The New York Times | http://nyti.ms/2ap8pHr

Harnessing the Immune System to Fight Cancer

New drugs and methods of altering a patient's own immune cells are helping some cancer patients — but not all — even when standard treatments fail.

By DENISE GRADY JULY 30, 2016

Steve Cara expected to sail through the routine medical tests required to increase his life insurance in October 2014. But the results were devastating. He had lung cancer, at age 53. It had begun to spread, and doctors told him it was inoperable.

A few years ago, they would have suggested chemotherapy. Instead, his oncologist, Dr. Matthew D. Hellmann of Memorial Sloan Kettering Cancer Center in New York, recommended an experimental treatment: immunotherapy. Rather than attacking the cancer directly, as chemo does, immunotherapy tries to rally the patient's own immune system to fight the disease.

Uncertain, Mr. Cara sought a second opinion. A doctor at another major hospital read his scans and pathology report, then asked what Dr. Hellmann had advised. When the doctor heard the answer, Mr. Cara recalled, "he closed up the folder, handed it back to me and said, 'Run back there as fast as you can.'"

Many others are racing down the same path. Harnessing the immune system to fight cancer, long a medical dream, is becoming a reality. Remarkable stories of tumors melting away and terminal illnesses going into remissions that last years — backed by solid data — have led to an explosion of interest and billions of dollars of

investments in the rapidly growing field of immunotherapy. Pharmaceutical companies, philanthropists and the federal government's "cancer moonshot" program are pouring money into developing treatments. Medical conferences on the topic are packed.

All this has brought new optimism to cancer doctors — a sense that they have begun tapping into a force of nature, the medical equivalent of splitting the atom.

"This is a fundamental change in the way that we think about cancer therapy," said Dr. Jedd Wolchok, chief of melanoma and immunotherapeutics services at Memorial Sloan Kettering.

Hundreds of clinical trials involving immunotherapy, alone or combined with other treatments, are underway for nearly every type of cancer. "People are asking, waiting, pleading to get into these trials," said Dr. Arlene Siefker-Radtke, an oncologist at the University of Texas M.D. Anderson Cancer Center in Houston, who specializes in bladder cancer.

The immune system — a network of cells, tissues and biochemicals that they secrete — defends the body against viruses, bacteria and other invaders. But cancer often finds ways to hide from the immune system or block its ability to fight. Immunotherapy tries to help the immune system recognize cancer as a threat, and attack it.

Doctors tried a primitive version of immunotherapy against cancer more than 100 years ago. It sometimes worked remarkably well, but often did not, and they did not understand why. Eventually, radiation and chemotherapy eclipsed it.

Researchers are now focused on two promising types of immunotherapy. One creates a new, individualized treatment for each patient by removing some of the person's immune cells, altering them genetically to kill cancer and then infusing them back into the bloodstream. This treatment has produced long remissions in a few hundred children and adults with deadly forms of leukemia or lymphoma for whom standard treatments had failed.

The second approach, far more widely used and the one Mr. Cara tried, involves mass-produced drugs that do not have to be tailored to each patient. The drugs free immune cells to fight cancer by blocking a mechanism — called a checkpoint — that cancer uses to shut down the immune system.

These drugs, called checkpoint inhibitors, have been approved by the Food and Drug Administration to treat advanced melanoma, Hodgkin's lymphoma and cancers of the lung, kidney and bladder. More drugs in this class are in the pipeline. Patients are clamoring for checkpoint drugs, including one, Keytruda, known to many as "that Jimmy Carter drug" which, combined with surgery and radiation, has left the former president with no sign of recurrence even though melanoma had spread to his liver and brain.

Checkpoint inhibitors have become an important option for people like Mr. Cara, with advanced lung cancer.

"We can say in all honesty to patients, that while we can't tell them we can cure metastatic lung cancer right now, we can tell them there's real hope that they can live for years, and for a lot of patients many years, which really is a complete game-changer," said Dr. John V. Heymach, a lung cancer specialist and chairman of thoracic/head and neck medical oncology at M.D. Anderson.

Yet for all the promise and excitement, the fact is that so far, immunotherapy has worked in only a minority of patients, and researchers are struggling to find out why. They know they have their hands on an extraordinarily powerful tool, but they cannot fully understand or control it yet.

