Cancer immunotherapy in adult patients with HIV

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ABSTRACT

The availability of antiretroviral therapy (ART) has increased the life expectancy of people with HIV (PWH) and reduced the incidence of AIDS-associated malignancies, yet PWH have a significantly increased incidence of malignancy and less favorable outcomes of cancer treatment compared with the general population.

Immunotherapy has revolutionized cancer therapy, becoming the standard of care for various malignancy treatments. However, PWH are an underserved population with limited access to clinical trials and cancer treatment.

This review of the available evidence on different classes of cancer immunotherapy in PWH is mostly based on case reports, case series, but few prospective studies and clinical trials due to the exclusion of PWH from most oncologic clinical trials. The results of the available evidence support the safety of immunotherapy in PWH. Immunotherapy has similar effectiveness in PWH, an acceptable toxicity profile, and has no clinically significant impact on HIV viral load and CD4-T cell count. In addition, there is no reported change in the incidence of opportunistic infections and other complications for PWH with well-controlled viremia. This review aims to briefly summarize the current state of immunotherapy in cancer, guide clinicians in the management of immunotherapy in cancer PWH, and encourage the inclusion of PWH in clinical trials of cancer immunotherapy.

INTRODUCTION

Multiple immune-based cancer therapies have been approved for the treatment of malignancy and have resulted in higher and more durable response rates with improved survival.[1–4] Moreover, cancer immunotherapies have a more acceptable toxicity profile when compared with traditional cytotoxic therapy, with fewer drug–drug interactions.[5] Currently available immunotherapy treatment is divided into five categories: cellular immunotherapy, immunomodulators, targeted antibodies, oncolytic virus therapy, and therapeutic cancer vaccines[5 6] (table 1). With a better understanding of the cancer tumor microenvironment and the advancement of bioengineering technology, immunotherapy continues to expand, and new potential targets are being developed. Cancer immunotherapy is anticipated to be used in an increasing number of patients with cancer.[7]

The introduction of antiretroviral therapy (ART) has dramatically improved the outcomes of people with HIV (PWH) and has reduced the incidence of AIDS-associated malignancies.[8] However, cancer remains a major cause of death in this population. PWH are at higher risk of malignancy compared with the general population.[9 10] Melanoma, Kaposi sarcoma (KS), non-Hodgkin's lymphoma (NHL), cervical cancer, and other viral infection-related malignancies such as malignancies related to human papillomavirus, Epstein-Barr virus, and hepatitis B and C viruses are significantly more common in patients with HIV.[11–13] Healthcare disparities,[2] and lack of knowledge of the safety and efficacy of cancer immunotherapy among PWH, limit access to treatment on this population at risk. Despite the recommendation from the American Society of Clinical Oncology supporting the inclusion of PWH in cancer clinical trials,[14] a recent study found that 72.9% of recent cancer immunotherapy trials specifically exclude PWH.[15] The data on the use of immunotherapy in PWH diagnosed with cancer are scarce. We aim to review the available evidence on the safety and effectiveness of the different classes of immunotherapy, including immunomodulators, cellular-based immunotherapy, therapeutic cancer vaccines, and targeted antibodies, in treating PWH and cancer. We will discuss only medications that have been approved by the US Food and Drug Administration (FDA) for cancer treatment.

METHODOLOGY

We systematically searched PubMed for articles on cancer immunotherapy treatment for PWH, using the following keywords: HIV, AIDS, immunotherapy, checkpoint inhibitors, chimeric antigen receptor (CAR)-T cell, monoclonal antibodies (MoAbs). We included any article type. We initially identified 8230 publications. We limited the search to the English language, human studies, cancer, and to a period between September 6, 2011 and September 6, 2021. The search resulted in 651 articles that were screened by 2 investigators (DD and SAK) for relevancy. We excluded duplicates, studies focusing on immunotherapy for HIV treatment, management of HIV reservoir, and context of HIV vaccine development. We also reviewed the reference lists of the retrieved publications for additional correlating studies.

