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Nivolumab Treatment for Cancers in the HIV-Infected Population

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Abstract

Nivolumab is a standard treatment option in several advanced malignancies, but safety and efficacy are still unknown in patients with human immunodeficiency virus (HIV) infection. We describe a case series of people living with HIV (PLWH) receiving nivolumab in the Veterans Health Administration (VA) and report responses and toxicities. We identified all PLWH who received nivolumab at any VA facility since 2000 in the Corporate Data Warehouse (CDW), which provides nationwide research access to VA electronic medical records. We identified 16 HIV-infected nivolumab recipients. The median number of nivolumab doses received was 6 (range, 1–32). Changes in CD4 count during therapy were variable, with 70% (7/10) of patients experiencing

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increases. Half of PLWH were treated for non-small cell lung cancer (NSCLC); 2 for Hodgkin lymphoma (HL), 2 for renal cell carcinoma (RCC), and 4 for off-label cancers. For NSCLC, 7 patients had evaluable responses. While 5 of these 7 patients immediately progressed, 1 had a partial response (PR) and 1 had stable disease (SD), which were both durable. Two of the 16 (14%) PLWH had complete responses (CRs); both with HL (2/2 HL, 100%). The prevalence of immune-related adverse effects (irAEs) was 40% overall (6/15); 27% (4/15) had pneumonitis. To our knowledge, this is the largest case series reporting outcomes with nivolumab in PLWH. Outcomes were comparable to those seen in studies of HIV-uninfected patients, and particularly interesting for HL. The reason for the high proportions of irAEs is unclear, but needs to be confirmed in larger studies.

Introduction

Nivolumab, a programmed death 1 (PD-1) immune-checkpoint-inhibitor antibody, has been approved by the FDA for the treatment of 8 malignancies since 2015: metastatic microsatellite instability-high colorectal cancer, recurrent or metastatic head and neck cancer, Hodgkin lymphoma (HL), unresectable or metastatic melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), urothelial cancer, and hepatocellular carcinoma (HCC). Moreover, *in vitro* and animal studies have suggested that PD-1 blockade may reverse some of the immune dysfunction in exhausted HIV-specific CD8+ cytotoxic cells.^{1, 2} Yet, the safety and efficacy of immune checkpoint blockade in people living with HIV (PLWH) is still unknown, and data are urgently needed as the aging PLWH population is at increased risk of both virally and non-virally mediated cancers. We report a case series of all known U.S. PLWH with malignancy who received nivolumab between 1/2015 and 7/2017 at the Veterans Health Administration (VA). Our primary objective was to describe this population and report an exploratory analysis of responses and drug tolerance.

Methods

We searched the Corporate Data Warehouse (CDW) to identify all HIV-positive patients who used the VA from January 1, 2000 through December 31, 2016. Inclusion criteria were: 1) at least 18 years old the time of HIV diagnosis; 2) at least 2 out of 3 of the following criteria: (a) presence of HIV viral load test or CD4 count test or positive HIV Western Blot or ELISA antibody test; (b) presence of prescription for antiretroviral therapy (ART); or (c) ICD-9/10 code for HIV. Within this cohort, we searched for patients who had received nivolumab between January 1, 2015, and July 26, 2017 in either inpatient or outpatient settings. To establish patterns of use in comparable veterans, we created a control cohort of HIV-uninfected patients, matched 4:1 to the HIV cases by 1) gender; 2) occurrence of an outpatient visit within one month of the case's index date (HIV diagnosis date); and 3) age within two years of the case's age at HIV diagnosis. In the control cohort, we measured the proportion of patients who received nivolumab.

We reviewed the electronic medical records of PLWH using the secure Compensation and Pension Records Interchange (CAPRI) and extracted age, sex, geographic location, smoking status at time of cancer diagnosis, smoking history by cumulative pack years, hepatitis B

(HBV) and hepatitis C (HCV) co-infection (based on hepatitis B surface antigen and anti-HCV IgG, respectively), cancer type, number of doses of nivolumab received, previous cancer therapy, adverse effects, response to therapy, and immune parameters such as CD4 count and viral load. We calculated summary descriptive statistics including proportions and medians for each variable with Microsoft Excel (v16.0), and significance using Fisher's exact test with IBM SPSS Statistics version 24. This study was approved by the Institutional Review Board (IRB) of Baylor College of Medicine, and administrative review was given by the VA IRB.

