Is Classical Stereotactic Radiotherapy the Optimal Partner for Immunotherapy?

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It is now well recognized that the host’s immune system senses the effects that ionizing radiation provokes in irradiated tissues. Evidence that the degree of integrity of the immune system determines the dose required to control experimental tumors is more than 30 years old.[1] However, it is only recently that the radiation oncology community has acknowledged the immunogenic effect of ionizing radiation[2] and started exploiting its clinical potential.

In 2005, we introduced the concept of a partnership between radiation and the immune system, and hypothesized that, with the correct immunotherapy, the irradiated tumor could become an in vivo vaccine.[3] Over the years, we and many others developed preclinical and clinical evidence confirming this original hypothesis, and have linked the abscopal effect of radiotherapy originally described by Mole et al[4] to immune-mediated mechanisms.[5] Recently, we suggested the addition of tumor immune “rejection” as the fifth “R” of radiobiology, joining the classical “R’s” of reassortment, reoxygenation, repair, and repopulation.[6]

Ten years later, many questions remain. From a therapeutic perspective, the most urgent of these questions concerns how best to harness radiotherapy to stimulate the patient’s immune system. Specifically, what are the optimal radiation technique, dose, and fractionation one should use with each immunotherapy intervention? In terms of techniques, the focused, targeted approach of stereotactic radiation offers the advantage of controlled delivery, with optimal exclusion of vulnerable normal tissue and draining lymph nodes. The latter particularly need to be preserved intact and functional in order to best mount an effective immune response. In this sense, we agree with Sharabi et al[7] on the advantages of stereotactic radiosurgery or a comparably focused approach, delivered by modern, intensity-modulated radiotherapy.

However, there is much less clarity regarding the choice of the site to irradiate, and the dose and fractionation of the radiation regimen—in particular, whether a large single dose or a biologically equivalent, multi-fractionated regimen is best. When combined preclinically with cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) blockade, fractionated—but not single-dose—radiation demonstrated abscopal effects in the 4T1 syngeneic murine model of mammary carcinoma,[8] and in two additional preclinical models of cancer.[9] Consistently, in each of the clinical cases in which abscopal effects were reported after CTLA-4 blockade and radiotherapy (summarized in the Table), the patient had received multifractionated radiotherapy targeting a visceral lesion.[10-12] It is possible that the lack of advantage from the addition of ipilimumab to radiotherapy in the large prospective randomized trial of castration-resistant metastatic prostate cancer may be explained by the facts that a bone lesion (instead of a visceral metastasis) was treated, and that a single dose of 8 Gy was used.[13]

It is notable that we demonstrated, in an in vitro assay, the induction of each of the three classic components of immunogenic cell death (translocation of calreticulin, release of high mobility group box 1 [HMGB1], and release of adenosine triphosphate [ATP]) after a single dose of radiation, in a dose-dependent fashion.[14] The in vivo inferiority of a single dose compared with a fractionated regimen may reflect a mechanism dependent on the tumor microenvironment, rather than on the immunogenicity of cancer cells.

Is radioablation (complete elimination of cancer cells within the field) required to best stimulate the immune system? The abscopal cases reported (see Table) and many emerging systemic responses in the setting of CTLA-4 and programmed death ligand 1 (PD-L1) blockade have occurred with biologic doses that are certainly not ablative. One could hypothesize that in these patients, the immunotherapy received contributed to the in-field response and determined which patients were successfully immunized against their tumor, both locally and systemically. The standing question is
whether more patients would have responded if their irradiated metastatic lesion had been ablated, or if ablative doses of stereotactic radiosurgery had been applied to all clinically and radiologically detectable metastatic sites. Only well designed prospective trials can help us address such questions.

An alternative to the use of ablative stereotactic radiosurgery with immunotherapy is a strategy that would consist of integrating radiotherapy as one of multiple components of a staged effort to immunize the patient against her or his tumor. In such an approach, an intervention that aimed at increasing priming (ie, toll-like receptor [TLR] agonists, granulocyte-macrophage colony-stimulating factor [GM-CSF], etc) could precede fractionated radiotherapy with concomitant CTLA-4 blockade. The approach could conclude with the addition of an anti–PD-1 or anti–PD-L1 intervention, to overcome T-cell exhaustion. Preclinical models in syngeneic murine tumors will elucidate the optimal sequencing and regimen of radiation for this approach.

In summary, Sharabi and coauthors provide a thoughtful and comprehensive review of the current evidence on radiation and immunotherapy, and offer their opinion on the key role of stereotactic radiotherapy in best realizing the promise of this partnership.

We reserve judgment about the need for ablative doses, particularly in view of the fact that, at least in our experience with CTLA-4 or transforming growth factor beta (TGF-beta) blockade, nonablative, fractionated regimens were superior to a large single dose at achieving immunization, and resulted in gene expression consistent with better activation of immunologic pathways.[15; unpublished data] Financial Disclosure: Dr. Formenti serves as a consultant or advisory board member for Bristol-Myers Squibb, Elekta, GlaxoSmithKline, Regereron, Sanofi, and Varian.

Table: Examples of Abscopal Responses After Treatment With Radiotherap...

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