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Current Clinical Trials Testing Combinations of Immunotherapy and Radiation

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Preclinical evidence of successful combinations of ionizing radiation with immunotherapy has inspired testing the translation of these results to the clinic. Interestingly, the preclinical work has consistently predicted the responses encountered in clinical trials. The first example came from a proof-of-principle trial started in 2001 that tested the concept that growth factors acting on antigen-presenting cells improve presentation of tumor antigens released by radiation and induce an abscopal effect. Granulocyte-macrophage colony-stimulating factor was administered during radiotherapy to a metastatic site in patients with metastatic solid tumors to translate evidence obtained in a murine model of syngeneic mammary carcinoma treated with cytokine FLT-3L and radiation. Subsequent clinical availability of vaccines and immune checkpoint inhibitors has triggered a wave of enthusiasm for testing them in combination with radiotherapy. Examples of ongoing clinical trials are described in this report. Importantly, most of these trials include careful immune monitoring of the patients enrolled and will generate important data about the proimmunogenic effects of radiation in combination with a variety of immune modulators, in different disease settings. Results of these studies are building a platform of evidence for radiotherapy as an adjuvant to immunotherapy and encourage the growth of this novel field of radiation oncology.
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Introduction

Although evidence for contribution of the immune system to the clinical response of radiotherapy dates as far back as the mid-1970s,[1] it is only in the past 10 years that trials have started exploring this novel approach in the clinic. For instance, there is now some evidence of tumor-specific immunity in patients following radiation. In one study, it was demonstrated that radiotherapy and antiandrogen hormone therapy induced autoantibody responses to a variety of tumor-associated antigens (Ags) in 25%-30% of patients with prostate cancer.[2] In another study, after radiation some patients with colorectal cancer or prostate cancer had T cells specific for an Ag that is overexpressed by tumors detectable by tetramer analysis.[3] The host's recruited immune response against the irradiated tumor has the potential to actively contribute to the success of the course of radiotherapy.

Moreover, if sufficiently robust, this newly acquired immune response could achieve systemic antitumor effects. In this scenario, tumor-specific effector T cells can target cancer cells at metastatic sites, achieving an abscopal effect of radiotherapy (ab scopus = away from the target).[4,5] Clinical abscopal effects of radiotherapy have been described, although very uncommon.[4] Their rare occurrence reflects the fact that by itself, standard radiotherapy is inadequate at subverting the existing immunosuppression or tolerance characteristic of the microenvironment of an established tumor. However, the ability of radiation to prime antitumor responses is likely to be key in obtaining a therapeutic synergy with immunotherapies that can unleash these immune responses.

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The first trial testing the ability of a combination of radiation and immunotherapy to induce abscopal responses, a proof-of-principle trial that has opened this field, is described in the following sections.[6] A brief summary of the ongoing trials of immunotherapy and radiation that are currently open for patient enrollment is given. Without the ambition of representing all the ongoing research on the subject, this report is meant to offer some examples of current investigations in this field and introduce the reader to some of the challenges intrinsic to the combination of the 2 modalities.

Initial Trials of Radiotherapy and Immunotherapy

Investigators at New York University (NYU) originally hypothesized that ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated, reporting out of the field responses in a murine model of syngeneic mammary carcinoma treated with FLT-3L and radiation.[5]

