One of the newest cancer treatments available to patients today is CAR-T cell (Chimeric Antigen Receptor T cell) therapy. CAR-T cell therapy uses a patient's own cells and re-engineers them to fight cancer.

**CAR-T Therapy: Advocating for Research and Treatment Access** is a recently published series of articles that spotlights the organizations and efforts dedicated to CAR-T research and helping patients access CAR-T therapy. Please accept this complimentary copy as our way of thanking you for your commitment to this community and advocating for healthier futures.

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CONTENTS

Search & Destroy: Chimeric Antigen Receptor T-Cells (CAR-T) ................. 3
   Emily Burke, Ph.D., Director of Instruction, BiotechPrimer.com

Does CAR-T Cell Therapy Belong in Community Clinics? ....................... 8
   Community Oncology Alliance

CAR T-Cell Therapy Gave Me Back My Life ........................................... 10
   Association of Community Cancer Centers

Multiple Myeloma Research Foundation: CART Cell Therapy Initiatives ..... 16
   Multiple Myeloma Research Foundation

The Evolution of CAR-T Therapy .............................................................. 18
   Lee Greenberger, PhD, Chief Scientific Officer, The Leukemia & Lymphoma Society

CAR-T Cell Immunotherapy: What to Expect ........................................... 20
   Claire Saxton, Vice President, Education and Outreach, Cancer Support Community
Search & Destroy: Chimeric Antigen Receptor T-Cells (CAR-T)

Editor's Note: The following article is reprinted, with permission from Biotech Primer. The original version appeared in the Biotech Primer WEEKLY. To subscribe to the Biotech Primer WEEKLY, click here.

The first (and so far, only) chimeric antigen receptor T-cell (CAR-T) therapies—tisagenlecleucel and axicabtagene ciloleucel were approved in 2017, and they remain one of the hottest types of immunotherapies on the market today. They work by boosting the body’s ability to recognize and attack cancer cells. This column reviews the basics of CAR-T technology and takes a peek at CAR-T innovations moving through the pipeline.

Term of the Week: Killer T-Cells

CAR-T therapy is based on a type of white blood cell called a killer T-cell. The job of these cells is exactly what the name implies — to kill dangerous cells. They target diseased cells in the body via cell-surface receptors: each has a uniquely shaped receptor and recognizes its intended target because the shape of its receptor “matches” or fits into a uniquely shaped surface protein found only on diseased cells. Once the killer T-cell “docks” onto its target, it injects an enzyme which triggers death. The result: no more bad cells.

Why CAR-T?

In theory, our immune system should recognize the unique proteins presented on cancerous cells. However, there are two main reasons this doesn’t always happen:

1. Early on in tumor development, the cell composition is similar enough to healthy tissue that it can be overlooked by the immune system.
2. Later, as a tumor progresses, it releases chemical signals that suppress the immune response, helping it to evade detection. This trickery is known as the tumor microenvironment and once again the dangerous cancer cells can pass by undetected.

So what’s a scientist to do? Figure out a way to train killer T-cells to ALWAYS recognize and destroy cancer cells…enter CAR-T.

**How to Train an Immune System**

CAR-T therapies boost the body’s ability to recognize and attack cancer cells. These “super” killer T-cells have been physically enhanced to go after cancer. Like the mythical chimera, this drug is composed of different parts. Genetic engineers fuse an antibody with a killer T-cell receptor to create a chimeric molecule—the “C” in CAR-T.

The transformation begins with technicians removing killer T-cells from a patient’s body and isolating them in the lab. Next, scientists use a viral vector—a virus that has been modified to contain a therapeutic gene—to deliver a gene that encodes the chimeric receptor to the T-cells.

The enhanced receptor includes two parts: a targeting domain and an activation domain. The first is the portion that remains on the surface of the T-cell. It’s an antibody that detects and locks onto a specific surface protein on the patient’s malignant cells. The activation domain part of the receptor is triggered once the targeting domain attaches itself to the desired cancer protein.

The engineered T-cells are then reinfused into the patient, at which point the targeting domain finds the proper surface protein on the tumor cell and attaches to it. Then, the activation domain signals the killer T-cell to:

- Stay alive.
- Make copies of itself (replicate).
- Release cytokines—chemical signals that activate other white blood cells to assault the tumor.
- Kill the target cell.
What’s in a Name?

Chimeric antigen receptor therapy broken down:

- **Chimeric**: Composed of components from two distinct parts, such as an antibody and a killer T-cell.
- **Antigen**: A protein that is recognized by an antibody, such as a protein on the surface of a tumor cell.
- **Receptor**: A protein that is embedded in a cell membrane and transmits signals to itself in response to being activated, for example a T-cell receptor transmits signals to the T-cell when it docks onto its target.
- **Therapy**: A treatment meant to manage or cure a disease

Tricky Terminology

The medical community classifies CAR-Ts as a “cell-based gene therapy.” They’re immune cells that have been engineered using gene therapy techniques.

Next-Generation CAR-T

The current generation of CAR-Ts have the potential to cause serious safety issues in some patients. While highly effective against blood cancers, their results have been less impressive when targeting solid tumors. Finally, existing CAR-T therapies are patient-specific, which adds to their expense and the time required for their production. Let’s take a look at each of these issues in turn and examine some steps that are being taken to address them.

