Immunotherapy: An Emergent Anti-Cancer Strategy

Editorial

Volume 7 Issue 3 - 2017

Alain L Fymat*

International Institute of Medicine and Science, California, USA

***Corresponding author:** Alain L Fymat, International Institute of Medicine and Science, California, USA, Tel: (760) 485-9149; Email: alain.fymat@fiimas.org

Received: January 28, 2016 | **Published:** February 02, 2017

Editorial

Diseases such as cancer, heart disease and stroke account for a major percentage of deaths worldwide and pose the greatest threat to modern global public health. The American Cancer Society estimated that by the end of 2015, approximately 1.66 million new cancer cases will be diagnosed in the United States, and the figure goes up once the global statistics are taken into consideration. But why hasn't cancer been cured despite a four-decade "war" against the disease and the expenditure of hundreds of billions of dollars? It is essentially because of our lack of understanding of the basic underlying molecular mechanisms that drive it. Early on, certain chemicals (such as nitrogen mustard - similar to mustard gas) were found to significantly reduce white blood cells. It was then thought that these chemicals may perhaps halt the growth of rapidly dividing cells, such as cancer cells. Thus, began an era of testing several chemicals to see if they could kill tumors. Chemotherapy was born! However, while at times effective, this approach does not elucidate the underlying molecular mechanisms or why it does not work universally or permanently. As cell biology and genetics became understood at a deeper level, newer targeted therapies have been designed to which the complementary procedures of surgery and radiotherapy were added and used either singly or in combination. It now appears that cancer is less an organ disease and more a disease of molecular mechanisms caused by the mutation of specific genes. More recently, the newly emerging "immunotherapy" has been successful in inducing long-term remissions of hard-to-treat cancers in about one-third of patients.

A Brief History of Immunotherapy

The year 2013 marked a turning point in the fight against cancer, as long-sought efforts to unleash the immune system against tumors were paying off, even if the future remains a question mark. The journal Science selected cancer immunotherapy as the Breakthrough of the Year. But, what is "immunotherapy"? It is the harnessing of the immune system to battle tumors. It represents an important paradigm shift in cancer treatment as it marks an entirely different way of treating cancer - by targeting the immune system, not the tumor itself. To this day, however, it has touched only a tiny fraction of cancer patients and has helped only some of them. Examples include: a woman with a grapefruit-size tumor in her lung from melanoma, who is alive and healthy 13 years later; a 6-year-old near-death from leukemia, now in third grade who is in remission; and a man with metastatic kidney cancer whose disease continued fading away even after treatment stopped. The early steps of immunotherapy are retraced below:

In 1987: French researchers identified a new protein receptor on the surface of T-cells. They called it cytotoxic T-lymphocyte antigen 4 (CTLA-4).

In 1996: James Allison found that CTLA-4 puts the brakes on T-cells, preventing them from launching all-out immune attacks. He wondered whether "blocking the blocker" (the CTLA-4 molecule) would set the immune system free to destroy cancer. The approach turned from considering immunosuppression as the focal point to manipulation of immunosuppression as the target. He showed that antibodies against CTLA-4 erased tumors in mice.

In the mid-1990s: A biologist in Japan discovered a molecule expressed in dying T-cells, which he called "programmed death 1" (PD-1) and which he recognized as another brake on T-cells. Whilst engineered T-cells are still experimental, antibodies are slowly going main stream. At least five major drug companies are developing antibodies such as anti-PD-1.

In 1999: Medarex, a small biotechnology company in Princeton, New Jersey, acquired the rights to the antibody, taking the leap from biology to drug development. Oncologist Drew Pardoll of the Johns Hopkins University urged the company to test an anti-PD-1 antibody in people. The first trial, with 39 patients and five different cancers, began in 2006. By 2008, doctors were jolted by what they saw: In five of the volunteers, all of them with refractory disease, tumors were shrinking, and survival in a few stretched beyond what was imagined possible.

In 2010: Bristol-Myers Squibb, which acquired Medarex, reported that patients with metastatic melanoma lived an average of 10 months on the antibody, compared with 6 months without it. It was the first time any treatment had extended life in advanced melanoma in a randomized trial. Nearly a quarter of participants survived at least 2 years.

Now, with anti-CTLA-4 and anti-PD-1 treatment options, physicians saw some tumors grow before vanishing months later. Some patients kept responding even after the antibody had been discontinued, suggesting their immune system had been fundamentally changed. However, some, particularly those on anti-CTLA-4, developed unnerving side effects, including inflammation of the colon or of the pituitary gland.

