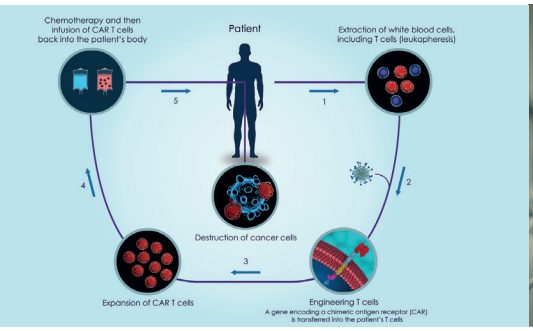
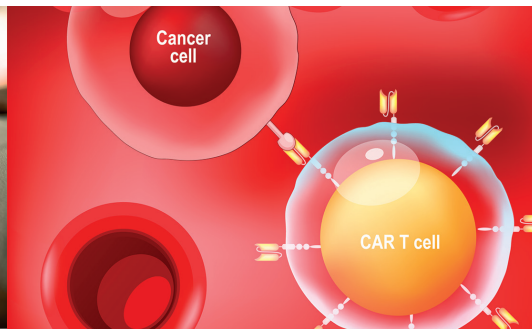
HNHCP
Haematology Nurses & Healthcare Professionals Group





Haematology Nurses and Healthcare Professionals (HNHCP)

CAR (Chimeric Antigen Receptor) T-Cell Therapy:

A Resource for Healthcare Professionals

Dear Colleague

It is with great pleasure that we present the "Haematology Nurses and Healthcare Professionals (HNHCP) – CAR (Chimeric Antigen Receptor) T-cell therapy: a resource for healthcare professionals.

As in many other disciplines, developments in haematology follow each other in rapid succession.

All these developments mean that the content of nurses' work has changed significantly, with increasing demands on theoretical knowledge and insight and on the ability to apply them in daily work.

Nurses and healthcare professionals will find useful information in this brochure, which will increase knowledge about CAR T-cell therapies, their administration and the recognition and treatment of associated toxicities.

A faculty consisting of specialist nurses working in the field of haematology/oncology, haematologists, and patient advocates have collaborated to develop this programme dedicated to increasing knowledge about CAR T-cell therapies.

This program features topics relevant to the multidisciplinary team approach to caring for patients receiving CAR T-cell therapies and their relatives. Nurses, other allied healthcare professionals and patient organisations play an important role in this process and the group is excited to share with you the most current information and up-to-date recommendations for addressing the unique long-term management of patients' needs.

The CAR (Chimeric Antigen Receptor) T-cell therapies: a resource for healthcare professionals learning program was made possible by an educational grant from Celgene / Bristol Myers Squibb Company, Janssen-Cilag AG, Novartis and Kite Gilead.

On behalf of the Haematology Nurses and Healthcare Professionals Group and the faculty who worked on this initiative, we hope that the CAR T-cell learning program will be of value to you in your care of patients undergoing CAR T-cell therapy.

Sincerely,

Erik Aerts

President

Haematology Nurses and Healthcare Professionals Group

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CAR T-cell therapies learning program: A Resource for Healthcare Professionals is also available online at

www.hemcare.org

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Contents

[1] This module contains information specific to the administration of CAR T cells in pediatric patients. Please see Modules 1, 2, 3, 4 and 5 for detailed information on the immune system, administering CAR T-cell therapy, managing side effects and follow-up and longer-term care.

Quick Facts

- Through innate (also referred to as non-specific, natural or native) and adaptive (also referred to as acquired) immunity, the immune system recognizes and eliminates pathogens
- T cells have a unique antigen-binding receptor on their membrane, known as the TCR (T-cell receptor), which requires activation through antigen-presenting cells (APCs) to be able to recognize a specific antigen
- Adoptive cell transfer (ACT) is a rapidly emerging immunotherapy, which involves collecting and using the patient's own immune cells to treat their cancer
- Chimeric antigen receptors (CARs) comprise three main components: the extracellular, which is responsible for antigen recognition, the transmembrane domain, which primarily supports CAR stability, and the intracellular signaling domain, which facilitates signal transduction to activate T cells during antigen recognition
- The chimeric antigen receptor on CAR T cells is a hybrid of the antigen-recognition region of an antibody combined with the killing power of a T cell

Module I: Overview of the Immune System and Introduction to Adoptive Cell Transfer

Overview of the Immune System

The primary function of the immune system is to defend the body against pathogens. Through immune surveillance, molecules that are identified as non-self are eliminated. Targets include not only cells infected with viruses, bacteria, parasites, or innocuous environmental substances, but also damaged cells such as those transformed through malignancy (Sharpe 2015). Substances recognized as being non-self by the immune system (antigens) act as a stimulus to trigger the immune response. By contrast, when an immune response is activated without a real threat or is not turned off once the danger passes, different problems arise, such as allergic reactions and autoimmune disease.

There are two subsystems within the immune system, which are closely linked and work together to recognize and eliminate pathogens:

- innate immunity (also known as non-specific, natural or native immunity), encompassing more primitive elements of the immune system including macrophages, natural killer (NK) cells and antigen-presenting cells (APC), and
- adaptive immunity (or acquired immunity), encompassing B and T cells

Innate immunity

The innate immune system is the first line of defense against pathogens and occurs naturally; it is not induced by infection or vaccination but works to reduce the workload for the adaptive immune response. The system's defense mechanisms include physical and chemical barriers (skin, low pH of the stomach and the process of urination), pattern recognition receptors (PRRs) and antiviral cytokines such as interferons (IFNs). The innate immune system is activated immediately or within hours of detecting the presence of an intruding pathogen and provides a general defense response. The innate immune response is an antigen-independent or non-specific defense mechanism. The assumption that repeated infection or vaccination cannot improve the efficiency of the innate immunity has recently changed since innate immune cells such as myeloid cells and NK cells can also adapt to previous encounters with pathogens. The adaptive characteristics exhibited by the innate immune system have been termed 'trained immunity'. Future research in this area will yield greater understanding of host defense mechanisms and the pathogenesis of immune-mediated diseases and open new avenues for clinical applications in vaccination as well as disease prevention and treatment (Netea 2020).

The primary function of innate immunity is to recruit immune cells to sites of infection and inflammation, which is accomplished through the production of cytokines, which are small proteins involved in cell-to-cell communication. In immunity, there are several categories of cytokines important for immune cell growth, activation and function (**Box 1**). These small signaling molecules are produced by many different immune cells, such as neutrophils, mast cells, macrophages and B- and T-cells. Cytokines bind to specific receptors on both immune and non-immune cells and may signal the cell to adjust its growth or behavior. Nearly every organ of the body contains cells with cytokine receptors.

The innate immune response involves a set of cells that produce cytokines/chemokines that participate in phagocytosis, inflammation and the synthesis of acute phase proteins.

Box 1. Categories of Cytokines

Colony-stimulating factors (CSF): essential for cell development and differentiation

Interferons: inhibit viral replication and modulate the immune response; necessary for immune-cell activation. Type I interferon mediates antiviral immune responses, type II interferon is important for antibacterial responses

Interleukins: provide context-specific instructions, with activating or inhibitory responses

Chemokines: produced in specific locations in the body or at a site of infection to attract immune cells. Different chemokines will recruit different immune cells to the site of infection

Tumor necrosis factor (TNF): family of cytokines, stimulates immune-cell proliferation and activation; critical for activating inflammatory responses

Cytokine production causes a release of antibodies and other proteins and glycoproteins that then activate the complement system, a biochemical cascade that functions to identify and coat (opsonize) foreign antigens making them susceptible to phagocytosis (Warrington 2011) (**Box 2**).

Box 2. Definition and Function of the Complement System

Complement system is part of the innate immune system. As the name implies, this system is complementary to the antibody response of the adaptive immune system. It is a cascade of soluble proteins and membrane-expressed receptors and regulators, which operates in plasma, in tissues, on cell surfaces and within the cell. It is composed of more than 40 proteins; the soluble ones being produced mainly by the liver. The complement system has many functions: in healthy individuals, it orchestrates the immunologically silent clearance of host cells after their programmed cell death; it plays a central role in the inflammatory process and modulates the activity of T and B cells; the complement system contributes to the clearance of immune complexes and pathogen elimination.
Source: Merle 2015

Innate immune protection involves cells of both hematopoietic and non-hematopoietic origin. Hematopoietic cells include macrophages, dendritic cells, mast cell, neutrophils, eosinophils, natural killer (NK) cells and natural killer T cells (**Table 1, Figure 3**) (Turvey 2010). Non-hematopoietic cells include epithelial cells of the skin, and respiratory and gastrointestinal tracts.

Adaptive immunity

Adaptive immunity is an acquired defense against foreign pathogens. The first exposure to an antigen stimulates a primary response and subsequent exposures stimulate a faster and strong secondary response. Therefore, adaptive immunity is defined by two important characteristics: specificity and memory. Specificity refers to the adaptive immune system's ability to target specific pathogens, and memory refers to its ability to quickly respond to pathogens to which it has previously been exposed. The primary functions of the adaptive immune system are:

- recognize specific "non-self" antigens
- generate pathogen-specific immunologic effector pathways to eliminate specific pathogens or pathogen-infected cells
- develop an immunologic memory to eliminate specific pathogens (Bonilla 2010)

Adaptive specific immunity involves the actions of T cells and B cells. Although both cell types arise from a common hematopoietic stem cell differentiation pathway, their sites of maturation and their roles in adaptive immunity are different.

B cells develop from hematopoietic stem cells in the bone marrow and are responsible for the production of glycoproteins called antibodies or immunoglobulins. Antibodies are involved in the body's defense against pathogens and toxins in the extracellular environment. Mechanisms of adaptive specific immunity that involve B cells and antibody production are referred to as humoral immunity.

T cells mature in the thymus. They play a role in both innate and adaptive immune responses and are also responsible for destruction of cells infected with intracellular pathogens. The targeting and destruction of intracellular pathogens by T cells is called cell-mediated immunity or cellular immunity.

Activation of the adaptive immune defense is triggered by pathogen-specific molecular structures called antigens, which are unique to a specific pathogen (**Figure 1**). While antigens play a role in the production of antibodies, they are also essential in stimulating cellular immunity and for this reason are sometimes referred to as immunogens.

Antibodies, also known as immunoglobulins, are glycoproteins present in both the blood and tissue fluids. There are 5 classes of antibodies: IgG, IgM, IgA, IgD and IgE. Each of these antibodies differs in size, arrangement, location within the body and function. Functions include neutralization of pathogens, opsonization for phagocytosis, agglutination, complement activation and antibody-dependent cell-mediated cytotoxicity. For most of these functions, antibodies also provide an important link between adaptive specific immunity and innate nonspecific immunity. Antibodies also activate the complement cascade, an important component of the innate response, and enhance the killing of pathogens that are too large to be phagocytosed through a function known as antibody-dependent cell-mediated cytotoxicity.

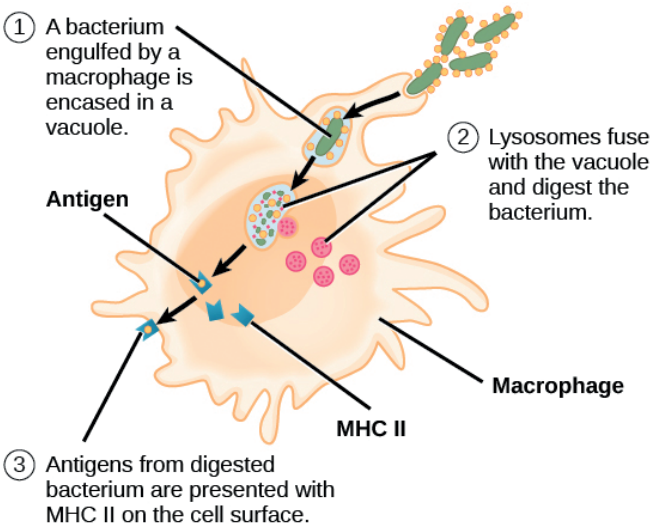


Figure 1. An APC, such as a macrophage, engulfs and digests a foreign bacterium. An antigen from the bacterium is presented on the cell surface in conjunction with an MHC II molecule. Lymphocytes of the adaptive immune response interact with antigen-embedded MHC II molecules to mature into functional immune cells.

Major histocompatibility complex (MHC) molecules are expressed on the surface of healthy cells identifying them as normal and "self" to natural killer cells. MHC molecules also play a role in the presentation of foreign antigens, which is a critical step in the activation of T cells. MHC genes are also refereed to as human leukocyte antigen (HLA) genes.

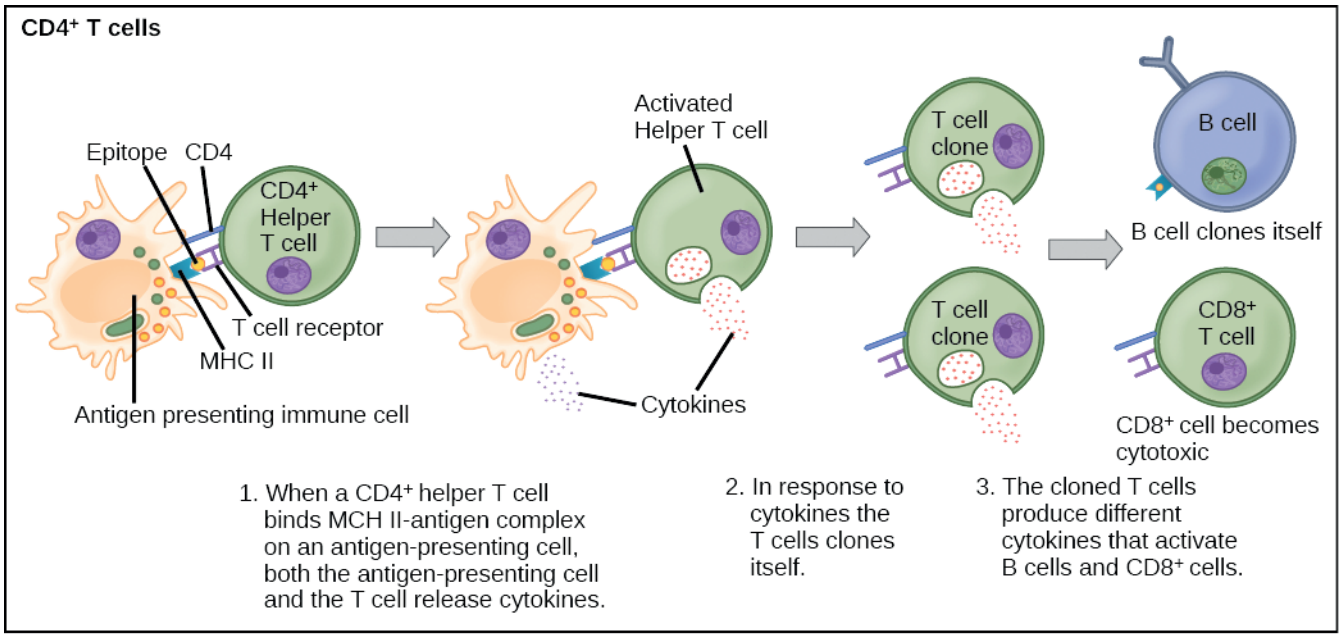
There are two types of MHC, MHC class I and MHC class II.

- MHC class I molecules are expressed by nearly all nucleated cells of the body except red blood cells, which lack a nucleus and do not express MHC molecules on their surface; they present normal self-antigens and abnormal or non-self pathogens to effector T cells involved in cellular immunity
- MHC class II molecules are only present on macrophages, dendritic cells and B cells; they present

abnormal/non-self pathogen antigens to activate T helper cells (also known as CD4+ T cells)

In organ transplantation, MHC proteins are matched between donor and recipient to lower rejection risk.

All nucleated cells have mechanisms for processing and presenting antigens in association with MHC molecules. The presentation of antigens helps the immune system to identify the cell as normal and healthy or infected with an intracellular pathogen. However, only macrophages, dendritic cells and B cells can present antigens specifically for the purpose of activating T cells and for this reason, these cells are known as antigen-presenting cells (APCs). Whereas macrophages and dendritic cells phagocytize pathogens, B cells play a role in the production and secretion of antibodies. Another difference is that B cells interact with foreign pathogens using antigen-specific immunoglobulin as receptors. Once the immunoglobulin receptor binds to an antigen, the B cell internalizes the antigen by endocytosis before processing and presenting the antigen to T cells.



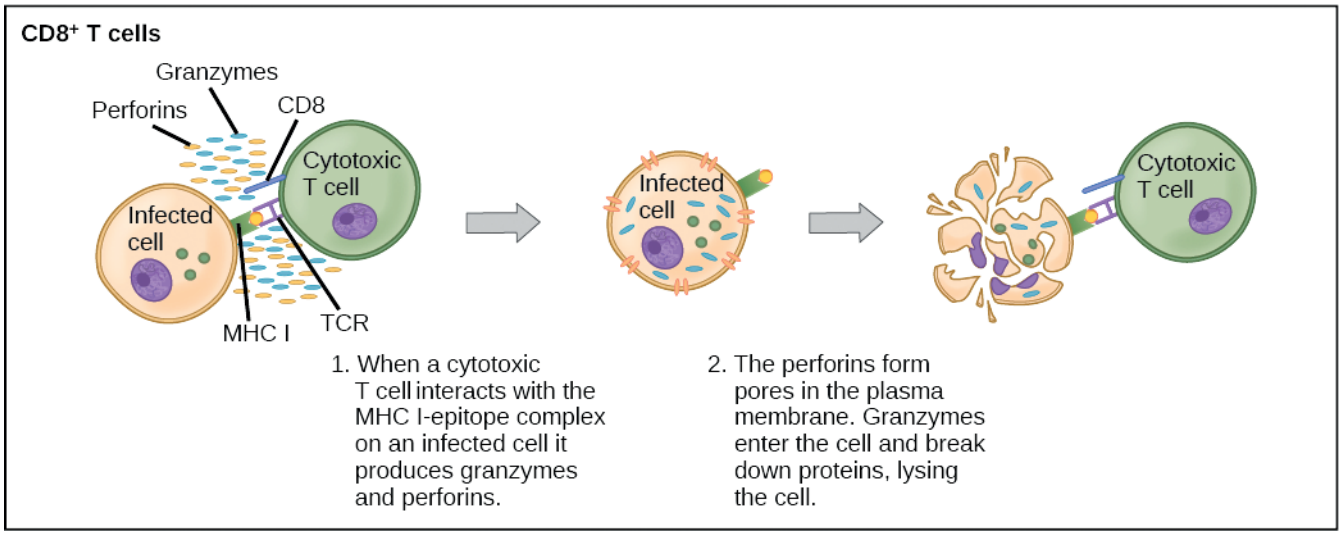


Figure 2. Naïve CD4+ T cells engage MHC II molecules on antigen-presenting cells (APCs) and become activated. Clones of the activated helper T cell, in turn, activate B cells and CD8+ T cells, which become cytotoxic T cells. Cytotoxic T cells kill infected cells.

Humoral and cellular immunity

There are two types of adaptive immune responses: the cell-mediated immune response, which is carried out by T cells, and the humoral immune response, which is controlled by B cells and the antibodies produced by B cell-derived plasma cells. The primary activity of humoral immunity is to fight pathogens in extracellular spaces; pathogens that penetrate host cells are largely protected from humoral antibody-mediated defenses. By contrast, cellular immunity targets and eliminates intracellular pathogens through the actions of T cells.

T cells are involved in innate and adaptive immunity. As stated above, T cells (thymocytes) mature in the thymus. In the first phase of thymic selection, which takes place in the thymus, T cells develop into functional T-cell receptors (TCRs), a process that requires APCs for activation. Cells with improperly functioning TCR are eliminated. In subsequent steps, cells that cannot appropriately interact with MHC molecules are destroyed. Those that can interact with MHC molecules continue through the process of maturation. In the last step, self-reacting thymocytes (T cells with a potential to attack healthy self-cells) are prevented from reaching the bloodstream.

T cells are categorized into three classes: helper T cells, regulatory T cells and cytotoxic T cells based on their expression of certain surface molecules, their mode of activation and their functional roles in adaptive immunity (**Table 1**). All T cells produce cluster of differentiation (CD) molecules, which are cell surface glycoproteins that identify and distinguish between various types of white blood cells. T cells can produce several CD molecules whereby CD4 an CD8 are the two most important. Helper T cells and regulatory T cells are characterized by the expression of CD4 on their surface and cytotoxic T cells are characterized by the expression of CD8 (**Table 1**).

T cells are also classified by the specific MHC molecules and APCs with which they interact for activation. Helper T cells and regulatory T cells are only activated by APCs presenting antigens associated with MHC II. By contrast, cytotoxic T cells recognize antigens presented in association with MHC I either by APCs or by nucleated cells infected with an intracellular pathogen (**Table 1**).

Because binding of the TCR to the MHC containing the antigen peptide is somewhat unstable and often insufficient to induce an adaptive immune response, activation using a co-receptor is often required. The CD4+ co-receptor is expressed by helper T cells and the CD8+ co-receptor by cytotoxic T cells (**Figure 2**). Although most T cells express either CD4+ or CD8+, some express both and a proportion does not express either. Once activated, the T cell secretes cytokines, which in turn stimulates T cells to differentiate into either cytotoxic T or T helper cells.

Similar to T cells, B cells possess antigen-specific receptors (B cell receptors [BCRs]), which are membrane-bound forms of Ig (immunoglobulin or an antibody) with diverse specificities. Although they rely on T cells for optimum function, B cells can be activated without help from T cells. Foreign antigens, such as viruses and bacteria, activate the proliferation and differentiation of B cells into antibody-secreting plasma cells. B cells also aid in the activation, anergy (inactivation of T cell response after encounter with an antigen), differentiation and expansion of T cells (Noonan 2015). B cells have a positive role in priming adaptive CD4+ T cells but not CD8+ T cells.

Activated B cells produce proinflammatory cytokines, such as IL-1 and IL-6, and granulocyte macrophage colony stimulating factor and tumor necrosis factor (TNF). T cells and other cells, such as dendritic cells, mediate the production of antibodies by plasma cells developed from B cells.

T and B cells differ in one fundamental way: whereas T cells bind antigens that have been digested and embedded in MHC molecules by APCs, B cells function as APCs that bind intact antigens that have not been processed. Although both T and B cells react with molecules referred to as "antigens", each responds to different types of molecules. B cells must bind intact antigens because they secrete antibodies that must recognize the pathogen directly rather than digested remnants of the pathogen (**Figure 4**).

