

# The outlook and potential of combined radiation therapy and immunotherapy

Mary Beth Massat

**T**he field of immunotherapy has progressed rapidly since the approval of the CTLA-4 blocking antibody ipilimumab for metastatic melanoma in 2011. Immunotherapy uses substances made by the body or in a laboratory to boost the body's natural immune system function to fight cancer. It includes monoclonal antibodies and tumor-agnostic therapies, T-cell therapy, nonspecific immunotherapies, oncolytic virus therapy, and vaccines.<sup>1</sup>

Excitement is also mounting for the potential to use immunotherapy in conjunction with radiation therapy (RT). This interest, says Ralph R. Weichselbaum, MD, chair of the Department of Radiation and Cellular Oncology at The University of Chicago Medicine, is partially due to the use of immunotherapy in patients who likely would have died from their disease, but instead had pro-

longed survival or have been cured.

“A healthy immune system is likely to be important for radiation therapy to be successful,” Dr. Weichselbaum says. “This knowledge comes to us from animal models and some clinical observation. Whether radiation therapy and immunotherapy have a successful interaction in the context that a lot of people, including myself, think it might, is still open to question.”

Much of the clinical data is preliminary and many confounding variables make interpretation difficult. However, initial experimental and human data in the context of case reports or small trials are impressive.

Although data are limited thus far, an array of clinical trials are examining combinations of RT and immunotherapy across different clinical settings, such as metastatic or locally advanced cancers, as well as in various types of cancers.

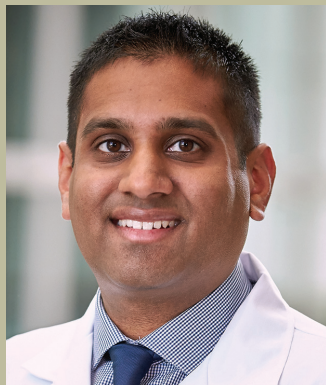
“Ultimately, what we need are hypothesis-driven studies that sci-

entifically look at each aspect of the combinations to really understand the mechanisms by which there is synergy between radiation therapy and immunotherapy,” says Abhishek Solanki, MD, an assistant professor with clinical expertise in radiation oncology at Loyola University Medical Center in Maywood, Illinois.

## **Trials to Watch, Trails to Forge**

Jonathan D. Schoenfeld, MD, MPH, associate professor of radiation oncology at Harvard Medical School, and radiation oncology director of the Melanoma Disease Center at the Dana-Farber Cancer Institute in Boston, is leading a phase II multi-institution trial sponsored by the National Cancer Institute (NCI). The trial is evaluating the immunologic effects of RT and the impact of combining radiation with durvalumab and tremelimumab in patients with metastatic colorectal or non-small cell lung cancer (NSCLC). He

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also believes that the most impactful studies will examine the use of radiation in patients for whom immunotherapy either hasn't worked or where only a minority of patients have responded.<sup>2</sup>

"We want to take these novel agents and then test in a step-wise fashion the addition of radiation therapy," Dr. Schoenfeld says. The study is comparing patients who receive immunotherapy alone against those who receive combined immunotherapy and RT.

Patients are randomized to three groups: group A receives only durvalumab and tremelimumab immunotherapy; group B receives immunotherapy and high-dose RT; and group C receives immunotherapy and low-dose RT.<sup>2</sup>

"We are collecting blood and tissue samples from these patients and looking before and after radiation therapy to look for changes in blood and the tumor that we don't see in the group receiving immunotherapy alone," Dr. Schoenfeld explains. "With biopsy and blood samples, we hope to understand what radiation therapy is adding to the immunotherapy or what the immunotherapy is adding to radiation therapy."

This potential synergistic relationship between RT and immunotherapy is a key research theme. Dr. Weichselbaum has been involved in numerous

studies assessing the combination of immunotherapy and radiation therapy. In 2018, a group from the University of Chicago examined the safety and toxicity of pembrolizumab and multisite stereotactic body radiation therapy (SBRT) in patients with metastatic solid tumors. While the combined treatments were well tolerated with acceptable toxicity in the phase I study, additional studies are needed to further examine the clinical benefit and predictive biomarkers.

"The use of combined immunotherapy and radiation therapy looks relatively safe—that's what these phase I trials will tell us," Dr. Weichselbaum says. "We also need to work out the timing, at least in terms of checkpoint inhibitors. How much do we treat with radiation? Is it a local or systemic effect, such as the abscopal effect?"

The abscopal effect is a systemic immunologic response initiated by localized radiation that results in activating the immune system to kill cancer cells distant to the primary target. A systematic review of studies on the abscopal effect suggests that the effect seems to occur in the setting of radiation therapy with immunotherapy.<sup>3</sup>

The optimal RT target site to maximize immune-activation is also unknown. Dr. Solanki is the lead author in

a review of published studies examining the combination of immunotherapy and RT in genitourinary malignancies. In the article, the authors note that in a phase I trial combining radiation with SBRT in patients with visceral metastases, irradiating the liver lesions led to a greater immunologic response than treating lung lesions.<sup>4</sup>

The PACIFIC Trial also examined the use of durvalumab after chemoradiotherapy in patients with locoregionally advanced NSCLC.<sup>5</sup> This study randomized patients with stage III lung cancer receiving standard chemoradiation and, if they didn't progress, patients were randomized to placebo or durvalumab immunotherapy. Patients receiving immunotherapy had significantly longer progression-free survival and overall survival in the group that received durvalumab.

