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# Influence of CAR T-cell therapy associated complications

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Since the introduction of chimeric antigen receptor (CAR) T-cell therapy, it has elicited an immense response in both targeted and residual cancers. Its clinical efficacy is often accompanied by a group of side effects that may become serious because of factors such as tumor burden, the extent of lymphodepletion, and the type of co-stimulus. It is also crucial to know the common toxicities associated with CAR T-cell therapy, including cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), cardiotoxicity, metabolic disorders, pulmonary toxicity, macrophage activation syndrome (MAS), prolonged cytopenia, coagulation disorders, and potential off-target effects on various organs. If not well managed, these can be fatal. However, knowledge about molecular pathways, calcineurin inhibitors, IL-6 receptor antagonists, steroids, suppression of nitric oxide synthase, various therapeutic approaches, and other recent advances have been developed to mitigate the fatal results of various short-term and chronic adverse events related to CAR T-cell therapy. This study provides a comprehensive perspective on contemporary management strategies and presumed causative processes of CAR T-cell-related adverse effects, albeit with several limitations. When CAR T-cell complications, costs, and challenges of toxicity management are properly considered, the CAR T-cell therapy of the future will include a number of toxicity-escaping options.

## KEYWORDS

CAR T-cell, immunotherapy, adverse of CAR-T, CRS, neurologic toxicities

## 1 Introduction

A novel approach called chimeric antigen receptor (CAR) T-cell immunotherapy amplifies T cells to combat cancerous cells. This potent immunotherapy targets cancer cells through accurate tracking with minimum risk to the healthy cells of the human body (1). In this approach, the chimeric antigen receptor (CAR) gene is fused into the genomic structure of the host cell by a viral vector, such as a retrovirus or lentivirus (Figure 1). This fusion of the CAR gene develops sustained transgenic expression. Chimeric antigen

receptors have the potential to detect, stimulate, and activate various receptor chains through the replication of genuine T cell receptors of a complex nature. CAR T cells can persist in the host circulatory system for a long duration and act as long-lasting memory cells. When cancer cells regenerate, they detect and eradicate them from the circulatory system (2).

Novel CAR T-cell therapy is widely considered a successful treatment against various blood and solid tumor malignancies. Despite that, its universal adoption is challenging due to adverse events (Figure 2) limiting the impressive early responses in clinical trials (3). In terms of the toxic effects (Figure 2) of this therapy, CAR T cells have particular toxicity due to their innate biological makeup (4). This study highlights the critical problems and toxicities resulting from CAR T-cell therapy and their revealed mechanisms are discussed to advance this approach or innovations in the domain of cancer treatment.

## 1.1 Cytokine release syndrome

The outstanding effectiveness of CAR T cells, however, has been associated with considerable potentially fatal toxicities, the most frequent of which is cytokine release syndrome (CRS) (5). CRS (Table 1) is caused by generalized immunological activation and is associated with significant increases in inflammatory cytokines such as granulocyte-macrophage colony-stimulating factor (GM-CSF),

interferon-gamma (IFN- $\gamma$ ), tumor necrosis factor-alpha (TNF- $\alpha$ ), and interleukin-6 (IL-6) (Figure 3). CRS is quite common, with a rate ranging from 60% to 93%, but grades 3 and 4 have rates as low as 13% to 14% (9). These increase the immune response via a cytokine chain that includes other immune cells. The subsequent cytokine storm causes elevated vascular permeability, activation of endothelial cells, and multiorgan dysfunction, which appears as hypotension, edema, neurotoxicity, and organ dysfunction (Figure 3). To manage CRS, medications such as tocilizumab target important cytokines, primarily IL-6, to diminish the inflammatory process and improve symptoms (6).

According to clinical trials, CRS initially causes fever in the patients following CAR T-cell treatment, and the fever duration is CRS grade-dependent (Table 1). Following the CAR T-cell therapy, patients with grade three or four CRS have a fever within 25 hours, while patients with a CRS grade lower than three experience a fever after 12 days (10, 11). Furthermore, the patients exhibit insufficient oxygen levels, low blood pressure, elevated heart rate, and various neurological abnormalities including language difficulties, impaired handwriting, and reduced focus abilities (12, 13). The levels of IFN- $\gamma$ , interleukin-2 receptor subunit alpha (IL2Ra), and soluble IL-6 serum indicators were found to determine the severity of CRS through a significant rise in severe CRS cases compared to those without the same severity (14). Severe CRS exhibits symptoms such as leakage of blood vessels, heart issues, impaired kidney function, accumulation of fluid in the lungs (pulmonary edema), abnormalities in blood clotting

