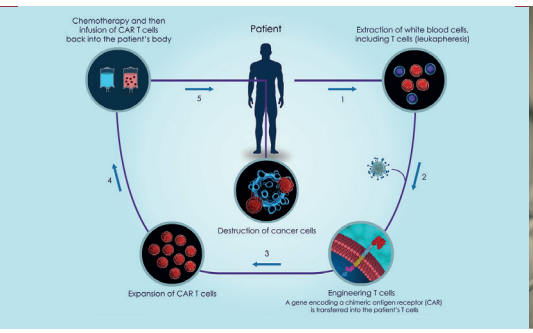
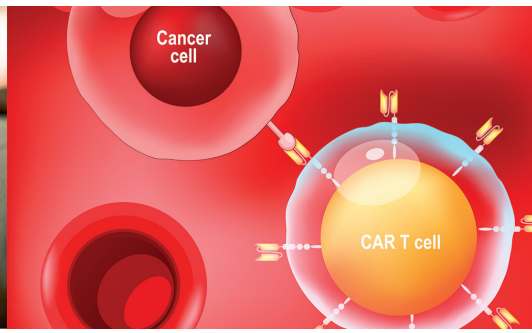
HNHCP
Haematology Nurses & Healthcare Professionals Group





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 updated version of 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 program 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 Bristol Myers Squibb Company, Janssen-Cilag AG, a Johnson & Johnson company, 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

The Haematology Nurses and Healthcare Professionals Group gratefully acknowledges the following individuals for their review and contributions to this learning program.

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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

- The immune system is capable of naturally recognizing and eliminating a variety of pathogens and malignant cells through two mechanisms: innate and adaptive immunity.
- T cells have a unique antigen-binding receptor on their membrane, known as the T-cell receptor (TCR), 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) are a type of receptor that has been genetically engineered to recognize and respond to specific antigens. These receptors are transduced into T-lymphocytes through a process of gene transfer, resulting in the reprogramming of the cell's biological functions. This reprogramming enables the T-lymphocytes to target and attack antigens in a more precise manner, enhancing their immune response capabilities.
- CAR T cells have been produced that target CD19 in order to treat B-cell malignancies, and that target B-cell maturation antigen (BCMA), which is expressed by multiple myeloma cells.

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 harmful processes through immune surveillance, by which all targets that are identified as non-self are eliminated. Targets include not only cells infected with pathogens such as viruses, bacteria, parasites, or harmless environmental substances, but also transformed (e.g., malignant) cells. Generally, substances that are recognized by the immune system as non-self elicit an immune response. The process of expression of neo-antigens is pivotal to the acquisition of antigenicity and therefore immunogenicity by malignant cells. Consequently, this occurrence can stimulate a response from the immune system (Sharpe 2015).

There are two main components of the immune system:

1. Innate immunity, also known as nonspecific, natural, or native immunity, which includes primitive elements such as barrier mechanisms of the body, macrophages, natural killer (NK) cells, and antigen-presenting cells (APCs). These cells respond uniformly to any pathogen or foreign substance.
2. Adaptive, or acquired immunity, which is comprised of T and B lymphocytes (**Figure 1**).

Innate immunity

The innate immune system serves as the body's primary line of defense becoming operational immediately upon detection of an intruding pathogen. In addition to cellular components, physical and chemical barriers such as the skin, mucous membranes, and secretions are elements of innate immunity that prevent pathogens from entering the body.

The innate immune response is a non-specific and thus antigen-independent defense mechanism. It was long hypothesized that innate immunity does not have a memory to help it recognize future infections more efficiently. Recent scientific proposals indicate that innate immune responses may include adaptive characteristics comparable to immunologic memory.

The main function of innate immunity is to attract immune cells to sites of infection and inflammation by producing cytokines and to unselectively present antigens to the cellular compartment of the adaptive immune system. Cytokines are small proteins involved in cell-to-cell communication. The immune system uses a variety of different cytokines to signal cell growth, activation and function (**Box 1**).

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

Cytokines act as chemical messengers to signal:

Cell activation: cytokines direct immune cells toward an infection site and heighten or lessen the processes associated with inflammation.

Cell differentiation: cytokines direct immature cells to develop into a specific type of cell.

Cell proliferation: cytokines direct cells to reproduce.

The release of cytokines and activation of the complement system are important events in the development of the inflammatory reaction and are involved in both the innate and the adaptive immune responses (**Box 2**).

Box 2. Definition and Function of the Complement System

The complement system is a crucial component of the immune system that plays a pivotal role in enhancing the ability of antibodies and phagocytic cells to clear microbes and damaged cells, promote inflammation, and attack pathogen cell membranes. It is composed of more than 30 proteins that interact in a cascading manner to facilitate antigen clearance and inflammatory responses. The complement system can be activated by antibodies bound to antigens or by components of innate immunity. It is crucial as a defense against bacterial infections, and is involved in inflammatory reactions.

Adaptive immunity

Adaptive, or acquired immunity is a slower, more potent response to pathogens that produces long-lived antibody-producing plasma cells and memory cells existing in a dormant state until the foreign substance is reintroduced. The primary functions of the adaptive immune system are:

- recognizing specific "non-self" antigens
- generating pathogen-specific immunologic effector pathways to eliminate specific pathogens or pathogen-infected cells
- and developing an immunologic memory to eliminate specific pathogens (Bonilla 2010).

Hence, the adaptive immune response is a critical component of the body's immune system, enabling it to recognize, eliminate, and survey pathogens more precisely than innate immunity.

The adaptive immune response relies on two main types of lymphocytes:

- B cells: responsible for humoral immunity, including plasma cells, which produce antibodies that bind to antigens, neutralizing pathogens or marking them for destruction by other immune cells and the complement system.
- T cells: involved in cell-mediated immunity, including:
  - o Helper T cells (CD4+) that assist other immune cells by releasing cytokines
  - o Cytotoxic T cells (CD8+) that directly kill infected or cancerous cells

T cells have a unique antigen-binding receptor on their membrane, known as the T-cell receptor (TCR), which requires activation through antigen presenting cells (APCs) to accurately recognize a specific antigen. APCs are found in the skin, and the gastrointestinal and respiratory tracts. APCs possess specific molecules on their surface which present an antigen to adaptive immune cells, called major histocompatibility complexes (MHC). There are two types of MHC, class I and II.

- MHC class I molecules are expressed in all nucleated cells and in platelets and are essential for presenting viral antigens to cytotoxic T cells and self-antigens to differentiate self from non-self.
- MHC class II molecules are expressed on the surface of antigen-presenting cells and play a crucial role in initiating cellular and humoral immune responses. Their expression can be induced in other cell types by inflammatory cytokines, particularly IFN-γ.

MHC molecules have been shown to signal whether a cell is a host or a foreign cell. In organ transplantation, the importance of MHC-matching between donor and recipient is well-established, with the objective of minimizing the risk of transplant rejection, and in stem cell transplantation the risk of graft-versus-host disease.

Because binding of the TCR to the MHC containing the antigen peptide is somewhat unstable and most of the time insufficient to induce adaptive immune system response, an activating co-receptor is often required. The CD4 co-receptor is expressed by T helper cells and the CD8 co-receptor by cytotoxic T cells. Although most T cells express either CD4 or CD8, some express both and a small proportion does not express either. Once activated, the T cell secretes cytokines, which in turn stimulates other T cells to differentiate into either cytotoxic T or T helper cells (Marshall 2018).

B cells, on the other hand, develop from hematopoietic stem cells in the bone marrow. Once matured, they leave the marrow expressing a unique antigen-binding receptor called the B cell receptor (BCR) on their membrane (Warrington 2011).

The main function of B cells is to become specific plasma cells, which produce large amounts of antibodies in response to antigens to inactivate, destroy and opsonize pathogens very potently. B cells are activated through CD4 T-cells (**Figure 2**).

Cell-mediated immunity is primarily a function of lymphocytes that protect the body against pathogens (Noonan 2015). Lymphocytes are found widely distributed within tissues and tumors. Cytotoxic T cells destroy virus-infected cells in the cell-mediated immune response, and helper T cells play a part in activating both the antibody and the cell-mediated immune responses. Regulatory T cells, which comprise approximately 5% to 10% of the total mature CD4+ T cell population, play a critical role in regulating the immune response. These cells function by deactivating T cells and B cells when needed to prevent immune response from becoming overly intense (**Table 1**).

Cancer immunotherapy, including check point inhibitors and chimeric antigen receptor (CAR) T-cell therapy, aims to enhance the ability of the immune system to specifically target and destroy cancer cells. The immune response is a multifaceted and dynamic system that protects the body against infections and diseases. Immunotherapy involves a coordinated effort between innate and adaptive immunity, utilizing a variety of cells, molecules, and mechanisms to identify and neutralize pathogens and malignant cells (Vaillant 2024).

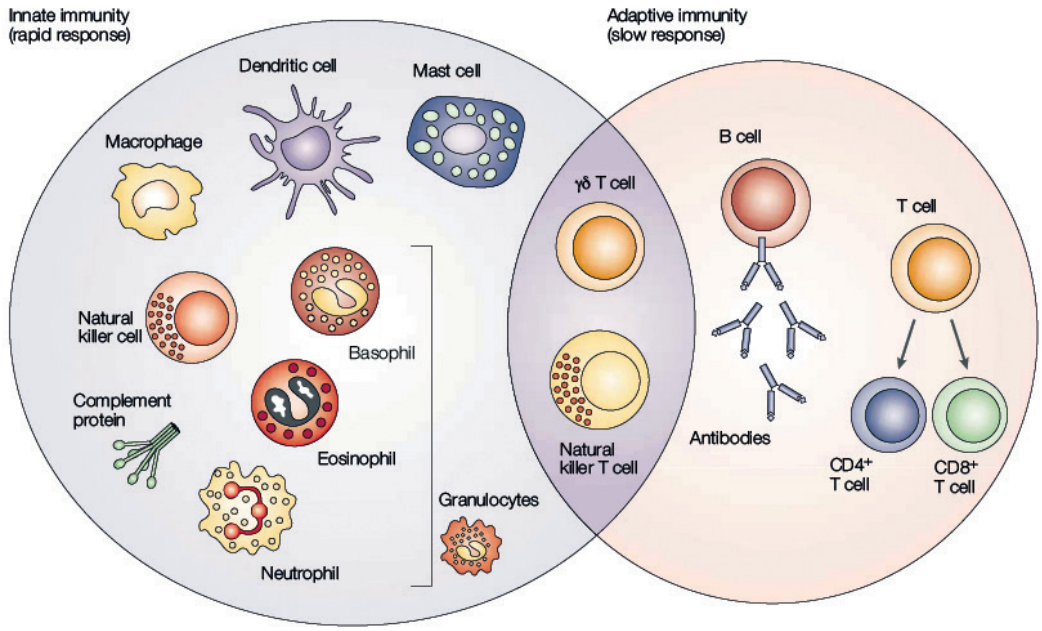

Figure 1. Overview of the cell types of the innate and adaptive immune system. All cells of the immune system are derived from a multipotent stem cell in the bone marrow. The innate immune system consists of a diverse set of cells as well as numerous soluble factors and proteins. The adaptive system consists of antibodies, B cells and CD4+ and CD8+ T cells, which enable a highly specific response against a particular target. **Source: Sharpe 2015; Dranoff 2004**

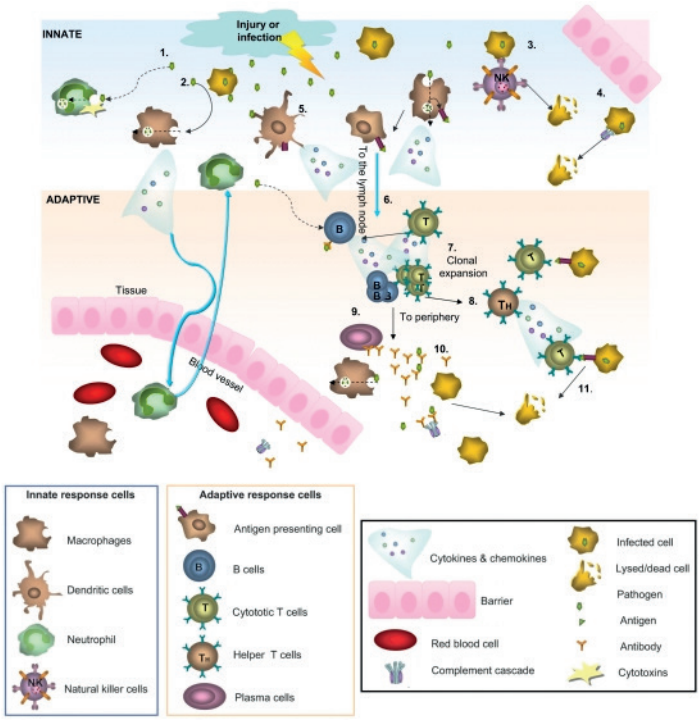

Figure 2. A schematic overview of the activities of the innate and adaptive immune systems following injury or infection. The innate immune system provides an immediate response to foreign targets, usually within minutes to hours (Steps 1–5). 1. Neutrophils engulf the pathogen and destroy it by releasing 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 via MHC II 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

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 (CD4+) and cytotoxic (CD8+) T cells; helper T cells activate T and B cells to stimulate immune response mechanisms; cytotoxic T cells have TCR receptors on surfaces which kill viral cells when receptor matches viral antigen
CD4+ T cell (also known as helper T cell)	Component of adaptive immune system	Helps activity of other immune cells by releasing cytokines; recognizes peptides presented on MHC II molecules found on APCs; play a major role in instigating and shaping adaptive immune response
CD8+ T cell (also known as cytotoxic or killer T cell)	Component of adaptive immune system	Most CD8+ cells express TCRs that recognize a specific antigen; recognizes 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

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 type of immunotherapy, which involves collecting and using the patient's own adaptive immune cells to treat their cancer. There are several types of ACT (**Box 3**), but CAR T cells have undergone the most extensive development and show the greatest promise in treating cancer at the present time.