Table 1: Overview of Characteristics of Cells in the Immune System

Cell type	Origin	Function
B cells (B lymphocytes)	Mature in bone marrow; involved in humoral immune response, essential component of adaptive immune system	Become plasma cells; plasma cells produce and secrete antibodies after antigen exposure, present antigens to T cells
T cells (T lymphocytes)	Mature in thymus; involved in cell-mediated immunity, component of adaptive immune system	Subdivided into helper (CD +4) and cytotoxic T cells; helper T cells release cytokines to stimulate defense against specific antigen; cytotoxic T cells have TCR receptors on surfaces which kill viral cells when receptor matches viral antigen
CD4+ T cell (helper T cell)	Component of adaptive immune system	Enhance pathogen-killing functions of macrophages and NK cells; activated by APCs presenting antigens associated with MHC II; play a major role in instigating and shaping humoral and cellular immune response
CD4+ T cell (regulatory T cell)	Component of adaptive immune system	Prevent potentially damaging immune responses; protect against autoimmune disorders; activated by APCs presenting antigens associated with MHC II
CD8+ T cell (cytotoxic or killer T cell)	Component of adaptive immune system	Most CD+8 cells express TCRs that recognize a specific antigen; reactivated by APCs or infected nucleated cells presenting antigens associated with MHC I. In order for the TCR to bind to MHCI molecule, it must be accompanied by a glycoprotein called CD8
γδ T cell (Gamma delta T cells)	Cytotoxic lymphocyte, overlap both innate and adaptive immunity	An unconventional T cell; involved in a broad spectrum of pro-inflammatory functions that are not restricted to MHC-mediated antigen presentation; may exhibit regulatory functions
Natural Killer (NK) T cells	Features of adaptive and innate immune systems; specialized population of T cells	Share characteristics of NK cells, produce large amounts of cytokines when stimulated; contribute to antibacterial and antiviral immune responses; promote tumor-related immune surveillance
Natural Killer (NK) cells	Develop in bone marrow; component of adaptive immune system	Provide rapid response to virally infected cells by altered expression of MHC I on the cell surface and respond to tumor cells in adaptive immune response; cause cell death through apoptosis. Can recognize stressed cells in the absence of antibodies and MHC while maintaining tolerance to normal, healthy cells
Dendritic cell	Derived from myeloid precursor cells; component of adaptive and innate immune systems	Capture and process antigens to aid T- and B-cell receptors; important APC; develop from monocytes. Produce high levels of type I interferon and play a role in antiviral host defense and autoimmunity
Macrophage	Component of innate immune system	Provide rapid and broad response to pathogens; critical for host defense
Mast cell	Component of innate immune system	Mediate inflammatory responses such as hypersensitivity and allergic reactions
Granulocyte	Component of innate immune system	Important mediators of the inflammatory response. Three types: neutrophils, eosinophils and basophils

APC, antigen-presenting cell; MHC, major histocompatibility complex; TCR, T-cell receptor
Based on content from Noonan 2015; Warrington 2011

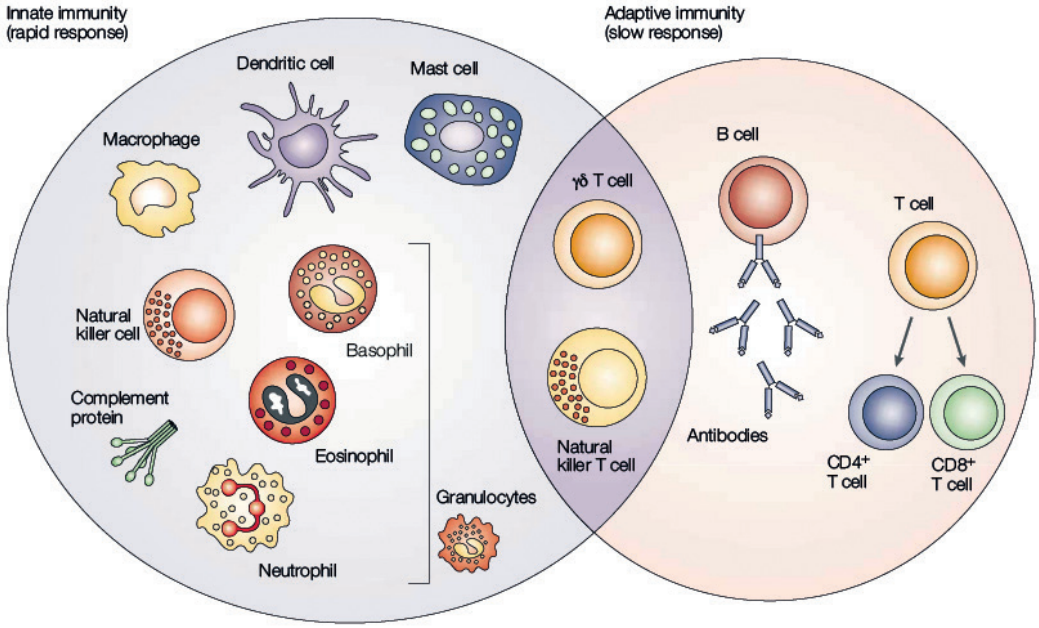


Figure 3. Cells of the innate and adaptive immune system. All cells of the immune system are derived from a multipotent stem cell in the bone marrow. The innate immune system consists of a diverse set of cells as well as numerous soluble factors and proteins. The adaptive system consists of antibodies, B cells and CD4+ and CD8+ cells, which enable a highly-specific response against a particular target. Source: Sharpe 2015; Dranoff 2004

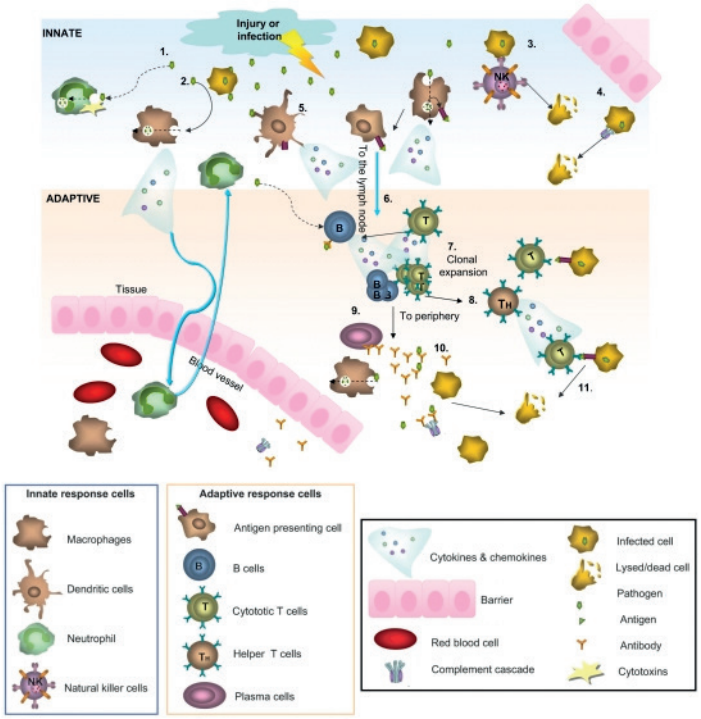


Figure 4. A schematic of the activities of the innate and adaptive immune systems following injury or infection. The innate immune system provides an immediate response to foreign targets, usually within minutes to hours (Steps 1–5). 1. Neutrophils engulf the pathogen and destroy it by releasing antimicrobial toxins. 2. Macrophages directly phagocytize pathogens leading to production of cytokines and recruitment of more cells from the blood. 3. Natural killer (NK) cells detect infected cells, which display MHCI (major histocompatibility class I) molecules on their surface. 4. Bacteria can also be recognized by the complement system, resulting in their lysis. 5. Macrophages and dendritic cells become antigen-presenting cells (APCs) by taking up peripheral antigens and migrating to lymph nodes to present antigen on their surface to naïve B and T cells. The adaptive system provides specific, long-lasting immune responses (Steps 6–11). 6. APC interaction with B and T cells in the lymph nodes leads to B and T cell activation and migration to the periphery where they mediate adaptive immunity. 7. Once activated, the T cell undergoes a process of clonal expansion in which it divides rapidly to produce multiple identical effector cells. Activated T cells then travel to the periphery in search of infected cells displaying cognate antigen/MHCI complex. 8. Peripheral APCs induce helper T cells to release cytokines and recruit cytotoxic T cells. 9. Activated antigen-specific B cells receive signals from helper T cells and differentiate into plasma cells then secrete antibodies. 10. Antibodies bind to target antigens forming immune complexes, which can then activate complement or be taken up by macrophages through Fc receptors. 11. Formation of cytotoxic T-cell synapses causes lysis of the infected cell. The two systems are linked; for example, dendritic cells are important adaptive immune system cell activators and natural killer T cells and γδ T cells are cytotoxic lymphocytes that overlap both immune systems. Source: Garay 2010

Overview of Adoptive Cell Transfer

Adoptive cell transfer ([ACT]; also referred to as adoptive cell therapy, cellular adoptive immunotherapy or T-cell transfer therapy), is a rapidly emerging immunotherapy that involves collecting and using the patient's own adaptive immune cells to treat their cancer. There are several types of ACT (**Box 3**), but chimeric antigen receptor (CAR) T cells have been developed the furthest and currently show the greatest promise in treating cancer. CAR T-cell therapy uses genetically modified T cells harvested from the patient to selectively target disease-causing cancer cells. In other words, T cells are re-engineered to harness the power of existing defense mechanisms in the body to fight cancer.

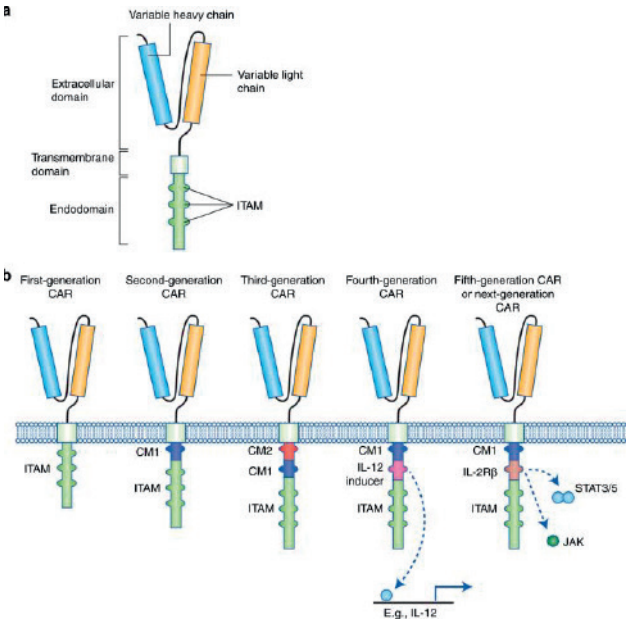
Box 3. ACT Types: TIL, TCR and CAR

TIL: uses immune cells from the patient's resected tumor that have penetrated the environment in and around the tumor, known as tumor-infiltrating lymphocytes (TILs). Has been used to successfully treat advanced melanoma, cervical, colorectal and liver cancers
Endogenous T-cell therapy: uses tumor-specific T cells grown from blood

TCR: involves the engineering of the patient's T cells to express a specific T-cell receptor (TCR). TCRs can recognize antigens inside tumor cells. Small pieces of these antigens are shuttled to the cell surface and presented to the immune system as part of a collection of proteins called the MHC complex. TCR has been tested in a variety of solid tumors and shows promise in melanoma and sarcoma

CAR: uses parts of synthetic antibodies (chimeric antibody) that recognize specific antigens on the surface of cells

Adapted from: Tokarew 2019



Mechanism of action of genetically modified T cells

CARs comprise three main components: the extracellular, which is responsible for antigen recognition, the transmembrane domain, which primarily supports CAR stability, and the intracellular signaling domain, which facilitates signal transduction to activate T cells during antigen recognition (**Figure 5**).

To create CAR T-cell therapy, T cells are extracted from the patient's blood through the process of leukapheresis. Then, using a disarmed virus, the T cells are genetically engineered to produce receptors on their surface called CARs. CARs are recombinant receptors for antigen, which, in a single molecule, redirect the specificity and function of T lymphocytes and other immune cells. When the modified T cell encounters the antigen to which it is directed, it becomes activated resulting in proliferation, cytokine secretion and target cell lysis (Chang 2017). The release of a large number of inflammatory cytokines is the underlying cause of the most life-threatening toxicity of CAR T-cell therapy, namely, cytokine release syndrome (CRS) (Ma 2019) [see Module 4 for more information on CAR T cell side effects]. As used in cancer immunotherapy, CARs rapidly generate tumor-targeted T cells by bypassing the barriers and incremental kinetics of active immunization (Sadelain 2013) [see Module 2 for a detailed explanation of the process of creating genetically modified T cells]. CAR T-cell therapy combines the specificity of an antibody with the cytotoxic and memory functions of T cells to kill cancer cells.

Figure 5. Structure of the different CAR generations. a) To make the process of gene transfer easier, a single, artificial gene that produced a functional protein that could both recognize antigen and transmit signals to the cell was designed. In these early CAR T cells, heavy and light chain variable domains were linked together with a flexible linker to create a single-chain variable fragment (scFv). The transmembrane is fundamental for surface expression and stability of the receptor. The endodomain (or intracellular domain) is the core component of most CARs and contains ITAM (immunoreceptor tyrosine-based activation motifs) that are important for signal transduction. b) The development of CARs has been based on the structure and composition of the endodomain. Whereas first generation CARs contained a single CD3ζ intracellular domain, second generation CARs were generated to enhance T cell proliferation and cytotoxicity by adding a co-stimulatory domain such as CD28 or CD137. A third intracellular signaling sequence using a co-stimulatory domain such as CD134 or CD137 was added to third generation CARs. Fourth generation CARs are similar to second generation but include a protein (such as interleukin 12 [IL-12]), that is expressed on CAR activation. T cells transduced with fourth generation CARs are called TRUCKS (T cells redirected for universal cytokine-mediated killing). Fifth generation CARs, currently being evaluated, are based on second generation CARs but contain a truncated cytoplasmic IL-2 receptor β-chain domain with a binding site for the transcription factor STAT3 to enhance T cell activation and proliferation. Source: Tokarew 2019

The CAR T cells are living drugs that can replicate rapidly and persist to provide anticancer activity for months. Further, CAR T cells may promote immune surveillance to prevent tumor recurrence through antigen release by assisting tumor-infiltrating lymphocytes to attack tumors, or by their own persistence (June 2018). To be successful as a cancer treatment, however, sufficient numbers of T cells must be obtained from the patient for genetic modification.

First generation CAR T cells could recognize and kill target cells in vitro but they did not persist in vivo and were not clinically effective: to increase activity and persistence, CAR T cells require co-stimulation [see Module 2]. Second and third generation CARs contain co-stimulatory domains (either CD28 or 4-1BB) to produce more T cells after infusion and increase survival in the circulation. Third and subsequent generations of CAR constructs are being investigated (**Figure 5**).

The majority of approved CAR T cell products to date target the B cell lineage antigen CD19 and are thus often referred to as anti CD19 therapies. CD19 is a protein on the surface of immature B cells that remains present until they become fully mature plasma cells. CD19 functions as the dominant signaling component of a multimolecular complex on the surface of mature B cells and acts as a critical co-receptor for BCR (B cell receptor) signal transduction [see Module 2]. CD19 is expressed on the surface of most forms of ALL (acute lymphoblastic leukemia), CLL (chronic lymphoblastic leukemia) and B cell lymphomas. In fact, the majority of B cell malignancies express CD19 at normal to high levels. In comparison to healthy cells where CD19 transmits signals to the B cell to alert it that the BCR has recognized an antigen, in cancer, this signaling becomes dysregulated and can occur without antigen binding thus stimulating inappropriate activation, survival and growth signals to the cell. In this way, CD19 aids the survival of cancer cells but, because of its significant role in cancer cell proliferation, the targeting of CD19 is advantageous in treating cancer. CD19 is only present on immature B cells, not on mature antibody-producing cells, hematopoietic stem cells or other tissues. However, because CD19 is present on normal cells, CD19-targeting CAR T cells destroy all healthy immature B cells causing B-cell aplasia, which can be successfully managed with infusions of immunoglobulin therapy [see Module 4].

CAR T-cell Therapy in the Clinical Setting

Anti-CD19 CAR T cells for the treatment of CD19 B-cell malignancies, including acute and chronic B-cell leukemias and B-cell non-Hodgkin lymphomas, are presently the most advanced T-cell therapy approach in use. While key studies have reported high remission rates (over 80%) in patients with treatment refractory ALL (Buechner 2017; Locke 2017), it remains to be proven that these remission rates will prolong overall survival for these otherwise untreatable patient populations (Tokarew 2019). Clinical development of other CARs for treating other hematologic cancers such as CLL and multiple myeloma are ongoing.

A newly approved CAR T cell targets plasma cell malignancies. These CAR T cells redirected to recognize B cell maturation antigen (BCMA) have induced potent antitumor responses in patients with advanced-stage multiple myeloma [see Module 3].

Outcomes following treatment of solid tumors with CAR therapy have been less promising than those achieved with B-cell hematologic malignancies. Severe, even lethal toxicities have been reported by clinical trials using TCR-modified T cells in solid tumors. The ineffectiveness of CAR therapy is primarily due to the hypoxic, poorly vascularized and extracellular matrix-rich tumor microenvironment, which prevents T cells from infiltrating the tumor tissue (Tokarew 2019).

Based on preclinical trials, five concepts need to be addressed to use engineered T cells as a viable therapy for solid tumors:

- improvement of T cell recruitment to tumors
- enhancement of T cell survival and activation
- an increase in tumor cell antigen recognition
- implementation of control strategies
- counteraction of the immunosuppressive microenvironment (Tokarew 2019)

The effectiveness of CAR T-cell therapy is dependent on two situations:

- expression of the targeted tumor antigen on the cell surface, and

- expression of the targeted antigen – ideally – only on tumor cells

There are, however, no truly tumor-specific antigens. Expression of the targeted antigen on non-cancer cells causes 'on target off tumor' treatment toxicities [see Module 5]. In light of these potentially life-threatening toxicities, mechanisms under investigation to make CAR therapy safer include:

- conditional and controllable activation of CAR T cells through switch compounds, such as a modified version of rapamycin
- depletion of CAR T cells upon the occurrence of undesired and uncontrolled side effects
- suppression of CAR activity in the vicinity of non-tumor cells through receptors that recognize non-tumor/healthy cells (Tokarew 2019)

At present, the most advanced modality to deplete T cells in the event of on target off tumor side effects is to use a suicide gene or agents to deplete cells bearing specific markers with monoclonal antibodies such as cetuximab. There is no evidence to date, however, that substantiates the reversal or prevention of severe toxicities or longer-term complications using these methods. Further, depletion or removal of biologically active CAR T cells could in effect promote cancer recurrence.

Because there are no cancer-specific antigens, the simultaneous targeting of two or more different cancer-associated antigens may enhance efficacy and improve the safety of CAR T therapy. The advantage of this approach is that full T cell activation would only occur when both antigens are present, which would probably occur on cancer but not normal cells. Dual CARs (the combination of two identical CARs), which enhances efficacy when both antigens are engaged, and split CARs (separation of the co-stimulatory domains from CD3ζ) are novel approaches currently being investigated in clinical trials (Tokarew 2019).

One of the most crucial factors affecting CAR T cell efficacy and overall survival is antigen escape through loss of CD19 expression or selection by B cells for mutants or variants that cannot be recognized by the anti-CD19 CAR T cells. Intensive lymphodepletion regimens, mostly using cyclophosphamide and fludarabine, as well as lymphopenia resulting from the underlying hematologic malignancy, might reduce the extent of anti-CAR cellular immunity by reducing the numbers of circulating lymphoid cells as well as of antigen-presenting cells (Wagner 2021).

Efficacy of CAR treatment is highly dependent on the extent of T cell expansion and persistence in the patient; sufficient numbers of T cells are required to effectively eliminate the target tumor cells. Under normal conditions, T cells require TCR engagement, co-stimulatory signaling and cytokine signaling to drive proliferation and survival. A strategy used to promote CAR T cell function involves the addition of co-stimulatory signaling moieties such as CD28 or 41BB to the CAR to promote T cell expansion and survival. Other approaches to promote T cell proliferation and survival are in the early stages of investigation.

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Quick Facts

- Chimeric antigen receptor (CAR) T cells combine the antigen recognition capabilities of an antibody with the direct killing capabilities of a T cell
- CAR T cells in current clinical use target the B cell antigen CD19, although research work is being conducted to design CAR T cells against many targets
- Because of the high risk of disease progression during the CAR T manufacturing process. bridging therapy (conventional chemoimmunotherapy, targeted therapies or radiation therapy) may be administered to keep disease under control between apheresis and CAR T-cell therapy administration
- Lymphodepletion therapy, intended to deplete T, B and natural killer cells to enhance and improve CAR T cell proliferation and potentially limit host T cell-mediated CAR T-cell rejection, may cause bone marrow suppression with resulting infection. Patients and caregivers should be educated to watch for signs/symptoms of infection and know when and whom to contact should it occur
- Strategies to address manufacturing challenges can lead to an improved CAR T cell product for all patients

Module II: Autologous CAR T-cell Therapy Process

Settings for Administration of CAR T-cell Therapy

Cellular therapies promise to revolutionize personalized medicine. T cells genetically engineered to express chimeric antigen receptors (CARs) or T-cell receptors (TCRs) in order to redirect their cytotoxic specificity towards tumor cells offer new approaches for treating, and possibly curing, previously intractable diseases. However, due to the risk of severe and potentially life-threating toxicities of CAR T therapy, regulations in most countries restrict their administration to facilities that have been granted permission to provide CAR T cell transfusions to patients [see Module 4]. Because of the similarities in facility services and supportive care required by hematopoietic stem cell transplant (HCT) procedures and CAR T delivery, many centers providing HCT have now also become designated centers for CAR T-cell therapy. The requirements that must be met for a center to administer CAR T cells, including special training for healthcare professionals involved in the administration of this new treatment, means the number of approved centers is small and patients may need to travel to a distant city for treatment. The wide distribution of centers also highlights the need for close and enhanced collaboration of patient care between referring oncologists/haematologist, the specialists at the CAR T center and primary care physicians (Beaupierre 2019).

Collection of T Cells and Preparation for CAR T Infusion

The clinical process related to the administration of CAR T-cell therapy is depicted in **Figure 1**.

Patient selection/eligibility (general requirements)

Most centers require a thorough check of eligibility as well as a discussion of each patient in a multidisciplinary board often including palliative care specialists, neurologists and ICU personnel. Patient and disease characteristics play a role in establishing eligibility for treatment (**Table 1**). Assessment of disease burden at the time of evaluation is critical; patients with a low disease burden tend to experience fewer treatment related toxicities and appear to derive more benefit from treatment (Park 2018). Similarly, because the turn-around time from leukapheresis to return of processed cells to the clinical site for patient infusion may take 2 to 4 weeks or longer,

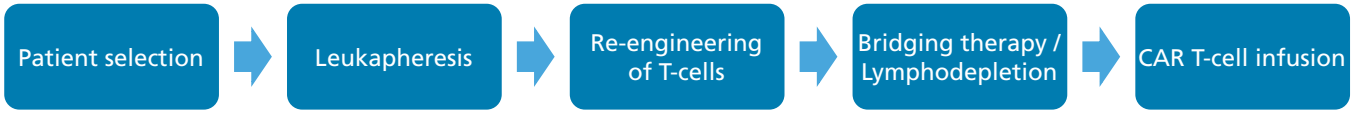

Figure 1. Process of preparing for CAR T cell therapy.

Table 1. Patient- and Disease-related Eligibility Considerations

Patient-related characteristics	Disease-related characteristics
Be well enough to receive therapy, good performance status[1]	Early identification of suitable candidates is advisable as ongoing chemotherapy can lead to T-cell depletion; Adequate amounts of T cells necessary for collection and generation of CAR T cells
Absence of residual complications/toxicities of prior treatment, adequate organ function and physiological reserve to tolerate pronounced fevers and accompanying symptoms	Disease should be responsive to CAR T cell treatment and fit the labeling indication for the product
Absence of infection proven with negative tests for bacterial and viral infections	Disease and remission criteria are according to published guidelines for specific indications
Have health insurance coverage or other sources to finance treatment have been arranged	Without central nervous system involvement
No history of significant autoimmune disease	Lack of other suitable low-risk treatment options
Type of previous chemotherapy treatment, in particular, T cell impairing agents (i.e., alkylating agents)	Not previously treated with allogeneic hematopoietic stem cell transplantation

[1] An ECOG performance status >2 is not recommended by EBMT, although real-world data have included patients with higher scores (Yakoub-Agha 2018)

evaluation of the aggressiveness of the disease should be performed to determine the potential for complications and/or disease progression during this waiting period. Screening laboratory tests and imaging to assess organ function and patient eligibility, as would be performed to assess eligibility for enrollment in a clinical trial, should be performed. An absolute neutrophil count > 1.0 x 10^9/L (evidence of adequate bone marrow reserve), and an absolute lymphocyte count > 0.2 x 10^9/L (evidence of count recovery following corticosteroid therapy as a surrogate marker of corticosteroid washout) are recommended (Yakoub-Agha 2018). Patients should have a central venous catheter for the procedure and for subsequent management [see Module 4 for detailed information on patient eligibility].