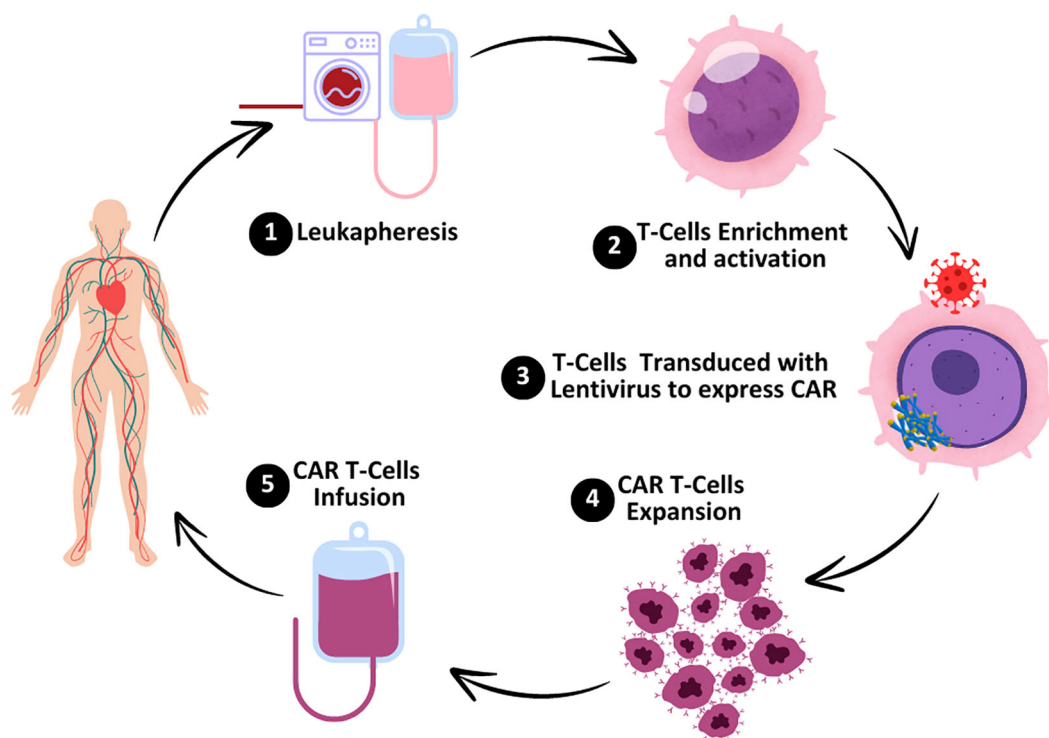
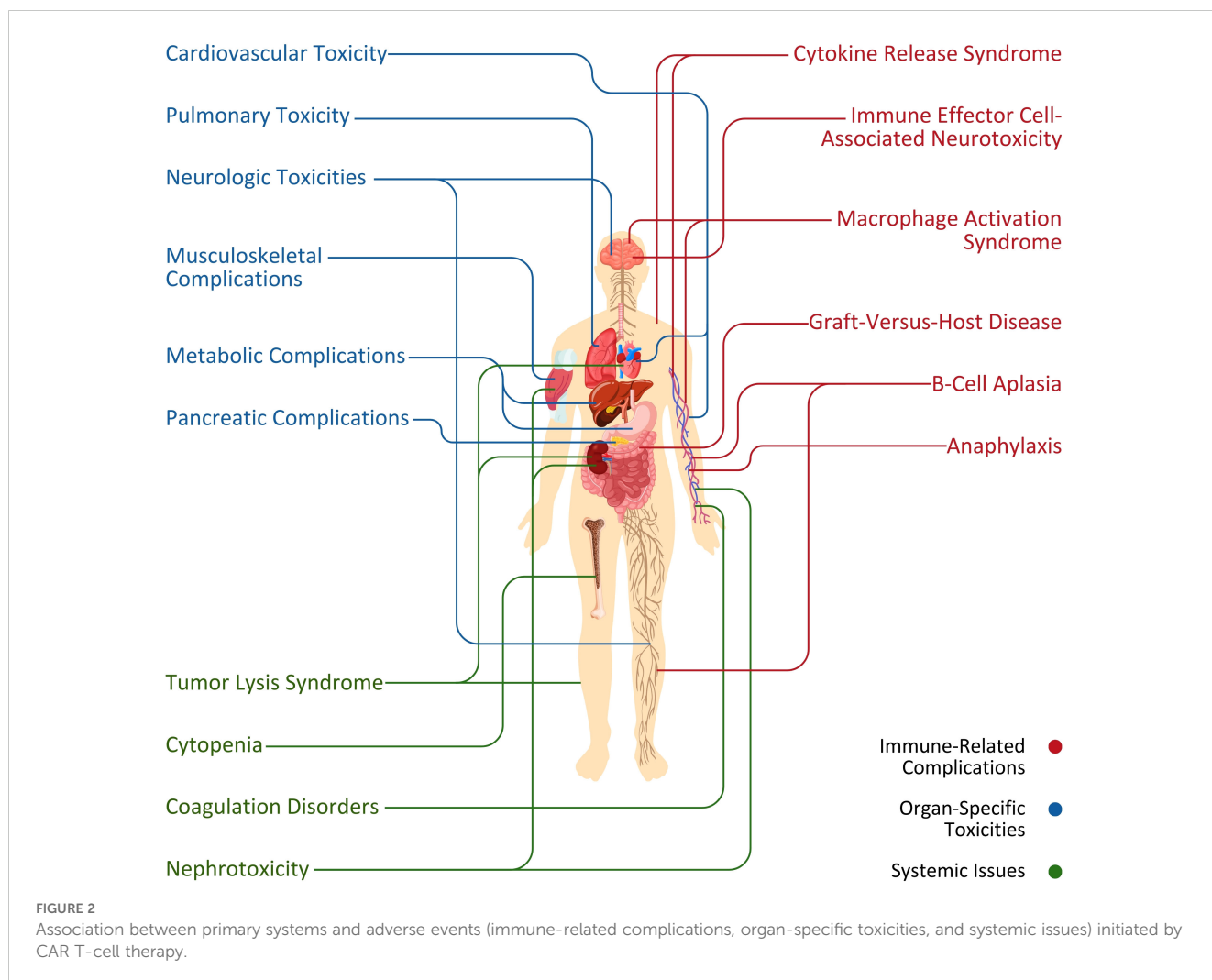


FIGURE 1

Preparation of CAR T cells. The process starts with leukapheresis, the process by which the peripheral blood is taken from the patient and T cells are isolated. T-cell enrichment and activation take place in the laboratory which enables the selection of T cells and stimulation. T cells are transduced with a lentiviral vector containing the gene of the chimeric antigen receptor (CAR) so that the T cell can identify and bind to specific cancer cells. In CAR T cells, there is a process of expansion where the cells divide and multiply in order to reach the necessary amount for administration. Finally, the genetically engineered CAR T cells are reintroduced into the patient's body to locate and kill cancer cells.



(coagulopathy), and hepatic failure (15). Park et al. (16) found severe CRS in 41% of patients with high disease stress, while only 5% of individuals with low disease stress exhibited CRS.

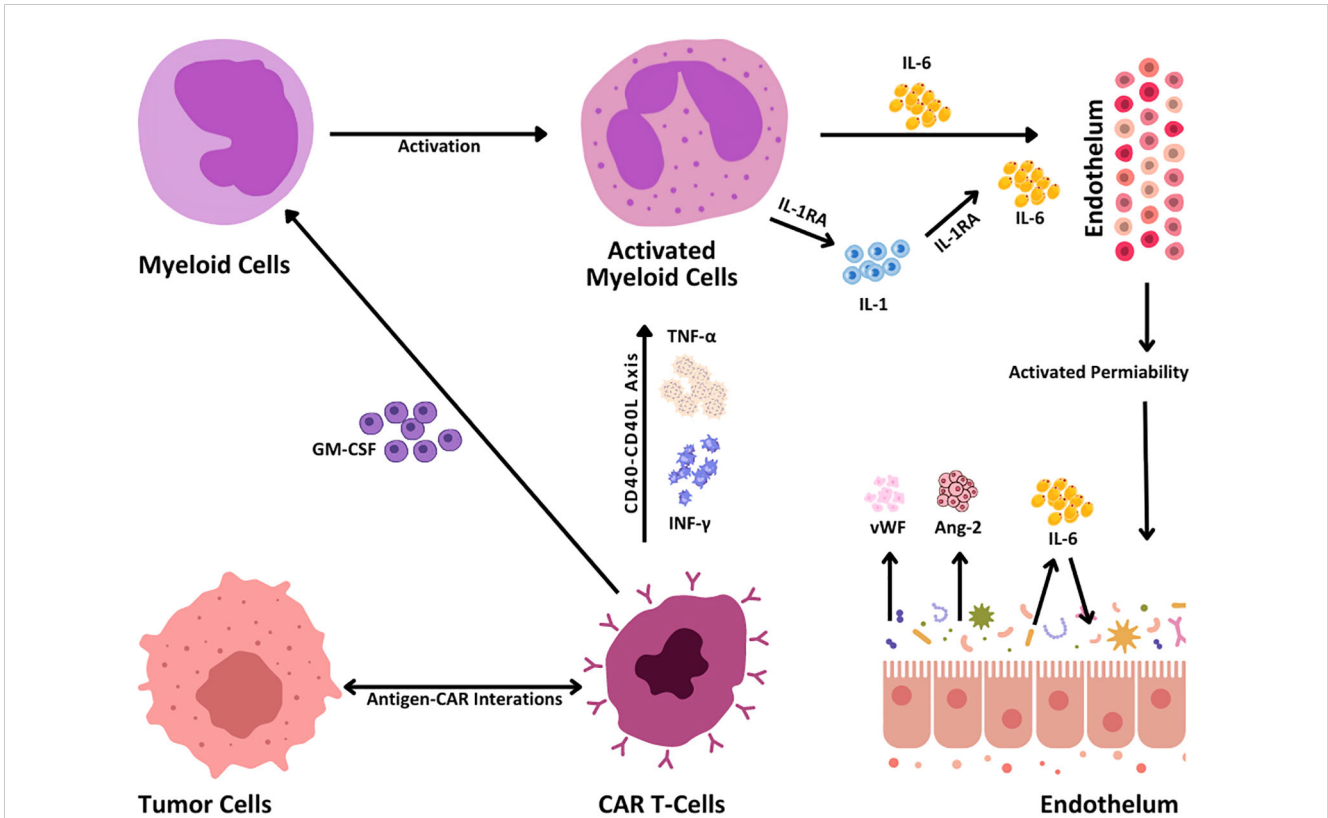
Early clinical studies using cluster of differentiation 19 (CD19) CAR T cells revealed considerably significant toxicities compared to the symptoms experienced in conjunction with further cellular therapies, demonstrating substantially widespread stimulation of the immune system (Table 2). The severity of CRS can vary significantly, with some patients experiencing mild symptoms while others develop life-threatening conditions (7).

