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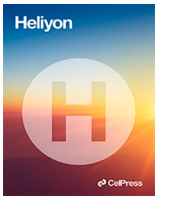

Review article

Improving cell reinfusion to enhance the efficacy of chimeric antigen receptor T-cell therapy and alleviate complications

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ABSTRACT

Adoptive cell therapy (ACT) is a rapidly expanding area within the realm of transfusion medicine, focusing on the delivery of lymphocytes to trigger responses against tumors, viruses, or inflammation. This area has quickly evolved from its initial promise in immuno-oncology during preclinical trials to commercial approval of chimeric antigen receptor (CAR) T-cell therapies for leukemia and lymphoma (Jun and et al., 2018) [1]. CAR T-cell therapy has demonstrated success in treating hematological malignancies, particularly relapsed/refractory B-cell acute lymphoblastic leukemia and non-Hodgkin's lymphoma (Qi and et al., 2022) [2]. However, its success in treating solid tumors faces challenges due to the short-lived presence of CAR-T cells in the body and diminished T cell functionality (Majzner and Mackall, 2019) [3]. CAR T-cell therapy functions by activating immune effector cells, yet significant side effects and short response durations remain considerable obstacles to its advancement. A prior study demonstrated that the therapeutic regimen can induce systemic inflammatory reactions, such as cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), tumor lysis syndrome (TLS), off-target effects, and other severe complications. This study aims to explore current research frontiers in this area.

1. Introduction

CARs are designed to equip T cells with the ability to target and damage cancer cells. They combine an external domain, which identifies cancer-specific antigens using a single-chain variable fragment (scFv) from antibody segments, with an internal domain that activates T cells through elements of the T cell receptor (TCR) and costimulatory signals. This structure ensures precise targeting and effective T cell activation against tumors [1,2]. CAR T-cell therapy is a powerful treatment option for hematologic malignancies [3–5]. In this approach, the patient's own T cells are collected and engineered to recognize target antigens. These cells are then expanded in vitro before being reintroduced into patients for *in vivo* treatment [6]. Subsequently, CAR T cells engage and eliminate targeted tumor cells they encounter. Briefly, the progress of CAR T-cell approach has been described as follows (Fig. 1). CAR T-cell therapy exhibits high effectiveness against certain challenging cancers, yet it can also lead to serious or even life-threatening side effects. This method activates CAR T cells when they identify particular antigens on cancer cells inside the body. As CAR T cells proliferate, they can release significant amounts of cytokines into the bloodstream, leading to heightened immune activity. This release may result in severe side effects such as high fever, chills, respiratory difficulties, intense nausea, vomiting, diarrhea, dizziness, headaches, rapid heartbeat, extreme fatigue, and muscle or joint pain [7–9]. Clinical strategies have been employed to enhance the efficacy of CAR T-cell therapy

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while mitigating potential risks. Studies have indicated that improving the CAR T cells reinfusion scheme can enhance the therapeutic impact and lower complication rates. Similarly, this study aims to summarize the research scope and application status of improving the CAR T cells reinfusion scheme to enhance its therapeutic effect and avoid complications.

2. Concise overview concerning CAR T-cell therapy

Artificial transmembrane receptors known as CAR T-cell receptors are composed of a single-chain extracellular antibody fragment and intracellular signaling domains taken from the T-cell receptor and costimulatory molecules. These receptors are designed for specific recognition and activation within T cells [10]. As engineered proteins, CAR-T cells can control cell activation and guide cytotoxic lymphocytes to specific antigens [11]. The antigen-recognition domain of CAR T cells primarily relies on sequences from monoclonal antibodies, which interact with tumor epitopes without the requirement for MHC presentation. Currently, CAR T-cell technology shows great potential in addressing hematologic malignancies and other medical conditions [12], suggesting its potential as a broadly applicable cancer treatment modality [13].

