Review Article

Immunotherapy in Special and Rare Situations: A Brief Review

Sujay Srinivas, Jyoti Bajpai

Department of Medical Oncology, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India

Address correspondence to Jyoti Bajpai (dr_jyotibajpai@yahoo.co.in).

ABSTRACT

Immunotherapy has established itself as an important component of the treatment armamentarium against various solid as well as hematologic cancers. Immune checkpoint inhibitors (ICI) provide for a very well-tolerated and efficacious treatment option that has improved survival in several cancers. The approved ICIs mainly consist of antibodies targeting cytotoxic T lymphocyte–associated antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) or its ligand, programmed cell death ligand 1 (PD-L1). However, most clinical trials of ICI have excluded patients from high-risk populations, such as those with autoimmune diseases, patients on chronic steroid intake for various reasons or preexisting HIV infections. The older adults are also an underrepresented section of the population enrolled into such trials, most probably due to the higher prevalence of comorbidities and frailty affecting their Eastern Co-Operative Oncology Group performance status, and thus the eligibility for clinical trial enrollment. This paper aimed to briefly review the available evidence and thus guide the decision-making process for use of ICI in such rare and special situations.

Keywords: immune checkpoint inhibitors, autoimmune, HIV, corticosteroids, elderly

AUTOIMMUNE DISORDERS

Approximately 13.5 to 25% of patients diagnosed with lung cancer are simultaneously being treated for several autoimmune diseases.[1] There are three retrospective studies on use of anti–CTLA-4 or anti–PD-1 agents in melanoma patients with autoimmune diseases.[2–4] The response rates reported in these studies was in the range of 12 to 33%, while the rates of flare up of the existing autoimmune disease was 27 to 38% (Table 1). The treatment discontinuation rates reported due to flare-up was 4 to 17% (Table 1). There are relatively fewer studies on the use of ICI in patients of non-small cell lung cancer (NSCLC) and urologic cancers (Table 1). Leonardi et al.[5] reported on the use of ICI in NSCLC patients with a response rate of 22% and 23% patients having flare up of preexisting autoimmune disease, while the safety was comparable to that in the general population with no treatment discontinuation due to autoimmune flare-up. The study by Martinez Chanza et al.[6] was a retrospective international study on the use of ICI in patients of urologic cancers and they reported rates of 35 and 36% in terms of response and flare-ups of autoimmune diseases, respectively. The treatment discontinuation due to flare up of existing autoimmune disease was 6%.

A multicenter study of 112 patients treated for various cancers with ICIs and having autoimmune diseases reported by Tison et al.[7] showed response rates of 49% in patients without prior ICI therapy. They reported relatively higher rates of flare up and treatment discontinuation, which were 47 and 21%, respectively (Table 1). The treatment discontinuation reported here was due to any immune-related adverse events (irAEs). Danlos et al.[8] reported the safety and effectiveness of anti–PD-1 antibodies in different cancer patients with autoimmune or inflammatory disorders from a French registry study. Of the 397 patients included in the study, 45 had preexisting autoimmune diseases and they noticed that although the rate of irAEs was significantly higher in these patients (44 versus 23%); there was no difference in the overall survival among either group.[8] A systematic review by Abdel-Wahab et al.[9] summarized the evidence on adverse events (AEs) with immunotherapy in 123 patients with cancer and preexisting autoimmune disease from 49 publications. There was an exacerbation of preexisting autoimmune disease, irAEs, or both in 75% of the patients. More disease flares were reported with anti–PD-1 or PD-L1 agents and more de novo irAEs were reported with ipilimumab in this study. Most flares and irAEs were managed with corticosteroids, and the

Table 1. Safety and efficacy of immune checkpoint inhibitors (ICI) in cancer patients with autoimmune diseases