Table 1 Cancer immunotherapy classes and approved FDA medications

Cancer immunotherapy types	Subtypes	Specific active cells/targets	FDA-approved medications
Immunomodulators	Checkpoint inhibitors	PD-1/PD-L1 inhibitors	► Atezolizumab ► Avelumab ► Cemiplimab ► Dostarlimab ► Durvalumab ► Nivolumab ► Pembrolizumab
		CTLA-4 inhibitor	► Ipilimumab
	Cytokines	Interferons and interleukins (ILs)	► IL-2 aldesleukin ► Interferon alpha-2a ► Interferon alpha-2b ► Peginterferon alpha-2b
Cellular immunotherapy, also known as adoptive cell therapy	CAR-T cell therapy	Anti-CD19	► Axicabtagene ciloleucel ► Brexucabtagene autoleucel ► Lisocabtagene maraleucel ► Tisagenlecleucel
		B-cell maturation antigen (BCMA)	► Idecabtagene vicleucel
Therapeutic cancer vaccines		T helper stimulator oncolytic viruses	► BCG
		Dendritic cells	► Sipuleucel-T
Targeted antibodies	Monoclonal antibodies	CD52	► Alemtuzumab
		VEGF/VEGFR	► Bevacizumab
		EGFR	► Cetuximab
		CD38	► Daratumumab
		RANKL	► Denosumab
		GD2	► Dinutuximab
		SLAMF7	► Elotuzumab
		CD38	► Isatuximab
		CCR4	► Mogamulizumab
		EGFR	► Necitumumab
		CD20	► Obinutuzumab
		CD20	► Ofatumumab
		PDGFRα	► Olaratumumab
		EGFR	► Panitumumab
		HER2	► Pertuzumab
		VEGF/VEGFR2	► Ramucirumab
		CD20	► Rituximab
		CD19	► Tafasitamab
		HER2	► Trastuzumab
	Antibody–drug conjugates	BCMA	► Belantamab mafodotin-blmf
		CD30	► Brentuximab vedotin
		Nectin-4	► Enfortumab vedotin
		CD33	► Gemtuzumab ozogamicin
		CD20	► Ibritumomab tiuxetan
		CD22	► Inotuzumab ozogamicin
		CD22	► Moxetumomab pasudotox
		CD79b	► Polatuzumab vedotin
		TROP-2	► Sacituzumab govitecan-hziy
	Bispecific antibodies	CD19 and CD3	► Blinatumomab ► Amivantamab
Oncolytic virus therapy			► Talimogene laherparepvec

CAR-T, chimeric antigen receptor T cells; CCR4, C-C chemokine receptor 4; CTLA-4, cytotoxic T-lymphocyte antigen-4; EGFR, epidermal growth factor receptor; FDA, Food and Drug Administration; GD2, glycolipid; HER, human epidermal growth factor receptor; PD-1, programmed cell death-1; PDGFRα, platelet-derived growth factor receptor α; PD-L1, PD-ligand 1; RANKL, receptor activator of nuclear factor kappa-B ligand; SLAMF7, signaling lymphocytic activation molecule family member 7; TROP2, a transmembrane glycoprotein encoded by the Tacstd2 gene; VEGF/VEGFR, vascular endothelial growth factor and its receptor.

References identified were imported into EndNote (Clarivate Analytics).

DISCUSSION

Immunomodulators

Immune checkpoint inhibitors

T-cell activation, proliferation, and differentiation are complex and are regulated by multiple levels of control. Inhibitory receptors expressed on T cells, called immune checkpoints, aim at regulating the immune system by preventing the activation of self-reactive T cells and autoimmunity. These checkpoints play a significant role in immuno-oncology.[16] Cancer cells evade immunosurveillance by stimulating these checkpoint pathways and subsequently suppressing the T cells and natural killer (NK) cells.[17] Similarly, HIV infection persists by evading immune recognition through establishing a latent infection and increased expression of checkpoints on CD4 and CD8 T cells.[18]

The most established cancer therapies targeting the checkpoint pathways either block cytotoxic T-lymphocyte antigen-4 (CTLA-4), programmed cell death-1 (PD-1), or its complementary PD-ligand 1.[19] Blocking these immune checkpoints prevents T-cell inhibition, resulting in the activation and proliferation of effector T cells which enhances the anti-tumor immune response but also leads to potential immune-related adverse events (AEs) of variable severity.[20 21]