3. Pretreatment of CAR T cells reinfusion

3.1. Mechanism of pretreatment to improve therapeutic effect

Pretreatment preceding CAR T-cell immunotherapy involves lymphocyte depletion primarily through chemotherapy or radiotherapy [14]. This pretreatment regimen aims to decrease lymphocyte numbers while maintaining stable cytokine levels, thereby facilitating enhanced contact between CAR T cells and cytokines to support their stable proliferation [15,16]. Some studies have shown that administering cyclophosphamide and fludarabine before CAR T cells reinfusion can inhibit the expression of indoleamine 2,

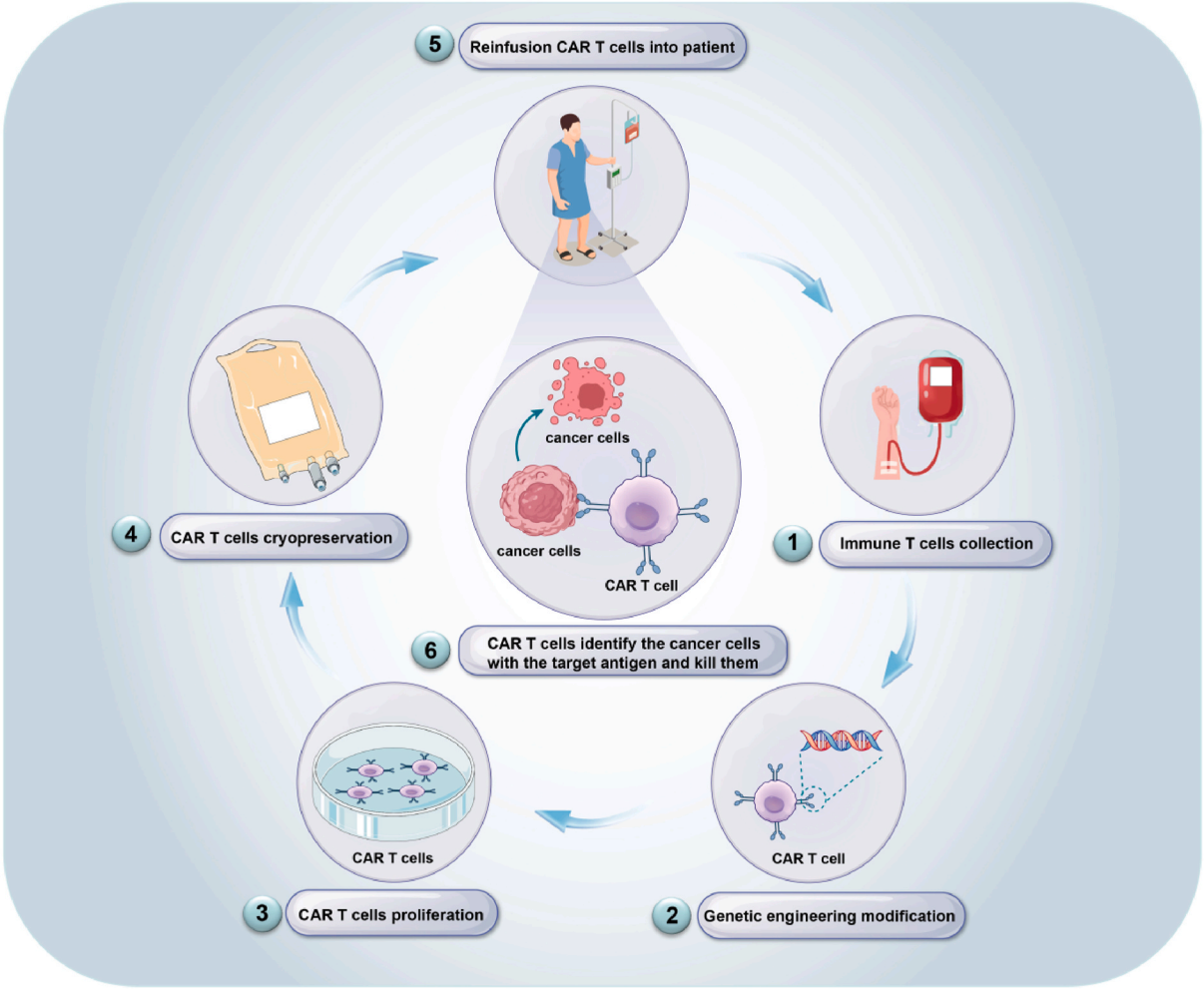

Fig. 1. Chimeric antigen receptor T-cell therapy.

