CAN WE AFFORD THE WAR ON CANCER?

Immunotherapy vaccines could extend survival in a handful of cancers. But personalizing treatment, payers argue, is not sustainable. Where should the line be drawn?

BY ED SILVERMAN

Two years ago, the U.S. Food and Drug Administration took a step that some thought would never occur — it approved the sipuleucel-T (Provenge) vaccine for late-stage prostate cancer. The move came after a protracted episode involving allegations of conflicts of interest among a pair of FDA advisory committee members who reviewed the treatment and convinced agency officials to withhold approval — even after an FDA panel recommended approval.

The maneuver, said to be motivated by questions about efficacy, subsequently generated probes, lawsuits, and patient protests. By the time Provenge was approved in April 2010, its maker, Dendreon, generated still more heat, thanks to Provenge's $93,000 price tag and concern among physicians who were expected to pay the full cost while awaiting reimbursement.

Then another debate emerged over differences between a statistical analysis plan submitted to the FDA and a key clinical study. Amid this roller-coaster ride, the manufacturer closed a plant, cut numerous jobs, and replaced its chief executive officer — hardly the expected outcome for a product that was touted as a paradigm shift that could set the stage for other oncology vaccines. Instead, the episode has raised doubts about whether extending a life by 4.1 months is worth the price of Provenge. It has also prompted larger questions about the underlying technology and the need to develop more vaccines.

Provenge is made by culturing a patient's immune cells with a recombinant antigen. The individualized product is then infused back into the patient, activating the immune system to target and attack the cancer. This "immunotherapy" underscores the move toward personalized medicine, but the high price also has served to intensify debate about the ability of the healthcare system to pay for such vaccines.

At what cost?

"I have to give a company credit where it's due. Dendreon was the first to get an immunotherapy vaccine approved, and it represents a generation of [vaccine] technology that is in the later stages of clinical development and may become more commercially palatable," says Mara Goldstein, senior biotechnology analyst with the financial services firm Cantor Fitzgerald. "But Provenge has also raised some eyebrows.

"Society has to make decisions around questions of cost and survival," Goldstein continues. "This is what I call the infrastructure perspective. What makes immunotherapy very expensive is that it's not scalable. With Provenge, everything is individual to the patient. Theoretically, by making immunotherapy scalable, costs should be reduced. But, if the best way to treat patients really is to personalize treatment, I don't know if the current health system can bear it."

"Vaccine-based immunotherapy should yield a more potent and durable response, leading to a significantly higher rate for overall survival," says James Merson, PhD, head of Pfizer's Vaccines Research West.

This is a conversation that is certain to last for some time given the turmoil over healthcare costs and the need to develop more effective treatments and to make them affordable.

The issue of cost underscores a crucial dilemma: satisfying patient expectations that are fueled by scientific advances even as hopes and theories are tempered by limited resources. It also encompasses questions about the willingness of drug makers to commit the resources required to develop and market oncology vaccines; whether such vaccines can be developed successfully for

small patient populations; and the ethics of prolonging life by what may be only a few months as healthcare dollars are stretched thinner every day.

"How are we going to pay for this innovation in order to continue the race against cancer?" asks Douglas Paul, PharmD, vice president and partner at Medical Marketing Economics, a consulting firm that specializes in evaluating effectiveness. "And as you get into small populations, you start to ask tough questions: What's the obligation to the cancer community and shareholders? How do I balance this knowing there's a huge risk? How is this drug financed? These are difficult questions to answer."

"I think we're headed toward a period of ambiguity," says Paul's partner, Kevin Patterson. "Expenses are rising. There's more pressure against charging high prices, so it becomes difficult to go after opportunities with high risks — is the reward justified or do you go after a lower threshold? You have to look at the competitive landscape, the reimbursement issues, and the advancements in different areas of science. It's hard to know what it's all going to look like in, say, 10 years."

More vaccines coming

Despite such uncertainty, there is a lot of research taking place. Pharmaceutical Research and Manufacturers of America, the industry trade group for large drug makers, earlier this year estimated that no fewer than 102 vaccines are currently under development to treat a variety of cancers, including pancreatic, lung, and breast tumors, and glioblastoma multiforme, the most common — and also very aggressive — form of brain cancer.

The increased research reflects the possibility of profits. The global value of the cancer vaccine market was nearly $1.7 billion in 2010 and is estimated to reach $7.1 billion by 2018, which represents a compounded annual growth rate of 20 percent, according to GlobalData Healthcare, a market research firm. The therapeutics portion represents the largest slice, growing from $48 million in 2010 to more than $4.8 billion by the end of 2018 — a compounded annual growth rate of 78 percent.

