Review Article

Immune Checkpoint Inhibitors in Challenging Populations

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Immune checkpoint inhibitors, including those targeting the programmed cell death 1/programmed cell death ligand 1 and cytotoxic T lymphocyte antigen 4 pathways, are revolutionizing cancer therapeutics. Both activity and toxicities largely stem from unleashing tumor- or host-specific cytotoxic T cells. Many patients seen in routine clinical practice have not qualified for or have been seriously underrepresented in immune checkpoint inhibitor clinical trials. Thus, a major gap in knowledge regarding the safety and efficacy of these agents persists in many populations, even after regulatory approval. To address this challenge, this review aggregates and synthesizes the available preclinical and clinical data surrounding immune checkpoint inhibitor therapy in challenging clinical populations to assist both academic and community oncologists in treatment decision making. Specifically, this review focuses on the safety and activity of immune checkpoint inhibitors in patients with autoimmune disorders, organ transplant patients, patients with chronic viral infections, patients with ongoing immunosuppressant use, patients with organ dysfunction, pregnant patients, patients with brain metastases, patients at extremes of age, and patients with an impaired functional status. ***Cancer*** **2017;123:1904-11.** © *2017 American Cancer Society*.

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INTRODUCTION

Agents that block the interaction between programmed cell death 1 (PD1) and programmed cell death ligand 1 (PD-L1) and that inhibit cytotoxic T lymphocyte antigen 4 (CTLA4) are transforming the therapeutic landscape in oncology. These so-called immune checkpoint inhibitors target these key immune regulatory pathways and thereby unleash restrained T cell–mediated antitumor responses. Anti-PD1/PD-L1–directed therapies have now received regulatory approval for melanoma, non–small cell lung cancer, renal cell carcinoma, and head and neck squamous cell carcinoma. Ipilimumab (anti-CTLA4) has a more narrow scope of activity as a single agent, with regulatory approval only for melanoma. However, anti-CTLA4 therapies may augment the activity of anti-PD1 in melanoma and other cancer types, and this may result in more widespread use.

Immune checkpoint inhibitors are appealing treatment options for patients and clinicians for several reasons. First, they have broad activity and demonstrate response rates ranging from 15% to 90% in more than 10 different cancer types.[1] Second, they frequently induce durable disease control. Nivolumab, for example, has now been associated with a 34% 5-year overall survival rate for patients with advanced melanoma, with similar durability observed for other cancers. Third, immune checkpoint inhibitors generally have favorable toxicity profiles (particularly with anti-PD1/PD-L1 monotherapy). Although immune-related adverse events (irAEs) may infrequently cause substantial morbidity and even mortality, many patients experience excellent quality of life with minimal symptoms while they are on therapy. Identifying reliable predictive biomarkers of efficacy and particularly toxicity has been a major challenge.

The safety and activity of immune checkpoint inhibitors have been well characterized in numerous clinical trials. The average oncologist's patient population in both community and academic practices, however, is frequently composed of many patients who would have been ineligible for these seminal clinical trials. Such trial-ineligible patients may now desire treatment, and in our experience, this presents an extremely common source of confusion for both academic and community oncologists alike.

Several small studies have begun to explore the safety and efficacy of these agents in excluded or underrepresented populations, including those with dysregulated immune activation (preexisting autoimmune diseases and hematopoietic/

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solid organ transplant), compromised immune function (long-term immunosuppression and chronic viral infections), and significant medical comorbidities (organ dysfunction, old age, and brain metastases). Despite these early efforts, there remains substantial uncertainty surrounding the safety and efficacy of anti-PD1/PD-L1 and anti-CTLA4 in these populations. Here we synthesize the current data to facilitate the appropriate utilization of these novel therapeutics.