Leukapheresis

Following approval of eligibility and before the initiation of leukapheresis, patients should be provided information on:

- The leukapheresis process
- Potential short- and long-term side effects
- Involvement of caregiver
- Relevant financial aspects of CAR T-cell therapy (cost of treatment, costs related to travel, accommodations and time spent away from home)
- Potential risk of manufacturing failure, which may prohibit or delay administration of CAR T cells [further information on patient and caregiver informational needs is presented in Module 4]

Leukapheresis (also referred to as apheresis) is the collection of non-mobilized mature CD3-positive T lymphocytes from peripheral blood for CAR T-cell production (**Figure 2**). The collection of T cells during leukapheresis takes about 2 to 3 hours and involves the removal of blood from the patient's body, the separation of leukocytes, and the return of the remainder of the blood to the circulation (Smith 1997). Timing of leukapheresis should be closely

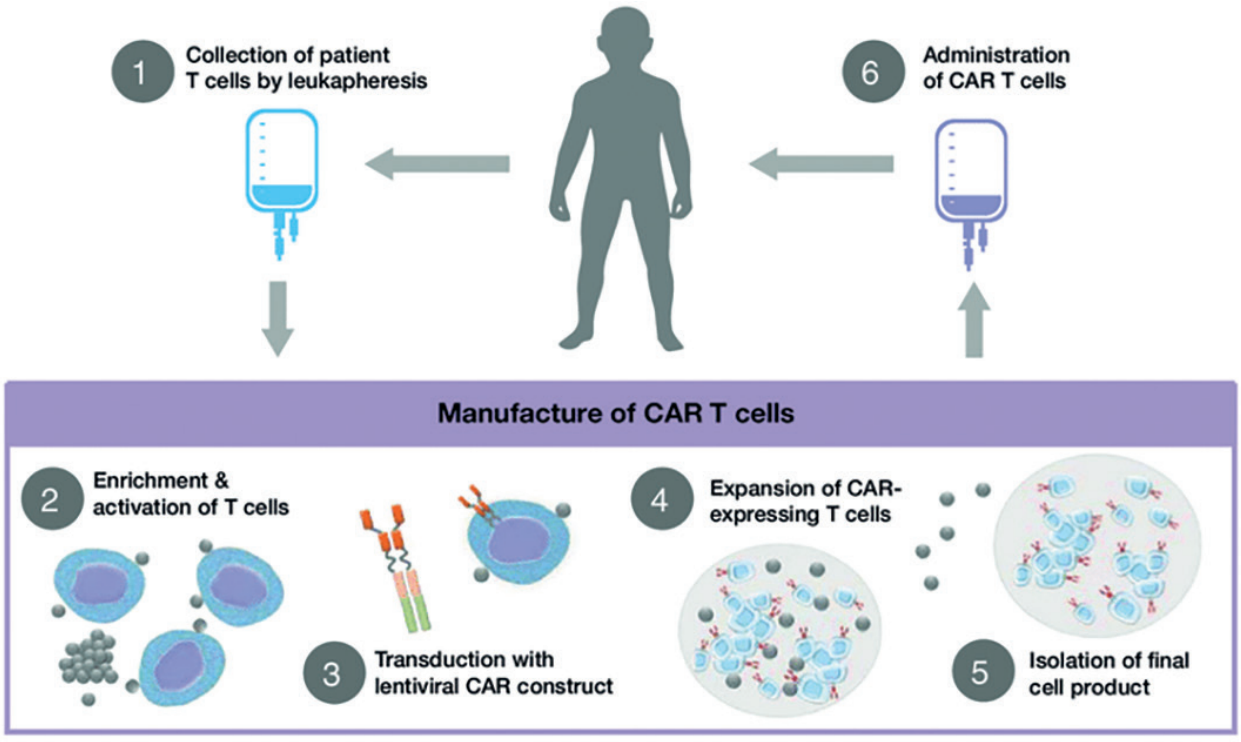

Figure 2. CAR T cell treatment process. The treatment process begins with leukapheresis of T cells. Once these are isolated, they are sent for manufacturing to produce genetically-modified CAR T cells, which are reprogrammed to target the killing of CD19+ B cells. The viral vector (step 3) might vary depending on the CAR T product being manufactured. The last step is the reinfusion of the CAR T cells. Source: Hucks 2019

coordinated with the primary oncologist, patient manager and CAR T team. Low leukocyte and lymphocyte counts due to previous treatment may make T cell collection for CAR T manufacturing more challenging. The specific CAR T cell product to be administered will determine the target number of cells to be collected, usually between 100 mL and 400 mL. One collection session is generally required.

Cryopreservation of samples collected shortly after the diagnosis of a hematologic cancer (if performed) may provide better efficacy than samples freshly collected after prior treatment. Some centers are collecting and cryopreserving cells earlier in the patient's treatment journey with the goal of increasing CAR T cell efficacy should the cells be needed at a later date. Cryopreserved specimens may allow for more flexibility in the CAR T-cell therapy process.

Regarding the treatment of mantle cell lymphoma [see Module 3], circulating CD19 expressing tumor cells in the product collected during leukapheresis are removed. This is done because patients with mantel cell lymphoma may have a high number of circulating tumor cells and/or leukemic blasts in the peripheral blood and relatively fewer T cells in the material used for manufacturing of CAR T cells. The removal of tumor cells reduces the risk of activation, expansion and exhaustion of anti-CD19 CAR T cells during the ex-vivo manufacturing process (Mian 2021).

Although leukapheresis is generally regarded as a safe procedure, there are some known side effects including:

- Fatigue
- Nausea
- Dizziness
- Feeling cold
- Tingling sensation in the fingers and around the mouth

Serious complications such as abnormal heart rate and seizures can occur during leukapheresis but are extremely rare (Maus 2016).

Bridging and Lymphodepletion Therapy

Bridging therapy

Disease progression is highly probable in patients with aggressive underlying diseases such as relapsed/refractory diffuse large B cell lymphoma (DLBCL) or relapsed/refractory B-cell acute lymphoblastic leukemia (ALL). These patients are, therefore, at high risk of their disease progressing during the CAR T manufacturing process, which can take 2 to 4 weeks. Initiation of conventional chemoimmunotherapy, targeted therapies or radiation therapy provides a bridge to keep disease under control between apheresis and CAR T-cell therapy administration. Patients with lower disease burden or slower disease kinetics who can be closely monitored during the manufacturing of CAR T products may not necessarily require bridging therapy (Jain 2019). At this time, the optimal choice and timing of bridging therapies is still unknown and often limited by factors such as patient comorbidities and refractory disease. Bridging therapy should not induce major complications, such as infections, bleeding or organ dysfunction that might interfere with the planned lymphodepleting therapy and CAR T cell infusion (Yakoub-Agha 2018).

Bridging therapy should only be given after leukapheresis is completed so that the quality of the harvested CAR T cells is not affected. Should the patient receive bridging therapy at the referring center, clear lines of communication between the treating and referring center should be established to manage any complications and measures should be in place for frequent monitoring of laboratory values and for early assessment of complications.

Lymphodepletion therapy

The intention of lymphodepletion chemotherapy prior to infusion of CAR T cells is to deplete T, B and natural killer cells to enhance and improve CAR T cell in vivo proliferation and potentially limit host T cell-mediated CAR T-cell rejection (Gust 2020). Regimens may vary by disease indication and manufacturers' recommendations but typically include fludarabine and cyclophosphamide administered over 3 days (Beaupierre 2019; Turtle 2016; Kochenderfer 2017). In one of the first studies to evaluate CAR T-cell therapy in patients with relapsed/refractory diffuse large B-cell lymphoma or follicular lymphoma, patients received personalized lymphodepleting regimens that were based on their response history, blood counts and organ function (Schuster 2017). Lymphodepletion is generally administered 2 to 7 days before scheduled infusion of CAR T. Patients with active infections should be excluded and any infections should be under control before starting lymphodepletion (Yakoub-Agha 2018). The availability of the CAR T must be confirmed prior to starting the lymphodepleting regimen (Kymriah 2020; Yescarta 2021).

Following lymphodepletion therapy, patients may be required to stay within 2 hours (or closer) of the CAR T center while awaiting administration of CAR T-cell therapy. Bone marrow suppression lasting 1 to 2 weeks can occur during this time and infection prophylaxis medications are often prescribed. A caregiver should remain continually with the patient and both the patient and caregiver should understand what symptoms may occur, what measures they should undertake, and know who to contact and when.

Engineering T Cells to Produce CAR T-cell Therapy

Once collected, the leukapheresis product is shipped to a commercial facility where T cells are isolated, activated, genetically modified with a CAR-encoding vector and expanded before cryopreservation (Perica 2018). CAR T cells can be either derived from T cells in a patient's own blood (autologous) or derived from the T cells of another healthy donor (allogeneic). In current practice, autologous cells are primarily used. During the activation process, the T cells are incubated with the viral vector encoding the CAR, and, after several days, the vector is washed out of the culture. The viral vector uses viral machinery to attach to the patients' cells and upon entry into the cells, the vector introduces genetic material in the form of RNA (**Figure 3**). In CAR T, this genetic material encodes the CAR. The RNA is reverse-transcribed into DNA and permanently integrates into the genome of the patient's cells. In this way, CAR expression is maintained as the cells divide and grow. The CAR is then transcribed and translated by the patient's cells and expressed on the cell surface. Lentivirus vectors, a type of retrovirus, are used for gene transfer although there are other methods currently under investigation including the Sleeping Beauty transposon system or mRNA transfection (Levine 2017).

Co-stimulation of T cells is necessary for them to recognize antigens [see Module 1]. To prevent inappropriate T cell activation, a second signal is provided by the interaction between co-stimulatory molecules expressed on the antigen-presenting cell and the T cell. In second-generation CAR T cells currently in use in the clinical setting, this second signal is provided by a co-stimulatory molecule (CD28 or 4-1BB) incorporated into the CAR construct, which activates the CAR T cell to destroy the cancer cell (**Figure 4**).

After processing, the product (now in a frozen state) is shipped back to the institution at which the infusion will take place. Manufacturers have a program for coordinating shipping and product identity and it is advisable that healthcare professionals are knowledgeable in the use of such programs (Perica 2018).

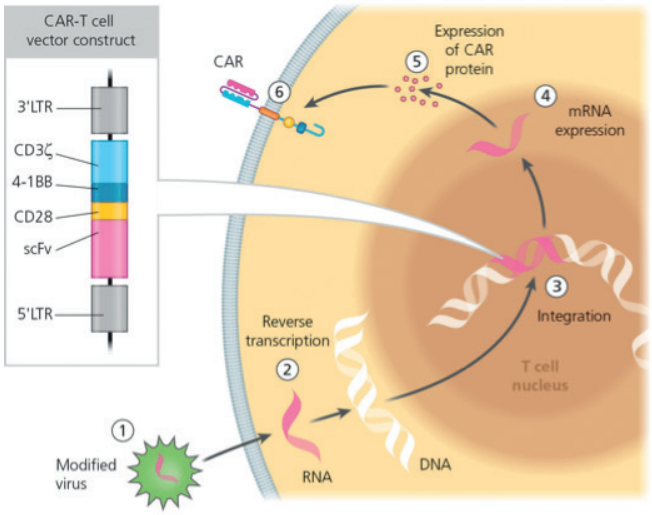

Figure 3. Retroviral gene transfer. LTR, long terminal repeat; scFv, single-chain variable fragment. 1) gene-encoding RNA enters the T cell in a modified lentivirus vector where it is 2) reverse transcribed into DNA and 3) integrated into the T cell genome. 4) The new DNA is transcribed into messenger RNA (mRNA), which then 5) directs the synthesis of a functional protein that enables 6) the T cell to express the antigen-specific chimeric antigen receptor. Source: Leukaemia Care

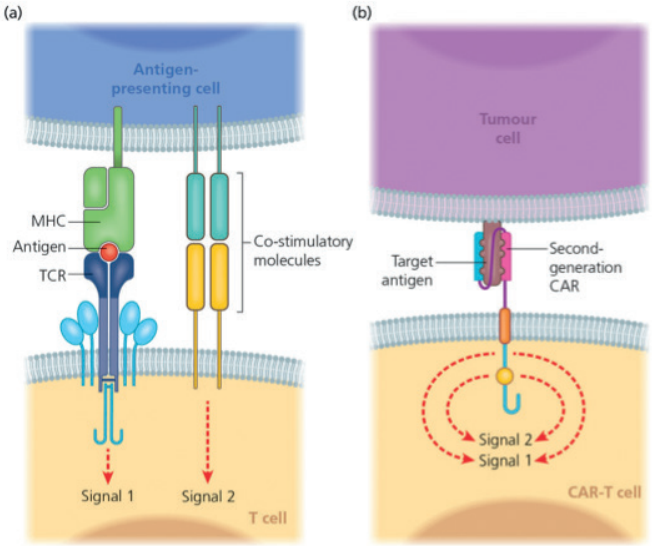

Figure 4. Co-stimulation of T cells. MHC, major histocompatibility complex; TCR, T cell receptor. T cells require a second signal that allows them to become activated. This stimulation (signal 2) is provided by the interaction between co-stimulatory molecules expressed on the antigen-presenting cell and the T cell (a). Infected cells increase the amount of co-stimulatory molecules that bind to co-stimulatory T cell receptors. Cancer cells evade detection by decreasing the amount of co-stimulatory molecules by increasing the amount of molecules that do the opposite and act as checkpoints. TCR-antigen binding provides both signal 1 and 2, thus circumventing the need for separate co-stimulation (b), which increases CAR T cell efficacy and persistence. Source: Leukaemia Care

Limitations of CAR T-cell therapy

Availability of qualified centers

CAR T-cell therapy involves multiple coordinated critical procedures including patient selection, bridging treatment, leukapheresis and management of complications. This therapy should be administered only in facilities with expertise in cellular therapies and an infrastructure that includes interdisciplinary designated specialists from hematology, intensive care medicine, neurology as well as specially trained nursing staff [see Module 4 for more details].

Treatment efficacy

In addition to the cost, CAR T-cell therapy does not work for every patient, although when it is successful a single dose can elicit a complete response. In some patients, the CAR T cells do not proliferate, which can negatively affect clinical response, or persistence of the CAR T cells is diminished, which can also, depending on the type of disease, influence clinical remission (Schultz 2019).

The timeline of 3 to 4 weeks from leukapheresis to administration of CAR T cells poses a risk for possible disease progression in aggressive diseases. Novel manufacturing techniques allowing expedient in-house manufacturing of CAR T cells are being developed and tested in clinical trials (Lock 2017).

Manufacturing issues

Although there are numerous scientific challenges relating to the optimization of CAR T-cell therapy, the need to make these therapies more widely available is an equally critical issue. Manufacturing currently in first generation system on a one-to-one basis needs to become automated and performed using robotics. Similarly, the scaling of production of CAR T cell-therapies from single centers to global manufacturing is challenging as the integrity and potency of the final product must be closely monitored. In addition, although the vector (e.g., lentivirus) is not difficult to produce and is able to be stored, the generation of consistently high-quality vector for predictable genetic modification of cells must be assured before global manufacturing of CAR T-cell therapy is possible (Levine 2017).

There is a possibility that the CAR T cell production may not be successfully manufactured and infusion cannot be provided if the product does not pass release tests. In some instances, a second manufacturing of the CAR T cell product may be attempted.

Financial considerations

Total treatment costs for CAR T-cell therapy can be unpredictable due to the newness of this novel cancer treatment and the probability of adverse events, which although mostly reversible, can be severe. List prices of approximately $373,000 in the US and €320,000 in Europe make CAR T-cell therapy one of the most expensive cancer treatments at the moment (Heine 2021) and an inaccessible treatment for some patients. These high costs are related to the manufacturing process in specialized facilities. Costs of hospitalization and intensive care treatment of complications such as cytokine release syndrome (CRS) and neurotoxicity substantially increase the cost of these novel treatments.

The current restriction on and limitation of designated treatment facilities may impose additional expenses due to relocation of residence to be closer to a treatment center. This means that issues related to patient disease status, treatment timeline and feasibility of therapy need to be discussed and planned (Taylor 2019). Product manufacturers may be able to provide financial assistance to patients with limited financial resources.

Future Perspectives

The feasibility of central manufacturing of CAR T-cell therapies and treatment with cryopreserved CAR T-cell products might help to make this therapy available to a broader population in the near future. The development of CAR T-cell therapies that use immune cells collected from healthy donors may favorably affect the cost of CAR T-cell therapy. This idea would create so-called off-the-shelf CAR T-cell therapies that are immediately available for use and do not need to be manufactured for each patient.

The major challenge in developing off-the-shelf T cells is avoidance of immune rejection in both host-versus-graft and graft-versus-host directions (June 2018). Another possible advantage of allogeneic T cells from healthy donors is the prevention of product contamination. Contamination of a CAR T-cell product with malignant cells is a theoretical risk for any patient with a hematologic malignancy. While this risk can be reduced when the product undergoes upfront T cell selection, the ability to select for T lymphocytes in patients with T-cell malignancies is difficult.

Other possibilities being explored to create a broader application of this treatment include combining techniques involving induced pluripotent stem cells and synthetic biology to generate off-the-shelf T cells with

favorable attributes, including antigen specificity, lack of alloreactivity, histocompatibility and enhanced functional properties (Themeli 2015).

Natural killer (NK) cells are being explored as an alternative off-the-shelf product, with early clinical trial results in B-cell malignancies rivaling the outcomes of autologous CAR T cells, albeit in a small number of patients (Chang 2017). There are numerous potential advantages to using NK cells over CAR T cells. Owing to their lack of a TCR, NK cells do not pose a risk for graft-versus-host disease (GVHD) and therefore require no additional gene editing to be used as a universal product. Theoretically, NK cells may retain lytic activity against the tumor cells in a non–antigen-dependent manner, which may prove useful in settings where antigen modulation is frequently encountered. In addition, there is less antigen overlap between NK cells and non–B-cell hematologic malignancies, which may allow a greater number of possible targets.

The combination of genetic engineering and synthetic biology offers a wide range of possibilities to design T cells with enhanced functions [see Module 1]. New prospects to increase efficacy (by preventing antigen escape or antigen loss) and safety (by reducing on-target off-tumor activity) of CAR therapy include combinatorial targeting and Boolean logic-grated T cells that may recognize either one or two antigens (i.e., both CD19 and CD22) (Sadelain 2017). CD19 antigen loss, in which B-cell malignancies no longer express CD19 due to epitope/antigen loss of the CD19 through splicing/mutation mechanisms (Chavez 2019), is a major driver of resistance or relapse as evident in the ELIANA study (Maude 2018). Increasing the safety aspects of CAR therapy may be achieved with the use of controllable suicide switches such as inducible caspase and truncated epidermal growth factor receptor (June 2018). Two other approaches being explored are the use of nanotechnology to create CAR T cells inside the body and the use of the gene-editing technology CRISPR/CAS9 to more precisely engineer T cells.

The prospect of on-target off-tumor toxicity is a great obstacle for successfully developing CAR T cells for solid malignancies. In this situation, the target antigen for CAR T cells is present in non-malignant tissues of vital organs and treatment with these agents might lead to severe and possibly fatal toxicity [see Module 1].

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Notes

Quick Facts

- The first two CAR T-cell therapies were approved in 2017 and approval of these types of therapies is likely to continue
- In contrast to conventional antineoplastic treatments, CAR T cells are living organisms and their expansion and antineoplastic activity is a dynamic process, which is poorly understood
- Unlike most conventional cancer treatments or hematopoietic stem cell transplant (HCT), no upper age limit has yet been defined for treatment with CAR T-cell therapies
- All CAR T-cell therapies come with a 'Boxed Warning' for several serious and potentially life-threatening toxicities
- To date, CAR T therapy has been approved for the treatment of refractory/relapsed ALL in children and adults, B-cell lymphomas and multiple myeloma in patients who progressed on or did not respond to at least four prior lines of therapy

Module III: The use of CAR T-cell Immunotherapy to Treat Hematologic Malignancies

Introduction

CAR T-cell therapy has initiated a revolution in the therapy of patients with relapsed/refractory B-cell hematological malignancies. In contrast to conventional antineoplastic treatments, CAR T cells are living organisms and their expansion and antineoplastic activity is a dynamic process, which is poorly understood.

Several phase 2 clinical studies of anti-CD19 CAR T cells have produced favorable results leading to the approval of these novel therapies for clinical use. Improved efficacy and safety of these agents has been shown to be influenced by doses of less than 10^8 cells/m^2, absence of IL-2 administration and the inclusion of fludarabine and cyclophosphamide in conditioning regimens (Cao 2019). Despite promising treatment responses in large subsets of patients with otherwise refractory disease, as experience with these agents increases, evidence that remissions may be brief in a substantial number of patients owing to poor CAR T cell persistence and/or cancer cell resistance resulting from antigen loss or modulation is emerging (Shah 2019).

Complete or partial response 3 months after CAR T-cell treatment might be predictive of long-term response durability, but many patients initially responding only partially convert to a complete remission even months after treatment (Locke 2018; Schuster 2019a). In patients treated with tisagenlecleucel in the JULIET trial, conversion from partial to complete response occurred in 54% of the patients, including conversion 15 to 17 months after initial response in two patients (Schuster 2019b).

Whereas there is an upper age limit for hematopoietic stem cell transplant (HCT), no upper age limit has yet been defined for treatment with CAR T-cell therapies. As of this time, CAR T therapy is only approved for relapsed/refractory disease; the potential benefits of treating with CAR T cells earlier in the lymphoma disease course are being investigated.

All CAR T-cell therapies come with a 'Boxed Warning' for cytokine release syndrome (CRS), neurologic toxicities, hemophagocytic lymphohistiocytosis/macrophage activation syndrome, and prolonged cytopenia [see Module 4]. These are the most common adverse events associated with CAR Ts and the events most commonly associated with serious and/or life-threatening consequences for the patient. It is still too early to describe the full list and scope of the longer-term safety risks associated with this treatment.

The US Food and Drug Administration (FDA) approved the first two CAR T therapies in 2017 (**Table 1**). These approvals represented milestones in the development of a completely new scientific paradigm in treating cancer. As of 2021, two more CAR T therapies received approval indicating that the approval of these types of therapies is likely to continue. Due to the novel nature of these therapies and to the relatively fast regulatory approval, manufacturers of CAR products are required to continually provide information on:

- their safety profile
- how risks will be prevented or minimized
- plans for studies and other activities to gain more knowledge about the safety and efficacy of the treatments
- how the effectiveness of risk-minimization measures will be evaluated

Table 1. CAR T-cell Therapies approved in the EU and the US

Approval Agency	Generic (Trade Name)	Target	Indication
EMA/FDA	Tisagenlecleucel/Tisa-cel (Kymriah®)	Anti-CD-19	B cell ALL, non-Hodgkin lymphoma (DLBCL)
EMA/FDA	Axicabtagene ciloleucel/ Axi-cel (Yescarta®)	Anti-CD-19	Non-Hodgkin lymphoma (DLBCL, PMBCL, HGBCL, follicular lymphoma)
EMA (conditional marketing authorization)/FDA	Brexucabtagene autoleucel/ Brexu-cel (Tecartus®)	Anti-CD-19	Mantle cell lymphoma
FDA	Lisocabtagene maraleucel/ Liso-cel (Breyanzi®)	Anti-CD-19	Non-Hodgkin lymphoma (DLBCL)
EMA (conditional marketing authorization)/FDA	Idecabtagen vicleucel/ Ide-cel (Abecma®)	Anti B-cell maturation antigen (BCMA)	Multiple myeloma

ALL, acute lymphoblastic leukemia; DLBCL, diffuse large B-cell lymphoma; EMA, European Medicines Agency; FDA, Food and Drug Administration; HGBCL, high-grade B-cell lymphoma; PMBCL, primary mediastinal B-cell lymphoma

In Europe, this monitoring procedure is referred to as a Risk Management Plan (RMP) as established by the European Medicines Agency (EMA), and in the US as Risk Evaluation and Mitigation Strategies (REMS) as established by the FDA. Long-term patient follow-up to detect and manage late effects of cellular therapy is recommended in the FACT-JACIE International Standards Accreditation Manual (FACT-JACIE 2018).

CAR T cells in the Treatment of Acute Lymphoblastic Leukemia (ALL)

B-cell ALL (acute lymphoblastic leukemia) is aggressive and associated with poor outcomes with an expected 5-year survival between 20% and 40%. Tisagenlecleucel (tisa-cel) was the first CAR T approved by the FDA and is indicated for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or later relapse (Novartis 2020).

Efficacy and safety results to date

Minimal residual disease-negative complete response rates of 60% to 93% have been reported in relapsed and refractory ALL (**Table 2**). The ELIANA study, which evaluated the use of tisa-cel in ALL, concluded that this therapy produced high remission rates and durable remission without additional therapy in high-risk pediatric and young adult patients with relapsed or refractory B-cell ALL (Maude 2018). However, the adverse safety effects associated with tisa-cel, at least in this study, were substantial often requiring intensive care- (ICU) level care (**Table 3**). These events were alleviated in most patients following intervention with supportive measures and cytokine blockade.

