Chinese expert consensus on the management of chimeric antigen receptor T cell therapy-associated coagulopathy

Introduction

Chimeric antigen receptor T-cell (CAR-T) therapy has greatly improved the disease remission rate and long-term survival rate of patients with relapsed/refractory hematological malignancies.[1-3] Currently, several commercial CAR-T products are available in the market and numerous CAR-T clinical trials have been conducted. Attention should be paid to the safety of CAR-T therapy. The main adverse effects of CAR-T therapy are cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).[4] Moreover, CAR-T therapy-associated coagulopathy (CARAC) is also prominent.[Supplementary Table 1] Among the patients with hematological malignancies, including B-cell acute lymphoblastic leukemia (B-ALL), non-Hodgkin lymphoma (NHL), and multiple myeloma (MM), more than half of them experienced thrombocytopenia or showed at least one abnormal coagulation parameter after CAR-T therapy.[13-15] Approximately 19.6% of coagulopathy patients experienced clinically significant bleeding and 14–50% of coagulopathy patients further developed disseminated intravascular coagulation (DIC); 6.7–42.9% of the DIC patients died.[13-14,17] The current international grading criteria and treatment guidelines for CAR-T therapy-related adverse events only focus on CRS and ICANS, while CARAC has not been systematically summarized. In order to standardize the management of CARAC and promote the safe application of CAR-T therapy, experts from Thrombosis and Hemostasis Group, Chinese Society of Hematology (CSH) and Biotherapeutics Committee, Chinese Research Hospital Association (CRHA) formulated this consensus based on worldwide clinical experience and research progress.

Definition and Characteristics of CARAC

Definition

In the studies using CAR-T therapy for hematological malignancies, researchers have found that the rate of coagulopathy is higher among severe CRS patients and its severity is positively correlated with the CRS grade.[10,13-15] Besides, coagulopathy often occurs at day 6 to day 10 after CAR-T cell infusion, closely following the elevated levels of interleukin (IL)-6 and other cytokines, and gradually relieves with the control of CRS.[13-14] Consequently, CARAC is a clinical syndrome, which occurs within a short term (mostly <28 days) after CAR-T cell infusion. It is related to the release of cytokines and is characterized by bleeding and/or thrombosis, which is accompanied by decreased platelets (PLT) levels and coagulopathy.

Clinical characteristics

(1) Bleeding: Clinical manifestations of CARAC are mostly bleeding.[10,12-14] About 19.6% of the coagulopathy patients show clinically significant bleeding, among which grade ≥3 bleeding includes extensive maxillofacial hemorrhage, gastrointestinal hemorrhage, and intracranial hemorrhage.[14] (2) Thrombosis: The incidence of thrombosis is 6.3–8.8% with a median onset time of 20–29 days after CAR-T cell infusion. Reported thrombosis involves pulmonary embolism, deep vein thrombosis, thrombotic stroke, and visceral vein thrombosis.[22-23] (3) DIC: About 14–50% of the coagulopathy patients develop DIC, manifesting as petechiae/ecchymosis, jaundice, hypotension, dyspnea, renal dysfunction, nervous system abnormalities, shock, severe bleeding, etc.[11-14,24]

Laboratory indicators characteristics

Abnormal laboratory indicators of CARAC always occur before its clinical manifestation. The higher the grade of CRS, the higher the incidence of related abnormal indicators.

Decrease in PLT count

Statistically, 50.9% of the B-ALL patients experience decrease in their PLT count after CAR-T therapy with the nadir value ranging from 5 to 47 × 10^9/L. Mild and severe CRS patients have no significant difference in the nadir value of their PLT count.[13] About 86% of the MM patients experience significant decrease in their PLT counts after CAR-T therapy as compared to the baseline PLT count. The levels of serum IL-6 and interferon (IFN)-γ are negatively correlated with the PLT count.[15]

