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Mini-review

Radiotherapy combined with immune checkpoint blockade immunotherapy: Achievements and challenges

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ABSTRACT

To date, several kinds of immunomodulating monoclonal antibodies (mAbs) have been applied in clinical trials, such as anti-cytotoxic T-lymphocyte antigen-4 (anti-CTLA-4) mAb and anti-programmed death-1 (anti-PD-1) mAb. With the recent success of cancer immunotherapy, especially the checkpoint inhibitors, the renewed interest in immunotherapy as a treatment modality has gained extensive attention. The irradiated tumor cell death can enhance antitumor immunity by inducing antigen expression on tumor cells and activating lymphocytes. Radiotherapy (RT) combined with immunotherapy has revealed promising outcomes in various animal models. However, this new paradigm is often considered as a medical spectacle without a unifying model, and its mechanisms have yet to be elucidated. The purpose of this review is to investigate previously published studies of radiotherapy combined with checkpoint blockades by the following aspects: exploring the potential mechanisms; identifying the most beneficial dose, fraction and target site for RT; finding an appropriate time window to combine these two treatments; and discussing the toxicity and suitable treatment evaluating criteria.

Introduction

Ionizing radiation has largely been recognized as a local targeted therapy by a variety of mechanisms, including inducing tumor and tumor-associated stromal cell DNA-damage directly, and eventually causing tumor cell death through mitotic catastrophe, senescence, apoptosis, and autophagy [1]. In terms of the tumor infiltrating lymphocyte (TIL) component of tumor stroma, radiotherapy (RT) has traditionally been regarded as an immunosuppressive strategy [2]. However, more complex systemic effects occur between radiation and local immune microenvironment [3]. The irradiated tumor cell death can enhance antitumor immunity by inducing antigen expression on tumor cells and activating lymphocytes. In this way, the whole therapeutic efficacy of RT may exceed the sum of treatment efficacy on each cell in isolation. Currently, more and more reports have demonstrated the clinical observations regarding the regression of a metastatic lesion outside the irradiated field, the so-called 'abscopal effect' or 'radiation-induced bystander effect' (RIBE) [4,5]. There are a variety of mechanisms including inflammation, dangerous signals, immune response and distant effects. So far, the specific mechanisms of this treatment efficacy are still not elucidated fully. Emerging evidence suggests that the generation of antitumor immune responses may play an important role in the effectiveness of this phenomenon [6]. However, this rare phenomenon is only reported in several cases, possibly because radiotherapy per se is generally insufficient to subvert the host's immune tolerance toward tumors [7]. It is reasonable to hypothesize that radiotherapy combined with immunotherapy will lead to enhanced antitumor immune responses and improved clinical outcomes. Based on this theory, since the term "abscopal" has been proposed, dozens of preclinical studies and reviews have discussed this phenomenon and demonstrated the priming clinical outcomes of combinatorial treatment from radiotherapy and immunotherapy [5,8–10].

However, this new paradigm of cancer treatment, RT combined with immunotherapy, is often considered as a medical spectacle without a unifying model, and its mechanisms have yet to be elucidated. The purpose of this review is to investigate previously published studies of radiotherapy combined with immunotherapy by the following aspects: exploring the potential mechanisms; identifying the most beneficial dose, fraction and target site for RT; finding an appropriate time window to combine these two treatments; and discussing the toxicity and suitable treatment evaluating criteria.

Development of checkpoint blockade immunotherapy

The aim of cancer immunotherapy is to stimulate the host's immune system for attacking and rejecting tumors, which can be summarized as the push–pull strategy [11], by pushing the immune response with vaccines based on tumor-specific-lymphocytes, costimulatory molecules, cytokines and toll like receptor (TLR) ligands as molecular adjuvants, and pulling suppressive cells such as

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myeloid-derived suppressor cells (MDSC), Foxp3 T regulatory cells (Tregs) or blocking inhibitory molecules such as PD-1 or CTLA-4 receptors or inhibitory cytokines including TGF-β and IL-13 (Fig. 1). Monoclonal antibodies have been extensively applied by oncologists because of their long-lasting clinical benefit. These agents are either agonists of immune-activating receptors (costimulatory receptors) or antagonists of immune-repressor molecules (coinhibitory receptors), which may be the most potential family of agents holding much more hope for anticancer efficacy [12]. To date, several kinds of immunomodulating mAbs have been applied in clinical trials, such as anti-CTLA-4, anti-PD-1, anti-PD-L1, anti-CD40, anti-CD137, anti-OX40, anti-CD137, and anti-transforming growth factor (TGF)-β mAbs. Based on the published reports [13,14], the present review focuses on the development of radiation combined with antibodies to block signaling via inhibitory molecules such as CTLA-4 or PD-1/PD-L1.

