Radio-Immunotherapy

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Radio-Immunotherapy: the combination effect of radiotherapy and immunotherapy on tumors, which may have much better therapeutic efficacy than each of them alone.

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1. Introduction

The impact of radiotherapy (RT) on the non-radiation field tumor caused by the immune response triggered by the local irradiated tumor and the combination of RT and immunotherapy to eliminate the tumor have become the focus of current research. As we all know, systemic RT can ablate the body′s immune system to lower the risk of xenotransplantation rejection in patients [1]. Conversely, a volume of studies have proved that local tumor irradiation can enhance the immune response, thereby allowing metastases away from the treatment site to be controlled [2]. The previous research indicated that the local RT of a tumor increased the expression level of major histocompatibility complex (MHC) class I molecules and improved the ability of presenting antigens of antigen presenting cells (APCs), the maturation of dendritic cells (DCs) was motivated, and the toxicity of nature killer (NK) cells and the tumor infiltration of CD8+ cytotoxic T lymphocytes (CTLs) were enhanced [3][4][5]. However, at the same time, ionizing radiation (IR) also mobilized some immunosuppressive cells, such as regulatory T (Treg) cells and M2 macrophage and myeloid-derived suppressor cells (MDSCs). The presence of these cells helped the tumor cells escape the supervision of the immune system, which greatly reduced the efficiency of IR treatment.

Targeting therapies against programmed cell death protein 1 (PD-1) and its ligand PD-L1, T-lymphocyte-associated antigen 4 (CTLA-4) has impelled the clinical treatment of cancer to move forward and has also been found to extend the response of RT on the antineoplastic function to the whole body through activating T cells. Building on this foundation, the combination of RT with immune checkpoints blockade (ICB) is increasingly used in the study of local RT and the RT-induced abscopal effect [6][7][8]. Monoclonal antibodies targeting CTLA-4 (ipilimumab), PD-1 (e.g., pembro-lizumab and nivolumab), and PD-L1 (e.g., avelumab, atezolizumab, and durvalumab) have been approved by the Food and Drug Administration of USA (FDA) in the treatment of various malignant tumors, such as melanoma, non-small cell lung cancer, renal cell carcinoma, urothelial carcinoma, and lymphoma [9]. Despite the great success of anti-CTLA-4 and anti-PD-1/PD-L1 therapy, due to the complex adjustment of anti-tumor immunity in the tumor microenvironment, only a small percentage of patients benefit from ICB. Therefore, a more in-depth exploration of ICB therapy is required.

2. Clinical Outcome on Combined Therapy

In many clinical cases, RT combined with ICB treatment has demonstrated considerable superiority in cancer patients. A 65-year-old woman was diagnosed with a metastatic mucosal melanoma which was found in early 2015, and her right buccal mucosa was discolored and diagnosed as a malignant melanoma, but the neck, chest, and abdomen were negative on CT. She underwent surgical resection in August 2015 and received adjuvant intensity modulated radiotherapy (IMRT) of 50 Gy in 20 fractions at the primary site between October and November 2015. Then, metastatic melanomas in her neck and lungs were found in June and July 2016 respectively. Starting from August 2016, she received four cycles of 200 mg pembrolizumab (anti-PD-1) (3 mg/kg) intravenously every three weeks, and then her neck was irradiated with 24 Gy in 3 fractions on days 0, 7, and 21, starting from 19 October 2016. The tumors in her neck had shrunk by 20% one week after the first radiotherapy, and then it was surprisingly found that the volume and number of lung lesions had subsided. During the period, the treatment performed well until July 2017, where two lung lesions were found to be growing, and then, with continued SBRT and 20 cycles of pembrolizumab administration, the overall disease remained stable [10].

In April 2004, a 33-year-old woman was diagnosed with cutaneous melanoma, and then the primary lesion was surgically removed. During this period, she was in good health. In 2008, a new lung nodule was discovered, and then standard chemotherapy was given. In February 2009, new lung nodules were surgically removed, and the pathological examination demonstrated that they were metastatic melanomas. In August 2009, a CT scan revealed a recurrent disease accompanied by a new pleural-based spinal mass and right hilar lymphadenopathy, which was followed by a total of 4 cycles of ipilimumab (anti-CTLA-4) (10 mg/kg) injection every three weeks. After that, ipilimumab treatment was continued, once every 12 weeks. By November 2010, her pleural-based paraspinal mass and new splenic lesions had increased, so a total of 28.5 Gy doses in 3 fractions of 6-MV photons were administrated to the paraspinal mass over 7 days. In February 2011, she received ipilimumab again. After 2 months, the lesions in the target irradiation field obviously regressed. What was even more surprising was that the lesions outside the irradiation sites (right hilar lymphadenopathy and splenic lesions) also regressed [11].