Abnormal coagulation indicators

The changes in the levels of activated partial thromboplastin time (APTT), prothrombin time (PT), thrombin time (TT), fibrinogen (FIB), fibrin degradation products (FDP), and D-dimer (D-D) are remarkably correlated with the expansion of CAR-T cells. The peak/valley values after infusion show significant differences as compared to the baseline values before infusion.[14-15] The incidences of abnormal coagulation indicators are remarkably elevated among patients with severe CRS.[13-14] As compared to patients with grade ≤3 CRS, the peak/valley values of coagulation indicators are significantly higher or lower among patients with grade ≥ 4 CRS.[14] The levels of IL-6, IFN-γ, C-reactive protein (CRP), and ferritin are positively correlated with those of PT and APTT, while the levels of IL-6, IFN-γ, and ferritin are negatively correlated with that of FIB.[14,15]
**Supplementary Table 1: Articles related to CARAC.**

| References | Patients (n) | CAR-T targets | Coagulation indicators | Hemorrhage and thrombosis | Treatment |
|------------|--------------|---------------|------------------------|----------------------------|-----------|
| Hay et al[^4] | 133 (B-ALL: 47; CLL: 24; NHL: 62) | CD19 | Prolonged PT, APTT (peak: 2–5 days); increased D-D, decreased FIB (2–5 days); hypofibrinogenemia (9–12 days); decreased PLT (nadir: 2–5 days) | N = 3 (≥3 grade bleeding); not found thrombosis | Anti-coagulant; Replacement treatment |
| Jiang et al[^13] | 53 (R/R B-ALL) | CD19 | N = 30 (56.6%); begin: 8–10 days; prolonged PT, APTT; increased D-D, FDP; decreased PLT, FIB | Petechiae and Ecchymosis on trunk or four limbs; bleeding in nasal and oral mucosa, and sclera; thrombosis not found | Cryoprecipitate; Human prothrombin complex |
| Wang et al[^14,50] | 100 (ALL: 36; B-NHL: 43; MM: 21) | ALL: CD19; B-NHL: CD19 + CD20; MM: CD19 + BCMA | N = 51 (51%); begin: 6–20 days; prolonged PT (10%); prolonged APTT (16%); increased D-D (50%); increased FDP (45%); decreased FIB (23%) | N = 10 (10/51), Gastrointestinal, extensive maxillofacial and intracranial hemorrhage | – |
| Shao et al[^13] | 37 (R/R MM) | BCMA | N = 34 (91%); begin: 5–7 days; prolonged PT (46%); prolonged APTT (84%); prolonged TT (49%); increased D-D (81%); decreased FIB (62%); decreased PLT (86%) | – | Replacement treatment |
| Buechner et al[^16] | 137 (B-ALL) | CD19 | FIB (g/L) <1 (8.3%); ≥1 and <1.5 (12.0%); ≥1.5 (72.2%); prolonged PT (45%); prolonged APTT (66%); decreased PLT (72%) | Cerebral hemorrhage, epistaxis, hematuria, hemoptysis | FIB concentrate; Cryoprecipitate |
| Johnsrud et al[^23] | 127 (LBCL: 111, B-ALL: 16) | CD19 (89); CD19/22 (38) | – | Bleeding (9.4%); Thrombosis (6.3%) | – |

ALL: Acute lymphoblastic leukemia; APTT: Activated partial thromboplastin time; B-ALL: B-lineage acute lymphoblastic leukemia; B-NHL: B-non-Hodgkin lymphoma; BCMA: B cell mature antigen; CARAC: CAR-T associated coagulopathy; CAR-T: Chimeric antigen receptor T cell; CLL: Chronic lymphocytic leukemia; D-D: D-dimer; FDP: Fibrin degradation products; FIB: Fibrinogen; LBCL: Large B cell lymphoma; MM: Multiple myeloma; NHL: Non-Hodgkin lymphoma; PCE: Platelets; PT: Prothrombin time; R/R: Relapse and refractory; TT: Thrombin time.

**Recommended grades**

The evidence is graded according to the US National Clinical Diagnosis and Treatment Guidelines Database Grading System [Supplementary Table 2].

