Whole-process management of complications during CAR-T therapy

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Abstract

Chimeric antigen receptor T cell (CAR-T) therapy has substantial efficacy in the treatment of relapsed and/or refractory hematological malignancies. However, despite this outstanding performance, various CAR-T complications challenge treatment success during the entire process of CAR-T therapy. Short-term (within 28 days) complications with a high incidence include cytokine release syndrome, immune effector cell-associated neurotoxicity syndrome and CAR-T associated coagulopathy. Many other complications may also occur during mid- (28–100 days) and long-term (>100 days) follow-up. Determining how to identify and standardize the management of adverse events in CAR-T therapy in an accurately and timely manner is crucial for its wide application. This review focuses on time periods after CAR-T cell therapy, and discusses the occurrence and management of adverse events, with an aim to improve the safety management of CAR-T cell therapy.

Keywords: chimeric antigen receptor T cell therapy, complications, whole-process management

1. INTRODUCTION

Since the concept of the chimeric antigen receptor (CAR) was first proposed in 1989, the development of CAR-T therapy has accelerated in the past 10 years [1]. As of June 2022, more than 1000 registered CAR-T clinical trials and five commercialized CAR-T products have been approved by the Food and Drug Administration (FDA), and another three are listed in China, mainly for the treatment of relapsed and/or refractory acute B lymphocytic leukemia, large B-cell lymphoma, mantle cell lymphoma and multiple myeloma [2, 3]. CAR-T therapy has achieved great success, with 54%–90% complete remission [4, 5], a 50%–77% 12-month progression-free rate and 76%–89% overall survival rate [3, 6]; moreover, its efficacy may last for decades. Currently, axicabtagene ciloleucel has become the main second-line therapy for large B-cell lymphoma, and it is even used as a first-line therapy for high-risk cases [7, 8]. Through combination with chemotherapeutic drugs, oncolytic viruses and other genetic engineering techniques, the properties of CAR-T cells have been optimized, thus enabling broader application prospects [9-11].

However, as a live drug, CAR-T therapy is accompanied by many adverse events during the entire process of hospitalization and follow-up after infusion [12]. The short-term (28 days) period after infusion is the most dangerous stage, in which life-threatening complications such as cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS) may develop with high incidence and require close monitoring [13, 14]. Mid- (28 to 100 days) and long-term (>100 days) complications, despite having a lower incidence than short-term complications, may affect patient prognosis and quality of life, and should not be ignored [15, 16]. Therefore, to provide clinicians with more detailed information for timely identification and intervention guidance, this review comprehensively summarizes the clinical features and manifestations, pathogenesis and management principles of complications that may occur in various stages after CAR-T cell infusion (Figure 1). The importance of multidisciplinary teams (MDTs) is additionally stressed.

2. SHORT-TERM COMPLICATIONS

Within 28 days after infusion, CAR-T cells are activated and massively expand after their CARs engage with specific tumor antigens. Meanwhile, perforins, granzymes and other cytokines are released and lead to killing of
tumor cells accompanied by the activation of monocytes and macrophages [17]. Massive release of proinflammatory cytokines, tumor cell lysis and immunodeficiency can trigger many complications, including CRS, ICANS, CAR-T associated coagulopathy (CARAC), infections, CAR-T-cell-associated hemophagocytic lymphohistiocytosis/macrophage-activation syndrome (carHLH/MAS) and tumor lysis syndrome (TLS) [15, 18] (Table 1).

2.1 CRS

CRS is the most-common complication of CAR-T therapy, with an incidence of 57%–100%; the incidence of severe CRS is approximately 1%–47% [19, 20]. CRS can occur as early as 24 hours after therapy, and the median onset-time is 2–3 days, the typical duration of CRS is 7–8 days [12].

Figure 1 | Management principles of complications in the entire process of CAR-T therapy.

When they encounter tumor cells and by subsequently activated bystander cells, CRS involves the rapid release of proinflammatory cytokines including interleukin (IL)-6, IL-1β, interferon-γ, tumor necrosis factor (TNF)-α, granulocyte-macrophage colony-stimulating factor (GM-CSF), granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF) and monocyte chemokine protein-1 (MCP-1) [21].

