Radiation redux

Could traditional radiation treatments work in concert with immunotherapy to mount a more effective assault on cancer?

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When Michael Postow started his fellowship training in medical oncology at the Memorial Sloan Kettering Cancer Center (MSKCC) in 2010, he wasn't familiar with the term "abscopal." Coined decades before he was born and then largely forgotten by physicians, it describes a phenomenon in which radiation delivered at one site in the body has an effect on distant tissues that are, literally, "outside" the "scope" of the radiation blast. "It wasn't something I had ever heard about," Postow says. That changed when a patient at MSKCC had an unexpected response to radiation therapy.

The young woman had been receiving a then-experimental immunotherapy drug, called ipilimumab, to treat her advanced case of melanoma. The drug, now marketed by Bristol–Myers Squibb as Yervoy, blocks a so-called checkpoint protein that normally blunts immune activation. Ipilimumab, in effect, takes the brakes off the immune system, freeing cancer-killing T cells to mount an attack against the tumor.

But this therapeutic strategy only works when there are tumor-targeted T cells in the immune system's tank, otherwise there's nothing to rev into action. That seemed to be the case for Postow's patient. Tumors continued to grow throughout her spleen, in a lymph node in her chest, and near her spine. The pain from the tumor in her back became excruciating.

Postow and his colleagues, led by physician-scientist Jedd Wolchok, chief of the melanoma and immunotherapeutics service at MSKCC, arranged for the woman to receive radiation. They expected to shrink the tumor near her spine and offer some relief from the back pain, nothing more. But scans came back showing tumor regression throughout her body. After more than a year of worsening disease, the patient was finally in remission (1). "That's when all the bells started going off for everyone," Postow says. "Maybe there was something we did with the radiation."

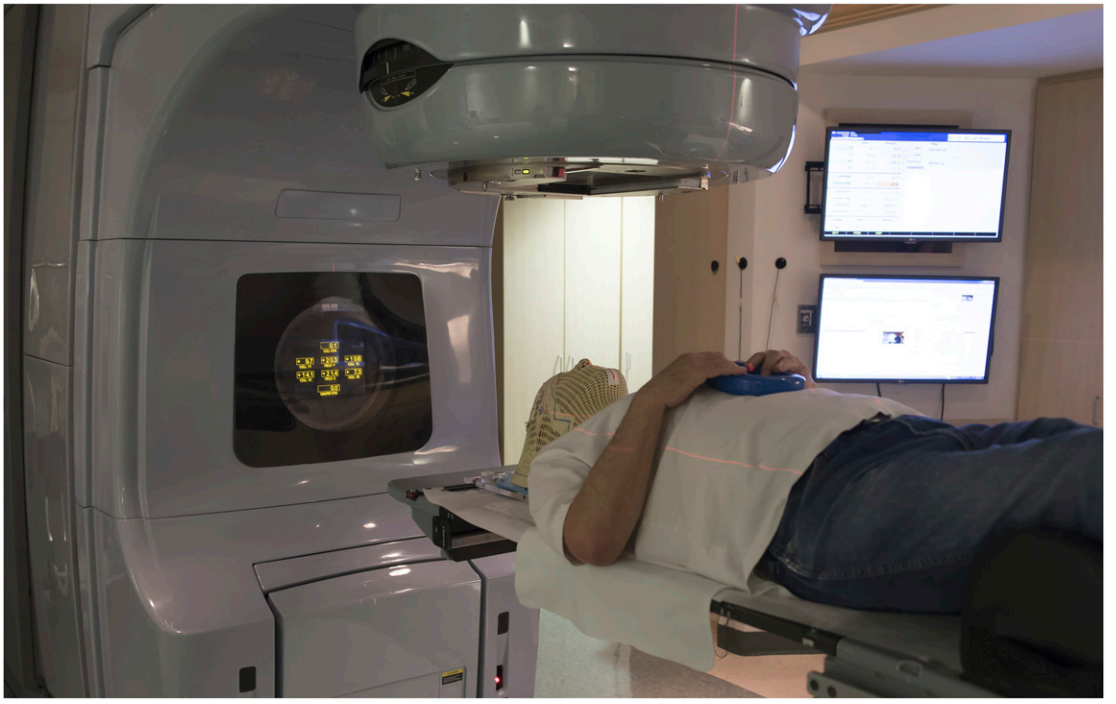

Fig. 1. Researchers are combining radiation therapy, here targeting brain cancer, with immunotherapy in hopes of finding a robust strategy for stymying various cancers. Image courtesy of Shutterstock/John Panella.