Author	Type of Study	N	ICI Used	Flare-Up of Preexisting Autoimmune Disease, %	Treatment Discontinuation due to Flare-Up of Preexisting Disease, %	ORR, %
Kähler et al.[2]	Restrospective	41	Anti-CTLA4	29	17	12
Johnson et al.[3]	Restrospective	30	Anti-CTLA4	27	NA	20
Menzies et al.[4]	Restrospective	52	Anti-PD1	38	4	33
Leonardi et al.[5]	Restrospective	56	Anti-PD1	23	0	22
Martinez Chanza et al.[6]	Restrospective	106	Anti-PD1 or anti-CTLA4	36	6	35
Tison et al.[7]	Restrospective	112	Anti-PD1 or anti-CTLA4	47	21$	49$$
Danlos et al.[8]	Restrospective	45	Anti-PD1	24	4	38

ORR, objective response rates; CTLA4, cytotoxic T lymphocyte–associated antigen 4; NA, not available; PD1, programmed cell death protein 1.
$This is the total discontinuation rates due to any immune-related adverse events (including flare-ups).
$$In patients without prior immunotherapy.

AEs improved in more than half without discontinuation of treatment. High-dose corticosteroids were required to manage AEs in 62% of patients, and other disease-modifying antirheumatic drugs or immunosuppressive therapies were required in 16%.[9] AEs improved in 90% of patients, with 50% of those with AEs having a partial or complete response as compared with 35.7% who did not have AEs.[9]

The candidates who can be considered for ICI are those who have good control of their underlying autoimmune disorder with low-level or no immunosuppression after informed patient consent and who are consulting with an appropriate autoimmune subspecialist.[10] Patients who have poor control of their autoimmune disease or require high doses of immunosuppressants for control, whereas patients with life-threatening autoimmune diseases and autoimmune neurologic or neuromuscular diseases are not appropriate candidates for ICI.[10]

HIV-POSITIVE PATIENTS

Cancer has become one of the leading causes of mortality in this high-risk population of HIV-positive patients. Because of the availability of better antiretroviral therapies (ARTs) and better coverage of AIDS treatment programs across the world the AIDS-defining cancers have declined in incidence while non-AIDS defining cancers, such as anal cancer, lung cancer, melanoma, head and neck cancer, or Hodgkin lymphoma have increased.[11] These tumors in the HIV population usually show a younger age of onset, more aggressive features, and poorer outcomes.[11] There are two review articles available in published literature that have attempted to address the issues of safety and efficacy of ICI in patients with advanced malignancies and HIV.[12,13] The first one by Cook et al.[12] reviewed data from 13 articles plus four meeting presentations and they found the ICI therapy to be well tolerated, with grade 3 or higher irAEs identified in 6 of 70 patients. Also, it had no association with adverse changes in HIV load or CD4 cell count. The authors

concluded the ICI therapy to be safe and efficacious in HIV patients with various advanced malignancies, including NSCLC, melanoma, and Kaposi sarcoma. The second review by Tapia Rico et al.[13] examined the available evidence on use of ICI in patients with advanced cancers and chronic viral infections (hepatitis B or C and HIV). In this comprehensive review, the authors have summarized the available evidence from all the prospective clinical trials, retrospective case series, and case reports published until December 2019. Here the authors also found ICI to be feasible in this specific patient population, with no deleterious effects on HIV infection, and with comparable safety and efficacy to that of patients without HIV and cancer. They concluded that for HIV-infected patients, it would be a good strategy to start ICI therapy once ART has been given for at least 4 weeks. Table 2 summarizes the findings from published prospective trials and retrospective series with a minimum of 20 patients on the use of ICI in HIV patients.[14–17]

Pembrolizumab was evaluated in a phase 1 study in HIV-infected patients and advanced cancers with a CD4 count of 100 cells/μL or more, ART for four or more weeks, and a viral load less than 200 copies/μL.[14] Of the 30 patients enrolled, 20% had grade 3 irAEs; HIV was well controlled in all patients with a nonsignificant increase in CD4 counts. Three of 30 patients had some response while 17 of 30 patients had disease stabilization for at least 24 weeks. DURVAST was a phase 2 study evaluating durvalumab in HIV patients with cancer.[15] In this study, with 20 enrolled patients, there were no serious irAEs (≥ grade 3) seen. Five of 20 (25%) patients had a partial response while 4 of 20 (20%) patients had stable disease. 8 of 20 (40%) patients remained on durvalumab at data cut off with median on treatment duration of 10.5 months.

