Considerations for immunotherapy in patients with cancer and comorbid immune dysfunction

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\textbf{Abstract:} Immune checkpoint inhibitors have been widely incorporated for cancer treatment in a variety of solid and hematologic malignancies. Multiple clinical trials have demonstrated the efficacy of PD-1/PD-L1 and CTLA-4 axis inhibition in the metastatic and adjuvant settings. Due to the risks of autoimmune toxicity with these agents, stringent inclusion/exclusion criteria were employed in those initial clinical trials. These criteria led to exclusion or underrepresentation of a variety of patient populations with underlying immune dysfunction. These populations included patients with preexisting autoimmune diseases, solid organ or bone marrow transplant recipients, patients with HIV or viral hepatitis infections, patients receiving concurrent chronic steroid therapy, as well as patients who were elderly, pregnant, or had poor performance status. Thus, established guidelines on the use of immune checkpoint inhibitors in these patients are lacking, and evidence to support efficacy or toxicity are overall limited to retrospective studies and case series. Fortunately, ongoing clinical trials are now including these patients and are shedding light on whether these underrepresented populations can also safely benefit from immune checkpoint inhibitor therapies. In this review, we summarize the most clinically relevant available data on the use of checkpoint inhibitors in immunocompromised patient groups with a primary focus on safety.

\textbf{Keywords:} Immune checkpoint inhibitors, cancer treatment, PD-1/PD-L1, CTLA-4, autoimmune toxicity.

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\section*{Introduction}

It has been almost a decade since immune evasion was recognized as a hallmark of cancer (1), and since then, cancer immunotherapy has been well integrated into the treatment of numerous solid and hematological malignancies. One of the most common cancer immunotherapy applications relates to the use of checkpoint inhibitors, which are monoclonal antibodies that block immune suppression mediated by PD-1/PD-L1 and CTLA-4 signaling. An array of agents is already approved by the Food and Drug Administration (FDA) and an even larger number of checkpoint inhibitors are currently in preclinical and clinical studies. Immunotherapy, contrary to cytotoxic chemotherapy, has a completely different mechanism of action and aims to disrupt the symbiosis between the immune system and cancer. A key step in the process of the cancer immunoediting shift, which eventually leads to tumor growth and proliferation, is mediated by the escape
of the tumor cells from the equilibrium state where tumor dormancy occurs with no apparent clinical disease (2). While these mechanisms are complex and not yet fully understood, what has become clear is that immunosuppressed patients do have a higher incidence of certain malignancies (3,4). By reversing immunosuppression with immunotherapy agents, immune attack against tumor can be restored, but often results in autoimmunity against normal cells. In patients with underlying immune dysfunction, including those with iatrogenic or acquired immunosuppression or preexisting autoimmune conditions, the risks of further disruption of the immune system's checks and balances with checkpoint inhibitors could outweigh potential anti-cancer benefits. However, limited data exist to date for whether this theory holds true in this unique population of patients. This review aims to provide an overview of the available data on immunotherapy applications in immunosuppressed patients.

Organ transplant recipients

Solid-organ and allogeneic hematopoietic stem cell transplant (HSCT) recipients must remain on chronic immunosuppression to maintain graft tolerance and prevent graft-versus-host disease (GVHD). GVHD most commonly occurs with stem cell transplantation, although it can occur with any transplanted graft which contains large amount of donor immune cells (5).

Graft rejection and GVHD are two major immunological complications of HSCT mediated by a complex crosstalk among predominantly T cells, innate lymphoid cells, intestinal epithelial cells, microbiota and stromal cells in secondary lymphoid organs (5). In allogenic HSCT, PD-L1 expression on donor T-cells is functionally implicated in regulating acute GVHD suggesting that inhibition of the axis may prevent GVHD (6). To investigate this, a phase 1 trial on the single-agent CTLA-4 inhibitor, ipilimumab, dosed at 0.1–3 mg/kg, for patients with relapsed hematologic malignancies after allogeneic HSCT, included 29 patients, none of whom developed any grade 3 or 4 acute GVHD. Still, four patients developed distinct irAEs (immune-related adverse events) (7), of which one was grade 3 polyarthritis and one grade 4 pneumonitis.

In contrast, when the same agent used at higher doses of 3 or 10 mg/m² in a subsequent study of 28 patients, GVHD rates were 14%, and six patients (21%) experienced irAEs, with two ≥ grade 3 toxicities and one treatment-related death (8). PD-1 inhibition has been used successfully in numerous case reports of patients with recurrent hematologic malignancies after HSCT (9-14) without major GVHD complications. Looking at larger retrospective studies, though, various degrees of GVHD have been reported. In a 30-patient study of patients who received anti-PD-1 therapy post allogeneic HSCT, the response rate was 77%; however, the GVHD rate was as high as 55% (grade 3-4 acute or severe chronic; 9 patients) with eight deaths related to new-onset GVHD (15). Fatal GVHD has also been reported with pembrolizumab after allogeneic GVHD (16). An interesting question raised in some successfully treated cases is whether lower doses of PD-1 antibody can mitigate the risk of GVHD and development of irAEs while maintaining efficacy.