Eye of the Storm

One of the reasons CAR-T treatments are so powerful is because once activated, they multiply inside of the body, and release inflammatory molecules called cytokines. Cytokines serve two core functions:

- They activate additional white cells to fight pathogens.
- They stimulate white blood cells to move towards inflammation.

Cytokine signaling makes for a quick, strong, and usually appropriate immune response via a positive feedback loop in which activated white cells release more activating cytokines. The response typically dissipates when the pathogenic cells have been destroyed. However, sometimes the feedback loop just keeps looping. This phenomenon is called a cytokine storm, and leads to acute inflammation with high fever, swelling, and/or nausea. It sometimes causes serious tissue damage and even death. For example, excess fluids can seep into the lungs and cause them to fail. Although uncommon, cytokine storms pose the biggest risk of CAR-T treatments.
Calming the Storm

Tocilizumab has been approved for the treatment of cytokine storms in patients undergoing CAR-T treatments. The drug is a monoclonal antibody therapy designed to "mop up" excess interleukin 6, an inflammatory cytokine.

Biopharma companies are also working on new CAR-T treatments with controls to regulate cytokines and minimize storms. First generation CAR-T therapies induce maximum white cell activity—a full cytokine barrage. Their intensity makes tamping down the cytokine response impossible.

In one example of next generation therapy, patients take an adjunct small molecule drug during their CAR-T infusion. This sidekick medicine provides an on/off switch for the CAR-T therapy. It turns on the therapy to fight the cancer. Should a cytokine storm ensue, doctors can immediately withdraw the adjunct drug, turning off CAR-T and ultimately stopping cytokine release.

Solid Tumors

So far, CAR-T has proven most effective against blood cancers. Targeting solid tumors is more difficult, in large part because tumors contain cells that secrete anti-inflammatory cytokines, or cytokines that turn the immune response down. Solid tumors can also be difficult to penetrate, meaning CAR-Ts can’t always effectively access malignant cells on the tumor’s interior.

One way to combat this immunosuppressive environment is to engineer CAR-Ts to secrete specific inflammatory cytokines designed to beef up their ability to attack solid tumors. One turbo-charged CAR-T in development releases interleukin 12 when triggered. Interleukin 12 is a cytokine known to combat the tumor’s immunosuppressive environment. When combined with small molecule controls for safe activation of the CAR-T, this immune-activating protein should be released in a safe and controlled manner.

Natural Killers

Another approach to targeting solid tumors with CAR technology is to use a different type of white blood cell that more easily penetrates solid tumors. Enter natural killer (NK) cells. These white blood cells are a part of our innate immunity, or the immune response that is activated immediately in response to any threat. Most immunologists think that NK cells play a role in recognizing and killing off cancer cells that arise in our body and are able to more easily penetrate solid tumors. However, early-stage cancers often aren’t recognized as a threat. By modifying NK cells with a CAR that targets them to a specific tumor type, their killing ability can be put to work. CAR-NK therapies are now in Phase I/II clinical studies for B-cell malignancies.

Chowing Down on Cancer

Macrophages are our body’s scavengers. The name derives from a Greek phrase meaning “big eater.” These cells kill infectious or diseased cells by surrounding and digesting them. Think of a sloppy Pacman. After a macrophage meal, minute bits of foreign cell proteins or antigens remain on its surface. The leftovers help activate some of the immune system’s other defenses, such as killer T-cells.

Biopharma companies are carrying out preclinical development of CAR-macrophages to destroy specific cancer cells. The amped up macrophages will simultaneously trigger other immune cells to recognize and attack those same antigen-bearing cells. Like other macrophages, CAR-macrophages can penetrate solid tumors much more effectively than basic T-cells.
Off-the-Shelf CAR-T

First generation CAR-T has been patient-specific, or autologous. In other words, T-cells are first removed from the patient to be treated, modified, and infused back in. Customizing CAR-T in this manner is time consuming and expensive but necessary to avoid immune rejection.

A few different companies are exploring ways to create allogeneic or “off the shelf” T-cell therapies that can be used with any patient. The trick is to remove the telltale signs that allow the recipient’s immune system to recognize the engineered T-cell as foreign. Strategies in preclinical development use genome editing to remove the genes responsible for immune rejection.

We’re still wowed by first-generation CAR-T, but biopharma companies have safer, more effective, and more versatile second-generation therapies coming down the pipeline. We’ll be watching their development closely.
Does CAR-T Cell Therapy Belong in Community Clinics?

CAR T-cell therapy (CAR-T) has emerged as a highly innovative and promising option for patients with cancer. Until recently, the use of CAR-T has been restricted to small clinical trials, primarily with patients with advanced blood cancers. These trials often are conducted at large, academic medical centers in major metropolitan areas.

As CAR-T continues to evolve, and new therapies are developed and brought to market, will they be accessible to all cancer patients, especially the large number of people with cancer who are treated in community oncology clinics? Real World Health Care sat down with Frank Senecal, MD, a medical oncology provider with Northwest Medical Specialties, PLLC, in the Tacoma, Washington area, to find out. Dr. Senecal is an active member of the Community Oncology Alliance (COA), a non-profit organization that advocates for community oncology patients and practices.

Benefits of Community Oncology

Real World Health Care: How does the COA help to support cancer patients?

Frank Senecal: The mission of the COA is to ensure that cancer patients receive quality, affordable and accessible cancer care in their own communities. Cancer treatments can be intense and span many years, requiring regular physician visits. Keeping patients close to their homes, families and support networks lessens the burden of this devastating disease.