One Patient's Story

Mr. Cara, an apparel industry executive from Bridgewater, N.J., had non-small-cell lung cancer, the most common form of the disease. The diagnosis shattered what had been an idyllic life: a happy marriage, sons in college, a successful career, a beautiful home, regular vacations, plenty of golf.

In December 2014, he began treatment with two checkpoint inhibitors. They cost about $150,000 a year, but as a study subject he did not have to pay.

These medicines work on killer T-cells, white blood cells that are often described as the soldiers of the immune system. T-cells are so fierce that they have built-in brakes — the so-called checkpoints — to shut them down and keep them from attacking normal tissue, which could result in autoimmune disorders like Crohn's disease, lupus or rheumatoid arthritis. One checkpoint stops T-cells from multiplying; another weakens them and shortens their life span.

As the name suggests, checkpoint inhibitors block the checkpoints, so cancer cannot use them to turn off the immune system.

Mr. Cara took drugs to inhibit both types of checkpoints. Every two weeks, he had intravenous infusions of Yervoy and Opdivo, both made by Bristol-Myers Squibb. He had no problems at first, just a bit of fatigue the day after the infusion. He rarely missed work.

But turning the wrath of the immune system against cancer can be a risky endeavor: Sometimes the patient's own body gets caught in the crossfire. About two months into the treatment, Mr. Cara broke out in a rash all over his arms, back and chest. It became so severe that he had to go off the drugs. A steroid cream cleared it up and he was able to resume treatment — but with only one drug, Opdivo. Doctors stopped the other in hopes of minimizing the side effects.

Checkpoint inhibitors can take months to begin working, and sometimes cause inflammation that, on scans early in treatment, can make it look like the tumor is growing. But Mr. Cara's first scans, in March 2015, were stunning.

His tumor had shrunk by a third.

By August, more than half of the tumor had vanished. The rash came back, however, and worsened. Steroids worked again, but in October a far more alarming side effect set in: breathing trouble.

Doctors diagnosed pneumonitis, a lung inflammation caused by an attack from the immune system — a known risk of checkpoint drugs. Continuing the treatment posed too great a danger.

Mr. Cara stopped the infusions, but the months of treatment seemed to have transformed his cancer to stage 2 from stage 4, meaning that it was now operable. This spring surgeons removed about a third of his right lung, and discovered that the cancer was actually gone.

“No cancer was seen in any of the tissue they took out,” Dr. Hellmann said. “‘One hundred percent treatment effect,’” he read from the pathology report. “It was pretty cool.”

Immunotherapy had apparently wiped out the disease. “It’s amazing. Unbelievable,” Mr. Cara said.

As of now, he needs no further treatment, but he will be monitored regularly. He is back to work, and golf.

“He’s had the best possible response,” Dr. Hellmann said. “I hope that remains permanent. Only time will tell, and I think he’s conscious of that.”

Mr. Cara acknowledged, “Is there something in the back of me that says this thing never goes away, it could come back any time? Sure. But it’s not the main thing I think. I’m young, I’m strong, I’m healthy, my pathology report came back clean.”

He considered framing that pathology report.

But, he said, “I don’t want to jinx myself.”

Drugs Help Some, but Not Others

When checkpoint inhibitors work, they can really work, producing long remissions that start to look like cures and that persist even after treatment stops. Twenty percent to 40 percent of patients, sometimes more, have good responses.

But for many patients, the drugs do not work at all. For others, they work for a while and then stop.

The vexing question, and the focus of research, is, why?

One theory is that additional checkpoints, not yet discovered, may play a role. The hunt is on to find them, and then make new drugs to act on them.

Despite the gaps in knowledge, checkpoint inhibitors are coming into widespread use and are being tried in advanced types of cancer for which standard chemotherapy offers little hope.

One example is anal cancer, a painful disease that carries a stigma because it is often linked to the sexually transmitted human papillomavirus or HPV, which also causes cervical cancer.

Lee, 59, who asked that her last name be withheld to protect her privacy, found out in 2014 that she had the disease, and that it had spread to her liver.

