How New Drugs Become Available to More Patients

Filling in the unknowns on the balance between risk and benefit

March 16, 2018 By Susan Keown

Change is coming in cancer treatment. Last year, the U.S. Food and Drug Administration approved its first-ever engineered cell therapies for cancer, which involve genetically reprogramming patients' T cells to aim the power of their immune systems squarely at their cancers.

Both of these new therapies are approved only for people with certain advanced cancers who have been failed by multiple conventional treatments, like chemotherapy. Some people may wonder: If these treatments are so promising, why aren't they available for more patients, including those who have just been diagnosed?

The short answer: We are not yet sure if the benefit outweighs the risk for patients at earlier stages of disease.

If these new treatments run a course anything like many other cancer therapies, however, they may eventually move up to the frontlines of therapy. What would it take for that to happen?

Let's take a look at the longer answer: how research can fill in the unknowns, shift the balance of evidence and make a new therapy available to more patients.

Medical research's delicate balance: risk vs. benefit

We do medical research to come up with ways to prevent and treat diseases that are better than what we already have. All medical research—and the FDA approval process built on the results of that research—is governed by the delicate balancing act between an experimental therapy's potential risk and potential benefits in comparison to the current best standard treatment.

When in-human research on a potential new therapy begins, both sides of that balance are filled with unknowns. Although scientists who develop new treatments do everything they can to understand in laboratory models what the potential risks of a new strategy might be—and they must submit this evidence to the FDA to get approval to move forward with a first-in-human trial—no one knows exactly how a new drug will act in a person until it is actually put into a person.

That's why a newly developed experimental therapy typically makes its debut in a patient who has limited treatment options for a life-threatening disease. For those with few options—situations in which there is no current good standard of care against which to compare a new therapy—the tipping point of the risk-benefit equilibrium can shift. The unknowns of an experimental therapy may thus become acceptable, both to the regulatory bodies who greenlight new trials and to the patients considering whether to enroll. In comparison, when there are good options for treatment, the ethical hurdle and scientific burden of proof needed to surmount it are both much higher.

Tipping the scales of evidence

As more trial participants receive a new therapy, researchers rack up more evidence about what's on both sides of that critical risk-benefit balance. If the earliest clinical trials show that a new approach is safe, researchers begin to look at whether it could offer more benefit, less risk, or both compared to existing treatments. Gradually the equilibrium can move toward allowing studies in patients who are not quite yet at the end of the line, whose disease is not quite so advanced. So, for many new drugs, that means a stepwise approach: First comes approval in late-stage disease, then as new trials open for individuals with earlier-stage disease, approvals for wider ranges of patients may follow.

One example is the path being taken by immune-modulating drugs called checkpoint inhibitors. They work by interfering in the braking systems cancer cells exploit to tamp down a patient's natural cancer-fighting immune response. The FDA first approved checkpoint inhibitors for patients with late-stage, treatment-resistant disease. Now these drugs are being tested in patients with earlier-stage cancers, reporting promising results and, in some cases (e.g., pembrolizumab [Keytruda]) winning approvals for earlier use.

This process can take years. It can take hundreds of patient enrollees and long follow-up to gather the type of rigorous evidence on efficacy and safety of a new approach compared to standard of care that is needed for an FDA approval. Other practical and scientific matters can affect timing as well, such as the company's interest in pursuing additional development of the drug, the rate at which participants enroll in trials and how long it takes for the drug's effects to become apparent.

For example, a targeted cancer drug called rituximab (Rituxan) was first approved in the U.S. in 1997 for treating certain patients with advanced non-Hodgkin lymphoma. It was nine years until the drug was approved by the FDA in the treatment of newly diagnosed patients with this disease. The second approval was based on three government- or industry-sponsored clinical trials, which enrolled more than 1,800 patients around the world—a significant undertaking.

Of course, in any given case, the evidence accruing from trials may point to a different answer: that the new thing isn't better than what we've already got for newly diagnosed or lower-risk patients.

So what about CAR T-cell therapy?

For new genetically engineered cancer therapies called CAR T-cell therapies, whether they could

be used at an earlier stage of treatment before the situation becomes dire "is a common question," said CAR T-cell expert Cameron Turtle, MBBS, PhD, FRACP, FRCPA, from his office at Fred Hutchinson Cancer Research Center.

Those studies haven't started yet. Researchers are first working to determine whether the therapies' potential toxic effects can be controlled, what proportion of patients get responses, and what the duration of those responses is, he said. If many patients' advanced cancers can be put into complete remission for the rest of their lives with relatively few side effects, that would tilt the risk-benefit scales toward kicking off studies of CAR T-cell products in patients with less-advanced disease.

At the same time, he noted, "there's a very different balance depending on the disease." T-cell therapies may never be used as a frontline therapy for some cancers that are usually cured with more conventional drugs, like chemotherapy. For such cancers, a T-cell therapy might make most sense only in high-risk patients or when chemotherapy has failed, he said. It would take many more years of evidence from clinical trials to know how T-cell therapies might best be incorporated into standards of care for different types of cancers.

A different balance: public health vs. individual need

It's not only the risks and benefits for individual patients that must be balanced in the process of bringing new drugs to people. There's also the delicate equilibrium between the well-being of the population as a whole and the urgent needs of a single patient who has no time to waste.

"Every part of the system, including the FDA, recognizes how much of a struggle it is to balance these needs: critical patient needs, and a responsibility for their mandate to protect public health, protect patient safety," said Jennifer Davies, a regulatory affairs associate at Fred Hutch who manages FDA-related matters for the institution's clinical researchers.

Patients nearing the end of their disease course simply have no time for evidence to build toward an FDA approval to treat people like them (if one ever comes) or for a clinical trial to open in which they could enroll. For such people, U.S. regulations allow for workarounds.

If there is no other good option available, doctors are allowed to prescribe an FDA-approved drug "off-label," meaning for patients or diseases the drug has not been proven to safely help. Off-label prescribing is common, especially in certain diseases and patient populations, such as pediatrics.

U.S. law also provides a means for a doctor to work with a drug manufacturer to gain access to an unproven, experimental medication to treat a patient with serious illness and no other options, via the FDA's expanded access program, also known as the "compassionate use exemption." Patients who are treated with an experimental medication under an expanded access protocol receive certain protections, including oversight by an institution's ethics board and the FDA. The FDA reports that it authorizes more than 99 percent of expanded access requests, and in late 2016, the regulations around expanded access were tweaked to make this process easier for patients and doctors to navigate.

These options, however, aren't always practical. For one, insurance companies typically don't cover treatment with a non-approved therapy, and oncology drugs can cost thousands of dollars (hundreds of thousands in the case of the first two approved CAR T-cell products). Experimental drugs are sometimes provided free of charge by the drug company through the expanded access program, but not always, especially in the case of products that are very expensive to make.

These practices become less feasible in the case of drugs that require specialized facilities and highly trained staff to administer, as genetically engineered T-cell therapies currently do.

So how these workarounds would apply to this new generation of therapy isn't clear, Davies said.

But what is clear, she said, is that no matter where the balance ultimately settles, cancer treatment will never be the same. "We're seeing medical precedents being set in front of our noses," she said.

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