For 17 years, COA has built a national grassroots network of community oncology practices, like mine, to advocate for public policies that benefit patients. One part of that work is that we identify treatments and technologies that can be safely provided in the community clinic environment and work with regulatory agencies to get those treatments approved for community clinic implementation. Our members, who come from all levels of cancer care delivery, volunteer their time on a regular basis to lead COA and serve on its committees.

Delivering the Promise of CAR-T

RWHC: How is the COA working to ensure that patients treated in community oncology clinics have access to new treatment options like CAR-T?

FS: The COA has stated formally that the Centers for Medicare & Medicaid Services (CMS) should not limit CAR-T site of care appropriateness strictly to hospitals. Limiting coverage for CAR-T therapy to the hospital setting will exclude other viable settings of care and limit patients’ options when trying to locate a provider. It is the COA’s position that any well-staffed and experienced sites, or clinics, that can meet the quality, safety and operational prerequisites for delivery of CAR-T treatment should be able to provide such treatment.
One key clinical trial supports this theory, in that 26 percent of adult patients in trials were infused in the outpatient setting. Another study showed decreased resource utilization for patients receiving CAR-T infusion in the outpatient setting, including a 40 percent decrease in their number of hospital days.

Many community cancer centers have the qualifications and experience to administer highly complex treatments like CAR-T. As a point of reference, consider stem cell transplants, which are similar in complexity to CAR-T therapy, and are performed successfully in the community oncology practice setting. Bispecific antibodies also are being administered in community, non-academic settings.

Indeed, some community oncology practices already have or are currently participating in studies on CAR-T and have demonstrated abilities in apheresis, cell processing and infusion, and lymphodepleting chemotherapy, as well as toxicity management.

For example, my clinic is involved in the TRANSCEND-PILOT-017006 trial, and enrolling patients to determine the efficacy and safety of a CAR-T line for aggressive B-cell non-Hodgkin lymphoma (NHL) in patients who have relapsed after conventional therapy and for whom stem cell transplant is not an option due to age or co-morbidities. Ours is the only site in the northwestern United States participating in this international trial and one of the few community clinics participating. Demonstrating the expertise to carry out a trial in the community clinic setting will be an important step toward bringing CAR-T therapy to more patients.

Managing CAR-T Side Effects in Community Clinics

**RWHC:** Are community clinics equipped to handle adverse side effects such as cytokine release syndrome (CTS) and neurotoxicity?

**FS:** Fortunately, we’re seeing CAR-T toxicities reducing as engineering improves and better CAR-T cell constructs are developed.

Safety is, of course, paramount when making decisions around site-of-care eligibility. As stated previously, a basic requirement to administer CAR-T therapy includes toxicity management. Community clinics aren’t going to get involved in CAR-T unless they have the staff and expertise to recognize and react properly to symptoms. They need a 24/7/365 organization of doctors, nurses and clinical staff that can be responsive to patients, for example, if symptoms develop at home, and get them in, evaluated and cared for.

Some community oncology clinics, including mine, participate in the oncology medical home model, which focuses on coordinating the highest quality care in an accessible, efficient manner and in the lowest cost setting for the patient. This structure is ideal for supporting emerging treatment options like CAR-T. Plus, many community clinics have established relationships with hospitals, which can be leveraged if needed.

The Cost of CAR-T Therapy

**RWHC:** How does the cost of CAR-T therapy affect the ability of patients in community clinics to access the treatment?

**FS:** Community oncology practices are less expensive settings for care, and studies show that the cost of care and the rate of emergency department utilization are lower for patients in the community setting than those in hospital outpatient departments. I expect that, while hospitals will continue to play an important role, we will eventually see more patients receiving CAR-T therapy on an outpatient basis.
Dr. Robyn Stacy-Humphries

CAR T-Cell Therapy Gave Me Back My Life

Editor’s Note: This week, Real World Health Care shares an inspirational story of a woman who was diagnosed with lymphoma and received treatment with CAR T-cell therapy. “CAR-T Cell Therapy Gave Me My Life Back” is reprinted with permission from the Association of Community Cancer Centers. Updated in April 2020, it was originally published on July 11, 2018 in ACCCBuzz Blog.

A Cancer Odyssey

When Robyn Stacy-Humphries, MD, was 48 years old, she discovered a supraclavicular lymph node. As a radiologist whose expertise lies in oncologic imaging, she knew right away that this discovery was “bad news,” since lymph nodes in this location are usually associated with lung, gastric, and ovarian cancer, as well as lymphoma. Ultrasound and a CT scan showed several tiny lymph nodes in her neck and core biopsy confirmed diffuse large B-cell lymphoma (DLBCL).

Although the news was devastating, Robyn knew that large cell lymphoma is potentially treatable with standard chemotherapy of RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone). She remembers RCHOP as “tolerable” and was able to work during treatment, having chemotherapy on a Friday and going back to work on Tuesday.

Robyn was declared in remission after three cycles of treatment but completed the full six cycles of RCHOP as per guidelines. Four years later she felt another lymph node in her neck, which was biopsy-confirmed as relapsed DLBCL. This news was “pretty devastating, because with even the first relapse your chance of survival — let alone cure — decreases dramatically.”

