Genomic Sequencing Initiative Advances Angiosarcoma Research

BY CHUCK HOLT

Corrie Painter, PhD, was confident everything was going to be OK. The huge lump had literally popped up overnight, moved freely under her skin and was located under the breast tissue. All of which was consistent with what she'd found while madly searching for clues online. Everything suggested the tumor was probably benign and not likely cancerous.

"And then when I went in for a consultation, the breast oncologist gave me a fine needle aspiration and the entire needle filled with blood," Painter recalled. "So then I searched 'blood' plus 'breast' plus 'lump' and it came up angiosarcoma. And that was the first inclination that I had it and that it might be something really bad."

Indeed. Angiosarcoma is an exceedingly rare cancer diagnosed in about 300 people a year in the U.S. and it has a very poor prognosis. Most patients with the soft tissue sarcoma develop metastatic disease and have only a 50 percent chance of surviving more than 5 years.

Today, Painter is a breast angiosarcoma survivor turned advocate who leads the Angiosarcoma Project, a patient-partnered genomic sequencing research initiative of the Broad Institute of MIT, Harvard Cancer Center/Dana-Farber Cancer Institute, and cancer research catalyst Count Me In.

Launched in 2017, the Angiosarcoma Project enrolled 63 patients within a week at the website www.ascproject.org. Three years later, more than 500 individuals have joined the project, representing a large portion of all the patients with angiosarcoma in the U.S. and Canada. The patients are continuously engaged through most all social media channels, the website, and e-mail updates.

Patients who register in the Angiosarcoma Project are asked to donate their stored tumor samples, saliva samples, blood samples, medical records, and their voices. Whole exome genomic sequencing is performed on the germline, tumor, DNA, cell-free DNA samples, and blood, which along with a review of medical records has generated a clinically annotated database. The Broad Institute's genome platform is used for the analysis of the biospecimens.

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> *—Corrie Painter, PhD, Associate Director of Operations and Scientific Outreach for the Broad Institute*

Recently, results from a study of 50 tumors samples from patients enrolled in the Angiosarcoma Project were published in *Nature Medicine.* The researchers identified dozens of mutations, including enrichment of the PIK3CA gene predominantly in primary breast angiosarcoma, and also a potential causative factor and therapeutic rationale for head, neck, face, and scalp (HNFS) angiosarcoma (2020; doi: 10.1038/s41591-019-0749-z).

The discovery of the mutation of the PIK3CA gene in breast angiosarcoma suggests a therapeutic rationale, this time for the PI3 immune kinase inhibitor which blocks the PIK3CA pathway, Painter noted.

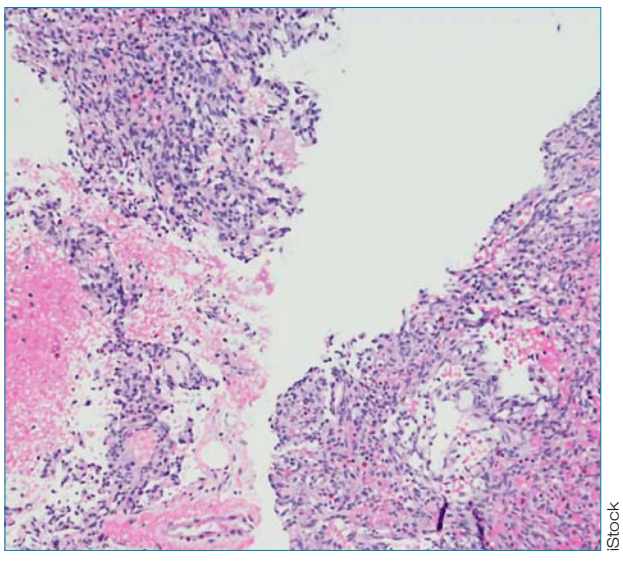
"PIK3CA is one of the most highly mutated genes in primary breast cancer, and so it is intriguing that about 30 percent of the people in our cohort who were sequenced for breast angiosarcoma had mutations in the same gene," she said. "Drugs already exist for treating patients with these types of mutations."

A second discovery revealed high tumor mutation burden (TMB) and UV damage in all patients with cutaneous angiosarcoma in the head, neck, and face region. The TMB is similar to cases of melanoma, which respond very well to immune checkpoint inhibitors, noted Painter, who is both Associate Director of Operations and Scientific Outreach for the Broad Institute and Associate Director of Count Me In.

CME/CNE Article

As the researchers suspected, a review of the medical records revealed that about a half-dozen patients had received immunotherapy previously in a compassionate care setting. Three patients who did not have HNFS angiosarcoma failed to respond to immunotherapy, while one patient with HNFS angiosarcoma had an adverse event upon receiving checkpoint inhibitors. Two other angiosarcoma patients with metastatic cancer of the HNFS region, however, had complete and durable responses in 2016 following off-label therapeutic use of the antibody to the programmed cell death-1 protein (anti-PD-1).

"Both patients actually had adverse events well after showing no evidence of disease. They were taken off the drug, but they remained disease-free the last time we looked at their medical record, which was earlier this year," Painter said. "Our numbers are small, so it doesn't mean that only patients with HNFS angiosarcoma will respond to checkpoint inhibition; it's just that those we evaluated did not. But it is a very exciting step forward."



