



Big Changes in the Pipeline for Cancer Treatment

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Published in Townsend Letter magazine
August/September 2016 edition

Former President Jimmy Carter is the poster boy for a new era of cancer treatment. He had a stage 4 melanoma that had spread to his liver and brain – usually a death sentence at any age. Last year, he was treated with immunotherapy and radiation. At this time, the former president is said to be cancer-free.

Immunotherapy represents a new and very different approach to treating cancer. Whereas chemotherapy drugs bombard all rapidly dividing cells – normal and cancerous – immunotherapies seek out specific molecular targets associated with cancer’s development. For example, some cancer cells seek to survive by emitting unique proteins which turn off the immune system so the body cannot see these unnatural cells and destroy them. Immunotherapy drugs and proteins can act as unclinking devices, allowing the immune system to recognize cancer cells once again and kill them.

The new treatment toolbox was the big buzz at the 2016 Best Answer for Cancer Conference in San Diego in April. It will usher in a paradigm shift in cancer treatment, a welcome light in the tunnel after decades of mostly stagnant results.

“Immunotherapy will be a game changer over the next five to ten years,” said Dr. Sean Devlin of Santa Monica. “We will move away from toxic chemotherapy to using the immune system for the systemic treatment of cancer.” Dr. Devlin serves as the Foundation’s medical director.

“We got chemo to work about as well as it is ever going to work,” said Dr. William Decker of Houston’s Baylor College of Medicine. “With chemo, you run into drug resistance and often unacceptable side effects. Chemo drugs poison the whole body, not just the cancer cells. Harnessing the power of the immune system has taken longer than expected because anyone trained before, say 1990, was taught that the immune system couldn’t recognize cancer, couldn’t do anything about it, and therefore it was completely irrelevant. There wasn’t enough acceptable evidence that the immune system was important in cancer. Change often comes slowly because people tend to irrationally cling to their beliefs. Right up until approval of the first mainstream immunotherapy treatments in 2010, those who believed the immune system could fight cancer were still viewed in some quarters as screaming lunatics. We were not trying to be anti-establishment; we were just trying to get mainstream medical oncology to acknowledge what should have been blindingly obvious. People like to say that they’re data-driven, but most people really aren’t.”

A human being will produce upwards of 10,000 cancer cells a day. A robust immune system is our first and best defense against cancer – it will clean out those cells each night while we sleep. Most medical experts agree that cancer is, first and foremost, a failure of the immune system.

What Is Old Is New Again

The very first form of immunotherapy was “Coley’s toxins,” a mixture of killed bacteria species developed in the late 1800s and approved by the FDA in the 1920s. It manipulated the immune system by introducing a bacterial infection with the idea that as the immune system geared up to fight the infection, it would begin to recognize the cancer cells too and knock them out. “Coley’s toxins” fell out of favor, however, when chemotherapy took center stage after WWII.

The immunotherapy used with Carter was an intravenous drug called pembrolizumab (brand name Keytruda[®]), approved in 2014 to treat late-stage melanoma that cannot be removed by surgery. A recent [study](#) sponsored by Merck Sharp & Dohme found that about one-third of advanced melanoma patients treated with pembrolizumab responded to the drug.

Cancerous tumors can grow and metastasize by expressing proteins that turn off the immune system and thus make the tumor invisible. Pembrolizumab blocks one of those proteins, PD-1, empowering the immune system to do what it is designed to do – kill off anything foreign, or “non-self” in the parlance of immunologists.

“With cancer you have immunological tolerance,” Thomas Ichim, PhD, of the Pan American Cancer Centers explained. “With cancer you want to break tolerance – the ability of the immune system not to kill what belongs to the self. In alternative medical approaches to cancer, the breaking of tolerance is a long process, mediated by nutritional and emotional therapies. Drug interventions are much faster acting – the immune system doesn’t have time to figure out what it should be tolerant of and not tolerant of. So we are trading a slower, safer process for an accelerated process. When you break the tolerance to the tumor, you can sometimes break tolerance to healthy tissue as well. The downside of that can be obvious but on the other hand if you have a stage 4 cancer, it’s great.”

Checkpoint Inhibitors, CAR, CRISPR, and Peptides

Pembrolizumab has fewer side effects than its earlier generation cousin, ipilimumab. Both are called checkpoint inhibitors. Other tools in the pipeline include chimeric antigen receptor (CAR) technologies, clustered regularly-interspaced short palindromic repeats (CRISPR), and peptides.

CAR is a genetically engineered T-cell that has been trained to recognize a specific protein (antigen) on tumor cells. These engineered immune cells can target tumors in a much more powerful way than normal immune cells can. A patient’s T-cells are collected in a lab, altered genetically to recognize a specific antigen, allowed to multiply into the billions, and then infused back into the patient like an army programmed to kill cancer cells.

“Think serial killers,” said Dr. Ichim. “In lymphomas we see a 50 to 70 percent cure rate. We see astonishing results, but they have severe side effects. They combine it with steroids and Humira[®]. These are still in human clinical trials.”