This time Robyn was treated with salvage chemotherapy followed by autologous stem cell transplant (ASCT) and external beam radiation. She describes the two cycles of chemotherapy as “brutal,” but continued working until she received ASCT. Treatment was complicated by sepsis and a stay in intensive care. Robyn remembers being “delirious for about two days, and that was frightening.” Following discharge on IV antibiotics, Robyn had head and neck radiation, after which she was unable to swallow solid food and her BMI plummeted from 22 kg/m$^2$ to around 16 kg/m$^2$.

Three and a half months after the transplant, Robyn was in complete remission. However, in April 2016, following a trip to the Galapagos Islands, the lymphoma relapsed a third time. This is a bleak prospect for any patient as the only option for treatment is allogeneic transplant. But Robyn has no siblings and knew she did not have a match.
What Is CAR-T Cell Therapy?

The annual report of the American Society for Clinical Oncology (ASCO) named chimeric antigen receptor (CAR) T-cell therapy 2018 Advance of the Year.¹ This accolade came four months after the U.S. Food and Drug Administration (FDA) approved tisagenlecleucel for the treatment of patients up to age 25 years old, with refractory or second or later relapse B-cell precursor acute lymphoblastic leukemia.²

This first approval for adoptive cell immunotherapy represented a major innovation for patients with hematologic malignancies and was followed by approval of a second CAR T-cell therapy, axicabtagene ciloleucel, to treat patients with several types of relapsed or refractory large B-cell non-Hodgkin lymphomas (NHL), including diffuse large B-cell lymphoma (DLBCL), after two or more lines of systemic therapy.³ The indication for tisagenlecleucel has also now expanded to include the treatment of adult patients with relapsed or refractory large B-cell lymphoma after two or more lines of systemic therapy.

CAR T-cell therapy involves filtering a patient’s own blood to remove T-cells and engineering them by gene transfer technology to express chimeric antigen receptor. These CAR T-cells are expanded in number and re-infused to the patient, who has typically undergone preconditional lymphodepletion with chemotherapy. The CAR receptor binds to the target antigen on the tumor cell, activates the signaling domains, and initiates CAR T-cell cytokine release, anti-tumor activity, expansion, and persistence.⁴⁻⁶ The re-infused CAR cells expand in vivo, amplify the anti-tumor response, and facilitate ongoing tumor surveillance.

Proactivity Pays Dividends

Because Robyn is a physician, she had prior knowledge of Phase 1 studies investigating CAR T-cell therapies and had been proactively researching Phase 2 trials via clinicaltrials.gov. In 2015 no trials were available for patients who failed first-line therapy, but by April 2016 Robyn had failed first and second-line therapy. She again researched clinicaltrials.gov and discovered that she met eligibility criteria for every chimeric antigen trial in the United States at that time. The catch was that all the trials were full.

After emailing contacts identified from the clinicaltrials.gov website, Robyn discovered a Facebook site called Physician Moms Group, which has 65,000 members across the world. She posted that she was a lymphoma patient in search of a CD-19 CAR-T trial but was unable to find a space. That afternoon, after a friend bumped her post up the Facebook feed, Samantha Jaglowski, MD, MPH, a hematologist in Ohio, posted that she had a spot that had just opened up in a Phase 2 trial at The James Cancer Center in Ohio.

“Like Ice Cubes Melting”

CAR T-cell therapies are currently limited to specialized treatment centers like The James that are involved in clinical trials and certified under a Risk Evaluation and Mitigation Strategy (REMS). Two weeks after Robyn’s relapse was diagnosed and four days after learning about this open spot, she flew to Ohio and was accepted into the trial, returning two weeks later to have her T-cells harvested.

There was a slight hitch, however. During the manufacturing process, Robyn’s cells expanded in number above the limit for dosing, so her case had to be reviewed by the FDA, which delayed treatment, creating considerable anxiety for Robyn and her husband. While she waited for FDA approval, Robyn received bridging chemotherapy with ibrutinib, which put her into remission.

Prior to commencing CAR T-cell treatment in September 2016, she had to stop her ibrutinib therapy and, with no treatment, her lymphoma returned with several palpable lymph nodes. Yet, Robyn recalls, within 24 hours of being infused with high-dose T-cells “the lymph nodes were half their size; within three days they were gone. It was like ice cubes melting.”
Managing Adverse Effects and Care Coordination

The initial side effects from CAR T-cell therapy can be significant. CAR T-cell therapies carry a black box warning for cytokine-release syndrome (CRS) and neurological events. Patients may also develop macrophage activation syndrome, hemophagocytic lymphohistiocytosis, tumor lysis syndrome, cytopenia, and febrile neutropenia.7-10

Although Robyn developed CRS with fever and hypotension five days after infusion and was readmitted to the hospital for adverse event management, she emphasizes that her side effects were relatively minor. Overall, she spent only four days as an inpatient (one for inpatient infusion and three for adverse event management) and the rest of her therapy as an outpatient. Since treatment Robyn has had three upper respiratory infections that were all treated with antibiotics as an outpatient.

Robyn says this is typical of other patients she has spoken with via a Facebook group (CAR-T Cell Patients and Carers) that she hosts for people who have been in clinical trials across the United States. Although the initial side effects can be significant, almost everybody returns to normal, and compared with radiation or stem cell transplantation, Robyn feels that CAR T-cell side effects are less intense. In fact, she continues to have permanent side effects from high-dose chemotherapy and radiation.

“I have osteoporosis and muscle mass loss from extensive chemotherapy,” she says. Due to radiation therapy, I have hypothyroidism, partial vocal cord paralysis and dry mouth. Unfortunate side effects but granted, I am alive and grateful to be here. I have no severe effects from CAR-T that I experience in everyday life.”

