CAR-T cell Therapy; Toxicities and Current aspects of Management

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Abstract

Chimeric antigen receptor (CAR) T cell therapy has redefined the treatment paradigm for hematological malignancies, offering remarkable remission rates and survival benefits. However, its clinical application is hampered by severe toxicities, notably cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), which pose significant management challenges. This review critically evaluates current toxicity profiles, elucidates underlying pathophysiological mechanisms, and assesses contemporary management strategies—including supportive care, corticosteroids, and cytokine inhibitors such as tocilizumab. Furthermore, we explore innovative approaches like dual CAR constructs, armored CAR-T cells, tonic signaling modulation, and the incorporation of suicide genes that promise to mitigate adverse effects while preserving therapeutic efficacy. By integrating emerging clinical evidence and novel therapeutic concepts, our analysis aims to inform future research directions and optimize patient outcomes in the evolving landscape of CAR T cell therapy.

1. Introduction

Chimeric antigen receptor T (CAR) T cell therapy has emerged as a groundbreaking immunotherapeutic approach for the treatment of hematological malignancies, including acute leukemia, lymphoma, and multiple myeloma.[1, 2] This therapy involves the genetic modification of patient-derived T cells to express CARs that target specific tumor antigens, such as CD19, CD20, and CD22, thereby facilitating more precise and robust immune responses against tumor cells. Despite its remarkable efficacy, CAR T cell therapy is frequently accompanied by significant toxicities that limit its broader application and impact patient outcomes. The most prominent adverse events include cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS), both of which can lead to severe and potentially life-threatening complications if not managed appropriately.

Current management strategies involve supportive care measures, corticosteroids, and cytokine inhibitors such as tocilizumab, which are tailored according to toxicity severity.[3] The assessment and grading of these toxicities vary significantly across clinical trials, which complicates management strategies. To address this issue, experts supported by the American Society for Transplantation and Cellular Therapy (ASTCT) have proposed standardized, objective definitions and grading systems for these toxicities (4). The grading systems can be calculated on the CARTOX app, which has been developed by the MD Anderson Cancer Center in the USA.

This review aims to synthesize current knowledge on the mechanisms underlying CAR T cell toxicities and to evaluate the efficacy of contemporary management strategies. By integrating clinical findings with novel therapeutic advancements we aim to provide a more comprehensive analysis of both the clinical challenges and the emerging solutions in the safe administration of CAR T cell therapy. Ultimately, this review seeks to inform clinical practice and guide future research toward mitigating toxicity while preserving the therapeutic benefits of this innovative treatment modality.

2. CART T Cell therapy overview

2.1 Structure of CAR T Cell

Chimeric Antigen Receptor (CAR) T cells are engineered immune cells designed to target and

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eliminate cancer cells. Their structure comprises four key components, as shown in figure 1.

A. Extracellular Antigen-Binding Domain – Typically a single-chain variable fragment (scFv) derived from antibodies, this domain enables specific recognition and binding to target antigens on cancer cells, ensuring selective cytotoxicity.

B. Hinge Region – Provides flexibility and optimal spacing between the antigen-binding domain and the transmembrane domain, facilitating efficient antigen engagement.

C. Transmembrane Domain – Anchors the CAR to the T-cell membrane, contributing to receptor stability and signal transmission.

D. Intracellular Signaling Domains – Responsible for activating the T cell upon antigen recognition. While first-generation CARs utilized CD3ζ alone, second and third generations incorporated co-stimulatory domains (e.g., CD28, 4-1BB) to enhance T-cell function. Fourth-generation CARs (TRUCKs) further enhance therapeutic potential by integrating cytokine-encoding transgenes.

2.2. Mechanism of CAR-T Cells in Hematological Malignancies

CAR T-cell therapy represents a transformative approach in the treatment of hematological malignancies, leveraging genetically engineered T cells to selectively target and eliminate cancerous cells. This innovative immunotherapy has demonstrated remarkable efficacy in conditions such as acute lymphoblastic leukemia (ALL) and chronic lymphocytic leukemia (CLL). The following sections outline the fundamental mechanisms underlying CAR T-cell therapy.

Genetic Engineering: Patient-derived T cells are harvested and genetically modified to express chimeric antigen receptors (CARs) that specifically recognize tumor-associated antigens, such as CD19 CD20, and CD22.[3]

Targeted Immune Response: Upon reinfusion into the patient, CAR T cells identify and bind to cancer cells, initiating their destruction through direct cytotoxic activity and cytokine-mediated immune responses.[5]

3.Toxicities of CAR- T Cell Therapy

3.1. Cytokine Release Syndrome

3.1.1. Pathophysiology of CRS

Cytokine release syndrome is the most common and severe toxicity, driven by overactivation of the immune response and endothelial dysfunction after administration of CAR T-cells.[6] It involves complex interactions between cytokines, immune cells, and the central nervous system, usually within days to a week after infusion, leading to severe clinical