The clinical symptoms, characterized by fever, hypoxemia and hypotension, usually begin with constitutional symptoms such as fatigue, myalgia or anorexia, and can progress to disseminated intravascular coagulation (DIC), multi-organ dysfunction syndrome and even death [22]. Several grading standards are used for evaluation of the severity of CRS; the most widely used is the American Society for Transplantation and Cellular Therapy (ASTCT) consensus grading [23].

Low-grade CRS usually requires symptomatic and supportive treatment, such as antipyretics, and infectious fever must be actively identified. Moderate to severe CRS requires active maintenance of oxygenation and hemodynamic stability, and concomitant treatment
### Table 1 | Clinical features of early complications of CAR-T.

<table>
<thead>
<tr>
<th>Complications</th>
<th>Incidence</th>
<th>Duration</th>
<th>Risk factors</th>
<th>Biomarkers</th>
<th>Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ALL</td>
<td>Lymphoma</td>
<td>MM</td>
<td>CLL</td>
<td>Median onset time</td>
</tr>
<tr>
<td>Any grade</td>
<td>74%–100%</td>
<td>30%–100%</td>
<td>76%–95%</td>
<td>63%–83%</td>
<td>4%–38%</td>
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<tr>
<td>severe</td>
<td>13–47%</td>
<td>1%–28%</td>
<td>4%–38%</td>
<td>4%–43%</td>
<td></td>
</tr>
<tr>
<td>ICANS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4–10 d</td>
</tr>
<tr>
<td>Any grade</td>
<td>28%–53%</td>
<td>19%–77%</td>
<td>18%–42%</td>
<td>8%–43%</td>
<td></td>
</tr>
<tr>
<td>severe</td>
<td>5%–50%</td>
<td>10%–28%</td>
<td>0%–23%</td>
<td>0%–25%</td>
<td></td>
</tr>
<tr>
<td>CARAC</td>
<td>36%–56.6%</td>
<td>43%</td>
<td>21%–91%</td>
<td></td>
<td>6–10 d</td>
</tr>
<tr>
<td>Early infections</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6–12 d</td>
</tr>
<tr>
<td>Any type</td>
<td>30%–64%</td>
<td>18%–52%</td>
<td>57%</td>
<td>21%</td>
<td></td>
</tr>
<tr>
<td>Bacteria (45.9%–56%)</td>
<td>25.5%–50%</td>
<td>9.7%–37.5%</td>
<td>50%</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>Viruses (8.2%–30%)</td>
<td>8.3%–10.6%</td>
<td>6.5%–10.7%</td>
<td>5%</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Fungi (4.1%–14%)</td>
<td>4.3%–5.6%</td>
<td>1.6%–3.6%</td>
<td>2%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>carHLH/MAS</td>
<td>3.5%–32.8%</td>
<td>10–14d</td>
<td>-</td>
<td>CD22 CAR-T therapy after prior CD19-targeted therapy</td>
<td>Ferritin, fibrinogen LDH, soluble CD25, IFN-γ, IL-6, IL-1</td>
</tr>
<tr>
<td>TLS</td>
<td>1%–10%</td>
<td>8–22 d</td>
<td>-</td>
<td>Peak of CAR T cell proliferation, cytokine release, and rapid reduction of tumor load</td>
<td>Potassium, phosphorus, calcium, uric acid</td>
</tr>
<tr>
<td>CVC</td>
<td>10%–39%</td>
<td>5–21 d</td>
<td>-</td>
<td>Baseline cardiovascular risk factors, cardiovascular disease, CRS and neurotoxicity</td>
<td>Body weight, serum myocardial markers (troponin, BNP)</td>
</tr>
</tbody>
</table>

