Melanoma Vaccines: Possible Progress After Years of Frustration?

By Charlie Schmidt

For decades, efforts to create a vaccine against melanoma, the most lethal type of skin cancer, have been exercises in frustration. As crafty as they are lethal, melanoma cells can mount evasive defenses that suppress a vaccine’s intended role to shrink tumors. Because of that, just 3%–10% of patients treated with experimental vaccines typically show clinical improvements—and some of these may be spontaneous. But far from conceding defeat, scientists are intensifying their efforts to create better immunotherapies against melanoma, and those under development today show more promise than ever.

In a recent phase II clinical trial, Steven Rosenberg, M.D., Ph.D., chief of the National Cancer Institute’s surgery branch, tested a new immunotherapy that shrank tumors in up to 72% of metastatic melanoma patients treated. This is the best “objective” result achieved yet in melanoma immunotherapy, according to Tom Gajewski, M.D., Ph.D., associate professor at the University of Chicago Medical Center. Objective endpoints—namely, progression-free survival and/or tumor regression—are better than the other endpoints that researchers more often report in the cancer vaccine literature. Such endpoints include, among others, a proliferation of immune lymphocytes, such as T cells, that will ideally attack tumors and destroy them. But without evidence of prolonged survival, or tumor shrinkage, T-cell proliferation has questionable clinical value, Gajewski said. Described in the Journal of Clinical Oncology on November 10, 2008, Rosenberg’s method is called adoptive cell therapy (ACT). With it, lymphocytes extracted from a patient’s own tumor are expanded in the laboratory and optimized for cancer-killing effects. Then, after radiation and chemotherapy have blunted the patient’s immune system, the superlymphocytes are put back into the patient. Scientists are developing several additional immunotherapeutic methods, each with similar goals: to focus the immune response against tumors with greater specificity and to block the natural suppressor mechanisms that tumors use to protect themselves from immune reactions.

According to Paul Chapman, M.D., an attending physician at Memorial Sloan–Kettering Cancer Center, these approaches offer new hope for immunotherapy in the fight against melanoma and other cancers. “At some point, we might be able to use vaccines to prevent metastatic disease among melanoma patients whose lymph nodes have been surgically removed,” he said. “Or perhaps we could immunize people at high risk of the illness while they’re still teenagers, but that’s a dream scenario that won’t happen anytime soon.”

Treatment Versus Prevention

The immunotherapies directed at melanoma differ from vaccines used against infectious disease. Made with fragments of dead, inactivated, or attenuated pathogens, infectious disease vaccines trick the immune system to recognize and attack live microbes that make people sick. Vaccines against cervical and liver cancer deploy a similar approach. Both these cancers can be triggered in response to foreign pathogens—cervical cancer is induced by human papillomavirus, whereas liver cancer can strike in the wake of hepatitis B, a virally induced illness. The only two cancer vaccines approved so far by the U.S. Food and Drug Administration target these viral cancers. Vaccines for nonviral cancers, on the other hand, including melanoma, are designed to boost immune reactions against malignancies that have already been diagnosed. So, whereas infectious disease vaccines aim for prevention, those used against melanoma—at least for now—are designed for treatment.

With first-generation cancer vaccines, scientists tried to jolt the immune system into attacking malignancies—for instance, by chopping tumor cells into fragments that could be put back into patients, either with or without additional drugs. Creating vaccines from the patient’s own cancer—a method still being explored today—offers the theoretical advantage of targeting all the antigens (i.e., cell-associated molecules recognized by lymphocytes) in a tumor, even if they’re not defined, Gajewski said. Cancer vaccines developed thus far target mainly melanoma, in part because melanoma cells are easier to culture than those of other tumors. In a September 2004 literature survey published in Nature Medicine, Rosenberg reported that among 440 individuals treated with 541 different cancer vaccines during the previous decade, 422 had metastatic melanoma, whereas 18 had other types of cancer.

One problem with first-generation vaccines is that they don’t target tumor cells with enough specificity because tumor antigens aren’t truly foreign. Rather, they originate from once-normal cells in the patient’s own body, and they contain subtle alterations that evoke weak immune responses. Over time, scientists have identified growing numbers of tumor antigens, for instance, MAGE-3, which is overexpressed by melanoma cells. These antigens have become useful as more specific vaccine targets.

But cancer cells can still evade these more sophisticated therapies. For instance, they can shed tumor antigens to limit the number of targets that they present for immune attack. Chapman points out that melanoma cells might not express human leukocyte antigen, a protein that presents surface antigens to T cells. “That’s what keeps me up at night,” he said. “Without [human leukocyte antigens], the T cells might be around, but since they can’t see the antigens, they don’t attack the tumor.”
Beyond Traditional Approaches
Rosenberg claims these shortcomings—in addition to other mechanisms that tumors use to resist immune attack—explain the lack of objective responses generally seen in clinical trials. Given their poor response record, he argues that new approaches to cancer immunotherapy are warranted, and he suggests that ACT in particular is promising. By genetically modifying lymphocytes from a patient’s malignancy, Rosenberg said, one can select for T-cell receptors that offer high tumor affinity. “And most importantly, by eliminating the body’s own immune system with chemotherapy and radiation, we get rid of the regulatory and suppressor mechanisms that prevent cancer immunotherapies from working,” he added.