Initially, the US FDA approved immune checkpoint inhibitors (ICIs) for the treatment of melanoma. Since then, their

usage has extended to other malignancies. Clinical data have demonstrated that ICIs have a favorable toxicity profile and potent activity on several malignancies.[21] PWH are historically excluded from clinical trials for cancer treatment with ICI due to concerns of tolerance, efficacy, and direct effect on HIV replication. However, PWH might potentially attain additional benefits from ICI therapy, in addition to activity against malignancy. For many years, the use of immunotherapy has been investigated as a curative strategy for HIV. ICI showed promising in-vitro results that are undergoing study in PWH.[19] The first clinical trial comparing the effect of nivolumab versus nivolumab and ipilimumab demonstrated that combination therapy, not monotherapy, induced a small HIV latency-reversing effect warranting additional investigation.[18]

There have been many case reports and case series published about PWH who received ICI for cancer treatment.[17 22–38] A systematic review[39] of PWH with advanced cancer treated with ICI, conducted in April 2018, identified 73 patients. The majority were male (90%) and received anti-PD-1 inhibitors, nivolumab (40%) and pembrolizumab (35%), and an unspecified anti-PD-1 (10%). The rest of the patients received either a CTLA-4 inhibitor, ipilimumab (8%), or combination ipilimumab with anti-PD-1 (7%). Cancer types were non-small cell lung carcinoma (34%), melanoma (22%), and KS (12%), anal cancer (7%), head and neck cancer (6%), and other (20%). AEs were similar to patients without HIV infection. Combination therapy of anti-PD-1 and anti-CTLA-4 was more likely to be associated with grade 3 or higher immune-related AEs. The overall response rate was consistent with trials of patients without HIV. Many of these patients did not have baseline HIV viral load or CD4 reported. However, among patients with HIV viral load and CD4 cell counts available before and after ICI therapy, there was no evidence of negative impact on viral suppression or CD4 cell counts.[39]

A more recent systematic review[19] identified 176 PWH who received ICI as cancer therapy (83%) or as HIV-targeted therapy (17%). The review included pooled data from 19 case reports, 9 case series, and 3 clinical trials. Non-severe AEs were reported in 49% of the patients, while severe AEs were reported in 12%, comparable with the incidence of severe AEs reported from patients without HIV (13%–14%). Severe AEs included pneumonitis, enterocolitis, autoimmune hepatitis, skin eruption, nephritis, neutropenia, and lymphopenia. One patient developed neurosyphilis soon after treatment with nivolumab and responded well to treatment. One patient had KS-lymphoproliferative disease and died. There was no immune reconstitution inflammatory syndrome noted in any of these reports. In addition, there was no significant impact on HIV viral load or CD4 cell counts.[19]

In table 2, we summarize 3 clinical trials and 1 prospective observational study on PWH treated with ICI for cancer

Table 2 Clinical trials and prospective study on patients with HIV treated with immune checkpoint inhibitors for cancer therapy