ALL, acute lymphoblastic leukemia; MM, multiple myeloma; CLL, chronic lymphoblastic leukemia; CRS, cytokine release syndrome; CAR-T, chimeric antigen receptor T cell; IL-6, interleukin-6; IL-10, interleukin-10; IL-1β, interleukin-1β; IFN-γ, interferon-γ; TNF-α, tumor necrosis factor-α; GM-CSF, granulocyte-macrophage colony-stimulating factor; MCP-1, monocyte chemokine protein-1; ICANS, immune effector cell-associated neurotoxicity syndrome; Ang-2, angiotensin-2; CARAC, CAR-T associated coagulopathy; TF, tissue factor; PECAM-1, platelet endothelial cell adhesion molecular-1; vWF, von Willebrand factor; DIC, disseminated intravascular coagulation; LC, lymphodepleting conditioning; CRP, C reactive protein; PCT, procalcitonin; carHLH/MAS, CAR-T-cell-associated hemophagocytic lymphohistiocytosis/macrophage-activation syndrome; LDH, lactate dehydrogenase; TLS, tumor lysis syndrome; CVC, cardiovascular complications; BNP, N-terminal-pro-brain-natriuretic-peptide.
with IL-6 receptor antagonists and/or glucocorticoids [24]. Tocilizumab (an IL-6 receptor antagonist) has been approved by the FDA for severe and life-threatening CRS after CAR-T, and has potent efficacy at a recommended dose of 8 mg/kg (12 mg/kg for patients <30 kg). If symptoms such as fever, hypotension or hypoxemia do not resolve, repeated use of tocilizumab should be considered [25]. Glucocorticoids are usually used for grade ≥2 CRS and tocilizumab-resistant CRS, particularly those with ICANS. Dexamethasone is most commonly used, and the recommended dose is 10 mg intravenously every 6 h; if refractory hypotension is encountered, the dose is increased to 20 mg every 6 h [14, 18]. However, whether the use of glucocorticoids affects the efficacy of CAR-T cells remains controversial. In addition, on the basis of understanding of the pathophysiology of CRS, preclinical models and clinical trials have been reported for other cytokine antagonists and signaling pathway inhibitor drugs targeting the pathophysiology of CRS, such as anakinra, siltuximab, lenzilumab, adalimumab and tyrosine kinase inhibitors [24-28].

### 2.2 ICANS
ICANS is the second most common complication associated with CAR-T therapy; approximately 19%–64% (grade ≥3, 7%–42%) of patients with CD19 CAR-T experience ICANS [6, 20, 29]. Moreover, 10% of patients may develop delayed ICANS >3 weeks after infusion. The median onset time is 4–10 days after infusion, and onset may occur concurrently with or shortly after CRS; the typical duration is 14–17 days [12, 15, 20]. According to the presence of CRS manifestations, Neelapu et al. have proposed biphasic ICANS. The first phase occurs concurrently with high fever and other CRS symptoms, typically within the first 5 days, and the second phase occurs after CRS symptoms, often more than 5 days after infusion [18]. Patients with B-ALL, baseline inflammatory status, high tumor burden, abundant CD19⁺ cells in the bone marrow, preexisting neurologic comorbidities or severe CRS are more likely to develop ICANS [24, 30]. Gust et al. have established a classification tree model and have proposed that patients with fever ≥38.9°C and serum IL-6 ≥16 pg/mL and MCP-1 ≥1,343.5 pg/mL in the first 36 hours after CAR-T cell infusion are more prone to grade ≥4 neurotoxicity [30]. The pathophysiological mechanism of ICANS remains unclear. According to laboratory findings, diffusion of cytokines (e.g., IL-6, IL-1β and TNF-α), inflammatory cell infiltration in the central nervous system, endothelial activation with subsequent blood-brain barrier disruption (elevation of angiotensin-2) and glial cell injury have been attributed to ICANS [24, 30].

ICANS usually occurs with toxic encephalopathy. Early manifestations include impaired attention, and language and writing function; headache; and delirium. Seizures, cerebral edema and even intracranial hemorrhage can occur in severe ICANS with low incidence [18, 30]. To assess ICANS severity, ASTCT consensus grading system incorporating the 10-point Immune Effector Cell–Associated Encephalopathy score is commonly used in adults, or incorporating the Cornell Assessment of Paediatric Delirium assessment in children [14, 23, 31]. Through use of a grading system, ICANS can be recognized early and reversed with aggressive treatment. When patients are suspected to have ICANS, a comprehensive neurological evaluation (e.g., cranial MRI, EEG and cerebrospinal fluid testing) is necessary to exclude other diagnosis [15].

