Plasma exchange as an effective treatment for cytokine release syndrome following T cell receptor-engineered T cell immunotherapy: A case report

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Abstract. T-cell receptor-engineered T-cell (TCR-T) immunotherapy is a promising approach for the treatment of solid tumors. However, TCR-T therapy can result in severe cytokine release syndrome (CRS), thus limiting its therapeutic application. The present study reported the case of a patient with TCR-T-related CRS, which was treated successfully with plasma exchange (PE). A 35-year-old male patient, who was diagnosed with hepatitis B virus (HBV)-related hepatocellular carcinoma (HCC) with lung metastases, was enrolled in a clinical trial for hepatitis B virus surface antigen-specific TCR-expressing autologous T-cell therapy for HBV-related HCC after failing multiple lines of targeted immunotherapy and local treatments. Therefore, TCR-Ts were infused after peripheral blood mononuclear cell collection, engineering and lymphodepletion chemotherapy. However, following engineered T-cell reinfusion, the patient developed a fever, hypotension, edema, multiple serous effusion and acute kidney injury, and was consequently diagnosed with grade 3 CRS and transferred to the Intensive Care Unit. The patient received three daily PE sessions (3,000 ml of fresh frozen plasma per session), renal replacement therapy, tocilizumab and 1,000 mg pulse methylprednisolone for 3 days. Following treatment, the patient's hemodynamic condition was stabilized and the C-reactive protein, ferritin and IL-6 levels were markedly reduced. During follow-up, a stable disease state was exhibited by the liver cancer and lung metastatic lesions. To the best of our knowledge, this is the first case reporting PE as a treatment approach for managing CRS following TCR-T therapy for solid tumors. The present study demonstrated that blood purification treatments, such as PE, which target inflammatory mediators and restore the balance between pro- and anti-inflammatory cytokines, could be a notable component in managing severe CRS associated with engineered T-cell treatment. However, additional clinical and translational studies are needed to further understand the mechanisms of T-cell immunotherapy to treat patients with solid tumors.

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Introduction

Hepatocellular carcinoma (HCC) is the sixth most common type of cancer and the third leading cause of cancer-related deaths worldwide (1). Current systemic therapies for HCC include immune checkpoint inhibitors, angiogenesis inhibitors and tyrosine kinase inhibitors. However, the response rates to these treatments are limited, and there is a high risk of HCC recurrence (2). Hepatitis B virus (HBV) infection is the primary risk factor for HCC development, accounting for ~50% of HCC cases worldwide and ~85% of cases in China. HBV-DNA integration is detected in >80% of HBV-related HCC tumor cells (3). Therefore, targeting the HBV-related surface antigen is seen as a promising strategy in the fight against HCC. Clinical trials exploring T-cell immunotherapy targeting HBV-specific antigens are underway.

T-cell receptor-engineered T cells (TCR-Ts) are autologous T cells modified to express a specific TCR that recognizes tumor-associated antigens presented by human leukocyte antigen molecules on cancer cells. These T cells are genetically engineered using viral vectors to enhance specificity and affinity for the target antigen. Upon reinfusion into the patient, the engineered TCRs guide T cells to recognize and eliminate tumor cells by triggering cytotoxic responses, including cytokine release and direct lysis (4). Similar to chimeric antigen receptor T-cell (CAR-T) therapy, which is another type of T-cell immunotherapy that mainly targets B cell lineages and is used to treat leukemia and lymphomas, TCR-T therapies can also be complicated by the potentially life-threatening adverse event of cytokine release syndrome (CRS). TCR-T therapy is being explored in clinical trials involving melanoma, synovial sarcoma, hepatocellular carcinoma, mesothelioma and various solid tumors (4). The incidence of CRS in these TCR-T clinical

trials ranges from 10-50% (5). While the precise mechanism remains to be elucidated, CRS manifests clinically as a severe systemic inflammatory response resulting in hypotension, hypoxia and multi-organ dysfunction (6). In severe cases of CRS, these systemic inflammatory responses can be fatal, with a reported mortality rate as high as 10% (7).

Apart from high-quality supportive care, tocilizumab and glucocorticoids serve as first-line treatments for CRS. However, for severe cases that are unresponsive to repeated tocilizumab and pulse glucocorticoids, limited second-line therapies are available. Plamsa exchange (PE) is a extracorporeal blood purification technique in which the patient's plasma is separated from the blood cells and discarded, while a replacement fluid, commonly fresh frozen plasma, is used to replenish the plasma. PE not only eliminates all inflammatory mediators and circulating damaged molecules, but also replenishes essential plasma components depleted by the disease process. Case reports and cohort studies have shown promising outcomes in using PE to manage severe CRS following chimeric antigen receptor (CAR)-T therapy (8-10). However, the efficacy of PE in the treatment of TCR-T-related CRS has not yet been reported.

