	Adeno	*KRAS* G12V	20%	2nd Pembro	PD	3 Months, discontinued due to PD	None	Yes[d]	Emtricitabine/ tenofovir alafenamide fumarate and dolutegravir	297/μL	<20	305/μL	<30[g]	Chronic HBV

[a]Best overall response (BOR) as assessed by the investigator according to the Response Evaluation Criteria in Solid Tumors, version 1.1.
[b]Toxicities assessed by National Cancer Institute Common Terminology Criteria of Adverse Events, version 4.
[c]Three weeks after pembrolizumab initiation, the patient started on ART with dolutegravir and emtricitabine/tenofovir disoproxil fumarate, which was later changed to a single tablet containing abacavir, dolutegravir, and lamivudine to improve adherence.
[d]Patient had intermittent adherence to ART regimen before starting on pembrolizumab.
[e]Baseline before starting PD-1 therapy.
[f]Units are copies/mL. A viral load of <20 copies/mL is considered undetectable.
[g]In this patient, the HIV viral load initially increased to 115 copies/mL after one dose of pembrolizumab but then decreased to <30 copies/mL after the fourth dose, which is considered detectable but below the quantifiable range of the assay.
M, male; F, female; pk-yr, pack-years; PD-L1, programmed death ligand-1; PD-1, programmed death 1; ART, antiretroviral therapy; Adeno, adenocarcinoma; TPS, tumor proportion score; N/A, not available; Pembro, pembrolizumab; Nivo, nivolumab; N/A, response not yet assessed; SD, stable disease; PD, progression disease; PR, partial response; VL, viral load; HCV, hepatitis C virus; HBV, hepatitis B virus.

paucity of data on the safety and efficacy of PD-1 pathway inhibitors in this population.[1–4] Because HIV is an independent risk factor for lung cancer, and more than 40% of people living with HIV (PLWH) in the United States have a history of tobacco use, lung cancer has emerged as one of the leading overall causes of death in PLWH.[7–9] In fact, PLWH who adhere to antiretroviral therapy (ART) but smoke are more likely to die from lung cancer than from acquired immune deficiency syndrome (AIDS) – related illnesses, highlighting the need to study effective lung cancer therapies among HIV-positive patients.[9]

A number of concerns have been raised about including PLWH in cancer clinical trials, such as possible impaired efficacy of immune checkpoint inhibitors in immunosuppressed individuals, potential exacerbation of immune reconstitution inflammatory syndrome (IRIS) in patients recently started on ART, and unknown effects on other HIV-related opportunistic infections or malignances.[10] To our knowledge, there have thus far only been three case reports of patients with NSCLC and HIV who were treated with an immune checkpoint inhibitor.[11–13] In this brief report, we describe seven additional cases of NSCLC patients with HIV who were treated with PD-1 inhibitors.

Methods

Clinicopathologic data and treatment outcomes were collected from retrospective chart review among patients with HIV and NSCLC who had consented to ongoing Institutional Review Board – approved studies at the Beth Israel Deaconess Medical Center and the Dana-Farber Cancer Institute.

Results

We identified seven patients with metastatic NSCLC and HIV infection who were treated with PD-1 inhibitors (Table 1); five received pembrolizumab and two received nivolumab. Six patients were male and one was female (age range, 43 to 59 years); all patients had lung adenocarcinoma histology and a history of tobacco use. In three cases, a *KRAS* mutation was identified, and oncogenic driver mutations were not detected in the other four cases. In the five cases where PD-L1 immunohistochemistry was performed, the PD-L1 TPS was $\geq$ 90% in four cases and 20% in one case. One patient (case 1) was ART-naïve at the time of pembrolizumab initiation and had a cluster of differentiation 4 (CD4) count of 423/μL and an HIV viral load (VL) of 12,589 copies/mL with a history of latent syphilis and cutaneous Kaposi sarcoma (KS) of the leg, left shoulder, and arm. One patient with intermittent adherence to ART

also had chronic hepatitis B (case 7) and another with intermittent adherence also had untreated chronic hepatitis C genotype 1a, with normal liver function, a CD4 count of 57/μL and an undetectable HIV VL at the time of pembrolizumab initiation (case 3). The other four patients had been adherent to ART for many years and had an undetectable HIV VL with no known history of opportunistic infections at the time of anti–PD-1 initiation.

In all cases, immune checkpoint inhibitor therapy was administered intravenously at standard doses (pembrolizumab 200 mg every 3 weeks or nivolumab 3 mg/kg every 2 weeks). The patients who had already been adherent with ART continued their HIV regimen without a change or interruption in ART. For case 1, ART was initiated 3 weeks after the start of pembrolizumab and intramuscular penicillin was also administered for latent syphilis. For case 3, ART was reinitiated at the start of pembrolizumab, and this patient also received trimethoprim/sulfamethoxazole for *Pneumocystis jiroveci* pneumonia prophylaxis and azithromycin for mycobacterium avium complex prophylaxis given the low baseline CD4 count.