For years, Steven Rosenberg of the U.S. National Cancer Institute had harvested T-cells that had migrated into tumors, expanded them in the laboratory, and re-infused them into

patients, saving some patients with dire prognoses. However, the technique worked only when doctors could access tumor tissue, though, limiting its application.

Again in 2010: Rosenberg published encouraging results from so-called chimeric antigen receptor (CAR) therapy - a personalized treatment that involves genetically modifying a patient's T-cells to make them target tumor cells. One group, led by Carl June of the University of Pennsylvania began reporting eye-catching responses to CAR therapy: patients with pounds of leukemia that melted away.

In 2011: The U.S. Food and Drug Administration (FDA) approved Bristol-Myers Squibb's anti-CTLA-4 treatment, called Ipilimumab, for metastatic melanoma. However, the cost is high as the company charges $120,000 for a course of therapy.

In 2012: Suzanne Topalian of the Johns Hopkins University, and Mario Sznol of Yale University and their colleagues reported results for anti-PD-1 therapy in nearly 300 people, and they provided an update earlier in 2015. Tumors shrunk by about half or more in 31% of those with melanoma, 29% with kidney cancer, and 17% with lung cancer.

In 2014: The FDA approved Pembrolizumab for the treatment of late stage melanoma. This is a monoclonal (therapeutic) antibody that blocks the inhibitor ligand of PD-1. This receptor is responsible for inhibiting the immune response against cancer cells. Normally, this effect is necessary to avoid an inappropriate over-reaction, such as an auto-immune disease, in healthy individuals. In patients with cancer, antibody blockade against this receptor (such as with Pembrolizumab reinvigorates the immune system, allowing it to target and destroy cancer cells. Pembrolizumab (one of a number of closely related therapies dubbed "immune checkpoint blockade") is sold under the brand name Keytruda. It belongs to the hot class of drugs called PD-1 inhibitors. By blocking the PD-1 protein, the therapy allows the body to make T-cells that can chase after a cancer. The treatment is also expensive (~ $150,000 a year). (See also below for a combined radiation+chemotherapy+Keytruda treatment of melanoma cancer.)

In 2015: At a meeting in New Orleans in September, June's team and another team at Memorial Sloan-Kettering Cancer Center in New York reported that the T-cell therapy in their studies put 45 of 75 adults and children with leukemia into complete remission, although some later relapsed. CAR therapy is now the focus of numerous clinical trials. Researchers hope that it, like the antibodies, can target an assortment of cancers.

In the fall of 2015: Bristol-Myers Squibb reported that of 1800 melanoma patients treated with Ipilimumab (sold as Yerzov), 22% were alive 3 years later. In June, researchers reported that combining Ipilimumab and anti-PD-1 led to "deep and rapid tumor regression" in almost a third of melanoma patients. Drugs blocking the PD-1 pathway have not yet been proven to extend life, although survival rates are highly encouraging.

Notwithstanding the above successes, immunotherapies do not help everyone (for example, for patients with metastatic cancer, the odds remain long). Researchers are largely clueless as to why more patients do not benefit and so they are racing to identify biomarkers that might offer answers and experimenting with ways to make therapies more potent.

Immunotherapy Using Pd-1 Inhibitors

In clinical trials, PD-1 blockers generally work in less than half the participants. Research published earlier in 2016 suggested that PD-1 inhibitors may work best on tumors with lots of mutations. A small clinical trial has found that people with advanced cancer were far more likely to respond if they had so-called mismatched repair mutations in their tumors. This could also help explain why, so far, PD-1 inhibitors have produced the best outcomes in people with lung cancer and melanoma, which often are both mutation-heavy tumors.

Case of Advanced or Unresectable Melanoma

In an accelerated approval, the FDA has approved Pembrolizumab (Keytruda) for treating advanced or unresectable melanoma in patients not responding to other therapies. As will shortly be described, the monoclonal antibody drug inhibits the PD-1 pathway, which prevents immune-mediated killing of melanoma cells. Pembrolizumab thus makes it possible for anti-tumor T-cells to attack melanoma tumors. In announcing its approval, the Agency noted that Keytruda is intended for use following treatment with Ipilimumab in patients with the V600 BRAF mutation. Patients should also have received a BRAF inhibitor before starting Pembrolizumab. With the recommended dose (2 mg/kg although a 10 mg/kg had a similar level of efficacy), Pembrolizumab's efficacy was demonstrated in uncontrolled studies involving 173 patients. It showed a 24% showed tumor shrinkage and safety data was provided in studies with 411 patients. The effect lasted at least 1.4 to 8.5 months and continued beyond this period in most patients. The drug's most common side effects included: Fatigue, cough, nausea, pruritus, rash, anorexia, constipation, arthralgia, and diarrhea. Severe immune-mediated adverse effects involving the lungs, colon, liver, and endocrine glands were seen less frequently.