3-dioxygenase in mouse B-cell malignant tumors, thereby reducing tryptophan metabolism and increasing CAR T-cell proliferation and activity [17]. Clinical evidence suggests that pretreatment can enhance the efficacy of CAR T-cell immunotherapy [18,19]. Brentjens studied 10 patients with acute lymphocytic leukemia and chronic lymphoblastic leukemia to compare the efficacy of cyclophosphamide pretreatment and non-pretreatment. The study showed that patients receiving cyclophosphamide pretreatment had stronger CAR T cells persistence and clinical activity than those with non-pretreatment [18]. Zhang performed a meta-analysis of the clinical data of 131 patients with recurrent/refractory B-cell malignancies and compared the 6 months progression free survival rate of patients with or without pretreatment before CAR T cells reinfusion [20]. The study showed that the progression free survival rate of patients with pretreatment before CAR T cells reinfusion was 94.6%, which was higher than the 54.5% of the with-pretreatment group ($P < 0.001$) [21]. A study by Caimi proved that administering tocilizumab prophylactically prior to CD19-CAR T cell reinfusion significantly mitigates CRS severity [22]. Therefore, the pretreatment scheme is of great importance for CAR T-cell immunotherapy.

3.2. Pretreatment scheme selection

To explore the best pretreatment scheme of CAR T-cell therapy, a series of clinical studies focused on the necessity of pretreatment scheme, the choice of drugs and dosage, and the treatment of subsequent adverse reactions [19]. In the selection of chemotherapy treatments, the combination of fludarabine and cyclophosphamide currently stands as the most commonly adopted regimen for lymphodepletion [23,24]. A clinical trial on 30 patients with B-cell acute lymphoblastic leukemia was carried out in the Fred Hutchinson Cancer Research Center [25,26]. Studies have found that the combination of fludarabine and cyclophosphamide is linked to improved disease-free survival and enhanced persistence of CAR T cells, in comparison to the cyclophosphamide-etoposide combination or cyclophosphamide alone. In addition to this scheme, various other schemes containing bendamustine, pentostatin, and polychemotherapy, although possible, are seldom used [27,28].

In addition to the pretreatment of chemotherapy drugs, total body irradiation (TBI) has also been applied to the pretreatment of adoptive cellular transfer immunotherapy, represented by CAR T cells reinfusion [29,30]. Researchers conducted a clinical trial on patients with metastatic melanoma. Patients were categorized into two cohorts: the first received pretreatment with fludarabine and cyclophosphamide, while the second underwent a regimen of chemotherapy in conjunction with total body irradiation (TBI). The results showed that the response rate of chemotherapy pretreatment alone was 49%, and that of the other group had a maximum of 72% [31]. Comparable studies have demonstrated that mice receiving radiotherapy before the infusion of CD19-CAR T cells exhibited extended survival times compared to those that did not undergo radiotherapy [32]. Therefore, chemotherapy combined with radiotherapy can improve the therapeutic effect, but confirming the efficacy and safety of this method requires further study.

Except of the above pretreatment schemes, some researcher established evidence-based approaches of prophylactic immunoglobulin. They made some suggestions that patients before CAR T cells reinfusion for B-cell malignancies with IgG $\leq$400 mg/dL shuold consider prophylactic IgG. Additionally, they recommend monitoring serum IgG levels both before and during the first three months following CAR T-cell approach for B-cell malignancies. Historically, corticosteroids have been omitted from the CAR T-cell therapy protocol because of their ability to harm lymphocytes [27]. However, some clinical trials have proved that prophylactic use of dexamethasone can effectively decrease severity of CRS [33]. Furthermore, research has shown that administering antihistamines and antipyretics prior to CAR T-cell reinfusion can aid in mitigating adverse reactions. The efficacy of this pretreatment approach, however, requires further empirical validation [34].

3.3. Pretreatment dose selection

Regarding the dosage of pretreatment, studies have shown that appropriately reducing the pretreatment dose can achieve similar clinical effects and reduce toxicity [35,36]. However, without any pretreatment, the effective remission rate of the disease is reduced [37]. The National Cancer Institute has conducted two studies at different times. In the first study, patients with B-lymphomas were administered high doses of cyclophosphamide and fludarabine as a preparatory regimen prior to receiving CAR T-cell infusion. The second study utilized low doses of cyclophosphamide and fludarabine for patients with non-Hodgkin lymphoma prior to CAR T-cell reinfusion. The outcomes indicated that 87% of patients in the first study experienced acute adverse reactions following CAR T-cell reinfusion. In contrast, the second study reported a significantly lower incidence of such reactions following CAR T-cell reinfusion [35,36]. The reasons for the different results may be due to different types of diseases or different dosag of chemotherapy drugs. However, these findings also highlight a valuable research direction, emphasizing that choosing the correct pretreatment dosage is crucial for augmenting treatment effectiveness and diminishing the occurrence of complications.