Results

The cohort of PLWH patients met at least 2 HIV-defining criteria were 96.9% male. Sixteen patients had received nivolumab during the study period (Table 1). In the control cohort, 69 patients had received nivolumab. The administration rates were thus 3.4 per 10,000 HIV-infected patients and 3.7 per 10,000 HIV-uninfected patients, respectively (data not shown).

The median age at nivolumab initiation in the HIV cohort was 65 years (range, 47–85); all were male. Half (8/16, 50%) received nivolumab for NSCLC; 2 patients for HL; and 2 for RCC. The other four patients were treated with nivolumab for off-label indications, including HCC, which was added as an indication to nivolumab's label after the study period, in September 2017. The median number of previous lines of therapy was 1 (range, 1–4). The median number of doses of nivolumab received was 6 (range, 1–24) and dose amount was 3 mg/kg, given every 2 weeks. PD-L1 expression was not reported for most tumors. For NSCLC, 7 patients had continued follow-up, with 1 patient who had a partial response (PR), 1 with stable disease (SD), and the remaining patients had disease progression. The median progression-free survival (PFS) was 2.75 months. The patient with a PR remained in PR, on nivolumab at the time of chart review, after 15 months of therapy (Table 1).

In the entire PLWH cohort, 2 patients (14%) had complete responses (CRs), both with nodular sclerosis HL, and each having received 4 prior lines of therapy. Both received nivolumab for at least 6 months. One patient was originally diagnosed with IIB disease almost 20 years earlier and treated with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD), then in the recurrent setting with ifosfamide, carboplatin, and etoposide (ICE), gemcitabine/vinorelbine, and brentuximab vedotin (hereafter called brentuximab) before receiving nivolumab. Despite no anti-neoplastic therapy for the last 2 years, he continues to have stable scans. The other patient, also stage II HL, did not respond to cyclophosphamide, vincristine, prednisone, and procarbazine (COPP), brentuximab monotherapy, brentuximab in combination with gemcitabine, or ICE. His CR by positron emission tomography-computed tomography (PET-CT) was seen after 8 cycles of nivolumab (Figure 1), and has so far persisted for greater than 10 months.

The median time between HIV diagnosis and cancer diagnosis was 18 years (range, 0–32). Fifteen of the patients received ART concurrently with nivolumab (Table 2). Most patients (10/16, 63%) had baseline CD4 counts > 200 cells/mm³ and baseline undetectable HIV RNA viral loads (7/10, 70%), and most (7/10, 70%) experienced increases in CD4 count

while receiving nivolumab therapy. All patients with follow-up HIV RNA data had either decreases in viral load or stability with nivolumab. The clinical benefit rate (CBR), the proportion of patients achieving CR, PR, or SD, was 50% (3 of 6) in patients with baseline CD4 counts ≤ 200 cells/mm³ and 25% (2 of 8, both with HL) in patients with baseline CD4 counts > 200 cells/mm³ (Table 2).

Six patients (40%) developed immune-related adverse events (irAEs): 4 (27%) with pneumonitis, 1 of whom also developed rash, 1 patient with hypothyroidism, and 1 patient with autoimmune diabetes mellitus. These were graded based on Common Terminology Criteria of Adverse Events (CTCAE). Most of the cases of pneumonitis were grade 3, while most of the other irAEs were grades 1–2 (Table 1).

None of the patients were co-infected with HBV; 4 of the patients were co-infected with HCV (Table 2). Ten (63%) patients were current smokers, 4 (25%) patients were former smokers, and 2 (13%) had never smoked (Table 2). Among current and former smokers, the median number of cumulative lifetime pack years was 35. One (25%) of the patients who experienced pneumonitis was a current smoker. There was no significant association between smoking history (less than 30 vs. greater than or equal to 30 pack years) and occurrence of pneumonitis ($p=0.876$).

