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An overview of the toxicities of checkpoint inhibitors in older patients with cancer

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ABSTRACT

Checkpoint inhibitors offer an exciting new option for treatment of a wide variety of cancers. By binding to surface receptors or their associated ligands on T cells, this class of drugs enhances immune activation and response to cancer cells. In available studies, the drugs are well tolerated, although toxicity involving skin, gastrointestinal tract, liver, lungs, and endocrine organs has been observed. Unfortunately, few studies to date have included patients older than 70 years of age. Since aging has been linked to changes in immune function, there are theoretical concerns that this patient population might experience a different profile of adverse events. This article reviews the tolerability of checkpoint inhibitors in older patients with cancer in clinical practice.

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1. Introduction

The immune system has long been an area of interest in cancer therapy. In 1907, Paul Ehrlick first hypothesized that through "immune

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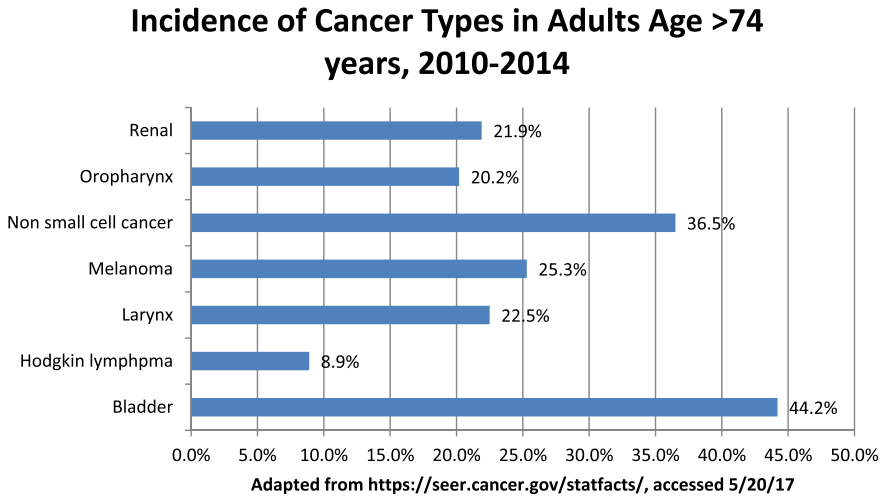


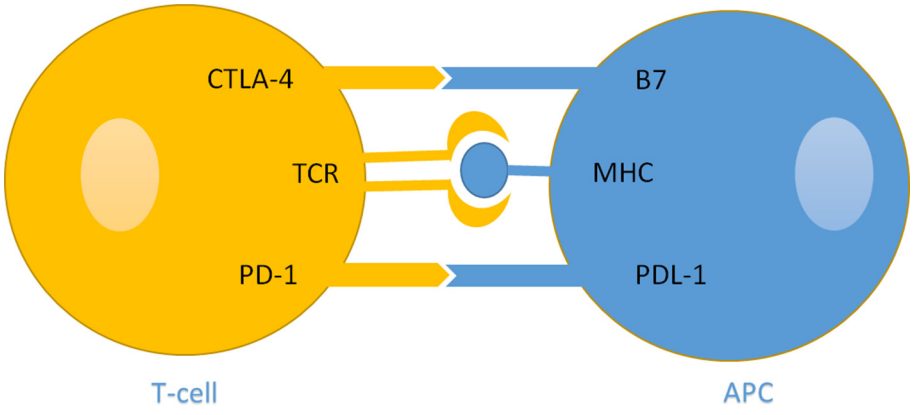
Fig. 1.

surveillance," the innate immune system "checks" tumorigenesis. The balance between activated and inhibited T cells is critical in maintaining an active immune response against foreign antigens and immune tolerance for host antigens. Immunotherapy seeks to activate the host immune system against tumor cells that escape normal immunosurveillance.

More than a century later, the anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) monoclonal antibody ipilimumab was approved by the Food and Drug Administration (FDA) for the treatment of advanced melanoma, the first of the new class dubbed "checkpoint inhibitors." In 2014, the first anti-programmed death 1 (PD-1) monoclonal antibody, pembrolizumab, was granted FDA approval for advanced or unresectable melanoma. Others soon followed and targeted the CTLA-4 and programmed cell death ligand 1 (PD-L1) pathways, with demonstrated efficacy in other tumors such as non-small cell lung cancer, head and neck cancer, renal cell cancer, bladder cancer, and Hodgkin lymphoma.

With expanding indications, immunotherapy has become a particularly attractive option given the tolerability and efficacy of these drugs in clinical trials. Yet the optimal role of checkpoint inhibitors is not well established in older adults, because this age group has been under-represented in clinical trials [1]. Despite the increasing incidence and prevalence of cancer among older adults, adults older than 75 years of age account for <10% of patients enrolled in National Cancer Institute (NCI) cooperative group trials. This lack of enrollment has been attributed to different factors, including advanced age, lack of adequate social support, poor performance status, and presence of multiple comorbid conditions. Of note, three-quarters of patients older than 70 years of age expressed willingness to participate in clinical trials [2,3]. At the ASCO 2017 annual meeting, Singh H. et al. presented the findings of the FDA experience with enrollment of older adults in clinical trials for cancer drug registration and demonstrated clear overrepresentation of patients below the age of 65 when compared to older adults [4].

Under-representation of older adults in trials of checkpoint inhibitors is important for three reasons. First, the cancers for which these drugs are indicated are common in older adults, as shown in Fig. 1. Second, the incidence or severity of drug-related adverse events could vary in an aging population because of co-morbidities, use of other medications, functional impairments, or physiologic changes of aging. Third, immunosenescence, or the waning function of the immune system with advancing age, could theoretically impair the efficacy of checkpoint inhibitors.



CTLA-4: Cytotoxic T-lymphocyte-associated antigen 4
TCR: T cell receptor
PD-1: Programmed cell death protein 1
PDL-1: Programmed death-ligand 1
MHC: Major histocompatibility complex
APC: Antigen-presenting cell

Fig. 2.

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