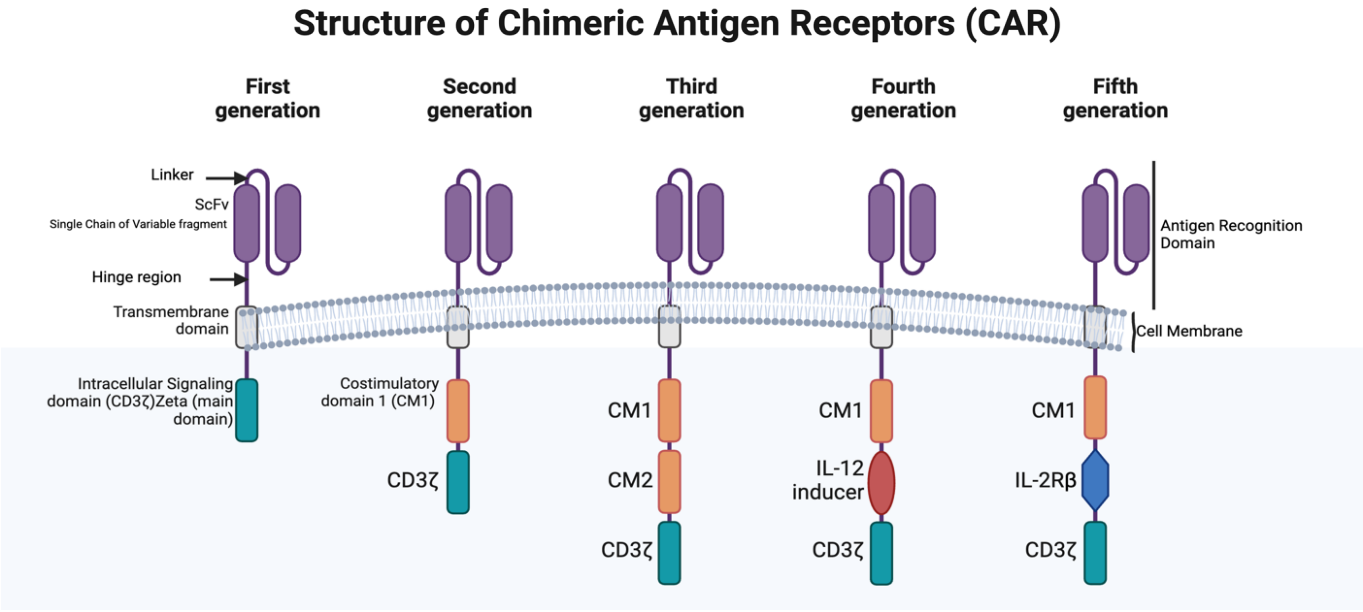

Fig. 1 : Schematic representation of the CAR T-cell structure, highlighting its key components, including the extracellular antigen-binding domain, hinge region, transmembrane domain, and intracellular signaling domains, which collectively enable targeted cancer cell recognition and activation.

manifestations.

The interaction of the CARs with their target on presenting cells leads to the activation and local expansion of the CAR T-cells, which triggers in-situ cytokine hypersecretion such as tumor necrosis factor α (TNF-α) and interferon-gamma (IFN-γ). As CAR T-cells expand in the peripheral circulation, a massive cytokine storm occurs, causing a solid systemic inflammatory response, with IL-6 being the major cytokine-driver.[7] Other cytokines involved are IL-1, the granulocyte-macrophage colony-stimulating factor (GM-CSF) and monocyte chemoattractant protein-1 (MCP-1), which, along with TNF-α and IFN-γ, play a role in migration and activation of macrophages and monocytes to produce IL-6. [8, 9]

3.1.2. Clinical Presentation of CRS

CRS usually presents with fever and constitutional symptoms such as rigors, anorexia, and fatigue. These symptoms can persist for several days and progress to severe CRS, with hypotension, hypoxia, and organ dysfunction.[6] Organ dysfunction may occur secondary to hypoxia or hypotension but can also result from the direct effects of cytokine release and includes cardiac, renal failure, and arrhythmia. Multi-organ dysfunction has been observed in patients with CRS. However, this is reversible or preventable in most cases if the symptoms and signs of CRS are promptly recognized and managed.[8] It has been observed that bispecific antibodies induced CRS occurs earlier compared to CAR T-induced CRS, within a few hours of administration, whereas CAR T-induced CRS is usually seen a few days after infusion when the cytokine release usually peaks.[6]

3.1.3. Diagnosis

The diagnosis of CRS is challenging, due to the nonspecific clinical symptoms and the lack of definite diagnostic testing. Patients require an extensive work-up to rule out any infectious process, including complete blood count, blood/urine cultures, and imaging if needed. IL-2, IL-6 and IFN-γ, although elevated, are not routinely measured. Inflammatory markers are elevated in CRS but are non-specific for diagnosis.[10] The diagnosis of CRS is mainly clinical, necessitating treatment with IL-6 inhibition (tocilizumab or siltuximab). CRS is graded on a scale from mild (grade 1) to life-threatening organ dysfunction (grade 4). A detailed grading and management of CRS is summarized in Figure 2.