On the same note, the evidence is also controversial on the safety of checkpoint inhibition in solid organ transplant recipients. The immunosuppressive state required for allograft tolerance, increases the risk of de novo malignancies and complicates the therapy of these secondary cancers. Preclinical evidence suggest that the PD-1/PD-L1 axis is important for solid organ allograft tolerance (17,18). In a 35-patient cohort study of solid transplant patients treated for second malignancies with immunotherapy, the overall response rate (ORR) of immune checkpoint inhibitors was 43.4%, and graft rejection rate was 31.4% in patients with liver, renal, or heart transplants (19). A systematic review of transplant patients receiving either PD-1 or CTLA-4 inhibitors reported the highest rejection rate in patients with kidney (40.1%), followed by liver (35%) and heart (20%) transplant (20). However, most of the patients included in that metaanalysis received renal (n=32) transplants followed by liver transplants (n=20) and only 5 received heart transplants (20). Interestingly, there was no association between the particular checkpoint inhibitor used and rejection rates, with most patient deaths ultimately attributed to disease progression rather than graft rejection (20). An analysis of exclusively renal transplant recipients receiving checkpoint inhibitors included 44 patients, 18 of whom had graft rejection, and 10 of them eventually died of various etiologies unrelated to irAEs (21). Overall, the advent of potent immunosuppressive therapy has led to a decreasing incidence of kidney acute rejection in the first year post transplant, which has been consistently less than 10% (22). Whether the degree of immunosuppression plays a role in this high graft failure in solid transplants with checkpoint inhibition or the actual transplanted organ is unclear. Although the data are limited thus far and derived mainly from retrospective case series and case reports, risks and benefits of this approach in this context should be carefully weighed considering the
type of the transplanted organ and the expected efficacy of checkpoint inhibitors.

**Autoimmune disorders**

Patients with pre-existing autoimmune disorders present a major common clinical challenge because of the immunosuppressive treatment often required and due to the inherent impairment of the immune system leading to those conditions. There is also the concern of worsening or exacerbating the underlying autoimmune disorder especially those driven mainly by T cells i.e., rheumatoid arthritis or multiple sclerosis. Although the precise pathophysiology mediating irAEs is not fully understood and there is a lack of predictive factors, pre-existing dysregulation of the immune system raises the concern of potentially impacting the severity, incidence and timing of irAEs with checkpoint inhibitors. Since these patients were initially almost universally excluded from the immunotherapy trials, most evidence is based on retrospective studies and case reports reported in the literature. A recent systematic analysis included 123 patients with a variety of autoimmune disorders - psoriasis, rheumatoid arthritis, autoimmune thyroid disease, ulcerative colitis, Crohn disease, multiple sclerosis, myasthenia gravis, and sarcoidosis (23). The majority of those patients, 83.5%, received prior treatment of their autoimmune disease, 46.5% had an active autoimmune disease, and 43.6% were receiving concurrent immunosuppression at the time of immunotherapy initiation. Overall, 41% of patients had an exacerbation of their pre-existing autoimmune disease with a similar presentation of their original disease, 25% had de novo irAEs, and 17.1% of all patients had to discontinue therapy due to irAEs (23). Half the patients who developed irAEs had either partial or complete response vs. 35.7% of patients who did not experience any irAEs (23). Interestingly there was no difference in the frequency of irAEs between patients with prior active autoimmune disorders versus inactive, and patients who were receiving immunosuppressive treatment concomitantly with immunotherapy had actually fewer irAEs (59% vs. 83%) (23). Importantly, in more than half of the patients, there was no need to discontinue immunotherapy. Another interesting point of this analysis is the observation that anti-CTLA-4 agents were associated with more de novo irAEs compared to PD-1/PD-L1 axis inhibitors (42% vs. 26%, respectively), which were associated more with the patients’ pre-existing autoimmune disease flares (23). A large multicenter French retrospective study on a similar patient population included 112 patients and reported similar results—overall, irAEs developed in 71% of patients, with 47% experiencing a flare of their autoimmune disorder, 42% developing de novo irAEs, and 18% developing both (24). Only 21% of patients discontinued their treatment because of irAEs (24). This study also reported a key observation that immunosuppressive treatment at the time of immunotherapy did confer a negative impact on cancer survival; shorter progression-free survival [HR 2.10 (95% CI: 1.08–4.07), P=0.028] and a trend towards worse overall survival although not statistically significant [HR 1.95 (95% CI: 0.89–4.64), P=0.134] (24). Lastly, in another recent retrospective study which included 46 patients with prior autoimmune conditions (hypothyroidism, psoriasis, rheumatoid arthritis, lupus, myasthenia gravis, inflammatory bowel disease and others) nine patients had flares with checkpoint inhibition, and only one patient required discontinuation of immunotherapy (25).

