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Hot Topic

Cancer immunotherapy in a neglected population: The current use and future of T-cell-mediated checkpoint inhibitors in organ transplant patients

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ABSTRACT

Although the indications for immune checkpoint inhibitors continue to grow, organ transplant recipients with advanced malignancies have been largely excluded from clinical trials testing the safety and efficacy of these therapies given their need for chronic immunosuppression and the risk of allograft rejection. With the rapid growth of transplant medicine and the increased risk of malignancy associated with chronic immunosuppression, it is critical that we systematically analyze the available data describing immune checkpoint blockade in the organ transplant population. Herein we provide a current and comprehensive review of cases in which immune checkpoint blockade was used on organ transplant recipients. Furthermore, we discuss the differences in efficacy and risk of allograft rejection between CTLA-4 and PD-1 inhibitors and make recommendations based on the limited available clinical data. We also discuss the future of immune checkpoint blockade in this subpopulation and explore the emerging data of promising combination therapies with mTOR, BRAF/MEK, and BTK/ITK inhibitors. Further clinical experience and larger clinical trials involving immune checkpoint inhibitors, whether as monotherapies or combinatorial therapies, will help develop regimens that optimize anti-tumor response and minimize the risk of allograft rejection in organ transplant patients.

Introduction

T-cell-mediated immunotherapy has rapidly become one of the most promising fields within oncology. The three most studied methods of T-cell-mediated immunotherapy include the use of immune checkpoint inhibitors, the adoptive transfer of anti-cancer T-cells, and vaccination with tumor-associated antigens or by delivery of neoantigens. Although optimal immunotherapy likely entails a combination of these methods, the most promising at this time is the use of immune checkpoint inhibitors [1].

It has been extensively described how tumor cells inhibit T-cell-mediated immunosurveillance by altering their microenvironment. One such way that tumor cells do so is by their upregulation of inhibitory checkpoint molecules, including programmed death-ligands PD-L1 and PD-L2, which interact with PD-1 on T-cells to suppress the appropriate T-cell-mediated activation and effector response [2]. Additionally, dendritic cells also express PD-L1 and PD-L2, as well as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which all serve to inhibit T-cell activity [3].

Anti-PD-1 checkpoint inhibitors, including nivolumab and pembrolizumab, and anti-CTLA-4 inhibitors, including ipilimumab, continue to revolutionize treatment for malignancies such as melanoma, renal cell carcinoma, non-small cell lung cancer, head and neck cancer, hepatocellular carcinoma, lymphoma, and urothelial cancer. These inhibitors take advantage of cellular autoregulatory pathways by blocking "checkpoint molecules" and effectively restoring immune function within the tumor microenvironment. Blockade of checkpoint molecules promotes T-cell activation, which consequently stimulates both the cell-mediated and humoral anti-tumor immune responses. However, it is important to understand that blockade of immune checkpoint molecules, such as CTLA-4 or PD-1, stimulates T-cell activation not only against malignant cells, but also against donor allo-antigens in solid organ transplant patients [4]. As use of such agents increases with time, it is critical to understand that both therapeutic benefit and associated toxicities are largely dependent on the relationship between allogeneic T-cell and tumor-specific T cell activation.

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Given the growing number of organ transplants, it is of the utmost importance to understand the safety and efficacy of immune checkpoint inhibitors in this patient population. Organ transplant patients represent a largely neglected population within the field of immunotherapy and would greatly benefit from further research, especially given the increased risk of malignancy from chronic immunosuppression. In example, epidemiologic literature has documented that when compared to the general population, transplant recipients on chronic immunosuppression are 65–250 times more likely to develop squamous cell carcinoma and up to 10 times more likely to develop basal cell carcinoma [5,6]. Given the paucity of data and clinical trials assessing the safety and efficacy of immune checkpoint blockade in this subpopulation, it is thus vital that we systemically analyze the existing preclinical and clinical literature.

Methods

PubMed search was performed with keywords, "immune checkpoint inhibitor, organ transplant, transplant, rejection, PD-1, PD-L1, CTLA-4, MEK inhibitor, BRAF inhibitor, ibrutinib, BTK, ITK, immune checkpoint blockade, regulatory T cell, immunotherapy." After an extensive literature search, 34 articles were used to describe the available preclinical data. Furthermore, 17 articles were used for pooled analysis describing the clinical outcomes of organ transplant recipients who were treated with immune checkpoint inhibitors.

Preclinical evidence

In solid organ or hematopoietic stem cell transplant patients, immune checkpoint blockade enhances T-cell activation and effector response upon recognition of both malignant cells and allograft cells expressing allo-antigens [2]. Understanding the mechanisms that influence tumor-specific T-cell and alloreactive T-cell activation after administration of immune checkpoint blockade is key for optimizing therapies for the organ transplant patient population.