Melanoma and Advanced Lung Cancer - Case of Error-Riddled DNA

New immune system-boosting cancer drugs have in clinical trials saved the lives of many people with seemingly untreatable melanoma or lung cancer, but the drugs seem useless against colon cancer. One exception - a man with colon cancer whose metastatic tumors vanished for several years after he was treated in 2010 - piqued researchers' interest. They suspected his recovery might have to do with the large number of mutations in his tumors. Now, a small clinical trial suggests that even cancer patients with types of tumors that were thought to be impervious to the new drugs could benefit if those malignancies have the right error-riddled DNA signature, a result that could help 3% to 4% of cancer patients.

The drug tested is an antibody that blocks a receptor called PD-1 on the surface of the immune system's T cells. Tumor cells can hide from T-cells by activating the PD-1 receptor. However, when this immune "checkpoint" is blocked by a PD-1 inhibitor,

the T-cells see the tumor cells and can attack them. Such drugs are among two new types of immune system-harnessing cancer treatments that have generated tremendous excitement because, in some patients with advanced cancer, they keep tumors at bay for years. One hypothesis about why melanoma and lung cancer respond best to PD-1 inhibitors is that these two cancer types tend to have more mutations than other cancers. Some of these mutations may alter genes so that they code for small stretches of abnormal proteins that the immune system sees as foreign proteins, or antigens. The more mutations, the more of these "neoantigens" that can trigger an attack from T-cells that have been unleashed by a PD-1 inhibitor.

Colon, Prostate, Uterine and Pancreas Cancers - Case of Mismatch Repair Genes

When researchers at Johns Hopkins University in Baltimore, Maryland, examined tumor tissue from a man with colon cancer who responded to a PD-1 inhibitor, they found a clue: His tumor had mutations in "mismatch repair" genes, so-called because their encoded proteins fix errors in DNA bases when cells replicate their DNA. When these genes don't work properly, they can lead to cancer-promoting mutations and result in a colon tumor riddled with 1000 or more mutations, 10 to 100 times the usual number. The Hopkins group wondered if patients with many cancer types who had tumors with errors in mismatch repair genes would respond to PD-1 inhibitors.

To explore this idea, Hopkins oncologists Dung Le, Luis Diaz, and others looked for mismatch repair mutations in tumor samples from patients with advanced colon cancer and other cancer types whose tumors had stopped responding to other treatments. They divided 48 patients into two groups, those with and without these mutations in their tumors. Then they gave all of them the PD-1 inhibitor Pembrolizumab (Keytruda) every 2 weeks. The difference in the results was dramatic. Those with mismatch repair mutations were far more likely to respond - of 13 with colorectal cancer, 8 saw their tumors shrink, 4 remained stable, and only one got worse. By contrast, not a single one of 25 colorectal patients lacking mutations in mismatch repair genes responded. Some of the patients who responded are still alive after a year or more, whereas the nonresponders lived on average only 7.6 months. Of 10 patients with other types of cancer - including pancreatic, prostate, and uterine - who had mismatch repair mutations, in seven their tumors shrank or remained stable; the other three progressed. The results suggest that the 3% to 4% (or 30,000-40,000 advanced cancer patients a year in the United States) of all cancer patients with mismatch repair defects in their tumors could benefit from PD-1 inhibitors.

The study also supports the idea that tumors with more mutations - whether from mismatch repair defects or for other reasons - are more likely to respond to PD-1 inhibitors and similar drugs. Jedd Wolchok of the Memorial Sloan Kettering Cancer Center in New York City and his team recently reported that melanoma and lung cancer patients with more neoantigen-coding tumor mutations are more likely to respond to immune checkpoint blockers. One implication is cancer patients with few mutations in their tumors might respond better to PD-1 inhibitors if they first receive radiation or chemotherapy, because these treatments can create new mutations in tumors.

Immunotherapy Using T-Cells

The technology used merges gene therapy, synthetic biology and cell biology in the laboratory. It involves the following steps: (a) First, a batch of certain T-cells known to respond best to a given disease are extracted from the blood; (b) a custom-built virus is used to implant them with new genes; (c) cells are created that target a molecule (CD19) that is found on the surfaces of some cancers; and (d) the modified cells are then returned to the body, where their new DNA gives them a fresh set of targets to attack (Riddell, 2016).

