REVIEW ARTICLE

Immune-mediated adverse events of anticytotoxic T lymphocyte–associated antigen 4 antibody therapy in metastatic melanoma

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Ipilimumab, an antibody that blocks cytotoxic T lymphocyte–associated antigen 4 (CTLA-4; CD152), was approved by the Food and Drug Administration in 2011 for the treatment of unresectable stage III or IV malignant melanoma. Although the addition of this particular immunotherapy has broadened treatment options, immune-related adverse events (irAEs) are associated with ipilimumab therapy, including dermatologic effects, colitis and diarrhea, endocrine effects, hepatotoxicity, ocular effects, renal effects, neurologic effects, and others. In this article, a critical evaluation of the underlying mechanisms of irAEs associated with anti–CTLA-4 therapy is presented. Additionally, potentially beneficial effects of combinational therapies to alleviate ipilimumab-induced irAEs in malignant melanoma are discussed. Future research is warranted to elucidate the efficacy of such combination therapies and specific biomarkers that would help to predict a clinical response to ipilimumab in patients with malignant melanoma. (Translational Research 2015;166:412–424)

Abbreviations: ADCC = antibody-dependent cell-mediated cytotoxicity; APC = antigen-presenting cell; BRAF = V-Raf Murine Sarcoma Viral Oncogene Homolog B; CIDP = chronic inflammatory demyelinating polyneuropathy; CT = cancer/testis; CTLA-4 = cytotoxic T lymphocyte-associated antigen 4; FcγR = fragment crystallizable γ receptor; FDA = Food and Drug Administration; IgG1 = Immunoglobulin G1; IgG2 = Immunoglobulin G2; IL-2 = interleukin-2; irAE = immune-related adverse event; LDH = lactate dehydrogenase; MEK = Mitogen-activated protein kinase kinase; MHC = major histocompatibility complex; NIH = National Institutes of Health; PD-1 = programmed cell death protein 1; PD-L1 = programmed death-ligand 1; PD-L2 = programmed death-ligand 2; SNP = single nucleotide polymorphism; TCR = T-cell receptor; Teff = Effector T cell; Treg = Regulatory T cell; T-VEC = talimogene laherparepvec; V-RAF = Virus-induced rapidly accelerated fibrosarcoma

INTRODUCTION

Melanoma, an increasingly prevalent cutaneous malignancy, is projected to cause 9710 deaths in the US in 2014.[1] Although early detected melanoma can generally be cured with wide excision (and possibly a lymph node biopsy), advanced stages of melanoma often require systemic treatment. Hence, localized melanoma has a much more favorable 5-year relative survival rate (up to 98%) than regional melanoma (62%) and distant melanoma (16%) based on the stage at diagnosis.[1]

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There are now several treatments for metastatic melanoma.[2] First, there is chemotherapy with dacarbazine or temozolomide. There is also targeted therapy with BRAF (*Virus-induced rapidly accelerated fibrosarcoma [V-RAF]* murine sarcoma viral oncogene homolog B) inhibitors (vemurafenib and dabrafenib), and inhibitors of mitogen-activated protein kinase kinase enzymes MEK1 and MEK2 (trametinib). Lastly, there is immunotherapy with interferon alfa-2b, interleukin 2 (IL-2), and an anticytotoxic T lymphocyte–associated antigen 4 (anti–CTLA-4; CD152) antibody, ipilimumab. Additional methods of immunotherapy include programmed cell death protein 1 (PD-1; CD279) antibodies, lambrolizumab,[3,4] now known as pembrolizumab (MK-3475),[5,6] nivolumab,[7,8] and the anti–PD-1 ligand (PD-L1; CD274) antibodies, BMS936559[9] and MPDL3280A.[10] This review article primarily focuses on immunotherapy, specifically with ipilimumab and also discusses combinational therapies with several of the agents discussed previously.

