Mining DNA in Blood for Fast, Specific Information About Tumors


Abhijit Patel, MD, PhD

Immunotherapy may be the most promising development in cancer treatment in the last decade, but so far it is only effective for about 30 percent of patients. Testing for biomarkers can sometimes predict which patients will benefit, but current tests do not provide absolute proof of how a patient will respond.

"While many patients derive remarkable benefit from immunotherapy, it fails to help many others," said Abhijit Patel, MD, PhD, Associate Professor of Therapeutic Radiology, "so these patients waste time when they could have been receiving some other therapy instead. There's a lot of interest in developing biomarkers that can predict response. But the biomarkers we have aren't correct as often as we would like them to be."

The stakes are high. What if a patient for whom immunotherapy could be lifesaving gets disqualified from receiving it because of a falsely negative biomarker test? Or, what if a patient tests positive for the biomarker but doesn't respond to immunotherapy while the tumor continues to grow?

Clearly all of these scenarios are unsatisfactory. Adding to the uncertainty, says Dr. Patel, tumors respond differently to immunotherapy than to other therapies, leading to confusing results on CT scans. With chemotherapy, for instance, CT scans reveal fairly quickly whether a tumor is shrinking.

"But with immunotherapy," said Dr. Patel, "the shrinkage can take time, sometimes many months. And sometimes it looks bigger on a scan before it shrinks, because the immunotherapy can make the tumor swell at first. So on your first scan, maybe a month after your therapy, your tumor can actually look worse. That can be confusing. Do we throw in the towel and say immunotherapy isn't working, or do we wait another month or two to see if it shrinks? The scans aren't giving us clear-cut data as they do for other therapies, so immunotherapy presents a unique challenge in monitoring and predicting response."

Since scans can't reliably detect the early effects of immunotherapy, Dr. Patel and a team of scientists at Yale began looking for blood biomarkers that could. They settled on circulating tumor DNA (ctDNA), a byproduct of dying cells shed by a tumor into the bloodstream. They theorized that measuring changes in ctDNA could provide a quicker and more reliable assessment of immunotherapy efficacy than CT scans because the amount of ctDNA in the blood reflects how many cancer cells are dying. To test this idea, they studied a group of patients with non-small cell lung cancer who were receiving immunotherapy, and published their eye-opening findings last year [2018] in *Clinical Cancer Research*.

Their basic question: Can ctDNA detect whether immunotherapy is working more quickly and reliably than a scan can? By comparing the levels of a patient's ctDNA before and after treatment, clinicians had confirmation, on average, just 24.5 days after treatment started, compared to 72.5 days when using scans. In other words, even very early in the treatment, before a scan could detect shrinkage, a patient's ctDNA showed that immunotherapy was killing the cancer—a clear sign to clinicians and patients to continue the treatment.

"Those patients whose ctDNA levels showed a clear drop shortly after starting immunotherapy also did a lot better in terms of overall survival and progression-free survival," said Dr. Patel. "We eventually saw substantial shrinkage of their tumors on scans, and these patients benefitted from immunotherapy for a much longer duration." Conversely, measuring ctDNA also offered an early indication of when immunotherapy was not working.

In September 2018, Dr. Patel and a multidisciplinary team from Yale, Harvard, Rice, and Microsoft Research received a $2.6 million grant from the National Institutes of Health to develop an assay that will use ctDNA-screening to detect early-stage lung cancer, which kills an estimated 154,000 Americans each year.

"The impact of this, if it works, could be tremendous," said Dr. Patel. "It's widely known that if you detect most types of cancer early, outcomes will improve, because you can surgically remove or eradicate all of the cancer cells and have a higher probability of achieving a cure."

He expects his multidisciplinary group to have made substantial progress toward a lung cancer early detection test within the five-year period of the grant. But his ultimate goal is a "pan-cancer assay" that could detect early-stage cancers of all types through a blood test that looks for ctDNA, sometimes called a "liquid biopsy." The theory is that ctDNA contains evidence of mutations specific to each tumor, evidence not typically found in healthy people. If ctDNA was detected, said Dr. Patel, imagining this future, "You could say, 'This patient very likely has cancer, and the three most likely cancers are X, Y, or Z,' then you could do a CT scan or an MRI to further diagnose. Such early detection could save countless lives."