4. Management in CAR T cells reinfusion process

4.1. Observation of the Patient's condition

Observation of the patient's condition is an important work before CAR T cells reinfusion. Patients shuold be hospitalized to monitor oxygen saturation, vital signs, urinary output and other indicators. Meanwhile, during reinfusion emergency materials should be placed beside the patients [27,28]. Studies have suggested that the possibility of CRS and adverse nervous system reactions after cell reinfusion is higher and more serious in patients with neoplastic fever before cell reinfusion [38]. Therefore, it is essential to promptly address any discomfort experienced by patients before reinfusion. In the process of reinfusion, the patients may have vomiting, nausea, fever, abdominal pain and tremors. Respiratory depression, neurological symptoms or cardiac arrhythmias also may be observed [39].

In such instances, healthcare professionals, including nurses and doctors, should consider slowing down or temporarily stopping the reinfusion process, initiating emergency interventions, and verifying the product being used [40].

4.2. CAR T cells thawing

A 10% DMSO solution is widely recognized as the standard freezing medium for CAR T cells [41]. Recently, studies have lowered the concentration of DMSO from 10% to either 7.5% or 5% [42,43]. Furthermore, investigations are underway into a cryopreservation solution comprised of 50/55% DMSO mixed with 5% dextrose as an innovative substitute for the DMSO-dextran combination. This alternative approach is targeted at preventing the aggregation of DNA and proteins from lysed cells, as well as mitigating cell swelling during the thawing phase, potentially improving the overall viability and functional integrity of the cells post-thaw [44]. The thawing process is crucial for ensuring the quality of infused cells and the clinical effectiveness of the product [45]. When thawing the CAR T cell bag, either on-site at the pharmacy or at a subcontracted cell processing facility, double-wrap it in protective plastic and place it in a dedicated 37 ± 2 °C water bath in a clean room, until the product is completely thawed [46]. Unsurprisingly, the optimal thawing rate is influenced by the rate of cooling employed [47]. It is advisable to double-wrap the CAR T cell bag in a waterproof plastic covering during thawing. This measure serves to safeguard the integrity of the bag and enables nurses to detect any unnoticed solution leakage during the transfer process [46]. Recently, researchers have introduced a thawing technique that eliminates the need for a water bath, thereby reducing the risk of contamination during thawing [41]. This alternative approach usually entails applying mechanical heat, such as utilizing a heated metallic plate or sealed warm liquids that do not come into direct contact with the thawed sample [48,49]. However, adoption of this technology remains limited.

4.3. CAR T cells reinfusion

Before reinfusing CAR T cells, patients' clinical status must be thoroughly reassessed, encompassing vital signs (body temperature, blood pressure, blood oxygen saturation, heart rate), presence of active infections, and organ function. Active infection and hypotension requiring vasopressor therapy are contraindications to CAR T cells reinfusion, and CAR T cells reinfusion needs to be delayed until infection or hypotension is completely treated or controlled [27]. Some studies suggest that patients with tumor fever before reinfusion are more likely to have CRS and nervous system adverse reactions after cell reinfusion, and are more serious [50]. In addition, corticosteroids should not be used before infusion unless in life-threatening situations, preventing the destruction of CAR T cells expansion and survival. Acetaminophen derivatives and antihistamines, like chlorphenamine maleate or diphenhydramine, are commonly given 30–60 min prior to CAR T cell reinfusion to decrease the likelihood of infusion reactions [27]. The widespread use of steroids is prohibited during and after transfusion (unless used to treat adverse reactions related to cells reinfusion, such as CRS or neurological adverse reactions) [27]. Mononuclear macrophages are significantly involved in the initiation and progression of adverse reactions associated with CAR T-cell therapy [51,52]. Granulocyte-macrophage colony-stimulating factor (GM-CSF) can stimulate macrophages, aggravating cell reinfusion related adverse reactions. Although some studies have shown that the application of GM-CSF neutralizing antibodies may be able to eliminate CRS and neurological adverse reactions and enhance CAR T cells function, but this mechanism needs further research to confirm [53,54]. In addition, the vital signs of the patients should be closely observed during the CAR T cells reinfusion process. The process should be carried out with reference to the product instructions, and the emergency equipment should be in a standby state [55,56].

