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Review article

Immunotherapy comes of age: Immune aging & checkpoint inhibitors

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ABSTRACT

Immune checkpoint inhibitors (ICIs) are based on the understanding that there are multilayered checks and balances which can be manipulated to unleash already existing, but paralyzed, immune responses to cancer. These agents are safer and more efficacious than classic cytotoxic drugs making them a very attractive therapeutic option, especially in older adults. Current available data do not suggest significant age-associated differences in the clinical profile of ICIs. It must be noted, however, that there is still relatively little information on the use of ICIs in adults over 75 years of age and aging is associated with a decline in the immune system or "immunosenescence" which theoretically can reduce the efficacy of these immune based therapies. In this paper, we review the mechanism of action of ICIs, current clinical data on their use in older adults, and age-associated immune changes that might have a direct impact on their activity in this population. We chose to focus on mainly adaptive cellular immunity, and especially on components of the immune system that are implicated directly in the immune checkpoint process.

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1. Introduction

Despite decades of effort aimed at harnessing the immune system to treat cancer, until recently clinical results have been limited in general and particularly so for older adults. Early attempts to harness the immune system to fight cancer included efforts to generally increase inflammatory responses in a non-specific manner with agents such as BCG or levamisole. Following this, use of cytokines [e.g. interleukin-2 (IL-2) or interferon alpha (IFN α)] which drive many aspects of immunity was tried with some benefit in certain cancers but with substantial toxicity. The relatively small impact of these efforts led to questions of the viability of immune enhancement as a broad-based approach to

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cancer therapy. Based on novel approaches, however, we now appear to be on the threshold of a revolution in immune based cancer therapy. Current exciting treatments known as immune checkpoint inhibitors (ICIs) are based on the more sophisticated understanding that there are multilayered checks and balances which can be manipulated to unleash already existing, but paralyzed, immune responses to cancer. In most cases, these agents are safer and more efficacious than classic cytotoxic drugs making them a very attractive therapeutic option, especially in older adults. On the other hand, aging is associated with a decline in the immune system or "immunosenescence" which theoretically can reduce the efficacy of these immune based therapies.

In this paper, we will review the mechanism of action of ICIs, current clinical data on their use in older adults, and age-associated immune changes that might have a direct impact on their activity in this population. We chose to focus on mainly adaptive cellular immunity, and especially on components of the immune system that are implicated directly in the immune checkpoint process. However, it should be noted that innate immune cells play important roles in cancer control or progression and these cells also have altered function with age (e.g. see discussion below of myeloid derived suppressor cells).

2. Mechanisms of action of checkpoint inhibitor antibodies

Immune checkpoints are essential for self-tolerance and protection of tissues from excessive immune related damage. Tumors can use these checkpoints as a pathway to escape immune response. Two immune-checkpoint receptors are currently the focus of cancer immunotherapy, cytotoxic T lymphocyte-associated antigen 4 (CTLA4) and programmed cell death protein 1 (PD1).

CTLA-4 antibodies act mainly by enhancing the interaction between antigen-presenting cells (APCs) and T lymphocytes (Fig. 1). APCs are a group of immune cells whose role is to capture, process, and present antigenic particles to lymphocytes initiating the cellular immune response. Multiple cells can function as APCs; however, in this paper we will focus on dendritic cells (DCs) since they are the most important APCs physiologically. After the capture and processing of antigenic particles, DCs migrate towards naïve T cells to prime them. This process is initiated by interaction between the T-cell receptor (TCR) on surface of T cells and the MHC on DCs, but a co-stimulatory signal is necessary to maintain it. This signal is provided by interaction of CD28 on the surface of T cells to CD80 and CD86 on the surface of APCs. Shortly after, CTLA-4 is expressed on the surface of T cells initiating a negative feedback that is necessary to avoid excessive immune reactivity and autoimmunity. CTLA-4 exerts its inhibitory action by outcompeting CD28 for its ligands, delivering direct inhibitory signals to T cells, sequestering CD80 and CD86 from surface of APCs, and downregulating T helper (Th) while enhancing T regulatory (Treg) immunosuppressive activity [1–5].

