

CAR T-Cell Therapy

Update on the state of the science

Misty Lamprecht, MS, APRN-CNS, AOCN®, BMTCN®, and Colleen Dansereau, MSN, RN, CPN



BACKGROUND: Chimeric antigen receptor (CAR) T-cell therapy leverages the power of the patient's own immune system by serving as a bridge to connect genetically modified T cells to the surface antigens of tumor cells based on targeted ligands. Clinical trials have demonstrated compelling overall response and survival rates in individuals with B-cell malignancies. The current approved agents target CD19, an antigen commonly overexpressed in B-cell hematologic and other malignancies.

OBJECTIVES: This article provides information on the current state of the science related to commercially available CAR T-cell products and examines how CAR T-cell science is evolving.

METHODS: An overview of pathophysiology, indications, and nursing implications of the currently approved CAR T-cell agents is presented. Future directions for CAR T-cell development and treatment indications are discussed.

FINDINGS: Tisagenlecleucel (Kymriah®) and axicabtagene ciloleucel (Yescarta®) received approval in 2017 for the treatment of B-cell precursor acute lymphoblastic leukemia in pediatric and young adult patients, and relapsed or refractory diffuse large B-cell lymphoma after two or more lines of systemic therapy in adult patients, respectively. Additional indications have since been approved, and new agents are in development.

KEYWORDS

chimeric antigen receptor T-cell therapy; indications; clinical trials; immunotherapy

DIGITAL OBJECT IDENTIFIER

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THE USE OF CELLULAR THERAPIES TO TREAT CANCER is a rapidly growing and promising new branch in the field of immunotherapy. Immune effector cell therapy is broadly defined as agents that can be leveraged to produce an immune response against targeted tumor cells, and currently include natural killer cells, cytotoxic T lymphocytes, regulatory T cells, dendritic cells, and engineered T-cell receptors (Maus & Nikiforow, 2017). Chimeric antigen receptor (CAR) T cells are described as a living drug; the use of genetically modified T cells, expanded *ex vivo*, to produce an antitumor effect (Fesnak, June, & Levine, 2016). Unlike many oncologic treatments, these cells are designed to target a single surface antigen, resulting in remarkable efficacy at eradicating malignancy. The efficacy of T cells is dependent on the interaction between the CAR T cell and this expressed target, allowing the CAR T cell to bind and initiate an immune response toward the underlying malignancy (Fesnak et al., 2016). Two agents directed toward CD19, a protein commonly overexpressed in many B-cell malignancies, received U.S. Food and Drug Administration (FDA) approval for the treatment of acute lymphoblastic leukemia (ALL) and diffuse large B-cell lymphoma (DLBCL) (Bach, Giral, & Saltz, 2017; Bouchkouj et al., 2018). Additional studies are ongoing to explore the use of CAR T cells and other immune effector cells directed to hematologic and solid tumor malignancies, with increasing products and indications anticipated for approval (Jackson, Rafiq, & Brentjens, 2016; Newick, O'Brien, Moon, & Albelda, 2017). This article presents an evidence-based overview of the current state of the science, including the pathophysiology of CAR T-cell therapy, current and potential future indications, and implications for nursing practice.

Pathophysiology

The premise for CAR T-cell therapy lies in the interactions between the receptors on the surface of healthy T cells and the co-stimulatory ligands on the surface of the antigen-presenting or tumor cell (Fesnak et al., 2016). The co-stimulatory signal from the tumor serves as an on or off switch to the body's innate T-cell response. T-cell receptors serve to either activate or inhibit that immune response, and cancer cells are inherently designed to overcome the body's immune response to proliferate. CAR T cells consist of three modules, extracellular target binding, transmembrane, and intracellular signaling domain (Guedan et al., 2018). These modules work as a bridge, expressing targeted receptors that increase binding to particular types of tumor cells and further unleash the antitumor effect of the T cells that are specifically programmed to engage with these particular tumor cells (Fesnak et al., 2016). A graphical representation of this process can be found in Figure 1.

Several generations of CARs have been produced, seeking the ideal signaling domains to target to elicit the maximum anti-tumor effect. Early CARs were ligand-based and targeted a single signaling domain focused on the CD3 ζ chain (Fesnak et al., 2016). Second-generation CARs have expanded to focus on co-stimulatory domains using single-chain fragment variable with an emphasis on CD28 or 4-1BB ligand (Fesnak et al., 2016). The single-chain fragment variable serves as a link, allowing the CAR to bind to the targeted surface antigen of the tumor cell to initiate the immune response (Fesnak et al., 2016). Third- and fourth-generation CARs are under review to evaluate how additional signaling domains may interact to produce an enhanced disease-specific antitumor effect.