Discussion

Malignancy is now the most common cause of mortality in PLWH receiving ART.^{3, 4} Evidence-based management of malignancies in this population is frequently not well-established because most clinical trials exclude PLWH. The role of nivolumab, an anti-neoplastic therapy approved in 2014, is similarly unknown in this population. Fewer than 10 PLWH patients' outcomes have been reported in the literature, mostly in case reports.^{5–9} Currently, two phase I clinical trials are evaluating the use of checkpoint inhibitors in patients with HIV infection and recurrent or refractory malignancies: one with pembrolizumab (NCT02595866), and the other with the combination of nivolumab and ipilimumab (NCT02408861). While we await the results of these trials, we report the largest case series of outcomes with nivolumab in PLWH to date. This is also the first study, to our knowledge, to report the high rate of irAEs.

In this case series, partial or complete responses were not limited to patients with CD4 counts greater than 200 cells/mm³; in fact, of the patients with baseline CD4 counts greater than 200 cells/mm³, the only responders were the patients with HL. Rather than responses being associated with CD4 count, we found that CRs were associated with cancer type. The 2 CRs in HL are hypothesis-generating, and the role of nivolumab as an addition in first-line as well as earlier in relapsed HIV-associated HL (HIV-HL) deserves further prospective study. The frequency of pneumonitis overall was higher than proportions reported in the literature (3–9%).¹⁰

Although this is a small sample, the number of irAEs is concerning. Epidemiologic studies have demonstrated higher rates of autoimmune phenomena occurring in PLWH. In a retrospective cohort study of 20,444 PLWH followed over 12 years in the post-ART era in

Taiwan, compared to 2 million HIV-uninfected controls, the standardized incidence rates (SIRs) were higher for incident Sjögren syndrome (SIR=1.6), psoriasis (SIR=2.1), systemic lupus erythematosus (SIR=2.6), autoimmune hemolytic anemia (SIR=35.1) and uveitis (SIR=2.5). Several mechanisms appear to contribute to the elevated risk of autoimmunity: 1) polyclonal activation of B cells¹¹ with hypergammaglobulinemia,^{12, 13} 2) dysfunctional T/B cell interactions,¹⁴ 3) molecular mimicry,^{15, 16} 4) increased production of autoantibodies,^{16, 17} and 5) the direct effect of HIV proteins on B cell function.^{13, 18} In one study, the rates of asymptomatic anti-nuclear antibodies (ANA), anti-neutrophil cytoplasmic antibodies (ANCA), and anti-glomerular basement membrane (GBM) autoantibodies was 23%.¹⁹ It is possible that many PLWH in this study who were thought to have no pre-existing pathological autoimmunity, may in fact have been harboring subclinical autoantibodies, which become symptomatic with the addition of checkpoint inhibitors.

The main limitations of our study are the small sample size and retrospective design. Though response rates are difficult to reliably assess in individual cancers due to small numbers in this series, the objective response rate in NSCLC observed in PLWH treated in the VA was comparable to that observed elsewhere: 14% in our series compared to 19–20% in other HIV-uninfected patients.^{20, 21} Additionally, because the PLWH in our cohort were not treated as part of a clinical trial, radiographic assessments of progression were not necessarily done by Immune-Related Response Criteria, and discontinuation of nivolumab was immediate upon radiographic progression, thus making distinction between progression and pseudoprogression difficult. Lastly, our retrospective design limited comprehensive assessments of adverse events, as we were dependent on documentation of patients' symptoms in the electronic medical record.

Conclusion

Nivolumab has been administered in the VA to PLWH and HIV-uninfected veterans with advanced cancer at comparable rates. Tumor response rates in PLWH are similar to those seen in the literature, with a subset of patients gaining durable benefit, regardless of baseline CD4 count. The potential efficacy of checkpoint inhibitors in HIV-HL is particularly promising. The reason for the high proportions of irAEs in PLWH compared to HIV-uninfected cohorts is unclear, but needs to be confirmed in larger studies.

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Figure 1.

Top row: trans-axial images from CT and PET, pre-nivolumab, with right supraclavicular lymphadenopathy. Most notable example measures 2.1 cm, with significant FDG uptake (max SUV of 6.7). Bottom row: trans-axial images from CT and PET post-nivolumab from a similar slice with complete response to therapy. The example node measures 0.7 cm and is no longer FDG-avid with max SUV of 1.5. Deauville score of pre-therapy PET/CT scan is 5a (uptake at initial site that is markedly increased compared to the liver), and of post-therapy scan is 1 (no uptake above background).

