Could a novel combination therapy cure metastatic melanoma?

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In medicine’s battle against metastatic melanoma, the odds are overwhelmingly in melanoma’s favor. Yet a novel treatment that pairs immunotherapy with high-dose radiation could offer new hope for patients with the deadly disease.

Steven Seung, M.D., Ph.D., Brendan Curti, M.D., and Marka Crittenden, M.D., Ph.D., all part of the Earle A. Chiles Research Institute at Providence Cancer Center, developed a clinical research trial using stereotactic body radiotherapy, or SBRT, with interleukin-2. Although this specific combination therapy had never been tried, they believed it held great promise. It did.

In the pilot study, which involved 12 patients with metastatic melanoma or renal cell carcinoma, 67 percent saw their tumors shrink. Results were published in the journal Science Translational Medicine on June 6.

“We are looking to understand why this worked so well,” says Dr. Curti, director of Providence Cancer Center’s Biotherapy and Genitourinary Oncology Research programs. “Just from standard IL-2 treatment we might have expected one or two patients to have a tumor response. In this study, five of seven patients with melanoma and three of five with renal cancer had significant regression of their cancer. Factoring in that it was a small study, this finding is very, very surprising.” Tumors in some patients completely disappeared during the six months of treatment and have not returned in more than two years of follow-up.

It is known that the immune system has the ability to attack cancer cells, primarily through T cells, which can recognize what is foreign in the body and eliminate it. However, cancers can hide from T cells in many ways, including concealing the proteins that the T cells would use to recognize and attack the cancer.
Providence researchers pursued the idea of using a high dose of sharply focused radiation — 10 times the strength of traditional radiation — to kill the cancer cells, helping to release proteins the T cells would recognize. Interleukin-2 gives a boost to those T cells, which when activated, proliferate and attack the melanoma or renal cancer.

Toxicities from IL-2 can be significant, including hypotension, pulmonary capillary leak with hypoxemia, fever, rigors, myalgias, arthralgias, pruritis, rash, diarrhea, peripheral neuropathy and more. Because of this, patients are hospitalized during IL-2 treatments. Although the side effects can be severe, they can be managed and resolved after the IL-2 is completed. There are only a small number of high-dose IL-2 programs in the United States, and Providence’s biotherapy program is among the busiest to offer this complex therapy.

The symptoms are not a substitute for the scans we use to measure the cancer, but we know that patients who have significant drops in blood pressure and platelet counts and who develop acidosis are more likely to respond to the treatment than those who do not,” Dr. Curti says. “The side effects are all manifestations of the immune activation needed to eliminate the cancer.”

A phase II study involving 44 patients with advanced melanoma is now under way. “If our preliminary work is confirmed, many more patients with advanced melanoma could find great hope in this combination therapy. Their cancer could be placed in remission,” Dr. Curti says. “In addition, if this therapy continues to show promise, we could apply it to other immune-based cancer treatments for renal, breast and prostate cancers. We’re already working on clinical trials to investigate this.”

HOW THE THERAPY WORKS

Radiation tightly targets the tumor.
The radiation breaks open the tumor to release hidden cancer proteins that T-cells recognize and attack.
IL-2 helps T-cells multiply, roam the body for cancer and create memory cells to thwart future invasions.

Providence joins global research network

Providence Cancer Center’s expertise in immunology has earned it a spot in the new International Immuno-Oncology Network, a research collaboration focused on using the body’s immune system to fight cancer.

The center’s Earle A. Chiles Research Institute is one of only 10 leading research institutions, and the only U.S. site west of the Mississippi River, invited to join the network formed by Bristol-Myers Squibb.

“We consider immunotherapy as the fourth method of treatment of patients with cancer,” says Walter J. Urba, M.D., Ph.D., director of Providence Cancer Center.

Researchers in the network will have access to many new drugs for further development and use in clinical trials. Patients will benefit substantially from these state-of-the-art, network-supported trials.

Providence anticipates the first of the new network trials to begin by year’s end.
PROVIDENCE inScope

A breakthrough aided by technology

Providence installed stereotactic body radiotherapy equipment that allowed for this novel approach when the new cancer center opened in 2008. SBRT does for the rest of the body what Gamma Knife radiosurgery does for brain tumors. By accounting for the movement of tumors during respiration, multiple beams of radiation deliver a high dose to the tumor while sparing the surrounding healthy tissue.

“Imagine taking a magnifying glass and focusing sunlight to burn your name on a piece of wood,” says Dr. Seung, director of The Gamma Knife Center of Oregon at Providence Cancer Center, and a radiation oncologist with The Oregon Clinic. “That’s exactly how this machine works.”

The combination therapy was tried about two decades ago, but with a very different radiation technique. That study had little success in eradicating the tumor treated with radiation and was no better than IL-2 alone.

“We built on that idea,” Dr. Curti says. “Radiation carefully applied has important and different effects on the immune system than conventional radiation, and these immune effects from SBRT can be amplified by IL-2 immunotherapy. This appears to be the reason we’ve had better clinical outcomes.”

