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RESEARCH ARTICLE

Management of cytokine release syndrome related to CAR-T cell therapy

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Abstract **Chimeric antigen receptor T (CAR-T) cell therapy is a novel cellular immunotherapy that is widely used to treat hematological malignancies, including acute leukemia, lymphoma, and multiple myeloma. Despite its remarkable clinical effects, this therapy has side effects that cannot be underestimated. Cytokine release syndrome (CRS) is one of the most clinically important and potentially life-threatening toxicities. This syndrome is a systemic immune storm that involves the mass cytokines releasing by activated immune cells. This phenomenon causes multisystem damages and sometimes even death. In this study, we reported the management of a patient with recurrent and refractory multiple myeloma and three patients with acute lymphocytic leukemia who suffered CRS during CAR-T treatment. The early application of tocilizumab, an anti-IL-6 receptor antibody, according to toxicity grading and clinical manifestation is recommended especially for patients who suffer continuous hyperpyrexia, hypotensive shock, acute respiratory failure, and whose CRS toxicities deteriorated rapidly. Moreover, low doses of dexamethasone (5–10 mg/day) were used for refractory CRS not responding to tocilizumab. The effective management of the toxicities associated with CRS will bring additional survival opportunities and improve the quality of life for patients with cancer.**

Keywords chimeric antigen receptor T cell; cytokine release syndrome; tocilizumab

Introduction

Chimeric antigen receptor T (CAR-T) cell therapy is a cellular immunotherapy that combines tumor associated antigen binding domain (usually a single-chain variable fragment, scFv) with the killing mechanism of T cells through gene conduction technique [1,2]. The targeted killing activity of modified T cells against tumor cells is independent of the major histocompatibility complex (MHC), which limits the molecular recognition of tumor antigens [3]. CAR-T immunotherapy has demonstrated potential clinical effects on patients with hematologic malignancies, especially B cell malignances [4–6]. Anti-CD19 CAR-T cell therapy has demonstrated therapeutic activities in $CD19^+$ malignancies. A 2014 study involving 30 patients with refractory and relapsed acute lymphoblastic leukemia (ALL) who received CAR-T cell targeting CD19 reported a complete remission (CR) rate of 90%, a 6-month event-free survival rate of 67%, and an overall survival rate of 78% [7].

CAR-T cell immunotherapy has shown certain curative effects and great breakthrough in treatment of hematological malignancies, but it leads to adverse events that cannot be underestimated. The toxicities caused by CAR-T cell immunotherapy include tumor lysis syndrome, off-target effect, anaphylaxis, and cytokine release syndrome (CRS) [8]. CRS is a potentially life-threatening toxicity and has been categorized into different grades in accordance with the revised grading system published by Lee to improve diagnosis and management [8] (Table 1). Several research centers have also shared their experiences

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Table 1 CRS grading system

Grade	Toxicity
1	Symptoms, e.g., fever, nausea, fatigue, headache, myalgia, and malaise, requiring only symptomatic management
2	Symptoms responding to moderate intervention, including oxygen requirement < 40%, grade 2 organ toxicity, or hypotension responding to IV fluids or low doses of one vasopressor (e.g., < 20 mg/min of norepinephrine)
3	Oxygen requirement > 40%, hypotension requiring high-dose or multiple vasopressors, grade 4 transaminitis, and grade 3 organ toxicity at other sites
4	Life-threatening symptoms requiring ventilator support or grade 4 organ toxicity other than transaminitis
5	Death