Table 1

Responses and Toxicities of U.S. HIV-infected Veterans Who Have Received Nivolumab

Patient	Age ^a	Indication	Doses of nivolumab received	Number of prior lines of therapy	Best response	PFS (months) ^b	Immune-related adverse events (grade) ^c
1	58	anal SCC	7	3	SD	8	pneumonitis (4), rash (2)
2	67	HCC	3	1	P	3	pneumonitis (3)
3	62	HCC + pancreatic	4	1	P	2	0
4	50	Hodgkin	14	4	CR	NR (> 32)	0
5	47	Hodgkin	18	4	CR	NR (>10)	diabetes mellitus (2)
6	65	NSCLC (SCC)	2	1	UTA	1	hypothyroidism (2)
7	71	NSCLC (adeno)	3	1	P	2.5	0
8	67	NSCLC (adeno)	5	1	P	2	0
9	82	NSCLC (SCC)	6	1	P	2	0
10	62	NSCLC (adeno)	6	2	P	3.5	0
11	56	NSCLC (SCC)	6	1	P	3	0
12	85	NSCLC	9	1	SD	NR (>10)	pneumonitis (3)
13	61	NSCLC	32	1	PR	NR (>15)	0
14	69	RCC	1	1	UTA	UTA	UTA
15	65	RCC	3	2	P	2	pneumonitis (3)
16	68	SCLC	2	1	P	1	0

Abbreviations: adeno, adenocarcinoma; HCC, hepatocellular carcinoma; NR, not reached; NSCLC, non-small cell lung cancer; P, progression; PFS, progression-free survival; RCC, renal cell carcinoma; SCC, squamous cell carcinoma; SCLC, small cell lung cancer; SD, stable disease; UTA, unable to assess.

^a Age at nivolumab initiation.

^b Patients were not necessarily receiving therapy the entire time.

^c Grade based on Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Smoking and Immunologic Status of U.S. HIV-infected Veterans Who Have Received Nivolumab

Table 2

Patient	Years diagnosed with HIV	ART regimen ^a	Baseline HIV parameters			Change with nivo ^c			HCV ^d	Smoking ^e	Smoking history: pack years
			CD4 (cells/mm ³)	VL (log [copies/mL]) ^b	CD4/CD8 ratio	CD4	viral load	CD4/CD8 ratio			
1	18	INSTI	164	1.5	0.2	↓40%	↓1 log	↑35%	–	former	5
2	67	NNRTI	304	UD	0.4	↑35%	---	↑31%	+	current	7
3	62	INSTI	180	UD	0.1	↑48%	---	↑36%	+	current	10
4	50	PI	300	UD	0.3	---	↓1 log	↑11%	–	current	20
5	47	NNRTI	391	UD	0.4	↑9%	---	↑16%	–	current	25
6	65	NNRTI	915	UD	0.8	UTA	UTA	UTA	–	current	55
7	71	PI	63	1	0.5	UTA	UTA	UTA	–	current	75
8	67	INSTI	400	UD	0.7	UTA	UTA	UTA	–	current	50
9	82	PI	374	1	0.5	↓39%	---	↓6%	–	former	200
10	62	INSTI	189	1.5	0.5	↑21%	↓1 log	↓20%	–	never	0
11	56	NNRTI	380	1.5	0.6	↑30%	---	↑67%	–	never	0
12	85	NNRTI	194	UD	0.7	↑51%	---	---	–	former	90
13	61	PI	189	2	0.9	↑114%	↓0.5 log	↓16%	–	current	40
14	69	None ^f	681	UD	1.6	UTA	UTA	UTA	+	current	25
15	65	PI	613	UD	UTA	↓90%	---	UTA	+	former	35
16	68	INSTI	280	UD	0.2	UTA	UTA	UTA	–	current	35

Abbreviations: +, positive; –, negative; ---, stable; ART, antiretroviral therapy; HCV, hepatitis C virus; INSTI, integrase strand inhibitor-based therapy; nivo, nivolumab; NNRTI, non-nucleoside reverse transcriptase inhibitor-based therapy; PI, protease strand inhibitor-based therapy; UD, undetectable; UTA, unable to assess; VL, viral load

^a ART regimen during nivolumab therapy.

^b Rounded to nearest 0.5.

^c “Stable” is defined as < 5% change

^d Based on presence of anti-HCV IgG.

^e Smoking status at the time of cancer diagnosis.

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