Immunotherapy: The Future of Cancer Therapy?

In December, researchers from around the world gathered at the 2014 San Antonio Breast Cancer Symposium (SABCS), the world’s largest breast cancer conference, to discuss the latest findings in breast cancer research and treatment. And what were they talking about? Much of the discussion focused on immunotherapy: the treatment or prevention of disease by stimulation of the immune system.

Using our own immune system to both protect us from cancer and fight off the disease once we have it sounds like science fiction, but it is one of the most active areas of cancer research today. Chosen as Science Magazine’s “Breakthrough of the Year” for 2013 (1) and selected in 2015 by the American Society of Clinical Oncology (ASCO) as one of the biggest changes in cancer care in the past decade (2), cancer immunotherapy “marks an entirely different way of treating cancer—by targeting the immune system, not the tumor itself.” (1)

This “new”—yet old, as in the 1890s Dr. William B. Coley, a renowned surgeon at Memorial Hospital in New York, attempted immune-modulating therapy for cancer by injecting tumors with “Coley’s Toxins” (a filtered mixture of inactive bacteria), resulting in a complete remission in his first patient (3)—has experienced a revival due to the careful decoding of basic biology that has happened over the past century.

Biotech companies, global pharmaceutical goliaths, and even the U.S. government are all funding immunotherapy research now. Some analysts predict that within the next decade, immunotherapies will be used for 60% of people with advanced cancer, resulting in a US$35-billion market (4). The National Cancer Institute includes Immunotherapy in its FY 2016 Professional Judgment Budget (commonly known as the “Bypass Budget”), marking its significance in its research portfolio by recommending an increase of $25 million dollars from the previous fiscal year (5).
To understand why immunotherapy is a topic of so much interest—not only at SABCS and to the editors and readers of scientific journals—we must appreciate the way our immune system works, both when we’re healthy and if we’ve been diagnosed with cancer.

The immune system acts as an “early warning” alert to notify us of things that might harm us and then attempts to eliminate these intruders. It recognizes harmful substances from the environment, neutralizes pathogens like bacteria, viruses, parasites or fungi that have entered the body and then removes them, and fights against the body’s own cells that have changed—as when they have become cancerous. The immune system has to differentiate between its own and foreign, or “non-self,” cells and substances, identifying which are invaders and which are not, and mount an attack.

The immune system can be activated by “non-self” substances called antigens. The proteins on the surfaces of cells foreign to the body are antigens, and these antigens bind to special receptors on the body’s defense cells, beginning the process to remove them from our system. We have a non-specific defense system called the “innate immune system” that attacks everything perceived to be a threat, and an additional type of protection that is smarter: adaptive immunity. With adaptive immunity our defense response is stronger and swifter with each exposure to a pathogen. Our body’s own cells have surface proteins, too, but usually (unless we have what is called an “autoimmune reaction”), the immune system does not fight them as it identifies these cells as “self.”

Just like any good defense, the immune system is complex and adaptable, providing protection with layers of increasing specificity. A major component of our innate immune system are leukocytes (white blood cells), which identify and eliminate pathogens either by attacking them through contact or by engulfing and then killing them, a process known as “phagocytosis.” Leukocytes include the phagocytes (macrophages, neutrophils, and dendritic cells), mast cells, eosinophils, basophils, and natural killer cells. The adaptive immune system allows for a stronger immune response as well as immunological memory, where each pathogen is “remembered” by a
signature antigen. The cells of the adaptive immune system are special types of leukocytes, called lymphocytes. B cells and T cells are major types of lymphocytes, and there are two major subtypes of T cells: the killer T cell and the helper T cells. Killer T cells kill cells that are infected with viruses or other pathogens, or are otherwise damaged or dysfunctional. Helper T cells regulate both innate and adaptive immune responses and help determine which immune responses the body makes to a particular pathogen. They do not kill infected cells directly, but instead control the immune response and tell other cells to accomplish the task.