**Diagnosis**

**Basic conditions**

CARAC is triggered by CRS after CAR-T cell infusion; therefore, CARAC is diagnosed by the presence of CRS (grade Ia). High tumor burden before infusion, rapid expansion of CAR-T cells in vivo, and high-grade CRS are the high-risk factors for CARAC (grade Ia). The patients with CRS are characterized by elevated serum levels of interleukin-1β (IL-1β), IL-6, IL-10, IFN-γ, tumor necrosis factor (TNF-α), etc. Among them, elevated IL-6 is the most common and significant marker (grade Ia).[^5-8,25] Consequently, the diagnosis of CARAC should be based on elevated levels of IL-6 and other cytokines. The ratio of post-infusion to baseline IL-6 level is suggested to judge whether IL-6 is elevated.

**Clinical manifestation**

According to its developmental process, CARAC can be categorized into the hypercoagulation stage, bleeding stage, and organ failure stage. Bleeding is the main clinical manifestation of CARAC and is usually spontaneous, involving multiple sites. The WHO bleeding scale is recommended to evaluate the degree of bleeding (grade IIa).[^26] Some patients may experience shock or microcirculation failure, which is life-threatening due to the dysfunction of multiple organs. The abnormal clinical manifestations always occur after the abnormal

**Supplementary Table 2: Recommendation grades.**

| Evidence level | Definition | Recommendation grade | Definition |
|----------------|------------|----------------------|-----------|
| Ia             | Meta-analysis of randomized controlled trials | A         | Ia        |
| Ib             | At least one randomized controlled trial | B         | Ib        |
| Iia            | At least one well-designed non-randomized controlled trial | C         | IIa       |
| Iib            | At least one well-designed quasi-experimental research | D         | IIIb      |
| III            | Well-designed non-experimental researches, such as control studies, correlation studies and case studies | E         | III       |
| IV             | Expert committee reports, authoritative opinion and clinical experience | F         | IV        |
laboratory indicators; therefore, clinicians should pay more attention to patients whose laboratory indicators turn abnormal.

**Laboratory indicators**

The diagnosis of CARAC should be based on progressive decrease in PLT count, prolongation in APTT and PT, decrease in FIB, and increase in FDP and D-D. The risk of DIC increases if the PLT count is <50 x 10⁹/L or decreases ≥50% within 24 h, D-D is ≥5 mg/L, prolongation of PT is ≥3 s, prolongation of APTT ≥10 s, or FIB <1.0 g/L (grade IIa). Thromboelastogram records the comprehensive functional status of all the parameters in coagulation process and can be used as a supplement to the traditional coagulation indicators (grade IIb). Platelet endothelial cell adhesion molecule-1, tissue factor, von Willebrand factor, angiopoietin-2, and other biomarkers, which reflect vascular endothelial function, can also be used to assist CARAC diagnosis (grade IIb).

**Application of DIC scoring system**

CARAC can progress to DIC. Therefore, it is important to diagnose and treat DIC at an early stage. Once the coagulation indicators turn abnormal, the Chinese DIC Scoring System (CDSS) or International Society on Thrombosis and Haemostasis (ISTH) DIC Scoring System is recommended to evaluate DIC (grade IIa).

**Differential Diagnosis**

**Sepsis-induced DIC**

Sepsis is defined as life-threatening organ dysfunction caused by the dysregulated host response to infection. Sepsis-induced DIC is characterized by systemic activation of coagulation and inhibition of fibrinolysis. It mainly causes a hypercoagulable state, which results in microvascular thrombosis, thereby affecting organ microcirculation and inducing organ dysfunction [Supplementary Table 3].

**Hemophagocytic lymphohistiocytosis (HLH)**

HLH occurs among a few severe CRS patients after CAR-T therapy and is mainly characterized by decreased PLT count and FIB level. Currently, the criteria of CAR-T related HLH have not yet been unified, but all criteria emphasized ferritin level, organ dysfunction, and hemophagocytosis. These may overlap with CARAC, but the cytokine profile is not the same; furthermore, HLH has a lesser effect on coagulation system than CARAC [Supplementary Table 4].