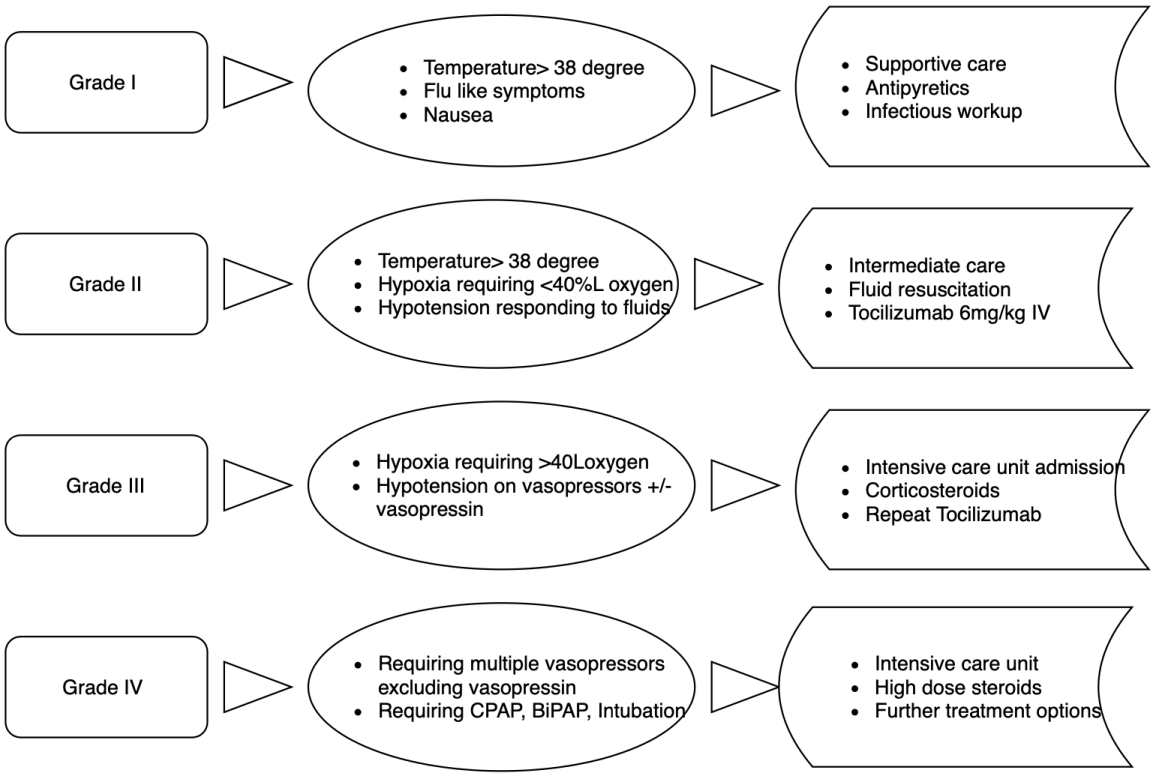

Fig. 2 : Depicting different grades of CRS and management strategies

3.1.4. Management of CRS

Supportive care with analgesics, antipyretics, intravenous fluids, pressors, supplemental oxygen and tocilizumab are sufficient for low-grade CRS.[11,12] Close monitoring in an intensive care unit (ICU) is often required, particularly in the first week following CAR-T infusion, as this is the critical period for the onset of CRS. In cases of severe CRS (Grade 3, 4) and CRS refractory to tocilizumab, steroids should also be administered to inhibit inflammatory cytokine production[12], but with caution, at the lowest possible dose, and for a short duration, due to potential negative impacts on CAR T-cell expansion and efficacy and therapeutic activity of bsAbs as well.[13] Other anti-cytokine agents for persistent and high-grade CRS include siltuximab (IL-6 inhibitor) or anakinra (IL-2 inhibitor), tumor necrosis factor (TNF) inhibitors (infliximab, adalimumab, etanercept), JAK-2 inhibitors (ruxolitinib), or other T-cell suppressing therapies such as anti-thymocyte globulin (ATG), cyclophosphamide (Cy), or cyclosporine may be used.[14]

3.2. Neurotoxicity

3.2.1. Pathophysiology

Neurotoxicity (NT) is another common toxicity, and its associated with CAR T-cell therapy. Most NT episodes in the KarMMa and CARTITUDE trials occurred near CRS; the most commonly reported symptoms were confusion and encephalopathy.[6] Acute early-onset NT is believed to be caused by immune effector cell–associated NT syndrome (ICANS), which is a well-described entity with CD-19 CAR T-cell therapies for B-cell acute lymphoblastic leukemia and non-Hodgkin's lymphoma.[6] The pathophysiology involves cytokine-induced endothelial activation with blood-brain barrier disruption and, thus, direct central nervous system (CNS) exposure to blood-circulating cytokines and inflammation. Microglia are then likely activated by cytokines migrating to the cerebrospinal fluid (CSF), triggering secondary cytokine production and local inflammation.

3.2.2. Clinical Presentation

The onset and duration of NT is highly variable. Early NT or ICANS is usually mild, and typical symptoms include confusion, delirium, transient aphasia, word-finding difficulties, agitation, hallucinations, tremors, dizziness, vertigo, encephalopathy, and polyneuropathy/nerve palsy. However, more severe symptoms that need immediate intervention, cerebral edema, obtundation, and seizures, have also been described. CRS often precedes ICANS, but sometimes, both entities can occur simultaneously.[15] In addition to CRS, other risk factors associated with ICANS development include high tumor burden, pre-existing neurologic conditions, and intensity of lymphodepletion chemotherapy.[16]

Apart from ICANS, non-ICANS late NT can occur, manifesting as movement and neurocognitive treatment-emergent AEs (MNTs). This usually develops after the recovery period from CRS and/or ICANS, a period that offers potential for significant improvement, and is irreversible.[17] A detailed grading and management of ICANS is summarized in Figure 3.