Regulatory T-cells (Tregs) play a vital role in allograft tolerance induction. Tregs, which comprise 5–10% of circulating CD4 T-cells, play a critical role in immune tolerance to self-antigens. Preclinical data has demonstrated that impaired Treg function increases the risk of organ-specific autoimmunity, such as type 1 diabetes mellitus and autoimmune hepatitis [7,8]. Tregs are able to suppress immune function and auto-reactivity via a combination of mechanisms, including cell contact-dependent suppression, cell contact-independent suppression, direct induction of apoptosis, and cytokine release [9]. Tregs may thus play a particularly important role in suppressing T-cell activation after exposure to allo-antigens in organ transplant recipients. The interaction of CTLA-4 on Tregs and B7 ligands on APCs promotes Treg-mediated suppression of both effector T-cell activation and APC maturation and function via recognition and endocytosis of APC's presented antigen and upregulation of the indoleamine 2,3-dioxygenase (IDO) pathway on APCs. The IDO pathway has been shown to be critical in acquired peripheral tolerance by promoting naïve CD4 T-cell differentiation into the "inducible" Treg phenotype and by direct activation of pre-existing Tregs. Thus, the IDO pathway may be critical in establishing and maintaining Treg-mediated immune suppression and peripheral tolerance [10]. Therefore, the use of CTLA-4 inhibitors in organ transplant patients may prevent Treg-induced immunosuppression and promote alloreactivity via increased stimulation and activation of effector T-cells.

Interestingly, preclinical data, prospective trials, and case reports also recognize the importance of the PD-1/PD-L1 axis for maintaining allograft tolerance in transplant recipients. PD-1 binds to both PD-L1, broadly expressed on both hematopoietic and non-hematopoietic cells, and PD-L2, mainly expressed on APCs. In multiple models that have described PD-L1 as a predominant inhibitor of T-cell alloreactivity, it's function has been highly dependent on the presence of Tregs [4]. PD-L1 signaling is critical for Treg induction, suppression of effector T cell function and expansion, and, ultimately, allograft acceptance. PD-L1 signaling, like CTLA-4 signaling, is thus pivotal in promoting the induction and maintenance of Tregs [3,11].

Clinical evidence

The initial ipilimumab trials, prior to the drug's FDA approval in 2011, excluded patients with active autoimmune disease and those receiving chronic immunosuppression after organ transplantation. Due to this initial exclusion, there remains a paucity of data assessing the safety and efficacy of immune checkpoint blockade in these high-risk populations. Given the increased risk of developing malignancy, especially cutaneous cancers, in transplant recipients on chronic immunosuppression, it is more important than ever to develop and standardize treatment options that maximize therapeutic benefit and minimize risk of allograft rejection. Although withdrawal of immunosuppression has been demonstrated to promote regression of metastatic melanoma in patients with underlying autoimmune conditions such as myasthenia gravis [12], organ transplant recipients are more reliant on some form of chronic immunosuppression and may thus benefit from concomitant use of immune checkpoint inhibitors.

Given the lack of randomized control trials, our data regarding the efficacy and safety of immune checkpoint inhibitors in transplant populations remains largely reliant on case studies. One such case study in 2015 details how an orthotropic liver transplant recipient with advanced cutaneous melanoma who received ipilimumab displayed partial response, and demonstrated only transient transaminase elevation and, ultimately, no evidence of graft rejection on biopsy. Although this data is promising, it is important to note that this patient received the liver transplant 8 years prior to ipilimumab administration, and was thus able to tolerate reductions in his immunosuppressive regimen [13]. Additionally, Lipson et al. reported two cases in which ipilimumab was safely and effectively used in patients diagnosed with metastatic melanoma who had previously received a kidney transplant and were concurrently being treated with low dose immunosuppression [14]. Once again, it is important to note that these patients had received their kidney transplant several years prior to induction of ipilimumab and may have already achieved full graft acceptance.

More recently, Spain et al. described a case in 2016 in which a kidney transplant recipient with metastatic melanoma underwent acute graft rejection after treatment with ipilimumab and nivolumab in sequence. This case report was one of the first to describe the occurrence of acute transplant rejection after initiation of immune checkpoint inhibitor therapy, as well as one of the first descriptions of the use of PD-1 inhibitors in an organ transplant recipient. It is important to note that in this case of acute graft rejection, the patient had received ipilimumab and then nivolumab in sequence a month apart due to tumor progression on ipilimumab monotherapy. It was hypothesized that acute rejection may have been triggered by a combination of augmented immune-related toxicity from the use of both agents in sequence and from nivolumab-induced loss of peripheral graft tolerance despite continuation of chronic immunosuppression with pred-