The same group conducted the first "proof-of-principle" trial, exploring the combination of subcutaneous (s.c.) administration of granulocyte-macrophage colony-stimulating factor (GM-CSF) with chemoradiotherapy to 1 metastasis in patients with metastatic solid tumors and at least 3 measurable metastatic lesions.[6] The trial was based on the hypothesis that, even in a setting of established and pretreated metastatic disease, the use of GM-CSF and radiation could stimulate the patient's immune system to overcome immune tolerance. GM-CSF increases the percentage of dendritic cells (DCs) and their maturation, facilitating cross-presentation of newly released Ags after cell death at the site of radiotherapy. In NYU01-02-81, enrollment was offered to pretreated patients with metastatic solid tumors after stable disease or progression on systemic chemotherapy; the same systemic therapy was maintained and radiotherapy was added to 1 lesion, 3.5 Gy × 10 daily fractions, for a total dose of 35 Gy for 2 weeks. Starting on day 7 (after 1 week of radiation), GM-CSF, 125 mg/m^2, was given s.c., and repeated daily for 14 days. An abscopal response was defined as a measurable response in any of the measurable lesions outside the radiation field. Assessment was performed by positron emission tomography-computed tomography (PET/CT). The results of this trial were reported at ASTRO in 2012, and a manuscript describing the long-term outcome of the treated patients is in preparation. Interestingly, patients displaying an abscopal response were also more likely to have longer survival, suggesting a better immune competence among responders. A clear weakness of this study is the lack of immune monitoring of these patients.

A different approach was aimed at optimizing available DCs to uptake and present tumor-derived Ags released by radiation in patients with hepatoma. DCs were injected intratumorally to patients with hepatoma 2 and 24 days after a single dose of 8 Gy of external-beam radiation therapy (XRT) to the tumor. Of 14 patients, 12 showed partial responses, and most patients had increases in α-fetoprotein–specific immune responses by enzyme-linked immunospot assay.[7] These data confirm the clinical effect of radiotherapy on the host's immune system and warrant accurate monitoring of immune biomarkers during combination treatment.

NYU Trials of Immunotherapy and Radiation

Currently, 4 institutional review board (IRB)–approved, investigator-initiated trials combining radiotherapy and immunotherapy are ongoing at NYU (Table 1).

NYU S11-00533 "Fresolimumab and Radiotherapy in Metastatic Breast Cancer"

This clinical trial is a component of Multi-Team Award BC100481 of the breast cancer program of the Department of Defense, which was conducted in collaboration with University of California, Los Angeles. The trial tests the effect of combining transforming growth factor β (TGF-β) blockade with radiation to a metastatic site of breast cancer. It directly translates the preclinical work on this combination. The 4T1 mammary carcinomas in the flank of syngeneic Balb/c mice were used to test the potential for combinations of TGF-β inhibition and radiation. TGF-β–neutralizing monoclonal antibody (mAb) 1D11.16 given 24 hours before radiation augmented the response of established tumors to radiation. Importantly, lung metastases were significantly reduced compared with each treatment alone ($P < 0.01$, 1-sided t test), which indicates that TGF-β inhibition in combination with radiation promotes systemic antitumor effects. Patients are randomly assigned to either 1 or 10 mg/kg dose of fresolimumab, a neutralizing antibody against all 3 TGF-β isoforms. A baseline and serial PET/CT scans are required to monitor the response. Immunomonitoring with tetramer and enzyme-linked immunospot assay and regulatory T (Treg) cells measurements are important components of this study.

NYUS11-0598 "Phase I/II Study of TLR7 Agonist Imiquimod, Cyclophosphamide, and Radiotherapy in Breast Cancer Patients With Chest Wall Recurrence or Skin Metastases"

Funded by NIH R01CA161891, this trial tests the combination of radiation and a toll-like receptor (TLR) agonist with and without low-dose cyclophosphamide (CTX) in women with metastatic breast cancer and skin metastases. The rationale for this study is derived by the fact that ability to generate an effective in situ vaccine can be potentiated by addition of a TLR agonist and by CTX-mediated regulatory T cell depletion. Imiquimod (IMQ) is a synthetic TLR7 agonist that activates DCs and primes Th1 and cytotoxic T lymphocyte (CTL) responses to coadministered Ags, including tumor Ags. Complete tumor regressions have been observed in patients with primary skin tumors after topical IMQ treatment without additional therapies, and in patients with skin metastases of breast cancer topical IMQ achieved a 20% response rate in a prospective trial.[7]