The model of cytokine release syndrome in CAR T-cell treatment for B-cell non-Hodgkin lymphoma

Jianshu Wei, Yang Liu, Chunmeng Wang, Yajing Zhang, Chuan Tong, Guanghai Dai, Wei Wang, John E. J. Rasko, J. Joseph Melenhorst, Wenbin Qian, Aibin Liang and Weidong Han

Chimeric antigen receptor T (CAR T) cell therapy has demonstrated efficacy in the treatment of haematological malignancies. However, the accompanying adverse events, the most common of which is cytokine release syndrome (CRS), substantially limit its widespread application. Due to its unique physiological characteristics, CRS in CAR T-cell treatment for B-cell non-Hodgkin lymphoma (B-NHL) may exhibit some special features. Although existing guidelines had greatly promoted the recognition and management of CRS, many recommendations are not fully applicable to B-NHL. Therefore, it is imperative to identify responses that are specific to CRS observed following CAR T treatment for B-NHL. Based on underlying biological processes and known pathophysiological mechanisms, we tentatively propose a new model to illustrate the occurrence and evolution of CAR T-cell-therapy-related CRS in B-NHL. In this model, tumour burden and bone marrow suppression are considered determinants of CRS. Novel phenomena after CAR T-cell infusion (such as local inflammatory response) are further identified. The proposed model will help us better understand the basic biology of CRS and recognize and manage it more rationally.

PERSPECTIVE

INTRODUCTION

Chimeric antigen receptor T (CAR T) cell therapy has emerged as a promising therapeutic approach for haematological malignancies, and overall response rates of 52–82% and durable remission could be achieved in patients with refractory or relapsed (R/R) B-cell malignancies. Consequently, two CAR T-cell products targeting CD19 have been approved for R/R B-cell acute lymphoblastic leukaemia (B-ALL) and B-cell non-Hodgkin lymphoma (B-NHL) by the U.S. Food and Drug Administration.19

In vivo, infused CAR T cells will specifically recognize and eliminate tumour cells expressing the target antigen. At the same time, these CAR T cells, activated by CAR mediated signals, will proliferate and release a variety of inflammatory factors to trigger a systemic inflammatory response.1,2 Therefore, CAR T-cell therapy often produces significant adverse events (AEs), with the most common being cytokine release syndrome (CRS).3,7,14 Progressive CRS can cause serious morbidity in patients or reduce the clinical benefit due to the use of measures intended to control CRS, such as corticosteroids.15,16 Therefore, proper recognition and management of CRS may not only alleviate toxicity but also improve the likelihood of therapeutic benefit.

B-NHL has distinct pathophysiological characteristics and clinical manifestations from other haematological malignancies, such as B-ALL. An obvious point of difference is that the lesions of B-NHL are generally localized. Given the nature of CAR T cells to pursue target cells, the in vivo dynamics of CAR T cells in B-NHL could be fundamentally different from those in other cancers. Consequently, the related toxicities could also exhibit unique features. For example, in B-NHL patients receiving CAR T-cell therapy, compartmental inflammation can be observed, manifested as redness, swelling and enlargement at the local lymphoma or around the periphery of lesions. Parallel local inflammatory reactions have also been reported in several other reports.7,17

To draw a contrast to the widely recognized systemic CRS (S-CRS), we tentatively define this local inflammatory response as local CRS (L-CRS).

Currently, our understanding of B-NHL-specific AEs induced by CAR T-cell therapy is still lacking, and published CRS grading and management guidelines give little specific recommendations for B-NHL.15,20,21 To better guide clinical work and basic research, we tentatively propose a new model to illustrate the occurrence and progression of CRS for B-NHL based on existing clues and our practical clinical experience.2 As shown in Table 1, the progression of CRS is divided into four stages: (1) CAR T-cell local expansion stage; (2) CAR T-cell overflow and inflammatory cytokine surge stage; (3) CAR T-cell redistribution and organ...