Similarly to that of CRS, the management of ICANS is also based on toxicity grade. For patients with grade ≥1 ICANS and concurrent CRS, anti-IL6 therapy is recommended; if CRS is not present, corticosteroids are the preferred treatment for patients with grade ≥2 ICANS and can be tapered gradually after symptoms improve to grade 1 [14, 18]. Patients should be closely monitored for symptoms of neurotoxicity during corticosteroids use and tapering. Glucocorticoids are considered the first-line treatment, and they usually lead to rapid resolution of ICANS. Short-term use of corticosteroids can decrease neurotoxicity without affecting the antitumor response. However, Strati has found that early and longer glucocorticoid use and higher cumulative doses are associated with faster disease progression and shorter overall survival, and has suggested that corticosteroids should be used at the lowest dose and for the shortest duration, and their initiation should be delayed [32-34]. For patients with grade ≥3 ICANS, ICU monitoring is necessary. For grade 3 ICANS with elevated intracranial pressure, corticosteroids and acetazolamide should be administered promptly; for grade 4 ICANS with cerebral edema, high-dose corticosteroids, hyperventilation and hyperosmolar therapy are recommended [18]. When patients develop ICANS with non-convulsive status epilepticus, in addition to evaluating the airway, respiratory and circulatory systems, as well as measuring blood glucose, treatments such as lorazepam, levetiracetam or phenobarbital should be used as appropriate. For convulsive status epilepticus, ICU transfer and increased doses are recommended [18]. IL-1β plays a major role in the pathogenesis of ICANS, and the use of anakinra (IL-1 receptor antagonist) has also shown encouraging results [35]. Moreover, novel drugs targeting cytokines and mechanistic pathways have shown significant therapeutic effects on CRS and neurotoxicity in preclinical models, and clinical trials are being conducted to verify their efficacy in patients [36-38].

### 2.3 CARAC
As reported by many studies, CARAC may become the third most common complication of CAR-T, with a 50%–56.6% incidence. Accompanying CRS, CARAC usually occurs in patients within 28 days (mostly 6–10 days) after CAR-T infusion, particularly in patients with poor vascular condition before infusion, high-dose CAR-T cells, high tumor burden or severe CRS [39-42]. The pathophysiological mechanism of CARAC
is closely associated with CRS. IL-6 and other cytokines cause endothelial activation and damage, including elevated tissue factor (TF), platelet endothelial cell adhesion molecule-1 (PECAM-1), P-selectin, angiopoietin-2 (Ang-2) and von Willebrand factor (vWF), which may lead to consumptive coagulopathy, i.e., CARAC [39-41].

Bleeding (19.6%) and hypofibrinogenemia are the most common symptoms of CARAC, and comprise primarily gastrointestinal, extensive maxilofacial and intracranial hemorrhage [42-44]. Among patients with CARAC, 14%–50% may show progression to DIC, particularly those with grade 3–5 CRS [39, 40, 44, 45]. Thrombotic events also occur frequently (6.3%–8.8%), involving pulmonary embolism, deep vein thrombosis, thrombotic stroke and visceral veins [46, 47]. Features include progressive decrease in platelet count, prolonged activated partial thromboplastin time, prothrombin time, hypofibrinogenemia, elevated D-dimer and fibrin degradation products, and similar cytokine profiles to those in CRS [42-44, 48]. In addition to ASTCT criteria, which can be used to infer the occurrence of CARAC by assessing the severity of CRS, the Chinese expert consensus on the management of CARAC suggests that the Chinese DIC Scoring System (CDSS) or International Society on Thrombosis and Haemostasis DIC Scoring System and WHO bleeding scale can be used to evaluate the CARAC severity and predict DIC [42, 49-51].

Because CARAC occurs and resolves after CRS, early identification of CRS and abnormal coagulation markers is crucial for the management of CARAC [42]. Corticosteroids and tocilizumab can be used in cases of concurrent CRS. Replacement therapy is the core of treatment for CARAC and should be actively applied in the setting of bleeding complications, abnormal platelet counts and coagulation indicators [19, 44]. Moreover, supportive and anti-infection treatment should be applied throughout the process; meanwhile, thrombopoietic drugs and plasma exchange can be used as appropriate.

2.4 Early infections
Because of the immunodeficiency caused by hematological malignancy (particularly acute lymphoblastic leukemia, ALL), ≥4 prior antitumor treatment regimens [52-54]. Infections that occur within 28 days are usually classified as early infections, whereas those occurring within 28–180 days are classified as late infections. Recent studies have found that the cumulative incidence of early infection within 28 days is approximately 23%–58.2%, and the infection density is 1.19–2.01 [52, 54]. The median time to the first infection is 6–12 days, and 80% of infections occur within 10 days after CAR-T cell infusion [52, 54, 55]. Most early infections are bacterial (45.9%–56%), followed by viral (8.2%–30%) and fungal (4.1%–14%) [52, 54].