INHIBITION OF CHECKPOINT WITH ANTIBODIES AGAINST CTLA-4, PD-1, AND PD-L1

Cellular mechanisms of action of CTLA-4. Anti–CTLA-4 antibodies augment tumor-specific cellular immunity by interrupting a negative signaling mechanism that inhibits cytotoxic T cells. In order for a naive T cell to become activated, 2 receptor-ligand interactions must occur (Fig 1). First, the T-cell receptor binds to a major histocompatibility complex molecule and an antigen on an antigen-presenting cell (APC). Second, there must be a costimulatory signal in the form of CD28 on the T cell interacting with B7.1 (CD80) and B7.2 (CD86) on the APC. CTLA-4 serves as a checkpoint in the immune system by binding to B7.1 and B7.2 with greater affinity than CD28.[11] This in turn compromises the costimulatory signal that must occur for a naive T cell to become activated, resulting in decreased IL-2 secretion and decreased expression of the IL-2 receptor. Thus, anti–CTLA-4 antibodies act as checkpoint inhibitors and better allow for the patient's own effector T cells to kill melanoma tumor cells.

In addition to inhibiting this costimulatory signal, CTLA-4 is highly expressed on regulatory T cells (Tregs), which serve to downregulate cell-mediated immunity. For example, the intratumoral ratio of effector T cells to Tregs with the use of anti–CTLA-4 antibodies has been investigated recently.[12] Treatment with anti–CTLA-4 antibodies increases the expression of effector and Tregs in the lymph nodes. However, in melanoma tumor lesions, anti–CTLA-4 antibody treatment depletes Tregs through an fragment crystallizable γ receptor (FcγR)-dependent mechanism, resulting in increased intratumoral ratio of effector T cells (Teff) and Tregs (Fig 1). There is a selective reduction in Tregs in melanoma tumors for several reasons. First, tumor-induced Tregs expressing CTLA-4 are abundant in the tumor microenvironment. Second, a particular FcR on macrophages within the tumor, called FcγRIV, is involved in the depletion of these Tregs. Macrophages with FcγRIV interact with anti–CTLA-4 antibodies, which bind to CTLA-4 on Tregs. Macrophages then deplete these Tregs via antibody-dependent cell-mediated cytotoxicity (Fig 2). Therefore, future research is warranted to further evaluate and compare the tumor microenvironment in malignant melanoma patients to predict the efficacy of anti–CTLA-4 treatment. Tumors with increased macrophages or macrophages with increased expression of FcγRIV could respond better to ipilimumab.

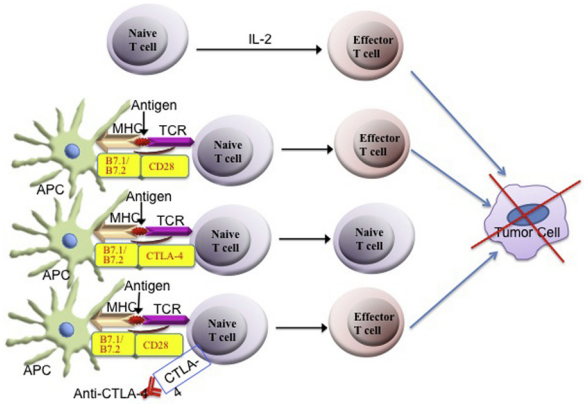

Fig 1. Schematic diagram showing the generation of effector T cells and the killing of the tumor cell. Normally, naive T cell differentiate into effector T cells in response to IL-2. Also, antigen is presented to naive T cells by APC via major histocompatibility complex (MHC) II and T-cell receptor, and this process is enhanced by the interaction of costimulatory molecules whereby CD28 molecule on T cells interacts with B7.1 (CD80) and B7.2 (CD86) on APCs, resulting into the generation of effector T cells to kill tumor cells. However, CTLA-4 binds with B7.1/B7.2 with greater affinity than CD28 and thus inhibits the differentiation of naive T cells into effector T cells. Blocking CTLA-4 with anti–CTLA-4 antibody will allow CD28 to interact with B7.1/B7.2 to generate effector T cells and promote killing of tumor cells. APC, antigen-presenting cell; CTLA-4, cytotoxic T lymphocyte–associated antigen 4; IL-2, interleukin 2; TCR, T-cell receptor.

Cellular mechanism of action of PD-1, PD-L1, and PD-L2. PD-1 is similar to CTLA-4, in that PD-1 attenuates effector T cell responses. PD-1 finds expression on activated T and B cells, Tregs, and natural killer cells.[13] The primary ligand for PD-1, PD-L1 (also known as B7-H1 or CD274), is found on activated immune cells and tumor cells. A second ligand, PD-L2 (also known as B7-DC or CD273), is found mainly on dendritic cells (APCs) and in a few tumor cell lines. When PD-1 interacts with its ligands, proinflammatory cytokines are diminished (Fig 2).