“I was told I’d be dead in 12 to 18 months with treatment, six months with no treatment,” she said.

Chemotherapy and radiation at a hospital near Dallas brought a remission that lasted only a few months. The cancer spread to her lungs.

Bedridden and in severe pain, she entered an immunotherapy trial at M.D. Anderson. In May 2015 she began receiving Opdivo every two weeks. The tumors in her liver and lungs have shrunk by about 70 percent. She is back at work.

While the drugs initially were given only to people with advanced disease, especially those who had little to lose because chemotherapy had stopped working, Dr. Heymach of M.D. Anderson predicted that soon some patients — including some with earlier stages of lung cancer — will receive checkpoint inhibitors as their first treatment.

Immunotherapy is also enabling doctors to help patients in unexpected ways.

Until recently, surgeons were reluctant to operate on people with advanced cancer because they knew from experience that it would not lengthen the patient's life. But checkpoint inhibitors are changing that. For instance, some patients have taken checkpoint inhibitors for an advanced cancer that had spread around the body, and wound up with only one stubborn tumor left. They then have had it surgically removed and have gone years without a relapse.

"Time has slowed down to the point where you can pay attention to individual tumors, since you're not running to put out the fire of wholesale systemic progression," Dr. Wolchok said.

If there is a potential downside to the advances, Dr. Hellmann said, it is that the buzz about immunotherapy has led some patients to think chemotherapy is passé.

"Immunotherapy represents a hugely important new tool, but chemotherapy can work too and has been the backbone of the way we've treated patients with lung cancer," he said. "Immunotherapy is not a replacement for that. It's a new weapon."

One of his patients, a 60-year-old man with lung cancer that had spread to his brain, was eager to try immunotherapy instead of chemotherapy. After having radiation treatment for one brain tumor, he began treatment with two checkpoint inhibitors.

But they did not work. So his doctors switched to chemotherapy. "He's had a tremendous response," Dr. Hellmann said.

He said it was impossible to tell whether the immunotherapy could have had some delayed effect and worked synergistically with the chemotherapy. Clinical trials are now trying to resolve that question.

But the potential for dangerous side effects cannot be overemphasized, doctors say. A 2010 article in a medical journal reported that a few melanoma patients had died from adverse effects of Yervoy.

In addition to causing lung inflammation, checkpoint inhibitors can lead to rheumatoid arthritis and colitis, a severe inflammation of the intestine — the result of an attack by the revved-up immune system that over-the-counter remedies cannot treat. Patients need steroids like prednisone to quell these attacks. Fortunately — and mysteriously, Dr. Wolchok said — the steroids can halt the gut trouble without stopping the immune fight against the cancer. But if patients delay telling doctors about diarrhea, Dr. Wolchok warned, "they could die" from colitis.

Checkpoint inhibitors can also slow down vital glands — pituitary, adrenal or thyroid — creating a permanent need for hormone treatment. Mr. Cara, for instance, now needs thyroid medication, almost certainly as a result of his treatment. Doctors have reported that a patient with a kidney transplant rejected it after taking a checkpoint inhibitor to treat cancer, apparently because the drug spurred his immune system to attack the organ.

Another of Dr. Hellmann's lung-cancer patients, Joanne Sabol, 65, had to quit a checkpoint inhibitor because of severe colitis. But she had taken it for about two years, and it shrank a large abdominal tumor by 78 percent. Patients like her are in uncharted territory, and doctors are trying to decide whether to operate to remove what is left of her tumor.

"I have aggressive cancer, but I'm not giving in to it," Ms. Sabol said. "It's going to be a big battle with me."

Coley's Toxins

Dr. William B. Coley, an American surgeon born in 1862, is widely considered the father of cancer immunotherapy. But he practiced a crude form of it, without understanding how it worked.

Distressed by the painful death of a young woman he had treated for a sarcoma, a bone cancer, in 1891, Dr. Coley began to study the records of other sarcoma patients in New York, according to Dr. David. B. Levine, a medical historian and orthopedic surgeon.

One case leapt out at him: a patient who had several unsuccessful operations to remove a huge sarcoma from his face, and wound up with a severe infection, then called erysipelas, caused by Streptococcal bacteria. The patient was not expected to survive, but he did — and the cancer disappeared.