AUTOIMMUNITY

Dysregulated immunity mediates autoimmune disorders such as inflammatory bowel disease, autoimmune hepatitis, and Guillain-Barre syndrome. The hallmark toxicities of immune checkpoint inhibitors, irAEs, result from aberrant activation of autoreactive T cells against host tissues. Clinically, irAEs recapitulate or closely resemble various autoimmune disease. Although most irAEs are resolved with corticosteroid administration, expectant monitoring, and/or hormone replacement, fulminant events occasionally lead to severe morbidity or even mortality.[2]

Naturally, the mechanism of action of immune checkpoint inhibitors led to fears that further immune stimulation would lead to clinically unacceptable immune activation in patients with preexisting autoimmunity in the form of underlying symptom flares or new autoimmune manifestations. Preclinical data supported these concerns because CTLA4-deficient mice succumbed to fulminant autoimmune activation with multiorgan involvement and a diffuse lymphoproliferative process.[3] PD1-knockout mice also developed immune-mediated myocarditis (at least in the BALB/c mouse model). Additional preclinical and gene association data have also suggested that CTLA4 and PD1/PD-L1 axes may play some role in autoimmune disorders, although the precise roles have not been fully elucidated.[4,5] Thus, patients with active autoimmune disease were excluded from all clinical trials. This population, however, represents 20 to 50 million people in the United States alone. One study using Medicare data demonstrated that a full 13.5% of lung cancer patients had a concurrent diagnosis of an autoimmune disease, and this suggests the urgency of exploring this population.[6]

To begin to address this question, our groups aggregated 30 patients with melanoma who had preexisting autoimmune disease and had received treatment with ipilimumab. Disorders included inflammatory bowel disease, rheumatoid arthritis, multiple sclerosis, and several others; 20% of the patients were receiving steroids or other immunosuppressants at the baseline. In this cohort, 27% experienced exacerbations of their autoimmune disease, and 33% experienced conventional irAEs requiring treatment.[7] The events that occurred resolved quickly with standard corticosteroid treatment algorithms, with the exception of 1 patient with psoriasis who died of colitis. This case was at least partially attributable to a long delay in seeking care and presentation after the onset of hypotension and multiorgan failure from volume depletion. Several patients with inflammatory bowel disease had low-grade disease flares but were manageable with corticosteroids. An objective response rate of 20% was observed, and this was consistent with ipilimumab clinical trials.

We also assessed 52 patients with preexisting autoimmunity treated with anti-PD1. Of these, 30% experienced an autoimmune flare (although only 4% required treatment discontinuation), and 29% experienced a classic irAE (8% discontinued treatment).[8] Interestingly, patients with rheumatologic disorders (rheumatoid arthritis, lupus, and psoriasis) tended to have low-grade disease exacerbations, whereas no patients with gastrointestinal or neurological disorders experienced flares. Again, these irAEs and autoimmune flares responded to standard treatment algorithms, and no patients died of treatment-related events. Notably, 33% of the patients responded to treatment; again, this was largely consistent with anti-PD1 therapeutic trials.

Thus, in our view, treatment with either anti-PD1 or ipilimumab is feasible for patients with preexisting autoimmunity, particularly in view of progressive, metastatic cancer. One caveat to these data is that our cohorts comprised patients to whom clinicians were willing to give immune checkpoint inhibitors, and they may not have included patients with the most severe autoimmune disease. We also would have great hesitancy in using combination immune checkpoint blockade (eg, ipilimumab and nivolumab) in patients with clinically significant autoimmune disease. Still, underlying autoimmune disorders are an important consideration and require close monitoring, but they do not pose an absolute contraindication to treatment.

TRANSPLANT

Patients who undergo solid organ or hematopoietic stem cell transplantation require fine-tuned modulation of immunosuppression to maintain allograft tolerance and prevent rejection or graft-versus-host disease (GVHD). Interestingly, preclinical data suggest that the PD1/PD-L1 axis may be particularly critical for maintaining organ tolerance, and PD1 gene polymorphisms are associated

with superior graft survival.[9-11] The relation appears complicated, however, because high expression of PD1/PD-L1 on various T-cell subsets has been associated both with inferior survival and with lower rates of GVHD after allogeneic stem cell transplantation.[12,13] Unfortunately, patients also develop cancer after transplantation at a high rate, at least in part because of their chronic immunosuppression, and often need systemic therapies. Immune checkpoint inhibitors in this setting are considered exceedingly high-risk for producing catastrophic posttransplant complications by breaking immune tolerance.

