INFERENTIAL FOCUS

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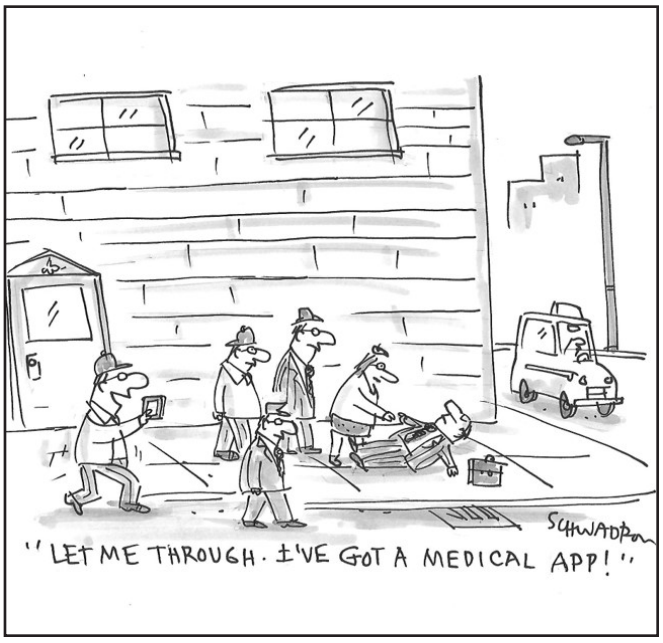
Healthcare

IMMUNOTHERAPY AND OTHER LEAPS IN CANCER CARE



Last year, former President Jimmy Carter had a surprising announcement. His late-stage metastatic melanoma, which had found its way into his liver and brain, had gone into remission. This March he concluded his treatment. Carter had found his way to a relatively new drug still in trials for various forms of cancer. The drug, pembrolizumab, functions as an **immunotherapy**. In such therapies, a patient's own immune system becomes the primary weapon against cancer, rather than debilitating radiation or chemotherapy. Surprise results like Carter's are becoming more common lately, as various new pathways to treating cancer gain traction. Have we reached an inflection point in cancer treatment?

TAKEAWAYS

- In recent months, a variety of new treatments for cancer have shown remarkable progress, even in cases where all traditional treatments failed.
- The most elegant of these new treatments involves a variety of approaches to immunotherapy, harnessing the body's own immune system to attack and kill cancer, rather than using radiation or chemotherapy.
- Traditional and even forgotten approaches to cancer treatment are also being revisited and showing promise.

IMPLICATIONS

- The next few years may see a marked uptick in human trials for new cancer treatments.
- "Surprise" recoveries, such as President Jimmy Carter's stage-4 cancer remission, may become more routine, prolonging lives.
- Healthcare costs for individual cancer patients rise with the approval of new treatments, and political questions emerge over what to cover. The government invests in cancer-prevention education.

The Targeted Approach to Cancer Therapy

In cancer, the "biological clocks" of cells go haywire and replicate *ad infinitum*, creating cancerous cells and deadly tissue damage. For much of the past 60 years, treatment of this disease has involved killing the cancerous cells with two somewhat blunt instruments, blasting them with radiation and/or poisoning them with toxic chemotherapies. The problem with those treatments is that, in addition to killing the cancerous cells, radiation kills or compromises healthy tissue and/or blood cells, and both radiation and chemotherapy cause various debilitating side effects, including nausea, fatigue and malaise, that hinder the patient's overall wellbeing.

In the past few years, an understanding of how cancer operates at the genetic and molecular levels has opened the door to several new forms of therapy. In an issue of *inFocus* earlier this year, we looked at how gene-editing capabilities have been accelerating in the past few years, in particular due to the advent of CRISPR as a tool for editing DNA. We were therefore struck by a related fact: Sixty-four percent of gene therapy studies since 1989 have focused on cancer. In fact, between 2010 and 2014, the FDA approved 37 cancer drugs, up from 19 approvals in the five years prior. The recent success of a variety of techniques to fight cancer suggests we are at a major inflection point in how cancer is treated and perhaps even cured. (*Foreign Policy,* 4/16; *New Scientist,* 4/18/15)

The new genetic and molecular understanding of cancer is enabling therapies that are precise and targeted, particularly immunotherapy. There are currently 3,400 immunotherapy-oriented cancer-treatment trials under way in the U.S. In studies of people with certain types of leukemia and lymphomas, where the patients did not respond to any other kinds of treatment, immunotherapies have cleared the cancer in up to 80 percent of the patients. In clinical trials for a new immunotherapy for a highly aggressive form of leukemia, 90 percent of patients enjoyed a complete remission. (*Scientific American*, 4/16)

Researchers have discovered that all cancer cells have biological markers on the surface that the immune system can be triggered to home in on and destroy. Normally, cancer evades such immune-system detection by producing another biological marker that tells the immune system, "Move along, there's nothing wrong here!" Deactivating that marker is one way to get the immune system back on task, to kill cancer. Pembrolizumab, the drug used to treat President Carter, is one such therapy that deactivates the marker. Use of this technique, in combination with other therapies, has been shown to have a tumor-shrinking effect in almost 60 percent of patients. (*Guardian Weekly*, 3/18/16; *New Scientist,* 3/5/16)