Current Indications

Tisagenlecleucel (Kymriah[®]) received initial FDA approval in 2017 for the treatment of patients who are aged 25 years or younger with B-cell precursor ALL that is refractory or in second or later relapse (FDA, 2017a). This was followed by a 2018 approval for treatment of adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy (Novartis Pharmaceuticals, 2018a). In late 2017, FDA approval was granted for axicabtagene ciloleucel (Yescarta[®]) for the treatment of adult patients with relapsed or refractory DLBCL after two or more lines of systemic therapy (FDA, 2017b; Kite Pharma, 2017). Tisagenlecleucel and axicabtagene ciloleucel are CD19-directed autologous T-cell products. CD19 is the antigen expressed on the surface of B cells and overly expressed on malignant B cells (Maude, Teachey, Porter, & Grupp, 2015). The primary difference in the products is the co-stimulatory domain used to enhance expansion. Tisagenlecleucel uses the 4-1BB ligand (Bach et al., 2017), while axicabtagene ciloleucel uses the CD28 protein (Bouchkouj et al., 2018). Both co-stimulatory domains act in conjunction with the CD3 ζ protein to activate the CAR T cells (Fesnak et al., 2016). Additional trials using these CD19-directed products for other B-cell malignancies are in progress (Jackson et al., 2016).

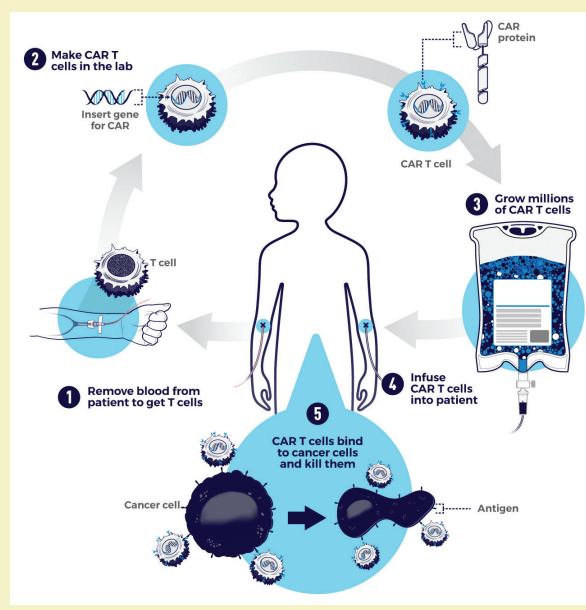
A product developed by Celgene (in collaboration with Bluebird Bio) for multiple myeloma, a disease with no known curative therapies, is expected to be the next FDA-approved CAR T-cell product. This product targets B-cell maturation antigen, which is expressed on the surface of plasma cells (Celgene, 2018).

Manufacturing Process

Manufacturing of autologous CAR T cells is a carefully defined and regulated process (Hollyman et al., 2009; Levine, Miskin, Wonnacott, & Keir, 2016; Wang & Rivière, 2016). The process for treating patients with these products is complex and can be time-intensive. The first step in the process is collecting T cells from the patient to be treated. This is accomplished via apheresis, during which blood is withdrawn from the body and separated using centrifuge (Levine et al., 2016). All blood components

except the one desired—in this case the buffy coat—are then returned to the patient. The buffy coat, including the desired T cells, is then shipped to the processing facility. Clinical concerns for the patient during this stage of the process include large-bore IV access, pain, and infiltration. If peripheral large-bore access is not an option, a central venous catheter is needed (Allen et al., 2017) and may be preferred based on institutional policy. Once in the laboratory, the T cells from the patient's product are isolated (Levine et al., 2016; Wang & Rivière, 2016). These cells are selected via exposure to anti-CD3/CD28-coated beads that trigger ex vivo T-cell activation (Levine et al., 2016; Wang & Rivière, 2016). Various selection options are available, including super-paramagnetic beads and biodegradable beads, which couple to CD3 and CD28 antibodies, allowing for the selection and activation of T cells (Wang & Rivière, 2016). The CAR gene is then attached to the patient's T cells through incubation using an inactivated viral vector, which enters the T cell and introduces the genetically modified material (Levine et al., 2016; Wang & Rivière, 2016). Following development of the CAR T cells, they are expanded in vitro to generate a sufficient number of cells for effective treatment. Target cell volume is product specific and can involve weight-based dosing of the patient. After expansion, the beads are removed and the product is cryopreserved before being shipped back to the treating facility. This process, from