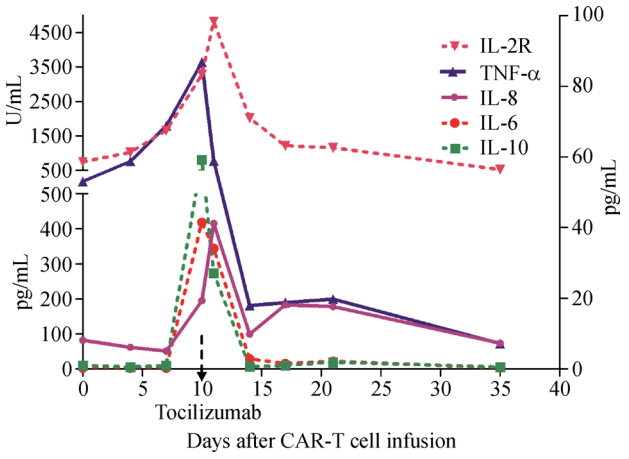

Fig. 1 Cytokine changes in case 1 with grade 3 CRS. IL-2R, IL-6, IL-8, IL-10, and TNF-α were significantly elevated through days 8 to 13 (IL-6 > 123-fold and IL-10 > 89-fold over baseline levels). Tocilizumab was given at a dose of 8 mg/kg on day 10.

of CRS. In this study, we attempt to analyze and discuss CRS management by presenting four cases who suffered CRS following CAR-T cell therapy.

Case 1: grade 3 CRS after CAR-T cell therapy for relapsed multiple myeloma

Patient 1 was a 57-year-old man with multiple myeloma (ISS III, R-ISS III, D-S IIA) for 2 years. His disease relapsed during first-line treatment involving nine cycles of bortezomib-based chemotherapy and lenalidomide. The patient was then enrolled in a phase 1 trial of LCAR-B38M CAR-T cell immunotherapy (NCT03090659). At the time of enrollment, his laboratory test results showed the presence of the M protein (IgG 3440.00 mg/dL) and 26.5% myeloma cells in his bone marrow (BM). Lymphodepletion using three doses of cyclophosphamide (CTX) 300 mg/m^2 on days 5, 4, and 3, followed by the infusion of engineered LACR-B38M CAR-T cells 5 days after the initiation of lymphodepletion chemotherapy. A total of 1.8×10^6 CAR-T cells/kg was split into three infusions (20%, 30%, and 50% of the total dose) administered on days 0, 2, and 6. The patient developed a fever accompanied by fatigue and nausea on day 9. His fever persisted for 4 days with the highest point reaching 41 °C. On day 10, he developed hypotension (86/44 mmHg), tachycardia, and acute respiratory failure (PO_2 52 mmHg, PCO_2 24 mmHg) with remarkably elevated levels of IL-6 and IL-10 (IL-6 > 123-fold and IL-10 > 89-fold over baseline levels, Fig. 1), grade II liver function damage, grade I renal function damage, and coagulation disorder. Lung imaging indicated lung infection and bilateral pleural effusion. He was treated with dopamine and aramine to maintain blood pressure and with 8 mg/kg tocilizumab. He was also given broad-spectrum antibiotics and supportive treatments, including antipyretics, transfusion support, volume resuscitation, vital sign monitoring, and input–output number record. Finally, his symptoms improved on day 12, and vasopressor support was discontinued on day 19. The cytokine level returned to the baseline level within 4 weeks. The patient's M protein level returned to normal on day 34, and his BM demonstrated CR on day 20. Eight-color flow cytometry on day 30 showed that minimal residual disease was negative. Long-term evaluation showed that the patient sustained strict CR for 25 months.

Case 2: grade 3 CRS after CAR-T cell therapy for B-ALL

A 19-year-old male patient with ALL underwent Philadelphia chromosome-positive relapse for 1 month after maintenance treatment with dasatinib. He was then enrolled in CD19-CAR-T cell therapy. At the time of enrollment, his BM had a lymphoblast level of 77.5%, and his white blood cell (WBC) count was 118×10^9/L. He received lymphodeleption chemotherapy with fludarabine 30 mg/m^2 and CTX 300 mg/m^2 on days –5 through –3. His WBC count was reduced to 2.38×10^9/L. He was treated with 12×10^6 CAR-T cells through intravenous injection on day 0. The patient suffered intermittent hyperpyrexia on days 1 to 5 that peaked at 40 °C but did not show evidence of infection. We terminated CAR-T cell infusion and provided supportive treatment. On day 5, the patient's WBC suddenly increased to 210×10^9/L, and his peripheral blood smear showed lymphoblasts. The same lymphodeleption chemotherapy was given again to reduce the tumor burden. After the second lymphodepletion chemotherapy cycle, the patient's WBC count was reduced to 1.21×10^9/L again. He received an infusion of 30×10^6 CAR-T cells on days 11 and 12. On day 13, the patient developed fever again with dizziness, headache,

