Efficacy of emapalumab in the management of anti-CD19 chimeric antigen receptor T-cell therapy-associated cytokine release syndrome: A report of two cases

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Abstract. Chimeric antigen receptor (CAR) T-cell therapy is an effective treatment for diffuse large B-cell lymphoma (DLBCL). However, it may activate the systemic immune system of the patient, resulting in cytokine release syndrome (CRS). Emapalumab is a human monoclonal antibody targeting interferon-γ, inhibiting its interaction with cell surface receptors and the subsequent activation of inflammatory pathways. The present report describes the cases of 2 patients with relapsed DLBCL treated with CAR T-cell therapy, in which the severe CRS associated with CAR T-cell therapy was attenuated without compromising antitumor efficacy after receiving emapalumab. Further prospective clinical trials are warranted to determine the role of emapalumab in CAR T-cell therapy.

Introduction

In total, 20-50% of patients with diffuse large B-cell lymphoma (DLBCL) will become resistant to initial immuno-chemotherapy or relapse after achieving a complete metabolic response (CMR), thus predicting a poor prognosis (1). Chimeric antigen receptor (CAR) T-cell therapy targeting CD19 has resulted in tremendous progress with regard to increasing survival rates in the past two decades (2-5). In the ZUMA-1 trial, patients with refractory large B-cell lymphoma received axicabtagene ciloleucel autologous anti-CD19 CAR T-cell therapy and the long-term survival analysis yielded an estimated 5-year OS rate of 42.6% (5), suggesting that further investigations are warranted to maintain long-term clinical remission, as well as to manage the potential infusion-related toxicities, namely cytokine release syndrome (CRS; grade ≥3 reported in 2-22% of patients) and immune effector cell-associated neurotoxicity syndrome (grade ≥3 reported in 5.1-28% of patients).

Cytokine release syndrome (CRS) is a potentially life threatening toxicity with a prevalence that can be as high as 93% (6,7). Currently, the commonly used treatment regimens for CRS include tocilizumab and corticosteroids (8). In patients with CRS who respond to tocilizumab, symptoms such as fever and hypotension typically resolve within a few hours. However, a subset of patients may show no improvement in symptoms or response. In these cases, the consideration of other drugs, such as corticosteroids, is warranted (9,10). Nevertheless, some studies have indicate that corticosteroids may adversely affect CAR T-cell function, and the cumulative dose could be linked to reduced survival rates (9,11,12). Additionally, some patients exhibit poor responses to both treatment regimens, resulting in limited options. Consequently, there is an urgent need to explore other medications for more effective management (10,13). The present study presented two cases of patients with relapsed DLBCL who received CAR T-cell therapy and aimed to investigate the efficacy of the interferon-γ (IFN-γ) antibody emapalumab in treating CAR T-cell induced CRS.

Case report

Patient 1. A 56-year-old male patient was diagnosed with germinal center B-cell (GCB) like DLBCL, Ann Arbor stage IV, an International Prognostic Index score (14) of 3 and MYC-BCL2 double expression in January 2022 at the Department of Oncology, The First Affiliated Hospital of Soochow University. The patient received 8 cycles (every 21 days