Fever is the main early symptom in most patients, and septic shock may occur in severe infections. Infections can occur in various locations, and bloodstream infections are more common with coagulase-negative Staphylococcus aureus, Streptococcal species, Enterococcus faecium and gram-negative bacteria [52, 54, 56]. Infectious disease screening should be routinely performed before CAR-T therapy, including serological viral testing for HIV, HBV, HCV, herpes simplex virus, varicella zoster virus and cytomegalovirus. If patients received tocilizumab, screening for Mycobacterium tuberculosis and invasive fungi is necessary [57]. Distinguishing infection from CRS is challenging. Luo et al. have found that double peaks of IL-6 in patients with CRS are associated with severe infection, and have proposed a predictive model using three cytokines (IL-8, IL-1β and IFN-γ) to facilitate the identification of infections; however, further verification is necessary [56]. Blood cultures should be obtained along with other relevant diagnostic tests to evaluate patients for infections and differentiate infections from other complications.

After CAR-T cell infusion, specimens from patients with neutropenia and fever ≥38°C should be promptly collected and cultured to assess etiology. Before the pathogens are identified, broad-spectrum antibiotics against gram-negative and gram-positive bacteria can be used empirically, and then the medication can later be adjusted according to the results of etiology and drug susceptibility testing. If necessary, MDTs should be consulted to guide the adjustment of antibiotic levels [57, 58].

2.5 carHLH/MAS
HLH/MAS is a hyperinflammatory syndrome caused by inherited or acquired factors such as infection, tumor or immune disease [59]. After CAR-T cell infusion, particularly targeting CD19 and CD22, some patients develop carHLH/MAS, whose clinical manifestations are similar to those of HLH/MAS, presenting high fever; multiple organ dysfunction; central nervous system disorders; hyperferritinemia; elevated levels of lactate dehydrogenase, soluble CD25 and cytokines (IFN-γ and IL-6); and hypofibrinogenemia [60]. The pathogenesis of carHLH remains unclear. A perforin-deficient CAR-T therapy mouse model suggests that perforin gene deficiency and CAR-T cell re-expansion may be associated with carHLH [61], a rapid and fatal complication of CAR-T therapy, occurring primarily in patients with CRS. According to recent clinical trials, 3.5%–32.8% of patients experience carHLH, often with CD22 CAR-T therapy after prior CD19-targeted therapy; the median onset time is 10–14 days postinfusion, usually after CRS resolution [60, 62]. Levels of IL-6, IFN-γ, IL-8, IL-15, IL-10, TNF and IL-1β are higher in patients receiving CD22 CAR T cell therapy, including CD8+ and CD4+ selection, which is associated with HLH/MAS-like toxicity [60].

Identifying carHLH/MAS, CRS and infection is difficult. Currently, the diagnostic criteria for carHLH/MAS proposed by Neelapu et al. are the most widely recognized. These criteria include elevated ferritin above 10,000 ng/mL and at least two organ toxicity symptoms, including the presence of hemophagocytosis in bone
marrow or organs, transaminitis of at least grade 3, renal insufficiency or pulmonary edema [18].

The principle of carHLH/MAS treatment involves actively controlling CRS, inhibiting over-activated CD8+ T cells and macrophages, and ultimately blocking and ameliorating multiple organ dysfunction caused by inflammatory storms. Symptomatic supportive treatment should be administered first after suspicion of carHLH/MAS; anti-IL-6 therapy and corticosteroids remain the main treatment options [59, 63]. If patients do not show clinical or serological improvements, additional treatment with etoposide should be considered; Intrathecal cytarabine may be considered in patients with concurrent neurotoxicity [18, 64]. Anakinra and glucocorticoids alone or in combination can resolve carHLH without affecting CAR-T efficacy and expansion [60]. In the future, new targeted drugs, such as humanized anti-IFN-γ mAb NI-0501 and IL-1 receptor antagonists may be applied in the clinical treatment of carHLH/ MAS [65, 66].