5. Observation of complications after CAR T cells reinfusion

5.1. CRS

Cytokine storm, known as CRS, is a severe systemic inflammatory response syndrome that can be initiated by infection or the use of specific medications [57,58]. CRS is accompanied by a series of biochemical changes. Davila argued that IFN-γ, IL-6, IL-5, IL-10, Flt-3L, GM-CSF, and fractalkine are closely related to severe CRS [59]. Different researchers have different conclusions in this respect. A number of cytokines peak after the occurrence of CRS, including ferritin, CRP, AST, ALT, and BUN, thus they are not helpful in

Table 1
ASTAC CRS consensus grading[a] [64].

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever[b]	Temperature ≥38.5 °C	Temperature ≥38.5 °C	Temperature ≥38.5 °C	Temperature ≥38.5 °C
Hypotension[b]	None	Not necessitating vasopressors	Necessitating the use of a vasopressor, with or without vasopressin	Necessitating multiple vasopressors (excluding vasopressin)
Hypoxia[b]	None	Necessitating the use of low-flow nasal cannula (≤6 L/minute)	Necessitating high-flow nasal cannula (>6 L/minute) or facemask	Necessitating positive pressure

[a] The CRS grade is determined based on the most severe event experienced by the patient: For instance, a patient with a temperature of 39.0 °C, hypotension requiring vasopressors, and hypoxia necessitating positive pressure is classified as grade 4 CRS.
[b] Fever hypotension and hypoxia are not attributable to any other cause.

predicting CRS [8,60]. Besides observing the biochemical changes, it is also necessary to observe the symptoms of patients. The symptoms of CRS may manifest progressively, with primary clinical presentations including fever, low blood pressure, hypoxia, and end-organ dysfunction. However, these symptoms are not exclusive to CRS [61–63]. Furthermore, there clinical manifestations must be a reasonable time relationship between diagnosis of CRS and cell therapy. Experts from the American Society for Transplantation and Cellular Therapy (ASTCT) have developed a grading system to accurately evaluate the severity of CRS. This system is currently the predominant standard utilized in the field [64] (Table 1).

5.2. ICANS

Research has shown that patients undergoing CD19-CAR T-cell therapy may develop ICANS at an incidence varying between 21% and 64%. Similarly, BCMA-CAR T-cell therapy has been associated with ICANS in 18%–21% of patients. The severity of ICANS, classified as grade $\geq$3, has been reported in 10%–30% of CD19-CAR T-cell cases and in 3%–9% of BCMA-CAR T-cell cases [65–70]. The onset typically occurs around one week after reinfusion [71–73]. Clinical manifestations of ICANS vary widely, spanning from tremors, confusion, and dysphasia/aphasia to deteriorating handwriting or seizures [64]. Schoeberl et al. discovered link between elevated preinfusion serum levels of neurofilament light chain, an indicator of neuroaxonal damage, and the intensity of ICANS [74]. Gust et al. suggest that pre-existing neurological comorbidities (e.g., peripheral neuropathy and headache disorder) are risk factors for ICANS [60]. Nurses should carefully observe the clinical manifestations of patients after CAR T cells reinfusion and strive to identify ICANS in advance to reduce its impact on patients.

5.3. TLS

TLS refers to the rapid release of cell contents into the blood due to the massive dissolution and destruction of tumor cells, where a series of complications are caused by the accumulation of metabolites due to exceeding the liver metabolism and renal excretion capacity. TLS mainly manifests as hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and metabolic acidosis [75]. TLS is not a specific complication of CAR T-cell therapy and can occur in patients undergoing chemotherapy. Therefore, it is very important to accurately identify the causes of TLS and early medication is beneficial to prevent the occurrence of TLS [76]. Allopurinol is recommended as the primary preventive medication for patients classified as low or moderate risk of TLS [77,78]. Conversely, rasburicase is the preferred choice for both prevention and treatment of TLS in patients at high risk [79]. To detect TLS, nurses must closely monitor the patient's vital signs and renal function, while accurately documenting their 24-h intake and output. Nurses should adhere to the physician's guidance and provide appropriate care accordingly.