Several prospective trials and case reports, however, suggest that these agents may be tolerated in some patients. Ipilimumab, a generally more toxic drug than anti-PD1/PD-L1 agents, surprisingly appears to have superior safety in this setting. An initial phase 1 study showed excellent tolerance of a single dose of ipilimumab (ranging from 0.1 to 3 mg/kg) in patients with relapsed hematologic malignancies after allogeneic stem cell transplantation without any episodes of GVHD in 29 patients.[14] A follow-up study of ipilimumab at 3 or 10 mg/kg for 4 doses was conducted in a similar population of 28 patients with relapsed hematologic malignancies after stem cell transplantation. At these doses, ipilimumab induced dose-limiting GVHD in 14% of the patients and irAEs in 21% (including 1 death), but it also induced several durable disease responses.[15] Several other case reports of advanced melanoma treated with ipilimumab after solid organ or stem cell transplantation have suggested reasonable tolerance with only a single episode of rejection in a renal transplant patient.[16-21]

Anti-PD1/PD-L1 has also been used safely in several patients after hematopoietic stem cell transplantation.[16,22-26] However, several cases of renal and cardiac allograft rejection and serious GVHD have also been reported soon after the initiation of anti-PD1 in patients with various advanced malignancies.[17,27-33] In particular, on the basis of these published case reports, renal transplant patients seem to be at high risk for rejection. It is unknown, however, how many patients have been treated without complications. One could speculate that the risk of rejection may be greater with allografts that are less well matched, have been in situ for a shorter period of time, and require higher doses of immunosuppression. We are currently conducting a more systematic multicenter effort to characterize the safety of these agents and risk factors for toxicities. Needless to say, immune checkpoint inhibitors carry a high risk of graft rejection and should be used with extreme caution and in a multidisciplinary setting in patients after transplantation with full disclosure of the risks.

CHRONIC VIRAL INFECTIONS

Hepatitis B, hepatitis C, and human immunodeficiency virus (HIV) infections have also been nearly universal exclusion criteria for immune checkpoint inhibitor trials. These chronic infections may suppress T-cell function and could theoretically compromise efficacy (particularly in the case of severe HIV/AIDS with low CD4 + T-cell counts). Interestingly, there are preclinical and limited clinical data suggesting that these agents could assist in viral clearance in infected patients.[34-38] In fact, therapeutic trials to test these agents in patients with HIV or hepatitis C have been conducted (NCT02028403 and NCT00703469), although the results have yet to be published. The role of immune checkpoint inhibitors in the management of chronic viral infections, particularly in view of numerous effective antiviral therapy options, is unclear.

Very little experience with immune checkpoint inhibitor therapy in patients with advanced cancer is available at this time. Initial data from a trial of nivolumab in patients with hepatocellular carcinoma (Child-Pugh score $\leq$ B7) included patients with chronic hepatitis B or C. This study demonstrated a 10% rate of grade 3/4 liver enzyme elevation, but it reported an overall manageable safety profile.[39] Responses to treatment were observed in patients with hepatitis B and C. Currently, a phase 3 study comparing nivolumab with sorafenib in patients with advanced hepatocellular carcinoma is underway (NCT02576509), and it will likely provide more insights into the safety and efficacy of nivolumab in this setting. Another ongoing trial is evaluating pembrolizumab in patients with HIV and advanced cancers; this study allows a variety of metastatic cancers and requires a CD4 + T-cell count $>$ 200 (NCT02595866). Pending the results of these trials, we do not view HIV or hepatitis C as a contraindication to treatment with anti-PD1. Patients with HIV/AIDS and low CD4 + T-cell counts should be monitored closely both for activity and for an immune reconstitution-type phenomenon, particularly if they are on concurrent antiretroviral therapy.