New developments (48) in managing CRS in the past few years include knowledge about the molecular pathways and the evolution of the approach to their management, which is significant in the context of CAR T-cell therapy. This is mainly orchestrated through the activation of cytokines such as IL-6 and IL-1 from the immune cells, especially the macrophages and the monocytes. These cytokines cause the dangerous inflammatory reactions that define CRS: developed fever, hypotension, and organ damage. Existing approaches (4, 49) are focused on reducing the off-target effects without any impact on the effectiveness of CAR T-cell therapy. Calcineurin inhibitors are still strong cornerstones in the treatment of CRS and tocilizumab, an IL-6 receptor antagonist, still plays a big

role in its management. Inflammation decreases and patients' conditions improve due to the use of this treatment, though it is more useful in patients with mild to moderate CRS. However, IL-1 is likely to have a critical role in both CRS and its neurotoxic assets, which is referred to as cytokine release syndrome-associated

TABLE 1 Cytokine release syndrome.

<b>Pathogenesis</b>	T cells are activated when they recognize a tumor antigen
<b>Timing</b>	Symptoms might not appear until few days and even weeks following therapy, determined by the rate at which T cells activate (6, 7)
<b>CRS Grading</b>	Grade 1: Fever $\geq 38^\circ\text{C}$ ; Nausea; Flu-like symptoms Grade 2: Fever $\geq 38^\circ\text{C}$ ; Hypoxia requiring low-flow nasal cannula; Hypotension not requiring vasopressors Grade 3: Fever $\geq 38^\circ\text{C}$ ; Hypoxia requiring high flow or face mask; Hypotension requiring one vasopressor with or without vasopressin Grade 4: Fever $\geq 38^\circ\text{C}$ ; Hypoxia requiring positive airway pressure; Hypotension requiring multiple vasopressors (8)
<b>Mediator</b>	IL-6 is a crucial mediator
<b>Management</b>	Inhibiting the IL-6 pathway or using corticosteroids can alleviate symptoms



**FIGURE 3**  
CRS mechanisms. When engaging the tumor cells, CAR T cells become activated via the interaction between antigens and CARs that leads to the production of inflammatory cytokines such as TNF- $\alpha$  and interferon-gamma (IFN- $\gamma$ ). This cytokine release in turn activates the CD40-CD40L signaling pathway, reacting more prospectively to immune activation. When secreting granulocyte-macrophage colony-stimulating factor (GM-CSF), CAR T cells activate myeloid cells, and subsequently IL-1, IL-6, and interleukin-1 receptor antagonist (IL-1RA) are hence secreted. These cytokines act upon the endothelium and result in enhanced permeability of blood vessels. Furthermore, the release of Von Willebrand factor (vWF), angiotensin 2 (Ang-2), and IL-6 promotes endothelial activation responsible for tumor growth and immune response.

**TABLE 2** Fatality percentage for major issues induced by CAR T-cell therapy.

Major issues	Prevalence	Observed patients	Fatality	References
CRS	Oklahoma City, USA	1	After 12h	Afzal et al. (9)
	Pittsburgh, Pennsylvania	1	After 2 months	Marker et al. (6)
	USA	1	After 9 days	Pemmaraju et al. (17)
	Paris, France	48	22.92%	Belin et al. (18)
	Hannover, Germany	15	No	Möhn et al. (19)
	Victoria, Australia	53	No	Sales et al. (20)
	France	238	4.8%	Le Cacheux et al. (21)
	Washington, Pennsylvania	43	7%	Gazeau et al. (22)
	Rennes, France	190	No	Mauget et al. (23)
	California, USA	26	3.84%	Nie et al. (24)
	California, USA	359	39%	Locke et al. (7)
	USA	148	3%	Jacobson et al. (25)
	USA	269	0.37%	Abramson et al. (26)
USA	57	5.26%	Shah et al. (27)	

(Continued)

TABLE 2 Continued

Major issues	Prevalence	Observed patients	Fatality	References
ICANS	Paris, France	48	22.92%	Belin et al. (18)
	Hannover, Germany	15	No	Möhn et al. (19)
	Victoria, Australia	53	No	Sales et al. (20)
	France	238	4.8%	Le Cacheux et al. (21)
	Washington, Pennsylvania	43	7%	Gazeau et al. (22)
	California, USA	1	No	Nie et al. (24)
	New York	3	No	Santomasso et al. (28)
	Rennes, France	190	No	Mauget et al. (23)
	Maryland, USA	79	No	Shalabi et al. (29)
	Xuzhou, China	60	No	Wang et al. (30)
TLS	Chicago, USA	1,595	12%	Obeidat et al. (31)
	Chicago, USA	8,779	32.3%	Moturi et al. (32)
	USA	9,034	32%	Gangani et al. (33)
	Mexico, USA	138	30.4%	Rios-Olais et al. (34)
	Arkansas, USA	1,808	19.7%	Roy et al. (35)
	Inglewood, Canada	930	14%	Adla Jala et al. (36)
	Shaanxi, China	480	17%	Feng et al. (37)
	Phoenix, Arizona	246	65.78%	Kelkar and Wang (38)
	Beijing, China	164	43.29%	Wang et al. (39)
	Istanbul, Turkey	107	12.38%	Bozkurt et al. (40)
	Karachi, Pakistan	400	36%	Ahmed et al. (41)
	USA	141	2.1%	Cairo et al. (42)
MAS	Minnesota, USA	5	2 died	Monteagudo et al. (43)
	Geneva, Switzerland	1,080	13.7%	Amikishiyev et al. (44)
B-Cell Aplasia	Spain	23	3 died	Molinos-Quintana et al. (45)
	Stanford, Canada	41	2.44%	Baird et al. (46)
	London, United Kingdom	151	4%	Gabelli et al. (47)

encephalopathy syndrome (CRES). However, another anti-interleukin-6 receptor (IL-6R) molecule, anakinra, an IL-1 receptor antagonist, appears useful in CRS prevention and other neurotoxicities that may not be treated by tocilizumab. Moreover, experiments with animal models identified that the suppression of nitric oxide synthase (NOS), which is enhanced during severe CRS, may eliminate life-threatening hypotonia and other toxic side effects. This has paved the way for the administration of nitric oxide synthase inhibitors as supplementary treatment, in order to enhance the patient prognosis in complicated cases. There are also changes in prophylactic treatment. Steroids and IL-6 blocking for prevention were thought to be counterproductive because they would suppress the anti-tumor effects of CAR T cells, however, this has recently been shown not to be the case when using anti-IL-1 or anti-IL-6 treatment. This has influenced the changes in clinical practice whereby tocilizumab or anakinra are administered early in

an attempt to decrease CRS-associated morbidity and mortality with no negative impact on cancer treatment.

## 1.2 Immune effector cell-associated neurotoxicity syndrome

Another common side effect of CAR T-cell therapy is immune effector cell-associated neurotoxicity syndrome (ICANS). It was once named CRES, chimeric antigen receptor T-cell-related encephalopathy, or neurotoxicity alone (12). When cluster of differentiation 28 (CD28) is used as a costimulatory domain in CAR constructs, high-grade ICANS is often also present, affecting up to 45% of treated patients (50). CAR T cells striking cluster of differentiation 22 (CD22), B cell maturation antigen (BCMA), and other hematological antigens have been shown to cause



neurotoxicity, in addition to CD19. The same neurotoxic outcomes have been documented concerning alternative immune effector cell (IEC) therapies, including blinatumomab (51). ICANS often causes impairment of concentration and disorientation. Expressive aphasia and alterations in handwriting are regarded as very specific and initial manifestations of ICANS. It usually leads to lowered consciousness and disorientation, leading to coma, convulsions, motor/muscular weakness, and cerebral edema. CD19-associated CAR T-cell therapy with 4-1BB or CD28 constructs has resulted in severe neurotoxicity owing to cerebral edema (3% incidence). All fatal cerebral edema cases were linked to CRS, and severe CRS was linked to severe ICANS (3).