CAR T cell therapy uses genetically modified T cells collected from the patient to selectively target disease-causing cancer cells. In other words, the T cells are engineered to harness the power of existing defense mechanisms in the body to fight the cancer cells.

Mechanism of action of genetically modified T cells

To create CAR T cells, lymphocytes are extracted from the patient's blood through the process of leukapheresis. Then, using a disarmed virus, selected T cells are genetically engineered to produce a chimeric antigen receptor

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

on their surface. The synthetic receptors now on the T cells allows them to recognize and attach to antigens on tumor cells and to be activated independently of the TCR [see Module 2 for a detailed explanation of the process of creating genetically modified T cells]. The chimeric antigen receptor on CAR T cells is a hybrid of the antigen-recognition region of an antibody combined with an activating domain which can directly activate T cells when the CAR recognizes the targeted antigen. The CAR T cells are therefore considered "living drugs" that can replicate rapidly and persist to provide anticancer activity for a long period of times.

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). In this way, CAR T-cell therapy combines the specificity of an antibody with the cytotoxic and memory functions of T cells to kill cancer cells. Cytokine release syndrome (CRS), which is a systemic inflammatory response and a potentially life-threatening side effect of CAR T-cell therapy, can occur when the immune system is overly activated during CAR therapy and over-excretes cytokine.

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 3**).

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 become more active and persistent, CAR T-cells require co-stimulation [see Module 2]. Second and third generation CARs therefore, contain co-stimulatory domains (either CD28 or 4-1BB) to more powerfully activate T cells so that they survive longer in the circulation. Research in CAR T-cell therapy has progressed and fifth generation CAR products are now being evaluated in clinical studies.

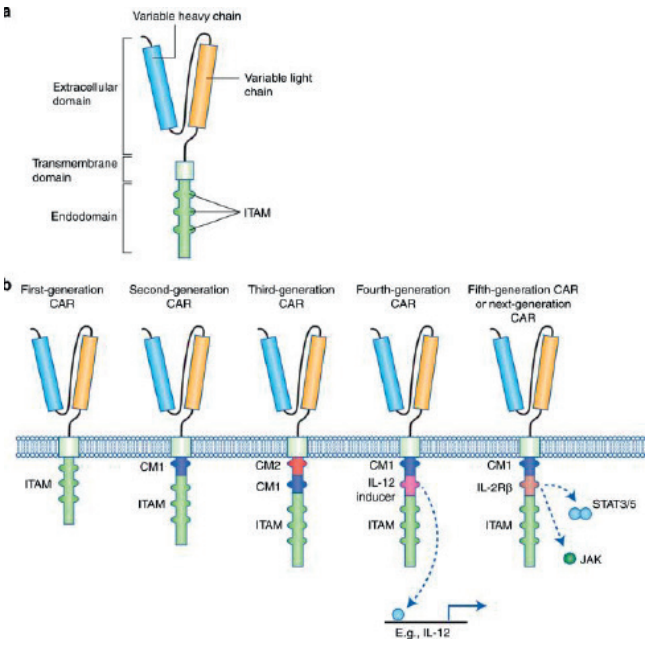

Figure 3. Structure of the different CAR generations. a) To make the process of gene transfer easier, a single, artificial gene that produced a functional protein that could both recognize antigen and transmit signals to the cell was designed. In these early CAR T cells, heavy and light chain variable 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 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 signal transduction [see Module 2]. CD19 is expressed on the surface of most forms of ALL (acute lymphoblastic leukemia), chronic lymphoblastic leukemia (CLL) 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, another adverse effect of CAR T therapy that is often chronic in nature but can be successfully managed [see Module 4].

In addition to CAR T cells engineered to target CD19, it is now possible to modify cells to target the B-cell maturation antigen (BCMA) that is expressed on the surface of myeloma cells. BCMA- targeting CAR T cells have exhibited impressive efficacy in multiple myeloma (MM) with two approved therapies, idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel), now standard of care for patients with relapsed and refractory disease.

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. Key studies have reported high remission rates (over 80%) in patients with treatment refractory ALL (Buechner 2017; Locke 2017), with recent results for large B-cell lymphoma indicating a curative potential of CAR T-cell therapy versus standard of care at 3-year follow-up in large B-cell lymphoma (Kamdar 2025). Clinical development of CARs for treating other hematologic cancers are ongoing.

CAR T-cell therapy for solid tumors remains in early stages of development and to date, no therapy has received FDA approval for solid tumors. CAR T therapy in solid tumors has been investigated in neuroblastoma, glioblastoma, and various carcinomas, with results obtained from both preclinical and clinical studies providing information for further advancements (Zhang 2025). As the incidence of solid tumors is significantly higher than that of hematologic cancers, there is an urgent need for innovative CAR-T strategies that are tailored to the challenges posed by these cancers.

The two key challenges impacting the success of CAR-T cell therapy in solid tumors include antigen escape and tumor heterogeneity, and the tumor immunosuppressive microenvironment (Tu 2025) as detailed below:

1. Antigen escape and tumor heterogeneity: Antigen escape refers to the phenomenon in which tumor cells downregulate or completely lose the expression of the antigens targeted by CAR T cells. Hence, the development of anti-cancer agents that target multiple antigens simultaneously or the modification of CAR T cells to recognize more than one antigen may be solutions to detection evasion. Antigen escape also limits long-term responses to CAR T-cell therapy in hematologic cancers.

   Solid tumors are composed of a diverse mixture of cell types, each potentially possessing different genetic and phenotypic characteristics, which ultimately helps cells to evade detection and plays a role in treatment resistance. This tumor heterogeneity also includes the expression of antigens on the surfaces of tumor cells that CAR T-cell therapies are engineered to recognize. The variability in antigen expression makes it difficult to identify a single or even a few target antigens that can be targeted by CAR T cells. Research is looking at using natural killer-like T cells expressing CARs to tackle tumor heterogeneity through the use of a combination of innate and adaptive immunity (Zhang 2025).

2. The tumor immunosuppressive microenvironment is characterized by a complex relationship between cellular and molecular components, which subsequently suppress immune responses, creating an adverse setting for CAR T cells attempting to infiltrate and destroy tumor cells. In addition to impairment of the immune response, physical barriers, including dense stroma and abnormal vasculature, negatively affect the infiltration and distribution of CAR T cells throughout the solid tumor and subsequently decreases the effectiveness of CAR T-cell therapy. A promising approach to this problem is to use a combination of CAR T-cell therapy and checkpoint inhibitors. Another strategy being evaluated is to genetically engineer CAR T cells to express cytokines or costimulatory molecules to improve their

proliferation, survival, and cytotoxic functions (Patel 2025).

In hematological malignancies as well as solid tumors, CAR T-cell therapy is associated with major toxicities that include on target/off tumor cytotoxicity, cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and immune effector cell-associated hemophagocytic lymphohistiocytosis-like syndrome [see Module 4]. Innovative techniques, such as modifying the structure of CAR T cells to achieve a therapeutic window during which they selectively target tumor-associated antigens while sparing normal tissues may prove beneficial to reduce toxicities (Tu 2025). Using switch mechanisms to control CAR T cell activation and inhibition post-infusion can provide a safeguard to enhance the safety of therapy. These switches involve several modalities, including the use of corticosteroids, inducible suicide genes, oncoclonal antibodies targeting engineered CAR T cells, protease inhibitors, and responsiveness to external stimuli like light and ultrasound (Tu 2025).

Long-term safety concerns persist, particularly the risks of insertional mutagenesis and cellular transformation (Patel 2025). Insertional mutagenesis occurs when viral vectors used to introduce CAR constructs integrate into the host genome at sites that may disrupt normal gene function or activate oncogenes, which may lead to malignant transformation (Patel 2025). Actual adverse events, such as secondary T cell malignancies, have been identified in patients treated with CAR T-cell therapies targeting BCMA or CD19 (Verdun 2024) [see Module 5].

In conclusion, although second-generation CAR T-cell therapies have demonstrated substantial clinical success, there are still many challenges. A new era in the field of CAR T-cell therapy will see more rapid manufacturing processes, durable responses, and improved safety profiles. Updates in indications including non-Hodgkin lymphoma and multiple myeloma, where next generation improvements ranging from dual targeting to neurotoxicity mitigation to frontline administration, will aim to offer novel therapeutic options for earlier intervention with broader patient accessibility and curative-intent strategies (Carre 2025).

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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

Adoptive cell therapies promise to revolutionize the fight against cancer. Human 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 malignant and non-malignant diseases. CAR T therapy was previously predominantly administered in inpatient settings due to the possibility of rapidly occurring and life-threatening toxicities. However, as knowledge and clinical experience with these products grows, as does the number of CAR T cell therapy options engineered for an improved safety profile, outpatient administration of CAR T cell therapy has been expanded. As expected, the change to outpatient care (for select patients) is a mechanism to overcome frequent hospital bed shortages and high costs of inpatient care.

Because of the similarities in facility services and supportive care required by hematopoietic stem cell transplant (HSCT) procedures and CAR T delivery, many centers providing HSCT 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 highlights the need for close and enhanced collaboration of patient care between referring hematologists/oncologists, the specialists at the CAR T center and primary care physicians (Beaupierre 2019). The coordination of patient care services is often the responsibility of a trained cancer nurse or advanced practice nurse.

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

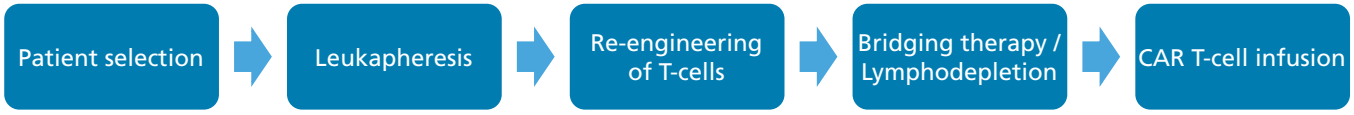

Figure 1. Process of preparing for CAR T cell therapy.

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)

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). Screening laboratory tests and imaging to assess organ function and patient eligibility, as would be undertaken to assess eligibility for enrollment in a clinical trial, should be performed. An absolute neutrophil count > 1.0 x 109/L (evidence of adequate bone marrow reserve), and an absolute lymphocyte count > 0.2 x 109/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]. Lastly, and importantly, manufacturer's guidelines as well as regulatory approval information should be consulted for patient-specific eligibility considerations.