CHRONIC IMMUNOSUPPRESSION

Immunosuppressants could potentially hinder immunotherapy responses by impeding various facets of T-cell function, including activation and effector function. Accordingly, ongoing high-dose corticosteroid or other immunosuppressant use has excluded patients from immune

checkpoint inhibitor trials. Thus, a paucity of experience exists regarding the safety and efficacy of these agents in patients receiving chronic immunosuppressants. By contrast, extensive experience surrounding the use of replacement (physiologic) dose corticosteroids exists because of the frequency of primary or secondary adrenal insufficiency experienced with ipilimumab; activity appears equivalent in this population.[40,41]

As for patients receiving supraphysiologic doses of steroids, our study of patients with prior autoimmunity suggested that responses may be less frequent in patients receiving high-dose steroids or other disease-modifying therapies (15%) than in those not requiring these agents (44%).[8] Furthermore, a study of ipilimumab in patients with metastatic melanoma with brain metastases showed that patients rarely experienced responses when requiring corticosteroids (although this could represent a more aggressive and refractory disease course).[42] Thus, we attempt to wean patients to replacement doses of corticosteroids ($\leq$10 mg of prednisone daily or the equivalent) before starting immune checkpoint inhibitors whenever possible.

ORGAN DYSFUNCTION

A vast number of patients with cancer have medical comorbidities, including chronic organ dysfunction. For example, an estimated 10% of the US population has chronic kidney disease, and this number is undoubtedly higher in the cancer population (particularly in patients with genitourinary malignancies). Although no clear contraindication to immune checkpoint inhibitors exists for patients with renal, hepatic, or cardiac dysfunction, these patients have been largely excluded from clinical trials, presumably because of difficulties in characterizing safety signals. In contrast to many cytotoxic chemotherapeutics and biologic agents, which undergo hepatic or renal clearance, immune checkpoint inhibitors and other monoclonal antibodies are metabolized to peptides and amino acids by circulating phagocytic cells.[43] Thus, renal or hepatic dysfunction would be expected to have minimal impact on drug levels, metabolism, or clearance.

To address the safety and efficacy of immune checkpoint inhibitors in patients with organ dysfunction, we recently assessed our experience with 27 patients who had preexisting cardiac, hepatic, or renal dysfunction treated with anti-PD1/PD-L1 agents. Somewhat arbitrarily, we included patients with creatinine levels $\geq$ 2.0 mg/dL or creatinine clearance $<$ 30 mL/min, with liver enzyme or bilirubin levels $\geq$ 3 times the upper limit of normal or radiographic evidence of cirrhosis, or with a cardiac ejection fraction $<$ 45%. In this cohort, we did not observe an excess incidence or unique pattern of organ-specific irAEs.[44] Several patients experienced volume overload and congestive heart failure exacerbations that were resolved with supportive care. Whether this represents systemic inflammation leading to cardiac strain and volume overload, excess fluid volume associated with infusions, or simply the natural history of the disease is unclear. In 3 patients receiving hemodialysis, we did not observe any irAEs or other concerning adverse events. Durable responses occurred in several patients. Other clinical trials have permitted mild organ dysfunction (eg, creatinine clearance of 30-60 mL/min) and have also reported efficacy comparable to that found in patients without these comorbidities.[39,45] One study of cisplatin-ineligible patients with urothelial carcinoma treated with atezolizumab reported equivalent response rates in patients with impaired renal function, although differential toxicity was not reported in that study.[46] Thus, in general, we do not consider even severe organ dysfunction to be a contraindication to anti-PD1/PD-L1 in patients with an adequate performance status and functional reserve.

Recently, fulminant myocarditis and other cardiac events have been reported after immune checkpoint inhibitors (particularly a combination PD1/CTLA4 blockade).[2,47] It is not at all clear whether preexisting cardiac conditions predispose patients to these more severe events. Indeed, 2 of the most severe cases lacked cardiac risk factors other than hypertension.[2] Some studies now mandate cardiac monitoring early during combination treatment (eg, weekly troponins and baseline electrocardiograms). However, it remains unclear whether treatment should be withheld if cardiac comorbidities are identified. One potential approach would be to use single-agent anti-PD1 rather than a more aggressive combination in patients with more severe cardiac comorbidities, although this recommendation is not supported by firm data.