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for a cycle) of R-CHOP (iv rituximab, 375 mg/m^2 on day 0; iv cyclophosphamide, 750 mg/m^2 on day 1; iv doxorubicin, 50 mg/m^2 on day 1; iv vincristine, 1.4 mg/m^2, dose cap of 2 mg on day 1; and oral prednisone, 100 mg daily on days 1-5). The fluorodeoxyglucose-positron emission tomography (FDG-PET) scan showed progression in both lungs, with a Deauville score (DS) (15) of 5 and an abdominal node with a DS of 4. A salvage chemotherapy comprising 2 cycles (every 21 days for a cycle) of R-GDP (iv rituximab, 375 mg/m^2 on day 0; iv gemcitabine, 1,000 mg/m^2 on days 1 and 8; iv dexamethasone, 40 mg on days 1-4; and iv cisplatin, 25 mg/m^2 on days 1-3) was administered. The patient was later referred to the National Clinical Research Center for Hematological Diseases, The First Affiliated Hospital of Soochow University for CD19-directed CAR T-cell therapy (16,17) in October 2022. The patient underwent lymphodepleting conditioning with cyclophosphamide 0.3 g/m^2 day-5-2 and fludarabine 30 mg/m^2 d-5-2. The patient was infused with 2x10^6 axicabtagene ciloleucel cells/kg. On day 4, the patient experienced a fever of 38.0˚C with tachycardia, but was normotensive with a normal respiratory exam. The patient had repeated negative blood cultures and was diagnosed with CRS (grade 1) based on the American Society for Transplantation and Cellular Therapy grading scale (18). Blood cultures testing for pathogenic microorganisms were obtained which was later reported to be negative, and broad-spectrum antibiotics (iv meropenem 1g q8h, and oral voriconazole 4 mg/kg) were administered. On day 6, the patient developed grade 3 CRS with hypotension (85/54 mmHg) and hypoxia. Supplemental oxygen was supplied at 6 l/min, as well as norepinephrine infusions initially at 0.15 μg/kg/min. Two doses of 8 mg/kg tocilizumab were administered intravenously every 12 h, but the patient did not exhibit a notable and persistent change in the fever or blood pressure. The temperature climbed back up to 39.6˚C and the blood pressure was 101/62 mmHg treated with norepinephrine infusions. Considering the lack of improvement in CRS symptoms, additional treatment is needed. Due to an increase in the level of IFN-γ, emapalumab, an anti-IFN-γ antibody, was administered at a dose of 1 mg/kg on day 7 after informed consent was obtained. The temperature of the patient rapidly normalized and the norepinephrine dose was gradually reduced (Fig. 1A). The levels of C-reactive protein (CRP) and inflammatory cytokines significantly decreased, with IFN-γ level particularly decreased to 0 pg/ml (Fig. 1B and C). The level of interleukin 6 (IL-6) descended from 1,162 on day 7 to 304 pg/ml on day 8 and continued to fall (Fig. 1C). The expansion of CAR-T cells were monitored by flow cytometry (Fig. 1D): The PE-labeled monoclonal anti-FMC63 antibody (ACROBiosystems, FM3-HPY53), CD3-FITC-conjugated antibody (Immunotech S.A.S, A07746), and CD45-PC7-conjugated antibody (Immunotech S.A.S, IM3548) were used to label CAR-T cells. The Beckman Coulter Navios (Beckman Coulter, Inc.) was used to acquire the data, and Kaluza Analysis Software (v2.1; Beckman Coulter, Inc.) was employed for data analysis. The number of CAR-T cells reached a peak less than 10 days after cell infusion (Fig. 1E). This also suggested that neutralizing IFN-γ may not affect the normal activity of CAR-T cells (19). The patient was followed up at 1, 3, and 6 months after treatment. At 3 months, the patient underwent an FDG-PET scan, showing a partial response (PR) status (16) (Fig. 1F). The response status remained stable at the last follow-up (at 6 months).

Patient 2. A 49-year-old female patient was diagnosed with DLBCL transformed from follicular lymphoma (FL; grade 3B, WHO grading system for FL) (20) in November 2020 at the First People's Hospital of Changzhou. The patient achieved a complete metabolic response (CMR) after 4 cycles of R-CHOP (as above) and 4 cycles of R-CHOP (as above) with zanubrutinib (oral, 160 mg, bid), but relapsed 6 months later. She was referred to the National Clinical Research Center for Hematological Diseases, The First Affiliated Hospital of Soochow University, in January 2023. The refractory disease was confirmed with a biopsy of the inguinal lymph node. Next-generation sequencing (NGS) showed an MCD subtype (a genetic subtype in DLBCL, based on the co-occurrence of *MYD88*^{L265P} and *CD79B* mutations) (21), with positivity for protein coding gene *CD79B*, *CDKN2A* (multiple tumor suppressor l), *CCND3* (protein coding gene), *FAS* (protein coding gene), *APC* (tumor suppressor gene), B-cell lymphoma 6 (*BCL6*) and *CREBBP* (protein coding gene). NGS was performed using a NovaSeq 6000 S1 Reagent Kit (cat. no. 20028319; Illumina, Inc.) and a GeneJET Genomic DNA Purification Kit (cat. no. K0721; Thermo Fisher Scientific, Inc.) to prepare the DNA sample. A Bioanalyzer 2100 (Agilent Technologies, Inc.) was used to verify the quality of the processed samples. The purified library was quantified using the KAPA Library Quantification Kit (KAPA Biosystems; cat. no. 07960140001; Roche Diagnostics). Enriched libraries were amplified and subjected to NGS on Illumina novaseq 6000 platforms (150 cycles; cat. no. 2002746; Illumina, Inc.). The quantitative concentration of the final library was 2 nM. The 2x150 bp paired-end sequencing was performed in a testing laboratory (Geneseeq Technology, Inc.) accredited by the Clinical Laboratory Improvement Amendments and the College of American Pathologists. Data analysis was performed using Trimmomatic 0.39 (https://github.com/usadellab/Trimmomatic).