1Department of Bio-therapeutic, the First Medical Center, Chinese PLA General Hospital, 100853 Beijing, China; 2Department of Oncology, the first Medical Center, Chinese PLA General Hospital, 100853 Beijing, China; 3State Key Laboratory of Biotherapy and Cancer Center, West China Hospital, Sichuan University, Chengdu 610041, China; 4Collaborative Innovation Center for Biotherapy, Chengdu 610041, China; 5Department of Cell and Molecular Therapies, Royal Prince Alfred Hospital, Sydney, NSW 2006, Australia; 6Gene and Stem Cell Therapy Program, Centenary Institute, University of Sydney, Sydney, NSW 2006, Australia; 7Central Clinical School, Faculty of Medicine and Health, The University of Sydney, Camperdown, NSW 2050, Australia; 8Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA 19104-515, USA; 9Department of Hematology, The Second Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou 310009, China; 10Department of Hematology, Shanghai Tongji Hospital, Tongji University School of Medicine, Shanghai 200065, China and 11State Key Laboratory of Kidney Diseases, National Clinical Research Center for Kidney Diseases, 100853 Beijing, China

Correspondence: Wenbin Qian (qianwb@zju.edu.cn) or Aibin Liang (lab7182@tongji.edu.cn) or Weidong Han (hanwdrsw69@yahoo.com)

These authors contributed equally: Jianshu Wei, Yang Liu, Chunmeng Wang, Yajing Zhang, Chuan Tong

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Clinical manifestations of local cytokine release syndrome (L-CRS). a–f In the early stage of CAR T-cell treatment, B-NHL patients may exhibit a significant local inflammatory response, mainly manifested as local swelling and redness. For example, patient 6 had a significant L-CRS response within 5 days after receiving CAR T treatment, but during this period, the proportion of CAR T cells to CD3 positive cells (g), the number of CAR DNA copies in PB (h) and the level of IL-6 in PB (i) remained at a low level. j The RNAscope results of patient 7 indicated that a large number of CAR T cells infiltrated into B-NHL lesions. B-NHL B-cell non-Hodgkin lymphoma, CAR chimeric antigen receptor, IL-6 interleukin-6, PB peripheral blood.

A new model to illustrate the occurrence and evolution of chimeric antigen receptor T (CAR T) cell therapy-related adverse events (AEs) in B-cell non-Hodgkin lymphoma (B-NHL). Stage 1: CAR T cells converge upon tumour cells and kill them. The early distribution of CAR T cells is localized, and the activated CAR T cells release cytokines that in turn trigger a series of local inflammatory reactions, defined in this paper as local cytokine release syndrome (L-CRS). Stage 2: Locally elevated CAR T-cell numbers and cytokine ‘overflow’ into the circulatory system occur, which may boost systemic cytokine release syndrome (S-CRS). Stage 3: CAR T cells redistribute into bone marrow and normal organs, such as the liver, lung and brain. The redistributed CAR T cells might activate tissue-resident immune cells to cause local organ damage and other AEs. TNF tumour necrosis factor, GM-CSF granulocyte-macrophage colony-stimulating factor, IFN interferon, CCL-3 C-C motif chemokine ligand 3 (also known as macrophage inflammatory protein 1α, MIP-1α), IL interleukin, SAP serum amyloid P component, CRP C-reactive protein, BM bone marrow.
Table 1. Four different stages of the occurrence and progress of CRS in CAR T-cell treatment for B-NHL

| Stage 1 | Local CAR T cells expansion stage; Stage 2. CAR T cells redistribution stage; Stage 3. CAR T cells over flow and inflammatory cytokines surge stage; Stage 4. Recovery (immune reconstruction) stage |
|---------|----------------------------------------------------------------------------------|
| CAR T kinetics | % CAR in PB increase mildly, sometimes with a minimal peak. | % CAR in PB increase rapidly until the peak. | % CAR in PB increase rapidly until the peak. | % CAR in PB increase mildly, sometimes with a minimal peak. |
| IL-6 in PB | IL-6 increases mildly, sometimes with a minimal peak. | IL-6 increase rapidly until the peak. | IL-6 increase rapidly until the peak. | IL-6 increases mildly, sometimes with a minimal peak. |
| Lesions | Swelling continuously begins to shrink. | Swelling continues to shrink. | Swelling continues to shrink. | Swelling continuously begins to shrink. |
| WBC | Continuous decline. | Myelosuppression: II. | Myelosuppression: III. | Little change can be observed. |
| ALAST | ALT/AST gradually gets to normal. | Against baseline: 1.2 times (fold change in diameter). | Against baseline: 5 times (fold change in diameter). | ALT/AST gradually gets to normal. |
| B-NHL | All | | | |

