First Oncolytic Viral Therapy for Melanoma

The FDA has approved talimogene laherpareovac (T-VEC; Amgen) to treat surgically unresectable skin and lymph node lesions in patients with advanced melanoma. Also called T-VEC, this is the first oncolytic virus to gain regulatory endorsement.

T-VEC, a genetically modified herpes simplex virus type 1, is thought to have two distinct means of antitumor activity: Its selective replication in cancer cells causes them to rupture and die; meanwhile, it also releases the cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF), which spurs the patient’s own immune system into tumor-fighting mode. However, Amgen has stated that T-VEC’s “exact mechanism of action is unknown and being further investigated.”

T-VEC’s approval was based on data from the multicenter phase III OPTiM study, in which 436 patients with surgically unresectable metastatic melanoma were randomized to receive injections of T-VEC directly into their lesions, or GM-CSF given subcutaneously (J Clin Oncol 2015;33:2780–8). Among patients in the T-VEC arm, 16.3% achieved durable responses—tumor shrinkage lasting at least 6 months—compared with 2.1% in the control group. The median overall survival with T-VEC was 23.3 months, versus 18.9 months with GM-CSF, which was not statistically significant, prompting the FDA and Amgen to emphasize that T-VEC “has not been shown to improve overall survival.” The therapy also had no effect on melanoma that had spread to other internal organs.

T-VEC was well tolerated by patients, with the most common side effects being fatigue, chills, and fever. Given the live nature of this therapy, cold sores and other herpetic infections were also observed.

According to preliminary data from a small phase I study, T-VEC plus the immune checkpoint inhibitor ipilimumab (Yervoy; Bristol-Myers Squibb) may also show promise in melanoma: Half of the study’s 19 patients responded, 22% completely. In addition, T-VEC is being evaluated alongside another checkpoint inhibitor, pembrolizumab (Keytruda; Merck), which blocks interactions between the ligand PD-L1 and its receptor, PD-1. A recent review noted that “as oncolytic viruses often induce interferon release in the local tumor microenvironment, and interferon is known to upregulate PD-L1 expression on tumor cells, this combination is especially interesting” (Nat Rev Drug Discov 2015;14:642–62).

Marc Ernstoff, MD, director of the melanoma program at Cleveland Clinic’s Taussig Cancer Institute in Ohio, notes that T-VEC has only “modest single-agent activity,” and “its place in the growing immunotherapy armamentarium is still unclear.” He adds, though, that “its unique mechanism of immune stimulation and high therapeutic index provide significant opportunities for multiagent regimens that can further leverage the immune path to durable tumor destruction.”

“It’s worth noting that we had only three approved agents for melanoma in the 30 years before 2011,” says John Kirkwood, MD, director of the melanoma skin and cancer program at the University of Pittsburgh, PA. T-VEC is the 10th new therapy approved for melanoma in the last 5 years, which the Melanoma Research Alliance has hailed as “a truly unprecedented rate of progress.” —Alissa Poh ■

Innate Immune Cells May Prevent Metastasis

A specialized type of white blood cell that helps defend the body from infection also appears to control the spread of cancer. Researchers have found that these innate immune cells, called patrolling monocytes (PMo), slow tumor metastasis to the lung in multiple mouse models (Science 2015;350:985–90).

Most of the body’s monocytes are the classic variety, which gobble up bacteria, viruses, and dying cells when recruited to sites of infection. Approximately 10% to 25% are PMo—active surveyors that can travel against blood flow to clear pathogens and other unwanted cells. In the context of cancer, the team discovered that PMo can “sense tumor cells, move toward them, help orchestrate their killing,
and clear the tumor cells’ debris before they metastasize,” says senior author Catherine Hedrick, PhD, of the La Jolla Institute for Allergy and Immunology in La Jolla, CA. Hedrick and lead author Richard Hanna, PhD, had long investigated the role of monocytes in atherosclerosis, but shifted their focus to cancer after research from Jeffrey Pollard, PhD, director of the MRC Center for Reproductive Health at the University of Edinburgh, United Kingdom, suggested that classic monocytes promote tumor growth and metastasis (Nature 2011;475:222–5). Meanwhile, others had shown that PMo could clear damaged endothelial cells, and Hanna observed a striking enrichment of PMo in the lung—a common site of metastasis (Cell 2013;153:362–75). This got him wondering if PMo might play a clean-up role in cancer, perhaps helping remove tumor cells within the lung.