In the present study, the case of a patient with HCC who underwent PE to effectively treat severe CRS following TCR-T therapy for metastatic HBV-related HCC is reported. To the best of our knowledge, this is the first reported case of PE being used to manage CRS following TCR-T therapy for solid tumors.

Case report

The present study reports the case of a 35-year-old male who presented to Peking Union Medical College Hospital (Beijing, China) in September 2023 with HBV-related metastatic HCC after failing previous multiline treatments. The patient was diagnosed with metastatic HCC at 1 year prior to the presentation to Peking Union Medical College Hospital, based on a biopsy of liver nodules and elevated serum α-fetoprotein levels. A positron emission tomography scan had demonstrated multiple metastatic lesions in both lungs and lymph nodes at an external hospital. Following diagnosis, the patient had undergone microwave ablation of liver nodules, followed by 3 months of immunotherapy with 200 mg sintilimab every 3 weeks and 0.4 g sorafenib twice a day, accompanied by transarterial chemoembolization (TACE), additional microwave ablation of liver lesions and microwave ablation of lung metastases. Systemic therapy was then transitioned to 200 mg toripalimab every 3 weeks and 0.2 g donafenib twice a day for 4 months, during which time, the lung metastases increased in size and number. The patient subsequently received another TACE and computed tomography (CT)-guided microwave ablation of the left lung metastases. Despite 1 month of Sintilimab 200 mg and bevacizumab 700 mg every 3 weeks, the lung lesions progressed (Video S1 and S2). The patient was then enrolled in a clinical trial of hepatitis B virus surface antigen-specific (HBsAg)-specific TCR-engineered autologous T cells for HBV-related HCC (trial registration no. CTR20222173; August 2022) (11). The patient had a medical history of HBV infection in 2003 and had been taking 5 mg entecavir orally once a day since then, with normal liver enzyme levels. The HBV DNA count and HBsAg levels prior to TCR-T therapy were <20 IU/ml (normal range, <20 IU/ml) and >250 IU/ml (normal range, <0.05 IU/ml), respectively.

Upon presentation in September 2023, no icterus or sclera were observed on the skin. Pulmonary auscultation demonstrated no rales. The patient's abdomen was soft and non-tender, and shifting dullness was negative. As part of the clinical trial treatment, peripheral blood mononuclear cells were harvested in advance to construct engineered T cells. SCG101, an autologous TCR-T designed to target specific epitopes of HBsAg, was used for the investigational cell therapy. SCG101 was engineered for high affinity and avidity toward intracellular antigens presented by major histocompatibility complex (MHC) on solid tumors (12). The engineered and expanded TCR-Ts were infused back into the patient 3 days after lymphodepletion with cyclophosphamide (900 mg on days 1-3) and fludarabine (45 mg on days 1-3). Prior to infusion, the vital signs were stable, with a blood pressure (BP) of 109/65 mmHg, a pulse rate of 61 bpm and a temperature of 36.4˚C (normal range of vital signs: systolic BP, 90-120 mmHg; diastolic BP, 60-80 mmHg; pulse, 60-100 bpm; temperature, 36.5-37.3˚C).

Prior to infusion, the patient was preconditioned with 12.5 mg promethazine, 650 mg paracetamol and 2 g ceftazidime once. A total of six bags, each containing $1.13x10^9$ TCR-T cells, were infused. At 30 min post-infusion, the patient experienced a fever, soreness and chills, with a temperature of 38˚C and a BP of 92/54 mmHg. Therefore, CRS was suspected. Aggressive hydration was initiated and tocilizumab at a dose of 560 mg was administered. Despite treatment, the fever persisted into the next day and the BP remained at <90/60 mmHg, which led to the diagnosis of grade 3 CRS. A norepinephrine infusion was initiated and two additional doses of tocilizumab were administered. The patient was also treated with dexamethasone (10 mg, every 6 h). Despite the aforementioned treatments, the patient developed peripheral edema, ascites and pleural effusion. Urine output declined and the serum creatinine levels rose from 86 to 155 μmol/l (normal range, 59-104 μmol/l). Due to hemodynamic instability and impending multiorgan failure, the patient was admitted to the intensive care unit (ICU) on the second day after infusion.