shortness of breath, and hypotension (85/38 mmHg). The laboratory tests showed extremely elevated levels of IL-6, IL-8, and IL-10 (IL-6 > 294-fold, IL-8 > 20-fold, and IL-10 > 20-fold over baseline levels, Fig. 2) and aminotransferase levels that reached grade III. He was given oxygen, dopamine, and blood component transfusion supportive treatment. Given that he presented unstable hemodynamics, we immediately treated him with tocilizumab (4 mg/kg, 2 days) on days 13 and 14. On day 17, his symptoms improved, and vasopressor support was terminated. Further assessment on day 45 revealed that the lymphoblast levels in his BM exceeded 80%.

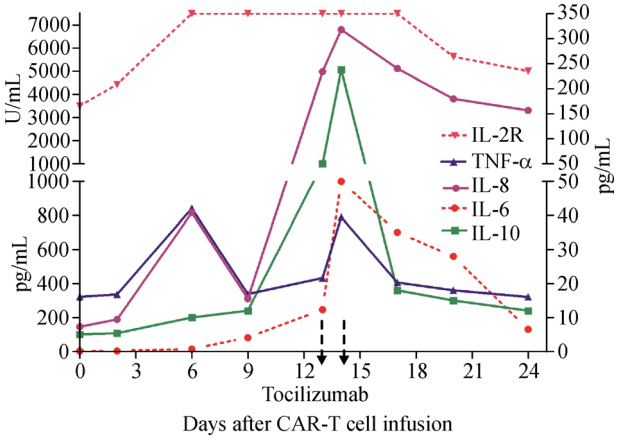

Fig. 2 Cytokine changes in case 2 with grade 3 CRS. IL-2R, IL-6, IL-8, IL-10, and TNF-α were significantly elevated through days 10 to 17 (IL-6 > 294-fold, IL-8 > 20-fold, and IL-10 > 20-fold over baseline levels). Tocilizumab was administered at a dose of 4 mg/kg on days 13 and 14.

Case 3: grade 3 CRS after CAR-T therapy for leukemia

Patient 3 was a 57-year-old man with chronic myeloid leukemia for 4 years and who had progressed to ALL for 9 months. He failed to achieve remission after 3 cycles of intensive chemotherapy and tyrosine kinase inhibitor treatment. At the time of enrollment, his BM mononuclear cells had 67.5% lymphoblasts and his WBC was 0.57×10^9/L. On days 5 to 3, the patient received fludarabine 30 mg/m^2 and CTX 300 mg/m^2. A total of 39×10^6 CAR-T cells were administered on days 0, 2, and 7. During the infusion of CAR-T cells, the patient was treated with oral dasatinib (100 mg/day, 2 days) to reduce the tumor burden. On day 9, the patient had a fever that peaked at 40 °C and was accompanied by sinus tachycardia. Although aggressive supportive treatments were given, the patient's symptoms progressed on day 10. The patient experienced chills; appeared flustered; and presented sinus tachycardia, acute laryngeal edema, and dyspnea, together with elevated IL-6 and IL-10 levels (IL-6 > 294-fold, IL-10 > 109-fold over baseline levels, Fig. 3), grade III liver dysfunction, grade I renal dysfunction, and disseminated intravascular coagulation (DIC). Lung imaging showed multiple high-density shadows on both lungs and right pleural effusion. Given that the patient suffered grade 3 CRS and lung infection, we gave him broad-spectrum antibiotics, low doses of tocilizumab (4 mg/kg, 2 days), low-molecular-weight heparin (LMWH), sodium, and supportive treatment. Once the patient experienced acute laryngeal edema, we treated him with dexamethasone at a dose of 10 mg. Finally, his acute respiratory distress symptoms released within half an hour. However, 2 days of treatment with tocilizumab failed to ameliorate CRS. We treated the patient with an additional dose of dexamethasone (10 mg/day, 2 days), and his vital signs stabilized on day 16. Additionally, the patient had neurological toxicity with ephemeral consciousness and gazing up for approximately 1 min. His head imaging revealed no abnormalities, and the symptoms did not occur after phenobarbital treatment.