ICI is thus an appropriate therapy for HIV-positive patients with CD4 counts more than 100/mm^3, as they have shown good clinical efficacy in these patients with no increased viremia, similar toxicity profile without any increased irAEs.

Table 2. Safety and efficacy of immune checkpoint inhibitors (ICI) in in patients with HIV and cancer

Author	Type of Study	N	ICI Used	Grade 3 irAEs, %	Response Rates, %
Uldrick et al.[14]	Prospective phase 1 study	30	Pembrolizumab	20	10 (CR/PR) 57 (SD)
Gonzales Cao et al.[15]	Prospective phase 2	20	Durvalumab	0	25 (PR) 20 (SD)
Shah et al.[16]	Restrospective	21	Anti-PDL1 ± chemotherapy	14	24 (CR/PR)
Spano et al.[17]	Restrospective	23	Anti-PD1	9	22 (PR) 22 (SD)

irAEs, immune-related adverse events; CR, complete response; PR, partial response; SD, stable disease; PDL1, programmed cell death ligand 1; PD1, programmed cell death protein 1.

PATIENTS ON CORTICOSTEROIDS

Typically, the clinical trials of ICI also excluded patients on corticosteroids, due to the concern that corticosteroid may counterbalance the therapeutic effects of immunotherapy. These corticosteroid drugs are often prescribed as a part of supportive medications for cancer patients either as an antiemetic, analgesic, or for those cases with brain metastases. They are often used in transplant patients for allograft rejection and are the drugs of choice for patients with irAEs.

In a study evaluating the potential impact of systemic corticosteroids at the start of immune checkpoint blockade on the efficacy of PDL-1 blockade in more than 600 patients with NSCLC, baseline corticosteroid use of more than 10 mg of prednisone equivalent was associated with poorer outcomes.[18] In another retrospective, single-center study of adult patients with melanoma, NSCLC, or renal cell carcinoma who received at least four cycles of nivolumab or pembrolizumab therapy, corticosteroids with more than 10 mg of prednisone equivalent for long durations (more than two weeks) during anti-PD1 therapy were associated with poorer survival.[19]

A systematic review from 27 articles on the concomitant use of corticosteroids and immune checkpoint inhibitors published by Garant et al.[20] suggested that the concomitant administration of corticosteroids and immune checkpoint inhibitors may not necessarily lead to poorer clinical outcomes. Thus, there exists contradicting literature on the concomitant use of corticosteroids and its correlation with outcomes with ICI therapy. However, most clinicians would prefer to avoid starting ICI especially until the corticosteroid dosage comes down to below 10 mg prednisone equivalent. The ongoing trials will further enlighten us in this regard.

EXTREMES OF AGE

Advancing age remains the single most important risk factor for most cancers because of age-related decline in immune surveillance. It is estimated that by 2030 more than 70% of all new cancers will be diagnosed in older adults.[21] Older adults with cancer are routinely underrepresented in clinical research. Fewer than 25% of patients enrolled in National Cancer Institute–cooperative group clinical trials are 65- to 74-years old and less than 10% are greater than 75 years of age.[22] Similarly, looking at the opposite end of age spectrum, cytotoxic chemotherapy remains the most commonly used antineoplastic agents in pediatric solid malignancies. Patients with recurrent and refractory solid pediatric tumors have dismal outcomes and researchers have increasingly looked at role of immunotherapy in this setting.

