Targeted therapy for chondrosarcomas

Cancer Center Trial Takes Aim at Treatment-Resistant Tumors

By Tyler Smith

University of Colorado Cancer Center has launched a clinical trial to bring new hope to patients with a bone and joint malignancy that is stubbornly resistant to treatment.

The target is chondrosarcoma, a group of tumors born of unchecked production of cartilage-producing cells. The disease originates in the bones but can metastasize to other parts of the body, particularly the lungs. The lesions are especially difficult to treat because they respond poorly to both chemotherapy and radiation, said Victor Villalobos, MD, PhD, director of the Cancer Center’s Sarcoma Medical Oncology program.

There are several varieties of the malignancy, including conventional, dedifferentiated, and mesenchymal chondrosarcomas, Villalobos said. They are treated slightly differently based on the “nuanced diagnosis,” but across the board, Villalobos said, “there is no good standard of care.” The response rate for chondrosarcoma patients to “heavy chemo,” he said, is only about 5 to 10 percent, for various reasons, including the lack of vascular systems in these tumors, which limits the absorption of chemotherapeutic drugs.

To date, surgical resection is the primary tool to fight chondrosarcomas, but that often means that patients lose portions of or entire limbs or undergo difficult cardiothoracic procedures to excise the cancer, said Villalobos.

Plan of attack. He hopes a new weapon is on the horizon: an oral medication that targets a genetic mutation associated with about 60 percent of chondrosarcomas. “We think it is a driver of some types of chondrosarcoma,” Villalobos said.

The mutation affects the protein IDH1 (isocitrate dehydrogenase). Normally, IDH1 catalyzes the conversion of isocitrate to the organic compound alpha-ketoglutarate. Roque DH1 converts the naturally occurring alpha-ketoglutarate into 2-hydroxyketoglutarate, which is an oncometabolite – that is, a molecule that lays the groundwork for the unregulated division of cartilage cells that is the hallmark of chondrosarcomas.

The new drug, AG-120, from Cambridge, Mass.-based biopharmaceutical company Agios, is designed to inhibit the IDH1 mutation. “We want to see how well the drug works as a selective inhibitor,” Villalobos said.

The Cancer Center is participating in a phase 1 multicenter clinical trial of AG-120, Villalobos said. Lia Gore, MD, associate professor of pediatrics-hematology and medical oncology at Children’s Hospital Colorado and University of Colorado Hospital, is principal investigator.

New path. The first part of the study established the optimal dose for patient safety. The second part, now underway, aims to further evaluate the drug’s safety, and how much of it patients can tolerate, as well as to assess patients’ response to the treatment. The trial is slated to run through May 2016.

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“It’s a great opportunity for patients,” Villalobos said, adding that the Cancer Center hopes to enroll 25 to 30 individuals in the trial. “We can’t rely only on local therapies. If the tumors don’t spread anywhere, we can treat them, but some are not resectable. We need better therapies.”

Especially problematic is the fact that chondrosarcomas frequently metastasize to the lungs, Villalobos added. “The lungs are fertile ground; we don’t know why,” he said. “That fertility allows the tumors to bloom.”

Michael Weyant, MD, a cardiothoracic surgeon at UCH, said chondrosarcomas are more likely to spread to the lungs as they get larger. When that happens, surgeons may have to cut them out because they lack therapeutic alternatives, he said. Preventing the lesions from reaching the lungs also presents significant surgical challenges, Weyant added.

“We often see these tumors as they arise from the bony structures of the chest wall,” he wrote in an email. Surgeons may have to remove “all layers of the chest wall, including bone, muscle and often skin,” Weyant added. Reconstructive work with synthetic material, such as Gore Tex grafts or polypropylene mesh, follows the resection. With larger defects, surgeons perform reconstruction with a prosthesis made of bone cement and grafts or mesh, he said.

“There is really no effective medical therapy for these tumors,” which highlights the importance of the trial, Weyant concluded.

Villalobos said AG-120 is just one example of a promising new direction in the treatment of sarcomas, which include a widely varied group of cancers that form in the bones and connective tissues. For example, researchers have isolated the c-Kit mutation in more than 80 percent of patients with GIST (gastrointestinal stromal tumors), another sarcoma, he noted. Patients treated with imatinib, an oral medication that targets c-Kit, have “responded dramatically,” Villalobos said.

“These discoveries have changed the way that we approach sarcomas,” he said.

For more information about the AG-120 trial, contact Sharon Hecker, phase I resource coordinator, at 720-848-0667, or sharon.hecker@ucdenver.edu.

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