After oral treatment with 3 cycles of R-ICE (iv rituximab, 375 mg/m^2 on day 0; iv ifosfamide, 5,000 mg/m^2 on day 2; iv etoposide, 100 mg/m^2 on days 1-3; carboplatin area under the curve 5, maximum dose of 800 mg, iv on day 2) and zanubrutinib (as above), the patient proceeded to undergo autologous stem cell transplant (ASCT) followed by CAR T-cell therapy. Pre-treatment with CEAC regimen (oral lomustine, 200 mg/m^2 on day 6; iv etoposide, 100 mg/m^2 q12h on days-5 to -2; iv cytarabine, 200 mg/m^2 q12h on days-5 to -2; and iv cyclophosphamide 1.5 g/m^2 on days-5 to -2) and iv cladribine (50 mg/m^2 on days-5 to -2) was administered, and autologous hematopoietic stem cells were infused (mononuclear cells, 6.8x10^8/kg; CD34$^+$ cells, 8.0x10^6/kg). After 7 days, the patient received a total amount of 100x10^6 relmacabtagene autoleucel cells/kg. A fever (39.6˚C) and hypoxemia developed on day 2 after CAR T-cell infusion, with negative repeat blood cultures, and the patient was diagnosed with rapid progression to grade 2 CRS (18). The serum IL-6 level reached a maximum of 506 pg/ml and the IFN-γ level reached 888 pg/ml. One dose of emapalumab (1 mg/kg) was administered after informed consent was obtained, as well as antifebrile therapy and supplemental oxygen. The body temperature rapidly decreased to 38.7˚C (Fig. 2A), with IFN-γ and IL-6 levels rapidly decreasing to 0 pg/ml and 141 pg/ml on day 4 after CAR T-cell infusion, respectively (Fig. 2B and C). The CAR T-cells continued to