The cytokine level returned to the baseline within 4 weeks. His peripheral blood cells returned to normal on day 34, and his marrow indicated CR. He did not undergo hematopoietic stem cell transplantation (HSCT) and remained disease free for 4 months.

Case 4: grade 2 CRS after CD19-CAR-T therapy for B-ALL

An 18-year-old man with primary refractory pre-B cell ALL (BCR/ABL$^+$, high risk) failed to experience remission after 8 cycles of intensive chemotherapy and dasatinib treatment. He then received anti-CD19-CAR-T cells therapy. Fludarabine 30 mg/m^2 and CTX 300 mg/m^2 were given on days 5 to 3. A total of 38×10^6 CAR-T cells were injected on days 0 through 2. On day 8, the patient experienced hyperpyrexia that peaked at 40 °C and was associated with rigor that persisted for 9 days. Lung imaging indicated pulmonary infection. No other infectious indications were observed. He was given broad-spectrum antibiotic therapy including biapenem, vancomycin, and voriconazole on day 8. Meanwhile, we closely monitored his vital signs and balanced his body fluid levels. On day 10, the levels of IL-6 and IL-10 were remarkably elevated in the serum (IL-6 > 185-fold and IL-10 > 36-fold, Fig. 4). All laboratory tests indicated that the patient suffered DIC, grade III liver function damage, grade I renal function damage, and premature atrial contraction. Continuous hyperpyrexia did not improve after aggressive antifebrile and antibiotic treatment and blood component transfusion. On day 11, we administered

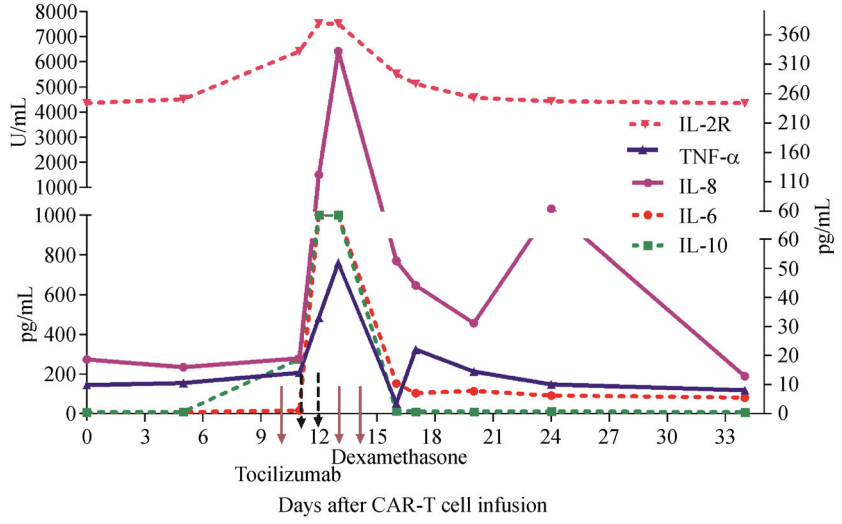

Fig. 3 Cytokine changes in case 3 with grade 3 CRS. IL-2R, IL-6, IL-8, IL-10, and TNF-α were significantly elevated on days 11 to 15 (IL-6 > 294-fold and IL-10 > 109-fold over baseline levels). Tocilizumab was administered at a dose of 4 mg/kg on days 11 and 12. Dexamethasone was provided at a dose of 10 mg/day on days 10, 13, and 14.