Ipilumumab, anti CTLA-4 mAb, has been approved by the Food and Drug Administration (FDA) following excellent clinical outcomes in patients with metastatic melanoma [15]. CTLA-4, a glycoprotein expressed on the surface of T cells, plays a pivotal role in attenuating the early activation of naïve and memory T cells in priming phases. The costimulatory receptor CD28 and the coinhibitory receptor CTLA-4 share the same ligands such as CD80 and CD86 on professional antigen-presenting cells (APCs). Ligation of CTLA-4 suppresses T lymphocyte responses by executing negative signaling at the immune synapse and outcompeting CD28 for ligand binding. Blocking inhibitory functions of CTLA-4 can stimulate the immune system to reject cancers. Another coinhibitory molecule, PD-1, primarily takes part in modulating T cell activity via interaction with PD-L1 and PD-L2 [16]. PD-1 is expressed upon lymphocyte activation in CD4+ and CD8+ T cells, natural killer (NK) T cells, dendritic cells (DC), as well as in monocytes and B cells. PD-1 is actively involved in the exhaustion process of activated T cells. PD-1 ligation by PD-L1 primarily controls the functions of effector cells by inhibiting the production of several cytokines and promoting apoptosis of T cells. Anti-PD-1/L1 mAbs show good outcomes in non-small cell lung cancer (NSCLC), renal cancer and melanoma. Pembrolizumab (MK-3475), mAb of PD-1, has been approved by FDA for clinical application in patients with advanced NSCLC [17]. With the recent successes of cancer immunotherapy, especially checkpoint inhibitors, the renewed interest in immunotherapy as a treatment modality has gained extensive attention.

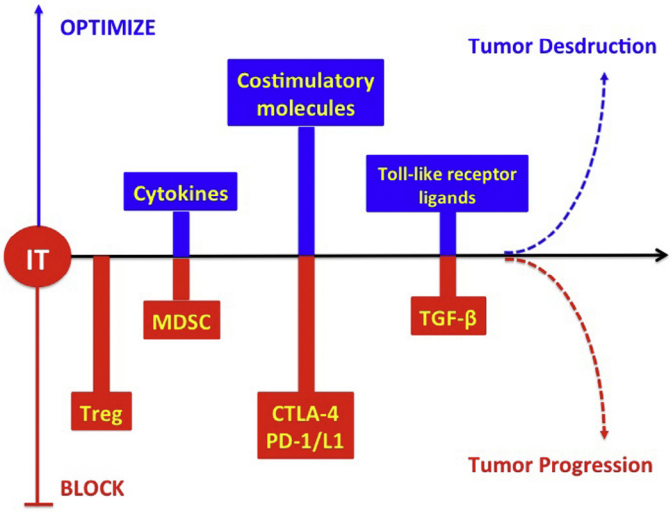

Fig. 1. Cancer immunotherapy aims to stimulate the host immune system for attacking or rejecting tumors by optimizing the immune response with vaccines based on tumor-specific-lymphocytes, costimulatory molecules, cytokines and toll like receptor (TLR) ligands as molecular adjuvants, and pulling suppressive cells such as myeloid-derived suppressor cells (MDSC), Foxp3 T regulatory cells (Tregs) or blocking inhibitory molecules such as PD-1 or CTLA-4 receptors or inhibitory cytokines including TGF-β and IL-13.

Achievements of RT combined with immunotherapy

In 2012, a case report has highlighted the treatment efficacy of RT combined with immunotherapy in melanoma. The patient reveals a slow progression despite treatment with checkpoint blockage through ipilimumab, but then exhibits a response after palliative radiation to the pleural metastasis and additional treatment with ipilimumab [5]. Subsequently, several case reports and studies have demonstrated priming outcomes of the combinatorial treatment in different cancer types [9,18]. In a retrospective analysis conducted by Grimaldi et al. [19], patients with metastatic melanoma who experienced disease progression after ipilimumab treatment and subsequent RT treatment are enrolled. Among 21 patients, 52% of patients have abscopal response and median OS for patients with abscopal response is significantly longer when compared with patients without abscopal response. Victor et al. have conducted a phase I clinical trial of 22 patients with metastatic melanoma [14]. A single index lesion is irradiated with hypofractionated radiation followed by four cycles of ipilimumab treatment. The disease progression of 36% patients has been controlled. In another phase III clinical trial [20], ipilimumab treatment is associated with better survival than placebo at a later time point among patients with at least one bone metastasis from castration-resistant prostate cancer. These reports and clinical observations focus on the potential of radiation to spark systemic antitumor immune response. In the last 5 years, a lot of preclinical studies have confirmed the augmentation of systemic antitumor immunity following local RT in combination with immunotherapy [10,13,14]. Although preclinical and clinical evidence suggests that RT may enhance therapeutic benefits of immunotherapy for cancers. The specific mechanisms, optimal treatment sequence and appropriate patient populations of the combinatorial treatment are still not elucidated. As a result, to date, no data are available from randomized clinical trials to determine whether these treatment approaches have synergistic antitumor effect.

Potential mechanisms of radiotherapy combined with immunotherapy

These immunomodulating antibodies are initially used as monotherapy, but with more and more attention on the abscopal effect, combinations of immunotherapy with radiotherapy have been tested both in preclinical studies and in ongoing clinical trials. Recently, RT combined with immunotherapy has revealed promising outcomes in various animal models. (Table 1) The relationship between radiation and the immune system is complex and multifactorial, which may largely depend on the radiation dose/quality and immune cell types [29]. In the combinatorial treatment paradigm, the critical role of radiation with appropriate dose and fraction is an in situ vaccination by inducing tumor immunogenic antigen release during antitumor immune response. In vitro and in vivo preclinical studies indicate that tumor irradiation exposed to a complex antigenic environment can generate new peptides and increase the pool of intracellular peptides for cross-presentation [30]. During combinatorial treatment between RT and immunotherapy, the tumor-specific immune response is triggered and enhanced subsequently. However, considering the heterogeneity of tumors, it is hard to select the best antigen for any specific tumors because it is unlikely for T cells to reject the tumor by recognizing only one or a couple of

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