In his recent phase II trial, the best results were from 25 patients given tumor antigen–specific lymphocytes after 5 days of pretreatment with cyclophosphamide and fludarabine, in addition to total-body irradiation, given twice daily for 3 days, for a total dose of 12 Gy. As noted earlier, 72% of these patients achieved objective responses. “And it looks like remissions for a third of these patients are complete and apparently durable,” Rosenberg said. “In developing this approach, we’ve had patients who remain disease free for more than 5 years.”

Other researchers question some of Rosenberg’s methods, however. Preparing tumor antigen–specific lymphocytes from a tumor takes 6–8 weeks, during which patients must stay healthy enough to tolerate the pending treatment. Both Chapman and Gajewski argued that patients who remain eligible during that interval might be unusually resilient. Thus, the waiting period weeds out sicker patients and selects for patients who might show better responses than average, they said.

Rosenberg dismisses these claims. In an e-mailed response, he wrote that his patients are heavily pretreated and that most have metastases at multiple locations, including some patients who have metastases in the brain. “So, those assertions are incorrect,” he countered. Outside Rosenberg’s laboratory, ACT for melanoma treatment is being developed at several other institutions, including the University of Texas M. D. Anderson Cancer Center in Houston and the H. Lee Moffitt Cancer and Research Institute in Tampa, Fla., among others.

Improving Vaccine Specificity
Meanwhile, cancer vaccine scientists aim to target ever-increasing numbers of tumor antigens. An experimental vaccine being developed by Sanofi Pasteur, a biopharmaceutical company in Lyon, France, targets five melanoma antigens in a vaccine coadministered with interferon alfa, a drug that heightens T-cell responses. Known as MEL11, the vaccine is delivered to melanoma cells in canary poxvirus, a microbe that grows only in avian cells, and is therefore safe for human use, said Neil Berinstein, M.D., a professor at the University of Toronto and head of Sanofi Pasteur’s cancer vaccine program. The vaccine will be tested at 21 locations in a phase III trial that has just begun, Bernstein said. “We’ll be testing our approach against a reference arm, which is interferon alfa alone,” he added. “So, the question to address is whether the vaccine–interferon combination produces a more effective antitumor response than interferon given by itself.”

With yet another approach, scientists are developing monoclonal antibodies that target CTLA-4, a molecule that—animal studies suggest—stops immune cells from overreacting upon exposure to benign pathogens, such as the virus that triggers a cold. Expressed on T cells, CTLA-4, when activated, also shuts down the immune response to cancer, Chapman explained. By targeting CTLA-4, scientists hope to block that suppressor mechanism and keep immune cells active. According to Chapman, two monoclonal antibodies against CTLA-4 are now under development: one by Bristol-Meyers Squibb and another by Pfizer. At the Memorial Sloan–Kettering Cancer Center, Chapman and his colleague Jed Wolchok, M.D., codirect a phase III clinical trial in melanoma that was recently completed. “The results aren’t available yet,” he said. “But multiple phase II trials have reported clear objective responses and complete tumor regression in some cases.”

Cancer immunotherapy, Chapman adds, takes time to work. “It can take 2–3 months to mobilize the T-cell response,” he explained. “The kinetics are different from what you have with standard chemotherapy.” Given that, some doctors might at first be challenged by melanoma vaccines as they become available, some experts say. “They’ll have to learn how to use them,” Chapman said. “People aren’t used to waiting so long for results, and that will take some educating.”

At the same time, some experts speculate that FDA protocols might not favor vaccine clinical trials in patients with early-stage cancer. Indeed, most clinical trials to date have occurred in patients with metastatic disease. These studies can typically be completed over relatively short durations. Determining progression-free survival in early-stage melanoma, on the other hand, might take 6–8 years, said Garo Armen, Ph.D., chief executive officer of Antigenics, a biotechnology company in New York, N.Y. Armen cites FDA barriers when explaining why Antigenics went to Russia for approval of Oncophage, a kidney cancer vaccine. He claims that Oncophage is the first cancer vaccine ever to obtain regulatory approval worldwide. The vaccine theoretically works by increasing the visibility of kidney cancer antigens to the immune system.

Gajewski hopes that vaccines will eventually become routine components of melanoma treatment. Ideally, doctors will prescribe them on the basis of a patient’s genetic makeup. Along those lines, scientists at the University of Chicago Medical Center are already identifying gene expression signatures that correlate with outcomes in cancer immunotherapy, Gajewski said. The goal is to target vaccines for specific patients, much as trastuzumab is given to HER2-positive breast cancer patients today. “We want to personalize our approaches,” he said. “But we also want to find ways to overcome resistance to immunotherapies among patients who don’t respond. It’s not to say that other therapies won’t continue to come up in the future.”

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