Three confirmed partial responses to pembrolizumab were observed; two patients remain on treatment (Fig. 1) and another patient with an ongoing response died due to complications from a non-ST elevation myocardial infarction unrelated to immunotherapy treatment. Two patients had stable disease, and two patients had progressive disease as a best overall response. Treatment with the PD-1 inhibitor was generally well tolerated in all seven cases. One patient experienced grade 1 fatigue and two patients developed grade 2 arthralgias. One patient developed grade 1 arthralgias, grade 1 headache, and grade 1 chest pain after the first nivolumab infusion, but these symptoms resolved spontaneously and did not recur. No grade 3-4 immune-related adverse events or treatment-related deaths occurred while on anti–PD-1 therapy. Autoimmune thyroiditis was not observed in these seven cases.

While on treatment with a PD-1 inhibitor, CD4 counts did not markedly change in the cases where follow-up values were available, although the CD4 count did decrease in one case (case 1) from 423/μL to 307/μL. In one patient, the HIV VL was initially undetectable but became detectable to 42 copies/mL (case 3). In another

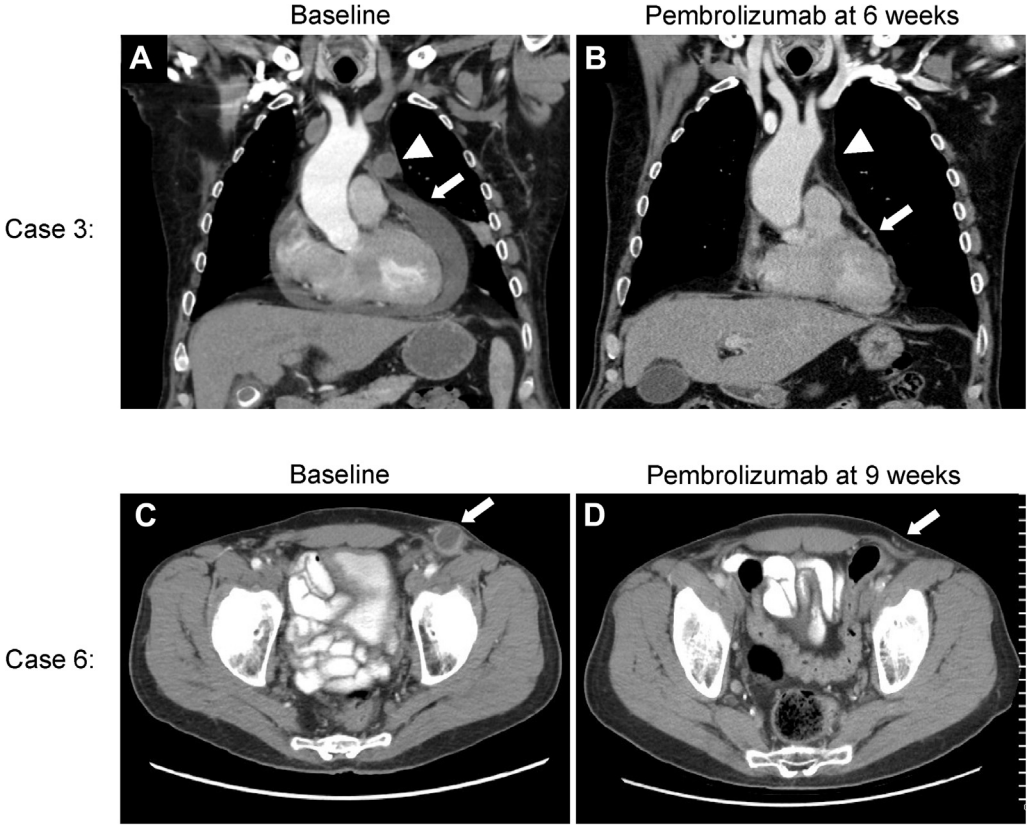

Figure 1. Computed tomography images showing disease response to pembrolizumab in two patients with HIV and NSCLC. (*A*) In patient 3, a malignant pericardial effusion (*arrow*) and mediastinal adenopathy (*arrowhead*) responded to pembrolizumab (*B*) after 6 weeks of treatment. (*C*) In patient 6, a left inguinal lesion (*arrow*) responded to pembrolizumab (*D*) after 9 weeks of therapy.

case, the HIV VL was also initially undetectable but increased to 115 copies/mL after one dose of pembrolizumab and then decreased to detectable but not quantifiable levels at <30 copies/mL (case 7). Both of these patients experienced an increase in CD4 counts during this time (from 57/μL to 140/μL and from 297/μL to 305/μL, respectively) and were fully adherent to ART. No opportunistic infections or manifestations of IRIS occurred even in the one patient who commenced ART 3 weeks after initiating pembrolizumab. The active KS lesions in this patient remain unchanged after 3 months of pembrolizumab therapy. The patients with chronic viral hepatitis infections continue to have normal liver function several months into therapy with pembrolizumab.