5.4. Off-target effect

Tumor antigens include tumor-specific antigens (TSA) and tumor-associated antigens (TAA). The TAS on the tumor surface are relatively lacking. Consequently, CAR T cells may identify and eradicate tumor cells, potentially causing unintended damage to normal tissues with low expression of target antigens, leading to off-target effects [80]. Therefore, CAR T cells can attack normal tissues and cause damage to them and organs while clearing tumors [81]. Beatty's study pointed out that the off-target effect can cause toxic reactions such as cardiac arrest, respiratory failure, intestinal obstruction, and abdominal pain [82]. To minimize off-target effects, it is recommended to regulate the reinfusion dose and route of CAR T cells. Typically, toxicity levels are positively associated with the dose of CAR T cells, underscoring the importance of carefully selecting the initial dose for the first treatment [83]. It is recommended to use a stepwise dose reinfusion scheme, that is, slowly increasing the dose of reinfused CAR T cells. Change the reinfusion route of CAR T cells can reduce the occurrence of off-target reaction, such as intrapleural injection of mesothelin-targeted CAR T cells for the treatment of malignant pleural tumors, intracranial injection for the treatment of glioblastoma multiforme. Intratumoral injection makes most CAR T cells accumulate in the range of lesions, enhances the therapeutic effect, and limits its targeted toxicity to normal tissues [84,85].

Table 2
Other complications and related factors.

Complications	Symptoms	Related Factors
Infections of CAR T cells reinfusion	Bloodstream infections, respiratory tract infections, hypogammaglobulinemia	Nosocomial infections, unreasonable use of glucocorticoids, B-cell dysplasia and hypogammaglobulinemia, high-grade CRS
Hemophagocytic lymphohistiocytosis	Fever, hepatosplenomegaly, abnormal liver function, decreased blood cell count, elevated triglycerides, increased serum ferritin, decreased fibrinogen levels	A large number of inflammatory cytokines release due to lysis of tumor cells and pro-inflammatory cytokines, released cytokines of activated CAR T cells, high levels of IFN-γ, increased serum ferritin, viral infections
Coagulation disorders	Increased D-dimer, prolonged prothrombin time, increased fibrinogen degradation products, decreased fibrinogen, thrombocytopenia	Liver damage, increased levels of cytokines, damage to endothelial cells, hypercoagulable blood of malignant tumor patients
Cytopenias	Neutropenia, thrombocytopenia, anemia	Higher-intensity chemotherapy, history of hematopoietic stem cell transplantation, high-grade CRS

5.5. Other complications and related factors

CRS, ICANS, TLS, and off-target effect are major complications. In addition, other complications also affect the patient's health. Some of the symptoms and related factors of complications are listed as follows (Table 2).

6. Conclusion

Many investigations have confirmed that the improved CAR T cells reinfusion scheme can improve its therapeutic effect and avoid or reduce the occurrence of complications. Administering cyclophosphamide and fludarabine prior to CAR T cell reinfusion has been demonstrated to improve the proliferation and efficacy of CAR T cells. Additionally, tocilizumab is frequently utilized as a pretreatment drug [17,18,22]. In terms of the choice of pretreatment dose some studies have shown that appropriately reducing the dose can achieve similar clinical effects [35,36]. In addition, a series of clinical trials have confirmed that TBI is also used as a pretreatment before CAR T cells reinfusion [27]. Further investigations are needed to confirm the efficacy and safety of chemotherapy combined with radiotherapy in improving the effectiveness of pretreatment. Monitoring the vital signs of patients undergoing CAR T cell reinfusion is crucial. In addition, future research directions may include exploring optimal concentrations for frozen solutions of CAR T cells. CRS, ICANS, TLS and off-target effect are common complications after CAR T cells reinfusion. Many cytokines have important predictive effects on them [8,59,60]. However, how to accurately and early identify the risk factors of complications and take appropriate treatment measures is an important issue for current researchers. In addition, some complications have different stages of development, and how to prevent the progression of complications is also an urgent problem for researchers.

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Data availability statement

There is no additional data available for this study.

Ethics declarations

Review and approval by an ethics committee were not necessary for this study, and informed consent was not required as the study did not involve animal experiments or human behavioral studies. Instead, we conducted a review of published research and provided appropriate references.

CRediT authorship contribution statement

Zhihao Han: Writing – original draft, Conceptualization. **Xiaoqin Ma:** Writing – review & editing, Methodology. **Guiyue Ma:** Writing – review & editing.

Declaration of competing interest

The authors declare no competing financial interests or commercial relationships that could be perceived as influencing the outcome of this research.

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