ICANS can manifest as a range of neurological symptoms, including confusion, delirium, seizures, and cerebral edema. The onset and severity of ICANS can vary (Table 2), with some patients experiencing mild cognitive changes while others suffer from severe and potentially fatal cerebral edema (18). Histopathological findings in cases of fatal ICANS often reveal neuronal death, neuronal and perivascular edema, and intraparenchymal hemorrhagic extravasations (21). According to Le Cacheux et al. (21), ICANS can be managed through supportive care and corticosteroids. Regular neurological assessments and advanced neuroimaging are important for the early detection and management of ICANS. In some cases, antiepileptic medications can also be utilized to manage seizures and other severe neurological symptoms that appear following CAR T-cell therapy.

Current investigations regarding ICANS resulting from CAR T-cell therapy exhibited a lower incidence, however, clinical studies reported intermediate to catastrophic ICANS in 30% to 60% of individuals (20, 25). In the study by Belin et al. (18), the mortality rate resulting from ICANS was modest. Nevertheless, the early detection of moderate to severe illness is imperative since patients frequently require extended hospitalization. Despite the variability, prompt detection is important to extend hospitalization due to the severity of the illness associated with moderate to severe ICANS. The low mortality rate (0% to 1.4%) of ICANS indicates the importance of appropriate and prompt treatment to avoid unfortunate results (20).

Clinicians completely understand the management of ICANS, including patients who have undergone chimeric antigen receptor CAR T-cell therapy in recent years. However, the management of ICANS is sometimes done in conjunction with the management of CRS (52) because they affect patients simultaneously. The first line of treatment for ICANS is the use of corticosteroids, specifically dexamethasone, once neurological signs are observed. For the scenarios that do not show an improvement with the first cycle of steroids, the administration of methylprednisolone in an increased dosage may be recommended. Recent studies (53) have discussed the use of an IL-1 blockade by anakinra in the treatment of steroid-unresponsive ICANS. Anakinra, an IL-1 receptor antagonist that treats neurotoxicity, has been effective in treating those patients who do not benefit from conventional management. This therapeutic approach is especially useful in severe or persistent ICANS where inflammation processes should be stopped as soon as possible to avoid devastating outcomes for the patient. Other adjunctive therapies such as antiepileptic drugs (AEDs) and

constant supervision, especially in the Intensive Care Unit, are important in the management of severe cases. However, investigations are being conducted into measures to prevent the development of ICANS. These include pretreatment with agents such as anakinra or newly developed treatments that selectively address the inflammatory processes more efficiently.

### 1.3 Tumor lysis syndrome

Tumor lysis syndrome (TLS) is induced by anticancer therapies for tumor cell lysis that develop metabolic content constellations that are dispersed into the bloodstream. Such constellated metabolic content can result in medical conditions such as hyperkalemia, hyperphosphatemia, and hyperuricemia (54, 55). Since TLS is induced by denatured cellular components, its development is directly proportional to the tumor cell proliferation speed or size of the tumor burden (56). Moreover, high levels of lactate dehydrogenase (LDH) with fever are also reported in the development of TLS in some patients (57).

TLS is a CAR T-cell therapy-induced complication that can lead to renal failure, arrhythmias, and fatality (Table 2) due to the destruction of cancerous cells by direct CAR T-cell therapy or lymphodepleting chemotherapy (3, 58). Patients treated with CAR T-cell therapy without lymphodepletion chemotherapy have also been reported to have TLS (59). Hence, in cases of high tumor burden according to TLS, prophylaxis as per standard medical guidelines and the use of hypouricemic agents (febuxostat, rasburicase, and allopurinol) should be employed before administering CAR T-cell therapy or initiating lymphodepleting therapy (3).

New developments in TLS treatment emphasize the prediction of TLS and prompt treatment to avoid complications. TLS is considered a potentially fatal condition and is most commonly associated with hematological malignancies such as acute lymphoblastic leukemia (ALL) and high-grade lymphoma. For high-risk patients, other preventive treatments (60) such as adequate hydration and administration of drugs that reduce serum uric acid levels, are critical. Xanthine oxidase inhibitors are described and remain an effective first-line strategy to protect the patient against hyperuricemia by blocking the synthesis of uric acid. Another drug in the category of xanthine oxidase inhibitors is febuxostat but it is rarely used because of its high cost and its side effects that are perilous in patients with cardiovascular conditions. A recombinant urate oxidase, rasburicase, assumes a central role in the management of developed TLS by reducing uric acid to the more soluble allantoin. This agent lowers the uric acid level much faster than any other agent and is therefore commonly recommended for patients with high-risk disease or preexisting hyperuricemia. Published literature (61) shows newer approaches to preventive and curative measures depending on the features of risk such as tumor load, impaired kidney function, or malignancy type. Additionally, the monitoring of urine output and managing electrolyte disturbances such as hyperkalemia is very important in managing TLS. Agents such as phosphate binders and sodium zirconium cyclosilicate have been used to address problems such

as hyperphosphatemia and hyperkalemia, respectively. Despite improvements in pharmacological options for modification of outcome, the concept of managing TLS has remained primarily preventive rather than curative through monitoring and early intervention.

## 1.4 Macrophage activation syndrome

Autoimmunity-associated hemophagocytic lymphohistiocytosis (HLH) is referred to as macrophage activation syndrome (MAS) (3, 62). MAS is a menacing problem that arises from the excessive proliferation and hyperactivation of T lymphocytes and macrophages (Figure 4) (55). Patients receiving CAR T-cell therapy also experience the symptoms of HLH/MAS (50, 63) due to its parallel criteria with grade 3 CRS. HLH/MAS associated with CAR T-cell therapy has been managed with CRS treatment including tocilizumab and corticosteroids (64, 65). According to Maude et al. (66), it was ambiguous whether MAS/HLH is a specific toxic entity or appears as a result of CRS hyperinflammation. HLH/MAS diagnostic criteria associated with CAR T-cell therapy were defined by the elimination of HLH/MAS from the terms of CRS following the ASTCT grading guidelines (3, 12). The proposed treatment, including etoposide and methotrexate or intrathecal cytarabine for refractory HLH/MAS, is still controversial. Administration of anti-IL-1 with anakinra has also been proposed for HLH/MAS treatment but has not been approved for the management or treatment of HLH/MAS (3, 14, 66).