Study	Patient characteristics	Baseline HIV status	Cancer type	Treatment	Primary outcome for evaluable patients	Non-immune-related AE	Immune-related AE	Effect on HIV and CD4
Scully *et al*[36] Prospective observational 2018	N=3 All men		2 H&N SCC 1 skin cancer	2 nivolumab 1 pembrolizumab	1 CR 2 SD	1/3 grade 1, 2 0 grade 3, 4	Possible autoimmune dermatitis	No significant change in HIV VL or CD4
Uldrick *et al*[40] Open-label phase 1 clinical trial non-randomized 2019 USA	N=30 93% men Median age 57 y	On ART HIV VL <200 CD4 >100	Advanced cancer 6 KS 5 NHL 19 non-AIDS-defining cancers	Pembrolizumab for up to 35 doses	1 CR 2 PR 17 SD 8 PD	73% grade 1, 2 20% grade 3, 4 4 anemia 1 increase ALT/AST 1 soft tissue infection 1 KS-associated B-cell lymphoproliferative disease and death	6 hypothyroidism 3 pneumonitis 2 rash	No significant effect on HIV VL or CD4
Lavole *et al*[41] Open-label phase 2 clinical trial non-randomized 2021 France	N=16 88% men Median age 58 y	On ART HIV VL <200 CD4 count any	Advanced NSCLC	Nivolumab Median duration 3.5 mo Median follow-up 23.6 mo	Disease control rate 62.5% 2 PR 8 SD 5 PD	75% grade 1, 2 6% grade 3, 4 1 pruritus, pemphigoid, and onycholysis	None	No significant effect on VL or CD4
Gonzalez-Cao *et al*[42] Open-label phase 2 clinical trial non-randomized 2020 Spain	N=20 80% men Median age 54 y	On ART HIV VL UD CD4 count any	Advanced solid tumor 14 NSCLC 2 melanoma 2 anal cancer 1 SCLC 1 bladder cancer	Durvalumab Median duration 4 mo Median follow-up 12.7 mo	Disease control rate 50% 4 PR 5 SD 7 PD (4 early deaths not drug related, secondary to rapid PD	0 grade 3, 4	None	No significant effect on VL or CD4

AE, adverse event; ALT, Alanine transaminase; ART, antiretroviral therapy; AST, Aspartate aminotransferase; CR, complete response; H&N, head and neck; KS, Kaposi sarcoma; NHL, non-Hodgkin's lymphoma; NSCLC, non-small cell lung carcinoma; PD, progressive disease; PR, partial response; SCC, squamous cell carcinoma; SD, stable disease; UD, undetectable; VL, viral load in RNA copies/µL.

therapy.[36 40–42] In most case reports and studies, at the time of ICI initiation, patients were on ART and had controlled HIV, with a range of CD4 cell counts. Several clinical trials studying the use of ICI, alone or in combination, in PWH with advanced cancer are underway.[43]

Cytokines

Cytokines are proteins that act to facilitate intercellular inflammatory interactions.[44 45] Cytokines as cancer monotherapy that failed to prove their efficacy through clinical trials, but appear to enhance the activity of checkpoint inhibitors.[46] Two cytokines were approved by FDA as monotherapy, interleukin (IL)-2 and interferon-alpha (IFN-α).[47] Another cytokine, IL-12 showed a potent anti-cancer effect in preclinical models, but use has been limited by systemic toxicities. Localized treatment to minimize systemic exposure is undergoing study in clinical trials.[48]

IL-2 is secreted by activated T-helper cells to stimulate proliferation of B and T cells[44 49] and is a major trigger in activating the proliferation of NK cells, and B and T lymphocytes.[50] IL-2 was approved for the treatment of metastatic renal cell carcinoma and metastatic melanoma. The overall response rate ranged from 15% to 20%.[51] The use of IL-2 in PWH was studied starting more than 20 years ago as an HIV treatment and yielded no clinical benefit despite leading to increases in CD4 cell counts.[52 53]

Subcutaneous IL-12 showed potent activity on AIDS-related KS. In a phase 1 study on 32 PWH and progressive KS despite ART, the observed overall response rate was 61%.[54] In a subsequent study, the combination of subcutaneous IL-12 with doxorubicin resulted in substantial tumor response. The primary AEs noted were influenza-like symptoms, neutropenia, anemia, elevated transaminases, and bilirubin.[55]

IFN also has immunomodulatory effects against tumors.[56] IFN-α was found to have pro-apoptotic, anti-proliferative activities, and antiangiogenic characteristics.[45] One of the first cytokine immunotherapies used in PWH is IFN-α for the treatment of HIV.[57] The response rate for treatment of HIV-associated KS with IFN-α was around 20%–40%.[58–62] IFN-α was approved by the FDA for the treatment of AIDS-related KS in 1988.[63 64] However, IFN-α is rarely used at present, especially as monotherapy, due to associated AEs, decreased incidence of KS, and the emergence of new agents.[64]