The other major side effect with CAR-T that can be significant is fatigue, which Robyn described as “like flu, with myalgias, aches, pains, and you want to sleep more. But you’re still functioning. In contrast, SCT fatigue was crushing and really difficult to get out of bed.” Many of the CAR-T patients that Robyn has talked to have had severe reactions to bug bites, although this adverse event has not yet been published in the literature.

However, Robyn cautions that after CAR-T treatment completion some patients experience sharp, intermittent pain wherever the tumors were located (e.g., neck or groin). Although this pain dissipates eventually, Robyn experienced this pain in tumor areas for a year. Muscle cramps can also be common and there can be secondary dermatology side effects due to B-cell aplasia.

Robyn is a determined person who faces life with grit and positive energy, so it should be no surprise to learn that she returned to work within four weeks of being treated with CAR-T, and one year after treatment she was managed solely by an internist and an immunologist in her community.

In order to optimize the process of transitioning from treatment center to home, Robyn emphasizes that, as in her own case, patients need to have an oncologist that understands the basics of chimeric antigen and who can communicate effectively with the treating oncologist about follow-up care. It is also important for clinicians to prepare families that “their loved one may be very confused for a couple of weeks but will come out of it.”

Paying for Treatment in a Clinical Trial

Like all immunotherapies, CAR T-cell therapies come with a high price tag. The $474,000 for tisagenlecleucel and $373,000 for axicabtagene ciloleucel include only the cost of therapy, engineering, and infusion, and not
costs for hospital stays not associated with infusion, supportive care, or physician visits, which can cost up to $500,000.\textsuperscript{11,12}

Robyn paid for her travel to The James for initial evaluation, after which the therapy manufacturer paid travel, accommodation, and caregiver (her husband) costs. She was initially required to stay in the area for blood draws every two to three days, and after 30 days returned home, traveling to Ohio for monitoring once per month for one year. The manufacturer also reimbursed these flights. Other medical expenses were not reimbursed, such as standard blood work, staging CT scans, and initial staging excisional biopsies, and Robyn emphasizes the importance of having insurance backup to cover these costs.

She also points out that although the costs associated with CAR T-cell therapy are high, they need to be compared with the cost of allogeneic transplant or ibrutinib, which has to be taken every day for an indefinite period. Although the average cost for allogeneic transplant in the United States is $800,000,\textsuperscript{13} allogeneic transplant is associated with higher transplant-related morbidity compared with autologous SCT, and treatment-associated mortality ranging from 20-50\%.

In contrast, CAR T-cell therapy is associated with a response rate of almost 60\% and an approximately 30\% remission rate. For this reason, Robyn says no cost would have been too high.

“The cost, I was willing to pay whatever,” she said. “I would have mortgaged my house. Whatever it would have taken, I would have done it. And the distance we were willing to go and do whatever we had to do. If the manufacturer had not paid for that, we would have paid for it. I knew it was my best chance, and it was my one chance for a cure really. And there are no guarantees this is a cure; but I am now in remission for 42 months. In the Phase 1 trial of my drug, there were 28 people, and 12 patients were in complete remission and still alive 3-4 years after CAR T-cell therapy.”

On August 7, 2019, the Centers for Medicare & Medicaid Services (CMS) issued a final National Coverage Decision (NCD) for CAR-T therapy. As outlined in the NCD, Medicare will cover CAR-T cell therapies nationwide; provide coverage when CAR-T therapy is administered in inpatient or in outpatient healthcare facilities that are enrolled in an FDA Risk Evaluation and Mitigation Strategies (REMS) with expertise in delivering cellular therapies; and cover off-label uses of CAR-T therapy that are recommended by CMS-approved compendia.\textsuperscript{15}

### Considerations in Clinical Trial Participation

Several clinical trials are being launched to investigate CAR T-cells in the treatment of multiple myeloma, relapsed DLBCL, follicular lymphoma, and solid tumors, and over 20 CAR T-cell therapies are currently in the clinical pipeline.\textsuperscript{16} Although Robyn knew that a clinical trial was her best bet for treatment and was able to draw on her clinical background to help navigate the available evidence and options, she has learned from other patients that there is a lot of anxiety associated with CAR T-cell clinical trials.

First, some patients have concerns about the origins of chimeric antigen. They have read that the HIV virus is used to insert the CAR onto the T-cell but do not understand that the therapy itself is not related to AIDS. Researchers used a deactivated virus to help them understand how to genetically alter T-cells.\textsuperscript{17}

Second, many patients assume that any therapies which are not FDA-approved are not legitimate treatments, and so the notion that patients are being used as “guinea pigs” is a significant barrier to participating in clinical trials.

To counter these myths and anxieties, Robyn suggests: “\textit{There needs to be patient education about the fact that clinical trials are cutting edge and often they’re your best chance for survival. It takes a long time to bring a life-saving treatment to commercial availability, so people should consider these trials because this is really}”
the best treatment they can get. Physicians can talk with their patients about the fact that this is often the best treatment.”

These conversations are especially important in the context of B-cell NHL, for which allogeneic transplant is the standard therapy.

“It is a difficult transplant that many people do not survive, and even when they do, they may be severely debilitated and unable to work,” she said. “But these statistics do not seem to reach the patient, versus hearing that a few patients died in a CAR-T clinical trial. Well, that’s a small percentage compared to the people who died with allogeneic transplant.”