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**Supplementary Table 3: The differences between CARAC and sepsis-induced DIC.**

| Differences | CARAC | Sepsis-induced DIC |
|-------------|-------|-------------------|
| **Etiology** | CAR-T therapy and other iatrogenic procedures | Bacterial and other microorganisms |
| **Characteristic** | Mainly in bleeding | Mainly in hypercoagulability |
| **Mechanism** | Coagulation activation | Coagulation activation |
| **Cytokines** | IL-6, IFN-γ, IL-1β | TNF-α, IFN-γ |
| **Treatment** | Tocilizumab | Heparin |
| | Glucocorticoid | |

CARAC: CAR-T associated coagulopathy; CAR-T: Chimeric antigen receptor T cell; DIC: Disseminated intravascular coagulation; IFN-γ: Interferon-γ; IL-1β: Interleukin-1β; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α.

**Supplementary Table 4: The differences between CARAC and CAR-T related HLH.**

| Items | CARAC | CAR-T related HLH |
|-------|-------|------------------|
| **Incidence** | Above 50% | About 3.5% |
| **Characteristic** | Mainly in bleeding | Mainly in organ dysfunction |
| **Mechanism** | Activation of mononuclear cells/macrophages and endothelial cells | Activation of CD8⁺ T cell and macrophages |
| | Hyperfibrinolysis | Hemophagocytosis |
| **Laboratory indicators** | Abnormal coagulation indicators | Elevation of Ferritin (>5000 ng/mL), transaminase and creatinine level |
| **Cytokine** | IL-6, IL-1β | IFN-γ, TNF-α, GM-CSF |
| **Treatment** | Tocilizumab | Glucocorticoid |
| | Glucocorticoid | Etoposide |

CARAC: CAR-T associated coagulopathy; CAR-T: Chimeric antigen receptor T cell; CAR-T related HLH: CAR-T related hemophagocytic lymphohistiocytosis; GM-CSF: Granulocyte-macrophage colony-stimulating factor; IFN-γ: Interferon-γ; IL-1β: Interleukin-1β; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α.
Chemotherapy-induced thrombocytopenia

Chemotherapy (including lymphodepletion)-induced thrombocytopenia (CIT) is defined as the peripheral blood platelet count of <100 × 10^9/L after chemotherapy. Its main cause is myelosuppression.\(^{36}\) Differentially, CIT recovers within 2–3 weeks after chemotherapy.\(^{37}\)

CAR-T therapy-related delayed-onset thrombocytopenia

CAR-T therapy-related delayed-onset thrombocytopenia is a form of late hematological toxicity, which appears ≥28 days of CAR-T therapy, and is far beyond the pretreatment chemotherapy period. Its incidence is as high as 76% and is significantly associated with previous transplantation and severe CRS.\(^{38}\)

Treatment

The principle of CARAC treatment is early diagnosis, accurate evaluation, removal of the cause, and management based on CRS levels. CARAC can be comprehensively managed according to the flowchart provided in Supplementary Figure 1. Specific measures are as follows.

CRS management

Cytokine antagonist

The most common and significantly elevated cytokine in CRS is IL-6. The IL-6 receptor antagonist tocilizumab has been approved by Food and Drug Administration (FDA) and has been widely used for the treatment of CRS after CAR-T therapy (grade IIa).\(^{39-42}\) The IL-6 monoclonal antibody siltuximab has also shown a beneficial effect on CRS (grade IIb).\(^{43,44}\) Additionally, other cytokines antagonists have also been applied for the CRS treatment, including IL-1 receptor antagonist anakinra (grade IIb) and TNF-α antagonist etanercept (grade III).\(^{45-47}\) Currently, tocilizumab, siltuximab, and anakinra are recommended to treat CRS according to the National Comprehensive Cancer Network (NCCN) guidelines.\(^{48}\) We suggest that patients with grade ≥2 CRS accompanied by CARAC use cytokine antagonists.