Table 2. Efficacy Results of Clinical Studies on CAR T-cell Therapy (Tisa-cel) for Acute Lymphoblastic Leukemia (ALL)

Clinical study	Participant age (yrs)	Response rate	Survival
Maude 2014 (pilot study)	5 – 22 (N = 25) 26 – 60 (N = 5)	90% CR at 1 month	78% OS and 67% EFS at 6 months
Lee 2015	5 – 27 (20 ALL pts)	70% CR in ALL 60% MRD-negative CR	51.6% OS at 10 months
Turtle 2016	20 – 73 (N = 32)	100% morphologic remission 93% MRD-negative remission	---
ELIANA Maude2018[1]	3 – 23 (N = 75)	81% overall remission, 60% CR at 3 months; 81% MRD-negative remission	73% EFS and 90% OS at 6 months; 50% EFS and 76% OS at 12 months
Park 2018	23 – 74 (N = 53)	83% CR 67% MRD-negative remission	6.1 months EFS 12.9 months median OS

ALL, acute lymphoblastic leukemia; CR, complete response; EFS, event free survival; MRD, minimal residual disease; OS, overall survival
[1] Global, phase 2 pivotal trial

Table 3. Safety Results of Clinical Studies on CAR T-cell Therapy (Tisa-cel) for Acute Lymphoblastic Leukemia (ALL)

Clinical study	Adverse event
Maude 2014	100% CRS, 27% severe; 43% neurotoxicity
ELIANA Maude 2018[1] N = 75	77% CRS, 46% ≥ grade 3; 40% neurologic events, 13% grade 3; 40% pyrexia; 39% decreased appetite; 36% febrile neutropenia
ELIANA (study update) Grupp 2018	77% CRS grade ≥ 3; 62% neutropenia; 20% hypoxia; 20% hypotension; 13% neurotoxicity grade 3
Park 2018 N = 53	85% CRS, 26% grade ≥3 36% neurologic events, 6% ≥ grade 3

CRS, cytokine release syndrome
[1] Global, phase 2 pivotal trial

Table 4. Efficacy Results of Clinical Studies on CAR T-cell Therapy in Relapsed or Refractory B-cell Lymphoma

Clinical study	Participant age (yrs)	Therapy	Response rate	Survival
ZUMA-1 (Neelapu 2017)	23 – 76 (N = 101)	Axi-cel	72% ORR, 54% CR, 40% CR at 15.4 months (median)	52% OS at 18 months
ZUMA-1[1] (Locke 2018)	23 – 76 (N = 101)	Axi-cel	58% CR at 27 months; 83% OR; response duration 11 months (median)	PFS 5.9 months (median)
ZUMA-5 (Jacobson 2020)	34 – 79 (N = 146)	Axi-cel	76% (indolent NHL), 80% (follicular lymphoma), 60% (MZL) CR at 17.5 months (median)	93% OS and 74% PFS at 12 months (estimated)
JULIET[1] (Schuster 2019a)	22 – 76 (N = 93)	Tisa-cel	40% CR, 52% ORR, 12% PR at 14 months	49% survival at 12 months (all pts, estimated), 90% (pts with CR); 2.9 months PFS; 11.7 months OS
JULIET 19 month F/U (Schuster 2019b)		Tisa-cel	64% relapse-free probability at 12 or 18 months 54% ORR at 19 months (median)	11 month (median) OS; 48% probability of OS at 12 months, 43% at 18 months
TRANSCEND[1] (Abramson 2020)	22 – 76	Liso-cel	73% ORR; 53% CR; 20% PR 93% ORR; 67% CR;	51.4% PFS at 6 months; 44.1% PFS at 12 months; 74.7% OS at 6 months; 57.9% OS at 12 months
ZUMA-2[1] (Wang 2020)	38 – 79 (N = 60)	Brexu-cel	57% in remission at 12.3 months (median)	61% PFS and 83% OS at 12 months

CR, complete response; F/U, follow-up; PFS, progression-free survival; PR, partial response; ORR, objective response rate; OS, overall survival
[1]Landmark paper

CAR T cells in the Treatment of Non-Hodgkin Lymphoma (NHL)

Diffuse large B-cell lymphoma (DLBCL), the most common type of NHL, is successfully treated in about two-thirds of patients following administration of a rituximab-based immunochemotherapy regimen (Feugier 2005; Pfreundschuh 2006). Outcomes for patients with relapsed/refractory aggressive B cell NHL are poor. Similarly, while the prognosis in follicular lymphoma after frontline therapy with rituximab-based therapies is excellent, 20% of patients relapse within 2 years after initial immunochemotherapy (Schuster 2017). The prognosis following early relapse is poor, with a 5-year overall survival of only 50% with currently available therapies (Tan 2013; Casulo 2015) and few effective treatment options for refractory/relapsed disease. The lack of validated and effective treatments for relapsed/refractory lymphoma has led to a need for new therapeutic approaches to achieve durable disease remission. The FDA recently approved lisocabtagene maraleucel (liso-cel) for treatment of relapsed/refractory DLBCL.

Brexucabtagene autoleucel (brexu-cel) recently received regulatory approval by the FDA for the treatment of relapsed/refractory mantle cell lymphoma (MCL). MCL is a rare and aggressive lymphoma. None of the therapies to date are curative and virtually all patients will eventually relapse or become resistant to Bruton's tyrosine kinase (Btk) inhibitors, which are commonly used to treat relapsed/refractory disease (Mian 2021). Brexu-cel differs from its predecessor (axi-cel) in having an additional T-cell enrichment phase during manufacturing to remove circulating tumor cells from the leukapheresis material [see Module 2].

Efficacy results to date

CAR T cells targeting the CD19 antigen on the surface of B cells in B-cell NHL are furthest in clinical development. Initial efficacy results from the ZUMA-1 study, which evaluated axi-cel in patients with DLBCL refractory to chemotherapy or relapsed after auto HCT, showed favorable efficacy results after a single dose of axi-cel (Neelapu 2017) (**Table 4**). These favorable efficacy results continued at 24 months as reported in the ZUMA-1 study submitted to the FDA for regulatory approval (Locke 2018). A large proportion of patients in this study achieved durable responses lasting more than 2 years and needed no further consolidation therapy. The estimated 24-month survival of 50.5% represents a major improvement in clinical outcomes for these patients.

Tisa-cel is approved for the treatment of adult patients with relapsed /refractory large B-cell ALL refractory or in second or later relapse and relapsed/refractory large

B-cell lymphoma after two or more lines of systemic therapy including diffuse large B-cell lymphoma (DLBCL) not otherwise specified, high-grade B-cell lymphoma and DLBCL arising from follicular lymphoma (Novartis 2020). Tisa-cel provided an overall response rate (ORR) at a median of 14 months of 52% and 12-month relapse-free survival of 79% in patients with relapsed/refractory DLBCL in the JULIET study (Schuster 2019a) (**Table 4**).

In the TRANSCEND NHL study, results using lisocabtagene maraleucel (liso-cel), a third CD19-directed CAR T therapy, showed 73% overall response and 53% complete response (Abramson 2020) (**Table 4**). This newest CAR T was approved by the FDA in February 2021 for the treatment of adult patients with relapsed/refractory large B-cell lymphoma (including DLBCL not otherwise specified, high-grade B-cell lymphoma, primary mediastinal large B-cell lymphoma and follicular lymphoma grade 3B) after two or more lines of systemic therapy. In comparison to the JULIET and ZUMA-1 studies, the TRANSCEND NHL study enrolled a broad range of patients with relapsed/refractory large B-cell lymphomas including B-cell lymphomas with diverse histological features and patients with low creatinine clearance or poor cardiac function, and high-risk features such as central nervous system (CNS) involvement. Patients aged ≥ 65 years were also eligible (median age 63, 42% of patients were ≥ 65 years of age) (Abramson 2020).

Safety

Cytokine release syndrome (CRS) and neurologic toxicities commonly occur following CAR T therapy. A precise and definitive comparison of safety data is difficult due to the different tools used to measure the severity of side effects (**Table 5**).

Real world clinical study results

Since completion of registration or landmark studies for CAR T-cell therapies, results of real-world or post-marketing studies have been published, which include either pooled or registry data on outcomes for patients who received CAR T outside of a stringently regulated clinical trial. The retrospective study by Nastoupil et al (2020) reports outcomes of therapy with axi-cel for aggressive B-cell lymphoma. This analysis included patients who, because of disease- and patient-related factors, would not have been eligible for participation in a clinical study. Safety and efficacy results were, however, comparable to those

Table 5. Safety Results of Clinical Studies on CAR T-cell Therapy in Relapsed or Refractory Large B-cell Lymphoma

Clinical study	Therapy	Adverse event
ZUMA-1 (Neelapu 2017)	Axi-cel	93% CRS, 13% grade ≥ 3 65% neurologic events, 28% grade ≥ 3 78% neutropenia grade ≥ 3
ZUMA-1 2-yr F/U[1] (Locke 2018)	Axi-cel	48% grade ≥ 3 serious adverse event 11% grade ≥ 3 CRS 32% grade ≥ 3 neurologic events 39% grade ≥ 3 neutropenia
ZUMA-5 (Jacobson 2020)	Axi-cel	7%, 6%, 9% CRS grade ≥ 3 in NHL, follicular, MZL, respectively 19%, 15%, 41% grade ≥ 3 neurologic events in NHL, follicular and MZL, respectively 86%, 85%, 95% grade ≥ 3 adverse event in NHL, follicular, MZL, respectively 33% neutropenia (all pts)
JULIET[1] (Schuster 2019b)	Tisa-cel	58% CRS, 22% grade ≥ 3 CRS 21% neurologic event, 12% grade ≥ 3 neurologic events 32% cytopenia > 28 days
TRANSCEND (Abramson 2020)	Liso-cel	42% CRS, 2% grade ≥ 3 30% neurotoxicity, 10% grade ≥ 3 60% grade ≥ 3 neutropenia
ZUMA-2[1] (Wang 2020)	Brexu-cel	68% serious adverse event 91% CRS, 15% CRS grade ≥ 3 63% neurologic event, 31% neurologic event grade ≥ 3 94% cytopenia grade ≥ 3 32% infection grade ≥ 3

CRS, cytokine release syndrome; MZL, marginal zone lymphoma; NHL, non-Hodgkin lymphoma

Table 6. Efficacy Results of a Clinical Study on CAR T-cell Therapy in Relapsed or Refractory Multiple Myeloma

Clinical study	Participant age (yrs)	Therapy	Response rate	Survival
KarMMa[1] (Munshi 2021)	33 – 78 (N = 128)	Ide-cel	73% ORR 33% CR 26% MRD	8.8 months (median) PFS

CR, complete response; MRD, minimal residual disease; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response
[1]Landmark paper

Table 7. Safety Results of a Clinical Study on CAR T-cell Therapy in Relapsed or Refractory Multiple Myeloma

Clinical study	Therapy	Adverse event
KarMMa (Munshi 2021)	Ide-cel	84% CRS; 5% grade ≥ 3 18% neurologic adverse events, 3% grade 3 97% cytopenia; 41% prolonged neutropenia grade ≥ 3

CRS, cytokine release syndrome

reported in the more strictly controlled ZUMA-1 study, except in those patients with poor Eastern Cooperative Oncology Group (EC)G) performance status and elevated lactate dehydrogenase levels. Similarly, an analysis of registry data of patients treated with tisa-cel for DLBCL provides evidence of efficacy and safety in the real world setting similar to data reported from the pivotal JULIET study (Jaglowski 2019). In that analysis, the administration of products with low cell viability provided efficacy and safety outcomes comparable to products meeting viability specifications.

CAR T Cells in the Treatment of Multiple Myeloma

In March 2021, the FDA approved idecabtagene vicleucel (ide-cel) for the treatment of multiple myeloma in patients who progressed on or did not respond to at least four prior lines of therapy. Ide-cel is the first agent in the class to target B-cell maturation antigen (BCMA). BCMA was chosen as a target for treating multiple myeloma because it is predominantly expressed in B-lineage cells and plays a critical role in B cell maturation and subsequent differentiation into plasma cells with a relatively higher expression on malignant plasma cells. The pivotal, phase 2 KarMMA trial (Munshi 2021), which evaluated patients with relapsed/refractory myeloma who had received at least 3 prior treatments, was the basis for approval (**Table 6**). The approval represents a new, personalized treatment option for this population. Almost all patients in this heavily pre-treated population experienced adverse events: prolonged cytopenia and incidences of infection were higher than in other comparable studies (**Table 7**).

Manufacturer Recommended Doses of CAR T cells

The unique process used to engineer T cells with CAR means that each product has its own recommended dose specified by the manufacturer (**Table 8**).

Table 8. Manufacturer's Recommended Dosages for Approved CAR T-cell Therapies	
Tisagenlecleucel (Kymriah): Pediatric/young adults with relapsed/refractory B-cell ALL	
Patients ≤ 50 kg	0.2 to 5 x 10^6 CAR-positive viable T cells/kg body weight
Patients > 50 kg	0.1 to 2.5 x 10^8 CAR-positive viable T cells (non-weight based)
Tisagenlecleucel (Kymriah): Adults with relapsed/refractory DLBCL	
	0.6 to 6 x 10^8 CAR-positive viable T cells (non-weight based)
Axicabtagene ciloleucel (Yescarta): Adults with relapsed/refractory DLBCL and primary mediastinal large B-cell lymphoma (PMBCL)	
	2 x 10^6/kg body weight (range: 1 x 10^6 – 2 x 10^6 cells/kg, maximum 2 x 10^8 anti-CD19 CAR T cells)
Lisocabtagene maraleucel (Breyanzi): Adults with relapsed/refractory large B-cell lymphoma	
	50-110 x 10^6 CAR-positive viable T cells
Brexucabtagene autoleucel (Tecartus): Adults with relapsed/refractory mantle cell lymphoma	
	2 x 10^6 CAR-positive viable T cells/kg body weight, with a maximum permitted dose of 2 x 10^8 CAR-positive viable T cells
Idecabtagene vicleucel (Abecma): Adults with relapsed/refractory multiple myeloma	
	300 to 460 x 10^6 CAR-positive T cells
DLBCL, diffuse large B-cell lymphoma; PMBCL, primary mediastinal large B-cell lymphoma Sources: Abecma (idecabtagene vicleucel) 2021; Breyanzi (lisocabtagene maraleucel) 2021; Kymriah (tisagenlecleucel) 2021; Tecartus (brexucabtagene autoleucel) 2021; Yescarta (axicabtagene ciloleucel) 2020	

Future Perspectives

The clinical success of CAR T cells in B-cell malignancies has resulted in their approval by regulatory agencies and continued development. The high response rates observed are unprecedented, especially considering that most patients treated with these agents are refractory to all other therapies (Weber 2020). Treatment-related mortality in large multicenter trials is currently less than 5%, which is not dissimilar from other standard treatment regimens for these refractory diseases (Locke 2018). The clinical use of CAR T cells is early in its evolution and it is, as yet, unclear whether this therapy represents a definitive treatment or whether disease cure will require further immunologically based consolidation such as allogeneic stem cell transplantation (Yakoub-Agha 2019). This issue can only be resolved with longer follow-up of patients.

In contrast to their success in refractory/relapsed hematologic malignancies, convincing evidence of efficacy has not been obtained in patients with solid tumors. Future research will likely focus on identifying a therapeutic window for CAR T cell targeting of cell surface molecules overexpressed on solid tumors (Weber 2020). In addition to exploring other applications for CAR T cells in cancer, work is ongoing on using CAR T cells for HIV infection and autoimmune diseases, among others.

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Quick Facts

- Because of the demanding process of CAR T administration and the associated significant toxicity profile of these products, a thorough patient consent process is highly recommended
- Patient and caregiver education, including verbal and written information on side effects and toxicities, is essential for prompt symptom recognition and reporting and supports the successful management of patients
- CAR T-cell therapy represents a promising approach for treating refractory B-cell malignancies but is associated with unique acute toxicities that require specialized monitoring and management
- CRS (cytokine release syndrome) and neurotoxicities commonly occur after CAR T-cell therapy but are, in most cases, temporary
- Intensive monitoring, accurate grading and prompt management of severe cases can reduce morbidity and mortality associated with these toxicities

Institutional Qualification

In some countries, regulatory agencies require that centers providing immune effector cell therapy, including CAR T-cell therapy, adhere to the Foundation for Accreditation of Cellular Therapy (FACT) (FACT 2018a) or the Joint Accreditation Committee of the International Society for Cellular Therapy and European Society for Blood and Marrow Transplantation (JACIE) immune effector cell standards (Yakoub-Agha 2020; Jain 2019; FACT 2018b). The FACT-JACIE guidelines serve as uniform criteria for the certification of CAR T treatment centers and ensure that certain standards are met with respect to cell collection, processing and clinical management of patients receiving immune effector cell therapy, including CAR T (FACT-JACIE 2018b). Hospitals and institutions should have provisions for intensive care and healthcare personnel working at these hospitals should be educated and trained to recognize and manage treatment toxicities.

Similar to institutions providing hematologic stem cell transplant, establishment of an immune effector cell coordinator, a healthcare professional designated to coordinate patient appointments and communications between inpatient and outpatient units as well as communication with referring physicians and institutions, is advisable. Establishment of open lines of communication between the CAR T cell center and the patient and caregiver is essential for achieving optimal outcomes.

In addition to meeting the complex medical, educational and regulatory requirements involved in administering CAR T-cell therapy, examples of some of the operational and logistical features required for CAR T-cell therapy include:

- Cellular processing
- An infrastructure that supports regulatory requirements
- Established research program
- Centralized patient intake process to optimize workflow
- Data and quality management teams responsible for identifying, investigating, documenting, reporting and implementing corrective and preventive actions in the event of errors, accidents, biological product deviations, serious adverse events and complaints in regard to performing CAR T-cell therapy
- Apheresis department to facilitate cell collection, storage, shipping and receiving modified T cells
- Adequately staffed and trained outpatient triage with extended hours of operation
- Pharmacy providing 24-hour availability of medications
- Availability of support services staff such as dietary, social services, psychology, physical therapy and data management (FACT 2018a)

Patient Preparation: Education and Informed Consent

Because of the demanding process of CAR T administration and the associated significant toxicity profile of these products, it is highly advisable that patients and their caregivers receive appropriate and sufficient information to be able to provide informed consent. As per the FACT (2018a) and JACIE (Yakoub-Agha 2020) recommendations, recipients should receive information regarding the risks and benefits of CAR T-cell therapy. A healthcare professional familiar with CAR T therapy should document informed consent.

Patient education, which includes verbal and written information on side effects and toxicities, is essential for prompt symptom recognition and reporting and supports the successful management of patients (**Table 1**) (Taylor 2019). Patients must be able to reliably contact a provider familiar with CAR T-cell therapy at the onset of new symptoms and to quickly access in-person assessment through clinic triage, the emergency department or direct admission to a designated unit (Taylor 2019).

Infusion of CAR T-cell therapy can occur in the inpatient setting and has more recently been extended to include ambulatory settings. The setting for infusion will depend on the onset, severity and management of any side effects of previous bridging and lymphodepletion therapies or of anticipated complications following CAR T cell infusion (Taylor 2019).

Those patients who return home for self-monitoring after infusion should be provided with instructions and a log to document any changes in their condition that might signal the onset of a toxicity. They should bring this log to clinic visits for review by nursing staff.

Table 1. Educational Topics to Address with Patient/Caregiver[1]

Topic	Educational content	Actions
CAR T	Purpose of CAR T-cell therapy and manufacturing process; Procedure for administration; Onset & types of side effects; Medication interactions	Assess patient/caregiver understanding of content
Common symptoms to watch out for	Fever, myalgia, headache, anorexia, nausea, vomiting, diarrhea, fatigue	Contact HCP if symptoms become severe
Infection/CRS	Monitor temperature twice/day for 3-4 weeks; Use of infection prevention measures; Be alert for feelings of a "racing heart", shortness of breath	Contact HCP immediately if elevated (generally, ≥38°C)
Neurotoxicity	Change in cognition, difficulty in naming/identifying objects Difficulty writing, onset of tremors Tiredness, generalized weakness Visual changes	Have caregiver assist in monitoring; Contact HCP immediately if any of these symptoms occur
General	Due to the risk of altered or decreased consciousness, confusion and seizures, patients should not drive, use machines or take part in activities that require alertness for about 8 weeks after infusion; Possibility of hospitalization to manage side effects should be explained to patient/caregiver	

[1]Many patients have received prior treatment for their hematologic malignancy and are thus familiar with side effects of CAR T-cell treatment such as infection risk, fatigue and gastrointestinal disturbances. Assessment of patient recall of knowledge of preventative measures, signs/symptoms and interventions of side effects should be performed.
CRS, cytokine release syndrome; HCP, healthcare professional
Kite Pharma 2021; Rivera 2020; Brudno 2019; Gust 2018; Lee 2014

Caregiver support

Caregivers should also receive education on what to expect with CAR T-cell therapy and patients will require the presence of a 24-hour caregiver for at least four weeks (Perica 2018). If several caregivers will be involved in providing care, then each should receive the appropriate information. Caregivers may experience challenges and stress while providing round-the-clock care during and after treatment. Social services and other support networks should be available for these caregivers to address their emotional needs and help them better cope with the situation.

The Administration Process

Healthcare professional preparedness

Nurses caring for patients receiving CAR T-cell therapy should be knowledgeable in the management of hematologic malignancies (i.e. treatments, disease and treatment-related complications, psychosocial issues, etc.) and principles of immunotherapy (FACT 2018b). Because tisa-cel is approved for use in patients up to 25 years of age, nurses specialized in the care of pediatric patients and/or pediatric oncology patients should be an integral part of the nursing team [see Module 6 for further details]. The evolving developments in types and targets of CAR T-cell therapies will mean that nurses will be required to continually update their knowledge and that nurses with expertise in other areas, intensive care for example, will need to be integrated into the team of nurses. Ideally, all healthcare professionals who directly or indirectly interact with patients receiving CAR T therapies should receive education and training to secure optimal patient outcomes. Educational content for all nurses involved in caring for patients receiving CAR T-cell therapy should include:

- Principles of CAR T-cell therapy (i.e. mechanisms of action, indications)
- Administration of CAR T-cell therapy including measures to ensure patient safety
- Care of the immunocompromised patient
- Causes and detection of complications/toxicities of CAR T-cell therapy
- Interventions to manage complications/toxicities of CAR T-cell therapy (FACT 2018a and 2018b; Taylor 2019)

Outpatient facilities providing CAR T-cell therapy administration should be designed in a manner that reduces the risk of infection transmission and allows for patient isolation (Taylor 2019). Comprehensive outpatient care is provided through extended hours of operation and availability of specially trained healthcare professionals.

Safety considerations

Current CAR T therapies are for autologous use only. It is therefore essential that the patient's identity matches the patient identifiers on the product. Documentation and verification procedures should be in place and part of standard of practice protocols when administering CAR T cells.

The manufacturer provides CAR T-cells in a frozen state. The procedure for thawing these products and the length of safe storage time once thawed should be verified with information provided by the manufacturer.

Manufacturers and approval agencies require that institutions stock at least 2 doses of tocilizumab for each patient before CAR T cell administration and have these doses ready for administration within 2 hours (Novartis 2018; Perica 2018). Similarly, approval agencies such as EMA (European Medicines Agency) and the FDA (US Food and Drug Administration) mandate prompt reporting of severe adverse events to institutional safety boards and to the manufacturers.

Infusion procedures

Infusions can be done in an outpatient setting with set-up and staffing similar to that used to monitor outpatient autologous hematopoietic stem cell recipients. Institutions should have guidelines and protocols in place for the administration of CAR T cells. Nurses should be familiar with and adhere to the recommendations provided by the manufacturer of the particular product being infused. Central venous access is recommended for the infusion of CAR T cells.

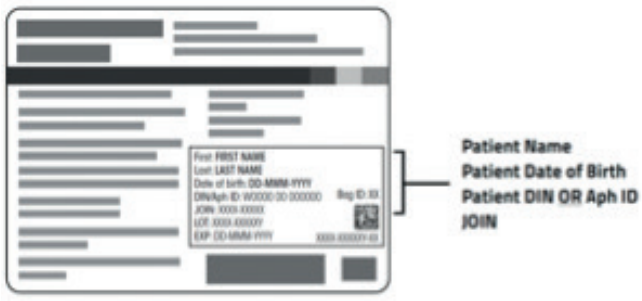

Figure 1. Sample of CAR T infusion bag.

Recommended steps to administer CAR T cells include:

- Verify patient identity as per local policy and match patient identity with the patient identifiers on the label of the infusion bag (**Figure 1**)
- Explain the procedure to the patient and caregiver
- Verify consent has been obtained
- Check prescription is correct
- Check vital signs and document
  - Ensure patient is hemodynamically stable and without infection
- Ensure all mandated pre-infusion assessments are complete
- Verify patent IV access
- Ensure bedside emergency equipment (suction/oxygen) is in full working order. Prepare IV fluids and fresh IV line, to be used in the event of a reaction during infusion
- Administer pre-medications as per institutional or manufacturers' (Kymriah 2021; Yescarta 2020) guidelines approximately one hour before infusion: steroids should not be administered
- Infuse thawed cells as per institutional guidelines, taking care to ensure that the infusion takes place approximately 30 minutes post thawing using the recommended administration equipment. Infusion time is approximately 10 to 15 minutes
- Observe for infusion related reactions and implement appropriate interventions as per institutional recommendations
- Ensure all necessary documentation is completed. CAR-T cells administered as part of a clinical trial will likely have additional documentation.
- Recommended monitoring of vital signs
  - every 15 minutes for one hour post infusion
  - hourly for 4 hours
  - 4 hourly thereafter
  - Monitor patients daily for at least 7 days after infusion (Novartis 2018; Kite Pharma 2021)

Delay the infusion of CAR T cells if the patients has:

- Unresolved serious adverse reactions from preceding chemotherapies (including pulmonary toxicity, cardiac toxicity or hypotension)
- Active uncontrolled infection
- Active graft versus host disease (GVHD)

- Worsening of disease burden following lymphodepleting chemotherapy (Novartis 2018)

Anaphylaxis

Serious hypersensitivity reactions, including severe anaphylactic reactions, can occur at the time of CAR T-cell infusion. These reactions are rare but can occur as a reaction to the cryoprotectant used (often dimethyl sulfoxide [DMSO]) (Kymriah 2021). Symptoms of anaphylaxis due to DMSO include shortness of breath, chest tightness, hypo- or hypertension, nausea, vomiting and headaches. Institutional policies for the management of anaphylactic reactions should be followed.