In addition to tocilizumab, pulse methylprednisolone and broad-spectrum antibiotics, daily PE was initiated on the second day until the fifth day after infusion. A total of three sessions were administered with a treatment volume of 3,000 ml per session. Fresh frozen plasma was used as the replacement fluid. Due to hyperkalemia, continuous veno-venous hemofiltration (CVVHF) was also initiated on the third day after infusion. Post-TCR-T therapy, the patient exhibited notably elevated interleukin-6 (IL-6), high-sensitive C-reactive protein (hsCRP) and ferritin levels. Notably, the levels of IL-6 rose to >1,000 pg/ml, while the normal range should be <5 pg/ml, and even in critically ill COVID-19 patients, the median IL-6 level is only 21 pg/ml (13). Following PE, the IL-6, hsCRP and ferritin levels were all notably decreased (Fig. 1), with the resolution of the patient's hypotension and fever. By the fifth day post-infusion, the patient no longer required vasopressors and the urine output was improved. The patient

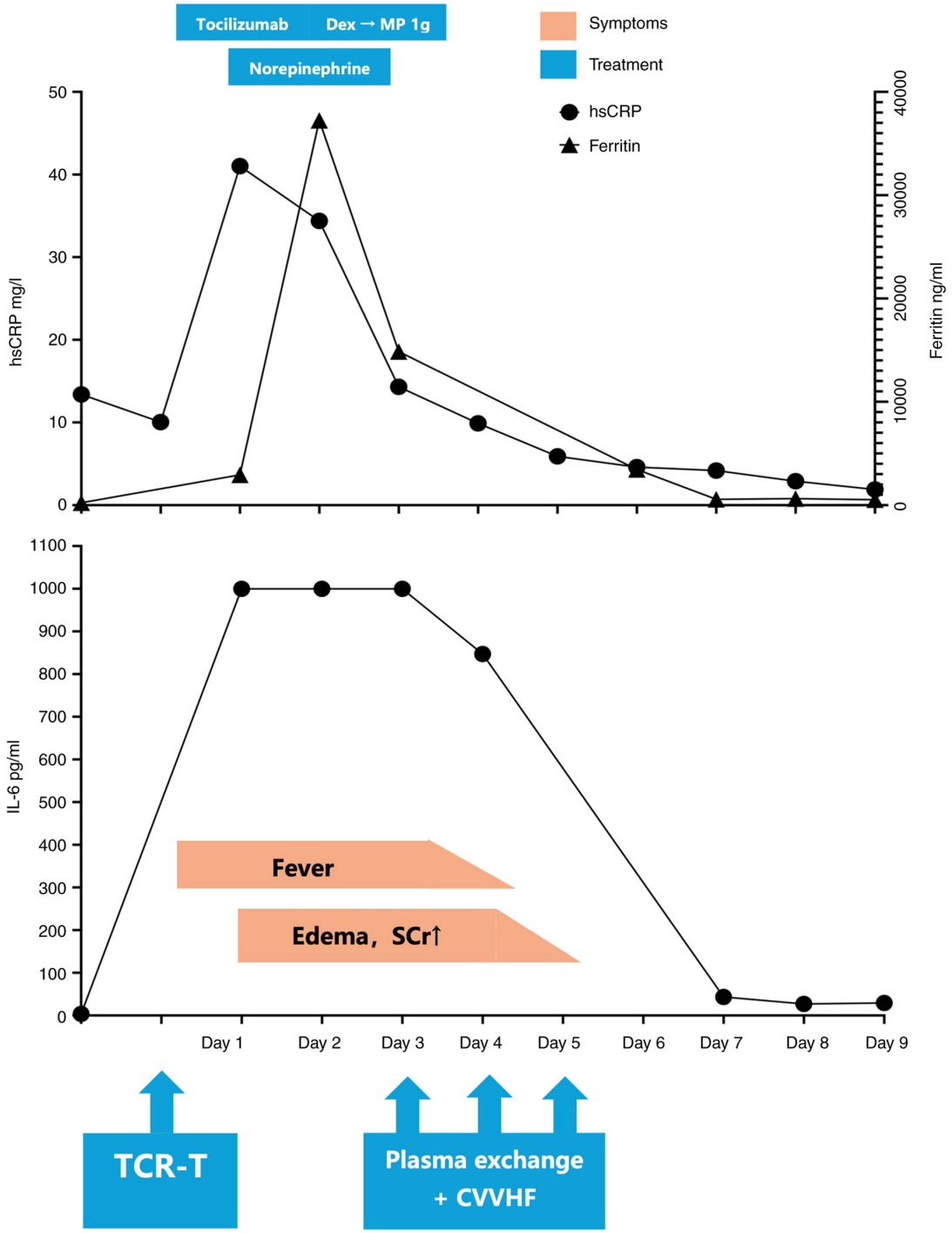

Figure 1. Change in inflammatory markers after TCR-T infusion and during PE treatment. The orange squares indicate the symptoms, and the blue squares indicate treatments. Arrows indicate the time of the treatments. The day count is started from TCR-T treatment. Methylprednisolone and norepinephrine were administered alongside PE therapy. TCR-T, T-cell receptor-engineered T cell; CVVHF, continuous veno-venous hemofiltration; hsCRP, high sensitivity C reactive protein; Dex, dexamethasone; MP, methylprednisolone; SCr, serum creatinine; PE, plasma exchange.

was discharged from the ICU and continued to receive 2 g ceftazidime twice a day for an additional week prior to discharge from the hospital.

After discharge, the patient was followed up in the outpatient clinic on a monthly basis. At 3 months after TCR-T infusion, the patient's renal and liver functions had returned to within normal ranges (Table I). Both metastatic and primary liver tumors were stable in size, thus indicating that the patient remained in a state of stable disease (Video S3 and S4).