Immunotherapy is a type of cancer treatment designed to boost the body’s natural defenses against cancer. Selected as a major advance in clinical cancer research and care by ASCO in their 2015 Annual Report on Progress Against Cancer, “immunotherapy can work in several different ways, by stopping or slowing the growth of cancer cells, by stopping cancer from spreading to other parts of the body, and by helping the immune system increase its ability to eliminate cancer cells by increasing the killing power of immune cells or flagging cancer cells for destruction.” (2)

There are several immunotherapy approaches, each acting in concert with our immune system:

- If the patient already has cancer, immunotherapeutic vaccines stimulate the body’s immune system to fight the cancer cells. These vaccines are not meant to prevent disease, like Gardasil, a vaccine used to protect against certain strains of human papillomavirus (HPV), but instead are used to treat cancer.
- Checkpoint blockade drugs take the “brakes” off the immune system, telling it to start attacking the cancer. Unfortunately, tumors can impede the immune response with certain molecules on the cell surface and by releasing products that inhibit the immune response, instructing the immune system not to destroy the cancer cell. Currently, two checkpoint molecules are the focus of the most drug development: CTLA-4 and PD-1.
Adoptive cell immunotherapies are an experimental approach in which immune cells from the patient or a donor are removed from the body, reengineered so that they can “learn” to attack cancer, and then re-infused into the patient (4).

According to the American Cancer Society, using the body’s own natural system for fighting disease may offer a lifeline for patients with certain types of cancer who have exhausted other treatment options (4). Advances in immunotherapy treatment for cancers such as melanoma and cervical cancer appear promising, and one cancer treatment vaccine has been approved by the Food and Drug Administration (FDA) —Sipuleucel-T (Provenge), for advanced prostate cancer patients who are no longer benefiting from hormone therapy. Other immunotherapy approaches have been developed, including interleukin-2 (IL-2), which was the first treatment approved by the US Food and Drug Administration (FDA) to fire up the immune system’s response to cancer: it was approved in 1992 (6).

These early immunotherapies didn’t work for every patient, however, and were sometimes accompanied by significant side effects. What has shown clinical promise are new targeted drugs that act on the “immune checkpoints”—proteins that control the immune system’s ability to attack and kill cancer cells. Immunotherapy advanced rapidly in 2011 when the FDA approved this new kind of immunotherapeutic drug for the treatment of metastatic melanoma. Yervoy (ipilimumab) binds to and blocks a “checkpoint protein” called cytotoxic T- lymphocyte antigen-4 (CTLA-4), which normally acts as a brake on the immune system by preventing T-cell activation (2). The drug essentially releases the brakes on the immune system, enabling the T cells to mount an attack against the tumor.

Researchers are now looking at other ways to use the immune system to battle cancer, including exploring the use of other checkpoint proteins. The programmed-death 1 (PD-1) receptor and its ligands PD-L1 and PD-L2 are part of the same family of coregulatory molecules as CTLA-4. The PD-1 receptor is expressed on the surface of activated T cells and a variety of other effector cells; its ligands, PD-L1 and PD-L2, are present on a lot of tissues—including tumors but also
some cells of the immune system itself, including T cells. Because some cancer cells have PD-L1 on their surface, drugs targeting the PD-1/PD-L1 pathway appear most effective in patients whose tumor cells make PD-L1 (7). Cancer cells exploit the PD-1 pathway to create an immunosuppressive environment in which they are able to thrive. Several agents targeting the PD-1 pathway have entered clinical testing, and current research also includes combining different immunotherapies with one another and with other types of existing cancer treatments to make them as effective as possible (8).

Now back to SABCS, the international breast cancer conference where immunotherapy sparked such interest. Results presented by Teemu Junttila and colleagues, researchers from Genetech, the California-based biotech company that is part of the pharmaceutical giant Roche, provided promising evidence on combination immunotherapies that can fully engage T-cell immunity. In an oral presentation entitled, “HER2 T cell dependent bispecific antibody (HER2-TDB) for treatment of HER2 positive breast cancer,” Juntilla reported on a T cell targeted therapy with a trastuzumab-based HER2 T cell-dependent bispecific antibody, HER2-TDB (9). Treatment advances for HER2 positive patients affect a large number of breast cancer patients: between 20-25% of invasive breast cancers overexpress the human epidermal growth factor receptor (HER2), and unfortunately the majority of patients with metastatic breast cancer who initially respond to the Genentech drug trastuzumab (Herceptin) develop resistance with one year of beginning treatment with the drug, and earlier stage patients treated with the drug also experience eventual progression of their cancer. Genentech hopes that HER2-TBD will overcome this resistance and destroy tumor cells in patients who have stopped responding to currently approved HER2 targeted drugs such as trastuzumab, providing proof-of-concept for combination therapy (9,10).

