Treating Cancer No Matter Where It Occurs

New treatment approaches target tumors with shared characteristics, regardless of where they appear in the body.

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Cancer treatments are traditionally developed, tested and prescribed for tumors in specific parts of the body. Breast cancer, lung cancer, colon cancer, melanoma—drugs for each type of cancer go through their own clinical trials, are reviewed separately by the Food and Drug Administration (FDA) and have distinct pharmaceutical marketing programs.

But what if new therapies could be tested and approved based on shared characteristics of the cancer—regardless of where it develops in the body? A growing understanding of the genomics of cancer is starting to make this so-called tumor-agnostic approach a reality.

Targeted therapies work against cancers with specific characteristics, such as genetic mutations that enable tumors to grow faster. Precision medicine involves analyzing an individual's cancer to determine which therapies are most likely to work against it.

For example, breast cancer that carries a receptor called HER2 (human epidermal growth factor receptor 2) is susceptible to HER2-blocking drugs like Herceptin (trastuzumab), while lung cancer with EGFR (epidermal growth factor receptor) gene mutations can be treated with EGFR inhibitors like Iressa (gefitinib).

But the good news is, precision medicine may not need to be quite so precise.

A seemingly endless stream of new drugs are designed to block the activity of various tyrosine kinases, enzymes that play a role in cell division and blood vessel formation. Many tyrosine kinase mutations are seen across multiple different types of cancer. This also holds true for other molecules that enable tumors to grow and spread.

Immunotherapy, too, works across cancer types. Rather than targeting cancer directly, this type of treatment helps the immune system detect and destroy cancer cells.

Two PD-1 checkpoint inhibitors that take the brakes off T cells, Keytruda (pembrolizumab) and Opdivo (nivolumab), are already approved for several different types of cancer, including lung

cancer, bladder cancer, Hodgkin lymphoma and melanoma.

Checkpoint blockers can work very well, but they do so only for a subset of patients. If doctors were better able to identify and treat just those with susceptible tumors, this kind of treatment would be more successful.

Redesigning Clinical Trials

Most randomized clinical trials in oncology still test one experimental drug regimen at a time in patients with one type of cancer—or what experts assumed was one type of cancer but may actually involve multiple different disease processes.

This approach greatly multiplies the time and money required to evaluate new drugs. What's more, less prevalent cancer types often have to wait their turn after more common types—and sometimes get left out altogether.

But this is not the only way to test new cancer treatments.

Umbrella trials enroll people with a single type of cancer but treat them with different targeted drugs as determined by biomarkers. In the ongoing ALCHEMIST trial, for example, lung cancer patients are assigned to study arms testing either an EGFR inhibitor or an ALK (anaplastic lymphoma kinase) inhibitor, depending on which mutations are found in their tumors after surgery.

The opposite approach is known as a basket, or bucket, trial. Here, a single drug is tested in people with specific cancer characteristics or biomarkers, regardless of where tumors are located in the body. This can benefit patients and researchers alike by grouping together enough people with uncommon characteristics to allow for a statistically valid study.

Though initially developed and tested in people with one type of cancer at a time, Keytruda broke ground as the first approved treatment for cancer with specific genetic features, regardless of where it occurs in the body.

In May, the FDA approved Keytruda for treatment of solid tumors at any location with mismatch repair deficiency or microsatellite instability.. Tumors with a broken mismatch repair system are unable to fix DNA damage that can shut down cancer growth. These tumors have many mutations for T cells to recognize and high PD-1 expression, making them susceptible to drugs like Keytruda. Mismatch repair mutations are seen in many types of tumors, including almost 18 percent of advanced endometrial cancers and about 6 percent of metastatic colon cancers.

At first, mismatch repair mutations were identified in tumor samples from patients in trials testing Keytruda for different types of cancer; Merck researchers then conducted additional studies that specifically enrolled people with the mutations.

Across five studies in which 149 participants with 15 different cancer types took Keytruda, 40 percent showed complete or partial tumor shrinkage, and 78 percent of those had responses

lasting at least six months.

The recent FDA approval means that people with all types of cancer—not just those whose cancer is common enough to have been studied in a dedicated trial—are eligible to take Keytruda if they have these mutations. Although doctors are allowed to prescribe marketed drugs to anyone based on their clinical judgment, insurance usually covers only FDA-approved uses.

Starting From Scratch

The promising experimental drug larotrectinib is among the first to be tested from scratch in people with a specific tumor mutation anywhere in their body. It is also one of the first to be tested simultaneously in adults and children. Recent studies showed that three out of four treated patients responded to the drug.

“These findings embody the original promise of precision oncology: treating a patient based on the type of mutation, regardless of where the cancer originated,” said David Hyman, MD, from Memorial Sloan Kettering Cancer Center, who presented the study results at the 2017 American Society of Clinical Oncology annual meeting.

Together these three clinical trials included 43 adults and 12 children with 17 different types of advanced or metastatic cancer, including lung, colon, thyroid and breast cancers. About a third had two uncommon cancer types, salivary gland cancer and infantile fibrosarcoma. Some of the cancers were so rare that patients traveled from across the world to join the trial.

What they all had in common was a tumor mutation known as a tropomyosin receptor kinase (TRK) fusion. When a TRK gene in a cancer cell fuses with another gene, it acts as an “ignition switch” to turn on cancer growth, Hyman explained. Larotrectinib, being developed by Loxo Oncology, blocks TRK and halts cancer progression. Because TRK plays a minimal role in normal biological processes, blocking it is less likely to cause side effects.

Overall, 76 percent of study participants showed complete or partial tumor shrinkage in before-and-after scans. Some patients reported that their symptoms began to improve within days after starting treatment. Responses were good across all tumor types.

At the time of the presentation, more than 90 percent of responders were still doing well on treatment, including two children who saw their tumors shrink enough that they could undergo curative surgery, Hyman said. A few people with longer follow-up were still responding after one and a half to two years.

Another 12 percent of patients had stable disease (no worsening) while 12 percent experienced cancer progression. As often occurs with targeted therapy, six people who initially responded to larotrectinib later experienced disease progression, mostly because their cancer become resistant to the drug.

TRK fusion mutations are uncommon, occurring in only around 1 percent of all cancers. However,

they’re found in more than 90 percent of some rare cancers. More than 5,000 people in the United States are diagnosed with TRK fusion cancers each year, but because testing is limited this is likely an underestimate, according to Hyman.

“This really brings us into a new era where treatment is truly based on mutation, not location,” Sumanta Kumar Pal, MD, from City of Hope Cancer Center told reporters at the conference.

Although the new Keytruda indication and larotrectinib are relevant only for a small proportion of cancer patients, they may help usher in a new tumor-agnostic treatment paradigm.

A growing number of experts suggest that more people with cancer should receive genetic testing to find those individuals who could benefit from new targeted therapies. But questions remain about how the cost of these tests will be covered and how best to treat people found to have no “actionable” biomarkers.

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