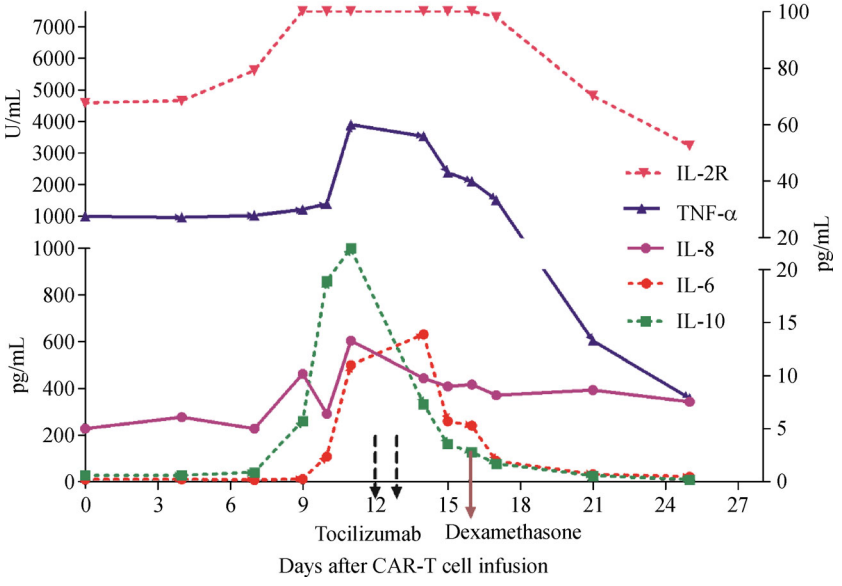

Fig. 4 Cytokine changes in case 4 with grade 2 CRS. IL-2R, IL-6, IL-8, IL-10, and TNF-α were significantly elevated through days 9 to 15 (IL-6 > 185-fold and IL-10 > 36-fold). Tocilizumab was administered at a dose of 4 mg/kg on days 12 and 13. Dexamethasone was administered at a dose of 10 mg/day on day 16.

low-dose tocilizumab (4 mg/kg, 2 days) for 2 days. The patient's symptoms, however, were not relieved. Finally, his temperature returned to normal, and his symptoms improved until dexamethasone (10 mg, 1 day) was administered on day 16.

The patient's peripheral blood cell levels returned to normal, and his marrow sample on day 36 demonstrated CR. The patient sustained CR for only 3 months, and no appropriate donor for HSCT was found.

Discussion

CRS is a systematic inflammatory response that arises as an adverse event of some disease or severe infection and is

a complication of therapy with CAR-T cells and monoclonal antibodies [9]. CRS is triggered by the activation of a series of immune cells, such as T cells, B cells, NK cells, monocytes and/or macrophages, dendritic cells, and endothelial cells [8,10]. Activated immune cells release inflammatory cytokines and chemokines, including IL-2, IL-6, IL-10, IFN-γ, TNF-α, and CXCL10. CRS can lead to widespread reversible multiorgan dysfunction that includes the cardiovascular, respiratory, gastrointestinal, hepatic, renal, hematological, musculoskeletal, and nervous systems [5,11–15]. The clinical features of CRS include not only some flu-like symptoms, such as fever, myalgia, fatigue, anorexia, nausea, and vomiting, but also life-threatening cardiac dysfunction, hypoxic respiratory failure, hypotension, DIC, and renal and/or hepatic failure [8]. The symptomatology and severity of CRS vary greatly. The intensive monitoring and early intervention of adverse events facilitate the safe and efficient use of CAR-T cells as a potential curative approach in clinics. Given that CRS occurs when inflammatory cytokine levels are elevated, researchers have focused on identifying circulating cytokines that can be used as predictive biomarkers or models for forecasting patients who may suffer severe CRS during CAR-T cell therapy [16]. Scientific and clinical experience has implied the relationship between the severity of CRS and the level of cytokines, including TNF-α, IL-6, IL-1, CRP, ferritin, and IFN-γ [6,7,10,11,13,17]. We monitored the levels of cytokines, including TNF-α, IL-2, IL-6, IL-8, IL-10, CRP, and ferritin before and after CAR-T cell therapy to predict patients who may develop severe CRS and other toxicities. No conclusion has been reached given the limited number of cases studied. Collaborative efforts to develop predictive models based on some biochemical markers remain underway. In addition, studies have indicated that the severity of CRS is associated with tumor type and burden, CAR structure, infused CAR-T cell dose, high-intensity lymphodepletion with fludarabine, preexisting endothelial activation, and cytokine gene polymorphism [18]. The involvement of increased malignancy burden in BM has been established as a risk factor for toxicity in patients with B cell malignancies receiving anti-CD19 CAR-T cell treatment [10] and in patients with multiple myeloma receiving anti-BCMA CAR-T cell treatment [19,20].