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"There are plenty in the pipeline," says oncology analyst Cheryl Strelko Gradziel, PhD, at GlobalData Healthcare. "People are in different camps about whether vaccines are really going to make a difference, but it's definitely not stopping companies from trying. And you know that quality of life is very important to cancer patients, so if you can find something like a vaccine that, theoretically, has minimal side effects but also does the same [thing] as chemotherapy, it could be awesome."

Off-the-shelf vaccines

For now, though, barriers exist. One issue is the direction of research and development, which will determine the best approach for turning out vaccines and the best potential combinations of therapy and sequencing for successful treatment, says John Sampson, MD, PhD, professor of surgery and immunology and associate deputy director of the Preston Robert Tisch Brain Tumor Center at Duke University Medical Center. "Now that it's clear that immunotherapy works, there will be a lot more work on targeting antigens and boosting immune response and promoting cell signals," says Sampson, who also has intellectual property rights to technology used by Celldex Therapeutics to develop cancer vaccines. "But everything depends on future results. I think cancer vaccines need to move to the off-the-shelf mode. Right now, oncologists find that a vaccine such as Provenge is very expensive and cumbersome."

What exactly is an off-the-shelf vaccine? As the phrase implies, it's a vaccine that a physician can administer to most any patient without requiring the sort of complicated process by which Provenge is made and delivered. In short, the concept relies less on personalized medicine and more on conventional thinking in which a manufacturer develops a vaccine for a large patient population.

As more knowledge is gained about tackling the immune system, however, developing vaccines for smaller patient populations with less common forms of cancer should become possible. But it will require a fundamental change in the approach to developing vaccines and a heavier reliance on immunotherapy, according to James Merson, PhD, senior vice president and head of Vaccines Research West at Pfizer.

"Detectable cancer is a product of an immune system that is unable to prevent the cancer from arising — that's quite important. If one can reset the immune system to recognize the cancer as foreign, even for weak tumor antigens, then the immune system has a greater chance of either

preventing metastases or tumors from occurring, debulking tumors, or both," Merson says. But therapeutic vaccines, per se, will not work in broad oncology populations, Merson adds. "They haven't for 20 years and are unlikely to work in the majority of cancer patients. When we talk about oncology vaccines, we're really talking about vaccine-based immunotherapy, which addresses the immune blockade afforded by the tumor microenvironment that has become increasingly understood over the past decade."

The attraction, Merson explains, is that vaccine-based immunotherapy should yield a more potent and durable response, leading to a significantly higher rate for overall survival — which means a greater level of efficacy that offers a higher quality of life. This is different from the approach taken by Dendreon to develop Provenge, Merson notes, which he likens to "adoptive T-cell therapy." "We're talking about a different process than incubating with an individual's T cells and asking them [the T cells] to remain active in the tumor microenvironment when re-infused back into the patient."

Merson cautions that it may be several years before any major clinical breakthroughs occur. In part, that reflects strategic thinking among pharmaceutical and biotechnology companies, some of which have devoted themselves to this area of research.

"But I think it's challenging for the smaller companies, because they don't have all the components to address the natural immune-response self-regulation that a vaccine-induced immune response has to overcome," says Merson. "Big pharma has some of the agents, so there will be an opportunity to partner these with the most promising vaccines."

Only in the past few years has this thinking caught on; big pharma has been reticent to exploit immunology to manage chronic disease, Merson explains. In fact, he says, "it's been a bit of a backwater." Now, however, more large drug makers are undertaking projects that have been made possible by the pioneering work of many scientists and clinicians around the world.

Merson acknowledges that attention is focused on the biggest cancer populations, but adds that "there are plenty of smaller cancers where we can apply our toolkit over time."

Personalize or not?

But which cancers to target? Given that more therapies exist for only a few tumors, one health policy expert maintains that drug makers and biotechs should focus on vaccines that combat cancers where the need for any sort of treatment is greatest. Instead, the biopharmaceutical industry is emphasizing research that targets the largest patient populations.

At what point do a few more months of life become justified when healthcare is increasingly expensive? And who should decide?

"We believe that manufacturers are responding more to the signal of large markets," says Matthew M. Davis, MD, associate professor of adult medicine and pediatrics and associate professor of public policy at the Gerald R. Ford School of Public Policy, University of Michigan. "Ask yourself: Why is it that the first therapeutic cancer vaccine available was for treating prostate cancer?"

The premise, says Davis, is that a new vaccine is most effective and has maximum market potential when two conditions are met: it is for an ailment that has more, rather than fewer, patients and it fills a therapeutic need that is not currently being met by other available options. "But if I were a payer, I'd be concerned that such a vaccine may not fill a need in my plan, unless it is substantially less toxic than available alternatives."