Overall immune checkpoint inhibitors are better tolerated than cytotoxic chemotherapy, but the toxicity to immunotherapy in the elderly population is described only by a few trials as patients above 70 years only make up for a very small fraction. In one study, grade 3 to 5 AEs were recorded less often in patients younger than 65 years of age (58.4%) than in patients 70 years of age or older (71.7%).[23] Findings suggested the occurrence of diarrhea or colitis and rash were lower in the younger group than in the elderly group (5.2 and 10.4% vs 2.4 and 7.6%, respectively).[23] However, a recently published review on the available data of efficacy and AEs of ICB drugs in older patients showed no age-dependent efficacy difference or any major increase in irAE incidence with increasing age, from the clinical trials.[24] In a systematic review and metanalysis including more than 5000 patients from nine randomized studies, equal efficacy was seen with immunotherapy in terms of overall survival of both younger and older patients.[25] The cutoff age was 65 years in eight of these studies while 70 years in the remaining study. The data on the safety of efficacy of ICI in children were scarce until the very recent publication of a multicenter study ADVL1412.[26] This was a multicenter phase I/II study of nivolumab in children and young adults with recurrent or refractory non–central nervous system solid tumors or lymphoma to determine its safety, pharmacokinetics, and antitumor activity. The disease cohorts enrolled in the trial were rhabdomyosarcoma, Ewing sarcoma, osteosarcoma, neuroblastoma, Hodgkin lymphoma, non-Hodgkin lymphoma, and melanoma. A total of 85 patients were enrolled in this study with a median age of 14 years and the nivolumab dose of 3 mg/kg was confirmed to be the recommended pediatric dose. The most common irAE seen was raised liver enzymes seen in approximately 28% of the patients and the next common irAE was hypothyroidism seen in 13%. Grade

3/4 irAEs was seen in less than 10% of total patients with elevated Lipase and pleural effusion being the most common (3% each).[26] In terms of response rates, responses were seen only in lymphoma patients with 30% for Hodgkin lymphoma (3/10) and 10% for non-Hodgkin lymphoma (1/10). Objective responses were not observed in other tumor types.

An interesting editorial by Hajjar[27] highlights the unique challenges of using ICI in patients with primary or secondary immunodeficiencies given the increased risk of malignancy in them and raised two key questions regarding the efficacy and the higher risk of autoimmune dysregulation with ICI in this often ignored high-risk population. Furthermore, in another paper Naing et al.[28] reflected on the absence of an evidence-based rationale for withholding use of ICI in the high-risk population comprising immune deficiencies, autoimmune diseases, prior transplantation, HIV, hepatitis B or C, or prior irAEs. The authors stressed on the need for maintaining national registry for such patients and to conduct prospective studies by including these high-risk patients so as to identify optimal anticancer therapies, class, and dosing strategies of ICI in them. They also proposed incorporation of close monitoring strategies and translational research as a part of these clinical trials to better understand the risk-benefit ratios, the underlying mechanisms of response and irAEs in such high-risk population.

CONCLUSION

Although immunotherapy has slowly revolutionized the treatment of several advanced cancers and improved oncologic outcomes there are still several patient subgroups where conclusive evidence on its efficacy and safety is lacking. Overall, there are several studies to suggest that ICI might be feasible and effective in high-risk patient subgroups that are typically excluded or underrepresented in the immunotherapy trials viz patients with preexisting autoimmune diseases, HIV-positive patients, those receiving corticosteroids, and the elderly patients with comorbidities. Nevertheless, due to limited data in these patient subgroups, a careful multidisciplinary tumor board–based assessment of potential benefit versus potential harm is mandatory before starting ICI in these patients. This includes evaluating the type and level of control of underlying autoimmune diseases, CD4 counts in HIV patients, the dosage of corticosteroids before starting treatment, and a comprehensive geriatric assessment in elderly patients. There is an unmet need for randomized controlled studies in these special population subgroups. The United States Food and Drug Administration has published guidance emphasizing on the importance of including adults over age 75 years and patients with HIV in cancer clinical trials.[29] National and international collaborative efforts including from authorities and lead societies like Society for Immunotherapy of Cancers, Immuno-oncology Society of India, and European Society of Medical Oncology particularly on investigational immunotherapy track would be vital. Collaborative trials would be highly recommended to better understand these rare and challenging situations adequately and streamline care across the globe.

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