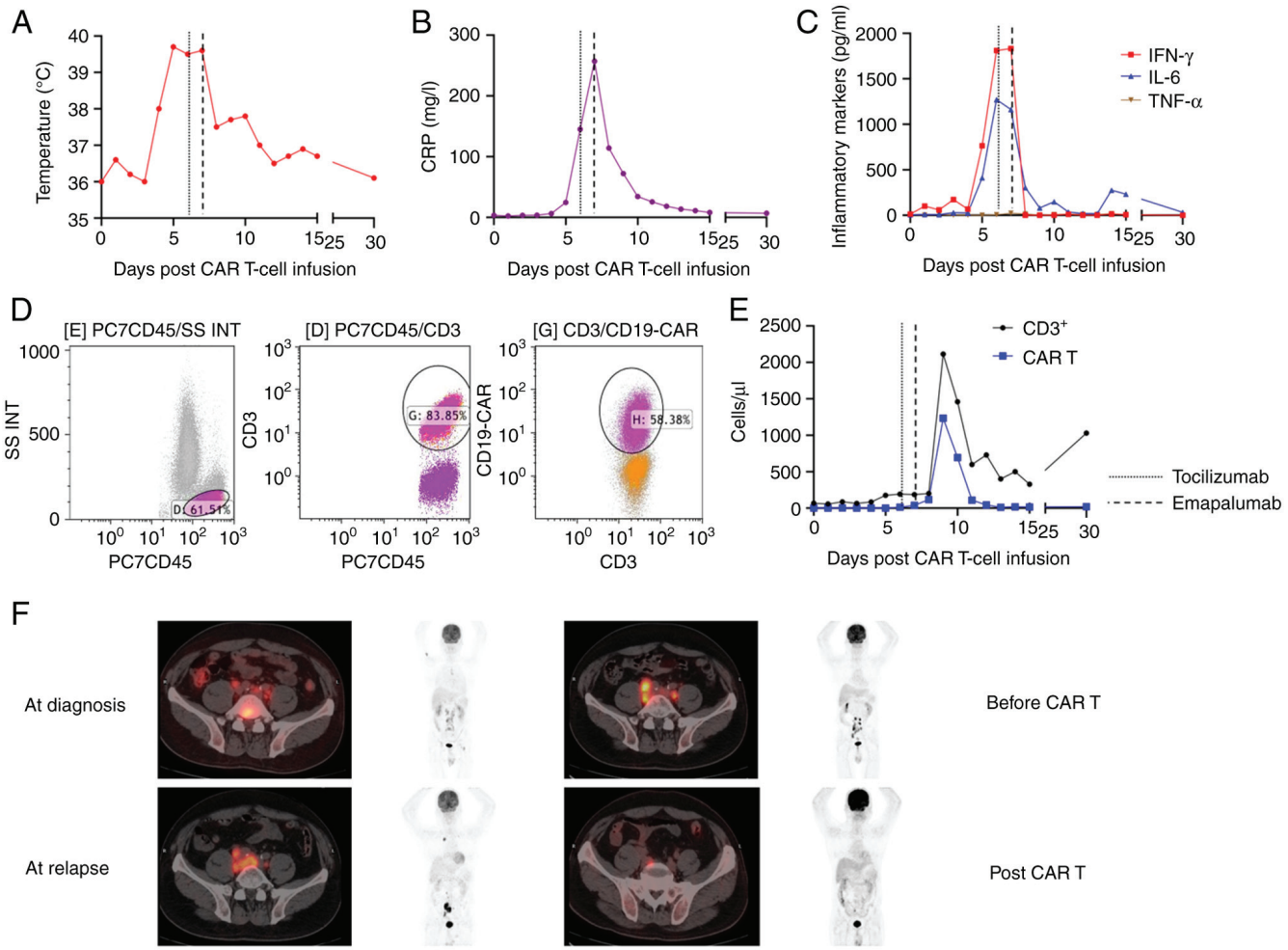

Figure 1. Clinical and laboratory features surrounding the use of emapalumab for CAR T-cell-induced cytokine release syndrome in patient 1. (A) Temperature in ˚C. (B) CRP levels in mg/l. (C) Serum cytokine levels in pg/ml of IFN-γ, IL-6 and TNF-α. (D) Representative flow cytometry of CAR T-cell. (E) CAR T-cell expansion in cells/µl examined by flow cytometry. (F) Efficacy of CAR T-cell therapy based on fluorodeoxyglucose positron emission tomography scans at diagnosis, at first relapse, and at 1 month before and 3 months after CAR T-cell therapy. CAR T-cell, chimeric antigen receptor T-cell; CRP, C-reactive protein; IFN-γ, interferon-γ; IL-6, interleukin 6; TNF-α, tumor necrosis factor-α.

expand (Fig. 2D and E). The patient was followed up at 1, 3, and 6 months after treatment. The 1-month FDG-PET scan showed a CMR (Fig. 2F), and circulating tumor DNA monitoring at 2 months revealed a negative disease state (Fig. 2G). The patient was still alive, taking zanubrutinib 160 mg bid orally, with no signs of occurrence at the 6-month follow-up.

Discussion

The pathophysiology underpinning the development of CRS stems from activation of immune cells of the tumor microenvironment, directly resulting in excessive production of inflammatory cytokines and chemokines (22). The most commonly affected cytokines are IL-6, IFN-γ, tumor necrosis factor-α, CRP and ferritin (23), which in turn lead to endothelial injury and tissue damage. IL-6 serves a crucial role in mediating CRS, and tocilizumab (anti-IL-6 receptor) has been approved for the management of CRS (24). However, some patients exhibit a poor response to tocilizumab and glucocorticoids (9,10), necessitating adjustments to their treatment regimen based on individual responses. Additionally, there is currently no standardized treatment protocol for CRS.