Discussion

TCR-T therapy is a promising form of immunotherapy for solid tumors. With ongoing clinical trials, novel targets and engineered T cells are emerging to bolster the treatment of various types of cancer. However, the mortality rate for severe cases of CRS remains as high as 10% (7) and treatment options are limited. The present study reports a case of TCR-T-related CRS successfully managed with PE as a salvage therapy to

Table I. Changes in biochemistry and coagulation parameters with treatment.

Parameter	Baseline (before PBMC harvesting and lymphodepletion)	Before TCR-T infusion, (after PBMC harvesting and lymphodepletion)	Day 2 after TCR-T infusion (before PE)	Day 6 after TCR-T infusion (after PE)	3-months after TCR-T infusion	Normal range
Alanine transaminase, U/l	38	22	3,084[a]	477[a]	26	9-50
Aspartate aminotransferase, U/l	28	34	4,153[a]	231[a]	29	15-40
Total bilirubin, μmol/l	6.1	15.3	45.1[a]	44.0[a]	8.3	5.1-22.2
Direct bilirubin, μmol/l	2.2	4.8	30.7	20.5	3.4	<6.8
Albumin, g/l	48	46	25[b]	36	49	35-52
Serum creatinine, μmol/l	61	53	155[a]	94	56	59-104
Urea, mmol/l	5.32	3.52	8.12[a]	11.80[a]	5.36	2.78-7.14
Potassium, mmol/l	4.4	4.1	6.5	3.6	4.0	3.5-5.5
Phosphate, mmol/l	1.06	1.12	NA	1.02	1.26	0.81-1.45
Fibrinogen, g/l	4.16	4.28	0.78	1.32	2.22	1.80-3.50
White blood cells, n ($x10^9$/l)	6.01	1.20[b]	0.52[b]	2.31[b]	3.63	3.50-9.50
Lymphocytes, n ($x10^9$/l)	1.26	0.04[b]	0.04[b]	0.34[b]	1.10	0.80-4.00
Platelets, n ($x10^9$/l)	162	103	73[b]	45[b]	107	100-350
Hemoglobin, g/l	158	144	133	83[b]	136	120-160
Hepatitis B virus DNA, IU/ml	<20	<20	<20	<20	<20	20
Hepatitis B surface antigen, IU/ml	799.52[a]	952.75[a]	819.07[a]	6.41[a]	3.74[a]	<0.05
α-fetoprotein, ng/ml	4.7	17.4	NA	NA	1.5	≤20.0

[a]Increased and [b]decreased compared with the normal range. TCR-T, T-cell receptor-engineered T cell; PBMC, peripheral blood mononuclear cells; NA not available; PE, plasma exchange.

tocilizumab and glucosteroids, which suggested that PE could be a potential strategy for the treatment of refractory CRS.

