Harnessing Ionizing Radiation to Enhance Immunotherapy: A Paradigm Shift

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The field of cancer immunotherapy, once the sole purview of immunology, has evolved toward the harnessing of newly described properties of ionizing radiation (IR). Cancer immunotherapy now includes the combination of established cytotoxic modalities with immune manipulations, as vaccines alone are unlikely to succeed at curing bulky, established tumors.[1] Combining chemotherapy with immunotherapy has shown promise, despite the fact that both are systemic modalities with overlapping effects.[2-4] In this regard, radiotherapy has a clear advantage, as its effects can be targeted to the primary tumor, converting the tumor itself into an “immunologic hub” ideally capable of subverting the immune defeat that has resulted in the clinical presentation of cancer. This approach is appealing since most immune impairment appears to occur at the tumor site.[5]

Dr. Hodge and coauthors have elegantly reviewed this field. They summarize the available evidence with regard to the effects of IR on the different mediators of an immune response, and they discuss the initial promising results that have been achieved with the translation of preclinical experience to the clinic.

New Investigational Horizons

As a novel application for IR, a partnership with immunotherapy has opened exciting new investigational horizons.[6] While many ongoing efforts are aimed at integrating immunologic strategies with traditional radiotherapy protocols, a conceptual shift in the investigational approach should be considered. Investigators need to determine how to best harness IR, a physical modality, to serve cancer immunotherapy.

In this novel role, IR optimization to enhance immunity takes priority over the classical aim of achieving successful cytotoxicity that translates into local control. Instead, radiation-induced cell death and its associated danger signals participate in a more global strategy to recruit the immune system to the primary tumor, achieving successful in situ immunization that translates into systemic, antimetastatic immune responses.[7-9] The traditional definition of the radiotherapy target will need to be reevaluated, as will all concepts of dose, fractionation, and schedule.

IR-Specific Peptides

The type of radiation dose and fractionation used in the clinic to treat cancer has evolved empirically as the best compromise between optimal tumor killing and recovery from damage to the normal tissue included in the treatment field. It is likely that the very inflammatory response that could be valuable to immunotherapy is in fact avoided in the current clinical practice of cancer radiotherapy. Nevertheless, important information could be derived by studying cancer patients who are currently receiving standard radiation treatments.

For instance, as described in the authors’ review, the original findings from the Neefjes’ lab—that after radiotherapy, IR-specific peptides are generated that are potentially capable of recruiting an immune response—warrants an accurate clinical exploration.[10] Since the antibody response to tumor antigens correlates with T-cell immunity, IgG responses against these antigens can be identified by applying the technique of seromics to detect antigens as being de novo or increasingly recognized following treatment.[11] This form of immune-monitoring, which does not require expression of a specific HLA allele by the patient, could detect which single dose currently used in
the clinic is most effective at generating IR-specific peptides (ie, radiosurgery-like fractions or fraction sizes used in more standard fractionation regimens).

**Ideal Target**

The ideal target for combining IR with immunotherapy is also not yet known. If the primary tumor is to be investigated as an “immunologic hub,” how can one best counteract the immunosuppressive effects of radiation?[12] Should margins of “normal” adjacent tissue be included to assure a vigorous inflammatory response? In addition, should the draining lymph nodes be included in the radiation field? While IR could eliminate immunosuppressive cell populations, this effect may not be a general rule. Breast cancer–specific immune profiles of draining nodes differ among patients and have been revealed to be robust, independent prognostic factors, thus favoring a more cautious and individualized approach, particularly if combined with immunotherapy.[13]

**Timing of Therapy**

Finally, it remains unknown when during its clinical course it is best to test the combination of IR and immunotherapy on a specific cancer. Ideally, an intervention earlier in the course of the disease would be expected to provide the best chance for success. From the point of view of immune surveillance, an intervention at the equilibrium phase—before the tumor coopts the immune system to enhance growth and angiogenesis—would be ideal, suggesting that testing in the adjuvant setting of radiotherapy is appropriate.

Conversely, preliminary data suggest that a lower degree of tumor response to radiotherapy may correspond to a favorable plasticity of the tumor to induce relevant signal transduction pathways that are crucial to immune system responses. For instance, IR induction of interferon-gamma influences antitumor immunity through a multiplicity of signal transduction pathways that involve MHC class I expression, induction of adhesion molecules like VCAM-1, and chemokines required for effector T-cell trafficking.[14] These processes are consistently associated with intracellular signaling by STAT1. Since increased STAT1 expression is associated with a radioresistant phenotype,[15] would carriers of recurrent tumors after radiation therapy be the best candidate for reirradiation with immunotherapy?

In summary, the review by Hodge et al calls for more collaboration between radiobiologists and cancer immunologists, while it encourages clinicians to recognize the fundamental role of the immune system in cancer and cancer therapies, and to revisit the field of radiation oncology with an open mind.

**References**


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