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PATTERNS OF PROGRESSION IN CRS

After infusion, CAR T cells will rapidly locate and gather around tumour masses and expand locally. This stage is usually observed 0–5 days after CAR T infusion. During this period, sustained intra-tumoral expansion of CAR T cells can be retained within the tumour mass, and few CAR T cells recirculate into the peripheral blood (PB) (Fig. 3). At the same time, activated CAR T cells release a large number of cytokines, by which a local inflammatory response is triggered. Tumour-infiltrating macrophages and dendritic cells may enhance local inflammation, although it is not clear how important their roles are and how they are activated. During this period, many local inflammatory manifestations can be observed clinically.23

In the second stage, locally expanded CAR T cells and cytokines begin to significantly enter the circulatory system. This stage usually occurs 3–12 days after CAR T-cell infusion according to our clinical observations. Early in this stage, a rapid increase in CAR T cells and inflammatory factors (such as IL-6) in PB can be observed (Fig. 3). In the following week or two, the levels of CAR T cells and inflammatory factors in PB will continue to rise until the peak. Usually, the most intense S-CRS occurs at this stage. The underlying mechanisms of CRS at this stage are likely similar to those of the CRS observed with CAR T-cell treatment for ALL. During this period, monocytes that are eliminated by pre-conditioning begin to recover gradually. Therefore, newborn monocytes in the circulatory system and bone marrow (BM) could be another contributor to S-CRS. The main clinical manifestations of this stage include intractable fever, decreased blood pressure, impaired lung function, liver damage, increased exudation in the serosal cavities, abnormal blood coagulation, BMS and so on. It should be noted that the first and second stages are sometimes blended in practice, especially when a patient has very large tumour masses or an inflammatory background (such as infection). Generally, serious systemic inflammatory responses start earlier than mild responses in CAR...
T-cell infusion. If not handled properly, they can lead to high mortality.

In the third stage, the proliferation of CAR T cells is retarded owing to the lack of antigen stimulation, leading to a lower number of CAR T cells in the peripheral blood (PB) increases slowly, accompanied by enlargement of tumour lesions, a mild rise in IL-6 in the PB and an initial minimal peak and further decline of white blood cell (WBC) counts caused by preconditioning chemotherapy. Within ~3–10 days after infusion, a large number of CAR T cells overflow from the tumour site into the PB, accompanied by obvious regression of tumours, a rapid rise in IL-6 in PB to a peak (of note, the peak level of IL-6 is generally seen 1–2 days earlier than that of CAR T-cell numbers), a slow rise in WBC count (due to the accumulation of CAR T cells in PB) and agranulocytosis and organ damage caused by cytokine release syndrome (CRS) or haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS). Within about 10–21 days after infusion, the peripheral CAR T cells redistribute into BM and normal organs (prompted by a rapid decrease in CAR T cells in PB), accompanied by ongoing tumour regression, a minimal peak and then continuous decline in IL-6 levels (possibly because the redistributed CAR T cells activate monocytes/macrophages in the BM and normal tissues) and WBC count recovery after a minimal dip accompanied by transient hepatic dysfunction. IL-6 interleukin-6, AST aspartate aminotransferase, ALT alanine aminotransferase, BM bone marrow

DETERMINANTS OF CRS

The intensity and kinetics of CAR T-cell-therapy-related CRS significantly vary among different patients. The accumulation of clinical cases suggests that CRS could be affected by a combination of factors, including tumour burden, individual immune status, the peak number of CAR T cells, IL-6 level, lymphodepletion and the gut flora. Clarifying how these factors contribute to the development of CRS is crucial for the development of strategies to prevent and manage this severe adverse event.
factors interact will help us better understand the general progression pattern of CRS and thus more effectively predict and manage the related toxicity.41