Some patients with severe CRS exhibit characteristics similar to those of hemophagocytic lymphohistiocytosis (HLH) (10). Notably, IFN-γ levels are elevated in both severe CRS and HLH, and in HLH, IFN-γ is regarded as a key driver of inflammation (10). A maximum fold-change in IFN-γ of >100 has been used to predict grade 3+ CRS, with a sensitivity of 83% and a specificity of 100% (25). The knockdown of IFN-γ preserves the benefits of anti-CD19 CAR T-cell therapy and inhibits the release of multiple cytokines from CAR T-cells and peripheral blood mononuclear cells, thereby reducing the effect of CRS and enhances the safety profile of CAR T-cell therapy (26). In addition, IFN-γ blockade can reduce macrophage activation and improve CAR T-cell function while reducing treatment-related toxicity in hematologic malignancies (27).

Emapalumab is a human anti-IFN-γ antibody that binds to both free and receptor-bound IFN-γ, inhibiting receptor dimerization and the transduction of IFN-γ signaling, thereby neutralizing its biological activity (28). A prospective clinical study has demonstrated its effectiveness as a targeted therapy for primary HLH (28). Additionally, it has shown efficacy in treating CRS following CAR T-cell therapy in patients with relapsed B-cell acute lymphoblastic leukemia (29).