2.6 TLS

TLS, a group of acute metabolic disorder syndromes caused by spontaneous or rapid dissolution of tumor cells, is characterized by hyperkalemia, hyperphosphatemia, hyperuricemia and secondary hypocalcemia [67]. TLS is relatively rare, occurring in 10% (1/10) of cases of chronic lymphocytic leukemia and 1/111 of cases of relapsed or refractory diffuse large B-cell lymphoma [29, 68]. It often occurs 8–22 days after CAR T cell infusion, a period generally correlating with peak CAR T cell proliferation, cytokine release and a rapid decrease in tumor load, and it is not significantly associated with pretreatment chemotherapy [68, 69].

TLS causes systemic metabolic disorders and serious complications, which require early prophylaxis, identification and close monitoring of high-risk patients. Timely monitoring and restoration of electrolyte balance, adequate hydration and lowering of uric acid are the basis for prevention and management of TLS [67]. Rasburicase has been reported in the treatment of TLS after CAR-T reinfusion. Dialysis or continuous renal replacement therapy is necessary when patients present with internal environment disturbances that cannot be corrected with conventional medications [2, 67].

2.7 Cardiovascular complications

Cardiovascular complications (CVC) are more likely in patients with baseline cardiovascular risk factors, cardiovascular disease, grade ≥2 CRS and neurotoxicity [2, 70, 71]. Alvi et al. have reported that the duration between CRS onset and tocilizumab administration is associated with CV events, with a 1.7-fold increased risk with every 12-hour delay in tocilizumab administration; the median time for the occurrence of cardiovascular complications is 21 days [72].

CAR-T cardiotoxicity is an early, largely reversible phenomenon. The main manifestations are decreased left ventricular ejection fraction, arrhythmia, heart failure, myocardial infarction, hypotension, systolic dysfunction and elevated troponin, with an incidence of approximately 10%–39% and mortality of approximately 30% [2, 70, 71]. Interestingly, a Cross-Sectional FDA Adverse Events Reporting System analysis has indicated that arrhythmia is the most frequent CVC, and that axicabtagene ciloleucel is associated with a higher incidence of arrhythmias than tisagenlecleucel, but the latter is associated with higher rates of heart failure [71].

CVC grade is based on symptomology, imaging abnormalities, and biomarker measurements, including troponins, according to the Common Terminology Criteria for Adverse Events [2]. A complete cardiovascular evaluation before infusion is necessary, which should include transthoracic echocardiography, serum troponin and N-terminal-pro-brain-natriuretic-peptide (NT-pro BNP)/BNP. When patients develop grade ≥2 CRS, troponin and the left ventricular ejection fraction should be monitored [2, 15]. Antiplatelet drugs and anticoagulants should be discontinued before CAR-T treatment, and beta blockers, angiotensin II receptor blockers, calcium channel blockers and ACE inhibitors should be changed from long-acting to short-acting as appropriate; early use of IL-6 blockers and/or glucocorticoids, or escalation of current treatment should be considered when CVC is suspected; dual-action anticoagulants should be discontinued when PLT < 100×10^9/L; all anticoagulants should be discontinued when PLT < 50×10^9/L; and the anticoagulant dose should be decreased when thrombosis or infusion of PLT occurs [2].

3. MID-TERM COMPLICATIONS: FROM DAYS 28 TO 100

Although the onset of complications at this stage is not as dangerous as CRS/ICANS, the complications last for long time periods, usually several months, and include cytopenias, late infections, B-cell aplasia and hypogammaglobulinemia and graft-versus-host disease (GVHD).

3.1 Cytopenias

Among grade ≥3 complications, cytopenia appears to be the most common complication after CAR-T therapy, including anemias, neutropenia, thrombocytopenia and leukopenia, which are associated with marrow tumor burden, the number of prior therapies, baseline cytopenias, and CRS and ICANS [40, 73-75]. The incidence of any grade neutropenia, thrombocytopenia and anemia is 16%–87%, 34%–47% and 58%–94%, respectively, whereas those of grade ≥3 neutropenia, thrombocytopenia and anemia are 3%–85%, 4%–51% and 2%–50%, respectively [74-76]. The duration and severity of cytopenia varies by CAR-T product and disease, but grade ≥3 cytopenia tends to lasts as long as 3 months after infusion [29, 73, 76]. The incidence of cytopenia in different CAR-T products and diseases is listed in Table 2.
Table 2 | Incidence of cytopenia in different CAR-T products and diseases.