CRISPR is like using scissors and scotch tape to go into a person's DNA, edit out an unwanted gene, and put the DNA back together in working condition. Don't want the BRCA gene which predisposes you to breast cancer? "CRISPR me!" The scissors in this scenario are an enzyme called Cas9 that can target a specific spot in the DNA and remove a gene or insert desired sequences. For cancer it is exciting because multiple genes can be targeted at once. Unlike other gene-editing methods, CRISPR is cheap, quick, easy to use, and it is displacing more cumbersome efforts in labs around the world. The technology is moving faster than some would like since changing DNA raises tricky moral and ethical questions for humans and farm animals alike.

Growth factors and peptides are considered molecular therapy and it is the fastest growing part of the pharmaceutical industry. A peptide is a tiny molecule, an individual little piece of protein that acts like a smart carrier.

"There are numerous known peptides that are identified for a particular receptor for a particular cancer," said Dr. Donese Worden of Arizona. "They can be used as a drug inside the nucleus of the cell. They can carry other drugs. They can be utilized as a vaccine, or as a radio nuclear carrier (take the radiation where it needs to go). They are very specific, very efficacious. They help the cell decide what to do. You can inhibit, stimulate (proliferate), or modulate. Antibodies are more of a shotgun approach. Peptides are in that space before anyone knows about them, but they are real and they have a lot of good science now."

We don't know all of the peptides yet, but we know quite a few of them. They have been researched since 1922 and are just now moving into mainstream use.

"In the United States, they have to be patented and it is one peptide at a time," she added. "In Mexico, for example, they are doing multiple peptides right now."

Better Cancer Detection Tests

Chances are, if you get screened today for cancer, it will be with a PAP smear, a mammogram, a PSA test, or a biopsy. This array of options is quickly changing too.

"Compared to the newer and more sensitive tests available today, those are late diagnostic," said Registered Nurse Jenny Hrbacek who wrote the go-to book on early detection tests, *Cancer Free! Are You Sure?*

"Conventional tests typically will not detect cancer until it has been growing for many years, perhaps a decade or more," she said. "At that point the cancer is harder to treat and the immune system is more overwhelmed by the complexity of the cancer. Newer tests are much more sensitive and some are even covered by insurance. I love that the medical community is now looking to harness the power of the immune system, but they are still waiting for the cancer to show up on conventional tests. The earlier you intervene, the shorter the course of therapy and the easier it is to have a successful outcome, not to mention it is probably going to be less expensive."

Dr. Rick Davis, CEO of Quicklab™ in Florida, is bringing some of the newest tests to market. At the conference, he announced he has devised two new tests that are faster, less expensive, and

more comprehensive than what has been available to date. One is a quantitative test for ENOX2, a protein that only cancer cells make. The second is a speedier measurement of nagalase, an enzyme secreted only by cancer cells, pathogenic bacteria, and viral cells.

The only measure of ENOX2 has been the ONCOblot[®] test which detects whether the ENOX 2 protein is present in the bloodstream, and it takes just 2 million cells to be able to give a positive result. It can also tell you the tissue of origin – prostate, breast, lung, kidney, etc. Knowing that you have cancer and what tissue type it is are very important. But is that tumor the size of a sesame seed or golf ball? Now Davis is taking it to the next level. He has devised an ENOX 2 test that will tell you *how much* of this protein is present in the blood and that's important because the amount is proportional to tumor burden. However, unlike ONCOblot, his test will not tell you the tissue of origin. But on the other hand, his lab gives results in 48 hours instead of 3 weeks. By sequentially using both tests together, physicians can get a more complete picture to approximate both the tumor's size and type. This is critical information when deciding how to proceed once the diagnosis of cancer is made.

Dr. Davis also improved the ability to measure the nagalase enzyme that cancer, pathogenic bacteria, and viral cells secrete into the blood stream. Nagalase is the weapon these cells use to cloak themselves from the immune system, thus the amount of nagalase in the blood is proportional to the amount of immunosuppression brought to bear by the disease. It used to be that physicians had to ship a patient's blood sample to labs in Europe and wait 5-6 weeks for the results. His test is done in QuickLab's U.S. facility and the results are back in 48 hours.

“Putting a patient's sample in the mail can be very problematic because the sample will quickly degrade if it is not kept at a precise temperature all throughout the shipping process,” he explained. “So using overnight delivery eliminates the need to ship it overseas and solves the transit problem. This gives a more accurate and faster result.”

By the end of 2016, Davis expects that doctors will be able to perform both nagalase and ENOX2 tests in their own offices using a rapid test strip technology he is developing (similar to a pregnancy test). Performing both of these tests in real time will provide powerful new tools for physicians to personalize a more effective treatment plan without having to send blood samples to an outside lab. More importantly, treatment effectiveness can be monitored as often as weekly to determine whether the current protocol is effective for the patient, providing an objective measure of: “Is my treatment working?”