Considering all these data, pre-existing autoimmune disorders should not necessarily be an absolute contraindication, especially when the potential anti-cancer benefits outweigh the risks. While there is a potential of reactivation of the autoimmune disorder, this is not universal, and more importantly, few patients required therapy discontinuation despite the development of irAEs or disease flare. Future research on the pathogenesis of irAEs will hopefully improve the ability to predict irAEs and guide the use of checkpoint inhibitors minimizing toxicity.

Lastly, a unique condition in this population is the cancer-associated dermatomyositis which can be present either at the time or years prior the diagnosis of cancer. This is a challenging disease and it represents a good example of the complex relationship between cancer and autoimmunity. Interestingly, a study recently showed that patients with dermatomyositis and cancer had significantly higher levels of soluble PD-L1 expression when compared to patients without cancer or those with cancer in remission (26). While causation cannot be elicited from this early study, it can be hypothesized that patients with cancer and dermatomyositis may have higher responses to immune checkpoint inhibitors.

**Acquired immunosuppression—viral infections or chronic steroid use**

Another challenging population is the patients who have acquired immunosuppression secondary to either viral
infections like HIV or chronic steroid use. Importantly, the patients with concomitant HIV or hepatitis infections were all excluded from the first clinical trials with checkpoint inhibitors, due to the viral immunosuppressive effects on T cells. Independently from the coinfection with HIV, human hepatitis viruses and in particular HCV activate innate immune responses and can lead to T cell exhaustion due to chronic antigen stimulation (27). This prolonged activation of the innate immunity which can potentially impair adaptive immune responses, may ultimately confer vulnerability to checkpoint inhibition. Limited data suggest the beneficial effects of checkpoint inhibitors not only against cancer but also on HIV viral clearance and increase of CD4, and CD8 T lymphocyte counts (28,29).

More recent retrospective series reported similar findings; a 50-patient study, which included both patients with HIV and viral hepatitis, showed an ORR to checkpoint inhibition of 28% and 18%, respectively (30). The incidence of any grade irAEs was 24% and 44% in the HIV and the HBV/HCV cohorts, respectively (30). A systematic review of 73 patients with HIV infection reported even better tolerance to checkpoint inhibitors with an overall irAE rate of 8.6% and ORR of 30% for lung cancer, 27% for melanoma, and 63% for Kaposi sarcoma (31). Patients with HIV and viral hepatitis infections appear to have similar tolerance to checkpoint inhibitors and in some malignancies possibly enhanced antitumor efficacy—with the most recent example of superior overall survival of patients with viral associated hepatocellular carcinoma when treated with Bevacizumab in combination with checkpoint inhibition compared to those with non-viral associated disease (32). Multiple trials in the last few years with checkpoint inhibitors are now including patients with HIV infections to answer these questions prospectively.

On the other hand, patients on chronic steroid use for multiple reasons beyond autoimmune disorders constitute another very common and challenging clinical scenario. There is accumulating evidence that chronic steroid use may harm immunotherapy responses depending on the dose and the timing of initiation. In the first study on a cohort of 640 patients with metastatic lung cancer and concurrent use of prednisone, dose ≥10 mg/day was associated with lower response rates and survival compared to those patients who were using prednisone at <10 mg/day (33). These findings were consistent with the results of several other retrospective studies, especially when steroid exposure was early during immunotherapy (34). Similarly, one of the first trials of CTLA-4 inhibition in patients with melanoma and brain metastases included patients who were on stable corticosteroid dose and showed worse survival compared to those patients who were off steroids at the time of treatment (35). Although these conclusions are mainly based on retrospective studies, they do offer a plausible hypothesis of why steroid use does not affect efficacy when given later for the treatment of irAEs (36) when T cell antitumor response is already established. Steroids affect T cell apoptosis (37), and induce T regulatory cell proliferation and recruitment (38), which can eventually lead to primary or adaptive resistance to checkpoint inhibitors.

**Other immunosuppressed populations—pregnancy and the elderly**

In contrast to the populations mentioned above, some patients represent a challenge due to functional baseline immunosuppression resulting from a physiologic state such as pregnancy or advanced age.