Anti CTLA-4 agents exert their action mainly during the "priming phase" in which naïve T cells are activated. Similar to CTLA-4, PD-1 is

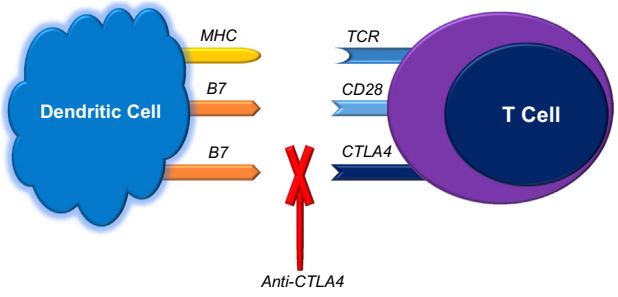

Fig. 1. T cells are activated after the T-cell receptor (TCR) recognizes antigens presented by the major histocompatibility complex (MHC). Shortly after, T-cells are activated and an inhibitory signal is initiated through interaction of CTLA4 and B7.

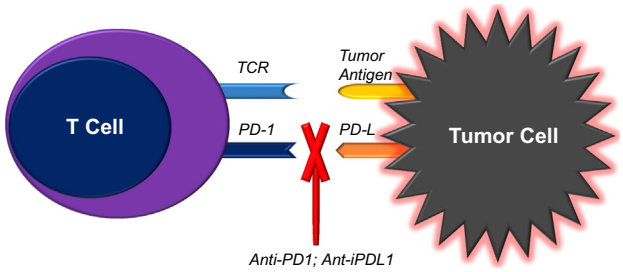

Fig. 2. PD-1 is expressed by T cells after they are exposed to antigens. The interaction between PD-1 and its ligands PD-L1 and PD-L2 results in negative regulation of T cells. Antibodies blocking the PD-1 pathway result in upregulation of T cells activity.

expressed on the surface of T cells after TCR is engaged by APCs [6]. In contrast to CTLA-4 which is focused in secondary lymphoid organs, the major role of PD-1 is within peripheral tissues and the tumor microenvironment [7] (Fig. 2). Interaction of PD-1 with one of its ligands, PD-1 ligand 1 (PD-L1) or PD-1 ligand 2 (PD-L2), inhibits effector T cells directly and by enhancing proliferation of the immunosuppressive Treg [8–11]. Persistent PD-1 activation can lead to a phenomenon termed T cell "exhaustion" [12]. PD-L1 is the main PD-1 ligand expressed on the surface of solid tumors [8,13]. Expression of PD-L1 on tumor cells can result from a physiologic reaction to protect tissues from excessive immune injury [10,14], or represent a constitutive mechanism within the tumor like in glioblastoma or ALK positive lung cancer [15,16]. Antibodies which bind to PD-1 or PD-L1 are now in use and have been proven to extend survival in various cancers with less autoimmune toxicity than CTLA-4 antibodies. The reduced toxicity may be due to the distinct mechanisms of activity of these two classes of antibodies. As noted PD-1/PDL-1 antibodies are likely acting upon T cells already within the tumor stroma and directed against tumor antigens. There is evidence for intrinsic declines in immune cell functions with age which may impact the effectiveness of either CTLA-4 or PD-1/PD-L1 antibodies.

3. Clinical trial data on use of ICIs in older adults

There have been no trials focused specifically on the use of ICIs in older adults. However, several papers have reviewed results of the limited number of older adults included in larger trials and found no clear evidence of age-associated difference in the effectiveness of ICIs, although a concern about higher toxicity has been raised. Elias et al. reviewed efficacy and safety of checkpoint inhibitors based on data from key clinical trials that lead to approval of ipilimumab, nivolumab and pembrolizumab in non-small cell lung cancer, melanoma, and renal cancer. No clear age-associated difference in efficacy or toxicity of ICIs among those older and younger than 65 years was found, although this information was more ambiguous for those older than 75 years due to very low number of patients enrolled in studies [17]. Nishijima et al. conducted a meta-analysis that included nine randomized controlled trials, where patients were separated into younger and older based on age cut-off of 65–70 years [18]. They showed that improvement in survival was comparable among age groups although based on preplanned subgroup analysis improvement in overall survival was not significant for PD-1 inhibitors in patients older than 75 years. A group from Memorial Sloan Kettering Cancer Center presented at the American Society of Clinical Oncology (ASCO) 2016 meeting their experience with patients older than 80 years treated with ICIs for melanoma [19]. They reported a comparable benefit and toxicity profile to published phase III data, although the rate of immune-related adverse events and early treatment discontinuation was modestly higher for older patients compared to a younger population. In another presentation from the ASCO 2016 meeting,

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