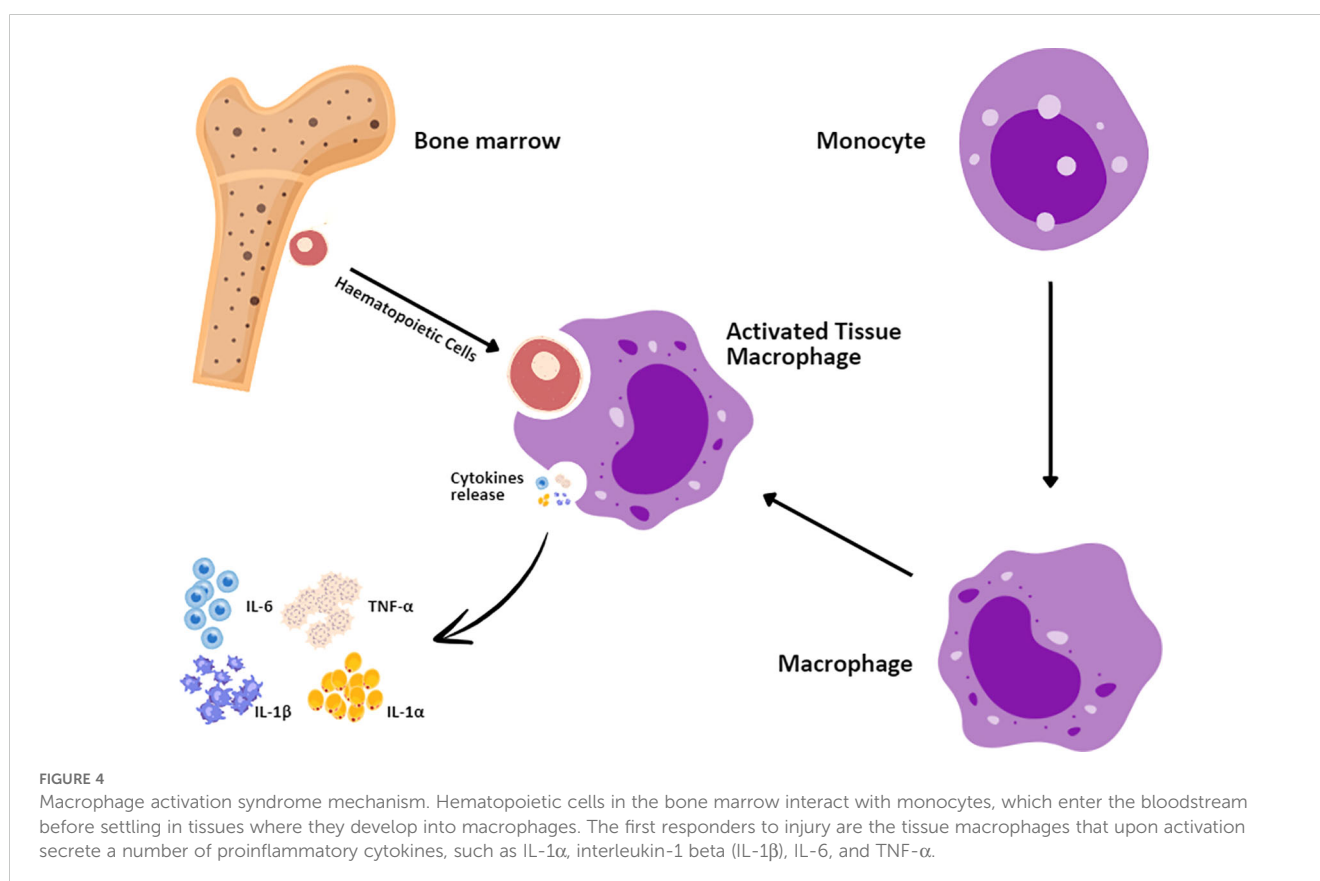
## 1.5 B-cell aplasia

B-cell aplasia and hypogammaglobulinemia are anticipated issues after CD19-directed CAR T-cell therapy because of the off-tumor-on-target effect of CD19-associated CAR T cells on natural B cells. CAR T-cells with 4-1BB as a secondary pathway lead to chronic B-cell aplasia up to 5 years after treatment by CAR T-cells for ALL (67, 68). Thus, the persistence of CAR T-cells can be predicted through B cell levels as pharmacodynamic biomarkers. Remission duration has a potential role in B-cell recovery for ALL (68–70). However, during perpetual remission after CAR T-cell therapy, recovery of B cells in lymphoma can manifest (71, 72).

Severe infections are associated with hypogammaglobulinemia developed from B-cell aplasia (67). During B-cell aplasia, empiric immunoglobulin (Ig) replacement in pediatric patients is executed on a standard basis (68, 73). Different approaches to Ig replacement and CD19-negative memory plasma cells (that secrete antibodies) that increase basic humoral immunities have been described to treat B-cell aplasia and hypogammaglobulinemia in adults due to CAR T-cell therapy (74, 75).

## 1.6 Anaphylaxis

The non-human elements of most CAR constructs pose a risk to clinical efficacy and could lead to allergic responses. CAR T-cell infusion followed by anaphylaxis has been published but allergic responses are rare after frequent CAR T-cell therapies (76). However,



CAR T-cell therapy with tisacel and axicel has been reported to lead to the production of preexisting anti-murine antibodies against CD19-directed CARs in patients (69). Although CD-19 antibodies associated with rising titers against CARs have been revealed, the expansion, efficacy, and persistence post-infusion of CAR T-cells are genuine. Fully human generated CARs to minimize immunogenicity have still not been reported (72, 77).

New developments in anaphylaxis and immunogenicity management (78, 79) in the current population underline the need for early detection, individual therapeutic approaches, and novel methods of monitoring. The management of anaphylaxis (80) has progressively shifted more toward the search for biomarkers, primarily serum tryptase, that facilitate speedy diagnosis and risk assessment. We, therefore, recommend the use of additional tryptase levels immediately after the onset of anaphylactic reactions to inform emergency management. Immunogenicity, especially in biological products and monoclonal antibodies, remains an issue thanks to the development of antidrug antibodies (ADAs). These ADAs can decrease the therapeutic effectiveness of the active substance and cause hypersensitivity reactions up to anaphylaxis. Some of the new approaches that are seen at the developmental stage relate to computational and *in vitro* modeling of immunogenic risk early in drug development. Immunogenicity is traditionally a highly litigious issue and derisking immunogenicity through methods such as T-cell epitope mapping and high-end *in silico* algorithms is now getting deployed more and more for late preclinical and early clinical validation (81). Furthermore, factors that can be related to the individual patient, for instance, the patient's heredity and previous treatment with related biologics, are included in the risk evaluation tools used to identify possible immunogenic reactions. Some strategies aimed at determining immunogenicity include using fully humanized or engineered antibodies so as to avoid immune identification. Further, in clinical management, it is common to prescribe antihistamines and corticosteroids before the procedure in patients who are sensitive to latex. It is crucial to enhance patient prognosis in therapeutic endeavors and to continue research on the molecular base of ADA formation and hypersensitivity reactions.

## 1.7 Graft-versus-host disease

CAR T-cell therapy has the potential to bind T cells to protein, carbohydrate structures, and glycolipids and contributes to the persistence and expansion of T-cells. It can be active in both CD8+ and CD4+ cells and there is a low chance of graft-versus-host disease (GVHD) and autoimmunity (82). GVHD, with adverse effects on the vital organs of recipients of CAR T-cell therapy, is an immune response and can be mitigated by immunosuppressive medication (83). GVHD has not been considered a threatening issue in patients posttransplant since this therapy was not accepted for the treatment of ALL in the early days (55). However, only one report of chronic GVHD with drastic skin GVHD 3 months after the CAR T-cell therapy has been published. Subsequently, corticosteroids were administered for the management of the incidence of GVHD (84).

## 1.8 Acute myelofibrosis

The investigations of Lai et al. (85) revealed acute myelofibrosis (AMF) as a serious threat that appeared by CD-19-associated CAR T-cell treatment, beyond the neurotoxicity and CRS. After receiving CD19 CAR T-cell therapy, 1 out of 17 patients diagnosed with B-cell acute lymphoblastic leukemia (B-ALL) exhibited AMF following grade IV CRS. Despite achieving complete remission (CR) from B-ALL, a 36-year-old male patient with grade IV CRS and Philadelphia chromosome-negative B-ALL eventually had a fatal relapse through worsening of bone marrow fibrosis. It was also concluded by primary myelofibrosis (PMF) mutations such as JAK2, MPL, and CALR that pre-existing genetic predisposition was not the reason for AMF. A CRS-induced cytokine milieu with IL-6 among other profibrogenic and inflammatory cytokines was the cause of AMF development (85). This was in line with the cytokine expression and inflammatory response involved in myelofibrosis.