3.2.3. Prevention and management

It is important to perform a baseline patient evaluation, to rule out other underlying etiologies and other comorbidities. Hospitalization for CAR T-cell infusion is currently recommended for transfusional support, in addition to CRS/ICANS monitoring. Daily inpatient laboratory evaluation should include a complete blood count with differential, comprehensive metabolic panel, coagulation studies, CRP, lactate dehydrogenase, uric acid, and ferritin, however some patients with electrolyte wasting, coagulopathies or need for transfusion may need more frequent lab work.[6]

3.3. Infections

The incidence of infectious diseases in immunotherapy recipients is a significant concern, particularly due to the immunosuppressive effects of various therapies. Infections account for over 50% of non-relapse mortality cases in CAR T-cell therapy, driven by factors such as neutropenia and impaired immunity.[18,19] Approximately 66% of CAR T-cell therapy recipients experience infections post-treatment, with bacterial (52%), viral (30%), and fungal (10%) infections being the most common.[20,21] Risk Factors such as prior infections, number of previous therapies, and the presence of cytokine release syndrome (CRS) significantly increase the risk of post-therapy infections.[20, 21] Infection-

related mortality is notable, particularly with fungal infections, which have a mortality rate of 20%.[20] In contrast, while immunotherapy can lead to increased infection risks, some studies suggest that certain therapies, like blinatumomab, may have a lower incidence of infectious complications compared to traditional chemotherapy.[22]

Infection rates vary depending on the therapy type, with 19–69% of patients experiencing infections after CD19-directed CAR-T therapy and 42–69% after BCMA-directed CAR-T therapy. Although life-threatening infections are rare, several factors influence infection risk, including lymphodepleting chemotherapy, patient health status, and infection timing post-therapy. Notably, infection-related mortality, excluding relapse cases, accounts for approximately 50.9% of such deaths.[23, 24]

3.3.1. Pathophysiology and timing of infections

The excessive cytokine surge can lead to immune dysregulation, increasing infection risk, while severe CRS has been associated with immune paralysis, further exacerbating susceptibility to infections.[25] Another key factor is immune effector cell-associated neurotoxicity syndrome (ICANS). Managing ICANS typically requires high-dose corticosteroids, which, while effective for neurotoxicity, suppress the immune system. This immunosuppression increases the risk of opportunistic infections, including fungal infections and cytomegalovirus (CMV) reactivation.[26]

The risk of infection varies over time following therapy. During the first 30 days, patients are particularly vulnerable to bacterial infections, largely due to neutropenia caused by lymphodepleting chemotherapy, such as cyclophosphamide and fludarabine, as well as the direct immunosuppressive effects of the therapy. Many patients develop fever, often necessitating broad-spectrum antibiotics.[27] As cytopenias resolve, the risk shifts toward viral and fungal infections. Conditions such as prolonged B-cell aplasia and hypogammaglobulinemia, commonly observed after CAR-T and bispecific TCE therapy, further contribute to infection susceptibility. Close monitoring and timely management of these delayed infections are essential for improving long-term outcomes.[28]

Effective infection risk management requires a comprehensive approach, including antimicrobial prophylaxis tailored to the patient's risk profile and treatment timeline. Routine laboratory monitoring is essential for early detection of infections, while IVIG administration can help mitigate infection