FIGURE 1.
STEPS FOR CREATING CAR T-CELL THERAPY



CAR—chimeric antigen receptor

Note. Image courtesy of the National Cancer Institute. Used with permission. Retrieved from <https://www.cancer.gov>

TABLE 1.
CAR T-CELL THERAPY COMMON TERMINOLOGY

TERM	DEFINITION
Antigen	Any substance foreign to the body that evokes an immune response either alone or after forming a complex with a larger molecule (such as a protein) and that is capable of binding with a product (such as an antibody or T cell) of the immune response
Buffy coat	A concentrated leukocyte suspension
CAR T cells	Artificial receptor that combines an antigen-specificity domain coupled with an intracellular signaling domain expressed by a T lymphocyte
CD	A surface marker that identifies a particular differentiation lineage recognized by a group of monoclonal antibodies
Co-stimulatory domain	A protein that combines with the endogenous T-cell receptor to signal full activation of T cells, resulting in activation, proliferation, and cytokine secretion
Immune effector cells	A cell that has differentiated into a form capable of modulating a specific immune response
iPSC	Cells derived from skin or blood cells that have been reprogrammed back into an embryonic-like pluripotent state that enables the development of an unlimited source of any type of human cell needed for therapeutic purposes
Off the shelf	CAR T cells derived from an allogeneic donor. The antigen-specific receptor is attached while the native T-cell receptor is removed to prevent graft-versus-host disease.
Single-chain fragment variable	Extracellular domain of the CAR T cell, which consists of a fragment of a tumor-specific monoclonal antibody
TCR	TCRs can recognize tumor-specific proteins on the inside of cells. When tumor-specific proteins are broken into fragments, they show up on the cell surface with another protein, called MHC. TCRs are engineered to recognize a tumor-specific protein fragment/MHC combination.
Transduction	The process by which foreign DNA is introduced into a cell by a virus or viral vector
Transgene	A gene that is taken from the genome of one organism and introduced into the genome of another organism by artificial techniques
TIL	TILs are isolated from tumor tissue and cultured with lymphokines, such as interleukin-2. The therapeutic TILs are then infused into the patient, where, after reinfiltration of the tumor, they may induce lysis of tumor cells and tumor regression.
Vector	A virus that carries a piece of foreign DNA to a host cell

CAR—chimeric antigen receptor; CD—cluster differentiation; iPSC—induced pluripotent stem cells; MHC—major histocompatibility complex; TCR—T-cell receptor; TIL—tumor-infiltrating lymphocytes

Note. Based on information from Foundation for the Accreditation of Cellular Therapy, 2018; Leukemia and Lymphoma Society, 2018; Medical Dictionary, n.d.; National Cancer Institute, n.d.; National Institutes of Health, n.d.; Poirot et al., 2015.

collection of the autologous product to return of the CAR T-cell product, takes at least two weeks and is dependent on the rate of cellular reproduction to produce the replication-defective viral vector (Levine et al., 2016).

Because underlying disease and prior treatment can affect the quality of the collected lymphocytes, defined parameters for leukapheresis are followed (Allen et al., 2017). Leukapheresis should occur at least three months after previous stem cell transplantation, with recommended infusion of tisagenlecleucel at least six months after transplantation because of risk for alloreactive lymphocytes (Buechner, Kersten, Fuchs, Salmon, & Jäger, 2018). This time off treatment, combined with time needed for product manufacturing, can require bridge therapy for the patient's disease between collection and CAR T-cell infusion because of the aggressive nature of the underlying malignancy (Beaupierre et al., 2019; Buechner et al., 2018; Shah et al., 2017). Steroids may also need to be limited during this period because of concern for their lympholytic properties, particularly T-cell suppression (Neelapu et al., 2018).

Prior to infusion of the CAR T-cell product, the patient receives lymphodepleting chemotherapy. Study results recommend a combination of cyclophosphamide and fludarabine, often via three daily doses of 250–500 mg/m² and 25–30 mg/m², respectively (Bot et al., 2015; Kochenderfer et al., 2017). The regimen is designed to deplete regulatory T cells to benefit the expansion of the CAR T-cell product (Wieczorek & Uharek, 2013). The cell product is infused approximately two days after completion of the lymphodepleting chemotherapy (Kochenderfer et al., 2017). Patients are premedicated according to institutional or protocol parameters, typically with acetaminophen and diphenhydramine, to reduce the risk for reaction to the product (Shank et al., 2017). Infusion of the product should occur within 30 minutes of thawing (Kite Pharma, 2017; Novartis Pharmaceuticals, 2018a). Once infused, CAR T cells continue to proliferate, reaching their peak expansion within two weeks postinfusion, with evidence of continued proliferation at one year or greater (Locke et al., 2017). This immune persistence has been associated with durable complete remission, allowing for continued immune surveillance by the activated T cells to promote eradication of current and potentially future malignancy (Guedan et al., 2018).