<table>
<thead>
<tr>
<th>CAR-T Products</th>
<th>Diseases</th>
<th>Patients (n)</th>
<th>Neutropenia Any grade</th>
<th>Grade ≥3</th>
<th>Thrombocytopenia Any grade</th>
<th>Grade ≥3</th>
<th>Anemia Any grade</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axi-cel [76]</td>
<td>Large B-cell lymphomas</td>
<td>108</td>
<td>44%</td>
<td>39%</td>
<td>35%</td>
<td>24%</td>
<td>68%</td>
<td>46%</td>
</tr>
<tr>
<td>Tisa-cel [94]</td>
<td>Large B-cell lymphomas</td>
<td>115</td>
<td>20%</td>
<td>20%</td>
<td>34%</td>
<td>28%</td>
<td>49%</td>
<td>39%</td>
</tr>
<tr>
<td>Liso-cel [95]</td>
<td>Large B-cell lymphomas</td>
<td>269</td>
<td>63%</td>
<td>60%</td>
<td>31%</td>
<td>27%</td>
<td>48%</td>
<td>37%</td>
</tr>
<tr>
<td>Citla-cel [3]</td>
<td>Multiple myeloma</td>
<td>97</td>
<td>96%</td>
<td>95%</td>
<td>79%</td>
<td>60%</td>
<td>81%</td>
<td>68%</td>
</tr>
<tr>
<td>Ide-cel [96]</td>
<td>Multiple myeloma</td>
<td>128</td>
<td>91%</td>
<td>89%</td>
<td>63%</td>
<td>52%</td>
<td>70%</td>
<td>60%</td>
</tr>
<tr>
<td>Brexu-cel [74]</td>
<td>Mantle-cell lymphoma</td>
<td>76</td>
<td>87%</td>
<td>85%</td>
<td>74%</td>
<td>51%</td>
<td>68%</td>
<td>50%</td>
</tr>
<tr>
<td>Brexu-cel [97]</td>
<td>B-precursor acute lymphoblastic leukemia</td>
<td>55</td>
<td>27%</td>
<td>27%</td>
<td>33%</td>
<td>31%</td>
<td>53%</td>
<td>53%</td>
</tr>
</tbody>
</table>

Presenting symptoms associated with CAR T–induced cytopenia may include fatigue, weakness, shortness of breath, poor concentration, frequent infections, fever, bleeding and bruising easily.

In addition to symptomatic and supportive care, growth factors are often used to stimulate hematopoiesis. Granulocyte colony-stimulating factor can be used prophylactically without effects on immunotoxicity, CAR-T expansion or prognosis [77, 78]. Symptomatic treatments such as dexamethasone (anti-inflammatory therapies) and erythropoietin/thrombopoietin agonists may also be helpful. However, GM-CSF is not recommended for cytopenias because it may theoretically aggravate CRS [2, 75].

3.2 Late infections
The infection risk rate is 0.67 per 100 days from day 29 to day 90 after infusion, and late infections are dominated by viruses, including upper respiratory tract virus and cytomegalovirus infection [52]. Reactivation of herpes simplex virus and varicella-zoster virus may also occur [57].

In patients with upper and/or lower respiratory tract viral infections, delaying CAR-T cell therapy should be considered until symptoms resolve. Ribavirin can be used to treat upper respiratory tract viral infections; ganciclovir and foscarnet sodium can be used to treat cytomegalovirus infections; and acyclovir and valacyclovir are effective against herpes simplex virus and varicella-zoster virus [57]. Because of the limited treatment options for viral infections, intravenous immunoglobulin can be used to boost immunity [79]. Invasive fungal infections, such as mold, can occur in as many as 8% of patients. Thus, during severe neutropenia, prophylactic fungal therapy, such as fluconazole, may be used until neutropenia has recovered [57, 80].

3.3 B-cell aplasia and hypogammaglobulinemia
B-cell aplasia, an immunodeficiency caused by an immune attack to normal B cells or B precursor cells by CAR-T cells targeting CD19/20/22, is characterized by persistent B cell and immunoglobulin deficiency as well as immunodeficiency [81-83]. It is a common on-target off-tumor effect that occurs in all responding patients; it persists for several years and can be used as a marker for monitoring CAR-T cell activity [5, 6]. Hypogammaglobulinemia is more common in children than adults, owing to their immunological immaturity. A total of 83% of pediatric patients with B-ALL have ongoing B cell aplasia at 6 months; 20.9%–25% undergo B cell aplasia at 12 months after infusion [6, 83, 84].