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The MSKCC team's 2012 case report was the first demonstration in a patient that radiation can synergize with a checkpoint inhibitor like ipilimumab. The report showed, says Sandra Demaria, a cancer immunologist at Weill Cornell Medicine, that eliciting a strong enough immune response will lead to the abscopal effect. "From there," Demaria adds, "everyone became interested, and things have progressed fast."

Just 5 years after that initial report, around 100 clinical trials are ongoing to test the mix of radiation and checkpoint inhibitors in patients with cancers of every stripe. The word abscopal is finally on the tongues of oncologists and drug executives everywhere.

"It's energized the field of radiation oncology and broadened the mindset of pharma as well," says William McBride, a tumor immunologist at the University of California, Los Angeles. "It's very early days to know where this is going to go, but it's certainly exciting."

Joining Forces

Around 60% of all cancer patients receive radiation at some point in their course of treatment, mainly to shrink tumors so drugs can finish them off or just to reduce pain and buy time. However, the therapy itself can be completely curative if given in the earliest stages of the disease, when tumors remain contained to one site in the body. That's why Jonathan Schoenfeld from the Dana–Farber Cancer Institute describes radiation as "one of the most effective forms of cancer treatment we have." But it's mainly local treatment. Adding immunotherapy to the mix, Schoenfeld says, should help give radiation system-wide powers.

Renewed interest in the abscopal effect comes as pharmaceutical companies all jockey to expand the markets for their competing—and lucrative—immunotherapy drugs. One way they hope to bolster both effectiveness and sales is by boosting response rates to these agents.

When taken alone, checkpoint inhibitors generally only work for around 20–30% of patients. To get those numbers up, drug firms are actively testing immunotherapeutic cocktails, either combining checkpoint inhibitors with one another or with other types of treatments, such as cancer-killing viruses, engineered T cells, and radiation.

The radiation-augmented strategy rests on the idea that high-energy blasts of X-rays or other particles act, at least in part, like a natural cancer vaccine. With any vaccine, a bolus of antigen prompts the immune system to recognize the same antigen later and to be on alert to destroy it. The radiation does the same by setting in motion the process of cancer cell death, during which the floundering tumor cells release bits of cancer debris—the antigens—that prime T cells not only for local clean-up but also for an onslaught against any tumor cells elsewhere in the body. Those immune cells just need to be given the chance. Add in a checkpoint inhibitor to unleash them, and they can surge into action.

"The radiation is changing what the immune cells are doing," says Christopher Barker, a radiation oncologist at MSKCC, who collaborated with Postow and Wolchok on the 2012 report (1). "And it's modulating them in a way that makes them more likely to have anticancer effects."

Slow Acceptance

This idea is now pretty well accepted, but it wasn't always so. Pathologist Robin Mole of the Medical Research Council's Radiobiology Unit at Harwell, United Kingdom, was clearly proud when he introduced the term "abscopal" in a 1952 lecture. It "conveys the exact meaning required," he noted (2).

Yet, it was a word ahead of its time. Clinicians simply had no use for it. Only rarely did they ever administer localized radiation to cancer patients and then see untargeted tumors disappear as well. Such responses were so uncommon, in fact, that a recent systematic review of the scientific literature by researchers at the Moffitt Cancer Center could find only 46 clinical case reports on the abscopal effect between 1969 and 2014 (3).