Cellular immunotherapy, also known as adoptive cell therapy

CAR-T cell therapy

This type of therapy uses harvested human T cells from peripheral blood and genetically modifies these cells to express CARs. These cells are multiplied, a process that takes 2–3 weeks. CAR-T cells are then reinfused to the patient to bind to specific antigens presented by the cancer cells and produce a potent anti-tumor effect.[65] Current CAR-T cell therapies have two cancer targets, the B-cell marker (CD19), typically expressed by leukemia, lymphoma, and myeloma cells, or the B-cell maturation antigen (BCMA), typically expressed by myeloma cells. Clinical trials of CAR-T cell immunotherapy have shown positive results.[66] The first CAR-T cell therapy was approved in 2017. The FDA has now approved 4 anti-CD19 CAR-T cells for the treatment of relapsed/refractory (R/R) acute lymphoblastic leukemia (ALL) in young adults up to age 25 years and specific subsets of B-cell lymphomas and 1 anti-BCMA CAR-T cell for refractory multiple myeloma (table 1).[67]

However, CAR-T cell therapies have significant side effects that could be life-threatening. The US FDA provides boxed warnings about the risk of cytokine release syndrome (CRS) and immune cell-associated neurotoxicity syndrome (ICANS). All CAR-T cell therapies are approved for use under a risk evaluation and mitigation strategy program.[68]

The use of cellular immunotherapy as a strategy to target and treat HIV has been studied in the past,[69] but the use of CAR-T cell therapy to treat cancer in PWH has not been studied.[70] The safety and efficacy of CAR-T cell to treat hematological malignancies might be different in patients with or without HIV. First, CAR-T cell therapy in PWH will be derived from HIV-infected T cells. PWH might have HIV-mediated T-cell depletion. There are concerns for interaction between ART and CAR-T cell therapy and a higher risk of infectious and immune-mediated complications. In addition, baseline cytokine levels could be different in PWH compared with patients without HIV, which could affect the incidence and the severity of CRS and neurological complications, as well as the expansion and persistence of CAR-T cell therapy.[71]

The FDA does not exclude PWH for the approved CAR-T cell therapies, yet in a small international survey sent in 2019 to physicians with experience in administering CAR-T cell therapies, there was a general agreement that patients with chronic viral infections, including HIV, should not be eligible for treatment.[72]

A total of 4 PWH were treated with anti-CD19 CAR-T cells (axicabtagene ciloleucel) for R/R diffuse large B-cell lymphoma (DLBCL). In 1 report, 2 PWH underwent successful autologous CAR-T cell therapy along with ART that resulted in long-term remission of the lymphoma. One patient had a CD4 cell count of 52 cells/mm^3 at the time of apheresis and the other patient had a CD4 cell count of 127 cells/mm^3. The side effects were consistent with expected CAR-T cell therapy in patients without HIV and were reversible with standard therapy.[73] A case series of 10 patients who received CAR-T cell therapy for R/R DLBCL included 1 PWH on ART. The patient had complete remission at 3 months and had no significant toxicities.[74] Allred *et al* reported a patient with well-controlled HIV on ART who underwent CAR-T cell for R/R DLBCL, had grade I CRS and grade II ICANS that resolved with standard protocol; however, at 2 months after CAR-T cell therapy, the patient had evidence of disease progression (table 3).[75]

These case reports have established that CAR-T cell therapy among PWH is possible, even in the context of HIV-associated T-cell depletion, and suggest that it has a comparable safety profile and effectiveness with those without HIV infection. Allred *et al* suggest several steps to optimize CAR-T cell therapy for PWH: engage a multidisciplinary team, achieve HIV control, review and change ART to minimize drug interactions and overlapping toxicities, screen for and treat opportunistic infections, closely monitor HIV control every 3 months for 1 year after CAR-T cell therapy, assess for immune reconstitution, and administer infection prophylaxis for pneumocystis pneumonia, herpes simplex virus (HSV), varicella-zoster virus, and mold.[75]

Table 3 Characteristics and outcomes of patients with HIV who received CAR-T cell therapy (ref)