Box 1. Topics for patient education before initiation of leukapheresis

- The leukapheresis process (duration)
- Potential leukapheresis reactions
- 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 require re-apheresis, prohibit or delay administration of CAR T cells [further information on patient and caregiver informational needs is presented in Module 4]

Leukapheresis

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 varies but usually takes between 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 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 T cells collected shortly after the diagnosis of a hematologic cancer (if performed) may provide better efficacy than T cells collected after cytotoxic 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 mantel 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 the 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. The goal of bridging therapy is to prevent rapid disease

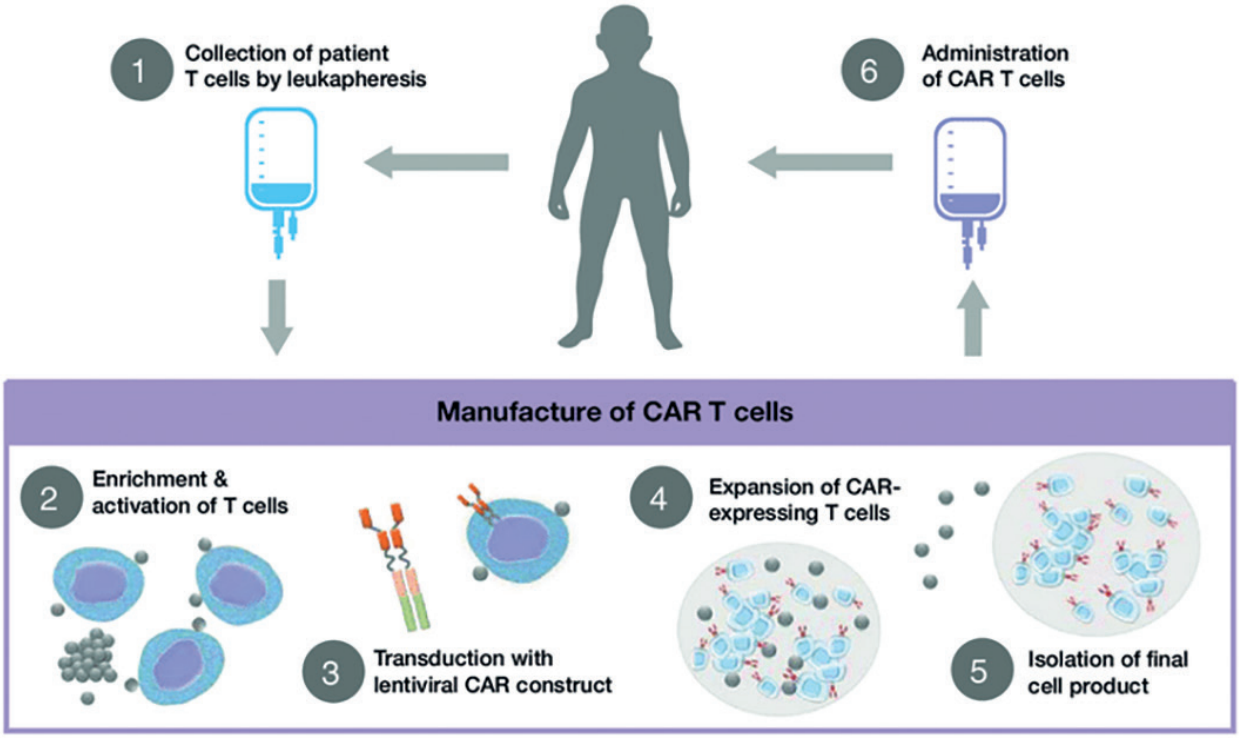

Figure 2. CAR T cell treatment process. The treatment process begins with leukapheresis of T cells. Once these are isolated, they are sent for manufacturing to produce genetically-modified CAR T cells, which are reprogrammed to target the killing of CD19+ B cells. The viral vector (step 3) might vary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

progression during this interval period and prior to CAR T cell infusion. 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).

Box 2. Topics for patient education at time of bridging therapy

- Monitoring for disease symptoms between leukapheresis and administration (palpable lymphadenopathy, functional status, infection risk)
- Potential difficulties in waiting for the CAR T cells to be manufactured
- Reassurance of patients/.caregivers by providing information of manufacturing process

Bridging therapy should only be given after leukapheresis is completed so that the quality of the harvested CAR T cells is not affected.

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). Thus, lymphodepletion creates a favorable immune environment for CAR T cells, which improves their expansion, persistence and clinical activity while reducing the potential for anti-CAR immune responses (Wagner 2021).

Regimens may vary by disease indication and manufacturers' recommendations but typically include fludarabine and cyclophosphamide administered over 3 days (Beaupierre 2019; Kochenderfer 2017; Turtle 2016). 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

Box 3. Topics for patient education at time of lymphodepletion therapy

- Patient and caregiver education on logistics, potential side effects and management of symptoms of lymphodepleting chemotherapy
- Patient and caregiver education on prevention and self-care of infection and when to contact healthcare professional
- Fever ≥ 38.5C requires urgent call to CAR T team
- Practice hand hygiene and avoidance of crowds and persons with infection
- Provide information on other signs/symptoms of infection and when to present at emergency department
- Need for caregiver to be continually present with the patient

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.

Engineering T Cells to Produce CAR T-cell Therapy

Once collected, the leukapheresis product may be shipped to a commercial facility where T cells are isolated, activated, genetically modified with a CAR-encoding vector and expanded before cryopreservation (Perica 2018). Alternatively, the cell modification process is performed at or near the treating center.

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

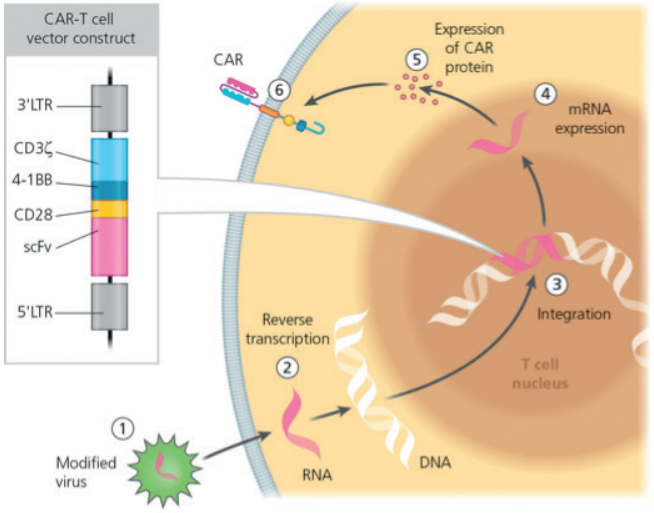

Figure 3. Retroviral gene transfer. LTR, long terminal repeat; scFv, single-chain variable fragment. 1) gene-encoding RNA enters the T cell in a modified lentivirus vector where it is 2) reverse transcribed into DNA and 3) integrated into the T cell genome. 4) The new DNA is transcribed into messenger 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

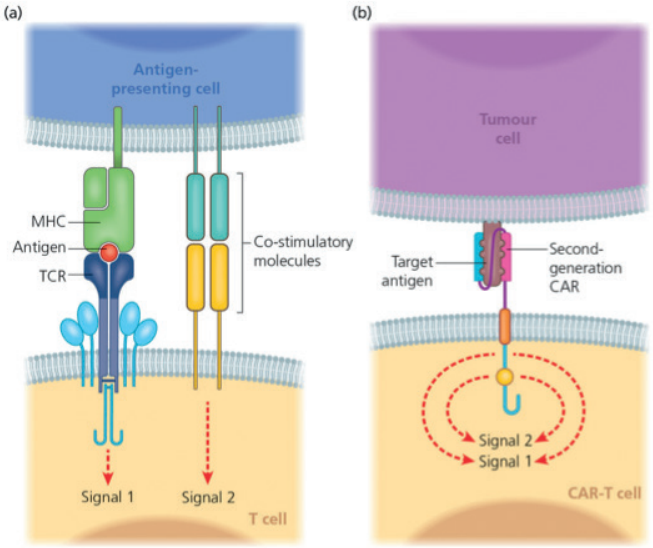

Figure 4. Co-stimulation of T cells. MHC, major histocompatibility complex; TCR, T cell receptor. T cells require a second signal that allows them to become activated. This stimulation (signal 2) is provided by the interaction between co-stimulatory molecules expressed on the antigen-presenting cell 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

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 Module1]. 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).

Problems and Limitations of CAR T-cell therapy

CAR T cell therapy has gained significant attention and has achieved numerous favorable results because of its impressive impact on the treatment of hematologic malignancies and other non-malignant diseases. Despite these successes, there are still challenges to overcome such as resistance, treatment toxicities, and the high cost of treatment.

Resistance and disease recurrence

CAR T cell therapy does not work for every patient and resistance remains a significant problem. There are differences between the biology of CAR T cells and natural T cells that provide both opportunities and challenges for the use of this therapy.

Antigen modulation is a major cause of CAR T cell resistance in B cell malignancies, and likely poses an even greater challenge in solid tumors. In children and young adults with B-cell ALL, the majority of relapses are associated with CD19 loss (Labanieh 2023). Tumor cells escape immunity and develop resistance usually caused by antigen loss on the tumor cell surface making them unrecognizable by CAR T cells. For example, B-cell maturation antigen (BCMA) is crucial for the normal function of plasma cells and the absence of BCMA is a mechanism of resistance in CAR T cells (BCMA is overexpressed in multiple myeloma and some types of leukemia and therefore a target in treatment of these disorders).

A second major cause of CAR T cell resistance is related to inadequate T cell potency, persistence, functional persistence and/or dysfunction, and is typically associated with disease recurrence in the absence of antigen modulation (Labanieh 2023). Dysfunction is often caused by T cell exhaustion that leads to low T cell proliferation and cytotoxicity. T cells in the manufactured CAR T cell product sometimes display exhaustion due to the poor quality of harvested T cells as a result of previous chemotherapy, age-related immune decline, or the advanced stage of the cancer (Yang 2025).

Treatment toxicities

Patients receiving CAR T cell therapy can experience numerous potentially life-threatening side effects such as cytokine release syndrome (CRS) [see Module 4]. There are several strategies either in practice or in development to alleviate "on-target, off-tumor" toxicities:

1) use iCasp9/AP1903 suicide gene technology to remove or destroy improperly activated CAR T cells to balance effective T-cell activation to ensure antitumor activity, and decrease the potential for uncontrolled activation, which may generate immune responses;

2) increase the targeting ability of CAR T cells;

3) develop dual-targeted CAR T cells to maximize their ability to prevent tumors from escaping immune system detection and limit their off-target toxicity;

4) precisely control the dose of CAR T cells at different time points by administering dasatinib as a CAR T cell on/off switch. Lenalidomide can also serve as an on/off switch for CAR T cells;

5) design CAR T cells that self-regulate the production of inflammatory cytokines to reduce the toxicity of CRS and increase the ability to attack tumors. Toci- (derived from tocilizumab) secreting CAR T cells have demonstrated in vivo antitumor efficacy.

High cost of CAR T cell therapy

The high cost of CAR T cell therapy is driven by several factors:

- The complexity and precision of the manufacturing process
- The presently limited use of the technology to hematologic malignancies, which limits large-scale application.

Thanks to engineering advances, automated closed-system manufacturing provides the opportunity to manufacture CAR T cells at the point-of-care. This has decreased not only costs, but delays and logistical challenges associated with centralized manufacturing as well (Labanieh 2023).

Costs of hospitalization and intensive care treatment of complications such as cytokine release syndrome (CRS) and neurotoxicity substantially add to the costs of treatment.

Future Perspectives

Innovations in CAR T therapies fall into two main categories: cell sourcing and engineering approaches.

The development of CAR T-cell therapies that use immune cells collected from healthy donors (allogeneic source) would expand the availability of CAR T therapy and address limitations with manufacturing and administration thereby increasing access to this treatment. T cells from a healthy donor could improve T cell potency by avoiding the engineering of T cells with preexisting dysfunction (due to previous cytotoxic treatment) (Labanieh 2023). While allogeneic products 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, they would still present a risk of graft vs host disease and rejection of the transferred cells by the host immune system.

In terms of cell engineering, the application of genome editing and synthetic biology tools to confer additional control over when, where and how strongly CAR T therapies are active could primarily improve safety and efficacy (Verma 2023). Examples of genome editing and synthetic biology tools include logic-grated, on/off, switchable, multi-targeting, and armored systems. These innovative approaches, especially logic-grated, on/off, and switchable, are likely to positively impact safety, efficacy, ease of administration and manufacturing cost and speed. Several studies, for example, have now reported control of toxicity while maintaining therapeutic efficacy using switchable CAR T technology.

> Switchable CAR T therapy (sCAR T) can be turned on and off allowing for controllable activity of the adoptively transferred cells. In this novel therapy, sCAR T cells are activated when the switchable CAR receptor binds to a tumor-specific antibody switch. This then activates the sCAR T cells against cancer cells (Scripps Research 2022).

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. CRISPR-Cas9 carries a risk of CRISPR-based mutagenic events longer term and this risk could be intensified when producing hundreds or thousands of allogeneic products with a singular manufacturing process (Labanieh 2023).

Increasing the effectiveness of CAR T cells by using them in combination with immune checkpoint inhibitors may achieve significant treatment results. Research suggests that combining CAR T cells with PD-1 blockade agents increases the survival of CAR T cells and promotes the killing of PD-L1-positive tumor cells and may help to improve the therapeutic efficacy and persistence of the CAR T cells.

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Notes

Quick Facts

- 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 (HSCT), no upper age limit has yet been defined for treatment with CAR T-cell therapies
- All CAR T-cell therapies come with a 'black box warning' for several serious and potentially life-threatening toxicities including a risk of secondary malignancies
- 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
- Real-world studies of CAR T-cell therapy, which usually lack tight inclusion and participation requirements, show patient outcomes that are comparable to those of clinical trials

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 such as B-cell acute lymphocytic leukemia, multiple myeloma, and non-Hodgkin lymphoma. Clinical studies are underway to investigate the use of CAR T-cell therapy in acute myeloid leukemia, solid tumors, and some autoimmune diseases such as systemic lupus erythematosus and myasthenia gravis. In contrast to conventional antineoplastic treatments, CAR T cells are living organisms and their expansion and antineoplastic activity is a dynamic process, which is not fully understood.