The symptoms of CRS, such as hypotension, hypoxia and capillary leaking, are associated with the supraphysiological levels of inflammatory cytokines due to the overstimulation of immune effector cells. Consequently, treatment of CRS primarily revolves around anti-inflammatory and anti-cytokine therapies, such as tocilizumab and glucocorticoids (14). Even as such, deaths have been reported for grade 3 and 4 CRS (15), thus limiting the application of T-cell immunotherapies, including TCR-T therapy.

Emerging evidence has suggested that blood purification techniques, including hemofiltration, immunoadsorption and PE, can mitigate systemic inflammatory reactions in inflammatory syndromes, such as sepsis (16), COVID-19-related cytokine storms (17) and hemophagocytic lymphohistiocytosis (HLH) (10), with some successful treatment outcomes reported in case studies. These techniques may be applied to CRS as well (9).

Hemofiltration effectively clears small molecules, such as ILs, via a method of convection. However, hemofiltration is unable to remove molecules larger than albumin (>66.5 kDa). Immunoadsorption can remove toxic substances or inflammatory cytokines by binding them with solvent or adsorptive materials in the extracorporeal circuit (16). Bottari *et al* (18) reported a case where hemoadsorption using a Cytosorb column and continuous renal replacement therapy were employed to manage grade 4 CRS associated with secondary HLH after CAR-T therapy for acute lymphoblastic leukemia. Both hemofiltration and adsorption have the disadvantage of being unable to replace plasma components (16).

PE is a blood purification technique in which the patient's plasma is separated from the blood cells and discarded, while a replacement fluid, commonly fresh frozen plasma, is used to replenish the plasma. PE not only eliminates all inflammatory mediators and circulating damaged molecules, but also replenishes essential plasma components depleted by the disease process (19). In CRS, multiple cytokines and activated immune cell products, including IL-6, IL-10 and INF-γ can contribute to the disease process (14). In the later stages of CRS, endothelial damage and tumor cell products further aggravate the clinical severity (20). Since CRS is multifactorial and the specific causative molecule is unclear, in our opinion, PE would be the preferred blood purification modality. The use of PE to address refractory CRS in CAR-T therapy has been reported by a number of studies. In 2019, Xiao *et al* (8) reported successful PE in a case of treatment-resistant CRS following CAR-T therapy for acute lymphoblastic leukemia. A recent study of a retrospective cohort reported the use of PE in 17 refractory cases of CRS after CAR-T therapy (9). In these cases, it was verified that PE could effectively mitigate CRS symptoms and reduce the serum levels of inflammatory mediators. Nonetheless, the use of TCR-T for the treatment of solid tumors is still under investigation and, to the best of our knowledge, there are currently no reports on the efficacy of PE for treating TCR-T-induced CRS.

Markedly increased ferritin levels in CRS could suggest the co-existence of HLH (6), although the distinction between the two is unclear without further diagnostic tests. Nonetheless, in the present study, PE therapy normalized the ferritin levels without necessitating additional immunosuppressive therapy, thus suggesting that an HLH-like presentation could represent a stage of CRS.

Whether PE interferes with the efficacy of T-cell therapy is another potential point of debate. PE primarily removes plasma and does not significantly affect infused effector T cell levels. However, T-cell therapies can induce the release of various cytokines and soluble factors that play a role in the antitumor response. PE can remove these cytokines and factors, potentially dampening the overall immune response against cancer cells. There is limited specific research directly addressing the interaction between PE and T-cell immunotherapy. In the present case study, the cancer remained in a stable disease state at the 3-month follow-up and we speculate that PE did not interfere with the effect of TCR-T therapy.

In summary, the present case study demonstrated the successful use of PE in managing CRS associated with TCR-T therapy. As TCR-T therapy expands across different types of solid tumors, more CRS cases are likely to arise. Nevertheless, tocilizumab and glucosteroids remain the first-line therapy for such cases. However, further research is needed to determine PE indications, optimal dosage and its potential combination with CVVHF and other blood purification modalities.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

XZ designed the study, analyzed patient data and wrote the manuscript. YW designed the study, advised on patient treatment and edited the manuscript. XZ and YW confirm the authenticity of all the raw data. SZ, HW and JX helped with the PE process, data collection and clinical management of the patient. KZ advised on patient treatment. YQ advised on patient treatment, helped with the PE process and obtained funding for the publication. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethical Committee of Peking Union Medical College Hospital (Beijing, China; approval no. I-23PJ1746).

Patient consent for publication

Written consent was obtained from the patient for academic use of their medical record.

Competing interests

The authors declare that they have no conflicts of interest.

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