Patient	Cancer type	HIV status	Treatment	Complications following CAR-T cell therapy	Outcome
#1	EBV-negative DLBCL	Pre-CAR-T cells: HIV VL: 1,760,000 copies/mL; CD4 count: 108 cells/mm^3 Post-CAR-T cells therapy: undetectable HIV VL and a CD4 count of 133 cells/mm	3 cycles of dose-adjusted EPOCH-R axicabtagene ciloleucel	CRS and neurologic toxicities	Follow-up imaging up to 1 y after CAR-T therapy showed complete remission
#2	EBV-positive DLBCL	Pre-CAR T therapy: HIV VL undetectable CD4: 127 cells/mm Post-CAR T therapy: disease activity remained under control	▶ EPOCH-R ▶ Rituximab plus lenalidomide ▶ Lymphodepleting fludarabine at a dose of 20 mg/m^2 (dose reduced for HIV and cytopenia)—cyclophosphamide axicabtagene ciloleucel	No documented CRS or neurologic toxicities	Follow-up CT and PET scan in 4 wk post CAR-T therapy showed complete remission
# 3	DLBCL EBV status unknown	Pre-CAR-T therapy: on ART, HIV VL undetectable, CD4 127 Post-CAR-T, last labs available showed HIV VL 683,817 and CD4 46 ~5 mo post-therapy	Fludarabine and cyclophosphamide prior to CAR-T cell therapy Axicabtagene ciloleucel	Neutropenia (absolute neutrophil count of <500 cells/μL	Complete remission at 3 mo
# 4	R/R DLBCL EBV status unknown	Pre-CAR-T therapy: on ART, HIV VL undetectable, CD4 378	1 cycle of ifosfamide, carboplatin and etoposide Subsequent therapy with fludarabine and cyclophosphamide Followed by axicabtagene infusion and concomitant ART	Grade I CRS and grade II ICANS that resolved with standard protocol	At 2 mo after CAR-T cell therapy, patient had evidence of disease progression

ART, antiretroviral therapy; CAR-T, chimeric antigen receptor T cells; CRS, cytokine release syndrome; DLBCL, diffuse large B-cell lymphoma; EBV, Epstein-Barr virus; EPOCH-R, etoposide phosphate, prednisone, vincristine sulfate (oncovin), cyclophosphamide, and doxorubicin hydrochloride (hydroxydaunorubicin) rituximab; ICANS, immune cell-associated neurotoxicity syndrome; PET, positron emission tomography; R/R, relapsed/refractory; VL, viral load.

Therapeutic cancer vaccines

Multiple efforts are underway to develop vaccines against HIV, but the following section will focus on the use of vaccines for cancer treatment in PWH.

Bacillus Calmette-Guérin

BCG is a live-attenuated strain of *Mycobacterium bovis*.[76] Intravesical BCG is indicated as adjunctive therapy for non-muscle-invasive bladder cancer (NMIBC) at high risk of disease progression.[77] It has been the gold standard and the most effective treatment for NMIBC in the last 40 years.[78] The BCG's mechanism of action is not fully understood. Intravesical BCG has a direct effect on tumor growth and an indirect effect. BCG triggers local inflammation and immune response and induces CD4 T cells and macrophages to improve recognition and destruction of tumor cells.[79]

Transmucosal absorption of intravesical BCG is limited. However, the risk of systemic BCG infection might be increased with mucosal damage, old age, and immunosuppression. Data on immunocompromised patients receiving BCG treatment are limited to draw any conclusions.[80–82]

PWH are theoretically at high risk of developing systemic infections.[83 84] The benefit of prophylactic anti-tuberculous agents such as isoniazid is not established.[85 86] In addition, BCG immunotherapy might not be effective in patients with impaired cell-mediated immune response.[76] There are only 2 case reports of PWH who received BCG intravesical therapy for bladder cancer. In the first report, 2 patients developed a culture-proven pulmonary infection after treatment with BCG, 1 of them HIV positive.[87] In a case series of 10 PWH and bladder cancer, 1 patient received intravesical BCG without infectious complications.[76] Given the critical shortage of BCG therapy, potential systemic infection, and lack of clear efficacy in this group population, alternative treatment should be considered in PWH and NMIBC.