In a trial of 31 patients with acute lymphoblastic leukemia (ALL), the approach brought about a complete remission in 93% of cases, an unprecedented result. A refinement of the technique consisted in overcoming the toxic effects that the treatments can trigger. As the number of T-cells doubles, roughly every 12 hours, a runaway immune reaction called a cytokine storm is triggered, which can be fatal to certain patients? The biggest cytokine storms seem to come from the patients with the most advanced cancers. The solution is to give the sickest patients the lowest dose so that the T-cells multiply more slowly, reducing the chances of an immune-system overreaction.

Although the ALL results are impressive, it is difficult to expand the approach to other cancers because to prime a T-cell to attack, it needs to be given precise co-ordinates. Otherwise it may lock onto and destroy something else in the body. Besides CD19, which is found in only a few cancers, scientists currently know of no other chemical target that is specific to cancer alone. The solution proposed by Kole Roybal (Cell, 2016) and his colleagues at the University of California, San Francisco consists in tweaking cells to attack when they sense two different target chemicals instead of one. In isolation, neither target may be unique to cancer cells - but the combination might be, which could allow the immune system to be unleashed on tumors whilst sparing healthy tissue.

While it is a long way from the laboratory to the clinic, engineered T-cells might be used to treat a wide range of diseases, including HIV, immune deficiencies, and autoimmune disorders. Besides the elegance of the idea of boosting the body's own defenses, the technology offers another big advantage over traditional drugs: once they have done their job, the engineered T-cells stick around in the body. That could offer protection against re-infection or the recurrence of a cancer possibly for a decade or more. Analogously, engineered B-cells could also perhaps be used to treat cancers that affect B-cells, another part of the immune system.

The Triple Attack Treatment

The treatment consists of surgery followed by focused radiation therapy to ablate melanoma lesions that have metastasized to the brain and further followed by a course of chemotherapy with Pembrolizumab (Keytruda). Likewise, for liver cancer, a similar triple attack technique combining chemotherapy, thermal ablation, and hyperthermia provides a highly targeted, yet

minimally invasive approach. It uses Bexarotene re-purposed and repackaged into a sensitive prodrug nanobubble form, inserted directly into the tumor using a flexible catheter, and ablated using ultrasound ablation therapy to pop the bubbles to release the agent.

Toxicities

After the huge success of the new class of cancer immunotherapies led by Pembrolizumab (Keytruda), the Association of Community Cancer Centers and its Institute of Clinical Immuno-Oncology, while making immunotherapy available in communities, want nonetheless to ensure that: (a) Non-oncologist physicians are made aware of immune-related toxicities from the new agents; (b) do not confuse them with chemotherapy or infection; and (c) save time and the risk of prescribing the wrong treatment. Two primary examples of toxic side effects are colitis and pneumonitis. They also want to educate cancer patients by providing them information about their immunotherapies.

With the evolution of modern radiation therapy techniques and targeted drugs, more patients with metastatic melanoma achieve complete and partial remissions, including remission of small brain metastases like the ones identified during the evaluation and initial treatment of former U.S. President Jimmy Carter. Carter's melanoma story began to emerge in early August 2015 when he had surgery to remove what was described as "a small mass" from his liver followed by focused radiation therapy to ablate four small melanoma lesions that had metastasized to his brain. This was further followed by a 12-week course of chemotherapy with Pembrolizumab (Keytruda). The radiation therapy-targeted therapy combination was a logical option for Carter, given observations that the PD-1 inhibitor has synergy with radiation. Whereas not every patient has the kind of robust response as suggested in the case of Carter, nowadays it would be more surprising when a patient does not respond. However effective was Carter's treatment, the optimism should be tempered by a long-term perspective. We would be careful to call it a "complete remission" and "disease control" but not a "cure" so far because in all likelihood, therapy will be resumed with follow-up of any autoimmune side effects.

Conclusion

Cancer immunotherapy represents an important paradigm shift in the treatment of cancer by targeting the immune system, not the tumor itself. Its early steps began with the identification of the antigen CTLA-4 to the protein PD-1, wherein cancer patients with few mutations in their tumors might respond better to PD-1 inhibitors. It continued with immunotherapy using T- and B-cells. Various types of cancer were considered (melanoma, colorectal, uterine, prostate, pancreas). With the evolution of modern radiation therapy techniques and targeted drugs, more patients with metastatic melanoma achieve complete and partial remissions, including remission of small brain metastases.

Citation: Fymat AL (2017) Immunotherapy: An Emergent Anti-Cancer Strategy. J Cancer Prev Curr Res 7(3): 00233. DOI: 10.15406/jcpcr.2017.07.00233