In principle, CAR T cells and their released cytokines coordinate in generating CRS. Therefore, the in vivo expansion of CAR T cells driven by target cell-mediated stimulation should be one of the core determinants.41 Generally, the higher the levels of CAR T cells are, the higher the degree of toxicity observed.2 Of course, CAR T-cell amplification is also positively correlated with clinical benefits.4,42 Tumour burden not only determines the peak value of CAR T cells but also may affect the time course of CAR T-cell proliferation. For most patients, a rapid rise in inflammatory factors occurs within 5–10 days after CAR T-cell transfection.64 After the peak, CAR T-cell amplification will slow down and the level of cytokines will decrease as the tumour burden subsides. However, if the tumour has not been eliminated substantially over a period of time (e.g., 1 month), the CRS might be prolonged. In practice, we also found that B-NHL patients with large tumour burden were more likely to experience severe L-CRS and S-CRS than those with a small tumour burden, and high-level CRS has been reported to have a longer duration than mild CRS.72

In addition to the tumour burden, another decisive factor of CRS intensity is the level to which haematopoiesis is suppressed. BMS is first caused by preconditioning regimens, of which the fludarabine/cyclophosphamide (FC) lymphodepletion regimen is the most widely used to improve therapeutic efficacy.65–67 Lymphodepletion can reduce the competition of other lymphocytes for growth factors, provide more ‘space’ for CAR T-cell proliferation and remove the inhibitory immune cells such as Tregs and MDSCs,68 thus promoting in vivo CAR T-cell expansion.69–71 During the BMS period, the expansion of CAR T cells is barely restricted, thereby facilitating target cell-mediated stimulation, a consequent peak of CAR T cells and acute systemic inflammatory response. Generally, more than 3 weeks are needed for the impaired haematopoietic function to return to normal after FC precondition.72 After this, CAR T-cell proliferation will be gradually limited along with the recovery of haematopoiesis, and CRS will also be alleviated.

This is the common progression pattern of BMS and CRS, but sometimes the BM recovery does not proceed efficiently,6,71,72 and it is even further aggravated by activated CAR T cells that redistribute into the BM.61 Poor haematopoiesis may increase the risk of secondary active proliferation of CAR T cells, especially for patients with high tumour burden. In addition, the persistent impaired haematopoietic function also increases the risk of infection,73–75 which is sometimes life-threatening. However, the mechanisms by which redistributed CAR T cells aggravate BMS remain to be further investigated.

The dose of administrated CAR T cells has also been considered a key factor of determining the intensity and kinetics of CRS by other scientists.41,76 Reducing the CAR T dose is considered a possible way to reduce CRS, as has been tested by several trials.77,78 Although there are some supporting data, the main concern is that the dose reduction will impair the therapeutic benefits, which is particularly concerning in B-NHL.51 Therefore, until clear evidence is provided, we do not recommend reducing the CAR T-cell dose to reduce the severity of CRS.

RECOGNITION AND CLINICAL MANAGEMENT OF AES

Local CRS

L-CRS can only occur in compartmental tumours and has only been reported in a few papers so far.17–19 In the case of solid tumours, the lack of examples is mainly due to the low effectiveness of CAR T-cell treatments.56,79 Heterogeneity and the immunosuppressive microenvironment are viewed as the main factors limiting the efficacy of CAR T-cell treatments for solid tumours.55,80 In addition, the infiltration of CAR T cells in the tumour bed could be further reduced by physical barriers.81

For B-NHL, significant L-CRS is also not frequently observed, mainly because patients with large masses are usually excluded or they are pretreated with chemotherapy to reduce the tumour burden before CAR T-cell treatment. In contrast, significant L-CRS was more frequently observed in our clinical trials for patients with large tumour masses. As shown in Fig. 1, several patients with B-NHL had a significant inflammatory response in the tumour site in the early stage after CAR T-cell infusion. The L-CRS is mainly affected by tumour burden and the consequent CAR T-cell amplification, and it usually occurs within 0–5 days after CAR T-cell infusion. During this period, S-CRS can also occur. However, the low number of CAR T cells and IL-6 levels in PB are in stark contrast to the conspicuous local inflammatory response (Fig. 1).17

L-CRS is the earliest AE observed following CAR T-cell treatment for B-NHL. Local proliferation serves as a reservoir of the continuous release of activated CAR T cells and cytokines that induce the systemic immune response. Therefore, timely control of L-CRS is helpful to prevent severe S-CRS. However, in early clinical practice, we found that IL-6 blocking antibodies could not effectively alleviate and instead aggravated the L-CRS response. This indicated that the underlying mechanisms of L-CRS might be specific.