The treatment of AMF has been recently improved (86) with an emphasis on combination therapy and new drugs. Ruxolitinib is and still remains an essential part of the management of this disease as it has been proven to be very effective in managing symptoms such as splenomegaly. Recent studies (87), however, show that an increasing number of studies have pointed towards the superiority of combining JAK inhibitors with non-JAK agents in the spleen with symptom control and reasonable tolerability. Further, the newer agents that have emerged, fedratinib, pacritinib, and momelotinib, have brought more options to the table particularly in managing patients with anemia and thrombocytopenia. Of these, momelotinib has emerged as potentially clinically effective in treating anemic AMF patients and improves their symptoms and transfusion dependence compared with conventional therapies. Currently, clinical studies are still being conducted to further understand other combinations and doses that are safe and effective for the patients with managed side effects.

## 1.9 Cytopenia

Cytopenia, including neutropenia, anemia, and thrombocytopenia, is a common chronic side effect of CAR T-cell treatment that adversely impacts the immune systems of patients (88). Alarming, prolonged cytopenia for 3 months or above has been observed following CAR T-cell infusion, and 15% of patients were diagnosed with B-cell lymphoma (89). Patients are also affected by cytopenia in continuous remission with no confirmation of myelodysplastic syndrome. However, the actual mechanisms behind these prolonged cytopenias have not yet been reported (90).

In some reports of CAR T-cell therapy, cytopenia was common after 4 to 39 months of CAR-T cell infusions but they characterized cytopenia as myelodysplastic syndrome (MDS) (91, 92). Such confusion raises the importance of ruling out the mechanisms of MDS or CAR-T therapy as the sources of cytopenia (93). Later, it was confirmed by Strati et al. (91) through statistical MDS diagnosis that cytopenia at day 30 after CAR T-cell infusion was not



associated with myelodysplastic syndrome. Meanwhile, it was reported by Jain et al. (94) that inflammation factors were significantly associated with hematopoietic recovery at 1 month and this imbalanced the observations about cytopenia.

After CAR T-cell therapies, grade 3 cytopenia is frequently reported. Febrile neutropenia of grade 3 was recorded in 17% and 31% of the patients examined within the JULIET trials and ZUMA-114, respectively (95, 96). Almost 30% of patients following CD19-specific CAR T-cell therapy with tisacel or axical exhibited prolonged severe cytopenia in a biphasic pattern beyond 30 days after administration (71, 97). Nevertheless, the etiology of late cytopenia is not fully described with the lymphodepleting chemotherapy being considered to be associated with early cytopenia (97, 98). Whereas, in severe CRS, prior hematopoietic cell transplantation (HCT), and frequent prior chemotherapies are attributed as the cause of late cytopenia (11, 96, 97). Patients with limited hematopoietic capacity who underwent a prior HCT showed a disturbance in their chemokine milieu following CAR T-cell therapy, and CAR-specific immunobiology has been described as a fundamental issue (11, 97). Platelet and erythrocyte replacement have been used in the treatment of thrombocytopenia and anemia. Similarly, patients with prolonged neutropenia should be treated with granulocyte colony-stimulating factor (G-CSF) (8, 99). However, according to previous studies, it might enhance the severity or incidence of CRS due to a lack of immune cell activation. However, CAR T-cell therapy can be useful as initial care in patients (99, 100). Anecdotally, the transfusion of allogeneic or autologous stem cells resolved the persistence of cytopenia after CAR T-cell therapy (96, 101).

## 1.10 Coagulation disorders

During the administration of CAR T-cell therapy, coagulation disorders, particularly hematological malignancies, have been observed in 51%-56.6% of patients within 6 to 20 days after the infusion (30, 102). Increased fibrinogen degradation products, decreased fibrinogen, increased D-dimer, thrombocytopenia, and prolonged prothrombin time are initiated by CAR T-cell therapy-associated coagulation disorders. Since the appearance of disseminated intravascular coagulation (DIC) is associated with severe coagulation disorders, only a few cases have been published regarding CAR T-cell therapy-associated DIC incidence (Figure 5). Various reports indicated an incidence of DIC of approximately 7% to 28.3% in patients following CAR T-cell infusion (30). In addition, the grade of CRS positively impacts the coagulation disorder's severity (30, 103). Patients with severe CRS have also been reported to have a higher incidence of DIC and coagulation disorders (102).

Conventional approaches for the treatment of patients with coagulation disorders are generally used for standard care and most of the patients are observed to recover without intervention (30). The development of DIC and the levels of multiple cytokines are decreased or eventually inhibited by the management of CRS (103, 104). Effective and timely treatment and interventions are essential once DIC symptoms appear in patients. New developments (105) in care and control strategies for coagulation syndrome are based on the

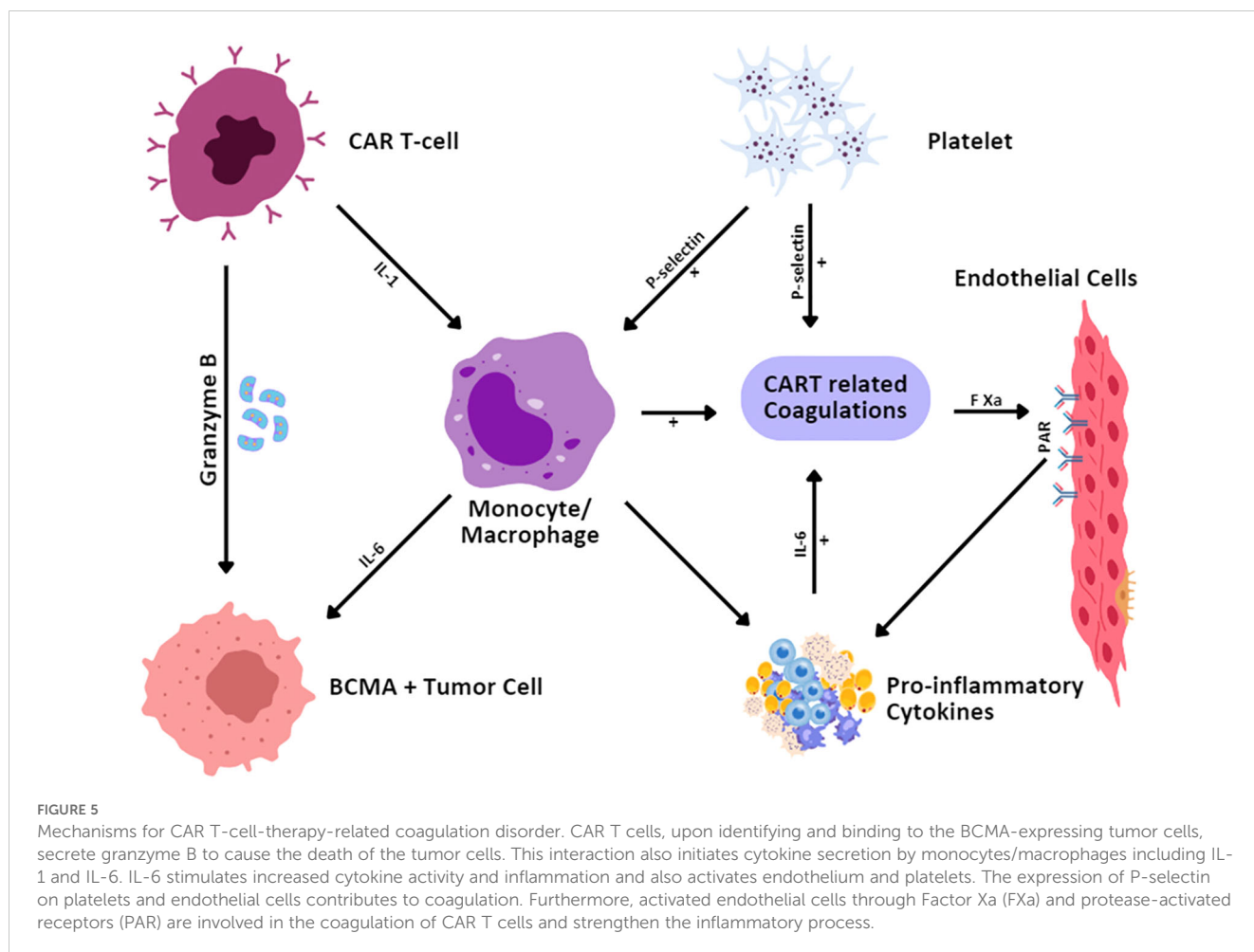
targeted intervention model. The early use of fibrinogen concentrates and antifibrinolytic agents has also demonstrated benefits in the treating of trauma (TR)-induced coagulopathy. Current attitudes toward the use of anticoagulants, especially in critically ill patients (106), are more focused on the choice between thrombotic and bleeding events; more novel antithrombotic agents and reversal approaches are needed. Coagulation disorders can be avoided with the help of normothermic management, correction of acidosis in the body, and normalization of calcium levels for the thickening of fibrin strands that support coagulation.