The European and US authorizations of these cellular adaptive immunotherapies (**Table 1**) was based on early evidence of anti-tumor activity from pivotal phase 1/2 clinical trials, provided that an unmet medical need (such as incurable malignancies characterized by a relapsing/remitting behavior and a progressive clinical course) is fulfilled and the benefit of early market access is greater than the risks resulting from the lack of comprehensive data (Bellino 2023). Early evidence indicated high response rates and the possibility for long-lasting disease control in heavily pre-treated patients with very limited treatment options.

Pre-clinical and early phase clinical studies of CAR T-cell therapy are numerous and on-going. These studies investigate the optimization of CAR-cell constructs by changing cell source (e.g., allogeneic natural killer (NK) cells, T cells with stem cell-like phenotypes), engineering CARs with dual binding domains, or secreting cytokines for improved activity and tumor cell killing (Yang 2025). While these developments are highly sophisticated and very promising, their implementation into practice has thus far only taken place in the form of clinical trials.

Whereas there is an upper age limit for hematopoietic stem cell transplant (HSCT), 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 disease course of B-cell hematologic malignancies and multiple myeloma are being investigated.

All CAR T-cell therapies come with a 'black box warning' for cytokine release syndrome (CRS), neurologic toxicities, immune effector cell hemophagocytic lymphohistiocytosis-like syndrome, prolonged cytopenia, and risk of secondary malignancies [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. While risks and management of the most common side effects of CAR T-cell therapy are fairly well understood and treatment guidelines have been established, novel and rare side effects continue to occur. The initial focus on cytokine release factor, for example, has now somewhat shifted to a focus on the relevance of immunodeficiency, infections,

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

Approval Agency	Generic (Trade Name)	Target	Indication[1]
EMA/FDA	Tisagenlecleucel/Tisa-cel (Kymriah®)	Anti-CD-19	B cell ALL; B-cell non-Hodgkin lymphomas (DLBCL, follicular)
EMA/FDA	Axicabtagene ciloleucel/ Axi-cel (Yescarta®)	Anti-CD-19	B-cell non-Hodgkin lymphomas (DLBCL, PMBCL, HGBCL, follicular lymphoma)
EMA/FDA	Lisocabtagene maraleucel/Liso-cel (Breyanzi®)	Anti-CD-19	B-cell non-Hodgkin lymphomas (DLBCL, PMBCL, HGBCL, follicular lymphoma grade 3B)
EMA/FDA	Brexucabtagene autoleucel/Brexu-cel (Tecartus®)	Anti-CD-19	Mantle cell lymphoma; B-cell precursor ALL
EMA/FDA	Idecabtagen vicleucel/Ide-cel (Abecma®)	Anti B-cell maturation antigen (BCMA)	Multiple myeloma
EMA/FDA	Ciltacabtagene autoleucel (Carvykti®)	Anti B-cell maturation antigen (BCMA)	Multiple myeloma

1 The current CAR T-cell therapy approval is for relapsed/refractory disease in all indications.
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
Adapted from: Bellino 2023

genotoxicity and secondary malignancies.

The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved six CAR T autologous cell products targeting CD19 or B cell maturation antigen (BCMA) for the treatment of relapsed/refractory B cell malignancies, such as acute lymphoblastic leukemia, large B-cell lymphoma, follicular lymphoma, primary mediastinal lymphoma, mantle cell lymphoma, and multiple myeloma (**Table 1**). Many more products are in the pipeline or in early phase clinical trials. Due to the novel nature of these therapies and to their 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

Tisagenlecleucel/Tisa-cel (Kymriah®) in the Treatment of B-cell Acute Lymphoblastic Leukemia (ALL)

The prognosis for adults with relapsed/refractory (r/r) B-cell ALL was once poor, but has improved due to immunotherapies and CAR T-cell therapy (Othman 2024). Tisa-cel was the first CAR T approved by the FDA and is indicated for the treatment of adults with B-cell precursor ALL that is refractory to treatment or in second or later relapse (Maude 2018).

Efficacy and safety

Minimal residual disease-negative complete response rates of 60% to 93% have been reported in clinical studies (**Table 2**). The ELIANA study concluded that tisa-cel 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 unit- (ICU) level care (**Table 3**). Most adverse events were alleviated in most patients following intervention with supportive measures and cytokine blockade.

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 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

Axicabtagene ciloleucel/Axi-cel (Yescarta®) and Lisocabtagene maraleucel/Liso-cel (Breyanzi®), Brexucabtagene autoleucel (Tecartus®), and Tisagenleucel (Kymriah®) in the Treatment of B-cell Non-Hodgkin Lymphomas

Outcomes for patients with any type of relapsed/refractory aggressive B-cell lymphomas treated with conventional chemotherapy regimens are poor. The treatment landscape has dramatically improved over the past 5 years with the availability of CAR T cells and more recently bispecific T-cell engagers and bispecific antibodies. At this point, adoptive T cell therapy using CAR T cells is has become the standard of care for relapsed disease in several B-cell lymphoma subtypes (Silkenstedt 2024).

Efficacy and Safety

Diffuse large B-cell lymphoma (DLBCL), the most common and most aggressive subtype of B-cell NHL), is successfully treated in about two-thirds of patients following administration of a rituximab-based immunochemotherapy regimen (Feugier 2005; Pfreundschuh 2006). The prognosis is poor, however, for patients with relapsed/refractory DLBCL.

Initial results from the ZUMA-1 study, which evaluated axi-cel in patients with DLBCL refractory to chemotherapy or relapsed after autologous HSCT, showed favorable efficacy results after a single dose (Neelapu 2017) (**Table 4**). These favorable 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 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 liso-cel, a third CD19-directed CAR T therapy, showed 73% overall response and 53% complete response (Abramson 2020) (**Table 4**). This study enrolled a broad range of patients with relapsed/refractory large B-cell lymphomas including 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).

Follicular lymphoma has an excellent prognosis with frontline rituximab-based therapies, but

20% of patients relapse within 2 years after initial treatment and outcomes following relapse are poor,

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

with a 5-year overall survival of only 50% with currently available therapies (Tan 2013; Casulo 2015).

CD19-directed CAR T-cell therapy with axi-cel or tisa-cel led to durable remissions in patients with refractory follicular lymphoma, leading to the approval of both of these products for relapsed follicular lymphoma (Jacobson 2022; Fowler 2021). In 2024 and then in 2025, liso-cel (lisocabtagene maraleucel) received accelerated approval from the US FDA and the European Commission (EC), respectively, for the treatment of adult patients with relapsed or refractory follicular lymphoma. The approval of both agencies was based on positive results from the TRANSCEND FL study, which demonstrated high response rates and durable remissions with a manageable safety profile (Morschhauser 2023).

Mantel cell lymphoma (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). After a median follow-up of 35 months, brexu-cel induced a durable overall response rate of 91% and a median progression-free survival of 25 months in patients with relapsed/refractory MCL (Wang 2022). Phase 1 studies are ongoing to evaluate the use of liso-cel in relapsed/refractory mantle cell lymphoma.

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). As previously mentioned, there are now published practice guidelines for managing CRS and neurologic toxicities, and as a consequence, their incidence and severity have decreased with increasing clinical experience and expertise.

Idecabtagene vicleucel/Ide-cel (Abecma®) and Ciltacabtagene autoleucel (Carvykti®) for the Treatment of Multiple Myeloma

Although the emergence of immune modulatory drugs, proteasome inhibitors, and CD38 antibodies have changed the treatment landscape and survival rates for patients with multiple myeloma, the disease remains incurable, and with each line of combination treatment, duration of response becomes shorter and the disease more refractory, especially in high-risk patients who rapidly become

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

refractory to conventional treatment options. Ide-cel was the first approved CAR T cell product to target B-cell maturation antigen (BCMA). The FDA (in 2022) and the EMA (in 2023) approved another product targeting BCMA, ciltacabtagene autoleucel (Cita-cel) (Carvykti®), which has two BCMA binding domains. 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. Both products are indicated for the treatment of adult patients with relapsed/refractory multiple myeloma and both products have demonstrated efficacy in clinical trials and real-world clinical practice.

Ide-cel was evaluated in patients with relapsed/refractory multiple myeloma; overall response rate was 73%, with a median duration of response of 10.6 months (Munshi 2021).

Cilta-cel was evaluated in patients with relapsed/refractory multiple myeloma who had disease progression; overall response rate was 97%, with a median duration of response of 21.8 months (Madduri 2020). Cilta-cel was found to provide early, deep, and durable responses with a manageable safety profile. The CARTITUDE-1 study provided the basis for regulatory approval of cilta-cel (Madduri 2020).

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 of ide-cel (**Table 6**). 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**). The CARTITUDE-1 study provided the basis for regulatory approval of cilta-cel (Madduri 2020).

BCMA-directed CAR T cell therapies, as used in multiple myeloma, have been shown to cause late and rare neurotoxicities including parkinsonism-like symptoms. These are discussed in Module 5.

Real world study results

Since completion of registration and 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 trials. An analysis of safety and efficacy results in real-world trials indicates similar outcomes to those reported in clinical trials thereby confirming the therapeutic effect of CAR T-cell therapies, particularly for those products with more available evidence:

- Summary results of a meta-analysis of clinical vs real-world studies in LBCL showed: CAR T therapies were used in a boarder patient population in real-world vs clinical trials; real-world effectiveness and safety results were comparable with trial results; axi-cel was associated with better effectiveness compared with tisa-cel; tisa-cel was associated with a lower risk of neurologic events compared with axi-cel in real-world outcomes (Jacobson 2024).
- Real-world safety profiles of tisa-cel and axi-cel were very similar to those reported in clinical trials (Westin 2021).
- In a large multicenter study, real-world outcomes were evaluated in patients with relapsed/refractory multiple myeloma who had received ide-cel. Overall response rate was 84%, median progression-free survival and overall survival were 8.5 and 12.5 months, respectively (Hansen 2023).

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

- In a European, multicenter study, real-world evidence of brexu-cel for the treatment of relapsed/refractory mantel cell leukemia indicated safety and efficacy similar to those obtained in the pivotal trial; ORR was 91%, the 6- and 12-month PFS was 77% and 51%, respectively; the 6- and 12-month OS was 83% and 61%, respectively (Iacoboni 2022)
- A comparison of CAR T products and their outcomes between patients from a clinical trial versus patients from a real-world situation showed that patients treated with cilta-cel were 3-fold more likely to respond to treatment, and had reduced risk of progression or death of 85% and 80%, respectively, although they experienced more adverse events (Mateos 2022).

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**).

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 favorable 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).

Today, 7 years after approval of CAR T-cell therapy in Europe, CAR T cells have become standard of care in certain subgroups of patients and have replaced high-dose chemotherapy with autologous stem cell transplantation in some patients with early relapse or refractory aggressive lymphoma in the second line of treatment. Long term data (> 5 years) demonstrate a plateau of overall and progression free survival, and suggest that CAR T cells can achieve cure in 35% to 45% of patients who previously had a very poor prognosis.

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.

Outside of non-malignant diseases, CAR T-cell therapy offers a promising therapy option in various autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis. However, the risk–benefit evaluation in the context of autoimmune disorders has not been established yet and must be reconsidered, as

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

certain complications are not tolerable in patients with autoimmune diseases.

Other emerging and potential novel applications currently under investigation include CAR-T cells to treat infectious diseases such as chronic viral (i.e., HIV) and opportunistic fungal diseases. CAR T cells are being tested in animals to reduce cardiac fibrosis.

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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 chimeric antigen receptor (CAR) T-cell therapy, adhere to the Foundation for Accreditation of Cellular Therapy (FACT) /Joint Accreditation Committee of the International Society for Cellular Therapy (JACIE) International Standards for Hematopoietic Cellular Therapy Product Collection, Processing, and Administration standards (FACT/JACIE 2021). The FACT-JACIE standards 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 therapies. According to these guidelines, 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. As experience with these products grows, their administration is increasingly taking place in outpatient rather than inpatient facilities. (As of July 2025, the FACT/JACIE standards are in the process of being updated.)

Based on clinical experience with the first generation of autologous CAR T therapies targeting CD19 and BCMA, the US Food and Drug Administration (FDA) in June 2025 relaxed the risk evaluation and mitigation strategies (REMS) for several CD19 agents (tisagenlecleucel, axicabtagene ciloleucel, lisocabtagene maraleucel), and BCMA-directed agents (idecabtagene vicleucel and ciltacabtagene autoleucel). Removal of REMS means (at least in the US) fewer patient monitoring requirements, therapies do not need to be administered at certified clinics, and the requirement for patients to remain in close proximity to the treatment center has been reduced from four weeks to two (FDA 2025).

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, including information regarding the short- and long-term risks and benefits of CAR T-cell therapy, expected remission rates and survival outcomes (Kisielewski 2024). A healthcare professional familiar with CAR T therapy should document informed consent.