It remains unclear which types of immune cells take part in this process and how these immune cells are activated. Tracking different infiltrating lymphocytes to clarify their changes in distribution and function may provide further insights into the pathogenesis of L-CRS. For this, a proper animal model for studying L-CRS is imperative. Considering the potentially important role of macrophage activation in the progression of L-CRS and S-CRS, we have previously attempted to control the inflammatory response by inhibiting macrophage activation using TNF-α blocking drugs82 in the patients with a high tumour burden (SPD ≥ 100 cm²).

For patients without compression symptoms, continuous clinical observation and supportive care are recommended. When compression symptoms occur, anti-TNF-α therapy and local intervention (if necessary), such as tracheotomy and drainage of serous effusion, should be implemented.

The specific damage caused by L-CRS can vary with the location of lesions. Of note are the masses located in or around the intestine. The local inflammatory response can cause damage to the intestines, such as intestinal mucosal damage, intestinal vascular rupture and bleeding. Such tissue damages provide more possibilities for the intestinal flora to boost the systemic immune response.83–86 For patients with tumours in proximity to the intestines, in particular with large tumours, gut purging before CAR T-cell treatment and oral antibiotics to inhibit the intestinal flora are recommended. The intestinal flora will be reconstructed after the S-CRS subsides. Recently, it was reported that antibiotic therapy may reduce the effectiveness of immunotherapy,87,88 whether the anti-tumour potential of CAR T cells will be weakened by the use of antibiotics needs further study. For these patients, prophylactic use of anti-TNF-α agents can also be considered. Another organ that needs attention is the heart, and more careful monitoring of cardiac function should be given when the B-NHL mass is located around the heart.

Systemic CRS

S-CRS, the most common AE associated with CAR T-cell treatment, is characterized by fever, hypotension, hypoxia and increased release of inflammatory cytokines,89,90 including IL-1, IL-6, IFN-γ, TNF-α, GM-CSF, MIP-1α, MCP1 and IL-10. S-CRS is commonly reversible following medical intervention. But severe S-CRS can lead to multiple organ dysfunctions, such as persistent cytopenias, cardiac complications, acute kidney injury and coagulation system abnormalities. According to published data, any grade CRS occurred in 42–93% of B-NHL patients receiving CAR T-cell treatment, with grade ≥ 3 toxicity occurring in 22–2% of patients.7,5,72
As discussed, the kinetics of S-CRS is closely related to tumour burden. Significant S-CRS generally occurs during the period when the number of CAR T cells increases in the PB, which usually peaks within 2 weeks after infusion. After this, the CRS response usually subsides due to the slowing down of CAR T-cell proliferation. However, sometimes S-CRS may persist for a longer time due to the continuous expansion of CAR T cells, which occurs if the residual tumour remains substantial. Due to the recovery of the haematopoietic function of the BM, some immunosuppressive cells can be reconstituted. Therefore, prolonged S-CRS is generally mild, characterized by persistent manifestations of low-level inflammation. For patients with incomplete BM recovery, chronic CRS can ignite secondary acute CRS under certain conditions, which is clinically dangerous.

As the most common AE, S-CRS can give rise to other CAR T-cell-therapy-related AEs, such as immune effector cell-associated neurotoxicity syndrome and haemophagocytic lymphohistiocytosis. Therefore, the recognition and management of S-CRS are very important issues, which have been widely reviewed. And some consensus guidelines have also been developed.

In early CAR T clinical trials, the Common Terminology Criteria for Adverse Events (CTCAE) v4.03 released in 2010 was used for CRS grading. However, the criteria were mainly for antibody drugs, which did not reflect the dynamics of CRS induced by CAR T-cell therapy. In 2014, Lee et al. proposed their CRS grading system. Specific clinical indicators such as patient response to vasopressors, oxygen requirement and organ toxicity were included in the criteria. In CTCAE v5.0 released in 2018, many criteria from the Lee grading system were used for reference. In 2018, the CRS grading system of the University of Pennsylvania was proposed. The greatest controversy over this grading system over other guidelines is that any fluid bolus or vasopressor use is indicative of CRS grade 3, and this is believed to improperly increase the proportion of high-level CRS. In the same year, Neeup et al. published the CAR T-cell-therapy-associated toxicity (CARTOX) grading system, which is very similar to the Lee’s guidelines. In CARTOX, body temperature, blood pressure, oxygen saturation and organ damage are used for CRS grading. In 2019, the American Society for Transplantation and Cellular Therapy released their consensus recommendations on CRS grading. Compared with CARTOX, these recommendations held that fever ≥ 38 °C was necessary for CRS recognition, and organ damage was removed from the grading system. Use of one or more vasopressors was employed as an indicator for CRS grading instead of the dose of vasopressor. In addition, consideration of the modality of oxygen delivery instead of just FiO2 was adopted.