This premise was discussed in a commentary Davis coauthored and published in *JAMA in* 2011* in which the annual incidence and 5-year survival rates of 23 different cancers were plotted in a chart. Three cancers — lung cancer, pancreatic cancer, and leukemia — showed up in what were called the "high-burden target profile." At first blush, Davis says, the interpretation might be that research and development should be focused on creating therapeutic vaccines for these cancers. But, Davis argues, this approach has limitations. How so? There can be differing views on thresholds for high incidence rates and effective treatment alternatives, Davis says. And these cancers include many subtypes with differing incidence or survival rates and, therefore, different prospects for treatment success. Also, scientific variables may hinder successful vaccine development "for otherwise appealing targets."

"There is so much creative energy going into new immunotherapies, and there's potential for a tremendous effect on cancer in the next decade," says Davis. "But the effect will be greater if we collectively aim for cancers that have an optimal combination of numbers and need. A company that makes decisions based solely on the number of new diagnoses each year acts at its own peril, because it may not consider other therapies that are accepted and in use for that cancer."

* Davis MM, Dayoub, EJ. *JAMA*. 2011; 305: 2343–2344.

Such views underscore the growing tension between the use of technologies that yield an off-the-shelf approach and the trend toward more personalized medicine.

Scientific advances may make it possible to produce effective oncology vaccines by pursuing immunotherapy. But some say the business model to support treatments for small patient populations will require drug developers, investors, payers, and physicians to make difficult choices. And that would lead to higher costs and higher prices.

For some, the answer may lie in relying on biomarkers to more readily identify the appropriate population for a given vaccine. This approach could provide incentives for those drug makers that may be able to develop a niche where there is less competition and, therefore, more opportunity to pursue pricing that yields a desired return on investment. This approach could also be applied to subsets of populations with a particular type of cancer.

"At first, you'll see interest in developing vaccines for the biggest markets," says GlobalData's Gradziel.

"These niche indications will prove attractive because it will be hard to demand premium pricing in crowded markets. So there will be more promise in smaller markets. What you really need to make that happen is specific markers. I think genetic testing or some kind of testing to look at protein expression levels will help [industry] figure out better targets for immunotherapies."

The goal, of course, is to develop therapeutic vaccines that sufficiently extend life at a cost that the system can sustain. But the current reality is more complicated.

Despite talk of immunotherapy, biomarkers, and off-the-shelf technology, physicians and patients will likely find themselves relying on treatments that carry high prices and offer limited survival benefits — at least for the near term. This may be especially true for cancers that are not the most common.

"In a small population, you still have all the costs associated with bringing a drug to market. So you get to a point where there's a trade-off," says Paul, at Medical Marketing Economics. And decisions have to be made in terms of opportunity costs, he adds. "The issue is framed by competitive alternatives and relative values. A few months of additional survival has been judged to be significant enough to say there's a difference in products. There's a long road of incremental benefit ahead."

As targeted populations get smaller and smaller, says Kevin Patterson, at Medical Marketing Economics, it will become more difficult to build a commercialization case. "Even if the science makes therapy more effective, you'll have new and different dynamics. So I see continued pressure on payers and the finite money supply. It's important that innovation be rewarded, but at the same time, we need appropriate lifecycle management. And we're going to need better outcomes to justify pricing."

The ethics of cancer care

Amid this widening conversation about scientific approaches, targeted populations, and outcomes, a vexing ethical issue arises — at what point does a few months' additional life become justified when healthcare is increasingly expensive? Should there be a no-holds-barred approach to paying for an expensive vaccine because a family wants to extend a relative's life as long as possible? If not, how should cutoffs be decided — and who should do it?

"It's a huge trap. We don't have the kind of healthcare system that allows us to deal with this issue," says Daniel Callahan, PhD, president emeritus of the Hastings Center, a bioethics institute, and author of *The Roots of Bioethics: Health, Progress, Technology, Death*. "If we spend $100,000 on a drug that doesn't give you a lot of survival time, what's the opportunity cost? Unfortunately, we're in no position to make a calculation.

"There's a huge resistance to allowing cost to be taken into account. Many physicians don't like to talk to patients about costs, and nothing forces them to do so. So we're stuck with a difficult problem. And if you really want to deal with cost, then you have to stand in the way of individuals and families and what they want and what may help them. No one wants to get into that discussion. But what may seem perfectly valuable to individuals may be a disaster for the healthcare system.

"Some people may be willing to bankrupt themselves," Callahan continues. "As for drug companies, they may not have to sell a lot [of drugs] to make a lot of money. But this also puts insurers in a difficult situation. If a $100,000-a-year vaccine gives you an extra year or two of life, how can you turn it down?"

Callahan sums up what he calls "a hype of hope and dramatic breakthroughs." In the past, he says, innovative medicine has accepted no limits and no boundaries. "It's like exploring outer space — you can keep going further. We're finding expensive ways to keep sick people alive a long time. And we have to think about what medicine is all about and what is best for society."

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