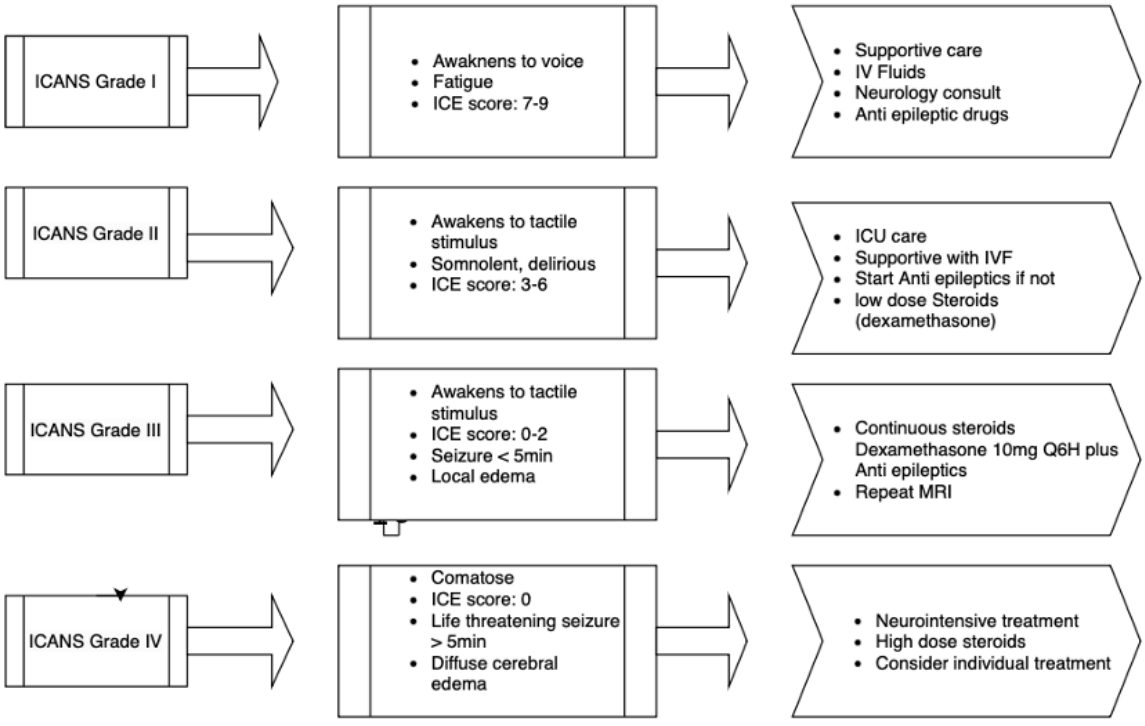

Fig. 3 : Depicting different grades of ICANS and management strategy

risks in patients with hypogammaglobulinemia.[29, 30] Additionally, patient education on recognizing and promptly reporting infection symptoms is crucial for timely intervention.

3.3.2. Screening, prevention, and management strategies

Given the heightened risk of infections associated with CAR-T therapies, implementing preventive measures and vigilant monitoring is essential to mitigate infection-related complications. A comprehensive patient history and thorough physical examination should be conducted before initiating therapy. If an active infection is detected, further evaluation is necessary, and treatment should be postponed until the infection is fully resolved.[6, 27]

A. Screening

Routine viral infection screening is recommended before starting CAR-T and bispecific TCE therapies due to the increased risk of reactivation, which can lead to severe complications.[31, 32] This includes HIV screening using the fourth-generation antigen/antibody combination immunoassay, as well as hepatitis B virus (HBV) markers, such as surface antibody (anti-HBs), surface antigen (HBsAg), and core antibody (anti-HBc), along with hepatitis C virus (HCV) antibody testing. If HBsAg is positive, HBV DNA testing should be performed. Additionally, reflex nucleic acid testing is required for positive HIV and HCV antibodies. Treponema pallidum (syphilis) testing may be considered in patients with relevant risk factors for sexually transmitted infections.[33, 34]

Additional screening should be tailored to individual risk factors. Patients not receiving acyclovir prophylaxis should be tested for varicella-zoster virus (VZV IgG) and herpes simplex viruses 1 and 2 (HSV-1 and HSV-2 IgG). Serologic testing for CMV and human T-cell lymphotropic virus type 1 (HTLV-1) may also be considered for high-risk population, while toxoplasma gondii serologies should be checked in patients with prior exposure.[6, 35]

Furthermore, the use of high-dose corticosteroids and/or tocilizumab for severe CRS and ICANS increases the risk of latent infection reactivation.[36] In patients from endemic regions or those with a history of exposure, Mycobacterium tuberculosis testing is recommended, though results should be carefully interpreted, particularly in cases of severe lymphopenia or prior lymphodepleting therapy.[35] Additionally, in patients from tropical or subtropical regions, serologic testing for Strongyloides stercoralis antibody or empiric treatment with ivermectin should be considered to prevent hyperinfection syndrome.[34]

B. Prevention

Due to the lack of clinical trials on prophylactic antimicrobial use during immunotherapy, standardized guidelines are currently unavailable. Existing recommendations are based on expert opinions and extrapolated from antimicrobial prophylaxis data used in stem cell transplantation protocols.[35, 37, 38]

Antibacterial Prophylaxis

The routine use of antibacterial prophylaxis remains controversial. In inpatient settings, some centers prioritize close monitoring, initiating intravenous antibiotics only in cases of febrile neutropenia. In contrast, in outpatient settings, prophylaxis with fluoroquinolones, such as levofloxacin (500–750 mg oral daily) or moxifloxacin (400 mg oral daily), may be considered during severe neutropenia. For patients with contraindications to fluoroquinolones, an alternative option is third-generation cephalosporin prophylaxis, administered until absolute neutrophil count (ANC) recovery > 0.5 $x10^9$/L for two consecutive days. [33, 34, 38]

Antiviral Prophylaxis

To prevent HSV and VZV infections, prophylaxis with acyclovir (400 mg oral twice daily) or valacyclovir (500 mg oral twice daily) is recommended. Prophylaxis should be initiated at the start of bispecific TCE therapy or lymphodepleting chemotherapy for CAR-T and continued for at least six months post-CAR-T infusion or throughout the duration of bispecific TCE therapy.[22, 27, 30] Currently, there is limited evidence supporting routine prophylaxis for CMV, human herpesvirus 6B (HHV-6B), and Epstein-Barr virus (EBV). Infectious disease (ID) consultation is advised for patients with seropositive CMV and a rising viral load. Routine serologic testing for CMV, HHV-6B, or EBV is not generally recommended, except in specific cases such as patients who received a stem cell transplant within one year prior to CAR-T or bispecific TCE therapy or those with a history of

significant immunosuppression.[6, 35, 38]