To help patients navigate clinical trial options, Robyn suggests that clinicians can share data that compares allogeneic SCT with CAR-T therapies and use specific examples of patients who have reaped the benefits of participating in clinical trials, and who, as Robyn notes, “have their lives back.”

“I want to stress though that CAR-T has given me my life back,” she said. “My theme is to live life like you are dying, because I was dying, and now I am taking every chance I can to do bucket list trips and make the most of every moment.

Conclusion

Not only does Robyn have her life back, but she is living it fully and sharing her story as widely as she can. She was named one of the Top Doctors in Radiology by Charlotte Magazine in 2018 and again in 2020.

“I’ve wanted to be a doctor since I was five years old,” she concluded. “I graduated from college in three years. I graduated from medical school in three and a half years, went straight to residency, fellowship. This is what I do. I’ve read hundreds of thousands of exams, I’ve done thousands of biopsies, but ironically my biggest contribution to medicine may be not as a doctor, but as a patient.”

About the Association of Community Cancer Centers

The Association of Community Cancer Centers (ACCC) is the leading education and advocacy organization for the cancer care community. Founded in 1974, ACCC is a powerful network of 25,000 multidisciplinary practitioners from 2,100 hospitals and practices nationwide. As advances in cancer screening and diagnosis, treatment options, and care delivery models continue to evolve, so has ACCC—adapting its resources to meet the changing needs of the entire oncology care team. For more information, visit accc-cancer.org or call 301.984.9496. Follow us on Facebook, Twitter, and LinkedIn; read our blog, ACCCBuzz; and tune in to our podcast, CANCER BUZZ.

References

Multiple Myeloma Research Foundation: CAR-T Cell Therapy Initiatives

Last year, the Multiple Myeloma Research Foundation (MMRF) launched a new, three-year strategic plan to help transform how multiple myeloma is treated and ultimately cured. One of the plan’s three strategic pillars focuses on immunotherapy, including chimeric antigen receptor T-cell (CAR-T) therapy.

Real World Health Care spoke with the MMRF’s Anne Quinn Young, MPH, Chief Marketing and Development Officer, and Hearn Jay Cho, MD, PhD, Chief Medical Officer, about the potential of CAR-T therapy and how the MMRF is supporting research on individualized, targeted therapies for multiple myeloma patients.

Building Partnerships for CAR-T Therapy Innovation

**Real World Health Care:** How does the MMRF support CAR-T research?

**Anne Quinn Young:** The MMRF is a bit different than other groups. From the very beginning, we’ve focused first on our strategic plan and then used that strategic plan to guide our scientific plan.

One of our initial tasks was to bring together all the critical players in the multiple myeloma ecosystem—researchers, clinicians, industry and the FDA—and through a series of topic-focused roundtables and workshops, create solution-driven action plans.

Our goal is to bring new, more precise treatments to patients faster, and we’ve implemented several important foundational elements to help us reach that goal. We established a multi-center tissue bank at the Mayo Clinic in Scottsdale, Arizona, from which samples were used to sequence a myeloma genome. We’ve helped to open more than 80 trials across a clinical network of more than 24 sites. And, we have a longitudinal study called CoMMpass, in which we’ve been collecting genomic and clinical data, and are now expanding to include immune data as well. This data and the tissue bank samples are huge assets.

Filling the ‘White Space’ in CAR-T Therapy Research

**RWHC:** What are some of the challenges MMRF faces in moving your CAR-T therapy research agenda forward?
Hearn Cho: There’s a bit of a paradox in CAR-T therapy research. We’re seeing unprecedented initial response rates, but progression-free survival has fallen short of expectations. Now, if we were talking about any other type of therapy that gave 12 months of progression-free survival, we would celebrate. But because it’s CAR-T therapy, it’s somehow viewed as disappointing.

CAR-T therapy research is unique because the capital costs involved in T cell engineering and trials are much higher than with standard drug or antibody trials. Although CAR-T therapies are born in academia, the transition to clinical trials requires the assets of industry, which is shouldering most of the costs. The MMRF respects that dynamic and strives to not be redundant in the trials we support. Instead, we strive to fill the “white space” in the clinical trial landscape.

One of those white spaces is mechanisms of action and resistance and understanding how an individual’s immune system and tumor state affects their outcomes. Also, because each CAR-T cell is unique in terms of its target, signaling domains and composition, each is a class of drugs unto itself. Understanding how these agents act in a different disease, under different circumstances, with different targets is essential.

Consortium Focuses on Collaborative Research

RWHC: Tell us about how MMRF is bringing the multiple myeloma community together to address some of these issues.

HC: MMRF has established the Multiple Myeloma Research Consortium (MMRC) to bring together academic and community cancer centers with industry, to advance innovative Phase I and Phase II clinical trials.

MMRF also is making an enormous investment in a project called the Immune Atlas, a gold-standard immune profiling platform for myeloma research and clinical studies. We are utilizing the assets from our collective tissue bank and CoMMpass samples and partnering with five leading academic centers from our MMRC, which will employ cutting-edge analytical technologies to comprehensively characterize the immune repertoire and activity of key immune cell populations in myeloma patients. We expect the platform to generate robust immune data that drives future research and eventually enables clinicians to customize treatments and therapies that will work best with individuals’ immune systems.