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Proof of Principle

Angiosarcoma is aggressive cancer that develops in the walls of blood and lymph vessels and typically presents as a bruise-like lesion that keeps growing. It is most prevalent in the HNFS region, but can arise anywhere in the body. It has a high mortality rate and there is no standard of care.

Like most rare cancers, which actually account for about 25 percent of all tumors, a big obstacle to finding therapies for angiosarcoma has been the low rate of incidence coupled with a geographically widely dispersed patient population, making it difficult to study clinically in a meaningful way.

"Historically speaking, there are a small number of physicians who see the equivalent of a high number of angiosarcoma cases," said Brian Van Tine, MD, PhD, Associate Professor of Medicine, Division of Oncology, Section of Medical Oncology, at the Washington University School of Medicine in St. Louis, a co-author of the study. "So, you are dealing with a group of diseases, all called angiosarcoma, that are often diagnosed late. And then by the time it gets figured out, nobody has a strong sense of what to do until you get to one of the sarcoma centers."

Trying to find a patient support group was next to impossible as well, Painter remembers. "There were none. And it was very difficult to go through this so isolated and alone," she said. "Then one day I was on Facebook and I found three other angiosarcoma patients, and it just changed my life for the better."

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Seeing an opportunity to spare other patients from the same lonely experience while also advancing research into urgently needed therapies for rare cancers, Painter jumped at the chance to join the Broad Institute of MIT in 2015 with the mutual goal of developing patient-partnered genomic research initiatives.

"I wanted to find ways that we could build an infrastructure that would enable deeper and richer research across a variety of different cancers, including rare cancers like mine," she said. "And to do that, we really had to generate a lot of data and make it publically available for as many people as possible rather than contributing to data silos."

The first genomics research Painter was part of was the Metastatic Breast Cancer (MBC) Project, which launched in October 2015 and was built with an infrastructure that included a strong social media presence and the website www.mbcproject.org with input from patients and advocacy groups. The patient-partnered project was led by Nikhil Wagle, MD, an Institute member at the Broad Institute, a medical oncologist at Dana-Faber, Assistant Professor at Harvard Medical School, and Director of Count Me In.

The MBC Project was the culmination of about a year's worth of work with patients that have MBC," Painter said. "We asked them if they would help us think through conducting genomic research that also would capture their voice; we wanted to hear what they had been through, and we wanted to understand the context of their clinical experiences. And we also wanted to sequence both their normal DNA and tumor DNA. And when we asked, 'Will you help us do that?' many of them said, 'Yes.'"

The project was a very early success and it became obvious that it was going to work the very first year, Painter said. "We started releasing data shortly thereafter, and right away we began seeing people citing the data in their own research and using it in their own investigations, which was the point," she said.

"And so we were able to expand into other cancers and the first one was angiosarcoma," Painter continued. "We wanted to show proof of principle that you could take this infrastructure and point it at MBC, which is a much larger patient population, and then point that same infrastructure at an exceedingly rare patient population and still enable that patient community to climb on board and be counted.

"And we still keep them updated to this day," she added, referring to both projects. "Any time we make a discovery, we will alert them usually with an email and then also through social media. And we always offer to talk by phone if they have any questions about the study as well. So it is a deep partnership."

Taking Control of a Disease

Painter and her team have since used the social media-based infrastructure they developed to launch a number of other projects for patients with rare cancers, including metastatic prostate cancer, stomach and esophageal cancer, brain cancer, and most recently, osteosarcoma. Privacy, a potential hurdle to the success of the patient-partnered projects, is protected by the removal of any patient identifiers and a re-classification of unique demographic responses from the data prior to it being released publically to the greater sarcoma community on the cBioPortal.

"I think one of the truly brilliant parts of this is how they were able to get archival samples despite academic blockades to sharing samples, and how they got families involved," Van Tine offered. "They actually drove patient-partnered research and really picked angiosarcoma apart. They've discovered a lot of things that I think are really incredible and transforming, and that are launching clinical trials, which are now possible due to Dr. Painter's group."

In one new prospective study involving angiosarcoma patients at the Siteman Cancer Center in St. Louis, investigators, including Van Tine, are examining the efficacy of induction paclitaxel followed by concurrent chemoradiation therapy with paclitaxel prior to curative surgical resection in patients with head and neck cancer (NTC03921008).

Patients with metastatic angiosarcoma have responded to taxane therapy, Van Tine noted. He believes results from the study, along with results of other upcoming clinical trials involving patients with angiosarcomas, will provide insight into the origins of rare cancers and better direction for sarcoma physicians in advancing treatments. He gives a lot of credit for it to the Angiosarcoma Project and their patient partners.

"We wouldn't be doing this if they hadn't driven the volume [of patients], which we are humbled about," he said. "Because they did, we are actually able to conduct prospective trials. So, instead of talking about something seen in the last decade, we're prospectively establishing data that tells us where we're going to go and how we are going to make this better.

"They are just a wonderful data-driven group of patients who, led by a former patient, are transforming their disease by taking control of it," he added. "I think angiosarcoma may have met its match." OT

Chuck Holt is a contributing writer.

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Learning Objectives for This Month's Activity:

After participating in this activity, readers should be better able to: 1. Synthesize recent discoveries from the Angiosarcoma Project. 2. Identify characteristics of angiosarcoma and social media-based work on angiosarcoma and other rare cancers.

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