Recognition and Management of Toxicities

Introduction

The genetic modification of autologous or allogeneic T cells to express chimeric antigen receptors (CARs) or T-cell receptors (TCRs) is emerging as a promising new treatment modality for cancer (Rosenberg 2015). Although this novel therapy can provide rapid and durable clinical responses, it is associated with unique and potentially serious toxicities that require specialized monitoring and management and are of significant concern (Maude 2018; Neelapu 2017; Schuster 2019). The two most commonly observed toxicities with CAR T-cell therapies are cytokine-release syndrome (CRS) and CAR T-cell-related neurologic toxicity, often referred to as immune effector cell associated neurotoxicity syndrome (ICANS).

Intensive monitoring, accurate grading and prompt management of toxicities with aggressive supportive care can reduce the morbidity and mortality associated with CAR T-cell therapy (Neelapu 2017). The overall goal of management is to maximize treatment benefit while minimizing the risk of life-threatening complications, particularly CRS and neurologic toxicities (Neelapu 2017). Unlike the toxic effects associated with cytotoxic chemotherapy, which are off-target effects and can cause permanent genetic modifications of cells, the toxicities from CAR T, including CRS, are on-target off-tumor and may resolve without intervention (Brudno 2019; June 2018).

It is imperative that nurses and other healthcare professionals are educationally prepared for the intensive monitoring that patients may require and that institutions providing CAR T-cell therapy are equipped to provide the complex interprofessional care required to manage severe side effects (Anderson 2019). Nurses play a pivotal role in assessing, identifying and managing treatment-associated toxicities and in coordinating the care of patients between hospital inpatient and outpatient units.

The magnitude and timing of the toxicities associated with CAR T cell therapy vary considerably, not only between different CAR T cell constructs, but also across different diseases (ALL versus NHL). Toxicity might also be influenced by other factors including patient age, the presence of co-morbidity and prior therapy. Because the risk of toxicity increases with patient age, children might be less likely than adults to have short-term or long-term CRS-related morbidity and/or mortality (Teachy 2018).

It is often difficult to distinguish some of the toxicities (i.e., CRS and hemophagocytic lymphohistiocytosis) as toxicities may occur simultaneously and/or have similar signs/symptoms. This means monitoring and assessing for toxicities requires being alert to toxicities occurring together.

Recommendations for Supportive Care of the Patient receiving CAR T-cell Therapy

Before and during CAR T-cell infusion

Consider baseline brain MRI to rule out any CNS disease
Central venous access, preferably with double or triple lumen catheter for intravenous fluid and other infusions in case of toxicities
Cardiac monitoring by telemetry or ECG for arrhythmias starting on the day of CAR T-cell infusion and continued until CRS resolves
Tumor lysis precautions for patients with bulky tumors
Consider seizure prophylaxis with levetiracetam at 750 mg orally every 12 hours for 30 days, starting on the day of infusion for CAR T-cell therapies known to cause CAR T-cell-related neurotoxicities
Hospitalization recommended for at least 7 days after CAR T-cell therapy

Patient monitoring after CAR T-cell infusion

Assess vital signs every 4 hours, close monitoring of oral and IV fluid input and urine output, daily bodyweight measurements
Daily review of patient history and physical examination
Daily blood counts, complete metabolic and coagulation profiling
Daily measurements of C-reactive protein and ferritin levels (may need to be performed more frequently in patients at high risk of severe CRS and/or neurotoxicity or those at risk of TLS)
Assessment and grading of CRS performed at least twice daily and whenever there is a change in patient's status
Assessment and grading of ICANS using the CAR T-cell therapy-associated toxicity 10-point neurological assessment (CARTOX-10) at least every 8 hours
Maintain IV fluids with normal saline to ensure adequate hydration

CNS, central nervous system; ICANS, immune effector cell associated neurotoxicity syndrome; IV, intravenous; MRI, magnetic resonance imaging; TLS, tumor lysis syndrome
Adapted from: Lee 2014, Neelapu 2018

Supportive care considerations

In addition to specific, toxicity-related interventions, supportive care considerations for managing patients receiving CAR T-cell therapy should be incorporated into the comprehensive plan of care for the patient (**Box 1**).

On target/off-tumor toxicity

Off target describes the effects that can occur when a drug binds to targets (proteins or other molecules in the body) other than those for which the drug was meant to bind. This occurs in CAR T-cell therapy in patients who have target antigen expressed on both tumor and healthy tissue. The severity of these events can range from manageable lineage depletion (B-cell aplasia) to severe toxicity. On-target/off tumor toxicity (sometimes referred to as off recognition) is seen in a variety of organ systems, including gastrointestinal, hematologic and pulmonary (Bonifant 2016).

Cytokine release syndrome (CRS)

CRS is the most common toxicity associated with CAR T-cell therapy (Brudno 2019; Brudno 2016). It is triggered by the activation of T cells on engagement of their CARs or TCRs with cognate antigens expressed by tumor cells. The activated T cells release cytokines and chemokines (e.g. IL-2, soluble IL-2Rα, IFNγ, IL-6, soluble IL-6R and GM-CSF) as do bystander immune cells, such as monocytes and/or macrophages (which secrete IL-1RA, IL-10, IL-6, IL-8, CXCL10, CXCL9, IFNα, CCL3, CCL4 and soluble IL-6R). CRS severity is related to high disease burden, intensity of lymphodepletion, tumor cell proliferation rate and cytotoxicity/dose of the CAR T-cell product (Shimabukuro-Vornhagen 2018).

The American Society for Transplantation and Cellular Therapy (ASTCT) defines CRS as:

> "A supraphysiologic response following any immune therapy that results in the activation or engagement

Table 2: Symptoms / Signs of CRS by Organ System

Constitutional: Fevers (temperature ≥ 38°C) Rigors Malaise Fatigue Anorexia Arthralgias	**Neurologic:** Headaches Changes in level of consciousness Delirium Aphasia Apraxia Ataxia Hallucinations Tremor Dysmetria Myoclonus Facial nerve palsy Seizures	**Cardiovascular:** Tachycardia Widened pulse pressure Systolic blood pressure < 90 mmHg (hypotension) Arrhythmias Low ejection fraction QT prolongation
Respiratory: Tachypnea Hypoxia Pleural effusion Dermatological: rash (less common) Coagulopathy: disseminated intravascular coagulation (less common)	**Gastrointestinal:** Nausea Vomiting Diarrhea	**Hepatic:** Increased serum ALT, AST or bilirubin levels
Renal: Acute kidney injury (increased serum creatinine levels) with decreased urinary output Hyponatremia Hypokalemia Hypophosphatemia	**Hematologic:** Anemia Thrombocytopenia Neutropenia B-cell aplasia Prolonged prothrombin time Disseminated intravascular coagulation Hemophagocytic lymphohistiocytosis	**Musculoskeletal:** Elevated creatine kinase Weakness Myalgia

ALT, alanine aminotransferase; AST, aspartate aminotransferase; SA O2, arterial oxygen saturation
Adapted from: Lee 2014

Table 3. Published and commonly used CRS Grading Systems

Grading System	Grade 1	Grade 2	Grade 3	Grade 4
ASTCT (Lee 2014)	Symptoms not life-threatening and require symptomatic treatment only (fever, nausea, fatigue, headache, myalgias, malaise)	Symptoms require and respond to moderate intervention: Oxygen requirement <40% FiO_2 or hypotension responsive to IV fluids or low dose of one vasopressor or Grade 2 organ toxicity	Symptoms require and respond to aggressive intervention: Oxygen requirement ≥40% FiO_2 or hypotension requiring high-dose/multiple vasopressors or Grade 3 organ toxicity[a] or grade 4 transaminitis	Life-threatening symptoms: Requirement for ventilator support or Grade 4 organ toxicity[a] (exluding transaminitis)
CTCAE version 5.0 (CTCAE)	Fever, with/without constitutional symptoms	Hypotension responding to fluids; Hypoxia responding to <40% FiO_2	Hypotension managed with one pressor; Hypoxia requiring ≥40% FiO_2	Life-threatening consequences; urgent intervention needed
Penn criteria (Porter 2018)	Mild reaction: Treated with supportive care such as antipyretics, antiemetics	Moderate reaction: some signs of organ dysfunction (grade 2 creatinine or grade 3 LFTs) related to CRS and not attributable to other condition. Hospitalization for management of CRS-related symptoms, including neutropenic fever and need for iv therapies (not including for resuscitation for hypotension)	More severe reaction: Hospitalization required for management of symptoms related to organ dysfunction, including grade 4 LFTs or grade 3 creatinine, related to CRS and not attributable to another condition Hypotension treated with multiple fluid boluses or low-dose vasopressors Coagulopathy requiring fresh frozen plasma, cryoprecipitate or fibrinogen concentrate Hypoxia requiring supplemental oxygen	Life-threatening complications such as hypotension requiring high-dose vasopressors Hypoxia requiring mechanical ventilation
ASTCT Consensus Grading (Lee 2019)				
Fever[1]	Temperature ≥38.5˚C	Temperature ≥38.5˚C	Temperature ≥38.5˚C	Temperature ≥38.5˚C
		WITH		
Hypotension	None	Requiring IV fluids but not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		AND/OR[2]		
Hypoxia	None	Requiring low-flow O_2 via nasal cannula[3] or blow-by	Requiring O_2 via high-flow nasal cannula, facemask, non-rebreather mask or Venturi mask	Requiring O_2 via positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

ASTCT, American Society for Transplantation and Cellular Therapy; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome; FiO2, fraction of inspired oxygen; IV, intravenous; LFT, liver function tests;
[1] Fever is defined as temperature ≥38.5°C not attributable to any other cause. If fever is no longer present due to antipyretics or tocilizumab or corticosteroids, fever is no longer required to grade CRS severity; CRS grading is driven by hypotension and/or hypoxia instead
[2] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS
[3] Low-flow nasal cannula is defined as oxygen delivered at ≤6L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6L/minute

of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia) and end organ dysfunction."

Patients at high risk of developing severe CRS include those with bulky disease, comorbidities and those who develop early onset CRS within 3 days of cell infusion (Neelapu 2018). There is not, however, a clear correlation between the development of severe CRS and clinical parameters meaning that more clinical input is required to identify predictive biomarkers for severe toxicity.

Clinical manifestations

The primary manifestations of CRS are constitutional symptoms, such as fever, malaise, anorexia and myalgia, but any organ system in the body can be affected (**Table 2**). The onset of CRS usually occurs within the first week of CAR T-cell therapy and typically peaks within 1 to 2 weeks of administration (Neelapu 2018). Depending on the type of therapy used, hospitalization for monitoring is recommended for at least 7 days after CAR T-cell infusion, or at the time of fever development with other agents (Teachy 2018).

Patient hospitalization with close monitoring is recommended for at least 7 days after CAR T-cell infusion, including cardiac monitoring by telemetry from the time of CAR T-cell infusion until resolution of any emergent CRS symptoms due to the high risk of arrhythmias (Neelapu 2017).

Management of CRS

The management of CRS is dependent on the grade of severity of CRS with several grading systems currently in clinical use (**Table 3, Table 4**). More recent systems identify fever as a hallmark of CRS and recognize neurologic toxicities such as confusion, delirium, aphasia and others to be a separate syndrome because of the differential time of presentation compared to other signs of CRS and lack of knowledge surrounding their etiology and pathophysiology (Lee 2019).

There is no clinical consensus on the "best" management of CRS. As would be the case in other disease entities, antipyretics are recommended for fever, fluid bolus and vasopressors for hypotension, and oxygen supplementation and correction of hypoventilation for management of hypoxia. Because corticosteroids may alter the effectiveness of CAR T cells, they should be avoided for the management of fever or for premedication before blood transfusions unless the patient is experiencing life-threatening treatment complications. Dexamethasone at a dose of 10 mg every 6 h for the treatment of grade 2 or 3 CRS refractory to anti-IL-6 therapy tapered as rapidly as possible depending on response (Neelapu 2018) or lower starting doses of intravenous methylprednisolone (starting at 1 to 2 mg/kg per day) may be sufficient to manage symptoms (Buechner 2017). Tocilizumab is a monoclonal antibody which binds to the IL-6 receptor and is licensed in most countries for treating CRS. The recommended dose is 8mg/kg, with a maximum dose of 800mg. It is given as an intravenous infusion over 60 minutes. Up to four doses can be given at intervals of at least eight hours.

Resolution of CRS, as defined by ASTCT, is the absence of all signs and symptoms that led to the diagnosis of CRS (Lee 2019).

Hemophagocytic lymphohistiocytosis (HLH)/Macrophage activation syndrome (MAS)

HLH or MAS can occur in the context of hematological malignancy, infection and autoimmunity/immune dysregulation. HLH/MAS encompasses a group of severe immunological disorders and is difficult to diagnose (Titov 2018), as its presentation is very similar to that of CRS; severe cases of CRS can progress to HLH/MAS (Sandler 2020). HLH/MAS following CAR T-cell therapy is observed in about 1% of patients and should initially be managed with interventions used for CRS (**Table 5**). Escalation of treatment might be necessary if improvement is not evident within 48 hours (Neelapu 2018).

Neurotoxicity

Neurotoxicity is the second most common, and dangerous, complication of CAR T-cell therapy (Gust 2018) and is sometimes referred to as immune effector cell associated neurotoxicity syndrome (ICANS). ICANS is a pathologic process involving the central nervous system that results in the activation or engagement of endogenous or infused T cells and/or immune effector cells (Lee 2019). ICANS is preferred over CRES (CAR T-cell-related encephalopathy syndrome) by some investigators as ICANS includes other symptoms and acknowledges other cellular immunotherapies, such as bispecific antibodies, that may have similar neurologic side effects (Lee 2019).

It is estimated that more than 60% of patients treated with CAR T cells may experience neurologic toxicities (Santomasso 2018), which are diverse and do not localize to one region of the central nervous system (Brudno 2019). A challenge for the wider application of CAR T-cell therapies is to better understand the pathophysiology, prevention and treatment of neurotoxicity (Gust 2018). Neurotoxicity associated with CAR T-cell therapy is thought to involve disruption of the normal blood-brain barrier function by an elevated cytokine level. In addition, endothelial activation and a disruption in the blood-brain barrier, and excitatory agonists are thought to have a potential role in the development of this toxicity.

Neurologic toxicities may occur simultaneously with signs of CRS such as hypotension, or in patients not having typical signs of CRS or after resolution of CRS (Brudno

Table 4. Recommendations for the Management of Cytokine-release Syndrome (CRS)

CRS grade	Symptom/sign	Medical/Pharmacologic intervention	Nursing intervention
Grade 1	Fever or organ toxicity	Acetaminophen; Ibuprofen (secondary treatment); Empiric broad-spectrum antibiotics and filgrastim if neutropenia; Maintain IV fluids; Tocilizumab 8 gm/kg[1] IV or siltuximab 11 mg/kg IV for persistent (> 3 days) and refractory fever	Close monitoring of vital signs; Hypothermia blanket; Assessment for infection, blood & urine cultures, chest x-ray; Management of symptoms of fever, constitutional symptoms
Grade 2	Hypotension	IV fluid bolus of 500-1000 ml of normal saline, administration of second bolus if systolic BP remains <90 mm Hg; Tocilizumab 8 mg/kg[1] IV or siltuximab 11 mg/kg for hypotension refractory to fluid boluses; repeat tocilizumab after 6 h if needed; Initiate vasopressors, consider transfer to ICU if lack of response from fluid boluses and anti-IL-6 therapy; Dexamethasone at 10 mg IV every 6 h for high-risk patients[2] or persistence of hypotension after 1-2 doses of anti-IL-6 therapy	Monitor BP; Supportive measures for fever and hypotension; Monitor fluid balance
	Hypoxia	Supplemental oxygen; Tocilizumab or siltuximab ± corticosteroids	Monitor administration of supplemental oxygen, monitor O_2 saturation; Supportive care measures for hypotension
	Organ toxicity	Symptomatic management of organ toxicities as per institutional standards; Tocilizumab or siltuximab ± corticosteroids	Monitor laboratory values; Supportive care measures for hypotension
Grade 3	Hypotension	IV fluid boluses as needed; Tocilizumab + siltuximab if not previously administered; Vasopressors as needed; Transfer to ICU; Echocardiogram, hemodynamic monitoring; Dexamethasone 10mg IV every 6 h, increase to 20 mg every 6 h if refractory	Hemodynamic monitoring; Management of fever and constitutional symptoms; Update report to ICU nurses
	Hypoxia	Supplemental oxygen including high-flow oxygen delivery and non-invasive positive pressure ventilation; Tocilizumab or siltuximab + corticosteroids	Monitor administration of supplemental oxygen, monitor O_2 saturation; Supportive care measures for hypotension
	Organ toxicity	Symptomatic management of organ toxicities as per institutional standards; Tocilizumab or siltuximab + corticosteroids	Supportive care measures as appropriate
Grade 4	Hypotension	IV fluids, anti-IL-6 therapy, vasopressors; Methylprednisolone 1 g/day IV; Medical management of fever & constitutional symptoms	Hemodynamic monitoring; Management of symptoms of fever, constitutional symptoms
	Hypoxia	Mechanical ventilation; Tocilizumab or siltuximab + corticosteroids; Medical supportive care	Supportive care measures as indicated
	Organ toxicity	Medical management of organ toxicities as per institutional guidelines; Tocilizumab or siltuximab + corticosteroids; Medical supportive care	Supportive care measures as indicated

; BP, blood pressure; ICU, intensive care unit; IV, intravenous;
[1] Maximum amount of tocilizumab per dose is 800 mg; [2] Patients with bulky disease, with comorbidities, those who develop early onset CRS within 3 days of CAR T-cell administration
Adapted from: Neelapu 2018

2019). Systemic cytokine release and the severity of CRS are the most clearly defined risk factors for ICANS (Gust 2020).

The development of neurotoxicity may be affected by:

- Type of disease (acute lymphoblastic leukemia rather than non-Hodgkin lymphoma)
- Prior treatment history
- Patient age (younger patients seem to be at higher risk)
- CAR design
- CAR T-cell manufacturing approach
- Lymphodepletion regimen (Gust 2018)

Studies on clinical experience with recognizing and managing the neurotoxicity of CAR T are continually emerging. In a study of 100 patients, high-grade ICANS was associated with worse outcome after CAR T-cell therapy, although reversible, grade ≥ 3 ICANS was associated with significantly shorter progression-free and overall survival (Strati 2020). In another study, 52% of recipients of CAR T cells developed grade 3 to 4 neurotoxicity, which was found to be associated with lower platelet counts at the time of CAR T cell administration, and in this study, grade 3-4 neurotoxicity, negatively correlated with overall survival (Karschnia 2019).

Clinical manifestations

Symptoms or signs of ICANS can be progressive. Early symptoms can include:

- Tremor
- Dysphagia
- Mild difficult with expressive speech (i.e. naming objects)
- Impaired attention
- Apraxia
- Mild lethargy
- Headache
- Visual changes
- Generalized weakness (Lee 2019; Gust 2018)

The most prevalent symptom is transient cognitive impairment (Gust 2020). While tremor and headache may occur, they are considered nonspecific symptoms, whereas expressive aphasia is a specific symptom and may progress to global aphasia, which is characterized by expressive and receptive difficulty whereby patients appear wide awake but are mute and unable to follow commands (Lee 2019).

Cerebral edema is the most serious complication, occurring in an estimated 1% to 2% of patients, and is fatal in most cases (Gust 2020).

The onset of neurotoxicity occurs at about 3 to 6 days after CAR T cell infusion, usually quite rapidly, with a peak on day 7 and resolution by days 14 to 21 (Gust 2020); persistent abnormalities are uncommon (Gust 2017). Severe symptoms are most often seen with an early onset of CRS and it is not unusual for ICANS to develop in the setting of improving or resolved CRS thereby supporting the hypothesis that cytokine release contributes to the development of neurotoxicity (Gust 2020).

Diagnosis of neurotoxicity

The ASTCT recently developed an encephalopathy screening tool, which includes an element for assessing the receptive aphasia seen in patients with ICANS. The presence of receptive aphasia is highly suggestive of the encephalopathy observed in patients with ICANS. This tool contains elements of the CARTOX-10, a 10-point neurologic assessment tool that incorporates key elements of the Mini-Mental State Examination (MMSE) to evaluate alterations in speech, orientation, handwriting and concentration (Neelapu 2017). ASTCT updated the CARTOX-10 by adding a command-following assessment (**Table 6**).

Table 5. Symptoms, Diagnosis and Management of HLH/MAS

Symptoms/Diagnosis	Management
High fever, multi-organ dysfunction, CNS disturbances; high serum levels of lactate dehydrogenase and low levels of fibrinogen; Peak serum ferritin > 10,000 µg/L with CRS and two of the following: grade > 3 increase in serum transaminases or bilirubin/ grade > 3 oliguria or increase in serum creatinine; grade > 3 pulmonary edema or histological evidence of hemophagocytosis in bone marrow or organs; fever, cytopenia; multi-organ failure	Supportive organ-specific treatment; administer broad-spectrum antibiotics, tocilizumab or siltuximab (anti-IL6 agents), corticosteroids; monitor lactate dehydrogenase, fibrinogen, transaminases, bilirubin, creatinine levels

CNS, central nervous system; CRS, cytokine release syndrome
Sources: Sandler 2020; Neelapu 2018

Table 6. Encephalopathy Assessment Tools for Grading of Neurotoxicity and ICANS

CARTOX-10 (Neelapu 2017)		**ICE** (Lee 2019)	
Orientation: orientation to year, month, city, hospital, president/prime minister of country of residence	5 points	**Orientation:** orientation to year, month, city, hospital	4 points
Naming: ability to name 3 objects (eg, point to clock, pen, button)	3 points	**Naming:** ability to name 3 objects (eg, point to clock, pen, button)	3 points
Writing: ability to write a standard sentence (eg, "I enjoy riding my bicycle")	1 point	**Following commands:** ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue")	1 point
Attention: ability to count backwards from 100 by 10	1 point	**Writing:** ability to write a standard sentence (eg, "I enjoy riding my bicycle")	1 point
		Attention: ability to count backwards from 100 by 10	1 point

CARTOX-10, CAR T-cell therapy-associated toxicity 10-point neurological assessment
ICE, Immune Effector Cell-Associated Encephalopathy score
Scoring systems are the same for both tools: 10 = no impairment; 7-9 = grade 1 ICANS; 3-6 = grade 2 ICANS; 0-2 = grade 3 ICANS; 0 due to patient unarousable and unable to perform ICE assessment = grade 4 ICANS

Table 7. ASTCT ICANS Consensus Grading

Neurotoxicity domain	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**
ICE score[1]	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness[2]	Awakens spontaneously	Awakens to voice	Awakens only to touch stimulation	Patient is unarousable OR requires vigorous/repetitive touch stimulation to arouse. Stupor/coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly OR non-convulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 min); or repetitive clinical OR electrical seizures without return to baseline in between
Motor findings[3]	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/ cerebral edema	N/A	N/A	Focal/local edema on neuro imaging	Diffuse cerebral edema on neuro imaging; decerebrate/decorticate posturing; OR cranial nerve VI palsy; OR papilledema; OR Cushing's triad

ICE, Immune Effector Cell-Associated Encephalopathy score; ICP, intracranial pressure; N/A, not applicable
ICANS grade is determined by the most severe event (ICE score, level of consciousness, seizure, motor findings, increased ICP/cerebral edema) not attributable to any other cause; for example, a patient with an ICE score of 3 who has a generalized seizure is grade 3 ICANS
[1] A patient with an ICE score of 0 may be classified as grade 3 ICANS if awake with global aphasia, but a patient with an ICE score of 0 may be classified as grade 4 ICANS if unarousable; [2] Depressed level of consciousness should be attributable to no other cause (i.e., sedation medications); [3] Tremors and myoclonus associated with immune effector cell therapies may be graded according to other tools but do not influence ICANS grading; [4] Intracranial hemorrhage with/without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading
Adapted from: Lee 2019

Using consensus, ASTCT developed an ICANS grading scheme in which various signs and symptoms of neurotoxicity are considered to establish the severity of ICANS and the final ICANS grade is determined by the most severe event among the different domains (**Table 7**).