Aggressive monitoring and treatment should be given once the patient exhibits hyperpyrexia. The symptomatic treatments of patients with severe CRS include tocilizumab, corticosteriods, vasoactive agents, organ protection treatment, antipyretic, transfusion support, volume resuscitation, and mechanical ventilation.

Tocilizumab

Tocilizumab is a humanized, anti-human IL-6-receptor antibody that has been approved for treatment of rheumatoid arthritis by the US Food and Drug Administration [21]. Tocilizumab prevents IL-6 from binding to cell-associated and soluble IL-6Rs and therefore inhibits classical and trans-IL-6 signaling [22]. Tocilizumab is now recommended as a first-line or standard approach for treatment of CRS-related toxicities following CAR-T cell infusion. Improvements occur within a few hours after using tocilizumab. Tocilizumab treatment also reduces the need for adjuvant therapy. However, the timing and method for the use of tocilizumab remain unstandardized. Numerous clinical programs administer tocilizumab to patients suffering from CRS of grade 3 or higher, whereas some recommend it when specific hemodynamic and organ function thresholds are crossed [8]. Tocilizumab dosing varies among centers and is given at a dose of 4 or 8 mg/kg [5,8]. Tocilizumab shows no evidence for affecting the clinical curative efficacy of CAR-T cells therapy [5,7,11].

According to our experience, tocilizumab should be provided early in accordance with toxicity grading and clinical manifestation, especially for patients whose CRS toxicities deteriorated rapidly. We suggest the early application of tocilizumab at a dose of 4 mg/kg for severe and partially moderate CRS patients. Patients who suffer continuous hyperpyrexia, hypotensive shock, acute respiratory failure, and CRS toxicities with rapid progression can be treated with tocilizumab at a full dose of 8 mg/kg (maximum 800 mg/dose). After tocilizumab administration, clinical manifestations, including fever, cytokine levels, and organ function should be continuously monitored. A second 8 mg/kg dose of tocilizumab could be administered, or other immunosuppression should be introduced, such as a corticosteroid, to patients with severe conditions that do not improve or stabilize within 8–24 h.

Some patients experienced neurological toxicity during CAR-T cells therapy. Given that tocilizumab cannot pass through the blood–brain barrier, this agent has no effect on patients suffering from central nervous system toxicity [8]. Some researchers have considered that elevated IL-6 levels in the cerebrospinal fluid promote disease progression [22].

Corticosteroids

Clinical experience indicates that corticosteroids are effective treatments for suppressing intensive inflammatory response and CRS [23]. However, physicians have different opinions on the timing and dosing of corticosteroids. Some physicians may choose to use corticosteroids as a first-line agent, whereas others do not [8]. This choice is based on emerging evidence that corticosteroids have widespread effects on the immune system and inhibit the antimalignancy efficiency of CAR-T cells [5]. In addition, corticosteroids may affect the amplification and persistence of CAR-T cells *in vivo* [5]. Indications for the dosing of

corticosteroids vary among centers. Some centers recommend administering methylprednisolone at a dosage of 1–2 mg/kg intravenously every 12 h to patients suffering from CRS toxicity refractory to tocilizumab. In addition, patients with grade 3 or 4 neurological toxicity are recommended to receive 10 mg IV q6h dexamethasone until either toxicity improves to grade 1 or less [4].

We suggest that corticosteroids be applied to patients with neurotoxic effects and cases of severe or life-threatening CRS, especially those who have no response to tocilizumab. Considering the antitumor efficiency of CAR-T cells, we attempted treatment with a low dose of dexamethasone (5–10 mg/day) until the patient's condition improved. In our report, cases 3 and 4 were treated with dexamethasone for severe CRS that failed to respond to tocilizumab. Case 3 suffered severe dyspnea after CAR-T cell infusion and was suspected acute laryngeal edema. We treated him with dexamethasone at a dose of 10 mg, and his symptoms improved immediately. Patient 3 was continuously treated with dexamethasone at a low dose of 10 mg for 3 days, and his disease maintained CR for 4 months. The dosing and choice of corticosteroid should be tailored to the individual patient. Further research is needed to assess the optimal timing and dosing of corticosteroids for managing CRS and neurological toxicity after CAR-T cell infusion.