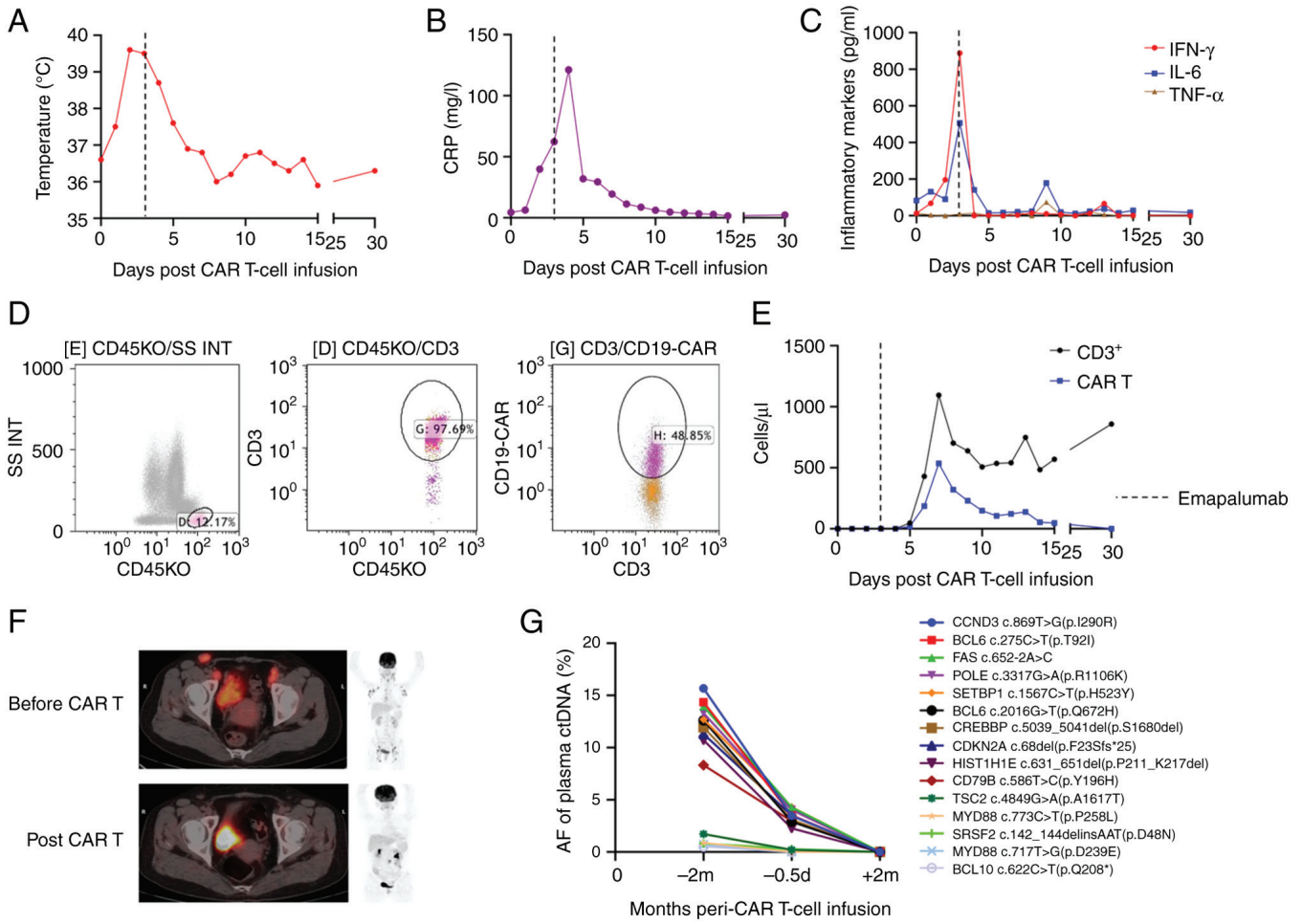

Figure 2. Clinical and laboratory features surrounding the use of emapalumab for CAR T-cell-induced cytokine release syndrome in patient 2. (A) Temperature in °C. (B) CRP levels in mg/l. (C) Serum cytokine levels in pg/ml of IFN-γ, IL-6 and TNF-α. (D) Representative flow cytometry of CAR T-cells. (E) CAR T-cell expansion in cells/μl examined by flow cytometry. (F) Efficacy of CAR T-cell therapy based on fluorodeoxyglucose positron emission tomography scans at relapse, and at 1 month after CAR T-cell therapy. (G) Efficacy of CAR T-cell therapy based on the ctDNA test. AF, allele fraction; CAR T-cell, chimeric antigen receptor T-cell; CRP, C-reactive protein; ctDNA, circulating tumor DNA; d, days; IFN-γ, interferon-γ; IL-6, interleukin 6; m, months; TNF-α, tumor necrosis factor-α.

McNerney and DiNofia reported the case of a patient with B-cell acute lymphoblastic leukemia who developed grade 4 CRS that was refractory to both tocilizumab and glucocorticoids. This patient was treated with tocilizumab, methylprednisolone, siltuximab and the IFN-γ inhibitor emapalumab, achieving complete remission for 12 months (10). Rainone *et al* (13) described a case of CAR T-cell therapy-associated macrophage activation syndrome/HLH that was successfully treated with emapalumab in combination with anakinra and corticosteroids.

In the present study, patient 1 developed severe CRS and received tocilizumab, but did not respond adequately, ultimately achieving a PR with emapalumab. In case 2, the IFN-γ levels were elevated, up to 888 pg/ml. A study has indicated that elevated IFN-γ levels are associated with severe CRS (30). Therefore, the patient was directly treated with emapalumab and achieved a favorable response. These findings are consistent with the limited previously reported cases (10,13), suggesting that the clinical use of emapalumab can effectively mitigate severe CRS in CAR T-cell-treated patients without compromising antitumor efficacy. Common AEs associated with emapalumab include infection, hypertension and infusion-related reactions (31). However, the 2 patients in the present report had no obvious AEs and the treatment was well tolerated. The patients felt no discomfort or dissatisfaction during the entire treatment. The cost of the medication was acceptable to the patients and they remained proactive and cooperative throughout the treatment. However, the present study also had certain limitations. It only reported two patients and lacked large-scale statistical data, and further prospective clinical trials are necessary to confirm the long-term efficacy and safety of emapalumab.

In summary, the present study trialed the use of the drug emapalumab to neutralize IFN-γ, in order to mitigate CRS while maintaining the efficacy of CAR T-cell proliferation. Prospective clinical trials are warranted to determine its role in CAR T-cell therapy.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available to protect patient privacy but are available from the corresponding author on reasonable request.

Authors' contributions

CL and DW were responsible for conception and design. WC and YL were responsible for providing study materials or patients. Collection and assembly of data was performed by HG, QY and LZ. Data analysis and interpretation was performed by WC and YL. HH, JL and SL advised on patient treatment, drafted the discussion and confirmed the authenticity of all the raw data. All authors helped to write the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University (Suzhou, China; approval number 2017-053-2).

Patient consent for publication

Written informed consent was obtained from the patients for the publication of any potentially identifiable images or data included in this article.

Competing interests

The authors declare that they have no competing interests.

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