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Bringing out the big guns to kill cancer

Providence Cancer Center News, spring 2008

People from all over the Northwest have access to the most sophisticated radiation therapy technology at Providence Portland Medical Center. An alternative to some invasive surgery procedures, stereotactic body radiation therapy (SBRT) safely delivers exceptionally precise, very high doses of radiation to tumors, with minimal radiation exposure to healthy tissue.

"SBRT does for the rest of the body what Gamma Knife radiosurgery does for brain tumors," says Steven Seung, M.D., Ph.D., a radiation oncologist with The Oregon Clinic and medical director of Providence's Gamma Knife Center of Oregon. "Individual beams of radiation, numbering into the hundreds, converge at a single point to destroy cancerous tissue. Because the procedure is noninvasive, these patients go home the same day and soon resume normal activities."

While the new technology represents a great leap forward in cancer treatment, Dr. Seung has even greater hopes for what it might mean for research.

"Because it is so precise, SBRT can safely administer very high doses of radiation to tumors. That ability is our opportunity to begin to answer basic questions about radiation can help the immune system to fight cancer."

In collaboration with Brendan Curti, M.D., director of the biotherapy program at Providence Cancer Center and also with The Oregon Clinic, Dr. Seung is studying using SBRT in combination with interleukin-2 (IL-2), a therapy that can cure metastatic kidney cancer and metastatic melanoma in certain patients.

"Recent studies have shown that SBRT is excellent for local control of tumors, with control rates of 90 percent or higher," says Dr. Curti. "Our proposal is to reduce the size of tumors with SBRT, and then to administer IL-2 therapy to encourage the patient's immune system to fight metastatic disease."

Preclinical studies have shown that SBRT used alone can improve the immune system's response to cancer. By combining SBRT with existing immunotherapies, Drs. Curti and Seung hope they will see a synergistic effect – one that optimizes the immune system's ability to seek out and destroy cancer cells.

A dream deferred

If high doses of radiation prove to be the key to unlocking the cancer-fighting potential of existing immunotherapy drugs and vaccines, we will be much closer to solving a problem that has puzzled researchers for half a century.

In 1957, a physician researcher out of the National Cancer Institute, Richmond Prehn, M.D., published a landmark study co-authored with his laboratory assistant, Joan M. Main. Its findings turned conventional wisdom about cancer and the immune system on its head.

What they discovered was that surgically removing tumors from sarcoma-ridden mice not only cured the mice of cancer – the treated mice also were immune to all subsequent efforts to reinoculate them with the same sarcoma.

"Prehn and Malin were revolutionary," Dr. Curti says. "Before their 1957 study, even the suggestion that the immune system had a role to play in cancer treatment would have been regarded in many scientific circles with skepticism. Now the hope was that new cancer therapies and vaccines could be developed that would rival both chemotherapy and radiation in their effectiveness."

But despite thousands of attempts to capitalize on Prehn and Main's success, that hope has gone largely unrealized.

"What we have learned is that a successful immune system response in humans depends on not just one event, but a series of events – from the presentation of a foreign marker on the surface of the cancer cell to the homing behavior of killer T-cells to the tumor site," Dr. Curti says. "These are like links in a chain, and any weak link can spell disaster for an effective immune system response."

IL-2 therapy that Dr. Curti administers to patients with advanced melanoma and kidney cancers at Providence Cancer Center is FDA-approved and is one of the most successful immunotherapies to date. Still, only about one in 10 patients has a complete response to this treatment.

"For the patients who respond to IL-2 therapy it's a godsend," Dr. Curti says. "But for most of our patients with advanced disease, we urgently need better answers."

New technology inspires new ideas

Inspired by the success of Japanese cancer researchers in provoking an immune system response with high doses of radiation, Dr. Seung recently conducted a series of experiments in collaboration with Marka Crittenden, M.D., Ph.D. Together they have achieved results comparable to those observed by Prehn and Main in 1957 – with a combination of radiation and immunotherapy.

"Our work demonstrates that the tumor environment in mice after radiation is exceptionally

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