## 1.11 Other cascade complications

The expression of tumor antigens, which is targeted in CAR T-cell treatment, is essential for effective targeted therapy. Such antigens, known as tumor-specific antigens (TSAs), should be visible to CARs on tumors. CAR T-cell therapy mainly targets tumor-associated antigens (TAAs) since TSAs are few during treatment (103). Tumor cells and normal cells indicating the target antigens are identified and killed by infused CAR T cells. This mechanism to kill the malignant cells appearing on normal cells is a known tissue-on-target effect that sometimes leads to serious complications and mortality. CAR T cells targeting ERBB2 (HER-2/neu) were developed by Morgan et al. (107) for the treatment of cancer patients with ERBB2 overexpression. Their team infused this treatment in one patient with liver and lung-propagated colon cancer and recorded respiratory distress within 15 minutes of infusion and pulmonary infiltration after chest x-ray analysis. The patient died within 5 days despite aggressive treatment. Later, according to the researchers' hypothesis, after infusion, CAR-T cells penetrated the lungs and targeted lung epithelial cells exhibiting low ERBB2 expression. This process resulted in CRS by inducing the release of a large number of cytokines. To reduce off-target effects, the utilization of TSAs to induce the respective CAR T cells is a potent approach but it is expensive and challenging to find new TSAs (103). Thus, studies are needed for the optimization of CAR T cells through the structure of the CARs by using novel techniques, particularly inhibitory CARs (iCARs) and synNotch receptors (103, 108).

### 1.11.1 Cardiovascular toxicity

Initially, cardiovascular toxicity following CAR T-cell therapy was observed in children suffering from ALL. In more than 5% of patients, pulmonary edema, hypotension, and fluid overload were observed, which are grade 3 cardiovascular toxicities, during the ELIANA trials (109). Additionally, retrospective analyses revealed cardiomyopathy causing left ventricular systolic disorder. In some cases, CAR T cells reversed such toxicities within weeks to months in most children (110). Two studies showed that CAR-T cell infusion resulted in acute cardiac tamponade and pericardial effusion through CRS (111, 112). These two cases were managed by eliminating CRS using dexamethasone and tocilizumab and one mortality was noted (112). Another clinical study of B-cell lymphoblastic lymphoma detected cardiac tamponade 5 months



after developing grade 2 CRS (113). The studies of Tao et al. (114) reported acute cardiovascular events in a 76-year-old patient with diffuse large B-cell lymphoma (DLBCL) during CAR T-cell infusion. Following autologous CAR-T therapy, a patient receiving CD-19 CAR T-cell therapy exhibited CRS-associated coronary vasospasm. Moreover, a few studies revealed that 13.3% of individuals with cardiovascular toxicity were associated with CAR T-cell therapy (115, 116).

Approved CAR T-cell constructs have been reported in two retrospective analyses. After CAR T-cell therapy, it was observed in 17% of patients that cardiovascular events usually occurred for 1 month (117). In parallel, among 60 consecutive adult patients of LBCL treated either with tisagenlecleucel or axicabtagene ciloleucel after CAR T-cell infusion, 32 patients exhibited 48 cardiovascular adverse events within 1 year (118). Fluid retention, atrial fibrillation, and hypotension have also been observed with cardiovascular toxicities in a pediatric population. Notably, patients with CRS normally have cardiovascular events, which confirms the CRS association with cardiovascular damage (109, 117).

### 1.11.2 Pulmonary toxicity

Pulmonary complications are common in immunotherapies, such as checkpoint inhibitor therapies. In recipients of CAR T-cell therapy, pulmonary toxicities in most of the cases have been

revealed to date. However, patients with severe CRS exhibit frequent pulmonary toxicities (118) with particular symptoms including pneumomediastinum, hypoxia, allergic rhinitis, pleural effusion, and pulmonary embolism (109, 118). However, in some patients who received a CAR T-cell infusion, no comprehensive analysis has been seen for lung toxicity, and there are no comprehensive long-term evaluation reports for the transfer capacity of lungs after CAR T-cell therapy.

Haas et al. (119) treated two cases with solid tumors with CAR-T therapy targeting mesothelin (MSLN) and observed severe pulmonary toxicities. Within 48 hours of the CAR T-cell infusion, symptoms consistent with CRS and hypoxemia were seen and grade 5 respiratory failure was revealed in one patient. CAR T-cell accumulation, acute lung injury, and extensive T-cell infiltration in the lungs were also observed in the autopsy findings. Further evaluation showed low levels of MSLN in the benign pulmonary epithelial cells of lungs in fibrotic or inflammatory conditions. This observation revealed that lung pneumocytes contribute to dose-limited toxicity rather than pleural cells (115).

### 1.11.3 Neurological toxicities

CAR T-cell therapy leading to toxicities that jeopardize the nervous system has captured the attention of numerous researchers seeking to develop this immunotherapy as a safe treatment. Severe IL-

TABLE 3 Summary of CAR-T cell therapy, traditional treatment methods, associated challenges, and overcoming strategies.

Aspects	CAR-T cell therapy	Traditional treatment methods	Studies
<b>Advantages</b>	Long-term efficacy in some hematological malignancies (e.g., leukemia, lymphoma), and high specificity and personalized approach.	Standardized protocols for treatment, broad applicability, and immediate results in some cases	Irizarry Gatell et al. (127) Qureshi et al. (128)
<b>Disadvantages</b>	High cost of production, risk of severe CRS and neurotoxicity, tumor relapse and antigen escape, and limited availability and access	Lack of specificity, systemic toxicity, and resistance and relapse in advanced stages	An et al. (129) Brudno and Kochenderfer (4)
<b>Challenges</b>	Cytokine release syndrome (CRS), CAR-T cell persistence and manufacturing difficulties, neurotoxicity, and tumor antigen escape (tumor heterogeneity)	Radiation therapy, Chemotherapy (e.g., cytotoxic drugs), and Conventional immunotherapy (e.g., monoclonal antibodies)	An et al. (129) Irizarry Gatell et al. (127)
<b>Overcoming strategies</b>	Improvements in CAR-T design to increase efficacy and reduce side effects (e.g., armored CARs). Targeting tumor microenvironment to enhance CAR-T persistence. Use of "off the shelf" CAR-T cells. CAR-T cell engineering improvements (e.g., co-stimulatory domains).	Combination with immunotherapies to boost efficacy. Improved screening and monitoring for side effects. Dual targeting and checkpoint inhibition. Enhanced targeting to reduce antigen escape.	An et al. (129) Brudno and Kochenderfer (4) Irizarry Gatell et al. (127)

6, IFN- $\gamma$ , and TNF- $\alpha$  levels at the beginning of the CAR T-cell therapy can result in neurotoxicity development with grade 3 or above (55, 84). According to univariate logistic analysis, the concentration of IL-6 is also a cause of grade 3 or higher neurotoxicity development (84). However, many reports demonstrated anti-cytokine therapies consisting of tocilizumab to prevent toxic neurological effects but resulted in no correlation between the neurotoxicity occurrence and CRS severity (55). Migration of cerebrospinal fluid (CSF) in the respective patients was determined as the main cause of the correlation between the administration of CAR T-cell therapy and the development of neurotoxicity due to their migration (70). Tremors, encephalopathy, headaches, hallucinations, confusion, and seizures are some neurological complications that influence the efficacy of CAR T-cell treatment (55, 70, 120). In a study by Turtle et al. (84), the total escape of the neurological issue over time was significant except for one fatality report.