In another case, a 46-year-old man was diagnosed with advanced non-keratotic nasopharyngeal carcinoma in November 2010 and then underwent a combination of radiotherapy and chemotherapy (cisplatin and fluorouracil). However, in October 2011, he first developed distant and local recurrent disease and was subsequently diagnosed with bone metastasis. Immunotherapy with pembrolizumab began in January 2016, but after 6 months, the tumor continued to spread. Thus, the recurrent lesions were re-irradiated at a total dose of 45 Gy in 25 fractions over 6 weeks, pembrolizumab was suspended during radiotherapy. 7 weeks after completion of radiotherapy; pembrolizumab treatment was started again. In December 2016, re-staging of PET-CT and MRI was performed and revealed that all the tumor lesions had regressed significantly, companied by marked swelling of the lacrimal and salivary glands, which indicated an enhanced immune response. Subsequently, pembrolizumab was used for treatment once more, and the tumor further regressed, inflammation symptoms resolved, and local control was achieved without metastasis [12].

3. Conclusions and Perspectives

RT plus immunotherapy has become a trend to fight against tumors, which breaks through the confined cognition in traditional radiobiology that radiation causing the cytotoxicity on tumor cells mainly originates from the production of DNA DSBs. The mobilization and tumor infiltration of CD8+ T cells are important guarantees for radiation to keep functioning [13]. After irradiation, the damaged tumor cells release neo-antigens, DAMPs, and some chemokines, which further induce CD8+ T cells priming. Among those, the antigens presentation of APCs is particularly important to activate CD8+ T cells. The activated CD8+ T cells can migrate and infiltrate the metastases outside of the irradiated field when a certain amount is reached, resulting in the subsequent sustained effects of anti-tumor [14]. Nonetheless, CD8+ T cells are not to fight a lone battle, multiple immune cells are also involved. Noticeably, some of these immunosuppressive cells can baffle the anti-tumor immunity and abscopal effects stimulated by local RT to promote the survival of tumors, including M2 macrophages, MDSCs, immature DCs, and Treg [15][16][17]. There is a balance between immunosuppression and immunostimulation. Without intervention, the function of CD8+ T cells is insufficient to completely eradicate residual tumor cells in this equilibrium, causing tumor recurrence and confining the therapeutic efficacy of local RT [18][19].

However, the accession of immune checkpoint inhibitors (ICIs) upsets the balance via enhancing CD8+ T cells' response. Immune checkpoints act as the "brake" of immune cells, which can invalidate the effector T cell response when specifically binding to its ligand, so that the cancerous cells can be free from immune surveillance and survive [7]. Therefore, local RT plus ICB induces a cascade reaction that magnifies and spreads the positive immune response continuously, and hence, it has become a promising treatment modality for both primary tumors and distant metastases in patients [20]. It has been clinically acknowledged that the anti-PD-1/PD-L1 axis and anti-CTLA-4 are remarkable for malignant tumors. In addition, although many new ICIs including anti-LAG-3, anti-TIGIT, and anti-TIM-3 are still in clinical trials, they also show unique advantages and huge potential and have been reported to reverse the exhaustion of T cells or NK cells to restore the lethality to tumors [21][22][23].

So, how does radiation affect the abscopal effects by modulating the immune cells? As we mentioned above, radiation increases antigen presentation by mediating the release of new antigens, increases surface antigens, and promotes the release of signaling molecules and inflammatory factors. Radiation-induced DNA damage also activates the cGAS-STING signaling pathway to release IFN. Both of these patterns are very critical for the activation and migration of T cells to distant sites to induce the abscopal effect. However, the radiation can also boost the expression of immune checkpoint ligands such as PD-L1, which makes the tumor escape the attack of the immune system. Thus, ICB application is of great significance for RT-induced abscopal effects and improves the cure of cancer. Although there have been extensive studies, the specific mechanism of radiation induced abscopal effect (RIAE) still needs to be further demonstrated.

Although the effect of ICIs is remarkable, its effect on certain tumors (such as gastrointestinal cancers, breast cancer, sarcomas, and part of genitourinary cancers) is still limited. How to improve the efficacy of immune checkpoint inhibitors is a critical issue. Two strategies are currently being taken into consideration. The first strategy is to improve the response rate of ICIs in patients via specific predictive factors (PD-L1 expression, tumor mutation burden (TMB), and clinical characteristics). The other strategy is the combination of therapeutics with ICIs. Among them, the abscopal effect induced by RT combined with ICIs is frequently used to evaluate the efficacy of cancer immunotherapy. However, recent studies have also focused on the potential functions of some molecules, which can modify the immune microenvironment to up-regulate the proportion of immune-activated cells and down-regulate the immune-suppressive cells to improve the efficacy of cancer immunotherapy. The drugs include microbiota modifiers, drugs targeting co-inhibitory receptors, anti-angiogenic therapeutics, small molecules, and oncolytic viruses [24].

As the superiority of RT combined immunotherapy is gradually emerging, some of the challenges faced cannot be neglected. The optimal dose and fractionation of RT, optimum administration point provided for the two therapeutic methods, and relevant biomarkers for tumor prediction are all variable factors for the efficacy of tumor treatment [25]. At the same time, the exploration of novel ICB and immune mechanisms and the collocation of different ICIs for RT to promote abscopal effects on more types of cancers are also issues that need to be considered in the future.

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