Comprehensive patient education 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 emergency treatment if needed (Taylor 2019).

Patients who return home for self-monitoring after infusion should be provided with instructions and a log

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 and to 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	Re-assess patient/caregiver knowledge of toxicity symptoms, symptoms to monitor for and their management, when to go to the treatment center, when to seek emergency care

CRS, cytokine release syndrome; HCP, healthcare professional
Kisielewski 2024; Kite Pharma 2021; Rivera 2020; Brudno 2019; Gust 2018; Lee 2014

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. Some treatment centers may require patients to be accompanied in the home setting by a 24-hour caregiver for at least four weeks following infusion (Perica 2018).

Psychosocial support

Patients come to CAR T therapy with complex physical, functional and psychological needs. Hence, they and their family members may be anxious about the treatment or experience anxiety because they are being treated at an unfamiliar center. Effort should be made to ask about any anxieties and offer referral to psychosocial services if needed. As these patients may have relapsed on previous treatment, and have an uncertain prognosis due to the risk of disease progression following CAR T treatment, the early and on-going integration of palliative care services to discuss advanced care planning and symptom control is advisable. The involvement of a multidisciplinary team together with a dedicated nurse specialist can offer a wide-range of supportive care services to help patients and families through survivorship and end-of-life care (Stenson 2022).

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 2021). 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. Further, nurses working in non-oncology areas where they may encounter patients treated with CAR T cell therapy (i.e., intensive care) will need to be integrated into the team of nurses and educated appropriately (**Box 1**).

Safety considerations

CAR T cells should be administered by nurses knowledgeable in immune effector cell therapy. Ideally, the infusion should take place during core hours of hospital/clinic operation to ensure the availability of medical and emergency staff should a critical adverse reaction occur.

Box 1. 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 2021; Taylor 2019)

Documentation and verification procedures for each step of the infusion process should be in place and part of standard of practice protocols when administering CAR T cells. Hospital/clinic safety protocols for CAR T cells should be followed and the following safety practices observed:

- Verify patient identity 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 if present
- Verify consent has been obtained
- Verify prescription with product label

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.

Both 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).

Approval agencies such as EMA and the FDA mandate prompt reporting of severe adverse events to institutional safety boards and to the manufacturers.

Infusion procedure

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. 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.

Recommended steps to administer CAR T cells:

- Compare written prescription to label on product for accuracy
- Check vital signs and document
    - o Ensure patient is hemodynamically stable and without infection
- Ensure all mandated pre-infusion assessments are complete, including a baseline sample of the patient's handwriting for the ICE assessment
- Verify patent IV access
- Ensure bedside emergency equipment (suction/ oxygen) is in full working order. Prepare IV fluids and new IV line, to be used in the event of a reaction during infusion
- Administer pre-medications as per institutional or manufacturers' guidelines approximately one hour before infusion
- Infuse thawed cells as per institutional and manufacturer guidelines, taking care to ensure that the infusion takes place immediately post thawing using the recommended administration equipment. Refer to manufacturer's guidelines for further information.
- 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

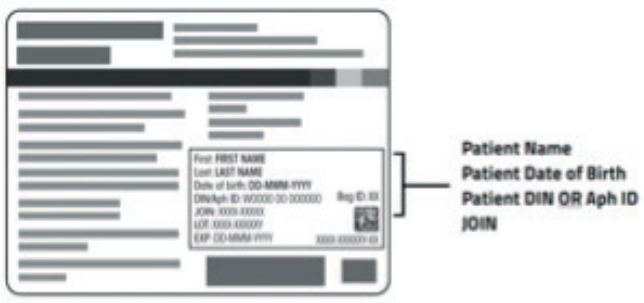

Figure 1. Sample of CAR T infusion bag.

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)
- Change in vital signs or signs of hemodynamic instability
- Active uncontrolled infection
- Active graft versus host disease (GVHD)
- Worsening of disease burden following lymphodepleting chemotherapy (Novartis 2018)

At the time of scheduling the CAR T cell infusion, inform the intensive care team and neurology services of the planned infusion date and follow institutional protocols for CAR T-cell infusion preparation..

Supportive measures

The regimen used for lymphodepletion can lead to prolonged (> 1 to 2 weeks) bone marrow suppression. It is advisable that patients receive anti-infective prophylaxis and other supportive measures similar to those prescribed f or autologous stem cell transplantation. Prophylactic medications may include

- Levofloxacin
- Acyclovir
- Fluconazole
- Co-trimoxazole
- Lansoprazole
- Consider levetiracetam for patients at high risk of neurological toxicity
- Tumor lysis prophylaxis as per institutional protocol

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 or transfusion reactions should be followed. These generally include

- Increase monitoring of vital signs
- Assess symptoms and treat appropriately
- Administer corticosteroids* **only if the situation is life-threatening** and authorized by a senior clinician
- Ensure patient comfort and provide information and reassurance
- Document as per local policy/trial protocol

** There is evidence that corticosteroids may adversely effect the efficacy of CAR T cells and should therefore be administered with extreme caution.*

Recognition and Management of Toxicities

Introduction

The three most commonly observed toxicities with CAR T-cell therapies are

- cytokine-release syndrome (CRS)
- immune effector cells associated neurotoxicity syndrome (ICANS)
- immune effector cell (IEC) hemophagocytic lymphohistiocytosis (HLH)-like syndrome (IEC-HS).

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). 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).

Managing treatment side effects requires a multidisciplinary team educationally prepared for the intensive monitoring that patients may require. Centers providing CAR T-cell therapy should be 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, prior therapy, and the lymphodepletion regimen used. Some degree of toxicity is expected to achieve an effective response to CAR T therapy (Chohan 2023). 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.

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 2).

Box 2. 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

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 T cell receptors (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 ASTCT (American Society for Transplantation and Cellular Therapy) defines CRS as:

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

CRS can occur at any time, often between days 0 and 14. 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).

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**): these symptoms are similar to those common to neutropenic sepsis. Patients treated in an outpatient setting should receive comprehensive education on the symptoms of CRS with specific instructions on what to do and who to contact should they occur.

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

Multidisciplinary management

The management of CRS is closely related to the grade of severity of CRS with several grading systems currently in clinical use (**Table 3**). 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 (Lee 2019). The ASTCT consensus grading of CRS is currently the most commonly used system in clinical practice (Lee 2019).

There is no clinical consensus on the "best" management of CRS (**Table 4**). However, tocilizumab, a monoclonal antibody which binds to the IL-6 receptor and is licensed in Europe for treating CRS and is used as first-line treatment. The recommended dose is 8mg/kg; with a maximum dose of 800mg administered as an intravenous infusion over 60 minutes. Up to four doses can be given, at intervals of at least eight hours. Second line treatment is usually steroids; the dose and choice of steroid is often recommended by the product manufacturer. Historically, caution was observed when using steroids as their use could reduce the persistence and efficacy of CAR T cells. Evidence now suggests a benefit from the early use of steroids in terms of lowering the incidence of CRS, reducing rates of high-grade CRS and shortening the duration of CRS symptoms in some patients (Lakomy 2023). 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.

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

Neurotoxicity

Neurotoxicity is a serious 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).

It is estimated that more than 60% of patients treated with CAR T cells 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). CAR T neurotoxicity 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 during or more commonly following CRS symptoms (but rarely before CRS), are variable between patients, and have an unclear pathophysiology, which is distinct from CRS (Lee 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).

Clinical manifestations

ICANS is an acute reaction and usually occurs within the first 10 days after infusion. Symptoms or signs of ICANS can be progressive. Severe symptoms are most often seen with an early onset of CRS and ICANS can develop in the setting of improving or resolved CRS; hence, it is hypothesized that cytokine release contributes to the development of neurotoxicity (Gust 2020).

Early symptoms can include:

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

Advanced symptoms include

- Somnolence
- Seizures
- Cerebral edema
- Coma.

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

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

Diagnosis of neurotoxicity

The ASTCT developed a 10-point encephalopathy scoring tool [Immune Effector Cell-Associated Encephalopathy (ICE)], which includes elements of the CARTOX-10, and neurologic assessment tool that incorporates items of the Mini-Mental State Examination (MMSE) to evaluate alterations in speech, orientation, handwriting and concentration (Neelapu 2017).

While the ICE score is helpful to assess patients for encephalopathy, grading of ICANS requires assessment of the ICE score as well as evaluation of other neurological domains such as level of consciousness, motor symptoms, seizures, and signs of raised intracranial pressure/cerebral edema, which may occur with or without encephalopathy (Lee 2019). The severity of ICANS and the final ICANS grade is determined by the most severe event among the different domains (**Table 7**).

Multidisciplinary management

As is the case for CRS, management of ICANS is dependent on the grade of severity (Box 3) and involves multidisciplinary care and proactive interventions to mitigate severe complications.

Corticosteroids are the mainstay of acute ICANS management, whereby higher doses are recommended for higher grades of ICANS. In most cases, steroid treatment results in rapid resolution of ICANS, even in severe cases.

The IL-1 receptor antagonist anakinra is frequently used in patients with steroid-refractory ICANS. Anakinra can be used as an adjunct to steroids but is associated with immunosuppression.

Supportive measures include seizure prophylaxis with levetiracetam, urgent referral to and reviews by neurology, and transfer to intensive care for monitoring (**Box 3**) 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).

Tocilizumab is usually prescribed in cases of neurologic toxicity in the presence of CRS 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.

Immune Effector Cell (IEC)-Hemophagocytic Lymphohistiocytosis (HLH)- like syndrome

In a patient who has received CAR T therapy, immune effector cell-associated hemophagocytic lymphocytosis-like syndrome (IEC-HS) is a life-threatening hyper-severe inflammatory state that is now understood as a complication of CAR T cell therapy and is unrelated to CRS and ICANS. It is characterized by an uncontrolled activation of natural killer cells, macrophages, and cytotoxic T lymphocytes that results in multi-organ dysfunction. Worsening cytopenia, in particular severe neutropenia, increased LDH, and often abnormal liver function tests are also commonly observed.

The incidence of IEC-HS is low and reported to occur in around 3.5% to 15% of patients following CAR T cell infusion; the diagnosis is dependent on correct recognition, patient characteristics and type of product infused (Sandler 2020). It is, however, considered a potentially fatal

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

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

complication. Although IEC-HS-like symptoms can occur in patients experiencing CRS, IEC-HS typically appears later, often after CRS has begun to resolve. Thus, a key factor in diagnosing IEC-HS is its chronological independence from CRS (Hines 2023).

Clinical manifestations

Clinical manifestations include progression or new onset of cytopenias, hyperferritinemia, coagulopathy with hypofibrinogenemia, and/or transaminitis. Patients exhibit signs and symptoms that closely resemble the onset of an exaggerated inflammatory response following CRS or CAR T cell expansion. Of note, all reported patients with IEC-HS-like toxicities to date have had a previous or ongoing CRS.

Multidisciplinary management

Early recognition and prompt treatment are critical to achieving favorable outcomes. High-dose corticosteroids are often used to treat IEC-HS (Ombada 2024; Hines 2023). There is wide variation on other types of treatments used in the clinical setting and most are generally selected based on etiology of disease. Targeted therapies like anakinra, ruxolitinib, and tocilizumab may help control inflammation. The FDA recently-approved emapalumab, effective in primary HLH, has gained off-label use in IEC-HS for its biologic impact and safety. The effect of any potential therapies on CAR T cell efficacy must be considered and treatments should be selected based on a lower risk of impeding CAR T cell activity and persistence (Hines 2023). However, in rapidly progressing or life-threatening IEC-HS, the patient's survival takes precedence over the longevity

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
General state	Drowsiness, delay in responded or mild disorientation to time/place; mild handwriting impairment	Handwriting may be poor; mild expressive aphasia and/or difficulty following commands; expressive aphasia	Severe global aphasia, not able to follow commands even if awake	Signs/symptoms of ICP (projectile vomiting with headache, papilledema; bradycardia,m hypertension, respiratory depression, decerebrate or decorticate posturing

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

Box 3. Schema for managing ICANS by grade

Grade 1
Assess physical and neurologic status routinely per institutional standards; frequent monitoring of vital signs, strict intake and output measurement, daily weights
Aspiration precautions: elevate head of bed to at least 30 degrees to minimize 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 if CRS is present

Grade 2
Supportive care, neurological work-up 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 if associated with concurrent CRS
Consider transfer to ICU if ICANS associated with grade ≥2 CRS

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)
Neurologic consult and consider repeat neuroimaging (CT or MRI), EEG and if patient has persistent grade ≥3 ICANS

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

Grade 5 ICANS
Clinically, Grade 5 ICANS is defined as death due to ICANS where another cause is not the principle factor leading to this outcome

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

Box 4. Multidisciplinary management of older/frail patients with ICANS

Older/frail patients may be at risk of prolonged deconditioning and corticosteroid-induced myopathy following treatment of ICANS. Geriatric assessment, physiotherapy, nutritional support, and rehabilitation are recommended in this vulnerable population (Lin 2023).

of CAR T cells and treatment options, such as T cell-targeted therapies or the interferon gamma (IFNγ)–blocking antibody emapalumab should be considered (Hines 2023).