Dr. Coley found other cases in which cancer went away after erysipelas. Not much was known about the immune system, and he suspected, mistakenly, that the bacteria were somehow destroying the tumors. Researchers today think the infection set off an intense immune response that killed both the germs and the cancer.

Dr. Coley was not alone in believing that bacteria could fight cancer. In a letter to a colleague in 1890, the Russian physician and playwright Anton Chekhov wrote of erysipelas: “It has long been noted that the growth of malignant tumors halts for a time when this disease is present.”

Dr. Coley began to inject terminally ill cancer patients with Streptococcal bacteria in the 1890s. His first patient, a drug addict with an advanced sarcoma, was expected to die within weeks, but the disease went into remission and he lived eight years.

Dr. Coley treated other patients, with mixed results. Some tumors regressed, but sometimes the bacteria caused infections that went out of control. Dr. Coley developed an extract of heat-killed bacteria that came to be called Coley’s mixed toxins, and he treated hundreds of patients over several decades. Many became quite ill, with shaking chills and raging fevers. But some were cured.

Parke-Davis and Company began producing Coley’s toxins in 1899, and continued for 30 years. Various hospitals in Europe and the United States, including the Mayo Clinic, used the toxins, but the results were not consistent.

Early in the 20th century, radiation treatment came into use. Its results were more predictable, and the cancer establishment began turning away from Coley’s toxins. Dr. Coley’s own institution, Memorial Hospital (now Memorial Sloan Kettering Cancer Center) instituted a policy in 1915 stating that inpatients had to

be given radiation, not the toxins. Some other hospitals continued using them, but interest gradually waned. Dr. Coley died in 1936.

Chemotherapy, developed after World War II, was another blow to his methods. And in 1965, the American Cancer Society added Coley's toxins to its list of "unproven" treatments. (The toxins were later taken off the list.)

After Dr. Coley's death, his daughter, Helen Coley Nauts, studied some 800 case records that he had left behind, and became convinced that he was onto something important. She tried to rekindle interest in his work, but she was thwarted by doctors who opposed it, including some with high rank at Sloan Kettering. However, in 1953 she founded the Cancer Research Institute in New York, a nonprofit that has become a significant supporter of research on the interplay between cancer and the immune system. The group awarded more than $29.4 million in scientific grants in 2015, and its advisory board includes Dr. Wolchok and the scientist credited with developing the first checkpoint inhibitor, James P. Allison.

The Scientist and the Doctor

"Are you Dr. Allison?"

James Allison and his wife, Dr. Padmanee Sharma, had just settled into their airplane seats when another passenger approached with tears in her eyes and thanked him for creating the drug that was keeping her husband alive. Dr. Sharma described the encounter during a joint interview with her and Dr. Allison in his office at M.D. Anderson in Houston, where both work.

"Every time Jim meets a patient, he cries," Dr. Sharma said.

"Well, not every time," Dr. Allison said.

Dr. Allison, 67, and Dr. Sharma, 45, have been research collaborators since 2005, and spouses since 2014, when he proposed by saying that nobody else could stand either of them — they talk about their work all the time — so they might as

well get married.

The drug the woman on the plane thanked him for was Yervoy, the first of the checkpoint inhibitors. It was approved for advanced melanoma in 2011. Dr. Allison — a scientist, not a physician — has won numerous research awards and is expected by many to win a Nobel Prize. He drives a Porsche convertible with a license plate bearing the name of the checkpoint he deciphered: CTLA-4.

A bearded, slightly rumpled figure, Dr. Allison plays harmonica with research colleagues in a blues-rock band called the Checkpoints. He is good enough to have accompanied Willie Nelson onstage at the Redneck Country Club in Stafford, Tex., this spring, playing, “Roll Me Up and Smoke Me When I Die.”

Immunology, particularly the study of T-cells, has been his life’s work. Cancer came later. “I became interested in cancer because I’ve lost a number of family members to cancer,” said Dr. Allison, chairman of the immunology department and executive director of the immunotherapy platform at M.D. Anderson. “My mother and two of her brothers, and my own brother, died of cancer.”