Sipuleucel-T

Sipuleucel-T uses stimulated dendritic cells (DCs) to produce an anti-tumor response. DC precursors are harvested from the patient's peripheral blood, primed ex-vivo to target prostatic acid phosphatase, and then reinfused.[88 89] Sipuleucel-T was the first therapeutic cancer vaccine to be approved by the FDA in 2010 for the treatment of asymptomatic patients with metastatic castration-resistant prostate cancer.[90]

AEs were mostly mild and resolved few days after treatment.[91] However, sipuleucel-T is not commonly used, secondary to controversies in regard to its effectiveness, high cost, and availability of other treatment options.[92] There are no available clinical data about the safety and efficacy of sipuleucel-T in PWH since they were excluded from clinical trials.[93] There are also no available case reports.

Oncolytic virus therapy

Oncolytic virus therapy uses genetically engineered viruses to target malignant cells. These viruses are modified by deleting and inserting new genes to decrease their ability to infect healthy cells and to enhance their tumor-specific tropism. After infection, oncolytic viruses cause lysis of tumor cells leading to the release and recognition of cancer

antigens and the activation of immune response overcoming the immune evasiveness of tumor cells.[94–96]

Talimogene laherparepvec is a modified HSV-1 and is the only currently FDA-approved oncolytic virus therapy, for the treatment of inoperable melanoma.[97] The main challenge of oncolytic viral therapy is the poor bioavailability when systemically administered. To achieve adequate drug delivery and clinical effectiveness, the treatment is administered by direct intratumoral injection. This led to improvement of durable response rates and even regression in distant non-injected tumor sites without significant serious AEs.[96 98–100]

Potential safety concerns include viral mutation with the potential ability for off-target infection, unexpected toxicities, virus shedding, and transmissibility of the virus.[101] Modified HSV oncolytic virus retained the thymidine kinase gene, a target for ganciclovir therapy that could potentially control an infection.[96] Clinical trials for oncolytic virotherapy have excluded patients who are immunocompromised. No clinical data are available on PWH receiving oncolytic virus therapy.

Targeted antibodies

The availability of MoAbs for cancer treatment has significantly expanded the options for cancer treatment while minimizing drug–drug interactions. Targeted antibody therapies include MoAbs, antibody–drug conjugates, and bispecific antibodies.

Monoclonal antibodies

MoAbs are proteins developed to target specific cancer antigens. After binding to cancer cells, antibodies disrupt different pathways of cancer cell activity. The FDA approved the first MoAb rituximab for cancer therapy in 1997, since then many more have been approved for cancer treatment.[102 103] MoAbs are either used as monotherapy or more likely in combination with chemotherapy.[104]

In PWH, the use of anti-CD20 MoAb, rituximab, has been the most studied in the management of HIV-associated lymphomas.[105 106] The only randomized controlled trial comparing the addition of rituximab with cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) versus CHOP in 150 patients with HIV-associated NHL did not show a statistically significant improvement in tumor response rate and was associated with an increase in infection-related deaths, 60% of these deaths occurred in patients with CD4 cell count <50 cells/mm^3.[107] Barta *et al* analyzed pooled individual data from 19 prospective clinical trials, including 1546 PWH with NHL; 84% were male, the median age was 40 years, 69% had DLBCL, 26% had Burkitt lymphoma/Burkitt-like lymphoma, or other (6%). Patients received various chemotherapy regimens, with CHOP the most used regimen (41%). Rituximab was added in 35% of the cases. In contrast to the previously described randomized controlled trial comparing R-CHOP with CHOP, these data have shown that the addition of rituximab improved overall survival, progression-free survival, and increased complete response rate by almost 3-fold in patients, notably in patients with CD4 cell count >50 cells/mm^3.[108] Rituximab-based therapy has improved the prognosis of HIV-associated multicentric Castleman disease (MCD) as well.[109] A retrospective analysis of 113 patients with HIV-MCD suggested that rituximab therapy lowered the risk of developing NHL by 11-fold.[110]