The main complications of B-cell aplasia are infections, which can be managed with infusion of intravenous immunoglobulins [6, 79]. Immunoglobulin replacement therapy can significantly decrease the rate of sinopulmonary infection in patients with persistent B-cell hypoplasia after CD19 CAR-T therapy [85]. No consensus exists regarding how to conduct immunization after CAR-T treatment, and international guidelines can be referred to for individualized evaluation and decision-making. The European Society for Blood and Marrow Transplantation guidelines suggest that patients be vaccinated at least 6 months after CAR-T cell therapy, preferably with inactivated influenza vaccine, 13-valent Streptococcus pneumoniae vaccine and Haemophilus influenzae vaccine [57, 86].

3.4 GVHD
CAR-T related GVHD has a low incidence, and is mild and controllable. GVHD generally manifests as a rash, but also includes abnormal liver function and gastrointestinal toxicity. Glucocorticoids alone or in combination with immunosuppressive agents can effectively treat CAR-T related GVHD [87]. With the broader development and application of donor-derived CAR-T cells after allogeneic hematopoietic stem cell transplantation, CAR-T cells derived from third-party healthy donors and universal CAR-T cells, GVHD is expected to be a complication of concern after CAR-T therapy [88].
application of γδ-T cells and gene editing technology can effectively prevent GVHD by knocking out the TRAC gene and inhibiting the expression of TCR; however, further clinical trials and mechanistic studies are needed to provide evidence of its prevention and treatment [89, 90].

4. LONG-TERM COMPLICATIONS: MORE THAN 100 DAYS

This stage may include cytopenia, B-cell aplasia and hypogammaglobulinemia infection, HBV reactivation and other complications, delayed recovery, disease recurrence and secondary tumors [6, 73, 83, 91]. Long-term B cell hypoplasia places HBV-infected or HBV-carrying patients at a higher risk of HBV activation after receiving CAR-T therapy, as reported by several teams [92, 93]. Therefore, such patients should be closely monitored for liver function and HBV DNA status. For patients with a history of HBV infection, anti-HBV drug prophylaxis can be used, and patients with positive HBsAg should receive regular anti-viral treatment.

5. MULTIDISCIPLINARY TEAM (MDT)

To successfully achieve the entire process management of CAR-T complications, collaboration among hospitals, patients and medical teams is indispensable. MDT involvement should start from patient screening, and should continue through mononuclear cell collection; pretreatment; CAR-T cell infusion; management of short-, mid- and long-term complications; and long-term follow-up [15]. Various types of CAR-T complications exist, often involving multiple systems, which must be promptly identified and addressed by hematologists on the basis of professional knowledge and sophisticated clinical experience.

To recognize CRS, ICANS, infection and CARAC early, laboratory, flow cytometry laboratory, and MRI physicians should be consulted to provide sufficient evidence support for diagnosis and treatment. Moreover, cardiovascular doctors and neurologists should be consulted if necessary. For HLH, DIC, grade 4–5 CRS or ICANS, gastrointestinal and respiratory tract hemorrhage, and other very dangerous and life-threatening complications, the intensive care, blood transfusion, gastroenterology and respiratory departments must urgently be contacted to provide technical and professional support. During the entire process, the nursing team is fundamental in managing all complications, and its importance should not be overlooked. A seamless connection among different disciplines is required to develop the best diagnosis and treatment plan for patients receiving CAR-T therapy.

6. CONCLUSION

Many types of complications are associated with CAR-T cell immunotherapy, and occur in various periods after treatment. Therefore, clinicians must manage the entire process after CAR-T treatment. At present, several guidelines exist for the assessment and management of CAR-T-associated toxicity, including the American Society of Clinical Oncology and European Society for Blood and Marrow Transplantation guidelines. This review comprehensively described the characteristics of CAR-T-associated complications, commonly used treatments and potential drugs, which are crucial for patient management and will ideally make cancer immunotherapy safer and more effective.

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CONFLICTS OF INTEREST

The authors declare no competing financial interests.

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Review


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