Around the time of his brother’s death from prostate cancer, Dr. Allison learned that he had the same disease himself. He was treated successfully, he said, adding with a laugh that he was more likely to die from inactivity than from cancer.

In the 1990s, Dr. Allison, then at the University of California, Berkeley, and Dr. Jeffrey Bluestone of the University of California, San Francisco, independently made a landmark discovery: They proved that a molecule widely believed to activate the immune system actually shut it down. The molecule was a protein on the surface of T-cells — a crucial checkpoint — and it was nature’s way of subduing the T-cells, apparently to dial back their ferocious activity and prevent them from attacking a person’s own tissue. Cancer cells can sometimes lock onto checkpoints, disabling the T-cells.

Dr. Allison wondered if it might be possible to block the checkpoint and launch the T-cells against cancer. He and a postdoctoral fellow, Dana Leach, developed an antibody — a molecule made by certain cells of the immune system — that would

stick to the checkpoint and block it. When the researchers gave the antibody to mice with cancer, tumors vanished.

Recalling those first tests in mice, Dr. Allison said it was astounding to see the cancers shrink and disappear. Veterinarians thought the mice had contracted an infection or a skin disease. But the sores that worried the vets were actually tumors that were ulcerating and rotting away under assault by T-cells.

Many drug companies were skeptical about the findings, but one, Medarex, created a human version of the antibody. Medarex was later acquired by Bristol-Myers Squibb, and the antibody, given the trade name Yervoy, was approved in 2011 to treat advanced melanoma.

It became the first drug to prolong survival in people with this deadly form of cancer. Major studies that started before it was approved found that among 1,861 patients treated for advanced disease, about 22 percent were still alive three years later, with no signs of recurrence — an astounding result for a disease that was almost always fatal. Some have survived 10 years or longer.

The discoveries that led to the drug, Dr. Allison said, came entirely from years of basic research in immunology — experiments in test tubes and mice — and not from the clinical or "translational" science, aimed at moving rapidly into humans, that is so heavily favored now by institutions that pay for studies.

"None of this came from cancer research, none," Dr. Allison said, adding that without support for basic research, "progress, if any, will be incremental, not a big leap."

His own work is well funded, he said, but he worries about an overall trend to shortchange basic science.

The focus of much of his and Dr. Sharma's research now is to understand how and why checkpoint inhibitors work in some patients and not others.

Dr. Sharma, a professor of genitourinary medical oncology, is a physician and

researcher who treats patients and oversees clinical trials, and she brings stories home to Dr. Allison about patients whose lives may be extended by his discoveries.

In general, checkpoint inhibitors seem to work best for tumors with many mutations, like most melanomas and cancers of the lung and bladder.

“It’s like buying a lottery ticket,” Dr. Sharma said. “The more genetic abnormalities, the more lottery tickets you’ve bought — and you have a much higher chance of a T-cell recognizing something to start the immune response.”

One area of particular interest is the tissue immediately in and around a tumor, what researchers call the microenvironment. By examining that zone, scientists can tell whether T-cells are fighting the cancer. Sometimes T-cells mob the margins of a tumor, but cannot get in. Other times, they get in but cannot kill it.

“How do we understand what drives the immune response in one patient to give a good clinical outcome, and how do we then drive that same immune response in all the other patients?” Dr. Sharma asked. “Did the T-cells get in? If not, is there another drug that can drive the T-cells in?”

Researchers also suspect that checkpoint inhibitors might work better if combined with treatments that kill tumor cells, because debris from dead cancer cells may help the immune system recognize its target. Studies are underway to test checkpoint drugs in combination with cell-killing treatments like chemotherapy and radiation. But it is a delicate balance to adjust the timing and doses, because in addition to killing cancer cells, those other treatments can knock out the immune system just when it is needed most.

Flying 3,300 Miles for Treatment

As word spreads about immunotherapy, a troubling fact remains: Patients do not have equal access to the new treatments, which can be prohibitively expensive. Insurers cover F.D.A.-approved treatments, but co-payments can be high for costly

drugs. Some people get costs covered by volunteering for clinical trials that are testing new drugs or novel combinations. But not everyone can, or wants to, enter a study. Participants tend to have the education, determination and means required to get second and third opinions, rearrange their lives, and buy plane tickets to get to cutting-edge medical centers. And they are willing to take risks for a chance to survive. Minorities have been underrepresented in studies, for reasons that are not clear.