EXTREMES OF AGE

Although very elderly patients were not specifically excluded from clinical trials, this population is underrepresented in nearly all studies.[48] One could speculate that age could influence immune cell function as well as the composition of the tumor microenvironment.[49] Efforts are ongoing to understand the interaction between young immune cells and aged immune cells and interactions with anti-PD1. Clinically, the impact of age on the immunotherapy response has not been systematically described. No clear differences have been noted in numerous trials

between response rates in patients older than 65 years and patients younger than 65 years. To assess this at a more granular level, our group performed a retrospective patient review assessing whether age influenced the rates of therapeutic responses or toxicities. In this cohort, we observed similar progression-free survival, overall survival, and toxicity rates in patients by decades.[50,51] Furthermore, in a meta-analysis of 9 randomized controlled trials that enrolled 5265 patients into immune checkpoint inhibitor arms or various control arms, improvements in clinical outcomes were seen in both younger and older patients receiving immune checkpoint inhibitors versus control therapies.[52] This study, however, did not directly compare outcomes for younger and older patients. A 28% response rate was also recently reported for urothelial bladder carcinoma patients older than 80 years who were treated with atezolizumab (vs 23% for all patients).[46] We have also reported cases of clinical benefit and response in patients older than 90 years, including a 90-year-old treated with a combination of ipilimumab and nivolumab who experienced a complete response and a 95-year-old with a partial response after pembrolizumab.[53] We think that old age is not a contraindication to immune checkpoint inhibition and instead that functional status is a more relevant consideration. However, the overall toxicity profile, efficacy, and relative risks and benefits in comparison with other therapies have not been studied comprehensively for tumor types other than melanoma, and they will need further study.

On the other extreme, the safety and efficacy of immune checkpoint inhibitors for pediatric patients are incompletely studied. One completed phase 1 study tested ipilimumab in 33 pediatric patients with refractory solid tumors (primarily melanoma and sarcoma) and noted no responses but stable disease in 18% of patients.[54] Toxicity profiles were similar to those observed in adults, but they frequently occurred early, even after the first dose (uncommon in adults). Heterogeneous immune checkpoint expression, including PD1 and PD-L1, has been described in a variety of pediatric cancers, although these tumors typically have a relatively low mutation burden (associated with lower response rates in some cancers).[55-59] Numerous studies are ongoing in pediatric patients with a variety of cancer types involving anti-PD1 with or without anti-CTLA4.[56]

POOR PERFORMANCE STATUS

Patients who present with advanced cancer and a poor Eastern Cooperative Oncology Group (ECOG) performance status present a challenging conundrum to oncology practitioners and, in many cases, overlap with other populations already discussed. In general, cytotoxic chemotherapy (particularly later lines of therapy) is associated with substantial toxicities, impaired quality of life, and a short lifespan in patients with an ECOG performance status ≥ 2.[60-63] By contrast, immune checkpoint inhibitors, particularly anti-PD1/PD-L1 monotherapy, often have favorable toxicity profiles, even in patients with a poor performance status. Moreover, some diseases such as Hodgkin lymphoma, Merkel cell carcinoma, and melanoma have response rates in the range of 40% to 90% (albeit in clinical trial populations), and this further complicates the decision.[64-67]

There is very little published experience to guide oncologists in terms of whether to use immune checkpoint inhibitors in patients with a poor performance status. One study of atezolizumab in cisplatin-ineligible patients with urothelial carcinoma reported a response rate of 25% for patients with an ECOG performance status of 2 (vs 23% for all patients).[46] In our anecdotal experience (largely in melanoma patients), we have observed excellent responses in this population, albeit less frequently than in patients with a preserved performance status. This issue will need further study, particularly because of the high costs of therapy. In our practice, we typically have a frank discussion about the likelihood of benefits and toxicities and often involve palliative care early. We would be less likely to recommend treatment to patients with concurrent high-dose steroids (eg, in the setting of progressive brain metastases) and more likely to treat patients with more responsive cancers (eg, Hodgkin lymphoma and melanoma). An accurate predictive biomarker of a response would have particular utility in this population for guiding treatment decision making.