New Indications

The early successes of CAR T cells in ALL and DLBCL provided a pathway to explore other hematologic and nonhematologic malignant indications. By its mechanism of action, the efficacy and utility of a CAR T cell is dependent on identification of a target surface protein to which the CAR can be directed. Although early CAR T-cell trials have been directed at the CD19 and CD22 proteins on the B-cell surface known to be responsible for B-cell ALL and DLBCL, new target proteins are being evaluated (Jackson et al., 2016). To date, more than 180 clinical trials

are ongoing, targeting proteins (CD19 and 22 or CD19 and 123) which are known to be overexpressed proteins on the surface of B cells responsible for leukemias and lymphomas (Leukemia and Lymphoma Society, 2018).

Of the hematologic malignant indications currently being evaluated, refractory or relapsed multiple myeloma holds the greatest promise. Late-stage clinical trials assessing the use of CARs directed at the B-cell maturing antigen protein, which is found on the surface of multiple myeloma cells, have demonstrated efficacy in achieving durable responses with a toxicity profile like those found in leukemia and lymphoma indications (Cho, Anderson, & Tai, 2018).

Solid tumors present a more complex array of surface proteins, which makes finding a common target for CARs more challenging. One common cell surface protein found in pancreatic, lung, ovarian, and mesothelioma tumors is mesothelin (Morello, Sadelain, & Adusumilli, 2016). Early-phase clinical trials are evaluating mesothelin-directed CAR T cells in this group of patients and has demonstrated some early efficacy and a tolerable

IMPLICATIONS FOR PRACTICE

- Understand how chimeric antigen receptor (CAR) T-cell therapy uses the body's innate immune defense to leverage T-cell functionality, attacking and eradicating malignancy.
- Identify those relapsed or refractory malignancies for which patients are currently being treated with CAR T-cell therapy products approved by the U.S. Food and Drug Administration.
- Explore the many additional CAR T-cell indications and cellular therapy products being developed to treat hematologic malignancies and solid tumors.

safety profile. Larger, later-stage clinical studies for these indications are ongoing. In 2019, funding was awarded by the National Cancer Institute to broadly explore the application of CAR T-cell therapy in solid tumor malignancies, specifically lung cancer and mesothelioma (Albelda, 2019).

Other solid tumor indications currently in clinical trials include neuroblastoma, glioblastoma, gliomas, and hepatocellular carcinomas. These tumors have identified targetable antigens or protein expression, such as EGFRvIII, GD2, or glypican-3, that can be CAR-directed (D'Aloia, Zizzari, Sacchetti, Pierelli, & Alimandi, 2018). Additional studies evaluate the delivery methodology of CAR T-cell therapy. Although most of the CAR T-cell infusion products are delivered via IV, studies continue to evaluate intraventricular administration for brain tumor indications (Migliorini et al., 2018) and direct administration to the tumor site, such as for hepatocellular tumors (Newick et al., 2017).

FIGURE 2.

EDUCATIONAL RESOURCES

FOR NURSES

ASSOCIATION OF COMMUNITY CANCER CENTERS

CAR T-cell therapy for your patients: What you need to know

- <https://bit.ly/2tthTFQ>

ASSOCIATION OF PEDIATRIC HEMATOLOGY/ONCOLOGY NURSES

Nursing management for the successful application of the CAR T-cell immunotherapy

- <https://bit.ly/2tpepLp>

LEUKEMIA AND LYMPHOMA SOCIETY

Facts about CAR T-cell therapy

- <https://bit.ly/2PIY6YT>

ONCOLOGY NURSING SOCIETY

Episode 1: Experiences with CAR T-cell therapy [podcast]

