Radiation and Melanoma: A Phoenix Rising

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Abstract

Although radiation therapy is a mainstay in the treatment of many cancers, many oncologists do not consider radiation as a treatment option for melanoma due to the outdated perception that melanomas are "resistant" to radiation. Fortunately, the advent of new modalities of radiation therapy allowing for precise targeting of high doses of radiation therapy and the recognition that these higher doses can synergize with emerging immunomodulatory agents such as the checkpoint inhibitors have changed, and will continue to expand, the role of radiation therapy in the treatment of melanoma.

Key words: radiation, immunotherapy, melanoma

Radiation therapy (RT) plays an integral role in the treatment of many cancers; however, for patients with melanoma, many oncologists do not consider radiation as a treatment option. This is due mainly to the outdated perception that melanomas are "resistant" to radiation. Much of this misperception is based on data using historical techniques and radiation doses that have long since been abandoned. Fortunately, the advent of new modalities of highly-focused RT, the increasing understanding of the role of the immune system in regulating the response to RT, and the recent development of a multitude of immune-oncologic treatment modalities should, and will, change the role of RT in the treatment of all stages of melanoma.

Highly-focused RT refers to a group of techniques including intensity modulated radiation therapy (IMRT), 3D conformal radiation therapy (3DCRT), and stereotactic radiation therapy (SRT), which allow for dramatic dose escalation due to the ability of these techniques to shape the radiation dose around normal dose-limiting tissue structures. Early trials suggesting that high-dose-per-fraction RT (hypofractionated RT) may be effective in melanoma focused on the treatment of brain metastases. Stereotactic radiosurgery (SRS) techniques allowed for large single doses of RT (eg, 24 Gy in a single fraction) to be delivered with limited toxicity, and retrospective data examining outcomes in melanoma brain metastases have shown local control rates of approximately 70% to 80%.[1,2] Other trials in melanomas of the head and neck in the postoperative setting have shown similar results with short courses of high doses per fraction RT (5-7 Gy).[3]

The main issue with hypofractionated RT is that for normal tissues it is associated with an increase in late radiation toxicity, particularly fibrosis. Modern advances in the delivery of RT have allowed for significantly more precise targeting throughout the body such that the amount of normal tissue for a given treatment can often be dramatically reduced. Current techniques such as stereotactic body radiotherapy (SBRT), similar to SRS for the brain, have allowed for the effective treatment of metastatic melanoma, with local control rates of >75% in locations such as spine, lung, and liver that previously would have been left untreated or treated to suboptimal doses.[4]

In addition to technical advances in the delivery of RT, there has been a recent breakthrough in the understanding of the role of the immune system in the biology of the response to RT. Specifically, the immune system has been found to play a critical role in mediating the efficacy of RT in multiple tumor types, including melanoma. Initial evidence from mouse models has demonstrated that the efficacy of RT depends in part on radiation triggering an antitumor immune response. These models revealed that RT generates an immune response by releasing pro-inflammatory molecules, such as type I interferons,[5] high-mobility group protein B1 (HMGB1),[6] and calreticulin,[7] that are sensed by the immune system, leading to the development of an antitumor response consisting largely of antitumor cytotoxic CD8+ T cells.[8,9] Absence of any of the immune components involved in this process leads to significant reduction in the efficacy of RT on a tumor. It remains unknown whether similar immunologic mechanisms operate in humans, and more studies collecting post-treatment tumor and peripheral blood specimens are needed to understand the immunologic events occurring in patients. Nevertheless, the promising experimental data has led many scientists and clinicians to explore strategies to target various pathways in the immune system in combination with RT in an attempt to improve the efficacy of both treatments.

With the advent of checkpoint inhibitors and the emerging

concept that the effect of high-dose per fraction RT is not only due to ablation of the irradiated site but also due to the potential to promote immune responses, combining RT with immunotherapy has become an important new avenue for investigation. Experimental evidence from animal models suggests that in melanoma and other cancers, RT can potentiate the effect of anticancer immunotherapies, such as dendritic cell vaccines[10] and checkpoint blockade.[11] In these settings, hypofractionated RT seems to be the critical component, as human trials with standard RT and immunomodulatory agents such as high-dose IL-2 did not have similar efficacy.[12] Intriguingly, these studies of hypofractionated RT and immunomodulatory agents suggest that in addition to improving local control, RT may also lead to a systemic anticancer immune response coined the *abscopal effect*.[13]

Although rare, the idea that RT in combination with immunomodulatory agents can be a systemic treatment has generated intense interest from researchers in radiation biology and immunology.[11] Early trials in melanoma using RT and immunotherapeutics have shown tremendous promise in terms of both local control and systemic responses, suggesting that RT in combination with cytokines or checkpoint inhibitors can be synergistic in terms of generating an antitumor immune response.[14,15] Seung and colleagues, in a phase 1 trial of SRT and high-dose IL-2, found a systemic response rate of 71.4%[14] compared with the 15% to 20% response rates reported for high-dose IL-2 alone.[16,17] Responses in these patients were associated with an increase in CD4+ effector memory T cells.[14] A similar dramatic systemic response was observed with ipilimumab and SRT in the case report by Postow et al who also found corresponding increases in activated CD4+ T cells and decreases in the myeloid-derived suppressor cells (MDSC), an inhibitory immune cell thought to suppress antitumor immune responses.[13] Mechanistically, animal models and human correlates have revealed that RT can alter the immunogenicity of tumors, making them more susceptible to immune-based targeting.[14,18] Current and future trials are testing the parameters for treating patients with RT and immunotherapeutic combinations in melanoma and a multitude of other tumor types.[19,20] Critical questions that need to be addressed in these trials include the timing of RT and immunotherapy and whether this timing differs by the agent, whether the synergy between RT and checkpoint inhibitors also applies to other immunotherapeutics that target other pathways, and, finally, what are the best conditions for RT delivery (site of irradiation, fraction size, and number) to optimize the immunologic response. Participation in the ongoing and future trials studying RT and immunotherapy will help address these questions and, in so doing, may change the standard of care for our patients with melanoma and other advanced malignancies.

Thus, despite the historical concept of melanoma as a radioresistant tumor, new paradigms that employ RT to treat melanoma are rapidly emerging. New techniques employing higher doses of RT have proven to be effective tools in the treatment of brain metastases and other metastatic sites in patients with melanoma. These new techniques that are allowing for higher ablative doses of RT to be employed, along with increasing evidence that RT can act as a powerful immunomodulatory agent, will make RT an essential consideration in future treatment algorithms for melanoma.

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