Glucocorticoid

The application of glucocorticoid can improve both coagulation indicators and bleeding symptoms (grade IIa).\(^{13,40-42}\) However, early clinical studies found that,

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Supplementary Figure 1: Clinical management pathway of CARAC. CARAC: CAR-T associated coagulopathy; CRS: Cytokine release.
Although glucocorticoid could control CRS, it affected the function of CAR-T cells or inhibited the proliferation of CAR-T cells in vivo, thereby showing potential adverse effects on the anti-tumor efficacy of CAR-T therapy.[49–51] The application of glucocorticoid in coagulation dysfunction needs to be adjusted according to specific clinical conditions.[52] Consequently, we recommend patients with grade ≥2 CRS accompanied by CARAC use glucocorticoid.

**Replacement therapy**

Bleeding is the main feature of CARAC. Replacement therapy can decrease the risk of bleeding and control active bleeding. Patients with grade ≥2 CRS accompanied by CARAC should receive replacement therapy. The dose of replacement therapy should be adjusted in a timely manner according to PLT count, FIB, PT, and APTT levels.

**Platelet suspension**

Platelet suspension should be transfused when the PLT count is <20 × 10^9/L or the PLT count is <50 × 10^9/L with active bleeding (grade III).[53]

**Fresh frozen plasma and prothrombin complex concentrates**

When the prolongation of PT is ≥3 s and/or that of APTT ≥10 s, fresh frozen plasma should be transfused at a dose of 10–15 mL/kg or prothrombin complex concentrates should be transfused as is appropriate (grade III).[53]

**FIB and cryoprecipitate**

Among patients with grade ≥3 CRS accompanied by CARAC, the risk of bleeding is very high. We suggest monitoring the FIB level daily and supplementing FIB concentrates or cryoprecipitate appropriately. The goal is to maintain the FIB level ≥1.5 g/L until CRS grade is ≤3 (grade IIa).[16,54] When the FIB level is <1.5 g/L, the suggested supplementary dose of FIB concentrates is ([1.5–measured level]/0.017) mg/kg. The cryoprecipitate contains factor VIII and FIB. If the FIB level is unknown but suspected to be very low, the supplementary dose of cryoprecipitate should be 0.1–0.2 U/kg of the body weight.[16] The patients with prolonged APTT can also use cryoprecipitate.

**Anticoagulant therapy**

Anticoagulant therapy can be applied based on the extent to which CRS is controlled. For patients with grade 2 CRS accompanied by CARAC, anticoagulant therapy should only be used at the time of replacement treatment (grade III).[13] For patients with grade ≥3 CRS accompanied by CARAC, anticoagulant therapy is not generally used. We recommend using low-molecular-weight heparin at a dose of 4000–6000 U/day. The dose should be reduced to half when PLT is <50 × 10^9/L and should be stopped when PLT is <20 × 10^9/L (grade IV).

**Anti-fibrinolytic therapy**

For patients with grade ≥3 CRS accompanied by CARAC, if the secondary fibrinolysis is the main reason for bleeding, anti-fibrinolytic therapy can be used (grade IV).[13]

**Other treatments**

**Infection prevention and treatment**

CRS and infection have overlapping symptoms; therefore, it is difficult to distinguish between them. In addition, severe infection can further aggravate coagulation dysfunction. Therefore, steps for the prevention and treatment of infections should be taken actively (grade IIIb).[13]

**Anti-inflammation and liver protection treatment**

Based on CARAC mechanisms, patients with grade ≥2 CRS should take anti-inflammation and liver protection treatment actively (grade IV).

**Thrombopoietic drugs**

The risk of bleeding remarkably increases in patients with grade ≥3 CRS. Thrombopoietic drugs, including thrombopoietin and thrombopoietin receptor agonist, can be applied to patients with persistent low levels of PLT (grade IV).

**Plasma exchange**

For patients with grade ≥3 CRS who have poor response to cytokine antagonists, plasma exchange can be applied (grade III).[135] The effect of plasma exchange in CARAC is better than that in sepsis-induced DIC.

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**Conflicts of interest**

None.

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