Checkpoint regulators like PD-1 and CTLA-4 play an important role in maintaining maternal-fetal immunotolerance in pregnancy (39). Anti-PD-1 and anti-CTLA-4 antibodies are categorized as pregnancy category D and C, respectively, by the FDA. While scarce case reports in the literature of patients who were found to be pregnant while on checkpoint inhibitors (40,41) or were treated with checkpoint inhibition during gestation (42) reported favorable pregnancy and oncologic outcomes, no prospective or large retrospective studies are available. Hence, treatment decisions in this setting should be highly individualized based on the potential benefits and risks for the patient and fetal safety.

Most elderly patients were excluded from immunotherapy trials as well, and information on the interactions of checkpoint inhibition and aged immune cells is limited. However, as the population older than 80 years in oncology is increasing, this is slowly becoming a challenge in clinical practice. While aging is associated with a decline in immune function, elderly are not considered strictly immunodeficient (43). The response to antigens with aging is reduced, and thus it can possibly affect the immune tumor microenvironment (43,44). However, clinically this impact has not been studied, and the functional status is more of consideration rather than patient’s biologic age when checkpoint inhibitors are prescribed. A large meta-analysis of 5,265 patients, which dichotomized patients into younger and older groups with an age cutoff of 65–70, showed a consistent benefit of immunotherapy in both age...
Poor performance status

While there is strong evidence that the administration of cytotoxic chemotherapy in patients with poor performance status is associated with worse toxicity which overcomes potential efficacy, the impact of performance status on the safety and efficacy of immunotherapy is unclear. Since the side effect profile of checkpoint inhibitors is drastically different than that of chemotherapy, immunotherapy may be an appealing option in patients whose only option would be the best supportive care. There are very few trials that included patients with an ECOG performance status of 2 (48-52), mainly of patients with lung or urothelial cancer. Most of these trials included a mix of elderly patients and performance status 0–2. The clinical benefit appeared to be consistent regardless of poor performance status with similar toxicity rates to that of patients with a performance status of 0–1 (48-52). A meta-analysis of 18 studies analyzed 11,354 patients who received immunotherapy for solid tumors did not show any significant difference between patients with a performance status of 0 versus 1–2 (53).

In contrast, a more recent meta-analysis of 3,600 patients with exclusively lung cancer, reported that patients with performance status ≥2 had overall inferior survival outcomes (54). This finding, however, could be confounded by multiple factors such as more aggressive disease biology and patient heterogeneity, not necessarily reflecting the lower efficacy of immunotherapy in this setting (54). Other trials specifically for patients with a performance status 2–3 are currently ongoing (e.g., NCT04221529, NCT02879617, NCT04108026).

Despite the data heterogeneity, in carefully selected patients with poor performance status regardless of age, checkpoint inhibition may be very efficient and lead to prolongation of life; the histology, tumor characteristics, and biomarkers of response such as PD-L1 expression and tumor mutation burden in certain malignancies should also be accounted for prior making the treatment decision.

Conclusions

Immunotherapy has been undoubtedly a breakthrough in cancer treatment and completely altered the treatment landscape of multiple malignancies. The side effect profile of immunotherapy can be similar to autoimmune disorders creating concerns of higher toxicity rates and decreased efficacy in patients with underlying autoimmune diseases and/or immunosuppression. Hence, this population was excluded from the majority of the initial clinical trials, and available data on the safety and efficacy of immune checkpoint inhibitors in immunosuppressed populations are mainly from retrospective studies and case series. Despite this, with the increased risk of cancers arising in immunosuppressed patients, there is an unmet need to expand the treatment landscape in this patient population.

As more literature becomes available and more trials are including those patients, this ambiguity will become less prevalent. For most immunosuppressed patient groups, checkpoint inhibitors appear safe or at least not more toxic than those without any underlying immunosuppression. In addition, strategies to mitigate the development of irAEs and to understand the exact mechanisms involved are currently under study and may be particularly relevant for this high-risk population if proven efficacious. A clinical trial of combining dual checkpoint inhibitors with CD24Fc in an effort suppress the danger-associated molecular patterns by binding to Siglec10 (NCT04060407) and decrease irAEs is currently ongoing. As far as efficacy, concurrent immunosuppression may ultimately have an adverse effect. In the metastatic setting, especially when no other therapies are available, even a modest efficacy may be clinically relevant when compared to best supportive treatment. What is important to emphasize is that these patients overall should not be automatically excluded from these treatments that could potentially benefit them. The caveat is, of course, that for specific groups such as pregnancy and vital organ transplant recipients, our knowledge is extremely limited, and the decision should always be made on an individualized basis with a multidisciplinary approach. As the checkpoint inhibitors move to earlier lines of therapy and/or maintenance, one must consider all those risks and carefully weigh them against the potential merits as the risk-benefit ratio in this setting may not be as favorable for this patient population.
Lastly, biomarkers to predict responses to immunotherapy and limit toxicities need further investigation for all cancer patients but would certainly be helpful to weigh the risks and benefits for high-risk populations.

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