Management of neurotoxicity

The optimal management of neurotoxicity is yet to be established. As is the case for CRS, management of neurotoxicity due to CAR T-cell therapy is dependent on the grade of severity (**Box 2**). Treatment with dexamethasone and other corticosteroids, which reduces the risk of life-threatening cerebral edema, and supportive measures (e.g. anti-seizure medications), is the frontline option, although there are concerns that administration of systemic steroids may suppress CAR T cell response. Administration of intrathecal hydrocortisone to reduce inflammation and chemotherapy showed rapid and sustained resolution of ICANS and no long-term complications in a limited-case trial (Shah 2020). In cases of neurologic toxicity in the presence of CRS, tocilizumab is usually prescribed according to CRS management guidelines (Anderson 2019). Tocilizumab, however, has limited efficacy in resolving neurologic toxicity, most likely because CAR T cells and inflammatory cytokines can cross the blood-brain barrier but tocilizumab has poor CNS penetration (Brudno 2019). Siltuximab has also been used to manage neurotoxicity and neurologic adverse events. The use of seizure prophylaxis using levetiracetam or prophylactic antiepileptic agents varies among institutions; some may initiate these agents on the day of CAR T cell infusion while others prefer to administer them at onset of neurologic toxicity (Rivera 2020).

Tumor lysis syndrome (TLS)

TLS is not unique to therapy with CAR T cells but rather can result from rapid destruction of tumor cells following various types of cancer treatment. The risk of TLS

Box 2. Schema for grading severity of neurotoxicity

Grade 1
Assess physical and neurologic status routinely per institutional standards; frequent monitoring of vital signs, strict intake and output measurement, daily weights
Elevate head of bed to at least 30 degrees to minimize aspiration risk and improve cerebral venous flow
Withhold oral intake of food, medicines, fluids; assess swallowing ability
Neurology consult; EEG daily until toxicity symptoms resolve; fundoscopic examination to rule out papilledema
MRI of the brain and/or spine (CT if MRI not available or not feasible); diagnostic lumbar puncture
Avoidance of medications that cause central nervous system depression
Low doses of lorazepam or haloperidol with careful monitoring if patient is agitated
Consider anti-IL-6 with tocilizumab 8 mg/kg IV or siltuximab 11 mg/kg IV if CRS present

Grade 2
Supportive care, neurological work-up and anti-IL-6 therapy as described for Grade 1
Continuous pulse oximetry and cardiac telemetry for patients receiving axicabtagene ciloleucel
Dexamethasone 10 mg IV every 6 h or methylprednisolone 1 mg/kg IV every 12 h if refractory to anti-IL-6 therapy or in the absence of CRS
Tocilizumab 8 mg/kg IV or siltuximab 11 mg/kg IV if associated with concurrent CRS
Consider transfer to ICU

Grade 3
Supportive care, neurological work-up and anti-IL-6 therapy (if not previously administered) as recommended for Grade 1
Transfer to ICU is recommended
Corticosteroids as recommended for Grade 2 if symptoms worsen despite anti-IL-6 therapy, or in the absence of CRS; continue corticosteroids until improvement then taper
Monitor papilledema with cerebrospinal fluid opening pressure
Pharmacologic control of seizures (benzodiazepine for acute management; antiepileptic drug therapy)

Grade 4
Control ICP using hyperosmolar therapy with mannitol or hypertonic sodium chloride
Assess need for mechanical ventilation
Anti-IL-6 therapy
High-dose corticosteroids until improvement to grade 1

CRS, cytokine release syndrome; CT, computed tomography; EEG, electroencephalography; ICP, intracranial pressure; ICU, intensive care unit; MRI, magnetic resonance imaging
Sources: Rivera 2020; Anderson 2019; Neelapu 2018

developing is higher in patients with significant disease burden, especially ALL with extensive marrow infiltration or NHL with bulky adenopathy (Hirayama 2019). Many centers administer prophylactic allopurinol prior to chemotherapy or cell infusion (Brudno 2016). Monitoring for TLS includes testing calcium, potassium, phosphorus, creatinine and uric acid levels 2 to 3 times per week. TLS is associated with hyperkalemia, hyperphosphatemia and hyperuricemia (Maus 2016).

Management

Most institutions involved in cancer treatment have standard protocols to effectively manage TLS, which usually include aggressive hydration and consideration of rasburicase administration.

Cytopenia and infection

Cytopenia can persist beyond 30 days after CAR T infusion and is associated with lymphodepleting regimens and CAR T-cell therapy. The etiology of cytopenia is unclear but likely related to ongoing CAR T activity and disruption of hematopoiesis with evidence of hypocellularity frequently shown in bone marrow examination (**Table 8**) (Neelapu 2019). Cytopenia, primarily exhibited as neutropenia and thrombocytopenia, eventually resolves in most patients.

Approximately one-fourth of patients (23%) experience infections after CAR T-cell therapy including fungal infections in 5% and life-threatening infections in 4% (Hill 2018). Infection may be a result of underlying immune suppression, the effects of lymphodepletion or the consequence of on-target, off-tumor toxicity resulting in B cell depletion (Hirayama 2019).

B-cell aplasia and hypogammaglobulinemia

CD19-specific CAR T cells target normal B cells, which can result in B-cell aplasia and is an expected and common adverse effect of anti-CD19 CAR T cells (Brudno 2016). B-cell aplasia and hypogammaglobulinemia may last 2 months to over 2 years following CAR T-cell therapy (Brudno 2016) and may lead to long-term disease surveillance and possibly prevent relapse (Maus 2016). The CTL019-mediated elimination of normal CD19-expressing precursors and maturing B cells is an on-target off-tumor toxicity. As prophylaxis from infection, intermittent infusion of pooled immunoglobulin (IV immunoglobulin [IgG]) may be necessary (Bonifant 2016; Brudno 2016). Patients should be monitored for infection and infection precautions should be applied.

Cardiac

Transient cardiac insufficiency and transient arrhythmia have been associated with CAR T-cell therapy and in association with CRS (Novartis 2018). Owing to a high risk of arrhythmias, cardiac monitoring by telemetry is advised from the time of starting CAR T-cell therapy until resolution of any emergent CRS symptoms (Neelapu 2018).

Future Perspectives

Approval of CD19 CAR T cell therapies was granted based on a relatively small number of patients from single-arm phase 2 trials. The limited amount of current data means that further data on toxicity and patient outcomes, especially potential long-term genotoxicity, should be collected and reviewed at regular intervals post-treatment. Similarly, the management of CAR T-cell toxicities is in its early stage highlighting a need for the development of universal grading scales for CRS and neurologic toxicity to develop better generalizable guidelines for managing toxicities.

Risk-adapted dosing of CAR T cells, with lower cell doses administered to patients with higher disease burden, may lessen toxicity, possibly without compromising efficacy, as higher disease burden is associated with a greater risk of CRS and neurotoxicity. Further evaluation of such risk-adapted approaches warrants investigation (Brudno 2019).

The cost implications and complexity of autologous T-cell therapies hampers the broader application of these therapies. The development of "off the shelf" products may be possible in the near future. The major challenge in developing off-the-shelf T cells is avoidance of immune rejection in both host-versus-graft and graft-versus-host directions (June 2018). Evaluation of autologous CAR T-cell therapies is currently being conducted.

Table 8. Assessment and Management of Cytopenias and Infection

	Assessment	Management
Cytopenias	As per institutional policies: monitor patient for signs/symptoms of bleeding, anemia, infection	Monitor blood counts; Administration of G-CSF for neutropenia; Prophylactic IVIG infusion; Blood product transfusion to support anemia and thrombocytopenia
Infection	Monitor vital signs (at least every 4 h if hospitalized); CBC with differential CMP; Blood/urine cultures if fever present; Targeted imaging based on symptoms of infection	Empiric broad-spectrum antibiotic therapy; Prophylactic antimicrobial agents if prolonged, grade 4 neutropenia; Acetaminophen and cooling blankets for fever/rigors; IV fluids; follow institutional protocols for prevention and management of infection

CBC, complete blood count; CMP, comprehensive metabolic panel; G-CSF, granulocytes colony-stimulating factor; IVIG, intravenous immunoglobulin
Sources: Brudno 2019; Neelapu 2019

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Quick Facts

- Patients and caregivers should understand the necessity to contact a healthcare professional should there be any change in their state of well-being not only in the immediate post-infusion period but also for months and even years after CAR T-cell therapy
- Hypogammaglobulinemia, a result of B-cell aplasia, occurs in all responding patients and can persist for several years placing the patient at increased risk for infection
- Regular monitoring of patients for relapse from the primary hematological malignancy and new complications such as second malignancies is recommended longer-term care
- Direct and indirect financial costs of treatment using CAR T cells are high and financial concerns may contribute to psychological sequelae that may further compound the anxieties and stressors associated with this novel treatment

Module V: Follow-up Monitoring and Psychosocial Implications

Introduction

The newness of CAR T-cell therapy and the limited number of patients treated with this novel therapy to date makes it challenging to identify longer-term adverse effects of treatment. One follow-up study reported rare occurrences of adverse effects, except for B-cell depletion and hypogammaglobulinemia, ≥ 3 years after treatment in a small group of patients (Cappell 2020). Because CAR T represents a novel class of therapy, currently approved products require close post-marketing surveillance. The European Medicines Agency (EMA), for example, requires the collection of 15-year follow-up data on treated patients in order to ensure the evaluation of the efficacy and safety of these treatments continues on a long-term basis.

While the majority of toxicities secondary to CAR T cells are known to resolve before day 30, some may persist beyond this time and a few complications may occur for the first time after 30 days. Common determinants of late toxicity are age, prior therapies, tumor type, acute toxicities and CAR construct

Currently, no clinical guidelines exist to define the longer-term care following CAR T-cell therapy, whether it is the surveillance plan for future malignancies, immune-related events, the optimal management of persistent cytopenias and hypogammaglobulinemia, or measures to screen for and address late-onset neurologic and psychiatric issues (Hossain 2020). The absence of such guidelines makes it necessary and important for institutions providing CAR T therapy to develop and implement their own institutional standards of practice to follow.

Medium-term Complications of CAR T-cell Therapy

The European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) define medium-term complications of CAR T as those occurring from day 28 to day 100-post infusion (Yakoub-Agha 2019). Several of these toxicities commonly occur in the period immediately following CAR T cell infusion. Others, such as graft versus host disease (GvHD), which is associated with allogeneic CAR T- cell therapy, can occur later but their frequency is relatively low. Hypogammaglobulinemia, a result of B-cell aplasia, occurs in all responding patients and can persist for several years serving as a marker for monitoring CD19-specific CAR T-cell activity over time (Yakoub-Agha 2019). Patients with B-cell aplasia are at sustained increased risk of infection. Other than IVIG as prophylaxis, no clear recommendations for treatment or prevention of severe hypogammaglobulinemia have been published so far (**Table 1**).

Table 1. Potential Medium-term Sequelae

Sequelae	Signs/symptoms	Management
Delayed or secondary macrophage activation syndrome/hemophagocytic lymphohistiocytosis [see Module 4]	Persistent high-grade fever, hepatosplenomegaly, lymphadenopathy, pancytopenia, fibrinolytic coagulopathy, elevated ferritin levels can develop concurrently with CRS	Supportive measures; administration of tocilizumab, steroids; follow standard treatment protocols when available
B-cell aplasia/ hypogammaglobulinemia [see Module 4]	Fever, chills (signs/symptoms of infection)	IVIG; transition to subcutaneous immunoglobulins after 6 months; infection prophylaxis
Infections [see Module 4]	Viral infections of respiratory tract common; fever, chills, shortness of breath, tachycardia	Administration of antimicrobial/antiviral agents; supportive measures
TLS [see Module 4]	Hyperkalemia, hyperphosphatemia, hyperuricemia	Prophylactic allopurinol; follow standard treatment protocols
CRS [see Module 4]	Fever, hypotension, hypoxia	Follow standard treatment protocols depending on grade
GvHD (in recipients of allogeneic HCT)	Rash, skin burning/redness; nausea, vomiting, abdominal cramps, loss of appetite, diarrhea; jaundice	Steroids; follow standard treatment protocols when available
Fatigue	Feelings of chronic tiredness/lack of energy; headache, dizziness	Exercise, yoga, meditation, Pilates, massage therapy; planned periods of rest during the day

CRS, cytokine release syndrome; GvHD, graft versus host disease; HCT, hematopoietic stem cell transplant; IVIG, intravenous immunoglobulin; TLS, tumor lysis syndrome
Sources: Sandler 2020; Yakoub-Agha 2019; Brudno 2019

Table 2. EBMT Recommendations for Tests to Monitor for Medium-term Complications	
Test	**Rationale**
CBC, biochemistry panel, LDH, fibrinogen, CRP	Standard follow-up tests for monitoring status
CMV, EBV, adenovirus	Monitor viral reactivation
Quantitative immunoglobulins or serum protein electrophoresis	Assess immune reconstitution
Peripheral blood immunophenotyping (CD3/4/8/16+56/19)	Monitor immune recovery; helpful to guide anti-infective prophylaxis
CAR T-cell monitoring (monitoring of anti-CD19 CAR T cells	CAR T-cell persistence
CBC, complete blood count; CMV, cytomegalovirus; CRP, C-reactive protein; EBV, Epstein-Barr virus; LDH, lactate dehydrogenase Adapted from: Yakoub-Agha 2019	

It may be difficult to distinguish the symptoms of one complication from those of another; for example, fever as a symptom of infection and fever due to cytokine release syndrome (CRS). Laboratory and refined diagnostic tests may assist in differentiating between two or more complications to confirm and appropriately treat a condition (**Table 2**).

COVID-19 vaccines

The dramatically changing scope and breadth of the SARS-CoV-2 pandemic make it difficult to provide current information on recommendations for COVID-19 vaccines for recipients of CAR T-cell therapy. Currently there is no data on the capacity of any approved vaccine to induce immune responses in CAR T-cell-treated patients. Therefore, these patients should continue to follow guidelines to limit their risk for exposure. Vaccination against COVID-19 should take priority over any regular vaccinations and the vaccine should be administered alone (EBMT 2021). For patients who received COVID-19 vaccination before CAR T-cell therapy, it is likely that the lymphodepletion procedure has wiped out all immune memory and these patients should be vaccinated as COVID-19 naïve patients. COVID-19 vaccination should be postponed if B-cell aplasia occurred earlier than six months after treatment (EBMT 2021).

Longer-term Complications of CAR T-cell Therapy

Little is known about the longer-term complications of CAR T as only a small cohort of patients has been followed for more than 2 years. Longer-term complications of CAR

Table 3. Potential Longer-term Events after CAR T-cell Therapy	
Event	**Management**
Cytopenia	Frequent monitoring of CBC with differential; G-CSF support and RBC and platelet transfusion as required
Hypogammaglobulinemia	Monitor monthly immunoglobulin levels; IVIG if recurrent infections; Consider IVIG for IgG level <200 mg/dL especially if IgA level is also low
Infections	Antimicrobial prophylaxis and vaccinations (i.e., acyclovir or valacyclovir for HSV and VZV)
Secondary malignancies	Frequent monitoring for MDS and skin cancers; Screening for solid cancers as per recommendations for general population
Neurologic disorders	Perform history and physical exam at each follow-up visit
Autoimmune disorders	Perform history and physical exam at each follow-up visit
GVHD (patients with prior or subsequent alloHCT)	Frequent monitoring for signs and symptoms of acute and chronic GvHD
Fertility	Consultation with fertility preservation specialist prior to lymphodepletion regimen
alloHCT, allogeneic hematopoietic stem cell transplantation; CBC, complete blood count: G-CSF, granulocyte colony stimulating factor; GvHD, graft versus host disease; HSV, herpes simplex virus; IVIG, intravenous immunoglobulin; MDS, myelodysplastic syndrome; RBC, red blood cells; VZV, varicella-zoster virus Source: Jain 2019; Buitrago 2019	

T are defined as those occurring from day 100 and beyond infusion (Yakoub-Agha 2019). In addition to the risk of relapse from their primary hematological malignancy, cellular therapy recipients are at risk of developing new complications beyond the immediate weeks following cell infusion such as second malignancies, as well as neurologic and other hematological disorders. For this reason, patients should be monitored for late effects every three months after day 100 to 1 year then on a yearly basis (Yakoub-Agha 2019).

The main complication is severe long-term immunosuppression resulting from lymphodepleting chemotherapy and/or previous cancer treatment (**Table 3**). Targeting CD19 can induce prolonged B-cell depletion depending on the highly variable persistence of CAR T cells, resulting in hypogammaglobulinemia, particularly in children (Maude 2018).

At present, there is insufficient clinical evidence to conclude that patients who receive CAR T therapy may be cured of their hematologic cancer. Therefore, follow-up management includes close monitoring for evidence of relapsed disease and possible late consequences of treatment. Because of the limited follow-up number of patients who have received this treatment, at this time there are no standard treatment recommendations for patients with relapsed disease or disease progression following CAR T-cell therapy.

The main concerns regarding potential long-term complications of CAR T therapy include subsequent malignancies and new incidence or exacerbation of neurologic or autoimmune disorders (Jain 2019). In theory, secondary malignancies could result from the use of retroviral and lentiviral vector to transfer the CAR gene into the host genome (Jain 2019). The random integration of the exogenous gene into the host genome may cause disruption of critical host genes at the integration site, including risk of activation of proto-oncogenes or inactivation of tumor suppressor genes, with the risk of insertional mutagenesis. This genetic manipulation of cells led regulatory agencies to mandate that healthcare providers follow patients who have received CAR T cells for 15 years.

Hematologic toxicities following CAR T therapy may be of a prolonged duration, which was found in one study to be independent of the myelotoxic effect of the lymphodepleting regimen (Fried 2019) (**Table 4**). These authors found that a second event of neutropenia and some cases of thrombocytopenia occurred independent of lymphodepleting therapy or CRS/ hemophagocytic lymphohistiocytosis but were rather related to prior stem cell transplant, as a likely result of poor marrow reserve, and to CRS grade. No major infectious events and no major bleeding events were observed with late neutropenia or thrombocytopenia, respectively, in this study. In one study, the presence of grade ≥ 3 CRS was the only factor independently associated with the occurrence of any infection, although it is unclear if CRS itself or pharmacologic intervention to treat CRS (i.e., tocilizumab or corticosteroids) contribute to this higher risk (Park 2018).

Adverse events that occurred or persisted beyond 90 days after the last CAR T cell infusion in patients with relapsed/ refractory NHL and CLL included hematologic disorders (11%) of which 7% were pancytopenia, new malignancy (14%) (myelodysplastic syndrome, skin/non-melanoma, non-invasive bladder cancer and neuropsychiatric and cardiac disorders; 8% each) (Cordeiro 2018). Severe hypogammaglobulinemia or IgG replacement beyond

Table 4. Cytopenias Present at Follow-up after Axi-cel

	Day 180	Day 270	Day 360
Grade 3-4 leukopenia Any leukopenia	16.7% (7/42) 64.3% (27.42)	9.4% (3/32) 56.3% (18/32)	3.2% (1/31) 51.6% (16/31)
Grade 3-4 neutropenia Any neutropenia	11.9% (5/42) 42.9% (18/42)	9.4% (3/32) 37.5% (12/32)	9.7% (3/31) 25.8% (8/31)
Grade 3-4 anemia Any anemia	7.1% (3/42) 31% (13/42)	3.1% (1/32) 31.3% (10/32)	3.2% (1/31) 22.6% (7/31)
Grade 3-4 thrombocytopenia Any thrombocytopenia	4.8% (2/42) 45.2% (1/42)	3.1% (1/32) 43.8% (14/32)	3.2% (1/31) 38.7% (12/31)
Any grade 3-4 cytopenia Any grade cytopenia	19% 8/42) 81% (34/82)	9.4% (3/32) 71.9% (23/32)	9.7% (3/31) 67.7% (21/31)

Source: Logue 2021

day 90 after last CAR T cell infusion were documented in 41% of patients and infections occurred in 74% of patients. These authors conclude that many long-term effects of CAR T may be related to prior hematopoietic stem cell transplant. Caution is advised in interpreting these study results as the follow-up period of 2.5 years is most probably not sufficient to estimate the frequency of secondary malignancies after CAR T and other factors, such as cytotoxic therapy before CAR T, may play a role (Penack 2020).

Currently, there are two published reports on the late effects of CAR T-cell therapy. According to a study by Cordeiro et al (2018), follow-up of patients (median time 23 months) showed: 20% with ongoing cytopenias requiring G-CSF support or RBC or platelet transfusions beyond 90 days after CAR T infusion; 8 with subsequent malignancies; neuropsychiatric disorders documented in 5 patients, 5 with cardiovascular events, 4 with renal dysfunction, 3 with respiratory disorders. Severe hypogammaglobulinemia beyond day 90 after last CAR T cell infusion was reported in 24 patients, documented infection in 40 patients, 25 of these required hospital admission. The authors conclude that long-term effects of CAR T are acceptable, most effects were not severe and many were most likely related to prior or subsequent therapies such as HCT before or after CAR T-cell therapy (Cordeiro 2018).

Schuster et al (2021) reporting on the JULIET study long-term outcomes (median time 40 months) identified the most common grade 3-4 adverse events to be anemia (39% of patients), decreased neutrophil count (34%), decreased platelet count (28%), CRS (23%) and hypophosphatemia (13%). The median time to resolution of first CRS was 7 days and the median time to resolution of all serious neurological events was 13 days. 19 of 23 patients with neurological events also had CRS. High concentrations of lactate dehydrogenase pre-CAR T infusion were independently associated with severe CRS and severe CRS was associated with severe neurological events. Patients who responded (had a complete or partial response) had clinically meaningful improvements in patient-reported health-related quality of life

Providing Support for Patients and their Caregivers

At this time, only certified specialist institutions and centers can provide CAR T-cell therapy meaning that patients and their caregivers often travel to an unfamiliar center for therapy. Being cared for in an unfamiliar environment may be stressful for patients. Separation from family or other support networks may add to anxiety. It is important that patients and caregivers understand the necessity to contact a healthcare professional should there be any change in their state of well-being not only in the immediate post-infusion period but also for months and even years after CAR T-cell therapy. Fortunately, many centers providing CAR T-cell therapy have established a CAR T cell coordinator role; a designated person responsible for coordinating appointment scheduling and the management of care of the patient between the multidisciplinary team as well as the patient's referring physician and/or oncologist.

Providing patients with a product-specific wallet card, which identifies that they have received a CAR T-cell product and provides information about the treating oncologist (Taylor 2019) may be beneficial in ensuring appropriate treatment is administered in emergencies. Patients should be instructed to carry this card with them at all times and to show it any time they present with symptoms to a site outside of the one in which they received treatment.

Quality of Life, Psychosocial Distress and Cancer Survivorship

Quality of life

Despite advances in therapy, a substantial proportion of patients diagnosed with aggressive B-cell hematologic malignancies will relapse or have disease that is refractory to treatment. Many of these patients experience significant physical and psychological symptom burden and impaired quality of life (QoL). Fear of recurrence, after failure of two or more previous treatments, is comprehensible. Furthermore, patients and their caregivers often conceal misunderstandings regarding their prognosis, which interferes with their ability to engage in informed decision making regarding their care (Odejide 2020).

Initiation of discussions on care options, which might include end-of-life care preferences, are ideally conducted in the context of prognostic information to promote informed decision-making (Gilligan 2017). Patients and their caregivers who share their goals for care are more likely to receive care that is consistent with their preferences and more likely to experience improvement in QoL. Patients who died of hematologic cancers and had participated in goals of care discussion more than one month before death were more likely to experience less intensive cancer-directed care close to death and were more likely to enroll in hospice more than 3 days before death (Odejide 2020). These authors conclude that promotion of patient-centered care that honors individual preferences at the end-of-life is accomplished through timely discussions related to goals of care that take place while the patient is still being seen in the

out-patient setting and involve hematologic oncologists (Odejide 2020).