Nurses play a key role in monitoring and assessing to identify changes in the patient's clinical condition.

- Monitoring of complete blood counts, renal function, and infection should be performed routinely.
- Supportive care, administration and monitoring of fluids, antibiotics, transfusions, and organ-specific interventions.

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 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).

Multidisciplinary management

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

Hypogammaglobulinemia, B-cell Aplasia and the Risk of Infection

Bacterial infections are more frequent in the early period post infusion whereas viral infections generally occur later (Kampouri 2022). Infection, but not relapse, CRS, or ICANS, was the cause of mortality in 50.9% of patients according to a systematic review/meta-analysis (Cordas dos Santos 2024). 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). The most extensively investigated CAR T cell therapies are specific for the CD19 antigen, which is expressed on B cells. The ability of anti-CD19 CAR T cells to target malignant CD19-expressing B cells also results in destruction of normal B cells, frequently producing hypogammaglobulinemia. Hypogammaglobulinemia results in decreased antibody production increasing the risk of infections. Because CAR T cells can persist for years in patients, there is a long-term risk of infection secondary to long-term B-cell aplasia and hypogammaglobulinemia.

Hypogammaglobulinemia is a condition characterized by low levels of immunoglobulins (antibodies) in the blood, which impairs the immune system and increases the risk of infections.

Multidisciplinary management

Due to lack of randomized, controlled clinical trials on treatment of hypogammaglobulinemia and infection risk, recommendations are based on expert opinion, center specific experience, and infection-prevention approaches and strategies from other contexts, such as following hematopoietic stem cell transplantation. Initially, treatment for cytopenias using G-CSF was deferred until acute toxicities had resolved. Now, real-world evidence has shown that G-CSF can be given as early as the first week, or even prophylactically, without increasing the risk of CRS or ICANS or negative effects on CAR T-cell expansion. Most patients will either spontaneously recover their neutrophil counts or have improvement in counts following G-CSF (Rejeski 2024).

Box 5. Multidisciplinary interventions for management of hypogammaglobulinemia, B-cell aplasia and the risk of infection

- Institute institutional care standards for infection precautions if patient is at risk
- Educate patient/caregiver on infection risk and the importance of self-monitoring and early recognition of increasing severity.
- Provide patient/caregiver information on who to contact and when to contact should symptoms become worse.
- Attain and maintain close contact between treating and referring hospital/clinic to ensure the patient is properly supervised during all time points along the cancer journey.

Future Perspectives

Despite the significant advancements in CAR T cell therapy, challenges remain in managing cytotoxicity. The future of these products may depend on improved medical management of adverse events and the development of innovate gene therapy strategies to decrease adverse events. Ongoing research is focusing on enhancing treatment strategies to improve CAR T therapy safety. Some of these strategies are

Suicide strategies: To avoid unexpected side effects or eradicate transduced T cells in cases such as graft vs host disease or on-target off-tumor toxicity, the use of inducible safety switch genes that selectively and permanently eliminate CAR T cells could be effective.

Insertion of herpes simplex virus thymidine kinase (HSV-TK) into the CAR T cells to allow them to be targeted and eliminated if necessary using ganciclovir. This strategy may help address some of the safety concerns of CAR T cell therapy such as CRS.

Dual-targeted T cells that have been altered to express two CARs that recognize two cancer-specific markers with separate signals and exhibit significant cytotoxicity with minimal side effects on normal tissues (Golmohammadi 2025).

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).

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Quick Facts

- The occurrence and severity of delayed (generally occurring from 29 to 100 days post transfusion) and long-term (occurring beyond 90 days post transfusion) complications may be influenced by patient age, type and duration of prior therapies, underlying cancer type, and previously experienced treatment toxicities.
- 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
- 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
- Second malignancies are a late complication of CAR T-cell therapy. Therefore, regular and age-appropriate cancer screening should be performed along with periodic monitoring of blood counts to screen for therapy-related myeloid neoplasms.

Module V: Longer-term and Psychosocial Implications of CAR T Therapy

Module V: Longer-term and Psychosocial Implications of CAR T Therapy

Introduction

CAR T-cell therapy is associated with early side effects that have been documented and researched and have now, as a consequence, become increasingly manageable by protocol-driven treatment algorithms [see Module 3]. As the indications for CAR T-cell therapy are extended, and the number of survivors steadily increases, there is a greater need to improve understanding and develop preventative measures of the late and long-term outcomes of these therapies.

While the majority of toxicities secondary to CAR T cells are known to resolve within the first 30 days, some may persist beyond this time and a few complications may occur for the first time after 30 days. Common predictors of late toxicity are age, type and duration of prior therapies (i.e., chemotherapy, radiation, autologous or allogeneic stem cell transplant), underlying cancer type, the nature and severity of acute toxicities and features of the molecular structure of the CAR. Of note, late toxicities of CAR T therapy may differ based on the relevant tumor target and CAR molecular construct (Puckrin 2023).

Addressing these unique challenges is critical to optimizing quality of life, supporting mental well-being, and ensuring comprehensive care throughout the post-treatment journey. This discussion explores the multifaceted long-term and psychosocial effects of CAR T therapy, highlighting the need for ongoing research and tailored survivorship support.

Delayed and Longer-term Complications of CAR T-cell Therapy

Delayed or intermediate-term toxicities are generally defined as occurring from approximately 29 to 100 days after infusion. Long-term complications are generally characterized as those toxicities occurring beyond 90 days after infusion. Data from studies designed to investigate delayed and longer-term adverse events, especially in patients who are in long-term remission after CAR T-cell therapy, identify four commonly occurring complications: B cell depletion (aplasia), hypogammaglobulinemia, cytopenias, and infections (Table 1) (Cappell 2023). It is known that CAR T-cell therapy has long-lasting effects on the immune system. CD19 for example, continues to be expressed on non-malignant B cells and BCMA on non-malignant B cells. Long-lasting B cell depletion following CD19-targeted CAR T therapy occurs in 25% to 38% of patients several years after CAR T cell infusion (Cappell 2023). Similarly, prolonged immunoglobulin depletion, leading to persistent hypogammaglobulinemia, has been observed in patients who received BCMA-targeted CAR T-cell therapy.

The occurrence of late toxicities seen with CAR T-cell therapy may be driven or modified by previous anti-cancer treatments. While response rates and durable remissions are encouraging, on-going studies are indicated to assess the incidence of non-relapse mortality to determine if CAR T cell survivors are at increased risk of mortality compared to the general population (Puckrin 2024).

Prolonged cytopenias

Cytopenias (or immune effector cell-associated hematotoxicity) are a common acute toxic effect of CAR T treatment. Chronic cytopenias can persist ≥ 3 months after infusion and persistent neutropenia affects about 10% of patients. The incidence of grade 3 to 4 cytopenias at ≥ 3 months is approximately 15% in patients with B-cell lymphoma (Logue 2021). Ongoing grade ≥ 3 neutropenia (in 20%) and thrombocytopenia (in 47%) was observed in patients with multiple myeloma at 100 days after infusion of ide-cel (Munshi 2021). Chronic cytopenias have also been observed following treatment with cila-cel (Martin 2023). The risk of cytopenias is associated with higher-grade CRS, multiple previous lines of therapy, receipt of allogeneic HSCT ≤ 1 year prior to CAR T cell infusion, baseline cytopenia, and the presence of bone marrow malignancy (Brudno 2022).

Generally, cytopenias resolve with time and appropriate supportive care (Puckrin 2024).

Late infections

Recipients of CAR T-cell therapy are vulnerable to infection due to the effects of prior anti-cancer treatment on the immune system, corticosteroids, prolonged neutropenia, B-cell aplasia, and delayed T cell rebuilding. Despite CAR-induced changes to the immune system, the incidence of severe infections > 1 month after therapy is relatively low compared to the incidence in the first month after CAR T-cell infusion; the incidence of severe infections decreases over time (Cappell 2023).

According to a meta-analysis, more than half of all non-relapse deaths were attributed to infectious complications (50.9%). However, the causative pathogen was not specified for most fatal cases (Cordas dos Santos

Table 2. EBMT Recommendations for Tests to Monitor for Medium-term Complications

Test	Rationale
Prolonged cytopenia	Frequent monitoring of CBC with differential; G-CSF support and RBC and platelet transfusion as required. Provide self-monitoring checklist and emergency contact details; discuss activity pacing, return to work/school plans
Hypogammaglobulinemia	Monitor monthly immunoglobulin levels; IVIG if recurrent infections; Consider IVIG for IgG level <200 mg/dL especially if IgA level is also low; identification and correction of infections, nutritional deficits, and myelosuppressive medications
Infections	Frequent and comprehensive assessment for infection; Antimicrobial and pneumocystis prophylaxis and immunizations (i.e., acyclovir or valacyclovir for HSV and VZV) recommended for > 6-12 months; consider antimould, antibacterial, and hepatitis B virus prophylaxis for high risk patients; immunoglobulin replacement for patients with hypogammaglobulinemia; SARS-CoV-2 vaccination; annual influenza vaccination. Patient education on self-monitoring and early reporting to enhance early management, provide "red flag" symptoms of infection list, discuss infection precautions (avoid crowds, wear mask)
Secondary malignancies	Regular and age-appropriate cancer screening performed along with periodic monitoring of blood counts to screen for therapy-related myeloid neoplasms; frequent monitoring for MDS and skin cancers; Advise to wear sunscreen and avoid peak hours of sun exposure, refer to reliable internet sources (i.e., ACS) for information on identifying changes/abnormalities in skin lesions
Delayed neurotoxicity	Perform neurologic monitoring throughout the first month post-treatment, be aware of subtle changes; Refer to physical/occupational therapy if needed. Instruct patient not to drive for 8 weeks. Provide a list of cognitive/neurological changes to watch for; provide supportive care as for ICANS; Promote physical activity, adequate sleep, and cognitive training exercises.
Psychosocial	Screen for and offer supportive measures for patients experiencing mental health disorders using validated instruments to characterize symptom burden, QoL, and patient-reported outcomes. Refer to psychosocial services if needed.
Fertility	Consultation with fertility preservation specialist prior to lymphodepletion regimen; Recommend effective contraception for at least 6-12 months after lymphodepletion.
Autoimmune disorders	Perform history and physical exam at each follow-up visit. Provide a symptom diary template; discuss when to seek medical care
GVHD (patients with prior or subsequent alloHCT)	Frequent monitoring for signs and symptoms of acute and chronic GvHD. Provide GvHD education on skin, oral, and eye care; discuss escalation pathways for flares and who/when to contact healthcare providers

ACS, American Cancer Society; 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; ICANS, immune effector cell-associated neurotoxicity syndrome; IVIG, intravenous immunoglobulin; MDS, myelodysplastic syndrome; QoL, quality of life; RBC, red blood cells; VZV, varicella-zoster virus
Source: Puckrin 2024; Jain 2019; Buitrago 2019

2024). Also, infections predominated as the cause of death in the real-world setting to a greater extent than in clinical trials, and infections were the primary cause of non-relapse death regardless of the underlying cancer or CAR T-cell product administered (Cordas dos Santos 2024).

Second primary malignancies

In theory, secondary malignancies such as myeloid and T-cell malignancies, could occur from adverse gene integration events (insertional mutagenesis) (Cappell 2023). Data from large-cohort follow-up studies indicate an incidence of secondary malignancies after CAR infusion of between 4% and 16% (Cappell 2023), although these low numbers do not provide conclusive evidence of the risk of second malignancies after CAR T therapy (Elsallab 2024). According to a meta-analysis, second malignancies (most commonly myelodysplastic syndrome or acute myeloid leukemia) follow infections as the most common specified cause of non-relapse-related death after CAR T treatment; these authors also acknowledge the difficulty in identifying whether the previous treatment burden or CAR T therapy contributed to the etiology of a second malignancy (Cordas dos Santos 2024).

Although malignancies have been observed to develop as early as a few weeks following infusion, incidences cited above are not higher than those for patients previously heavily treated with chemotherapy. However, the risk was sufficient to lead the FDA and EMA to mandate that CAR T cell products include a written black box warning of an associated risk for secondary hematologic malignancies with CAR T products. [The FDA has eliminated Risk Evaluation and Mitigation Strategies (REMS) for CAR T-cell therapies. The products are still subject to safety monitoring through adverse event reporting requirements which include the reporting of second primary malignancies. See: FDA Eliminates Risk Evaluation and Mitigation Strategies (REMS) for Autologous Chimeric Antigen Receptor CAR T cell Immunotherapies | FDA.]