So, perhaps it's no surprise that Demaria was also unaware of the abscopal effect when in the early 2000s, shortly after completing her medical training in anatomic pathology at the New York University (NYU) School of Medicine, she started studying the immune effects of chemotherapy given to women with breast cancer ahead of surgery. Demaria's research showed that immune cells often infiltrated the tumors of women who responded to the therapy (4).

> "It seemed like whatever we were doing locally in the tumor was converting the tumor into an immunogenic hub."
> —Silvia Formenti

Silvia Formenti, a radiation oncologist who had joined NYU around that time, had her own investigation testing the benefits of adding radiation to chemotherapy for this exact kind of patient, many of whom had tumors that had spread locally to nearby lymph nodes in the underarm area (5). The therapy was remarkably effective, and when Formenti heard about Demaria's immunological findings, she wondered if radiation might be having a similar immune-stimulating effect.

"It seemed like whatever we were doing locally in the tumor was converting the tumor into an immunogenic hub," recalls Formenti. She didn't dare make the analogy to a vaccine among fellow oncologists, Formenti adds, but that's what she was thinking.

The two women decided to team up to test the idea. Demaria and Formenti implanted mice with breast tumors in both flanks, one to represent the primary cancer, the other a metastatic site. They then irradiated the primary tumor and saw that the distant tumor shrank when the mice also received a growth factor that increases numbers of the antigen-presenting immune cells that activate T cells. But the distant tumor grew unabated in mice that got the drug without radiation (6). The abscopal effect was indeed immune-mediated, contrary to other leading explanations for the distant antitumor effects.

Few in the radiation oncology community initially accepted the conclusions. "They treated us like we

were crazy," recalls Formenti. But one expert who thought there might be something to the findings was James Allison, the pioneering immunologist who first identified the checkpoint protein CTLA-4 that led to the eventual development of ipilimumab (7). "He was totally open to the concept," Demaria says.

Allison sent Demaria and Formenti an experimental precursor to ipilimumab, a mouse version of the anti–CTLA-4 antibody that he'd developed. Together, the researchers showed in a 2005 paper that only the dual treatment of radiation plus the immunotherapy drug could eliminate nonirradiated lung metastases in a mouse model of breast cancer (8). "This opened the way to combining radiotherapy and checkpoint inhibitors [in patients]," Formenti says.

Still, it would take 6 more years for ipilimumab to win marketing approval and another year after that before the MSKCC researchers described their landmark case report, at which point many oncologists were already taking the immune effects of radiation for granted. What that meant, says radiation oncologist James Welsh, is that the trailblazing preclinical work of Demaria and Formenti now often gets overlooked.

"It kind of pisses me off that they don't get the credit they deserve," says Welsh, who's at the University of Texas MD Anderson Cancer Center. "They were doing immuno before immuno was cool."

Runaway Enthusiasm?

With immunotherapy now the coolest thing in all of cancer drug development, some researchers fear that the pharmaceutical industry is racing ahead to add radiation to the equation without necessarily deliberating on the best ways to deliver the ionizing therapy. "It's like a freight train," says Phuoc Tran, a radiation oncologist at the Johns Hopkins University School of Medicine. "And it's happening in a very helter-skelter way." Many trials, he says, are "just thrown together without much thought about how radiation is best positioned."

Take, for example, a phase III trial in which 799 men with advanced prostate cancer received a single, large palliative dose of radiation to a bone lesion followed either by ipilimumab or placebo. The combined therapy showed no statistical evidence of added benefit (9). But was that simply because the wrong radiation dose was selected? Or perhaps the bone was the wrong site to irradiate?

Researchers may never know because, after that large-scale trial failure, few drug companies now seem willing to pursue the dual strategy for prostate cancer. Tran's worry: "If you don't design these trials right, all this enthusiasm about extending the reach of radiation therapy could result in a big let-down."