Psychosocial distress

As the indications for using CAR T-cell therapy include disease that is refractory or has relapsed on standard therapy, patients and their families have been dealing with cancer and cancer treatment and its side effects for some time. Few studies have explored the psychological implications of CAR T therapy or included QoL assessments. A recent study reported a prevalence of anxiety and depressive symptoms of 13.8% and 40%, respectively, in patients hospitalized with hematologic malignancies at week 4 after CAR T-cell therapy (Dai 2021). Factors associated with a lower risk of anxiety symptoms were high school education and higher, and middle age. Increased risk of depressive symptoms was associated with older age, non-manual occupations before illness and higher healthcare expenditure and a lower risk of depression was associated with rural household location and being cared for by spouse (Dai 2021). Another study reported similar results of at least one clinically meaningful negative neuropsychiatric outcome (anxiety, depression or cognitive difficulty) reported by 50% of patients at a median of 3 years after CAR T therapy (Ruark 2020). These authors identified younger age, pre-CAR T-cell anxiety or depression and acute neurotoxicity as possible risk factors for long-term neuropsychiatric problems.

By contrast, one of the few studies to evaluate the effects of CAR T-cell therapy on health-related QoL showed durable and clinically meaningful patient-reported health-related QoL benefits in patients who responded to tisa-cel (Maziarz 2020). These improvements across multiple subscales were evident at month 3 and were maintained throughout month 18.

Cancer survivorship

Cancer survivorship has been defined as starting at the time of cancer diagnosis and lasting throughout the lifespan and is focused on the health of a person, including physical, emotional and financial well-being, after therapy. Thus, the care of survivors should be included as an integral part of the cancer care continuum. Family members, friends and caregivers are included in survivorship definitions as in most cases cancer is not experienced alone.

While not all late effects of treatment can be prevented, close monitoring may help to recognize and treat problems in an expedient manner, which may lessen their severity and impact on the patient's QoL.

Psychological consequences of being a cancer survivor can include depression and anxiety, post-traumatic stress disorder (PTSD), fear of recurrence, and return to work and financial issues (Shapiro 2018). Despite the common occurrence of these psychosocial issues, they frequently remain undiagnosed and untreated, although management interventions such as mindfulness practice and stress-reduction therapy, increasing physical activity and patient education are relatively easy to implement (Shapiro 2018).

Distress has been proposed as a word to describe the emotional concerns experienced by cancer patients (Holland 2007). Distress occurs on a spectrum ranging from adjustment disorders to diagnosable psychiatric illnesses. A simple way to screen for distress is to use the single-item question recommended by the NCCN, which allows patients to identify their level of distress using a scale from 0 to 10 ("On a scale of 0 to 10, how would you rate your level of distress?"). A self-reported score of 4 or higher is indicative of the need for healthcare professionals to ask additional questions to determine the cause of distress and refer the patient to psychosocial or supportive care services as appropriate (Holland 2007).

The number of older patients who survive a cancer diagnosis continues to increase. This special population poses challenges to healthcare systems and when asked about their goals, they may respond that they value independent functioning and preservation of cognitive capabilities more than extending their length of life. Assessment tools specific for screening problems in older patients may more precisely identify late effects of treatment in this population.

Health promotion is a foundation for improved health and wellness, especially for cancer survivors. Practicing health promotion can include measures such as:

- Weight management
- Increased physical activity
- A healthful diet
- Smoking cessation
- Reduced alcohol consumption

Needs of caregivers

Patients receiving CAR T cells are required, at most institutions, to have a caregiver during their recovery period. The often advanced stage of disease at the time of treatment means these patients are dependent on the assistance of others to carry out activities of daily living. While providing physical and emotional support to the cancer survivor, these providers of care often themselves experience adverse health effects and emotional distress such as distress as a result of the patient's relapsed/refractory disease and uncertainty regarding CAR T-cell therapy outcomes (Barata 2021).

Caregivers experience the same problems as cancer survivors: fatigue insomnia, loss of physical strength, loss of appetite and weight, depression, anxiety, PTSD and lost income (Girgis 2013). The needs of the caregiver change with the changing needs of the recipient of care. However, caregivers are less likely than patients to use mental health services despite high levels of distress. In the first published study of CAR T-cell caregivers, for example, worse patient health status was associated with worse caregiver depression and distress over time (Barata 2021). These study results suggest that early identification and referral to appropriate support, such as a social worker or psychologist, is needed for this group of caregivers. Results further highlight the need to address caregiver well-being, preferably prior to CAR T-cell therapy, and to follow-up on possible longer-term effects of CAR T therapy on caregiver outcomes.

Financial Aspects of CAR T-cell Therapy

A discussion of survivorship following CAR T therapy would not be complete without mentioning the impact of cost of treatment on the patient and family. Financial costs are high [see Module 2] and financial concerns may contribute to psychological sequelae that may further compound the anxieties and stressors associated with treatment (Buitrago 2019). While the cost of the treatment itself is high, the accumulation of ancillary costs, such as the costs of transportation, accommodations if relocating for treatment and daily living expenses can be prohibitive.

Some consequences of the financial burden of cancer are:

- Medication non-adherence
- Poorer health-related QoL, mental health, satisfaction with social activities and relationships
- Depletion of financial savings, declaration of bankruptcy, which is associated with an increased risk of mortality (NCI 2018)

The financial burden of cancer treatment, especially CAR T-cell therapy is not only an economic concern, but a situation that may cause acute distress and have psychological sequelae. Patients and their families should be encouraged to seek financial advice and be provided with resources that may provide assistance (**Box 1**). Of note, health insurers in some countries pay the cost of CAR T-cell therapy.

Box 1. Interventions to help patients/caregivers cope with financial aspects of treatment

- Open discussions with patients and caregivers about the realistic and total costs of treatment with CAR T cells should take place at the outset of treatment.
- Patients should be referred to and encouraged to seek and use financial assistance resources
- Perform on-going assessment of patient/caregiver for psychosocial sequelae of financial burden of treatment including fear of recurrence

Adapted from: Buitrago 2019

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Quick Facts

- CAR T-cell therapy represents a favorable shift in the treatment of refractory-relapsed ALL in children and young adults but is associated with unique, severe toxicities
- Leukapheresis of T cells may be more challenging in children due to physiology and greater susceptibility to hypothermia or hypocalcemia during the process
- Early detection of cytokine release syndrome (CRS) may be difficult in pediatric patients but can lessen the risks of life-threatening sequelae
- Tools specifically designed for the pediatric population are recommended to assess signs/symptoms of neurotoxicity associated with CAR T cells such as tremors, changes in speech, delirium
- According to study results, the timeframe of improvement in QoL following CAR T cell-therapy was shorter than that experienced with traditional therapy for relapsed/refractory ALL
- Treatment-related second cancers and coexisting medical conditions are the most pressing problems for survivors of pediatric cancer

Module VI: CAR T-cell Therapy in the Pediatric Population

This module contains information specific to the administration of CAR T cells in pediatric patients. Please see Modules 1, 2, 3, 4 and 5 for detailed information on the immune system, administering CAR T-cell therapy, managing side effects and follow-up and longer-term care.

Introduction

Acute lymphoblastic leukemia (ALL) is the most common cancer among children, representing 75% to 80% of acute leukemias in children (Chessells 2003). B cell precursor ALL (B-ALL) is the most common form of ALL, comprising more than 20 subtypes of variable prevalence according to age. Dramatic improvement in survival has been achieved over the past several decades for pediatric ALL, largely due to greater understanding of the molecular genetics and pathogenesis of the disease, the use of risk-adapted therapy and new targeted agents, and the use of allogeneic hematopoietic stem cell transplantation (HCT) (NCIa). During the period between 1975 and 2010, 5-year survival for ALL increased from 60% to approximately 90% for children younger than 15 years and from 28% to more than 75% for adolescents aged 15 to 19 years (Howlader 2015), with a definite trend towards a decrease in overall survival with increased age (Buchanan 2000).

About 2% to 3% of patients will present with refractory disease that is unresponsive to chemotherapy and 15% to 20% will relapse. Site of relapse and time from diagnosis to relapse are two important risk factors used to determine prognosis and the approach to further treatment (NCIa). In B-ALL, mutations in genes influence relapse as these mutations confer chemotherapy resistance (Meyer 2013). Refractory/relapsed ALL in this population is difficult to treat with a historically poor prognosis, especially in those with Ph-negative disease (NCIa). Using the conventional approach to therapy, chemotherapy intensity has been raised to the limit of tolerance and further improvements in outcomes and reduction of adverse effects now require novel therapeutic approaches (Inaba 2020).

Briefly, CAR T cells are generated through genetic modification of the patient's own T cells obtained through leukapheresis. The isolated cells are activated and genetically modified via viral transduction or non-viral gene transfer (**Figure 1**). Following modification or re-engineering, the CAR T cells express an engineered chimeric cell-surface receptor (CAR) comprising an extracellular antigen-recognition domain. This extracellular portion of the CAR enables recognition of a specific antigen (such as CD19) and the signaling domains stimulate T cell proliferation, cytolysis and cytokine secretion to enable elimination of the target cell (such as a B cell) (Mahadeo 2019). [See Module 2 for detailed information on the CAR T cell manufacturing process.]

Indications

CD19-targeted chimeric antigen receptor (CAR) T-cell therapy is a therapeutic strategy for pediatric B-ALL patients with refractory disease or those in second or subsequent relapse (NCIa). One widely utilized target of CAR-modified T cells is the CD19 antigen expressed on almost all normal B cells and most B-cell malignancies. In 2017, the FDA (US Food and Drug Administration) approved the first CAR T-cell therapy, tisagenlecleucel (tisa-cel, a CD19-targeted agent), which has been associated with an overall response rate of almost 90% among patients up to 25 years of age with B-ALL that is refractory or in second or later relapse (Maude 2018). Because CAR T cells can migrate to extramedullary sites such as the CNS and testes, they can be considered not only for patients with isolated bone marrow relapses but also for those with isolated or combined extramedullary relapses (Maude 2014). There is some evidence that patients who receive CAR T cells can maintain long-term remission without subsequent HCT (Nishikawa 2012). While this therapy represents a shift in treating cancer in the pediatric population, it is associated with unique toxicities, which can lead to very rapid and life-threatening cardiorespiratory and/or neurological deterioration (Mahadeo 2019). Although reported side effects of this treatment may be severe, they have been reversible (NCIa).

Study results

The pivotal phase 2, multicenter study, ELIANA, conducted in pediatric and young adult patients with relapsed/refractory B-ALL provided clinical evidence for the approval of a CD19-targeted CAR T-cell therapy by the FDA. Key results of this study are presented in **Table 1**.

The median time to onset of cytokine release syndrome (CRS; see below), a life-threatening toxicity, in this population was 3 days (range: 1-51 days) and the median duration was 8 days with 47% requiring admission to the intensive care unit. The majority of neurologic events occurred during CRS or shortly after resolution of CRS and were managed with

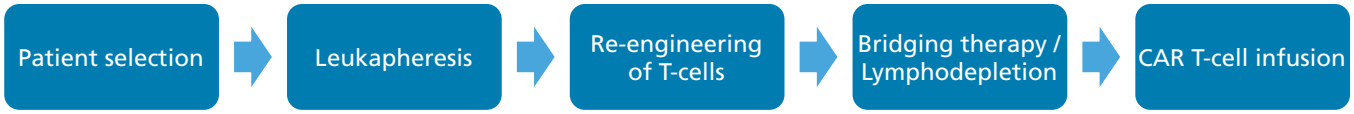

Figure 1. Steps in CAR T-cell therapy administration.

Table 1. Key results from the Phase 2 ELIANA Study in Pediatric/Young Adult Patients (N=75)	
Variable	**Results**
Overall remission rate (ORR) within 3 months Complete remission (CR)	81% 60%
Overall survival at 6 months Overall survival at 12 months	90% 76%
Grade 3 - 4 treatment-related adverse events[1] CRS CRS grade 4 Neurotoxicity Neurotoxicity grade 3 (no grade 4)	73% 77% 25% 40% 13%
Thrombocytopenia grade 3 - 4 not resolved by day 28 Neutropenia grade 3 - 4 not resolved by day 28 Probability of B-cell aplasia at 6 months	41% 53% 83%
CRS, cytokine release syndrome [1] Adverse events occurring within 8 weeks after CAR T infusion Source: Maude 2018	

supportive care. Ongoing persistence of the CAR T cells was observed more than 1 year after infusion in patients with a treatment response (Maude 2018).

Patient Selection

Eligibility for CAR T cells should adhere to criteria stated in clinical trial protocols or governmental approved indications, although there may be patients who could benefit from CAR T-cell therapy not necessarily meeting these criteria (Laetsch 2021) as has been demonstrated in non-clinical trials (Grupp 2019). Institutions administering these therapies should comply with product information labels and guidance from risk evaluation and mitigation strategy (REMS) and risk management plans (RMP).

Considerations for patient selection and evaluation:

- No evidence of uncontrolled infections
- No evidence of active graft-versus-host disease (GvHD)
- No recent donor-lymphocyte infusion (at least 6 weeks since last infusion)
- Not receiving immunosuppression after allogeneic hematopoietic stem cell transplantation (alloHCT)
- Evaluation of sites of active disease and presence of immune activation

Consent for the treatment should include descriptions of the risks and benefits associated with leukaphereisis, lymphodepletion, treatment-related side effects and complications, bridging chemotherapy, intensive-care support and anti-IL-6 therapy (Mahadeo 2019). Patients identified as candidates for CAR T-cell therapy who are not participating in a clinical trial should be referred for financial counseling as soon as possible to avoid delays in initiating treatment.

Screening for infections

Infectious disease screening, within 30 days prior to leukapheresis is recommended. These tests include screening for:

- Hepatitis B surface antigen (HBsAg)
- Anti-hepatitis B core antibody (HBcAb)
- Anti-hepatitis C virus antibody (HCVAb)
- Anti-human immunodeficiency virus (HIV) antibody
- HIV-1 / HCV / HBV Nucleic Acid Test
- HHV-6 IgG (Herpesvirus 6 Ab panel)
- Cytomegalovirus (CMV) IgG and IgM (MD Anderson 2021)

Most patients who receive CAR T receive a fludarabine-based chemotherapy regimen prior to CAR T-cell infusion. Fludarabine causes immunosuppression and can increase the risk of opportunistic infections. Additionally, CAR T-cells that target B-cells increase the risk of infection due to B-cell aplasia. Therefore, infection prophylaxis according to institutional standards of care should be implemented.

Preparation for CAR T cell Administration

Leukapheresis

To ensure optimal response and to reduce toxicities, patient and disease characteristics, such as therapeutic and disease history, are critical factors when determining the timing of leukapheresis and the need for and type of bridging therapy (Laetsch 2021).

Advance collection of T cells, which can be stored for up to 30 months before manufacturing begins, should be considered for patients at high risk of non-response, as there is evidence that the ability of T cells to proliferate decreases with increasing chemotherapy exposure (Das 2019). In some centers, early collection is performed in patients with high-risk disease after the first attempt of salvage therapy post-relapse.

Current guidelines for leukapheresis before tisa-cel manufacture suggest an absolute lymphocyte count of > 100 /µL can be acceptable, however a count of > 500/µL or a peripheral CD3 count of > 150/µL will ensure sufficient collection of T cells (Mahadeo 2019). Leukapheresis may be more challenging in children due to physiology and small extracorporeal volume and greater susceptibility to hypothermia or hypocalcemia during leukapheresis (Ceppi 2018). Pediatric patients should undergo pre-collection testing to ensure they are medically eligible for the procedure and should be hemodynamically stable and free of uncontrolled infection (Mahadeo 2019). During the procedure, patients should be closely monitored for hypotension, hypocalcemia and catheter-related pain, especially infants and younger children who may not be able to verbalize symptoms.

The wash-out period, (time between last administration of therapeutic agents or GvHD agents and collection of T cells) varies according to the type of treatment/ medications administered but is usually between 4 to 8 weeks and can be up to 12 weeks.

[See Module 3 for a full description of the process of re-engineering T cells.]

Bridging chemotherapy

Most patients will require bridging therapy to maintain disease control. The primary goal is to decrease disease burden while minimizing toxicity that could delay or prevent CAR T cell infusion. The type of bridging therapy used is based on disease burden, past treatments and the washout periods of chemotherapy regimens. Patients with rapidly progressing disease may require intensive therapy, which is associated with an increased risk of infection and organ toxicity. Periodic intrathecal central nervous system-directed treatment should also be considered during bridging therapy (Laetsch 2021). Radiation therapy may also be used as a bridging therapy to control disease burden, especially if disease is located where local inflammation from infiltrating CAR T cells could affect nerve function (i.e., spinal cord, optic nerve) (Laetsch 2021).

Lymphodepletion

As in adults, lymphodepleting chemotherapy with fludarabine and cyclophosphamide is necessary to allow engraftment and expansion of adoptively transferred CD19 CAR T cells. The usual recommended dose of fludarabine is 30 mg/m^2 x 4 days and the dose of cyclophosphamide is 500 mg/m^2/day x 2 days. A comparison of dose intensity of cyclophosphamide on safety and efficacy (high dose cyclophosphamide at 3 gm/m^2 and ≤ 1.5 mg/m^2) suggests that dose intensity of conditioning chemotherapy has a positive impact on response without a negative effect on toxicity (Curran 2019). This study also suggests that minimal pretreatment disease burden may have a positive impact on treatment response and the low rate of severe CRS, which, along with severe neurotoxicity, was reversible in the study. Patients should be re-assessed on the day of initiation of lymphodepletion to identify any new complications, which should include evaluation of infection and any new organ toxicity (Mahadeo 2019).

A 2 to 5 day window should be used between lymphodepleting therapy and CAR T cell infusion, although it may be necessary to wait up to 14 days if infection or clinical instability delay the infusion.

Administration and Monitoring of CAR T-cell Infusion

Institutional considerations

As is the case in the adult setting, only those institutions with provisions for intensive care, which have the necessary laboratory and support resources in place and in which healthcare professionals have received special training should administer CAR T therapy. The information provided in this section is specific to the administration of CAR T-cell therapy in the pediatric population.

The decision to administer CAR T-cell therapy in the inpatient or outpatient setting involves consideration of the toxicity profile of the product used, the clinical status of the patient and the ability of the institution to deliver prompt and comprehensive out-patient management as well as the ability of the patient to access such care (Mahadeo 2019). Benefits of inpatient delivery include ease of patient monitoring, which facilitates early detection and immediate treatment of adverse events.

Adverse events may also be identified early if the patient is treated as an outpatient and remains in close proximity to the treatment center, and outpatient infusion may have a positive impact on the patient's quality of life (QoL) and help reduce costs. Patients treated as outpatients must have a caregiver who has been educated to recognize symptoms of adverse events and can notify healthcare professionals promptly as required. Regardless of whether the patient is treated as an in- or outpatient, as CAR T cells are presently only administered at accredited institutions, pediatric patients may need to receive their treatment in a new setting and need to adjust to unfamiliar staff and routines. Coping with these changes can increase feelings of uncertainty and anxiety for patients and their families.

Clinical investigators representing the Pediatric Acute Lung Injury and Sepsis Investigators Network Hematopoietic Stem Cell Transplantation Subgroup and the MD Anderson Cancer Center CAR T Cell Therapy-Associated Toxicity Program have collaborated to provide comprehensive consensus guidelines on the care of children receiving CAR T cell therapy. These guidelines are available at Mahadeo 2019.

Managing patients receiving CAR T cells

CAR T cells are delivered as a frozen product, which allows flexibility in the timing of the infusion dependent on the child's condition.

Interventions prior to the initiation of the infusion include the following:

- Imaging of the brain
- Baseline ECG/EKG
- Central venous access with port or double/triple lumen catheter is recommended
- Tumor lysis precautions for patients with high tumor burden
- Seizure prophylaxis with levetiracetam 10 mg/kg PO or IV every 12 hours for 30 days starting on the day of infusion
- Consider filgrastim products if patient is neutropenic and concern for infection is evident

The following activities are recommended before and during the infusion of CAR T cells:

- Administration of pre-medication
- Double check CAR T cell label with patient identification
- Confirm blood return
- Monitor vital signs
- Infuse product over 30 minutes to 1 hour
- Agitate bag with CAR T cells every 15 minutes

Please refer to Module 4 for detailed information on administering and monitoring this therapy.

Education of patients, parents and caregivers

Involvement of parents or other caregivers from the beginning of the CAR T cell process is essential to minimize risks and ensure patient safety and well-being. (**Table 1**)

Management of infusion reactions

Citrate toxicity symptoms must be promptly recognized and treated immediately. Classically, symptoms are perioral numbness, paresthesia of the hands and feet, muscle cramps; nausea and vomiting. In low body weight children, abdominal pain and restlessness may be the first and only signs. Calcium supplement by intravenous or oral routes may be required. As a precautionary measure, oxygen, suction and emergency medications should be readily available at the time of infusion. Pre-medications as per

Table 1. Educational Instructions for Home Monitoring

Actions to be taken for home-monitoring:	Seek emergency care should the following occur:
Encourage oral fluid intake Have available self-care instructions and healthcare professional contact information Take oral temperature every evening	Oral temperature ≥ 38°C Measurement of hypotension defined as: --Age 1 – 10 years: systolic BP < [70 + (2 x age in years)] mmHg --Age > 10 years: systolic BP < 90 mm Hg Presence of tremors or jerky movements in extremities

Table 2. ASTCT Grading for CRS

CRS parameter	CRS Grade 1	CRS Grade 2	CRS Grade 3	CRS Grade 4
Fever[1]	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C	Temperature ≥ 38°C
WITH				
Hypotension	None	Requiring IV fluids but not requiring vasopressors	Requiring one vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
AND/OR[2]				
Hypoxia	None	Requiring low-flow O_2 via nasal cannula[3] or blow-by	Requiring O_2 via high-flow nasal cannula, facemask, non-rebreather mask or Venturi mask	Requiring O_2 via positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)

ASTCT, American Society for Transplantation and Cellular Therapy; BiPAP, bilevel positive airway pressure; CPAP, continuous positive airway pressure; CRS, cytokine release syndrome; FiO_2, fraction of inspired oxygen; IV, intravenous; LFT, liver function tests
CRS grade should be determined at least twice daily and any time there is a change in patient status.
[1]Fever is defined as temperature ≥38°C not attributable to any other cause. If fever is no longer present due to antipyretics or tocilizumab or corticosteroids, fever is no longer required to grade CRS severity; CRS grading is driven by hypotension and/or hypoxia instead; [2] CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5°C, hypotension requiring 1 vasopressor and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS; [3] Low-flow nasal cannula is defined as O_2 delivered at ≤ 5 L/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 5 L/minute and may vary based on the size of the pediatric patient. The definition of low-flow and high-flow nasal canula for pediatric patients may differ from the published ASTCT consensus grading guideline
Adapted from: Lee 2019; MD Anderson 2021

institutional policy or manufacturer's recommendation should be administered 30 to 60 minutes prior to infusion. In low weight children, assessment for blood priming should be performed according to center policy.

Recognition and Management of Treatment Toxicities

Early recognition of toxicities of CAR T-cell therapy, particularly CRS and neurotoxicity, in pediatric patients requires detection of variations from baseline in heart rate, blood pressure, temperature and irritability, mood and cognition (Mahadeo 2019). The information provided in this section is specific to managing infants and children receiving CAR T-cell therapy. Please refer to Module 4 for detailed information on recognizing and managing the toxicities of this therapy.

Cytokine release syndrome (CRS)

CRS is a systemic inflammatory response caused by a rapid and excessive secretion of cytokines that is associated with a spectrum of symptoms ranging from fever to multi-organ dysfunction. While early detection of CRS may be challenging in pediatric patients, early diagnosis and prompt management can lessen the risks of life-threatening sequelae. Sinus tachycardia can be an early presenting sign of CRS and continuous cardiac monitoring is therefore strongly advisable.

Historically, a number of grading systems have been used in CAR T clinical trials, which has made comparisons of incidence of CRS and outcomes difficult. An expert panel from the American Society for Transplantation and Cellular Therapy (ASTCT) developed a set of consensus grading criteria, which lead to a more universal CRS grading scale (**Table 2**). No single standard clinical laboratory test can predict the onset of severe CRS. Reports of severe CRS (grade ≥ 3) vary greatly; the severity of CRS is largely contingent on the disease burden present at the time of CAR T cell infusion: a lower burden is associated with a lower incidence and severity of CRS. The median onset of CRS grade ≥ 3 is 3 to 5 days post infusion (Laetsch 2021).

CRS grading should be performed at least once every 12 hours and more often if there is a change in the patient's clinical status (Mahadeo 2019).