Supportive care and hemodynamic management

Fever is frequently the first clinical symptom of CRS. Continuous hyperpyrexia generally occurs within few hours or days following CAR-T cell infusion [4,24]. Antipyretics, volume resuscitation, and physical cooling treatments are all needed to treat hyperpyrexia, and vital signs are monitored every 2 h. Infection may occur concurrently with or after CRS. Imaging, blood cultures, and other laboratory tests, such as G test, GM test, endotoxin, and sputum culture, provide additional evidence for diagnosis of infection. However, distinguishing the cause of fever between CRS toxicity and infection is difficult [25]. In our practice, antibiotics should be administered to prevent infection in neutropenic patients. Additionally, antifungal prophylaxis treatment is recommended for patients who have a history of pulmonary fungal infection. Patients with severe CRS can suffer from hypotensive shock after CAR-T cell infusion because of factors, such as persistent high fever and capillary leakage [26–29]. Hypotension must be recognized early and managed aggressively. In our clinical practice, we first considered the deficiency of blood volume and offered volume resuscitation. Volume resuscitation treatment contains normal saline, 5% glucose, human albumin solution, human immunoglobulin, and hydroxyethyl starch. The early application of vasoactive drugs is needed for patients with hypotension who did not respond to volume resuscitation. Norepinephrine and metaraminols are common vasopressor agents. In our center, we offer liquid crystal and colloidal liquid supplementation to treat hypotension. Cases 1 and 2 in our report suffered hypotensive shock, but their vital signs stabilized after using vasoactive agents.

Patients experience coagulation disorders following CAR-T cell infusion. These disorders appear as prolonged PT and APTT, hypofibrinogenemia, and elevated D-dimer and fibrinogen degradation product levels. To reduce the risk of bleeding, we provided transfusion support, such as fresh frozen plasma, cryoprecipitate, and fibrinogen. Additionally, we administered 4000 IU/day LMWH sodium to DIC patients who had no contraindication. Our clinical experience demonstrated that the administration of LMWH sodium is an efficient and safe approach for improving DIC and reduces transfusion support. Additional studies are needed to assess the efficiency and safety of anticoagulant drugs for improving DIC after CAR-T therapy.

Conclusions

Given the potential of CAR-T cell therapy, we expect to prevent life-threatening CRS while maximizing the antitumor effects of CAR-T cells therapy. First, we suggest the early application of tocilizumab at a dose of 4 mg/kg for patients with severe and moderate symptoms. Patients who suffer continuous hyperpyrexia, hypotensive shock, acute respiratory failure, and rapidly progressing CRS toxicities can be treated with tocilizumab at the full dose of 8 mg/kg (maximum 800 mg/dose). If patients with severe conditions do not improve or stabilize within 8–24 h of tocilizumab administration, then a second 8 mg/kg dose of tocilizumab could be administered. In addition, low doses of dexamethasone (5–10 mg/day) can be administered to patients with refractory CRS not responding to tocilizumab. Finally, severe or life-threatening grades of CRS require vasopressors and aggressive supportive treatments.

Compliance with ethics guidelines

Hongli Chen, Fangxia Wang, Pengyu Zhang, Yilin Zhang, Yinxia Chen, Xiaohu Fan, Xingmei Cao, Jie Liu, Yun Yang, Baiyan Wang, Bo Lei, Liufang Gu, Ju Bai, Lili Wei, Ruili Zhang, Qiuchuan Zhuang, Wanggang Zhang, Wanhong Zhao, and Aili He declare no competing interests. The clinical trials of LCAR-B38M therapy and CD19-CAR-T cells therapy were approved by the Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 *Helsinki Declaration* and its later amendments or comparable ethical standards.

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