AQY: We are trying to get to the point where we can identify subgroups of patients and better predict which treatments they will benefit from. Correlative studies and translational research—two areas in which MMRF excels—are important to achieving this end. We know that CAR-T therapy has a place for some patients. Now we need to identify who those patients are. We also need to consider the patients who lie outside of the typical response rates. Do we focus on making the treatment better, or do we just not treat those patients who aren’t likely to benefit?
The Evolution of CAR-T Therapy

Over the past two decades there’s been tremendous progress in understanding how to harness the body’s immune system to fight cancer. Today, immunotherapy is a mainstay of cancer treatment. One of the most exciting areas of immunotherapy is CAR (chimeric antigen receptor) T-cell therapy. This treatment involves purifying a special type of white blood cell, called a T cell, which is isolated from a cancer patient’s blood and then genetically engineering in the laboratory to find and kill cancer cells. Once complete, the re-programmed T cells are reintroduced to the patient’s body to fight their cancer. It’s now very clear that this method works!

Early CAR T Development

The first CAR T cells were created more than 30 years at the Wiesmann Institute of Science in the laboratory of Dr. Zelig Eshhar. It took more than two decades to learn how to super-activate the CAR T cells, mass produce them and understand how to use them to control cancer. The Leukemia & Lymphoma Society (LLS) recognized the great promise of this treatment for blood cancer patients and has been supporting research and development of CAR T cells since the 1990s. LLS has awarded grants to many researchers dedicated to immunotherapy including Dr. Carl June of the University of Pennsylvania, who is considered a pioneer of immunotherapy. The nonprofit not only funded research and development in academic laboratories, but used its venture philanthropy effort, known as the Therapy Acceleration Program (TAP), to partner with industry to speed up the clinical development of CAR T-cell therapy for blood cancer patients.

LLS’s investment of more than $50 million in cutting-edge gene therapies for blood cancer patients has yielded tremendous returns in progress. Tisagenlecleucel, the first-ever CAR T-cell therapy approved by the U.S. Food & Drug Administration (FDA) in 2017, was developed Leukemia & Lymphoma Society by Dr. June and his team with LLS support. This ground-breaking treatment is used to treat pediatric and young adults patients with B-cell acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma, (DLBCL), the most common type of non-Hodgkin lymphoma (NHL), and several more rare types including primary mediastinal large B-cell lymphoma (PMBCL), high-grade B-cell lymphoma, and DLBCL arising from follicular lymphoma (transformed follicular lymphoma or tFL).

Axicabtagene ciloleucel is approved for the treatment of certain lymphomas. The clinical results have been stunning. When used in many cancer patients who have relapsed or did not respond to all other therapies, CAR T-cell therapy has eliminated the disease for years after a single dose of cells. Nevertheless, CAR T-cell therapy does have significant, but manageable side-effects (most are transient) that require careful monitoring.
Supporting CAR-T Research

LLS continues to support scientists dedicated to advancing CAR-T including Dr. June and his team as they work to develop CAR-T targeting a different molecule, CD38, to work on different blood cancers including adult and pediatric acute myeloid leukemia (AML), T-cell ALL and multiple myeloma.

Significant progress has been made in CAR-T for myeloma targeting the B-cell maturation antigen (BCMA), which is close to FDA approval. LLS is also supporting new work at Dr. Mahdav Dhodapkar at Emory University to further improve BCMA CAR T-cell therapy. Plus, there is convincing clinical data for the use of CAR-T to treat two other types of lymphoma – follicular and mantle cell – that will support FDA filings for approval in the near future.

Safe, Effective Treatment

The next generation of CAR T-cell therapy is focusing on making the treatment safer, more effective, less costly, and accessible to patients with other types of cancers. Expanding on its original concepts, innovations in development will propel CAR-T to new levels. And there are exciting breakthroughs on the horizon – LLS is funding new work under the guidance of Dr. Renier Brentjens (Memorial Sloan Kettering Cancer Center) to develop “armored” CARs – a two-pronged approach to unleashing a patient’s immune system to fight cancer, which will not only target cancer cells, but will release a chemical that knocks out proteins that block the immune system from activating. Off-the-shelf CAR-T, where the T cells can be reprogrammed from healthy donors and used immediately as needed, promises to be less costly and labor-intensive option for patients. In this case, scientists are working to remove the mechanism that will cause donor T cells to attack a patient’s own cells.

Beyond blood cancer, the future of CAR T-cell therapy is promising. Multiple studies are under way to target cancers of the brain, lung, breast and other solid tumors. Laboratory studies have also demonstrated that CAR T-cell therapy can be used to control cardiac fibrosis and other inflammatory diseases in mice. In short, the full potential of CAR T-cell therapy has yet to be realized.

About the Leukemia & Lymphoma Society

The Leukemia & Lymphoma Society® (LLS) is a global leader in the fight against cancer. The LLS mission: cure leukemia, lymphoma, multiple myeloma, and improve the quality of life of patients and their families. LLS funds lifesaving blood cancer research around the world, provides free information and support services, and is the voice for all blood cancer patients seeking access to quality, affordable, coordinated care. Founded in 1949 and headquartered in Rye Brook, NY, LLS has chapters throughout the United States and Canada. To learn more, visit www.LLS.org. Patients should contact the Information Resource Center at (800) 955-4572, Monday through Friday, 9 a.m. to 9 p.m., ET.