Hepatitis B and C Prophylaxis

Given the potential for fatal HBV reactivation in patients receiving B cell-directed therapies, entecavir (0.5 mg once daily, oral) is recommended for patients who test positive for HBsAg or have detectable HBV DNA. Prophylaxis should begin with bispecific TCE therapy or lymphodepleting chemotherapy for CAR-T and continue for 6–12 months post-CAR-T infusion or while the patient remains on bispecific TCE therapy.[33, 34] For patients with negative HBsAg but positive anti-HBc (chronic HBV carriers), management options include either entecavir prophylaxis or active monitoring, with HBV DNA and serum alanine aminotransferase (ALT) levels checked every 1–3 months.[33, 34]

Patients with chronic hepatitis C virus (HCV) infection should be referred to a hepatologist for further evaluation and management. Given the limited data on CAR-T and bispecific TCE therapy in HIV-positive patients, an ID consultation is recommended before and during immunotherapy. The primary goal is to maintain continuous antiretroviral therapy (ART) with minimal interruptions.[6, 35]

Antifungal Prophylaxis

Fluconazole (200 mg oral daily) is the preferred antifungal prophylaxis during periods of severe neutropenia (ANC $< 0.5 \times 10^9$/L) and should be continued until neutrophil recovery. For patients with contraindications to fluconazole, micafungin (50 mg IV daily) serves as an alternative. In cases of severe and prolonged neutropenia (>3 weeks), a history of significant immunosuppression, or CRS, the use of mold-active antifungal prophylaxis may be warranted.[34, 38]

Additionally, prophylaxis against Pneumocystis jirovecii pneumonia (PJP) is recommended using trimethoprim-sulfamethoxazole (1 double-strength tablet, oral, three times weekly). Prophylaxis should begin at treatment initiation with bispecific TCE therapy or after ANC recovery ($> 0.5 \times 10^9$/L), typically by day 28 post-CAR-T infusion, and should continue for at least six months or until CD4 count exceeds 200 cells/mm³. For patients with sulfa allergies, alternative regimens include atovaquone (1500 mg oral daily), dapsone (100 mg oral daily), or aerosolized pentamidine (300 mg once monthly).[33, 34]

Hypogammaglobulinemia

HGG is a common treatment-related complication of CAR-T therapies and represents an independent risk factor for infections. Serum immunoglobulin (Ig) G levels should be assessed before treatment initiation and closely monitored during the first three months of therapy.

While the routine use of IVIG replacement remains controversial, supplementation with 400–500 mg/kg IVIG every 3–4 weeks is recommended when IgG levels fall below 400 mg/dL, aiming for a trough level > 600 mg/dL. For patients with IgG levels between 400–600 mg/dL, IVIG may be considered in cases of severe or recurrent infections, particularly those affecting the sinopulmonary tract.

Patients with IgG levels above 600 mg/dL who experience recurrent or severe infections should undergo further evaluation, including measurement of total IgG, IgA, and IgM, as well as CD19+ and CD20+ B-cell counts and IgG serotypes for Streptococcus pneumoniae, tetanus, and diphtheria. If protective immunity is insufficient, IVIG supplementation or vaccination challenge may be considered.[33-35, 37, 38]

C. Management of Infections

Patients presenting with signs or symptoms of infection should undergo a comprehensive diagnostic evaluation, including blood cultures, urinalysis, urine culture, stool studies, or Clostridium difficile testing if diarrhea is present. Sputum culture, multiplex viral polymerase chain reaction (PCR), SARS-CoV-2, or Influenza PCR should be performed based on clinical presentation. If indicated, further imaging studies, such as chest radiography or dedicated computed tomography (CT) scans of the chest or abdomen, may be necessary. Empiric broad-spectrum intravenous antibiotics with anti-pseudomonal coverage, with or without vancomycin, should be initiated promptly. Early ID consultation is typically recommended. Once an infection is confirmed through clinical, microbiological, or imaging findings, antimicrobial therapy should be adjusted accordingly. However, if no infection is confirmed and the patient has been afebrile for over 48 hours, discontinuation of antibiotics should be considered. CAR-T therapy should be delayed until the infection is fully resolved.[6, 33, 34]

D. Vaccinations

Vaccination plays a crucial role in preventing severe infections, though patients undergoing CAR-T or bispecific TCE therapy often exhibit a reduced immunologic response compared to immunocompetent individuals. To optimize protection, seasonal inactivated influenza and SARS-CoV-2 vaccines are recommended at least two weeks before initiating bispecific TCE therapy or lymphodepleting chemotherapy for CAR-T. For patients in disease remission who do not require additional therapy, inactivated vaccines can be administered six months post-treatment, while live and non-live adjuvant vaccines are recommended one year after therapy completion. Additionally, the SARS-CoV-2 vaccine may be given three months post-CAR-T infusion or bispecific TCE therapy.[6, 33, 35]

Due to immunologic deficits following CAR-T therapy, re-vaccination is advised for Streptococcus pneumoniae, Clostridium tetani, Bordetella pertussis, Corynebacterium diphtheriae, hepatitis A virus, and HBV (HBV in the absence of seroprotection). Conjugated vaccines are preferred over polysaccharide vaccines due to their superior immune response in immunocompromised patients. Shingrix vaccination is recommended for adults over 50 years old with a history of chickenpox, shingles, or VZV seropositivity.[35]