The CRS-associated symptom management algorithm defines a prodromal syndrome (grade 1 CRS) as fevers (≥ 38°C) with or without constitutional symptoms, fatigue, or anorexia. Observational therapy to rule out infection, empiric antibiotics per local standards of care and symptomatic support are commonly used. Patients who are being managed in the outpatient setting should be admitted to the hospital if low-grade CRS develops,

including at the onset of the first fever (Laetsch 2021). Although IV fluids are used early to manage CRS, fluid overload due to capillary leak can increase the severity of respiratory complications and early use of vasopressors instead of IV fluids is recommended. Severe CRS can have symptoms similar to hemophagocytic lymphohistiocytosis/ macrophage activation syndrome (HLH/MAS), such as prolonged fever, cytopenias, coagulopathy and liver dysfunction. Some centers have begun to initiate treatment with tocilizumab early in the management algorithm for CRS; clinical studies are required to clearly define the effect of early treatment on CRS severity and other safety and efficacy outcomes. A suggested pattern for treating CRS is shown in **Figure 2**.

Hemophagocytic lymphohistiocytosis (HLH)

Hemophagocytic lymphohistiocytosis (HLH) is a rare syndrome with severe clinical sequelae resulting from a dysregulated, hyperinflammatory immune response. HLH and macrophage-activation syndrome (MAS) are serious, life-threatening complications of CAR T cell therapy. As mentioned above, symptoms of HLH may overlap symptoms associated with CRS. A peak serum ferritin level > 10,000 ng/ml during the CRS-risk period with development of any two of the following is used to diagnosis HLH/MAS (macrophage activation syndrome): grade ≥ 3 organ toxicities involving the liver, kidney, or lung; or hemophagocytosis in the bone marrow or other organs (Mahadeo 2019).

Management includes administration of anti-IL-6 therapy and/or corticosteroids. In cases where this treatment does not resolve the condition, additional therapy, including consideration of systemic and/or intrathecal therapy or use of the IL-1 receptor antagonist anakinra can be administered (Mahadeo 2019).

Neurotoxicity

Pediatric patients with ALL may have residual neurocognitive impairments from prior neurotoxic therapies; these impairments may lead to further decline in functioning following CAR T. Using tools specifically designed to assess neurotoxicity in children and adolescents, investigators identified a range of neurotoxicity symptoms including pain, depressed mood, visual and auditory hallucinations, unresponsiveness and disorientation occurring at the time of CRS that subsequently resolved without irreversible neurotoxicity (Shalabi 2018).

The neurotoxicity associated with CAR T cells is termed immune effector cell-associated neurotoxicity syndrome (ICANS). Early symptoms include tremor, dysgraphia and mild difficulty with expressive speech; expressive aphasia has been shown to be linked with severe neurological toxicity [see Module 4 for detailed information on ICANS]. Early recognition of and intervention for ICANS are essential to avoid life-threatening complications. The Cornell Assessment of Pediatric Delirium (CAPD) is a validated screening tool for recognition of delirium among children and adolescents and is recommended to

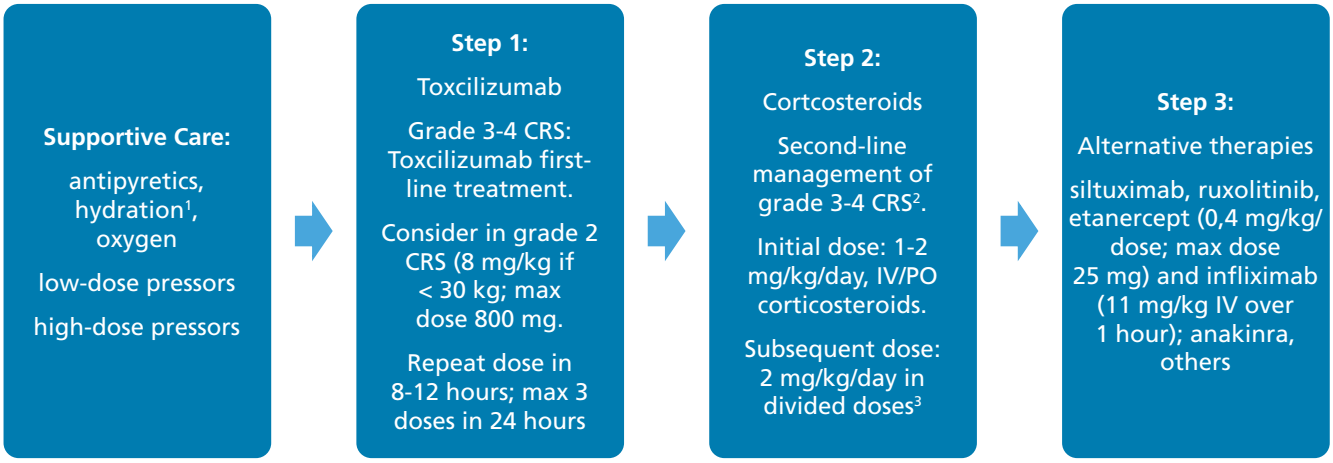

Figure 2. Stepwise treatment suggestions to manage CRS. [1] Defined as multiple fluid boluses for blood pressure support. Hydration status should be monitored closely to avoid overhydration and associated complications. [2] Grade 3 - 4 CRS defined as hemodynamic instability despite IV fluids and vasopressor support, worsening respiratory distress and/or rapid clinical decline. [3] Dexamethasone may be substituted as an alternative to methylprednisolone, with doses of 5-10 mg IV up to every 6 hours. Other pharmacologic options should be considered. CRS, cytokine release syndrome; IV, intravenous; PO, per mouth. Adapted from: Laetsch 2021

Table 3. Cornell Assessment of Pediatric Delirium (revised)

	Never 4	Rarely 3	Sometimes 2	Often 1	Always 0	Score
1. Does the child make eye contact with the caregiver?						
2. Are the child's actions purposeful?						
3. Is the child aware of his/her surroundings?						
4. Does the child communicate needs and wants?						
	Never 0	**Rarely 1**	**Sometimes 2**	**Often 3**	**Always 4**	**Score**
5. Is the child restless?						
6. Is the child inconsolable?						
7. Is the child underactive/very little movement while awake?						
8. Does it take the child a long time to respond to interactions?						
					Total	

Score: Grade 1 ICANS = 0 (no impairment); Grade 2 ICANS = 1 - 8 and awakens spontaneously; Grade 3 ICANS = 1 - 8 awakens in response to a voice; Grade 4 ICANS = ≥ 9
Sources: Traube 2014; Laetsch 2021

assess ICANS symptoms (**Table 3**). This assessment tool is based on observation and interaction with the child and takes less than 2 minutes to complete. A score of > 8 on the CAPD is indicative of delirium. A trend in scores within an individual patient is important: increasing scores can be used as a marker for ICANS severity.

Frontline management of CAR T-cell therapy-associated neurotoxicity is supportive care, which includes prophylactic anticonvulsants such as levetiracetam for 30 to 60 days following CAR T-cell administration and radiographic imaging and lumbar puncture to rule out other causes of neurologic dysfunction (Laetsch 2021; Hucks 2019) (**Table 4**). Patients should be monitored twice weekly for the first month in the outpatient setting or daily if in the hospital.

Psychosocial Sequela of Treatment and Quality of Life

The diagnosis of a life-threatening disease can be intensely distressing for children and their families, disrupting family life and routines and involving lengthy treatments, hospital admissions and uncertainty about the future. Shorter-term treatment side effects such as nausea and vomiting, mucositis, fatigue and infection following standard chemotherapy treatments are unpleasant and perhaps frightening for the child. Long-term adverse effects can include both behavioral and emotional problems as well as impaired intellectual function, neuroendocrine abnormalities, cardiotoxicity, impaired reproductive capacity and secondary malignancy (Bhatia 2003).

Assessment of quality of life (QoL) is an important outcome measurement in children with cancer not just in the long term but also during courses of treatment (Savage 2009), and is becoming increasingly important in the assessment of new oncology therapies (Laetsch 2019). In a component of the ELIANA trial, investigators evaluated the impact of tisa-cel on patient-reported QoL in 58 patients aged 8 to 23 years (Laetsch 2019). Results showed rapid improvements in broad aspects of patient-reported QoL beginning as early as day 28 and persisting at 6, 9 and 12 months. These improvements occurred most notably for physical functioning, although only 50% of patients achieved the physical functioning normative mean score at 12 months. Some delay in QoL improvement was seen in patients who had severe CRS or neurotoxicity but

Table 4. Management Recommendations for ICANS in Pediatric Patients

Grade 1	Grade 2	Grade 3	Grade 4
-Supportive care with aspiration precautions and IV hydration -Withhold oral intake of food, medicines, fluids and assess swallowing -Substitute oral medications and/or nutrition with IV if swallowing impaired -Avoid medications that cause CNS depression -Low doses of lorazepam (0.05 mg/kg) IV every 8 hrs or haloperidol (0.05 mg/kg) IV every 6 hrs with careful monitoring -Neurology consultation -Fundoscopic exam to assess for papilledema -MRI of the brain with/without contrast and diagnostic lumbar puncture -EEG -Consider anti-IL-6 therapy if ICANS associated with CRS	-Supportive care/neurological assessment -Administer anti-IL-6 if associated with CRS -Dexamethasone 0.5 mg/kg IV every 6 hrs or methylprednisolone 1-2 mg/kg per day if not associated with CRS -Consider transfer to PICU	-Supportive care/neurological assessment -PICU transfer -Administer anti-IL-6 if associated with CRS -Dexamethasone 0.5 mg/kg IV every 6 hrs, increase to 20 mg IV every 6 hrs if required or methylprednisolone 1-2 mg/kg per day divided every 6-12 hrs around the clock if symptoms worsen if not associated with CRS -Continue corticosteroid treatment until improvement to grade 1, then taper or stop -Consider repeat neuro-imaging (CT or MRI)	-Supportive care/neurological assessment -PICU monitoring; consider mechanical ventilation -Neurosurgical evaluation -Consider repeat CT scans -Obtain chemistry panels frequently, adjust medication and provide osmotherapy to prevent rebound cerebral edema, renal failure, hypovolemia and/or hypotension and electrolyte abnormalities -Anti IL-6 therapy -Consider high-dose corticosteroids -Continue corticosteroid until improvement to grade 1, then taper -Treat patients with convulsive status epilepticus accordingly

Grading of neurotoxicity should include patient history, physical examination and Cornell Assessment of Pediatric Delirium (CAPD) assessment performed at least twice a day and when a change in clinical status is observed.
CNS, central nervous system; CRS, cytokine release syndrome; CT, computer tomography; EEG, electroencephalogram; hrs, hours; ICANS, immune effector cell-associated neurotoxicity syndrome; MRI, magnetic resonance image; IV, intravenous; PICU, pediatric intensive care unit
Adapted from: Mahadeo 2019

meaningful improvement was evident in these patients by months 3 to 6. This timeframe of improvement in QoL was shorter than that experienced with traditional therapy for relapsed/refractory ALL, which might include months of chemotherapy followed by HCT and the potential for GvHD and other life-threatening toxicities.

Longer-term Complications and Follow-up

Monitoring for longer-term complications

While it is still too early to clearly identify longer-term complications of CAR T cell treatment, a systematic plan for lifelong screening, surveillance and prevention of secondary complications is advisable. General considerations for monitoring patients include the following:

- Type of previous cancer
- Type of previous cancer therapy
- Genetic predisposition
- Lifestyle behaviors
- Comorbid conditions
- Sex
- Screening of educational and vocational progress

Long-term follow-up studies are ongoing to evaluate for potential late adverse events including secondary malignancies, pregnancy, complications from prolonged B-cell aplasia and chronic sequelae of neurotoxicity (**Table 5**).

Management of on-target off-tumor effects should be well coordinated between treatment and referring centers if the patient returns to local providers following treatment. Patients should be monitored, usually monthly for the

Table 5. Possible Complications of CAR T-cell Therapy and their Management		
Possible long-term complication	**Clinical manifestation**	**Management**
Prolonged neutropenia	Increased risk of infection, including fatal encephalitis and systemic mycosis	Frequent monitoring for infections; prophylactic antibiotic and antifungal medications; possibly viral prophylaxis; possibly G-CSF (after 21-28 days)
B-cell aplasia/hypogammaglobulinemia	Increased risk of infection	Monitor for signs and symptoms suggestive of neuropsychological deficits, visual and motor deficits; Monitor immunoglobulin levels; administer intravenous immunoglobulin (IVIG) or subcutaneous immunoglobulin;
Risk of secondary malignancies		Regularly monitor for signs/symptoms

first 6 to 12 months, for minimal residual disease (MRD) and the persistence of the infused CAR T cells. Because there is currently no approved method to directly monitor the persistence of CAR T cells, B-cell aplasia, an on-target effect of CAR T cells, is used as a surrogate (Laetsch 2021). A loss of B-cell aplasia before 6 months following CAR T cell infusion is most likely a sign of increased risk of relapse. B-cell aplasia/hypogammaglobulinemia is common and may persist longer-term.

Multiple factors may affect the risk and severity of infectious complications. A variety of pathogens has been associated with both acute and prolonged neutropenia, including bacterial, fungal and/or viral infections. An increased risk of viral respiratory tract infections is associated with persistent hypogammaglobulinemia.

In addition to risk-based screening for medical late effects, current health behaviors should be taken into consideration and patients encouraged to exercise health-promoting behaviors. Educational efforts focused on healthy lifestyle behaviors include:

- Avoidance of smoking, excess alcohol use and illicit drug use
- Promotion of healthy dietary practices and an active lifestyle

Complications of CAR T-cell therapy should be reported to appropriate registries, such as the one established by the Center for International Blood and Marrow Transplant Research (CIBMTR), to ensure that these toxicities are documented to establish quality benchmarks, facilitate retrospective research, recognize potential delayed toxicities and ultimately improve future care (Mahadeo 2019).

Box 1. Common late effects of pediatric cancer

- Cardiopulmonary (heart abnormalities, reduced lung function)
- Musculoskeletal (scoliosis, asymmetry of bone or soft tissues)
- Bone morbidity (fractures, vertebral deformity)
- Dental (short roots, missing teeth)
- Eyes (cataracts)
- Nephrology (kidney disease, hypertension)
- Endocrine (growth failure, thyroid hypofunction, infertility)
- Neurocognitive (learning disabilities, memory loss)
- Psychological (depression, post-traumatic stress)

Late effects of pediatric cancer treatment

While many childhood cancer survivors are doing well and have few, if any, medical problems related to their cancer therapy, some survivors will experience side effects of their treatment later in life (**Box 1**). In fact, 60% to more than 90% of adults treated for cancer during childhood develop one or more chronic health conditions and 20% to 80% experience severe or life-threatening complications during adulthood (NCIb). The prevalence of late effects increases as time from cancer diagnosis elapses. By age 50, for example, the cumulative incidence of a self-reported severe, disabling, life-threatening or fatal health condition was 53.6% among childhood cancer survivors

Table 6. Findings from Long-term Follow-up of Pediatric Cancer Patients		
Study	**N**	**Findings**
Median age at diagnosis: 5 years Median time from diagnosis: 30 years (Mulrooney 2019)	980	Significantly more growth hormone deficiency, hypogonadism and neuropathy; 5.4 grade 1-4 health conditions; 3.2 grade 2-4 health conditions (musculoskeletal and endocrine disorders)
Median age at diagnosis: 21 years Median time from diagnosis to last follow-up: 8.2 years (Muffly 2020)	1069	High incidence of endocrine (28.7%) and cardiac disease (17%); avascular necrosis (9.6%), liver disease (6.5%), respiratory disease (6.2%), seizure and/or stroke (4.3%), renal disease (3.1%), second neoplasms (1.4%) at 10 years

versus 19.8% among a sibling control group (Armstrong 2014).

Although treatment advances have improved overall survival, the burden of late morbidity remains high for pediatric ALL patients (Mulrooney 2019). The most pressing problems for pediatric cancer survivors are treatment-related second cancers and coexisting medical conditions (**Table 6**) (Robison 2014). A significant decline in functional status, increased activity limitations, poorer mental health status and poorer general health is higher in adult survivors of childhood cancers than in matched sibling controls (Oeffinger 2006).

As measured at 25 years after completing cancer treatment, childhood ALL survivors reported more adverse general and mental health, functional impairment and activity limitations compared with siblings. Survivors who received radiation therapy as part of their treatment or had a leukemia relapse were at greatest risk for adverse outcomes (Mody 2008).

Common problems of adolescent and young adult survivors are infertility, other reproductive health problems and psychosocial issues.

Risk stratified therapy has reduced late morbidity and mortality in survivors of ALL. Health-related late mortality and secondary cancer risks among 5-year survivors of therapy administered in the 1990s are comparable to the general population (Dixon 2020). Survivors of ALL treated in the 1990s also had fewer severe chronic health conditions and lower prevalence of impaired memory and task efficiency than those treated in the 1970s and 1908s.

Using interview, authors found dominant themes of survivors revolved around successful adaption to life with late effects, a shift in the perception of own health alongside an increased body awareness, long-lasting impacts on peer relationships, contrasts between own and surrounding perceptions of survivorship identity and an unmet need to process these issues (Andres-Jensen 2020).

Financial aspects of CAR T-cell treatment

Whittington and colleagues (2018) performed an estimate of the long-term survival and value of tisa-cel for pediatric patients with B-ALL. The authors compared tisa-cel to clofarabine in terms of life-years gained, quality-adjusted life-years gained and incremental costs per life-year taking into consideration additional costs such as hospital markup, preparation, administration and management of adverse events for both agents. Their analysis suggests that tisa-cel provides clinical benefits in quality-adjusted and overall survival compared with clofarabine and that tisa-cel seems to be priced in alignment with benefits observed over a patient lifetime horizon. A similar cost effectiveness analysis concluded that tisa-cel represents reasonable value if it can keep a substantial fraction of patients in remission without transplantation. If all patients require transplant to remain in remission, it will not be cost effective at acceptable thresholds (Lin 2018).

Future Perspectives

At this time, it is unknown if CAR T cells represent a definitive treatment for relapsed/refractory ALL in children and young adults. Disease recurrence is related to ALL cells no longer expressing CD19, known as antigen loss or antigen escape, or to non-persistence of CAR T cells and CD19 relapses. In children and young adults with advanced ALL, evaluation of CAR T cells that target the CD22 protein, which is often overexpressed by ALL cells, is being undertaken. In a trial of CD22-targeted CAR T cells, most treated patients had complete remissions, including patients whose cancer had progressed after initially having a complete response to CD19-targeted therapy (Shah 2020; Fry 2018).

Researchers are also working on developing new therapies that reprogram a patient's own immune system cells to kill other types of cancer besides blood cancers. So far, solid tumors have generally resisted CAR-T cells. For patients with unresectable, metastatic or recurrent synovial sarcoma — a rare form of soft tissue cancer — clinical trials are testing a different kind of engineered T cell, referred to as T-cell receptor (TCR) engineered T cells. CAR-T cells are being developed for another pediatric cancer, neuroblastoma. In addition, the possibility is being explored that solid tumors will respond to CAR-T therapies when they are combined with another agent intended to boost T cell function.

Further immunotherapeutic options for patients who fail to respond or relapse after CAR T include reinfusion of alternative CAR T-cell therapies or further treatment with commercially available immunotherapies. While these alternative treatments are being developed, one option is to consider alloHCT for patients who have achieved remission following CAR T-cell infusion. This decision should be based on the patient meeting standard eligibility requirements, a risk-benefit assessment and the long-term outcomes associated with the specific CAR T cell product used.

Consolidative allo-HCT may provide durable remission in this patient population in which CAR T cells are used as a bridge to alloHCT (Curran 2019). This option is influenced by prior history of allo-HCT, available donor options, recovery from CAR T-cell toxicity and persistence of CAR T-cell activity.

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Glossary of Terms

Term	Definition
Antigen-presenting cells (APCs)	A heterogeneous group of cells that mediate a cellular immune response by processing and presenting antigens for recognition by T cells
Antigenicity	The capacity of a molecule or an antigen to induce an immune response, i.e. to be recognized by and interact with an immunologically specific antibody or T cell receptor.
Autologous	derived from the same individual and hence genetically identical to the host.
Chemokines	Any of a group of cytokines produced by various cells (as at sites of inflammation) that stimulate chemotaxis in white blood cells (such as neutrophils and T cells)
Clinical response/ complete remission	An important indicator of treatment response; often used in clinical trials to identify and quantify anti-tumor activity of new agents; limited value in predicting survival
Colony stimulating factors (CSF)	Any of several glycoproteins that promote the differentiation of stem cells especially into blood granulocytes and macrophages an that stimulate their proliferation into colonies in culture
Complete response (CR)	The disappearance of all signs of cancer in response to treatment. This does not always mean the cancer has been cured. Also called complete remission
Disease-free survival	A concept used to describe the period after successful treatment during which there are no signs and symptoms of the disease
Genotoxic	Damaging to genetic material
Human leukocyte antigen (HLA):	highly polymorphic molecule required for antigen presentation encoded within the human major histocompatibility complex
Immune effector cells	A cell that has differentiated into a form capable of modulating or effecting a specific immune response
Interferons	A considerable range of antiviral protein substances produced by cells that have been invaded by viruses
Interleukins	A range of cytokines secreted by white blood cells of the immune system. Effector ells have surface receptors for the various interleukins
Macrophage	Any of the large, mononuclear, highly phagocytic cells derived from monocytes, occurring in the walls of blood vessels and in connective tissue; originate in the bone marrow
Major histocompatibility complex (MHC)	proteins that control immune responses, encoded by a genetic locus encompassing a family of highly polymorphic genes.
Neo-antigens (or tumor antigens)	Antigenic proteins formed by metabolic pathways (for example, drug metabolism)
On target off tumor	Occurs when CAR T-cells attack non-tumor cells expressing the target antigen. For example, those CAR T-cell therapies that target CD19, which is found on the surface of both normal and cancerous B-cells
Overall response rate (ORR)	The proportion of patients who have a partial or complete response to therapy; it does not include stable disease and is a direct measure of drug tumoricidal activity
Overall survival (OS)	The length of time from either the date of diagnosis or the start of treatment that patients diagnosed with the disease are still alive; used in clinical trials to measure the efficacy of a treatment
Progression free survival	The time from random assignment in a clinical trial to disease progression or death from any cause
Proto-oncogenes	Any gene capable of becoming a cancer-producing gene (an oncogene)
Tumor necrosis factor (TNF)	A protein produced chiefly by monocytes and macrophages in response especially to endotoxins and that mediates inflammation and induces the destruction of some tumor cells and the activation of white blood cells
Viral transduction:	the transfer of genetic material to a cell via a viral vector.

Resources

Educational Resources for Patient/Caregiver(s)	
National Comprehensive Cancer Network (NCCN) Immunotherapy Side Effects: CAR T-cell Therapy	CAR T-cell Quick Guide for Patients. Available at: https://www.nccn.org/patients/guidelines/content/PDF/nccnquickguide-immunotherapy-se-car-tcell-patient.pdf CAR T-cell Guidelines for Patients. Available at: https://www.nccn.org/patients/guidelines/content/PDF/immunotherapy-se-car-tcell-patient.pdf
Pediatrics	Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers, Version 5.0 (October 2018). Available at: Children's Oncology Group (survivorshipguidelines.org)
Cancer Support Community	Immunotherapy for Cancer: Is it right for you? https://www.cancersupportcommunity.org/car-t-cell-therapy?msclkid=6272f0722c3b1fc6f653924a436cf8b8
Memorial Sloan Kettering Cancer Center	CAR T-cell therapy: A guide for adult patients & caregivers https://www.mskcc.org/pdf/cancer-care/patient-education/car-cell-therapy-guide-adult-patients-caregivers
Educational Resources for Healthcare Professionals	
Nursing education	Introduction to immunotherapy: What nurses need to know about emerging therapies (myamericannurse.com)
Nursing-directed education	CAR T-Cell Therapy: An overview for oncology nurses. https://www.medscape.org/sites/townhall/public/2018-nurse-cart#:~:text=Overview%20Chimeric%20antigen%20receptor%20%28CAR%29%20T-cell%20therapy%20is,therapy%20involves%20and%20its%20potential%20benefits%20and%20risks.
CAR T-cell therapy in Europe	The Process of CAR T-cell Therapy in Europe: EHA Guidance Document https://journals.lww.com/hemasphere/Documents/EHA%20Guidance%20Document%20CAR-T%20Cell%20Therapy.pdf
National Cancer Institute	CAR T cells: Engineering patients' immune cells to treat their cancers https://www.cancer.gov/about-cancer/treatment/research/car-t-cells
National Comprehensive Cancer Network	CAR T-cell therapy: recent advances and future consideration https://education.nccn.org/car-t
Professional Organizations	European Society for Blood and Marrow Transplantation (EBMT)

Notes

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