Our recognition and management of S-CRS in CAR T-cell treatment for B-NHL are presented in Table 2, which are generally consistent with the CARTOX criteria. Briefly, S-CRS can be effectively controlled below grade 3 by the use of tocilizumab in most cases. For cases of S-CRS refractory to tocilizumab therapy, corticosteroid therapy is recommended when the grade ≥ 3 is observed. Of note, corticosteroids have been shown to significantly inhibit T-cell activity, leading to impaired clinical outcomes. When CRS reaches grade ≥ 4, more intense treatments, such as methylprednisolone and mechanical ventilation, should be provided in a timely manner to prevent severe morbidity and death.

IL-6 plays an important role in the occurrence of S-CRS, and anti-IL-6 therapy has greatly improved the management of S-CRS. In addition, many clinical trials have shown that the use of tocilizumab does not impair therapeutic outcomes. Therefore, in various CRS management guidelines, tocilizumab is widely accepted and recommended across different CRS grades. However, some controversy remains regarding the use of anti-IL-6 agents. First, whether IL-6 blockade impairs the in vivo proliferation of CAR T cells is still debated, because IL-6 has been clearly proven to promote the proliferation of T cells. In addition, it has been reported that the serum IL-6 levels may rapidly rise after tocilizumab administration. According to our clinical observations, it is noteworthy that L-CRS can be aggravated by the use of tocilizumab. Although we are uncertain as to the mechanism behind this phenomenon, the rapid rise of IL-6 after tocilizumab administration may be an important factor. Therefore, when significant L-CRS occurs, tocilizumab is cautiously recommended for S-CRS management, and anti-TNF-α therapy might be a better choice. In our guiding principles, anti-TNF-α drugs are also recommended for patients with persistent fever, even if the S-CRS is below grade 2.

Two recently published articles demonstrated that monocytes and macrophages were the major contributors to CRS. Therefore, we believe that early blocking of the activation of monocytes and macrophages activation may be a reasonable strategy for CRS management. In addition to agents targeting TNF-α, blocking GM-CSF-mediated activation of monocyte and macrophage activation has been reported to effectively control the CAR T-cell-therapy-induced CRS response.

SUMMARY AND EXPECTATION
The in vivo kinetics of CAR T cells in B-NHL is different from that in ALL. As a result, CAR T-cell-treatment-related AEs in B-NHL exhibit some unique features, of which L-CRS is the most significant one. L-CRS is the earliest AE in CAR T-cell treatment for B-NHL, and we believe that timely management of L-CRS is beneficial to the prevention and control of serious S-CRS. However, the underlying mechanisms of L-CRS are not clear. Further active basic research will provide an important reference for the management of L-CRS. To guide clinical work and basic research, we tentatively proposed a new model to illustrate the progression of CRS in CAR T-cell treatment for B-NHL. In addition, we discussed how tumour burden and BMS interact to determine the progression of CRS. The recognition and management of L-CRS and S-CRS were also presented.

Some AEs are the result of differences in CAR T-cell manufac-
ture, which should be avoided in the future because it is difficult to identify whether these AEs are universal. Although CAR T-cell products are individualized, the standardization and industrialization of CAR T-cell preparations may rise above some of the problems. At present, the number of CAR T-cell-treated B-NHL cases is still limited. The strict criteria for clinical trials may not enable a full understanding of real-world outcomes. More samples, especially from multiple institutions, need to be accumulated and studied to enrich our understanding of AEs. Only in this way can a more widely applicable clinical management consensus be formed. Most of the aforementioned AEs were first recognized in the clinic and not observed in animal models, so the understanding based on current animal models is far from adequate. Clinical findings are in need of appropriate animal models to study mechanisms and developmental processes, to promote more appropriate AE recognition, management and the development of therapeutic drugs. At present, there is still a lack of drugs that can effectively manage L-CRS. Elucidation of the mechanisms of L-CRS will be helpful for the screening of drugs. Some emerging candidate drugs that inhibit inflammatory responses, such as adrenergic receptor inhibitors and JAK inhibitors, could be further explored in clinical trials.