Stem cell transplant (HCT) history also influences vaccination recommendations in CAR-T recipients. Patients who never received HCT or those who completed the post-HCT vaccination series do not require additional vaccines if they remain seropositive for the first post-CAR-T vaccine series, which includes DTaP, pneumococcal conjugate vaccine, and hepatitis A or B vaccines. However, HCT recipients who did not complete the post-HCT vaccination series but achieved seropositivity after initial post-CAR-T vaccination should complete the remaining post-HCT vaccines. For patients without a positive immune response to post-CAR-T vaccines, vaccination should be deferred until immune reconstitution occurs.[34]

Additionally, travel vaccines should be considered for patients planning to visit endemic regions, following consultation with an ID specialist.[37] Lastly, seasonal immunization against SARS-CoV-2 and influenza is also recommended for caregivers of patients undergoing CAR-T or bispecific TCE therapy.[33, 37]

3.3.3. Distinguishing CRS/ICANS from Infection

Given the clinical overlap between CRS, ICANS, and infections, initial management should focus on ruling out an underlying infectious process. Moreover, therapeutic agents used to manage CRS and ICANS, including corticosteroids, tocilizumab, and second-line treatments such as anakinra or siltuximab, can further increase the risk of opportunistic infections, invasive fungal pathogens, latent viruses, or mycobacterium tuberculosis.[6, 39] As a result, a high index of suspicion is necessary, and targeted testing for these pathogens should be performed, particularly in cases of persistent or recurrent fever. Patients receiving more than three days of corticosteroids or more than one dose of tocilizumab for CRS or ICANS are at high risk for CMV reactivation. Therefore, either weekly CMV surveillance for 4–6 weeks post-immunosuppressive treatment or prophylaxis with a mold-active antifungal agent is recommended to reduce infection risk.[34, 38]

3.4. Other toxicities

3.4.1. Hemophagocytic lympho histiocytosis (HLH)

HLH represents a severe toxicity observed in both CAR T-cell and BiTE therapies for follicular lymphoma, stemming from excessive immune activation that may culminate in multi-organ failure. Notably, HLH occurs in approximately 14.8% of patients undergoing CD19-specific CAR T-cell therapy, with high disease burden serving as a critical risk factor(40). Clinically, HLH manifests as profound immune dysregulation, cytopenias, and organ dysfunction, with treatment frequently necessitating aggressive immunomodulatory interventions such as dexamethasone and etoposide.[41] Despite these measures, mortality rates can reach 69.9%, and affected patients typically exhibit diminished response rates and overall survival.[40]

3.4.2. Tumor Lysis Syndrome (TLS)

Tumor lysis syndrome is an important consideration, especially in patients with high tumor burden. TLS results from rapid tumor cell destruction, leading to metabolic disturbances, such as hyperuricemia, hyperkalemia, and hypocalcemia. In the ZUMA-5 trial for Axi-cel, TLS was reported in 4% of patients

The ELARA trial for Tisa-cel reported a lower incidence of TLS at 2%, while mosunetuzumab, had a TLS incidence of 3%.[42-44] Epcoritamab showed similar results, where TLS occurred in 3.5% of patients.[45] Preventive measures, such as aggressive hydration and uric acid-lowering therapies, were specifically implemented to mitigate the risk of TLS.[46]

3.4.3. Organ Toxicities

Organ-specific toxicities such as hepatotoxicity, gastrointestinal and kidney dysfunction are primarily driven by immune activation secondary to CRS and off-target effects. Diarrhea is a commonly reported adverse effect in patients undergoing both CAR-T cell and BsAb therapies. In the ELARA trial for Tisa-cel, diarrhea was observed in 15% of the patients, primarily as a low-grade event.[43] Similarly, in the EPCORE NHL-1 trial, diarrhea occurred in 18% of the patients treated with epcoritamab.[45]

Elevated transaminase levels have been reported in 10% of Axi-cel patients (ZUMA-5 trial) and 6% of Tisa-cel patients (ELARA trial), with most cases being low-grade and manageable with supportive care.[43, 44] The EPCORE NHL-1 trial reported grade 3 or higher liver enzyme elevations in 5% of patients with epcoritamab, managed with dose modifications and supportive care; Mosunetuzumab, in the GO29781 trial, showed 3% of patients with grade 3 or higher liver toxicities.[42, 45] Kidney dysfunction, although less common, often results from complications such as CRS or TLS.[46]

3.4.4. Serious Adverse Events

Serious adverse events (SAEs) encompass a broad range of severe outcomes that require medical intervention, such as hospitalization, drug treatment, or other forms of clinical care. In the context of clinical trials, SAEs include severe infections, organ toxicity, and neurotoxicity. SAEs have been frequently documented in clinical trials of CAR T-cell and BsAb therapies. The ZUMA-5 trial reported SAEs in 52% of patients treated with Axi-cel, including severe infections, organ toxicity, and neurotoxicity.[44] Similarly, the ELARA trial for Tisa-cel documented SAEs such as severe cytopenia, febrile neutropenia, and immune-related toxicities.[43.] In the EPCORE NHL-1 trial, 20% of patients experienced SAEs, predominantly infections and infusion-related reactions The trial for mosunetuzumab reported a 28% SAE rate, with serious infections and infusion-related reactions being the most common.[42, 45, 47]

For CAR T-cell therapy, beyond the early detection of cytokine release syndrome and neurotoxicity, there is a critical emphasis on identifying high-grade events, including cardiotoxicity,HLH,GI and skin toxicities which often correlate with more severe complications.[48] This necessitates rigorous and personalized monitoring approaches, such as the integration of circulating tumor DNA (ctDNA) assessments to inform timely interventions with agents like tocilizumab or corticosteroids.[49] Consequently, regular evaluations focused on response rates and mild adverse events are essential to optimize dosing and mitigate long-term risks.