While the above approach involves disabling cancer's biological camouflage using a drug, another approach involves engineering immune system cells known as T cells so that they are especially well adapted to finding cancer, by giving them a receptor protein on their surface that can identify a corresponding protein on the surface of cancer cells – allowing T cells to identify and then kill the cancer. Doctors can extract a patient's own blood cells and then isolate cancer-fighting T cells from the blood. These cells can be genetically modified to more specifically identify and target cancerous cells that are marked with unique surface proteins. The modified cells are duplicated and injected back into the patient's body as a hyper-personalized form of treatment – the patient's own amped-up immune system does the attack. T cells can also be borrowed from a healthy donor, modified and given to hundreds of patients. Normally, a donated T cell would be seen as "foreign" by a recipient patient and rejected much in the way donated organs can be rejected by the recipient's body. But now, researchers can actually alter the genetics of the donated T cells, disabling a gene that will identify them as foreign to the recipient's body. (*New Scientist*, 11/5/15; *Time*, 4/4/16)

The Long-Lasting Potential of Immunotherapy

In another immunotherapy approach, scientists have engineered cells from a patient's own immune system to fight blood cancers in a treatment called CAR-T cell therapy. The therapy involves engineering a particular kind of immune cell, known as memory T cells, to target specific forms of cancer. The T cells are engineered to track down cancerous cells in the body and kill them. In preliminary trials, such CAR-T cell therapy eliminated cancer in 27 out of 29 patients with acute lymphoblastic leukemia, for whom other conventional treatments had failed. The therapy also dissolved tumors in six out of seven patients in whom the cancer had spread from the bone marrow to other parts of the body. Only a few hundred to a few thousand of the memory T cells

were needed to shrink the tumors. Unlike conventional treatments, these memory T cells stay in the body for at least 14 years after the patient has gone into remission, much like the antibodies for a disease like chicken pox stay in the body for years to prevent a future infection. Therefore, if the cancer returns, the memory T cells might be able to attack and clear the cancer before it gains any traction in the body again. (*Science News*, 3/5/16)

In a similar vein, researchers are creating something called a dendritic cell vaccine, by mixing human dendritic cells with cancer proteins in the lab. This creates dendritic cells that seek out and destroy cancer cells. When injected in the body, those dendritic cells recognize and target the cancer for years to come. (*Scientific American*, 4/16)

Other "New" (Sometimes Old) Approaches

While immunotherapy is one way to attack and kill cancer in a more targeted and refined way than chemotherapy or radiation, scientists are also exploring new ways to update old approaches:

• Building on a form of therapy first used over 100 years ago, but which fell out of fashion, researchers are re-exploring the idea of injecting cancer patients with certain bacteria that home in on cancerous cells. The bacteria not only infect and injure the cancer cells but also draw the body's own immune system to the cancer location as part of a double-whammy attack, while sparing other parts of the body that remain healthy. Recent trials of this updated and modified nineteenth-century treatment are showing positive results.

• Patients with aggressive skin cancer have been successfully treated for the first time with "virotherapy," in which a virus is programmed in the lab with a capability to attack and kill cancer cells. Such a virus can find cancer wherever it is hiding in the body, an example being of cancer that has metastasized and is located in dozens of small pockets that would otherwise be hard to detect and treat.

• In traditional cancer therapy, medicines are chosen based on what part of the body the cancer first emerged in. But now, doctors have a new approach: identifying which genetic mutations caused the cancer, regardless of where it appeared, and using the drugs that best treat those mutations anywhere in the body. That has been possible only recently, with the falling cost of genetic tests.

• Last year, a federally funded national program began screening tumors in thousands of patients to see which might be attacked by any of a dozen new drugs, a so-called "basket study" that tries many approaches at once to see what works.

• Traditional chemotherapy is undergoing a reassessment and adjustment that may improve its use. A new technique has been demonstrated in mice which suggests that the dose of chemotherapy should be ratcheted down as therapy progresses so that some of the cancer cells actually survive. Those surviving cancer cells can keep chemotherapy-resistant cells in check, which prevents a reemergence of a tumor for a longer period of time than simply trying to kill the entire tumor off does. (*Guardian Weekly,* 6/5/15; *New York Times*, 2/25/15; *New Scientist*, 3/5/16; *Discover,* 4/16)

In early June, Vice President Biden announced the launch of a first-of-its-kind, open-access cancer database, the Genomic Data Commons, to allow researchers to easily access the work done before them and to better understand the disease. The database contains the raw genomic and clinical data for 12,000 patients and includes both a detailed molecular makeup of cancers as well as which treatments were used and how patients responded. During the announcement, the Vice President also called for an overhaul in how the nation does clinical trials, in the way scientists collaborate in different disciplines and in the current "cult of the individual" research model, suggesting a move toward team science. The database will bring together work done thus far in the variety of new treatment possibilities outlined in this *inFocus* and will likely help push treatments forward as genomic science advances. New methods suggest we are at a major inflection point in the fight against cancer. (*Washington Post*, 6/6/16)