Dr. Davis is an engineer, chemist, medical doctor, and entrepreneur with more than 400 patents and trademarks. A few years ago, he found himself dealing with a surprise diagnosis of stage 4 rectal cancer – two years after a “clean” colonoscopy. He dived deep into the literature of cancer diagnosis and treatment. He chose not to use either chemo or radiation – “because I didn't want to kill my immune system” – and two years later was cancer free.

“Traditional oncologists are not encouraged to engage in a lot of critical thinking about what they do – it is a very blindfolded existence. I saw many flaws in conventional cancer treatment, and I recognized that early detection is critical and that it is possible to do it a lot better.”

The field of early detection tests is growing so fast now that Hrbacek's book is on its third revision in one year's time. “Wow – that's great news for people,” she said. “You don't have to

wait for a lump or bump. Why wait until the immune system has to deal with trillions of cells when we can find cancer now when there are only a few million cells – 2 million cells looks like a small dot that you would make on a piece of paper with a ball point pen. That’s how good these early detection tests are. But typically if your doctor even knows of them, he doesn’t know what to do with the information. It takes a functional oncologist to know how to interpret and adjust the plan of care accordingly.”

Economics of Cancer

Why is this all coming to the forefront now? Probably because of a combination of education and economics.

“Because of the internet, patients are able to access a lot of scientific information on their own,” Dr. Devlin offered. “They are no longer restricted to dumbed down literature that is essentially a sales pitch for a particular treatment. They can look at options themselves on line. Then in the medical world, you saw the silos start to break down; there was more crossover between specialties. That meant allergy and immunology doctors began to share info about the immune system with the oncology doctors. Patients saw it too through everyone’s experiences and made demands upon their doctors to use things other specialists were using.”

The economics of the new paradigm are pretty simple: the business model is one that the pharmaceutical industry can package.

“Pharma recognizes you can do this in conjunction with chemo and that you have distinct molecular entities which can be mass produced, patented, and sold,” said Dr. Ichim. “That includes the checkpoint inhibitor PD-1 that was used with Carter. That drug costs \$100,000 to \$300,000 for a 3 month course. Yes, there is a huge markup. And, it works a lot better than anything else anyone has seen yet.”

Some analysts are [predicting](#) pembrolizumab will be a \$5-billion-a-year blockbuster drug by 2018.

The “moon shot” effort recently announced by the Obama Administration is tasked to study the development of cancer vaccines, sensitive approaches to early detection, advances in immunotherapy and combination therapies, single-cell genomic profiling of cancer cells and cells in the tumor microenvironment, enhanced data sharing, and new approaches to the treatment of pediatric cancers. The cancer community, including the American public, will be provided a forum to post comments to help impact the recommendations ultimately made by National Cancer Institute. It is an open sourced, cross referenced, transparent collective that has to share information. No more sequestering of intellectual property. Think Homeland Security forcing the FBI and CIA to talk and share info.

Finding “the cure” has never been approached this way since President Richard Nixon famously launched the war on cancer in 1971 by signing the National Cancer Act, saying, “The same kind of concentrated effort that split the atom and took man to the moon should be turned toward conquering this dread disease.”

Yet, despite more than \$100 billion spent since then in research, many say the biggest advance has been in the realm of prevention – getting people to stop smoking drastically drove down the incidence of lung cancer. Most cancers are still fatal once they metastasize.

“The moonshot initiative is saying we must take the brakes off and get these new therapies out there quicker,” Dr. Worden said. “As insurance picks them up, they will trickle down to the average oncology office and patient.”

The Cancer Conundrum

“Immunotherapy will soon be the norm because ultimately a lot of cancer patients will benefit from using these modalities, allowing them to avoid chemo and radiation which may have worse side effects,” Dr. Devlin added.

He sees a bit of irony, however, in a widespread approach to harness the power of the body’s own immune system to defeat cancer.

“The immune system of today is not the same as it was in the 1950s because it has been so abused from what is in our environment – plastics, adrenal exhaustion, houses full of mold and allergens – the list is nearly infinite,” he said. “We crippled our immune system by diverting its attention to so many other pathogens; the world is a more toxic place.”

Also, we have an epidemic of obesity and diabetes, both of which increase the risk for cancer.

A significant challenge moving forward with these new therapies is our understanding of exactly how the immune system works. It is exceedingly complex. We know much more than we did 50 years ago, but not nearly as much as we will 50 years from now.

“No matter how many new therapies like this come down the pipeline, I don’t foresee that they can be the total answer because patients need holistic care,” said Annie Brandt, founder and president emeritus of the Best Answer for Cancer Foundation. “Most cancer patients have had a life trauma, for example, that needs to be dealt with just as much as the tumor if the goal is to achieve a real ‘cure.’ You can be done really quick with conventional treatment, and the cancer can come back really quick. I’ve seen it too many times. With the kind of functional oncology practiced by our International Organization of Integrative Cancer Physicians (IOICP), patients deal with the cancer today, *and* they learn how to greatly lessen the odds their cancer doesn’t come back in the future. Patients need education about how to strengthen their immune system and vital organs. This often opens up new avenues for them about how they eat, the toxins in their environment, unresolved emotions, and getting in touch with their spirituality. These avenues often make the difference between a cure – or not.”

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