3.4.5. Potential for Secondary Malignancies

The risk of secondary malignancies, although less common, is a concern regarding the delayed effect of CAR T-cell therapy. Long-term follow-up data from the ZUMA-5 trial indicated that a small percentage of patients (approximately 2%) developed secondary malignancies, including myelodysplastic syndromes (50); however the exact mechanism is not fully understood, although it is believed to be related to the genotoxic effects of prior therapies combined with CAR T-cell-induced immune dysregulation. Other studies have raised concerns regarding the development of secondary malignancies after CAR T cell therapy. Ghilardi et al. conducted a detailed analysis of patients who developed secondary cancers, and found that chronic immune activation and persistent inflammation might significantly contribute to secondary malignancy risk.[51] Their study highlighted the importance of monitoring inflammatory markers and immune activation over the long term to identify high-risk patients. Hamilton et al. focused on the emergence of secondary T-cell lymphomas and found that immune dysregulation following CAR T-cell therapy, particularly involving persistent T-cell activation and an imbalance in immune homeostasis, was linked to an increased risk of developing secondary lymphomas.[52]

4. Novel Therapies to Mitigate CAR-T Toxicities

Next-generation CAR-T therapies are currently being developed to mitigate the risk of toxicity and improve efficacy. Dual-targeting CAR-T cells,

Table 1: Comparative Incidence of Different Toxicities in CAR T-cell Therapies

Toxicity	Trial/Agent	Incidence (%)	Key Findings/Comments
Tumor Lysis Syndrome (TLS)	Axi-cel (ZUMA-5)	4%	Aggressive hydration and uric acid–lowering therapies implemented
	Tisa-cel (ELARA)	2%	
	Mosunetuzumab	3%	
	Epcoritamab	3.5%	
GastroIntestinal Toxicities – Diarrhea	Tisa-cel (ELARA)	15%	Primarily low-grade
	Epcoritamab (EPCORE NHL-1)	18%	
Hepato Toxicities – Elevated Transaminases	Axi-cel (ZUMA-5)	10%	Mostly low-grade and manageable
	Tisa-cel (ELARA)	6%	
	Epcoritamab (EPCORE NHL-1)	5% (Grade ≥3)	Managed with dose modifications
	Mosunetuzumab (GO29781)	3% (Grade ≥3)	
Serious Adverse Events (SAEs)	Axi-cel (ZUMA-5)	52%	Includes severe infections, organ toxicity, and neurotoxicity
	Epcoritamab (EPCORE NHL-1)	20%	Predominantly infections and infusion-related reactions
	Mosunetuzumab	28%	Serious infections and infusion-related reactions
Secondary Malignancies	Axi-cel (ZUMA-5)	~2%	Includes myelodysplastic syndromes; long-term risk from immune dysregulation

which can simultaneously recognize multiple tumor antigens, are being investigated as a means of reducing antigen escape and improving the long-term remission rates. These developments may pave the way for safer and more effective immune therapies that deliver sustained remission with fewer adverse effects.[53]

4.1. Dual CAR Constructs

These cells are designed to recognize multiple antigens and increase the activation threshold, potentially decreasing off-target effects and minimizing toxicity. Moreover, they can limit immune hyperactivation, lowering the incidence of toxicity.[54]

4.2. Armored CAR-T Cells

Armored CAR-T cells are engineered to produce immunomodulatory molecules, like IL-10, that can dampen the immune response. They suppress excessive cytokine release, protecting against severe CRS without compromising the therapeutic efficacy of the CAR-T therapy.[55]

4.3. Tonic Signaling Control

One mechanism leading to toxicity in CAR-T cell therapeutic signaling is that CAR-T cells are activated even in the absence of antigens. Modifications to the CAR design, such as incorporating inducible co-stimulatory domains or "on-switches," have been developed to limit tonic signaling.[55]

4.4. Incorporation of Suicide Genes

Suicide genes are being incorporated into CAR-T cells, and upon activation, CAR-T cells undergo apoptosis, effectively halting their activity in case of severe toxicity. This strategy provides a rapid and definitive means of managing life-threatening complications.[54]

5. Conclusion

CAR T cell therapy has revolutionized the treatment landscape for hematological malignancies, offering unprecedented remission rates and long-term survival benefits. However, the significant toxicities—primarily CRS and ICANS—pose considerable challenges that must be addressed to optimize patient outcomes. Standardized toxicity grading and prompt, tailored interventions remain critical to managing these adverse events effectively.

Emerging strategies, including dual CAR constructs, armored CAR-T cells, modifications to control tonic signaling, and the incorporation of suicide genes, represent promising advancements aimed at mitigating toxicity without compromising efficacy. Continued research and clinical trials are essential to validate these novel approaches and

refine management protocols, ensuring that the transformative potential of CAR T cell therapy is fully realized while minimizing its associated risks.

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