Discussion

Because HIV infection has typically been an exclusion criterion for immunotherapy clinical trials, our knowledge about the safety and efficacy of PD-1 pathway inhibitors among patients with HIV and cancer is quite limited. A case report recently described a patient with well-controlled HIV on ART (CD4 count of 684 cells/μL, undetectable VL) who experienced a complete response to nivolumab for recurrent squamous NSCLC (PD-L1 TPS unknown) without any significant side effects.[11] Another patient with squamous NSCLC (PD-L1 TPS 3%) experienced disease progression after 4 cycles of nivolumab and had a decrease in CD4 count from 370/μL to 130/μL while on nivolumab; HIV VL remained undetectable.[12]

Partial and complete responses to immune checkpoint inhibitors have also recently been observed in HIV-positive patients with melanoma, and in one HIV-positive patient with Merkel cell carcinoma.[14] Patients who were already on ART at the start of immunotherapy treatment continued receiving ART without incident, and no opportunistic infections arising during treatment with immune checkpoint inhibitors have been identified.[11,12,14] Treatment with immunotherapy has generally been well tolerated among cancer patients with HIV although one patient developed grade 3 colitis and another developed grade 4 myositis while on ipilimumab plus nivolumab as a treatment for melanoma.[11,12,14]

Here, we report seven additional cases of patients with HIV and advanced NSCLC who were treated with anti–PD-1 therapy. Three partial responses were observed and treatment with immunotherapy was well-tolerated among these seven patients with only grade 1-2 adverse events occurring. When data were available, the HIV VL did not markedly change, and the CD4 count remained under control while on treatment. No IRIS, opportunistic infections, or other AIDS-defining illnesses were identified while on treatment.

In addition to their potential antitumor activity, the effect of immune checkpoint inhibitors on control of chronic viral infections is also of immense clinical interest. Ongoing antigenic stimulation from chronic viral infections such as HIV can increase expression of inhibitory receptors on T cells such as PD-1 and cytotoxic T-lymphocyte associated protein 4, leading to a state of T-cell exhaustion, and a decrease in immunologic responses against HIV-infected cells.[15] A phase I study of a single dose of the PD-L1 inhibitor BMS-936559 at 0.3 mg/kg among six patients with well-controlled HIV showed that treatment with an immune checkpoint inhibitor was generally safe with grade 1-2 adverse events occurring in three patients, and no grade 3-4 adverse events. Enhanced HIV-specific immunity was observed among two patients in this study, suggesting a potential therapeutic role for PD-1 pathway inhibitors among HIV-positive patients.[16] Another phase I study aims to investigate the safety and effect of a single dose of pembrolizumab on PD-1 expression and HIV-specific antibody responses in the cerebrospinal fluid in HIV-positive patients without cancer (NCT03239899). Recently, a patient with NSCLC treated with nivolumab experienced a transient increase in the HIV VL followed by a significant decrease in HIV reservoir along with an increase in HIV-specific CD8 T lymphocytes, highlighting the potential therapeutic benefit of immune checkpoint inhibitors among patients with chronic viral infections, although further studies must verify the generalizability of this finding.[13]

With our initial experience in this small cohort of patients, anti–PD-1 therapy appears to be safe, and in some cases, very effective in HIV-positive patients with lung cancer. However, additional research must address several unanswered questions regarding the use of immune checkpoint inhibitors among patients with NSCLC and HIV. A detailed characterization of PD-L1 expression and tumor mutational burden in NSCLCs from patients with HIV is currently lacking. Furthermore, the safety of immune checkpoint inhibitors in this population warrants further investigation with respect to the incidence of serious immune related adverse events and IRIS particularly among patients who commence ART around the same time as initiation of immunotherapy. The overall response rate to anti–PD-1 therapy and factors that might impact response to immunotherapy (e.g., degree of immunosuppression) are also unknown. There are currently several ongoing clinical trials examining the use of nivolumab (NCT03304093), durvalumab (NCT03094286), pembrolizumab (NCT02595866), or the combination of ipilimumab with nivolumab (NCT02408861), in a variety of tumor types, including NSCLC, among patients with HIV. Because HIV-positive patients are highly underrepresented in oncology

clinical trials, we eagerly await the results of these prospective immunotherapy studies.[17]

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