Based on the recent clinical success of tumor immunotherapies that block immune suppression to restore T cell function, the research team from Genentech produced an antibody (HER2-TDB) that activates T cells, resulting in the destruction of HER2 expressing cancer cells. Because the therapy works in a way unrelated to HER2 signaling or sensitivity to chemotherapy, HER2-TBD
can overcome the resistance to currently approved HER2 therapies. To do so, HER2-TBD uses a combination of two immune therapies, directly recruiting T cells together with inhibiting T cell suppressive signaling. In mouse models, the researchers demonstrated that PD-L1 expression inhibited the ability of antibodies to recruit T cells. This sign of cancer resistance was reversed, the researchers reported, with anti-PD-L1 therapy and the combination of HER2-TDB with anti-PD-L1 immune therapy resulted in inhibition of tumor growth. While these findings are promising, HER2-TDB must undergo evaluation for safety in its next step towards use in the clinic (9,10).

Another oral presentation at SABCS focused on the PD-1 receptor-ligand pathway. In her talk entitled, “A phase Ib study of pembrolizumab (MK-3475) in patients with advanced triple-negative breast cancer,” Rita Nanda, assistant professor of medicine and associate director of the Breast Medical Oncology Program at the University of Chicago, presented findings on pembrolizumab, a drug designed to block PD-1 interaction with its ligands PD-L1 and PD-L2, thereby reactivating the immune system to seek out and destroy tumor cells (7). Pembrolizumab is a humanized monoclonal antibody that targets PD-1, “taking the brakes off” the immune system to allow it to attack the tumor. In 2014, pembrolizumab became the first PD-1-targeted drug to receive FDA approval; it was granted breakthrough therapy status due to unprecedented results in recent early clinical trials in patients with melanoma (2).

In a multicenter, non-randomized phase Ib clinical trial, called KEYNOTE-012, 32 women with PD-L1 expressing triple-negative breast tumors were given intravenous infusions of the single agent MK-3475 (pembrolizumab, also known as KEYTRUDA), which was assessed for safety, tolerability, and anti-tumor activity. This was the first report of clinical activity of an immune checkpoint inhibitor in triple negative breast cancer (TNBC), an aggressive form of breast cancer where the cancer cells do not have estrogen or progesterone receptors and do not have too much HER2, a growth-promoting protein. Approximately 15-20% of breast cancer patients are diagnosed with TNBC, which has no approved targeted therapies and a poor prognosis (7).
Preliminary results from this study suggest that pembrolizumab is a well-tolerated and effective therapy in a subset of patients who have undergone numerous previous treatments for advanced TNBC, although 5 patients (15.6%) experienced at least one drug-related serious adverse event. The overall response rate was 18.5%, which included one patient with complete response and four (14.8%) partial responses. In addition, seven patients (25.9%) had stable disease. Nanda commented that this study shows that a small proportion of patients may respond to treatment with pembrolizumab, and those that do tend to be long-term survivors. A Phase 2 study is planned for 2015 (7).

Pembrolizumab is also being tested for use in other cancers: the KEYNOTE-012 trial is looking at not only patients with advanced TNBC, but also advanced head and neck cancer, advanced urothelial (bladder) cancer, and advanced gastric cancer. Results from the studies of pembrolizumab in advanced non-small-cell lung cancer (NSCLC), melanoma, gastric cancer, urothelial cancer and head and neck carcinoma, presented during the ESMO 2014 Congress (Madrid, Spain), show promising activity and tolerability (11).

So while we may never be able to prevent all forms of cancer, by harnessing our own immune system we may be able to more effectively fight it. The advances presented at SABCS describing the use of the PD-1 checkpoint blockage drugs pembrolizumab and HER2-TDB are evidence of the promise of immunotherapy to extend the lives of cancer patients and, hopefully, someday cure them.

REFERENCES:


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