David Wight, a retired oil engineer in Anchorage, is a study participant who has been able to take every possible step to save his life. When bladder cancer began to spread in his abdomen, he was given three to 12 months to live. That was four and a half years ago.

On a recent Saturday, Mr. Wight, who is 75 but looks younger, refereed a boys' soccer game, racing up and down the field with the players. The following Wednesday he rose at 3 a.m. to fly 3,300 miles to Houston, where he would arrive at about 5 p.m. He has been making that trip every other week for over two years to receive immunotherapy at M.D. Anderson. For about a year and a half, his disease has been in complete remission.

Until recently, he paid his own airfare. But a few months ago, Bristol-Myers Squibb, the maker of the drug being studied, began picking up the tab, even reimbursing him retroactively — about $50,000 so far.

He has five children: three in their 40s, a son, 16, and a daughter, 10. The younger two were only 10 and 5 when he learned he was ill, and the thought that he might not have survived to raise them still brings tears to his eyes. Describing the time he has gained to be with his family, he said, "I won a lottery that's bigger than anybody could imagine."

His cancer was diagnosed in summer 2010, after a test during a routine physical found cancer cells in his urine. A small tumor had invaded the wall of his bladder. Mr. Wight had his bladder removed at a hospital in Anchorage, and was told he needed no further treatment.

A year after the surgery, he and his doctors were horrified to find that a large tumor had wrapped itself around his colon. Only then did the doctors discover that he had a rare, aggressive type of bladder cancer, called plasmacytoid. His doctors consulted with a hospital in Seattle, which devised a treatment plan.

"They said one word that told me I was not where I wanted to be: 'palliative,'" Mr. Wight said. He knew palliative treatment was meant to ease symptoms, but not cure the disease. "I said, 'No thank you. We can do better than that,'" he recalled.

His next stop was M.D. Anderson. Months of chemotherapy shrank the tumor enough to allow colon surgery in May 2012. But the disease kept coming back: spots in one lung, then the other, then a tumor under his kidney.

"I was getting a new tumor every six to eight months," he said.

Chemotherapy and an experimental gene therapy cleared his lungs and shrank the tumor near his kidney but could not get rid of it.

In June 2014, Mr. Wight became one of the first patients with bladder cancer at M.D. Anderson to enter a study of two checkpoint inhibitors. For three months he received Yervoy and Opdivo every two weeks, and then continued with only Opdivo.

The tumor under his kidney shrank, then disappeared. It has been gone for a year and a half, and he has had no other signs of cancer. He is still receiving Opdivo — the reason for his regular trips to Houston.

"I'm very fortunate," Mr. Wight said. "It has for me a single irritating side effect. It makes me itch like you wouldn't believe. I itch all the time but it's a small price to pay to stay alive and be feeling pretty well."

An antihistamine helps. Regarding how long he will keep being treated, he said: "It's experimental. You don't know the answer. As long as I have positive results I'm eligible for the treatment."

His oncologist, Dr. Siefker-Radtke, called his response to immunotherapy

"fantastic" and said other patients, also in complete or partial remission, were flying or driving to Houston for treatments every two or three weeks. Many do not want to stop taking the drugs.

But doctors do not know how long the treatments should continue. They wonder how long the remissions will last, and whether some will even turn out to be cures, Dr. Siefker-Radtke said. Some studies were planned to last just a year or two, longer than the life expectancy of most patients with advanced disease. Researchers did not think they would have to decide whether to keep treating people for years.

"We were not expecting to see patients going this long," Dr. Siefker-Radtke said.

Correction: July 30, 2016

An earlier version of this article overstated the initial effect of a new treatment against cancer for the patient, Steve Cara. His tumor had shrunk by a third, not half, at the time of his first scanning in March 2015. By August, more than half, not 90 percent, of the tumor had vanished.

A version of this article appears in print on July 31, 2016, on page A1 of the New York edition with the headline: A Sickened Body as Cancer Weapon.