To help prevent such disappointments, leading experts gathered last week in Bethesda, Maryland, for a radiation immunotherapy workshop convened by the American Society for Radiation Oncology, the National Cancer Institute, and the Society for Immunotherapy of Cancer. Tran, who co-organized the workshop together with Demaria, Formenti, and others, relished having all the leading figures in radiation oncology and cancer immunology together in one room. They discussed the latest mechanistic understanding of radiation's effects

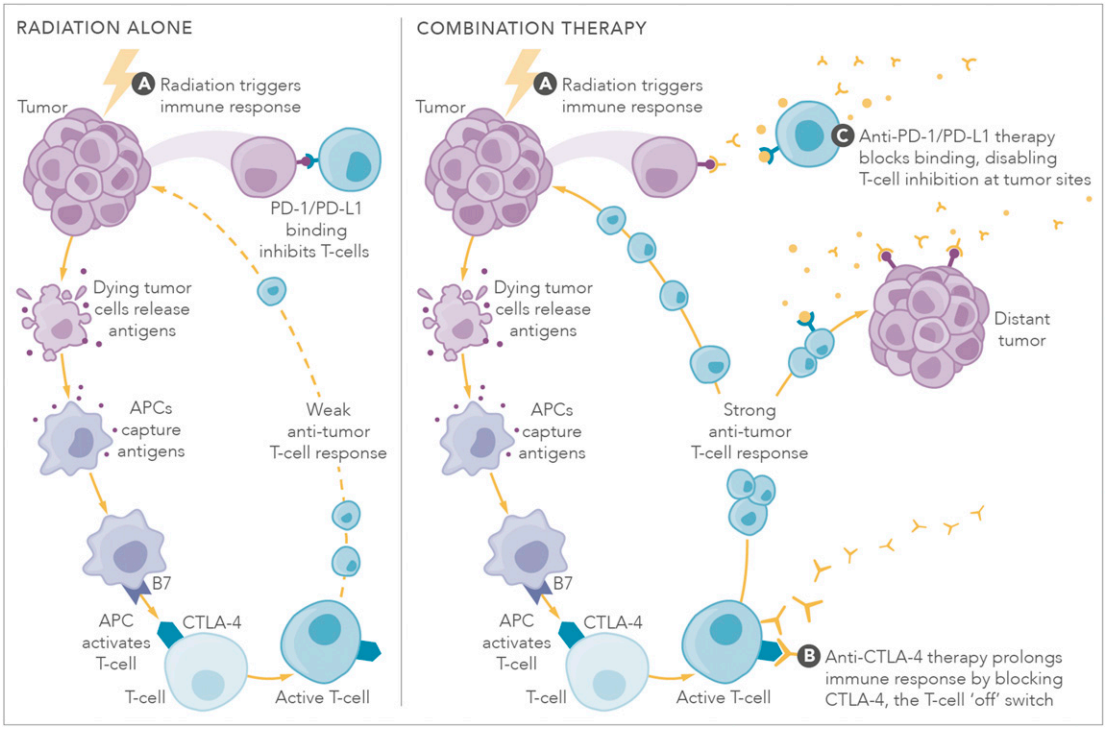

Fig. 2. Radiation alone fails to elicit a strong systemic antitumor response because of checks on the immune system's cancer-killing T cells. But adding immunotherapy drugs, known as checkpoint inhibitors, unshackles the immune system. T cells, prompted by the antigens produced through radiation, then mount an attack on tumors throughout the body. Image courtesy of Lucy Reading-Ikkanda (artist).

on the immune system and how to better design clinical trials involving the newest checkpoint inhibitors, most of which target the PD-1 pathway, which constrains the immune system in a slightly different way than does CTLA-4 (Fig. 2). "As a field," Tran says, "we really have to consider the known variables that are likely to affect how radiation and immunotherapy interact."

The main variables that need to be nailed down are the dose, schedule, sequence, and timing of radiation. For decades, the standard of care has involved giving patients low radiation doses every weekday for a month or more to slowly and gradually attack the local tumor, while leaving other tissues mostly unscathed. Yet, technological improvements in recent years have made it possible to accurately deliver a precision strike of radiation.

