Novel Opportunities to Use Radiation Therapy with Immune Checkpoint Inhibitors for Melanoma Management

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KEYWORDS

• Abscopal effect • Bystander effect • Immune checkpoint inhibitors
• Radiation therapy

KEY POINTS

- Anti–cytotoxic T lymphocyte antigen 4 and anti–programmed cell death 1 agents are immune checkpoint inhibitors with a proven role in the management of advanced melanoma.
- Preclinical models have revealed radiation therapy to stimulate the immune system.
- Based on preclinical evidence, numerous prospective studies are currently underway to assess radiation therapy in the management of advanced melanoma alongside immune checkpoint inhibitors.

INTRODUCTION

Immunotherapy is shifting the oncologic landscape in the management of malignancies. The immune system plays a critical role in the body's ability to clear neoplastic cells. Tumor evasion of the host immune system is crucial to its survival and proliferation. Through various mechanisms, tumors are able to evade the body's innate and adaptive immune system. Immune checkpoint inhibitors (ICIs) are a new class of targeted agents, which directly target various machineries used by tumor cells to suppress the immune system. These drugs have displayed impressive results in both solid tumors and hematological malignancies. Nowhere have these impressive survival results been more detailed than in melanoma. Melanoma was the first tumor model to study the efficacy of ICIs. As a result, substantial survival benefits have been noted in the use of these agents over conventional chemotherapy.[1]

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The role of radiation therapy (RT) in advanced metastatic melanoma has traditionally been part of the larger effort to improve local tumor control either intracranially or extracranially.[2,3] However, over the past decade studies have suggested the potential for RT to work synergistically with ICIs priming the immune system to enhance the efficacy of these systemic agents. Although the exact mechanism behind this synergistic effect is not known, several theories have been proposed.[4–7] These theories include the use of RT microenvironment modification with cytokine and danger signal release resulting in immunogenic cell death.[8] Multiple case reports have reported on the existence of such an effect whereby localized radiation alongside immunomodulating agents may have an effect in treating distant sites of disease.[9–13] In addition, several case series detailing results both systemically and intracranially with combined modality management have been reported. The purpose of this review is to highlight the research, which has been conducted to date with ICIs alone and in combination with RT for the management of advanced melanoma.

ANTI–CYTOTOXIC T LYMPHOCYTE ANTIGEN 4 THERAPY

Numerous receptors on the antigen-presenting cells and T cell are responsible for the immune response to tumor cells[7] (**Fig. 1**). Cytotoxic T lymphocyte antigen 4 (CTLA-4) is a receptor expressed on the surface of T cells that interacts with CD80 and CD86 on antigen-presenting cells to downregulate the T-cell response on tumors.[14] The anti–CTLA-4 monoclonal antibody, ipilimumab, inhibits the effect of the CTLA-4 receptor in inhibiting the immune response. The effect of CTLA-4 blockade is to allow CD28 (T

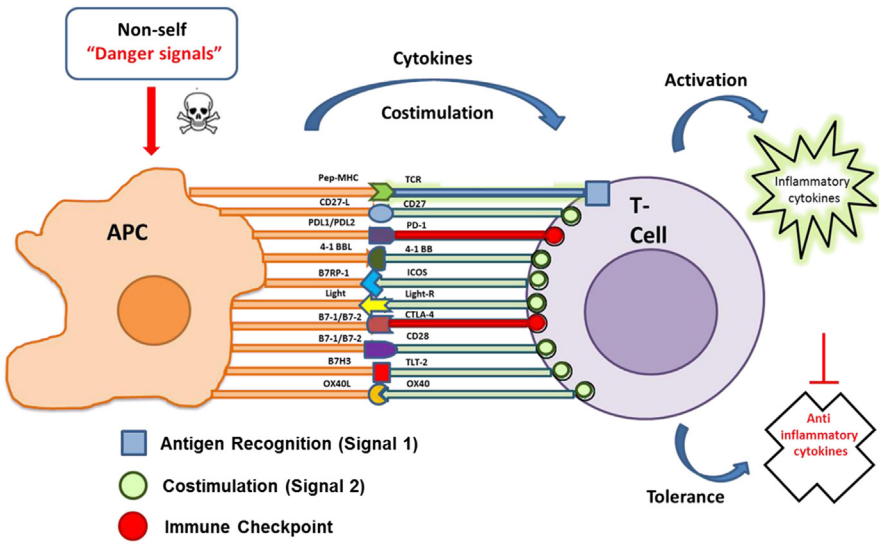

Fig. 1. Immune synapse. A snapshot of an immune synapse between antigen-presenting cell (APC) and effector cell (T cell) during immune priming is depicted. The APC stimulated by the danger signal will present antigen (signal 1) and costimulation (signal 2) via ligand-receptor interaction or cytokines. The immune response is restrained by immune checkpoint receptors and antiinflammatory cytokines. CTLA-4, cytotoxic T lymphocyte antigen 4; MHC, major histocompatibility complex; PD-1, programmed cell death 1. (*From* Grass GD, Krishna N, Kim S. The immune mechanisms of abscopal effect in radiation therapy. Curr Probl Cancer 2016;40:12; with permission.)