Bevacizumab is a MoAb targeting the vascular endothelial growth factor and its receptor. Main AEs include cardiovascular, such as stroke and myocardial infarction, as well as non-cardiovascular, including proteinuria, hypertension, bleeding, and gastrointestinal perforation. A phase II clinical trial investigated the use of systemic bevacizumab in 17 PWH-associated KS. It was well tolerated, with an overall response rate of 31%.[111] A subsequent study by the same group investigated toxicity and efficacy of combination liposomal doxorubicin with bevacizumab for PWH and KS, who failed to respond to ART or had advanced KS. The overall response rate was 56%, suggesting that combination therapy might result in improved response, compared with bevacizumab monotherapy. However, this study included 2 patients out of 16 who were HIV negative.[112] In an open-label phase 2 study, 14 PWH with KS in the upper airway were randomized 1:1 to ART alone versus ART and intralesional bevacizumab. No difference in tumor response was observed between these two groups.[113]

The use of other MoAbs in PWH and different types of cancers has been described in several case reports: bevacizumab in 2 patients with colorectal cancer (CRC)[114 115] and 1 patient with metastatic hepatocellular carcinoma[116]; cetuximab in metastatic CRC[117]; alemtuzumab in a patient with Sezary syndrome[118]; and the successful treatment of primary effusion lymphoma with daratumumab.[119] The treatment was well tolerated in these cases. For trastuzumab adjuvant chemotherapy, 2 PWH with human epidermal growth factor receptor 2-positive breast cancer were unable to receive the intended regimen due to cardiotoxicity, 1 possibly attributable to trastuzumab.[120]

Antibody–drug conjugates

Antibody–drug conjugates are MoAbs conjugated with a highly potent cytotoxic drug that will be directly delivered to cancerous cells.[121–124] Many antibody–drug conjugates are now approved for the treatment of hematologic and solid malignancies.

Brentuximab vedotin, an antibody–drug conjugate, in combination with doxorubicin, vinblastine, and dacarbazine, was studied in 6 patients with HIV-associated HL. All patients showed a complete response. It was well tolerated with minimal complications.[125]

Bispecific antibodies

Bispecific antibodies (BsAbs) have 2 different antigen-binding sites, 1 directed to tumor-specific antigen and the other targeting immune cells to activate the anti-cancer immune response.[126] The advantages of BsAb over MoAb include higher binding specificity, enhanced cytotoxic effect by bridging immune cells to the cancer cells, and lower risk of resistance by targeting 2 different receptors on the same tumor cell.[127] Blinatumomab is an FDA-approved BsAb, bispecific T-cell engager for treatment of R/R B-lineage ALL. Blinatumomab binds the CD19 on B-lymphocyte cancer cells to the CD3 on cytotoxic T-cell lymphocytes, activating and directing T lymphocytes to destroy cancer cells.[127] In May 2021, the FDA granted accelerated approval

to amivantamab, the second BsAb for adult patients with metastatic non-small lung cancer based on the overall response rate of 40% and median response duration of 11.1 months.[128] Unfortunately, there are no available clinical data, including case reports, regarding the treatment of patients with HIV with these agents, although a recent trial with amivantamab for adenoid cystic adenocarcinoma allows patients with well-controlled HIV to be included.

CONCLUSION

ART has improved clinical outcomes, reduced the incidence of AIDS-associated malignancies, and increased life expectancy for PWH, yet PWH continue to have a significantly increased incidence of malignancy with less favorable outcomes and decreased access to clinical trials and cancer treatment, compared with the general population. This review of the available literature on cancer immunotherapy in PWH suggests that using immunotherapy is likely to be feasible and effective, similar to its effects in patients without HIV infection, and without unexpected toxicities.[37] These results suggest that barriers need to be addressed and efforts implemented to include this underserved population in future clinical trials, so that PWH may also benefit from the therapeutic advances in cancer therapy. Bender Ignacio *et al* question the use of CD4 absolute cell count as a criterion for clinical trial eligibility since CD4 lymphopenia is partly related to the immunosuppressive effects of cancer. Moreover, the higher mortality associated with a chemotherapy-related decline in CD4 cell counts is particularly why immunotherapy should be introduced early in HIV-associated cancer to avoid additional immunosuppression.[129] Criteria for PWH that are well controlled should be similar to non-HIV-infected patients, avoiding the exclusion of those patients with well-controlled HIV and similar comorbidities to other patients undergoing evaluation for cancer treatment or inclusion in clinical trials.

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