Hanna, Hedrick, and their team tested this idea in three mouse models. First, they injected mice with lung carcinoma cells and saw that PMo swarmed to tumor sites, preventing tumor cells from attaching to lung blood vessels. Next, the researchers injected melanoma cells into PMo-deficient mice, which developed lung metastases earlier and in greater numbers compared to control mice.

A third line of evidence for PMo’s role in preventing metastasis came from experiments with mice that spontaneously develop breast tumors that spread to the lung. When the immune system in these animals was replaced with that of PMo-deficient mice, the number of spontaneous lung metastases rose dramatically, suggesting that PMo guard against metastasis. This was confirmed with “rescue” experiments where, prior to tumor injection, PMo were reconstituted in mice that lacked these immune cells; in this setting, very few lung metastases formed.

The researchers suspect CX3CL1 (fractalkine) is important for drawing PMo to the lung. This protein is highly expressed in lung epithelial and tumor cells, and its receptor, CX3CR1, is abundant on the surface of monocytes. In the lung, it’s hard to tell if PMo are directly killing tumor cells.

But “we know they orchestrate it,” says Hedrick. “They make a lot of the chemokines that recruit natural killer cells,” which are known for their ability to kill tumor cells.

All told, the new research suggests there is a balance of protumor and antitumor activities within the innate immune system, says Pollard, who wasn’t involved with this study. “From a therapeutic point of view, enhancing patrolling monocytes might help tilt the balance toward an antitumor metastatic role.” —Esther Landhuis

CRUK Launches “Grand Challenges”

Cancer Research UK (CRUK) plans to invest £100 million, or about $150 million, over the next 5 years in an ambitious grant program aimed at tackling some of the most vexing unsolved problems in cancer research. The group has issued seven initial challenges and aims to present its first award next fall.

Each year, the “Grand Challenges” program will award at least one 5-year grant of up to £20 million (approximately $30 million) to teams chosen by an international panel of nine accomplished scientists, which also set the initial challenges. Expressions of interest are due in February, with select teams making final submissions by the end of July. The winner will be announced in September.

“We are looking for scientists to approach these problems from multiple coordinated angles and to make use of the latest technologies,” says panel member Suzanne Cory, PhD, laboratory head in the Division of Molecular Genetics of Cancer at the Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia. “In developing these challenges, we deliberately looked for things that would provoke researchers to think outside the box.”

Although CRUK’s grants have traditionally supported UK-based projects, the Grand Challenges initiative requires only that teams have a strong UK component, and encourages international collaboration, says Nic Jones, PhD, CRUK’s chief scientist. Teams are also expected to cross disciplines, have a principal investigator and up to seven co-investigators from academic institutions or industry, and include a patient advocate.

“We’d like to see 25% of overall activity occur in the UK, but the rest could be based and led from elsewhere—and that’s a very different approach for CRUK,” Jones says. “Our main goal is to have the very best people apply their knowledge and expertise towards these challenges.”

While similar in spirit to the National Institutes of Health’s Provocative Questions grant program, Grand Challenges is larger in scale and more focused on teams versus individual investigators, says Jones. The NIH recently committed $40 million to fund Provocative Questions grants over the next 2 years (Cancer Discov 2015;5:569–70).

CRUK hopes to attract other funding partners as the project gains momentum. With the participation of other organizations, the group may eventually be able to sponsor more than one challenge per year, Jones adds.

During the selection process, the panel will look for new or unusual collaborations involving multiple disciplines, says Cory. For example, teams might include biomedical researchers, software developers, engineers, and experts in the physical, behavioral, health, population, and social sciences.

Proposals must provide details on how team members will communicate and work together effectively, she adds. “These should be very real teams, not just collections of individuals.”
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