As CAR T therapies are extended to nonmalignant conditions, it will become increasingly important to track and identify the incidence of second malignancies to gain valuable insights for patient care and future development (Elsallab 2024).

Delayed-onset neurotoxicity

Approximately 10% of patients experience delayed onset ICANS with confusion and seizures occurring as late as 3 to 4 weeks after infusion (Neelapu 2018) and late neurotoxicity occurring as late as 6 to 9 months after treatment (Bader 2021). Symptoms include mood disorders, cognitive decline/impairment, cerebrovascular accident, and neuropathy. Risk factors possibly include severe ICANS or higher levels of baseline fatigue, anxiety, and depression.

The form and type of late-onset neurotoxicity differs according to the product administered. BCMA-targeting CAR T-cell therapy, for example, has been associated with delayed-onset parkinsonism-like symptoms (Karschnia 2025), which may not be reversible (Gust 2023). By comparison, acute-onset neurotoxicities might be fully reversible, whereas delayed-onset toxicities could have less favorable outcomes (Karschnia 2025). Hence, close monitoring and further research are essential to better identify, manage, and possibly prevent late neurological complications to improve long-term outcomes for CAR T recipients.

Of note, not only CAR T but also fludarabine-associated delayed neurotoxicity can occur. Symptoms include rapidly progressive visual disturbances, progressing to quadriparesis, dementia, peripheral neuropathy, blindness, coma, and death. Signs of acute toxic leukoencephalopathy are evident on brain MRI (Graham 2025).

Psychosocial effects

Numerous studies have revealed a significant burden of psychologic distress among patients who have received CAR T cells including frequent symptoms of anxiety, depression, and post-traumatic stress disorder (Puckrin 2024). Although patients may experience a short-term decline in quality of life (QoL) during the first 2 weeks after infusion, successful CAR T treatment can provide rapid, meaningful, and enduring QoL improvement [see following section].

Fertility

Little is known about the potential effects on fertility in women and men and the consequences of transmitting CAR T cells through placental transfer or breastfeeding are unknown. Further research is needed into the reproductive considerations of CAR T-cell therapy and the impact on a developing fetus. This research will be essential for counseling patients on fertility preservation options and for developing recommendations regarding pregnancy and breastfeeding following CAR T-cell therapy.

Organ dysfunction

Generally, late-onset organ toxicities are uncommon following CAR T therapy. However, severe CRS may lead to severe acute cardiopulmonary complications, which in turn may cause persistent cardiac dysfunction in patients with pre-existing risk factors. The cumulative effects

of prior chemotherapy, radiation, stem cell transplant, and corticosteroids may place patients at risk of delayed organ dysfunction.

Psychosocial Implications of CAR T-cell Therapy

Introduction

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 accumulated experience to coping 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. Prior to receiving CAR T therapy, patients reported experiencing a range of emotions and distress, including excitement, nervousness, anxiety, and emotional, physical, relational, and spiritual distress, according to a meta-synthesis (Xie 2024). Another 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). Similarly, at a median time of 3 years after CAR T therapy, at least half of interviewed patients reported feelings of anxiety, depression or cognitive difficulty (Ruark 2020).

CAR T therapies were previously administered in the inpatient setting due to the risk of CRS and ICANS. There is now movement toward administering these products in outpatient settings when it is determined from the patient's standpoint to be safe to do so. This is possible if several factors are considered, including the efficacy and safety profile of the product, patient and disease characteristics, center infrastructure, logistic aspects, economic implications, and regulatory considerations (Perez 2024). Driving this change in setting is the need to reduce healthcare costs, optimize resource utilization, and increase patient satisfaction and convenience (Oluwole 2024). Certainly, it will take some time until outpatient CAR T therapy becomes widely available and a majority of patients are eligible to undergo outpatient treatment. Still, many of the obstacles and hardships encountered by patients, families, and caregivers when treatment is delivered in inpatient facilities such as being away from home and support networks, could be overcome or minimized should outpatient treatment become standard care.

Psychosocial distress

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 National Comprehensive Cancer Network (NCCN), which allows patients to identify their level of distress using a scale from 0 to 10 (Ön 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).

Patients and their caregivers often conceal misunderstandings regarding their prognosis or hesitate to ask questions, which interferes with their ability to engage in informed decision making regarding their care (Odejide 2020). The updated EBMT guidelines (Graham 2025) recommend that all patients with planned CAR T-cell treatment should be offered a routine pretreatment psychological assessment or consultation that focusses on discussing the patient's thoughts and feelings about treatment and establishing the need for ongoing support. The EBMT recommendations stress using a validated patient-reported outcome tool to regularly collect information and monitor the patient's status. Longer-term, patients and families should be encouraged to participate in support groups (Grahan 2025), which offer emotional and moral support, as well as the opportunity to share experiences and foster a sense of community.

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 communicate their goals for care are more likely to receive care that is consistent with their preferences. Further, the 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 early-on in the care trajectory (Odejide 2020).

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. Because cancer is rarely experienced alone, survivorship frameworks explicitly include family

members, friends and care partners as part of the unit of care.

Psychological consequences of being a cancer survivor can include depression and anxiety, post-traumatic stress disorder (PTSD), fear of recurrence and return to work, concern over financial issues (Shapiro 2018), frustration, and difficulty planning for the future. 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).

Older patients are commonly part of the population of real-world studies and 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, older patients may respond that they value independent functioning and preservation of cognitive capabilities more than extending their length of life. The use of validated geriatric assessment tools specific for screening and identifying problems in older patients, such as cognitive deficits (e.g., the Modified Mini-Mental State Exam) and/or frailty (e.g., Clinical Frailty Scale), may be beneficial in identifying late effects of treatment and developing age-appropriate interventions in this population.

Health promotion is a foundation for improved health and wellness, and this is especially true for cancer survivors. Interventions aimed at promoting health may help to overcome the physiological and psychological problems experienced by cancer survivors (Lopez 2021). For example, exercise improves breast cancer survivors' physical and psychological functioning (Courneya 2002), Qigong was an effective nursing intervention to reduce fatigue (Hong 2003), and mindfulness training was shown to help cancer survivors better manage stress and emotions, and to feel more relaxed (Goei 2019). When considering wholistic health promotion, the availability and utilization of a social network that includes sources of emotional support was identified as an important factor directly related to better health-related quality of life (HRQoL) in adult cancer survivors (Gudina 2021).

Box 1: Health promotion interventions to support survivorship

- Weight management
- Regular physical activity and/or exercise
- A healthful diet
- Smoking cessation
- Reduced alcohol consumption
- Seek out and remain open to receive social and emotional support from family and friends.

Quality of life studies

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 QoL. Fear of recurrence, after having experienced relapse following two or more previous treatments, is comprehensible. While patients (and caregivers) obviously have hope for cure, realistically and medically, at the current time CAR T offers patients, in most cases, control of their disease for an undetermined period of time.

Key points from studies on QoL/HRQoL in patients who had received CAR T-cell therapy are mentioned below. While there are data from clinical trials, data from real-world settings are required to support informed shared decision-making.

- The symptom burden experienced by patients undergoing CAR T-therapy is substantial during hospitalization (week 4 after infusion), and is closely associated with a diminished QoL. The prevalence of self-reported fatigue in the study group was 89.7%, 79.4% reported sleep disorders and 66% a decrease in appetite. Authors recommend enhancement of symptom management interventions post-infusion (Dai 2025).

- Similarly, QoL, depression, anxiety, and physical symptoms worsened by 1 week post-infusion followed by improvements in QoL, psychological distress and physical symptoms by 6 months after CAR T-cell infusion (Johnson 2023).

- QoL improved or remained stable in the first year after CAR T. However active disease and a greater number of previous lines of therapy were associated with worsening QoL. Overall toxicity burden decreased up to day 180, with subsequent worsening at day 360 (Hoogland 2024).

- Improvement in HRQoL was clinically relevant at 3, 6, and 12 months. Improvement in global HRQoL, fatigue, and anxiety was clinically relevant, although 20% to 40% of patients experienced persistent fatigue, psychological distress, and cognitive

complaints over time (Perthus 2024), underscoring the need for support beyond the early post-treatment period.

- Patient reported outcomes indicated median time to sustained worsening of symptoms was significantly longer in patients treated with cilta-cel versus standard treatment; although health scores decreased within the first 6 months after treatment, by 12 months post-treatment a higher proportion of patients treated with cilta-cel reported a clinically meaningful decrease in their total symptom burden and a clinically meaningful increase in their global health score (Mina 2025).

- Patient reported outcomes at about 18 months post-treatment identified significant and clinically meaningful improvements in fatigue, pain, and physical functioning compared with the standard treatment regimen group. Ide-cell improved both the quality and duration of survival in heavily pretreated, relapsed/refractory multiple myeloma. Following CAR T therapy there was improvement of QoL vs stabilization of QoL with standard treatment (Delforge 2024).

Addressing the needs of caregivers

Patients receiving CAR T cells are required, at most institutions, to have a caregiver present during their recovery period. 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).

The needs of the caregiver change with the changing needs of the recipient of care. Still, some problems are predictable such as fatigue, insomnia, loss of appetite and weight, anxiety, and lost income (Girgis 2013), and caregivers often experience significant levels of burnout and emotional exhaustion. Caregivers are less likely than patients to use mental health services despite high levels of distress. In the first published study of CAR T caregivers, for example, worse patient health status was associated with worse caregiver depression and distress over time (Barata 2021). Similarly, a newer study observed that caregivers reported QoL impairments that did not change over time such as clinically significant depression and anxiety symptoms (Barata 2024). However, those caregivers with greater emotional coping with prognosis experienced fewer symptoms of anxiety and those who were able to adapt to the situation displayed less psychological distress. Overall, it seems that caring for a patient receiving CAR T has an intense impact on caregivers' QoL and that they should be provided with proactive support.

Early identification and referral to appropriate support, such as a social worker or psychologist, is recommended for caregivers. Those interventions aimed at providing emotional support strategies can improve psychological distress in caregivers (Treanor 2020) and in particular, interventions that promote emotional coping with prognosis may be beneficial (Barata 2024). Study results 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 and, accommodations if treatment does not take place locally, can be prohibitive. Some consequences of the financial burden of cancer are:

- Medication non-adherence

- Poorer health-related QoL, mental health, and satisfaction with social activities and relationships

- Depletion of financial savings, declaration of bankruptcy, which is associated with an increased risk of mortality (NCI, 2018).

Patients and their families should be encouraged to seek financial advice and be provided with resources that may provide assistance (Box 2). Coverage of treatment and associated costs varies greatly between countries and individual insurance carriers and should be investigated prior to the initiation of treatment.

Box 2. 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 should take place at the outset of treatment.
- Patients should be referred to and encouraged to use financial assistance resources.
- Perform on-going assessment of patient/caregiver for psychosocial sequelae of financial burden of treatment including fear of recurrence and refer to psychosocial services as appropriate

Adapted from: Buitrago, 2019

The future of CAR T therapy depends not only on scientific breakthroughs, but also on reorganizing supply chains, logistics, and increasing manufacturing of CAR T products, all of which may positively impact the cost of treatment. According to a recent business analysis, the industry is moving toward achieving a cost of USD 30,000 per dose of CAR T (KPMG 2025) as opposed to the present average cost of outpatient treatment of USD 414,393. The recommendations to achieve a lower cost per dose include

- Optimizing treatment centers and logistics capacity: regularly assess capacity and adapt to growing demand, possible initiation of point-of-care and/or on-site manufacturing of CAR T cells
- Achieving operational excellence: optimize operational processes, create flexibility to adapt to future technologies
- Ensuring economic viability: balance costs while maintaining quality and innovation (KPMG 2025).

Research findings indicate that CAR T-therapies tend to be overall more effective than comparator treatments. More evidence, especially evidence obtained in cost-effectiveness studies, is needed to better understand the value of CAR T in diverse patient populations.

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Notes

Quick Facts

- CAR T-cell therapy represents a favorable shift in the treatment of refractory-relapsed B-cell ALL in children and young adults but is associated with unique and potentially 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 is essential to 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, and these improvements in QoL continued throughout 36 months of follow-up

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

[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 longer-term care.

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

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 (HSCT) (NCIa 2021).

About 2% to 3% of patients experience 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 2021). 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 Philadelphia (Ph) -negative disease (NCIa 2021). 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 patients with refractory B-ALL disease or those in second or subsequent relapse (NCIa 2021). 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. To date, only one product, tisagenlecleucel (tisa-cel, a CD19-targeted agent), has been approved in children, adolescent and young adults (AYA) 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). At present, the development of CAR T-cell therapies for children and AYA patients has not progressed as rapidly as for adults.

Study results

The pivotal phase 2, multicenter study, ELIANA, conducted in pediatric and AYA 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.**

In the follow-up of the ELIANA trial, tisa-cel provided an overall remission rate of 81% with 59% of children and AYA patients remaining relapse-free at 12 months. The overall survival at 3 years was 63% (Laetsch 2022).