About the Author

As the chief scientific officer of The Leukemia & Lymphoma Society (LLS) since 2013, Dr. Lee Greenberger is responsible for planning and executing the strategy for all LLS research programs. This effort includes a grant portfolio with more than 250 active research projects worldwide, as well as the Therapy Acceleration Program, a venture philanthropy initiative currently with 16 assets – three of which have earned FDA approval in the past two years. Dr. Greenberger holds a BA from the University of Rochester and a Ph.D. from Emory University.
CAR-T Cell Immunotherapy: What to Expect

As the largest professionally led nonprofit network of cancer support worldwide, the Cancer Support Community (CSC), including its Gilda’s Club affiliates, is dedicated to ensuring that all people impacted by cancer are empowered by knowledge, strengthened by action, and sustained by community. CSC achieves its mission through three areas: direct service delivery, research, and advocacy.

This article about the side effects of Chimeric Antigen Receptor T (CAR-T) cell therapy is excerpted from CSC’s Frankly Speaking About Cancer series, which can be downloaded from CSC’s web site.

What is CAR-T Cell Therapy?

CAR-T therapy uses a patient’s own immune cells and “re-engineers” them to fight cancer. Some researchers have called these re-engineered cells a “living drug,” and every patient who undergoes CAR-T cell therapy receives CAR-T cells created in a lab just for them.

CAR-T therapy is a very complex treatment. Collecting and altering the cells is difficult and the therapy is only offered at some major cancer centers, primarily to patients with blood cancer. It also is an expensive treatment. Ask if your insurance will cover the drug and hospital costs and if you qualify to get the therapy as part of a clinical trial where the drug cost is covered. Patients may have to travel long distances, so also ask if you can get assistance to cover travel, lodging and food costs for you and a caregiver.

CSC offers no cost Airbnb housing for qualified patients (and/or their caregivers) traveling at least 50 miles for treatment. Since CAR T requires many steps and at times long visits at or near the CAR T center, this program can be very helpful.

Is CAR-T Cell Therapy Right for You?

Patients treated with CAR-T cell therapy typically have cancers that have recurred or progressed following other treatments. The U. S. Food and Drug Administration has approved CAR T Cell therapy for specific types of Leukemia and Lymphomas. Many of the patients eligible for CAR T cellular therapy have few or no other treatment options available. Eligibility for CAR T depends on cancer sub type, general health status and other factors, including having disease(s) other than cancer. Some people respond very well to CAR-T cell therapy while others do not. Some who respond initially relapse over time.

There is great interest in treating other types of cancer, including solid tumors, with adoptive T-cell therapies. Clinical trials are now enrolling patients with different tumor types. Over time, scientists will learn from these trials which CAR-T cell therapies work best for which cancers.

Side Effects of CAR-T Cell Therapy

The side effects of CAR-T cell therapy can be severe and very serious. This is a major reason why this treatment is done only in hospitals that have a team of physicians, nurses and support staff with the expertise
Cytokine release syndrome (CRS) is by far the most serious possible side effect. After CAR-T cells are infused back into the body, they release a large amount of cytokines into the bloodstream. This can cause a wide range of problems. Patients at first experience high fevers, and sometimes nausea, fatigue and muscle aches. Unfortunately, the CRS can progress to more serious life-threatening situations with difficulty in breathing and low blood pressure.

Patients who have more cancer in their bodies are more likely to have severe CRS than patients with less cancer in their bodies. It’s a sign that the treatment is working and there is a positive response. The worst symptoms usually occur in the first days or weeks of treatment. As the number of cancer cells goes down, the symptoms tend to go down as well. Doctors use a variety of medicines to help manage these issues and get patients through the first phase of treatment. These include steroids and drugs that can directly block the action of cytokines. Researchers also are working on ways to minimize the chances of CRS occurring.

Some patients have nervous system side effects, including becoming delirious or having hallucinations or seizures. Problems affecting the brain and nervous system can be very severe and life-threatening, lasting from days to weeks for some patients.

Another possible side-effect is B cell aplasia, or the loss of normal B cells. Many CAR-T cells target a specific protein called CD19. The protein is found on both normal and cancerous B cells. This means some normal B cells can also be destroyed. This can reduce the body’s ability to protect itself from infections. Doctors use injections of immunoglobulin (immune defense proteins made by healthy B cells) to help prevent infection. B cell aplasia can continue as long as the CAR-T cells persist in the body. So far, this side effect seems to be well managed with immunoglobulin infusions.

Living with CAR-T Cell Therapy Side Effects

Patients who start CAR-T cell therapy will be told about all of the side effects they might have. It is very important that patients and their caregivers tell their doctors about any side effects they experience. Most side effects can be managed if they are treated early.

Patients who do respond to CAR-T cell therapy and get beyond the initial side effects often have few or no long-lasting side effects and live normal lives. However, patients may have long-lasting side effects from their other treatments.

Getting Support

Patients who get CAR-T cell therapy and their caregivers need a high level of support during the process. If you are considering CAR-T cell therapy, you should:

- Have an open and honest discussion with your oncology team about your cancer and its treatment.
- Be willing to change doctors or travel to a different cancer center if your current cancer center does not offer CAR-T cell therapies or CAR-T cell clinical trials.
- Have a caregiver who can provide physical and emotional support before, during and after the treatment.

Patients and caregivers can find support and additional materials about immunotherapy from the Cancer Support Community’s Helpline (888-793-9355) and website as well as your local CSC or Gilda’s Club. The Cancer Support Community’s Open to Options® program offers help for asking questions of your health care team when facing a cancer treatment decision.