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Renal complications of immune checkpoint blockade

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ABSTRACT

Immune checkpoint inhibitors have been approved for a variety of cancer species. Renal complications in use of these agents are not very common compared with other immune-related adverse events (irAE). However, it is crucial for physicians to recognize and manage renal manifestations of irAE. In this review, we will summarize the up-to-date knowledge of the clinical presentation, pathologic features, and management of renal irAE. In addition, we will discuss the safety of immune checkpoint inhibitors in patients with chronic kidney disease as well as in kidney transplant recipients.

Introduction

Over the past decade, the emergence of immune checkpoint inhibitors has revolutionized the treatment of cancers. Since their initial clinical trials in melanoma,[1] the checkpoint inhibitors have obtained Food and Drug Administration approval in a variety of cancer species, such as melanoma,[2] non–small-cell lung carcinoma,[3,4] renal cell carcinoma,[5] classical Hodgkin's

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lymphoma,[6] and urothelial carcinoma.[7] Currently, there is one anti-cytotoxic T-lymphocyte antigen 4 (CTLA4) antibody (ipilimumab), two anti-program cell death protein-1 (PD-1) antibodies (nivolumab and pembrolizumab), and one anti-program cell death protein ligand 1 (PD-L1) antibody (atezolizumab) available in market as immune checkpoint inhibitors. Though immune checkpoint inhibitors have provided a dramatic improvement in patients' survival, immune-related adverse events (irAE) are common. In this review, we summarize the up-to-date knowledge on renal complications of immune checkpoint inhibitors and their clinical management. We also review the current available information on the safety and efficacy of immune checkpoint inhibitors in patients with chronic kidney disease (CKD) population and kidney transplant recipients.

Immune checkpoint inhibitor—A double-edged sword

Immune checkpoint inhibitors have been developed with a goal of restoring anticancer immunity. The importance of the immune system in protecting the body against internal threats such as malignant cells has been described by Chen and Mellman[8] as the "cancer-immunity cycle" (Fig). The process starts with the release of cancer cell antigens (neoantigens), which are uptaken and processed by antigen-presenting cells, followed by presentation to T cells at secondary lymphoid organs. This leads to the activation of effector cytotoxic T cells that then migrate and infiltrate the tumor, recognizing and killing cancer cells. There are many factors that can regulate this process and current immune checkpoint inhibitors modulate mainly 2 phases of the immune response (Fig): (1) enhancing T-cell activation in secondary lymphoid organs and (2) increasing tumor cell killing by cytotoxic T cells at target sites. Cytotoxic T-cell immune responses require 3 signals to be fully activated: signal 1—engagement of T-cell receptor and

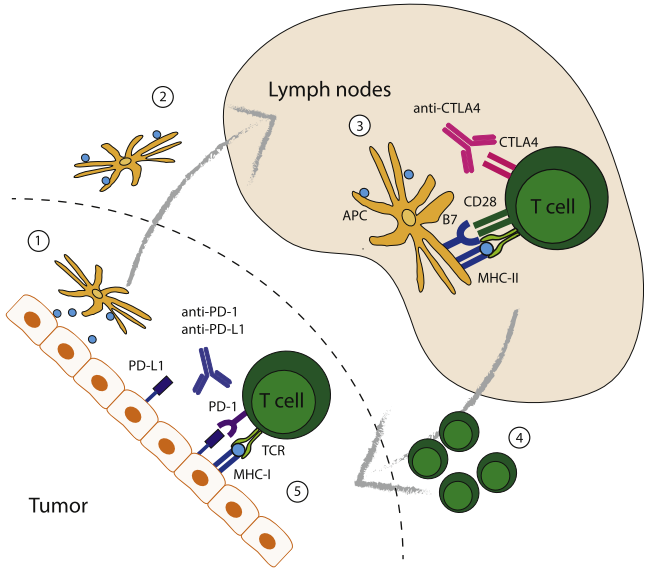

Fig. Cancer-immunity cycle and immune checkpoint inhibitors. Cancer cells release tumor neoantigens (1), which are carried to lymph nodes by antigen-presenting cells (APCs) (2). APCs present tumor antigens to T cells, which are primed and activated (3). Once T cells are activated, they migrate from the lymphoid organ to the tumor (4), where they identify target tumor cells and deliver killing signals (5). Anti-CTLA4 antibody blocks CTLA4-B7 interaction (3) thereby helps B7-CD28 engagement and T-cell activation in the secondary lymphoid organ, whereas anti-PD-1 antibody unleashes the inhibitory PD-1:PD-L1 signal (5), and enables cytotoxic killing of tumor cells by T cells in the target tissue. (Color version of figure is available online.)