"Perhaps debulking the tumor with stereotactic radiation decreases the T-cell exhaustion and this could be one mechanism by which radiation therapy may help immunotherapy be more active," Dr. Solanki says. "Or, treating multiple tumors may release different tumor antigens that are local to that tumor and the tumor microenvironment, so there may be a larger milieu of antigens for the immune system to work



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against. We don't yet know the right number of lesions or sites to treat with radiotherapy to augment immunotherapy."

There is also the question of how chemotherapy fits in with immunotherapy and radiation therapy or does it interfere or decrease the interaction between radiation and immunotherapy?

"In general, we don't know what additional modality will help immunotherapy the most," says Dr. Solanki. "We as a field need to find something that works."

Another area of investigation in the use of immunotherapy and radiation therapy is biomarker discovery. Current biomarkers for immunotherapy include PDL1 expression, T-cell type and characteristics, and tumor mutational burden, although Dr. Weichselbaum says some of these biomarkers remain under evaluation.

"Whether biomarkers can predict success of immunotherapy and radiation therapy combinations where neither were successful alone is a longer story and a harder question to answer," says Dr. Weichselbaum.

There is also interest in how radiation therapy changes inflammation in the blood and changes DNA damage in a way that stimulates the immune system,

Dr. Schoenfeld explains. "Probably the most exciting work that's been done is investigating if radiation therapy wakes up the immune system to recognize parts of the tumor that weren't recognized before."

For example, T-cells may be recognizing more or different parts of the tumor after radiation when it is combined with immunotherapy. A recent study by Silvia Formenti, MD, et al, reported that radiation therapy in combination with a CTLA-4 blockade induced systemic anti-tumor T-cells in several chemo-refractory metastatic NSCLC cancer patients for whom the previous use of the anti-CTLA-4 antibodies by itself and with chemotherapy did not demonstrate significant efficacy.<sup>6</sup>

Toxicity is another area where data is unclear, although the combination of radiation therapy and immunotherapy appears to be relatively safe.

"We are not seeing high toxicity rates or unexpected toxicity developing in patients receiving combination treatments of radiation and immunotherapy," says Dr. Schoenfeld. However, he cautions that extended patient follow-up is needed to ensure that radiation doesn't increase long-term toxicity. Also, newer immunotherapy treatments will need to be carefully evaluated for

both initial and late toxicity.

"Based on the data we have today, we know enough that for most patients who need palliative radiation therapy and could benefit from immunotherapy, it is probably safe to try those treatments either at the same time or close in time to each other," Dr. Schoenfeld adds.

The bottom line is, there is still much to learn about immunotherapy and what factors will help patients the most. Adding to the challenge are the many variables in cancer care—from the location of the primary disease and metastatic involvement to prior treatments and response. That's where personalized medicine, artificial intelligence (AI) and machine learning (ML) are poised to help.

### Personalizing Care

"Radiation therapy may be a way to personalize immunotherapy, to use radiation as a personalized vaccine," says Dr. Schoenfeld. "That's a big subject of research, however, [and] we are still developing the capabilities to give radiation to a patient, targeting more than two to three areas at the same time. We are almost at the limit of what we can do with limited manpower and limited time to plan and deliver treatments. That's one area



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where artificial intelligence and machine learning can offer an opportunity to help us integrate all this information that gets increasingly complex and take it into account [for each patient].”

Personalized medicine, guided by AI and ML, could also be invaluable in helping identify patients who will benefit the most from immunoradiotherapy.

“Where AI and machine learning may be most useful is to help us with precision medicine to best select treatments that are most likely to help the patient in front of you,” says Dr. Solanki. While the jury is still out regarding a synergy between radiation therapy and immunotherapy, Dr. Solanki believes immunotherapy will play a greater role in patients with localized disease who are receiving RT and, conversely, radiation will play a larger role in patients with stage 4 metastatic disease.

“It is possible that we will see a shift in the general radiation oncology clinic toward a higher volume of metastatic patients who we are treating with radiation, both potentially for synergy with immu-

notherapy but also in the setting of oligo-metastatic disease. There are increasing data showing that in the setting of oligo-metastatic disease, radiation or surgery as metastasis-directed therapy can help improve survival in patients with limited metastatic disease,” Dr. Solanki adds.

Dr. Weichselbaum also notes that immunotherapy may be used earlier in the disease process to treat primary tumors and prevent metastases. Ideally, more organizations such as the National Institutes of Health and the American Society for Radiation Oncology (ASTRO) will fund more radioimmunotherapy research.

“We need skilled investigators looking at interactions,” he says. This includes biomarker discovery — biomarkers that can indicate who will and who will not respond as well as biomarkers that may potentially block the combination effect of immunotherapy and radiation therapy.

“There is also the idea of personalized vaccines, where we can determine the antigenic peptides and develop a

vaccine that could be combined with radiotherapy,” adds Dr. Weichselbaum. “These are some of the ways we might be able to personalize future cancer treatments.”

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