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Table 2. The recognition and clinical management of CRS in CAR T-cell treatment for B-NHL

| CARTOX grading and management | CRS grading and management for B-NHL | L-CRS | S-CRS |
|-------------------------------|-------------------------------------|-------|-------|
| Occurrence time Day 1-14      | Day 1-10                            | Grade 1: Consistent with CARTOX. |
| Grading                      | Low-risk: (1) Diameter max < 10 cm. (2) No risk of tumour compression. |
| Grade 1: (1) Temperature ≥ 38°C (2) Grade 1 organ toxicity. | Grade 2: Consistent with CARTOX. |
| Grade 2: (1) Hypotension responds to IV fluids or low-dose vaspressors. (2) Hypoxia requiring FiO₂ < 40%. (3) Grade 2 organ toxicity. | Grade 3: Consistent with CARTOX. |
| Grade 3: (1) Hypotension needing high-dose or multiple vasopressor. (2) Hypoxia requiring FiO₂ ≥ 40%. (3) Grade 3 organ toxicity or grade 4 transaminitis. | Grade 4: Consistent with CARTOX. |

| Management                   | Grade 2: Consistent with CARTOX. |
| Grade 1: (1) Life-threatening hypotension. (2) Needing ventilator support. (3) Grade 4 organ toxicity (excluding transaminitis). | Grade 1: (1) Anti-TNF-α agents as recommended for persistent and refractory fever. (2) Other management as consistent with CARTOX. |
| Grade 2: (1) IV fluid bolus and supplemental oxygen. (2) Tocilizumab or siltuximab ± corticosteroids and supportive care, as recommended for the management of hypotension. (3) Manage fever and constitutional symptoms as in grade 1. | Grade 2: (1) Anti-IL-6 therapy ± anti-TNF-α agents as recommended. (2) Other managements are consistent with CARTOX. |
| Grade 3: (1) IV fluid boluses and vaspressors as needed. (2) Transfer to ICU, and supplemental oxygen as needed. (3) Manage fever and constitutional symptoms as in grade 1. (4) Tocilizumab or siltuximab plus corticosteroids and supportive care, as recommended. (5) Symptomatic management of organ toxicities as per standard guidelines. | Grade 3: (1) Anti-TNF-α agents as recommended if accompanied by L-CRS. (2) Plasma exchange as recommended. (3) Other managements are consistent with CARTOX. |
| Grade 4: (1) IV fluids, anti-IL-6 therapy, vaspressors and methylprednisolone as recommended. (2) Mechanical ventilation. (3) Manage fever and constitutional symptoms as in grade 1. (4) Tocilizumab or siltuximab plus corticosteroids and supportive care, as recommended. (5) Symptomatic management of organ toxicities as per standard guidelines. | Grade 4: (1) Cyclophosphamide as required. (2) Other management as in grade 3. |

CARTOX CAR T-cell-therapy-associated toxicity, CRS cytokine release syndrome, B-NHL B-cell non-Hodgkin lymphoma, CAR chimeric antigen receptor, L-CRS local cytokine release syndrome, S-CRS systemic cytokine release syndrome, TNF-α tumour necrosis factor-α, IL-6 interleukin-6, ICU intensive care unit, IV intravenous injection

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**ADDITIONAL INFORMATION**

**Competing interests:** W.D.H. certifies that the contribution and competing interests statements included in this paper are correct and have been approved by all coauthors. The authors declare no competing interests.

**AUTHOR CONTRIBUTIONS**

J.S.W., Y.L. and W.D.H. conceived and designed the work. J.S.W., Y.L., C.M.W., Y.J.Z. and C.T. collected and analysed relevant reports. J.S.W., Y.L., C.M.W. and Y.J.Z. wrote the manuscript. J.E.J.R., J.J.M., C.M.W., Y.J.Z., W.W., W.B.Q., G.H.D. and A.B.L. provided substantial contributions to improve the content of the article. J.S.W., Y.L., C.M.W., Y.J.Z. and C.T. contributed equally to this work.
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