- <https://bit.ly/2T5q93U>

FOR PATIENTS

AMERICAN CANCER SOCIETY

CAR T-cell therapies

- <https://bit.ly/2TRaPFb>

FOUNDATION FOR THE ACCREDITATION OF CELLULAR THERAPIES

Patient education sheet for participation in immune effector cell therapies

- <https://bit.ly/2ttB09s>

LEUKEMIA AND LYMPHOMA SOCIETY

CAR T-cell therapy

- <https://bit.ly/2jvbB4z>

CAR—chimeric antigen receptor

Off-the-Shelf CARs

One of the key benefits of CAR T-cell therapy is its use of an autologous patient-specific product, eliminating the potential for graft-versus-host disease found with allogeneic infusions. However, this process is lengthy and involves multiple steps for collection and manufacturing. To make the treatment more readily accessible with greater production efficacy, alternative methods are being explored. Multiple academic and biotechnology laboratories are investigating the development of an off-the-shelf CAR T-cell product (Cooper et al., 2018; Poirot et al., 2015). This method involves creating a master cell bank derived from induced pluripotent stem cells that are grown from donor cells. Using gene-editing techniques, these blood cells are reprogrammed to become immature (undifferentiated) stem cells that provide a blank slate for creating an immune cell line that can be expanded and easily reproduced (Ruella & Kenderian, 2017). To avoid the immune response that would be expected by using donor cells, the T-cell receptor is removed during the gene-editing process, making these cells incapable of attacking recipient T cells. This process renders universal use of the new cells. These new T cells can be transduced to insert the desired CAR for the proposed disease indication or target and then cryopreserved and stored for ready access for patients.

Although the methodology of creating these off-the-shelf CAR T-cell products has demonstrated feasibility, the safety, efficacy, and comparability to existing autologous CAR T-cell products

continues to be explored. To date, trials evaluating these new methods are still in early phases of clinical development.

Implications for Nursing

As CAR T-cell therapy approvals expand agents and indications, as well as first line-therapy applications for disease progression, nurses will be expected to provide safe and effective patient care. Safe nursing practice is based on continuing education about these evolutions in care. Familiarization with the language of CAR T-cell therapy, including common terms associated with treatment, is important (see Table 1). Although CAR T-cell administration is currently limited to select centers throughout the United States, patients return to primary oncology and community-based care settings for follow-up or management of other acute and chronic illnesses. This requires education for nurses practicing in oncology and non-oncology settings, including emergency centers (Hanley, 2018), to ensure preparation to care for these individuals. Nurses in the apheresis setting are fundamental to the safe and effective collection of CD3-positive cells and should, therefore, be included in comprehensive education about the CAR T-cell collection process. For those administering the drug or managing patients during and immediately following administration, the FDA requires Risk Evaluation and Mitigations Strategy (REMS) education for each approved agent (Kite Pharma, 2018; Novartis Pharmaceuticals, 2018b). Nursing knowledge can translate to enhanced education for patients and their caregivers about what to expect throughout the CAR T-cell therapy process (McConville et al., 2017). Resources for nurse and patient education are listed in Figure 2.

CAR T-cell therapy is FDA approved for treatment across the lifespan and, as such, care that is sensitive to the unique physiologic and psychosocial needs of patients across developmental stages is important. Family-based care is recommended, particularly in the pediatric population, to ensure the needs of the patient and the family caregivers are met (Callahan, Baniewicz, & Ely, 2017; Callahan et al., 2019). Establishing defined guidelines, standard operating procedures, and CAR T-cell-specific plans of care can also help to support transitions throughout the various stages of CAR T-cell therapy from cellular collection, through conditioning chemotherapy and CAR T-cell infusion, and ultimately through survivorship (Beaupierre et al., 2019; Buitrago, Adkins, Hawkins, Iyamu, & van Oort, 2019; Halton, Llerandi, Diamonte, Quintanilla, & Miale-Mayer, 2017; Taylor, Rodriguez, Reese, & Anderson, 2019). Toxicity management is a significant component of the care management and is well addressed in other articles (Anderson & Latchford, 2019; McConville et al., 2017).

Conclusion

The efficacy of CAR T-cell therapy shows much promise. These products are characterized as living drugs because of their intrinsic mechanisms with the capacity for long-term persistence

“Safe nursing practice is based on continuing education about these evolutions in care.”

of the therapy. However, the same mechanisms of activation, expansion, and persistence are believed to be responsible for the potentially severe complications of cytokine release syndrome and neurologic toxicity often associated with these therapies. New and improved management techniques for these toxicities are receiving much attention in the literature as use of CAR T-cell therapy expands (Anderson & Latchford, 2019). Nurses are integral to the safe and effective care of these patients and can support best practice through continuing education as these therapies evolve.

Misty Lamprecht, MS, APRN-CNS, AOCN®, BMTCN®, is a clinical nurse specialist in the Blood and Marrow Transplant Program in the Arthur G. James Cancer Hospital and Richard J. Solove Research Institute at the Ohio State University in Columbus; and **Colleen Dansereau, MSN, RN, CPN**, is the director of clinical research nursing and director of clinical operations for the Gene Therapy Program at the Dana-Farber/Boston Children's Cancer and Blood Disorders Center in Boston, MA. Lamprecht can be reached at misty.lamprecht@osumc.edu, with copy to CJONEditor@ons.org. (Submitted January 2019. Accepted January 31, 2019.)

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