The median time to onset of cytokine release syndrome (CRS; see below), a life-threatening toxicity, in this population was 3 days (range: 1 to 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 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).

In the ELIANA follow-up study, no new adverse events or treatment-related mortality were observed. The proportion of patients with grade 3 or 4 events declined over time, and the most frequent grade 3 or 4 event occurring 1 year after infusion was infection (Laetsch 2022).

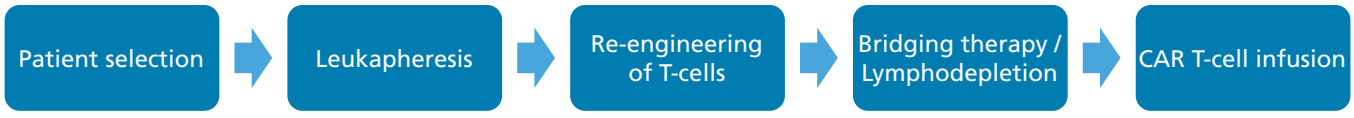

Figure 1. Steps in CAR T-cell therapy administration. CAR T-cell therapy is a type of treatment in which the patient's T cells are re-engineered in a laboratory, so they bind to cancer cells to kill them. The re-engineering involves the insertion of a gene for a receptor, chimeric antigen receptor (CAR), into the T cells. Millions of the CAR T cells are grown in the laboratory and then infused into the patient. The CAR T cells are able to bind to an antigen on the cancer cells to destroy them.

Table 1. Key results from the Phase 2 ELIANA Study in Pediatric, Adolescent and 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	

Patient Eligibility

Eligibility for CAR T cells should adhere to criteria stated in clinical trial protocols, governmental approved indications, or manufacturers' recommendations.

Consent for the treatment should include descriptions of the risks and benefits associated with leukapheresis, 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 infection

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 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.

Manufacturer suggested guidelines for leukapheresis 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.

Adverse events associated with leukapheresis

Citrate is used as an anticoaguloant during the leukapheresis procedure. In general, citrate anticoagulation is considered safe and serious side effects are uncommon. However, metabolic complications, such as citrate toxicity, can occur. Citrate toxicity symptoms must be promptly recognized and treated. 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.

[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/m2 x 4 days and the dose of cyclophosphamide is 500 mg/m2/day x 2 days. A comparison of dose intensity of cyclophosphamide on safety and efficacy (high dose cyclophosphamide at 3 gm/m2 and ≤ 1.5 mg/m2) suggests that dose intensity of conditioning chemotherapy has a positive impact on response without adding to toxicity (Curran 2019). 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

The information provided in this section is specific to the administration of CAR T-cell therapy in the pediatric population. Module 3 provides information that may be more appropriate to older (adolescents and young adults) patients.

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. Early identification of adverse events is also possible if the patient is treated as an outpatient and remains in close proximity to the treatment center and family caretakers receive and understand information on recognizing adverse symptoms and are knowledgeable and confident to contact healthcare professionals promptly as required. Outpatient infusion may have a positive impact on the patient's quality of life (QoL) and help reduce overall costs, especially those incurred due to hospitalization.

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.

Management of patients receiving CAR T cells

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

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

- Imaging of the brain
- Baseline ECG/EKG
- Availability of a 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
- Possibly 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 and/or institutional standards of care 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. 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 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 immune effector cell-associated neurotoxicity syndrome (ICANS), in pediatric patients requires detection of variations from baseline in heart rate, blood pressure, temperature and irritability, mood and cognition (Mahadeo 2019). Early detection and intervention for these toxicities may mitigate their morbidity and possibly mortality. The information provided in this section is specific to managing infants and children receiving CAR T-cell therapy. The information in Module 4 regarding monitoring and managing toxicities may be more appropriate for adolescents and young adults.

Generally, risk factors for toxicities, particularly CRS and ICANS, relate to higher levels of leukemic disease burden before infusion, CAR T-cell dose, activation, and expansion (Schultz 2020).

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. Typical onset is between 1 and 14 days post-CAR T cell infusion and duration is commonly between 1 and 10 days. While early detection of CRS may be challenging in pediatric patients, early diagnosis and prompt management can lessen the risks

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

of life-threatening sequelae. CRS is almost exclusively characterized by fever ≥ 38.5oC, hemodynamic instability, and hypoxemia.

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.

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 (≥ 380C) with or without constitutional symptoms, fatigue, or anorexia. Observational therapy to rule out infection, empiric antibiotics per local standards of care and symptomatic support with antipyretic drugs and intravenous fluids 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. Siltuximab has been used as a rescue drug for refractory CRS and in patients treated with tandem CD19/CD22 CAR T-cell therapies due to the high risk of CRS/ICANS development in these children and AYA patients (Galan-Gomez 2025). A suggested pattern for treating CRS is shown in **Figure 2**.

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

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; FiO2, 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.
1Fever is defined as temperature ≥38oC not attributable to any other cause. If fever is no longer present due to antipyretics or tocilizumab or corticosteroids, it is no longer required to grade CRS severity and CRS grading is driven by hypotension and/or hypoxia instead; 2CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5oC, 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 O2 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

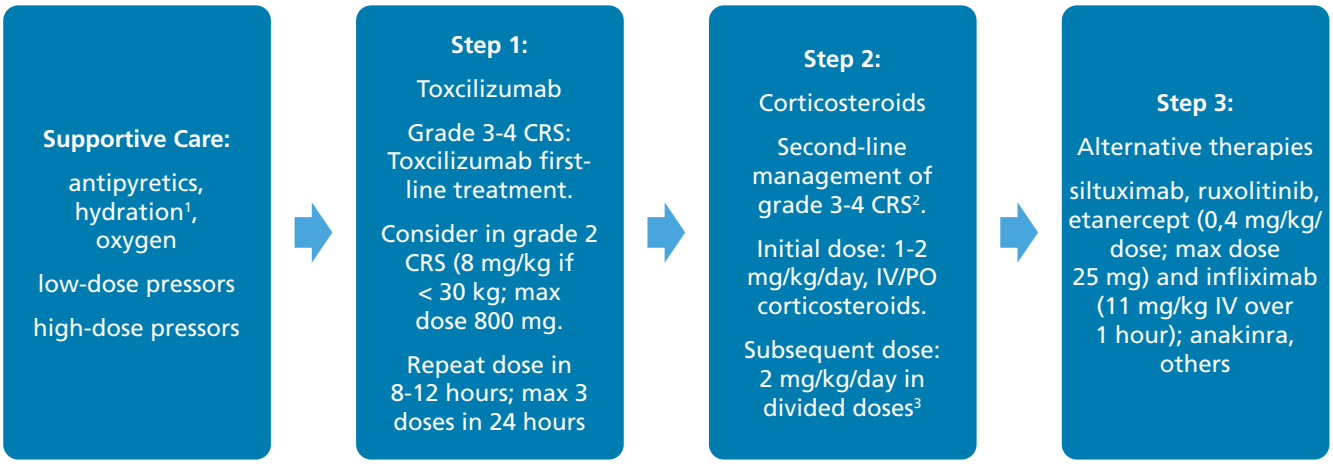

Figure 2. Stepwise treatment suggestions to manage CRS. [1] Defined as multiple fluid boluses for blood pressure support. Hydration status should be monitored closely to avoid overhydration and associated complications. [2] Grade 3 - 4 CRS defined as hemodynamic instability despite IV fluids and vasopressor 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

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 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.

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

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 CAR T-Cell 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. 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 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 HSCT and the potential for GvHD and other life-threatening toxicities.

The analysis of the ELIANA follow-up study compared QoL assessments at baseline and at least one post-baseline visit. Results indicated meaningful improvement in health-related QoL that began as early as 3 months after infusion and continued to improve through the subsequent 36 months (Laetsch 2022).

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

Steineck (2024) evaluated supportive care needs during CAR T therapy from the child and parent perspective. Most families remarked that it was a clear decision to proceed with CAR T-cell therapy, symptoms were tolerable, and the challenges they faced were primarily due to emotional and financial burdens of relocating and the unpredictability of navigating a novel therapy. Families pursuing novel cancer therapies are at risk for distress from decision making, symptoms, and uncertainty. Supportive care practices that minimize the impact of these risk factors and support hope, trust, and self-efficacy present opportunities to improve clinical care and patient and parent quality of life.

Longer-term Complications

There is little data on longer-term follow-up of pediatric recipients of CAR T-cell therapy. One unfortunate reason for this lack of data is the high and relatively early relapse rate in this population. Patients who do obtain remission with CAR T then receive additional treatment, including HSCT. A long-term study that followed patients for 4.8 years reported an overall survival of 10.5 months, and patients who achieved a complete response proceeded to a consolidative allo HSCT, those who did not experienced relapse (Shah 2021).

A few longer-term follow-up studies have investigated potential late adverse events including secondary malignancies, fertility, complications from prolonged B-cell aplasia and chronic sequelae of neurotoxicity. One study retrospectively evaluated outcomes at a median follow-up time of 6.7 years. Across this cohort, 2 patients developed a new primary cancer (papillary thyroid and cholangiocarcinoma), 4 a new neurologic disorder (including focus/attention, memory and problem-solving difficulties), 1 a significant infection, and 17 other illnesses (e.g., non-malignant tumors, endocrinopathies, chronic graft vs host disease) (Yates 2025). Although the study sample was small, these toxicities do not seem to be in excess of the toxicities experienced by pediatric patients who had a transplant without prior CAR T-cell therapy.

According to a global survey in which 22 pediatric cellular therapy experts contributed, there have been no reported cases of post CAR T cell malignancies, including insertional mutagenesis, in the pediatric B-ALL setting, and if there is a risk of secondary T-cell malignancy, the incidence is likely very low (Lamble 2024). These authors do recommend, that although secondary CAR-induced malignancies have not emerged as a major challenge for children and AYA patients over the first decade of CAR use, due to the seriousness of this risk, ongoing monitoring and longitudinal surveillance should remain a clinical standard.

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

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

Late effects of cancer treatment in pediatric patients

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 2021). 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 versus 19.8% among a sibling control group (Armstrong 2014).

Box 1. Common late effects of pediatric cancer treatment

- 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)

Although treatment advances have improved overall survival, the burden of late morbidity remains high for pediatric ALL patients (Mulrooney 2019). The prevalence of late effects of cancer treatment increases as time from diagnosis elapses (**Table 6**). Among adults who were treated for any type of cancer during childhood, late effects contribute to a high burden of morbidity including:

- 60% to more than 90% of survivors develop one or more chronic health conditions.
- 20% to 80% of survivors experience severe or life-threatening complications during adulthood.
- Morbidity accumulation is accelerated in young adult survivors of childhood cancer, compared with that of siblings and the general population. Accumulation of chronic diseases predicts risk of early mortality (Ebenshade 2023).

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

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

Disease recurrence is a significant problem in pediatric patients and 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 AYA with advanced ALL, evaluation of CAR T products that target both CD19 and CD22 protein, which is often overexpressed by ALL cells, are being undertaken to enhance clinical outcomes and overcome treatment resistance and antigen escape (Martinez-Gamboa 2025). The challenge remains in patients without a response to CAR T cells (,20%) or relapsing, representing approximately 40% to 50% of patients and occurring within the first 2 years after infusion, confirming the gap between early response and long-term survival (Dourthe 2025).

The package insert for tisa-cel provides broad dose ranges and various doses have been studied in real-world settings. An analysis of cell dose showed that higher doses of tisa-cel were not associated with increased toxicity, but did provide improved overall survival, event-free survival and relapse-free survival (Stefanski 2023). Another area of research is the use of allogeneic and other off-the-shelf strategies of CAR T-cell therapy to avoid contamination with tumor cells and better quality of the collected T cells. However, this strategy carries the risk of graft vs host disease and immune rejection.

CAR T products have been investigated in other hematologic malignancies in children and AYA. Real-world experience, for example, shows a benefit of tisa-cel in B-cell lymphomas in pediatric patients. A retrospective analysis revealed positive outcomes in these patients for whom few other treatment options exist. Overall response rate was observed in 10 patients, and 7 had a complete response. A majority of patients had CRS, only 2 (15%) with a CRS grade 3, and one patient experienced neurotoxicity grade 3. The authors conclude that tisa-cel

may be safe and efficacious in children and AYAs with relapsed/refractory B-cell lymphoma (Bender 2024).

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.

Several factors currently pose challenges to the development of pediatric CAR T products including complex production logistics, limited clinical site access, restrictive eligibility criteria, and financial constraints (Martinez-Gamboa 2025). Clinical trials for children and AYA populations face challenges in patient enrollment, trial design, and funding. By addressing these barriers, it may become possible to advance CAR T-cell therapy in pediatric oncology, improve outcomes, and ensure equal access to these innovative treatments (Martinez-Gamboa 2025).

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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

HNHCP
Haematology Nurses & Healthcare Professionals Group

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