#### 1.11.4 Genotoxicity

CAR T-cells are manufactured by the transduction of lymphocytes and viral vectors are utilized for the transduction process. Such viral particles are the cause of insertional mutagenesis (IM). When retroviral and lentiviral vectors transduce hematopoietic stem cells, IM is seen, but to date, no genotoxicity has been reported in differentiated cells through gene transfer (3, 121). Similarly, patients treated with manipulated T cells did not indicate any transformational event associated with retroviruses (122). However, in a patient with ALL receiving CAR T-cell therapy, the transduction of a leukemic B cell resulted in developing leukemia, relapse, and prompt death (123). After CAR T-cell therapy, non-melanoma skin cancer, bladder cancer, and myelodysplastic syndrome are reported secondary malignancies, but in some cases, the development of these malignancies is considered to be associated with previous therapies (93, 95). Overall, a longer observation period of almost 15 years will be required for CAR T-cell therapy toxicity

data collection and evaluation, and the authorization of commercially available constructs (3).

#### 1.11.5 Musculoskeletal complications

CAR T-cell therapy is associated with musculoskeletal complications such as myositis and is characterized by muscle inflammation. CAR T-cell infusion also elevates creatine phosphokinase (CPK) levels which cause both weakness and muscle pain. Following CAR T-cell therapy, myalgias associated with CRS is a common clinically adverse event that influences the muscular system (55, 120).

#### 1.11.6 Metabolic complications

After CAR T-cell therapy metabolic toxicities have been recorded as a frequent complication in 60 patients by Wudhikarn et al. (118). Hypophosphatemia, hypocalcemia, and hypokalemia were common electrolyte abnormalities observed after CAR T-cell Infusion. Hypoglycemia and hyperglycemia have also been reported frequently [Penack and Koenecke, (109)]. However, such complications are not persistent and can be managed.

#### 1.11.7 Pancreatic complications

Complications observed in the pancreas after CAR T-cell therapy should be considered. However, there are few published reports on such toxicities in the literature. Pancreatic complications have been described due to the development of pancreatitis in five patients after the administration of CAR T-cell therapy (120).

#### 1.11.8 Nephrotoxicity

Clinical syndromes causing acute kidney injury (AKI) are characterized by low renal excretions caused by sepsis and the aggregation of nitrogen-based metabolic products (55). This toxicity has rarely been reported due to CAR T-cell adverse events and has been found in stage 2 to 3 syndromes with renal electrolyte imbalances and other renal toxicities (59, 120).

## 1.12 How to avoid cascade complications

Avoiding cascade complications is important in cardiovascular and pulmonary conditions, especially in subjects with comorbid conditions where early evaluation and management are important. Screening with echo, electrocardiography (ECG), and pulmonary function tests (PFTs) is useful for identifying at-risk subjects in the population. Where the patient has had prior heart failure, reduced left ventricular ejection fraction (LVEF), or chronic obstructive pulmonary disease (COPD), caution is needed during therapy, and prior preventive actions are recommended (124). Steroid-induced side effects are common in CAR T-cell therapy such as musculoskeletal complications involving osteonecrosis and adrenal suppression. The management process includes reducing the steroid dose where possible and providing supportive care that includes physiotherapy and pain control (125). For genotoxicity and related effects, frequent blood count and genetic tests should be conducted while for treatment of the genotoxicity, the treatment depends on the severity of the effect and the type of genotoxicity. The possible side effects of corticosteroids, including hyperglycemia, are controlled by periodic modulation of corticosteroid doses and administration of insulin if required. Pancreatic side effects, though rare, need immediate intervention through the use of enzyme supplements (126) and frequent blood sugar level checks. Molecular pathways, including cytokine release syndrome, also cause nephrotic complications and are addressed in terms of fluid and electrolyte disorders. A summary containing information on the problems related to CAR-T cell therapy, conventional therapy, the pros and cons of the conventional approach, and approaches to address the challenges is presented in Table 3.

## 2 Conclusion and future prospects

Treatment for several blood-related malignancies and their associated off-target complications has been improved by CAR T-cell therapy and achieved remarkable success, especially in relapsed or refractory patients when prior therapies failed. Although CAR T-cell therapy has established a remarkable image as a promising cytotoxic therapeutic, according to our extensive data and historical review, it also induces severe toxicities such as CRS, ICANS, TLS, HLH, B-cell aplasia, GHVD, anaphylaxis, cytopenia, and coagulation disorders, and some off-target complications such as cardiovascular, musculoskeletal, pulmonary, metabolic, and pancreatic toxicities. These unavoidable toxicities are significant hurdles that patients encounter, which must be recognized early and sorted out swiftly. The implementation of standardized grading systems such as those offered by the American Society for Transplantation and Cellular Therapy (ASTCT); conventional approaches; corticosteroids; fully human generated CARs; etoposide, methotrexate, or intrathecal cytarabine; the use of hypouricemic agents; and the inhibitory CAR (iCAR) and synNotch receptor methods has been critical in improving clinical management of CAR T-cell-therapy-associated toxicities. As we learn more about the underlying mechanisms of CAR T-cell therapy-associated toxicities so will the strategies to mitigate these risks develop, leading to harmless and highly efficacious CAR T-cell

treatments. Further research and progress regarding early detection, precise risk stratification, and personalized interventions for these toxicities are essential to broaden the lifesaving performance of CAR T-cell therapy to a wider pool of patients while limiting toxicity.

Despite the current limitations of CAR-T cell therapy, innovative approaches and streamlined research promise to enhance its efficacy and safety. Initially, these limitations can be tackled through careful dosing plans and innovative approaches after a clear understanding of the mechanisms underpinning them. Neurotoxicity, CRS, and cancer recurrence rates can be managed by incorporating off switches, CARs, tandem CARs, and their constructs. Gene editing innovations and artificial intelligence integration are predicted to revolutionize CAR T-cell therapy through manufacturing processes and optimizing target identification. CAR-T efficacy is expected to be boosted through the combination of therapies with immune checkpoint inhibitors and other agents that exhibit synergistic effects. Despite these innovations, its global adoption is restricted by limited availability and high cost. However, its accessibility can be widened by reducing manufacturing costs. Additionally, continuous monitoring, rapid detection, and accurate intervention with supportive care and prophylactic strategies are crucial for managing CAR T cell-associated toxicities. Overall, the future of CAR-T cell therapy has the capability of managing various toxicities provided that the costs and limitations of toxicity management are effectively addressed.

## Author contributions

UM: Writing – original draft. YH: Supervision, Writing – review & editing. XB: Writing – review & editing. LX: Writing – review & editing.

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## Conflict of interest

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