BRAIN METASTASES

Patients with brain metastases represent a challenging clinical population with a traditionally poor prognosis, and they may present with a limited performance status or ongoing steroid use. Although it remains unclear whether immune checkpoint inhibitors cross the blood-brain barrier, animal models suggest that they may have modest penetrance, and clinical studies have confirmed that they can induce intracranial responses.[68] A phase 2 study of ipilimumab was conducted in 72 patients with melanoma and brain metastases, including 51 without neurological symptoms and not receiving corticosteroids (cohort A) and 21 with stable symptoms on corticosteroids (cohort B).[42] In cohort A, 18% of the patients had disease control at 12 weeks, whereas only 5% (1 patient) did in cohort B.

We have also recently reported a retrospective analysis of 89 patients with stage IV melanoma treated with standard-of-care pembrolizumab, 36 (40%) of whom had brain metastases before commencing therapy.[69] The overall survival data were consistent with other pembrolizumab data, with a 6-month overall survival rate of 86% and an estimated median survival of more than 20 months. In addition, patients with brain metastases treated with radiation therapy and/or surgery before pembrolizumab had a time to progression (median, 5 months; hazard ratio, 0.27; 90% confidence interval, 0.12-0.64) similar to that of patients without brain metastases (median, 6 months; hazard ratio, 0.19; 90% confidence interval, 0.08-0.42) but unlike that of patients with untreated brain metastases (median, 1.2 months). In addition, concurrent radiation therapy with pembrolizumab was performed in 15 patients without unexpected toxicity. These data support the use of pembrolizumab in patients with brain metastases and suggest that surgery or radiation before systemic therapy is ideal, but concurrent therapy with radiation is feasible.

Early results from a phase 2 study of pembrolizumab in patients with brain metastases and melanoma and non–small cell lung cancer (limited to PD-L1–expressing tumors) have also demonstrated efficacy. In this study, 22% of melanoma patients and 33% of non–small cell lung cancer patients experienced intracranial responses, and 3 melanoma patients (17%) developed grade 3 neurological toxicities.[70] A phase 2 study of ipilimumab in combination with nivolumab in patients with melanoma brain metastases is ongoing (NCT02320058). Other ongoing studies are prospectively evaluating interactions between brain radiation therapy and immunotherapy because early results have suggested that combining these modalities may augment efficacy and perhaps toxicity.[71-73]

PREGNANCY

Metastatic cancer in pregnancy is a devastating condition leading to difficult decisions involving the mother and the developing fetus. PD1/PD-L1 interactions appear to play a key role in maintaining fetal tolerance; indeed, the placenta is often used as a positive control for PD-L1 expression because of its strong and ubiquitous expression. In animal studies, anti-PD1/PD-L1 clearly increased the risks of spontaneous abortions.[74,75] However, in surviving animals, no increased risks of birth defects were noted. At this time, anti-PD1 agents are categorized as pregnancy category D by the Food and Drug Administration, whereas ipilimumab is pregnancy category C (because of the less clear role of the CTLA4 axis in fetal immune tolerance). The use of these agents in pregnancy, particularly anti-PD1/PD-L1, would likely pose a great risk of spontaneous abortion, with unknown maternal risk and unknown risks of birth defects, and would ultimately be an individualized decision made in light of the risks and potential benefits.

CONCLUSIONS

The use of immune checkpoint inhibitors across the spectrum of human cancers is rapidly expanding. Thus, characterizing their efficacy and safety in real-world patient populations not included in clinical trials is a critical objective. Available studies suggest that these agents often have acceptable safety profiles even in trial-ineligible populations, with the likely exception of anti-PD1 in solid organ transplant recipients. Larger prospective studies would help to extend and validate these experiences but may be challenging to complete. Furthermore, identifying reliable predictive biomarkers of efficacy and toxicity may also help with treatment decision making. In the interim, clinicians should consider these data when making treatment decisions in challenging patient populations, balance the risks of toxicity with potential benefits, and make such decisions in a multidisciplinary setting.

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CONFLICT OF INTEREST DISCLOSURES

Douglas B. Johnson serves on advisory boards for Bristol-Myers Squibb and Genoptix and receives research funding and travel support from Incyte. Ryan J. Sullivan has consulted/advised for Amgen, Novartis, Astex, and Prometheus and receives research funding from Merck. Alexander M. Menzies serves on advisory boards for Merck Sharp & Dohme and Chugai and receives honoraria from Bristol-Myers Squibb and Novartis.

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