“That’s the beauty of this study,” Dr. Seung adds. “We didn’t create anything new, but the approach was novel with how we combined the two.”

Science has had some breakthroughs recently in treating metastatic melanoma, which kills 95 out of 100 patients within five years. The newly approved Yervoy (ipilimumab), for example, has been found to slow the progression of the disease and can improve survival in a small percentage of patients.

“These new medicines have the potential to slow down melanoma but rarely, if ever, cure it,” Dr. Curti says. “So our goal, of course, is to find treatments that work not just at a high rate, but also for the long term.”

Learn more at www.ProvidenceOregon.org/cancer
When it comes to screening for cardiovascular health, most physicians stress the cardio part. However, evidence shows that screening for vascular disease is as important as a focused cardiac evaluation. Patients with peripheral artery disease, for example, are five times more likely to have an ischemic cardiac event. Yet because many of these patients are entirely asymptomatic, the disease goes largely unnoticed.

Carotid stenosis is another major vascular disease category worthy of focused screening. For many physicians, listening for a carotid bruit may be the extent of a screening unless a patient has presented with a focal neurological issue or a history of cerebrovascular disease.

Studies have shown, however, that bruits present in only 30 to 40 percent of patients with carotid lesions. This means that 60 percent of patients with high-risk carotid lesions may never be identified.

Lastly, abdominal aortic aneurysm, while the least prevalent of the above conditions, is a silent killer. Generally asymptomatic until a catastrophic rupture occurs, AAAs are more common in populations with certain risk factors, including a family history of aneurysms; hypertension; high cholesterol; age; male gender and smoking.

For symptomatic patients, it’s best to contact a vascular specialist. For those with no symptoms, consider the following guidelines:

1. An abdominal ultrasound screen beginning at age 55 for patients with a family history of AAA and a history of smoking
2. An ankle-brachial index for patients 60 or older with a history of smoking, diabetes, coronary disease or hypertension; family history of vascular disease; or prior stroke or heart attack
3. Carotid disease screening, particularly for men who are 60 or older with a history of diabetes, smoking, peripheral artery disease, hypertension or coronary disease

Vascular disease is a leading cause of death and disability in the United States. Screening remains a powerful weapon to combat the potentially devastating effects of these conditions.

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Quick Tip
Treating the chronic insomniac
Studies show that when standard sleep hygiene fails, six to eight weeks of formal cognitive behavior therapy can be as effective as, or better than, pharmacotherapy. Cognitive behavior therapy also can be used when medication is tapered.

Courtland Childers, M.D.
Providence Portland Internal Medicine Residency Program’s e-learning series

Visit us online at www.providence.org/oregon for more information.
John Zurasky, M.D.
Stroke neurologist, neurointensivist, Providence Brain and Spine Institute

Past lives
Medical director of Intermountain Healthcare stroke program; neurologic intensive care/stroke fellow at Washington University in St. Louis; economics major at Harvard University; teacher in Japan; stockbroker in San Francisco

What is neurointensive care?
A neurointensivist-led care model helps to standardize care processes for patients with complex neurologic trauma. Initially this subspecialty was found only in academic centers, but as improved outcomes were documented, the model has moved into advanced medical centers.

Under a neuro-ICU model, who is the final authority?
It’s a collaboration involving our partner neurosurgeons, other consulting physicians, nurses, respiratory therapists and other staff. The surgeons make the final surgical decisions. Otherwise, the neurointensivist is trained to balance the patient’s cardiovascular, respiratory and metabolic needs to optimize the neurologic outcome. We make the final decisions, but only with the help of our colleagues at all levels.

Why did you choose this specialty?
Neurology is fascinating, and the field is in an innovative phase that’s exciting to be a part of.

You were a teacher, then a stockbroker. What drew you to medicine?
I wanted life to mean a little more at the end of every day.
The doctor can see you now
Oregon state employees in Salem can now visit a Providence clinician with the click of a mouse. Providence Health eXpress is the first worksite health care clinic where public employees with minor complaints can have a video visit with a board-certified clinician.

The telehealth program is a partnership between Providence Health & Services and the Oregon Public Employees’ Benefit Board.

Providence joins national network
Providence Orthopedic Institute is now part of the High Value Healthcare Collaborative, a national network founded by Mayo Clinic, Intermountain Healthcare and other leading institutions to improve health care, lower costs and share best practices. The work will set the standard for national models of orthopedic care. The collaborative is also working on improving care for patients with diabetes and heart failure.

Cancer lab receives major grants
Providence research scientist Keith Bahjat, Ph.D., received two grants to support his laboratory’s work on new cancer immunotherapies. Susan G. Komen for the Cure awarded $450,000 over three years for work on a breast cancer vaccine. A $296,000 grant from the U.S. Department of Defense will fund research on how the protein SOCS-1 interferes with the body’s immune response to cancer vaccines.

Grant expands specialty dental services
A $25,000 grant from the Walmart Foundation will help Providence Specialty Pediatric Dental Clinic at Providence Child Center expand oral health services for children with special health care needs. The grant funds a second dental suite for the clinic as well as oral health outreach and education.