This means that doctors can now administer higher doses over a shorter period of time, a technique known as "hypofractionation." And although some combination trials with immunotherapy drugs continue to dole out radiation in the conventional manner with small daily doses, most are now employing these more intensive delivery schedules.

The newer timetables could be essential for reliably eliciting an abscopal response, at least if the preclinical data are to be believed. For example, McBride and his colleagues have shown that only higher doses of radiation can induce tumor immunity in mice (10). But go high enough, and you might overshoot, as Demaria and Formenti found out when they tried three different radiation protocols in combination with an anti–CTLA-4 drug in mouse models of breast and colon cancer. Broken-up, medium-dose radiation schedules induced an abscopal effect, but a single high dose of radiation does not (11).

Early clinical reports seem to bear out these preclinical findings, with most case studies of abscopal responses following immunotherapy happening in patients treated with radiation regimens similar to those that are effective in mice. Demaria's and Formenti's experience is no different. In 2013, they described a man who was rid of lung cancer that had spread to his liver and bones following treatment with ipilimumab and 30 Grays of radiation administered in five medium-sized batches over the course of 10 days (12). That man remains disease-free to this day. "Everything melted away," says Formenti. "He never got another treatment, and he's doing great."

A Bit of Black Magic

Why this intermediate-dose strategy produces the strongest anticancer immune responses is a matter of intense investigation. It's thought that too little radiation on a regular basis causes sustained damage to white blood cells known as lymphocytes, thereby suppressing the immune effect, while too much radiation wipes out cancer-killing T cells. The search is on for the sweet spot, but for now, says Ralph Weichselbaum, a radiation oncologist at the University of Chicago's Ludwig Center for Metastasis Research, "it's still a little bit of black magic."

It's also something of a mystery why only some people respond to combination treatment. In the MSKCC team's 2012 case report, the patient's response to therapy seemed to track with levels of an antibody against a tumor antigen called NY-ESO-1. These antibodies could provide one biomarker of anticancer immune action, although much more validation work is needed to determine which immunologic surrogates will provide the best predictors of clinical response.

Another question requiring further exploration: Is it better to give immunotherapy after radiation or radiation after immunotherapy? As it turns out, that depends.

In a study published last year, Marka Crittenden and her colleagues from the Providence Portland Medical Center in Oregon treated tumor-bearing mice with radiation and one of two different immunotherapy drugs (13). Mice given an anti–CTLA-4 agent responded best when the immunotherapy came before the radiation, presumably because the drug helped eliminate unwanted regulatory immune cells that can dampen radiation's effects.

"As a field, we really have to consider the known variables that are likely to affect how radiation and immunotherapy interact."

—Phuoc Tran

But mice that got a drug that activates a protein called OX40—which, like CTLA-4, is found on the surface of T cells, but unlike CTLA-4 has a stimulatory effect on immune responses—exhibited abscopal responses only when the animals received the immunotherapy shortly after the radiation. It's during that brief window when the immune system is picking up bits of tumor debris left over from the radiation blast that OX40 is known to be most active. "Timing matters," says Crittenden, and when to administer the immunotherapy agent relative to the radiotherapy "depends on what we think that agent is doing."

The sequence could also impact the safety of regimens that combine radiation and immunotherapy, both of which are known to cause serious side effects. In a retrospective analysis of lung cancer patients presented at the Multidisciplinary Thoracic Cancers Symposium in March, researchers from the Moffitt Cancer Center found that the problematic lung inflammation sometimes caused by checkpoint-inhibiting drugs seemed to be exacerbated when radiation was delivered after immunotherapy but not before.

Formenti concedes that many details still need to be worked out. She's just happy to have so many colleagues working alongside her on the problem. As recently as 2014, Formenti was onstage at the annual meeting of the Radiation Research Society debating one of the most prominent radiation oncologists in the United States about whether the abscopal effect was even relevant to curing cancer with radiation. Now, no one doubts it. The challenge is to make it happen more often.

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