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Letter Open Access

Unlocking Novel Therapeutic Targets in Hypofractionated Radiotherapy Through the Abscopal Effect

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Dear Editor

Hypofractionated radiotherapy has rapidly transitioned from experimental modalities to mainstream clinical approaches in oncology. This technique entails the delivery of higher doses of radiation per fraction. For instance, doses in the range of 5-10 Gy per fraction might be prescribed. Advanced radiotherapy techniques such as SBRT and SRS, frequently enabled by technologies like IMRT, have provided the means to deliver these high doses per fraction without serious side effects in normal tissues.[1] Experimental studies have shown encouraging findings. The superiority of this approach compared to conventional radiotherapy is not only due to convenience and improved local tumor control. Experimental and clinical findings suggest that hypofractionated radiotherapy has the potential to act as an instigator of systemic antitumor immunity.[2] Central to this immune phenomenon is the abscopal effect. Classically, this phenomenon is known as a rare but compelling observation in which localized irradiation leads to regression of metastatic lesions outside the radiation field. Once considered anecdotal, the abscopal effect is now receiving renewed interest as a therapeutic target rather than a serendipitous outcome.[3] This shift from anecdote to target was catalyzed by case reports and trials, such as those in melanoma patients showing systemic responses after local radiotherapy and ipilimumab, providing proof-of-principle for this combinatorial approach.[3]

The immunological underpinnings of the abscopal effect lie in the ability of hypofractionated radiation to enhance immunogenic cell death. Tumor cells irradiated at higher doses per fraction undergo a distinctive demise that releases damage-associated molecular patterns (DAMPs), tumor-associated antigens, and pro-inflammatory cytokines. These signals can stimulate the function of dendritic cells (DCs), prime naïve CD8+ T lymphocytes, and generate systemic cytotoxic responses.[4] These modulatory effects are crucial for the treatment of some tumors with low immunogenicity. These tumors have shown low responses to immunotherapy and are also resistant to various anticancer agents such as radiotherapy and chemotherapy.[5,6] These tumors are characterized by low infiltration of CD8+ T lymphocytes. In addition, the infiltrated CD8+ T lymphocytes are exhausted and show low activity against tumoral cells. These tumors, commonly seen in pancreatic cancer, prostate cancer, and certain breast cancer subtypes, represent a significant therapeutic challenge.[7] The cold phenotype of these tumors is responsible for drug resistance and typically results in disappointing response rates to conventional immunotherapy, often below 20%.[8] SBRT and SRS with a high dose/fraction can stimulate immunogenicity by awakening DCs and improving the infiltration and activity of cytotoxic CD8+ T lymphocytes. These effects can improve responses to immune checkpoint blockers (ICBs) and arrest the growth of tumors. Checkpoint blockade of the PD-1/PD-L1 and CTLA-4 pathways after SBRT or SRS has shown good clinical responses.[3]

Although this combination modality has shown promise, it has some challenges and limitations. Achieving a good clinical response can be affected by key factors, including radiation dose per fraction, total dose, target volume, and others. Optimal fractionation remains under investigation for each type of tumor and needs to be explored in clinical trials. SBRT is often administered before or concurrently with immunotherapy to trigger the release of inflammatory cytokines. The expression of checkpoint molecules in response to these inflammatory molecules can provide a rationale for utilizing ICBs. However, the response of tumors to radiotherapy might vary among different tumors and individuals.[9] In addition, selecting an appropriate timing for prescribing ICBs might also be challenging. Identifying predictive biomarkers of the abscopal effect, such as tumor mutational burden, PD-L1 expression, CTLA-4 expression, and circulating immune cell subsets, can refine patient selection for combination therapy with ICBs following radiotherapy.[10]

Remodeling the tumor microenvironment is a strategy to enhance the efficacy of radioimmunotherapy. For instance, inhibiting immunosuppressive cells like regulatory T cells (Tregs), cancer-associated fibroblasts (CAFs), and myeloid-derived suppressor cells (MDSCs) may help sustain abscopal immunity. These cells promote the exhaustion of cytotoxic CD8+ T lymphocytes by expressing and liberating several factors.[11] Therefore, inhibiting these cells can prolong antitumor immunity against malignant cells. Some novel combinations such as dual checkpoint blockade, oncolytic virotherapy, and targeted radiosensitizers alongside SBRT/SRS can further potentiate systemic immunity. For example, using gold nanoparticles can potentiate immunogenic cell death, which may enhance the abscopal effect and response to ICBs.[12] The translation of these findings requires further experimental and clinical trials. Ultimately, the abscopal effect should be reframed not as a chance occurrence but as a therapeutic endpoint, systematically elicited through combinatorial strategies.

Acknowledgment

None.

Competing interests

None.

Abbreviations

Damage-Associated Molecular Patterns: DAMPs; Dendritic Cells: DCs; Immune Checkpoint Blockers: ICBs; Cancer-Associated Fibroblasts: CAFs; Myeloid-Derived Suppressor Cells: MDSCs.

Authors' contributions

The author read and approved the final manuscript. He takes responsibility for the integrity of the data and the accuracy of the data analysis.

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