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LEADING ARTICLE

Clinical Impact of Checkpoint Inhibitors as Novel Cancer Therapies

Kent Shih · Hendrik-Tobias Arkenau · Jeffrey R. Infante

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Abstract Immune responses are tightly regulated via signaling through numerous co-stimulatory and co-inhibitory molecules. Exploitation of these immune checkpoint pathways is one of the mechanisms by which tumors evade and/or escape the immune system. A growing understanding of the biology of immune checkpoints and tumor immunology has led to the development of monoclonal antibodies designed to target co-stimulatory and co-inhibitory molecules in order to re-engage the immune system and restore antitumor immune responses. Anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibodies were among the first to be tested in the clinic, and ipilimumab was the first immune checkpoint inhibitor approved for an anticancer indication. Agents targeting the programmed death 1 (PD-1) pathway, either PD-1 or one of its ligands, programmed death ligand 1, are in active clinical development for numerous cancers, including advanced melanoma and lung cancer. Understanding the different mechanisms of action, safety profiles, and response patterns associated with inhibition of the CTLA-4 and PD-1 pathways may improve patient management as these therapies are moved in to the clinical practice setting and may also provide a rationale for combination therapy with different inhibitors. Additional immune checkpoint molecules with therapeutic potential, including lymphocyte activation gene-3 and glucocorticoid-induced tumor necrosis factor receptor-related gene, also have inhibitors in early stages of clinical development. Clinical responses and safety data reported to date on immune checkpoint

This article is part of the topical collection on Immuno-Oncology.

K. Shih (🖂) · H.-T. Arkenau · J. R. Infante Sarah Cannon Research Institute and Tennessee Oncology PLLC, Nashville, TN 37203, USA e-mail: kshih@tnonc.com inhibitors suggest these agents may have the potential to markedly improve outcomes for patients with cancer.

Key Points

Immune checkpoint inhibitors are designed to interrupt inhibitory immune signals and restore immune responses against tumors.

Numerous immune checkpoint inhibitors are in advanced stages of development and show activity across multiple tumor types, including advanced melanoma and advanced non-small-cell lung cancer.

Understanding the mechanism-associated adverse events and response patterns is important to the management of patients as these drugs are moved into the clinical practice setting.

1 Introduction

Rudolph Virchow may have been one of the first physicians in modern times to observe the link between the immune system and malignancy in what he termed "lymphoreticular infiltrates". These infiltrates were leukocytes surrounding malignant tumors, and he hypothesized that proinflammatory states might induce normal tissues to become malignant [1]. Since then, we have learned a great deal about how the immune system responds and reacts to tumors, which tumor-specific antigens are recognized as foreign, and how immune responses can be manipulated and harnessed to enhance tumor cell killing.



Recently, it has been recognized that, on its own, tumor peptide presentation by major histocompatibility complex (MHC) to T-cell receptors is inadequate for successful T-cell activation and immune destruction of cancer cells. Co-regulatory signals, either inhibitory or stimulatory, are also required [2, 3]. T cells play a critical role in cellmediated tumor immunity, and do so through an intricate counterbalance of co-stimulatory and co-inhibitory cell-tocell signals between various components of the immune system. This system of checks and balances is necessary not only to allow a powerful destructive response against both pathogens and malignancies, but also to prevent immune responses from being generated against normal tissues. Critical 'checkpoints' control and fine-tune the immune system through regulation of this complex network of co-stimulatory and co-inhibitory signaling [3]. In this paper, we review some of the important immune checkpoint molecules elucidated to date, as well as efforts to block these molecules in order to shift the balance towards antitumor immunity. We also describe some of the complexities and challenges encountered using these checkpoint inhibitors in the clinic.

2 Cytotoxic T-Lymphocyte-Associated Antigen (CTLA)-4

2.1 Background

More than 40 years of research has led to the development of a two-signal theory of T-cell activation: antigenic stimulation of the T-cell receptor (TCR) (signal 1) together with co-stimulation by other molecules on the cell surface (signal 2) [2, 3]. One of the key co-stimulatory mechanisms involves the interaction of CD28 on the surface of the T cell with B7 molecules CD80 or CD86 on antigen-presenting cells. CTLA-4, a transmembrane glycoprotein with considerable homology to CD28, binds to the same B7 ligands, as such (Fig. 1). Upon TCR stimulation by antigens, T cells express CTLA-4, which can bind B7 molecules; however, unlike CD28, CTLA-4 inhibits T-cell responses and is important for maintenance of immune tolerance. Expression of CTLA-4 raises the activation threshold and attenuates clonal expansion; thus, a productive T-cell response ensues only upon a net co-stimulatory signal.

2.2 Efficacy of CTLA-4 Inhibitors

2.2.1 Ipilimumab

Ipilimumab, one of the best-studied monoclonal antibodies targeting CTLA-4 (Table 1 [4–16]), has been evaluated in

Antigen presenting cell/Tumor

T cell

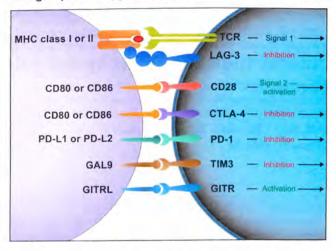


Fig. 1 T-cell activation and immune checkpoint pathways. T-cell activation requires two signals: (1) presentation of antigenic peptides by MHC to the TCR and (2) co-stimulation, typically via CD28:CD80 or CD28:CD86 ligation. Immune checkpoint pathways comprising receptors on T cells and ligands on antigen-presenting cells and/or tumors fine-tune immune responses via T-cell activation or inhibition. CTLA-4 cytotoxic T-lymphocyte-associated antigen 4, GAL9 galectin-9, GITR glucocorticoid-induced TNF receptor-related gene, GIT-RL glucocorticoid-induced TNF receptor-related gene ligand, LAG-3 lymphocyte activation gene-3, MHC major histocompatibility complex, PD-1 programmed death-1, PD-L1 programmed death ligand 1, PD-L2 programmed death ligand 2, TCR T-cell receptor, TIM3 T-cell immunoglobulin and mucin domain 3, TNF tumor necrosis factor

a clinical trial program of more than 2,000 patients with a variety of solid tumors [4, 5, 17-19]. Ipilimumab (Yervoy®), administered every 3 weeks for four doses, gained US FDA approval in 2011 for the treatment of unresectable or metastatic melanoma, based on data from two phase III randomized trials showing improvement on median overall survival (OS) over control arms in patients with melanoma [4, 5, 20]. One of the pivotal phase III trials evaluated ipilimumab with or without gp100 vaccine in previously treated patients with advanced melanoma. Although the best overall response rates were modest, 10.9 % in the ipilimumab-alone group and 5.7 % in the ipilimumab plus gp100 vaccine group, some patients in both groups maintained an objective response for at least 2 years [4]. In this trial, the 3-year OS rate for ipilimumab monotherapy was 20 % [4], which compares favorably with the 3-year OS rate of 17 % for historical control patients receiving standard of care chemotherapy in a separate clinical trial [21] (Table 2 [4, 5, 7, 18, 19, 21–33]). The other pivotal phase III trial was conducted in treatment-naïve patients with metastatic melanoma and compared ipilimumab plus dacarbazine versus dacarbazine plus placebo [5]. Although the dose and schedule were slightly different, the rate of best overall response was 15 % in the ipilimumab plus dacarbazine group versus 10 % for the dacarbazine plus



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