Chronic graft-versus-host disease secondary to donor-derived CAR-T cells treatment in children: a report of two cases and a literature review

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Abstract

Donor-derived CD19-directed chimeric antigen receptor-modified T (CAR-T) cell therapy seems be effective and safe for relapsed B-ALL after allogeneic haematopoietic stem cell transplantation (allo-HSCT). We report two cases of children who received Donor-derived CAR-T cell therapy. After transfusion, the children experienced different degrees of chronic graft-versus-host disease (cGVHD). Early intervention included strengthening immunosuppressant, FAM regimen, tyrosine kinase inhibitor, and auxiliary cell therapy. Their dyspnoea and lung function were significantly improved and recovered. They did not receive the second transplant. Timely and effective intervention is crucial to improve both prognosis and quality of life.

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Donor-derived CD19-directed chimeric antigen receptor-modified T (CAR-T) cell therapy seems be effective and safe for relapsed B-ALL after allogeneic haematopoietic stem cell transplantation (allo-HSCT). We report two cases of children who received Donor-derived CAR-T cell therapy. After transfusion, the children experienced different degrees of chronic graft-versus-host disease (cGVHD). Early intervention included strengthening immunosuppressant, FAM regimen, tyrosine kinase inhibitor, and auxiliary cell therapy. Their dyspnoea and lung function were significantly improved and recovered. They did not receive the second transplant. Timely and effective intervention is crucial to improve both prognosis and quality of life.

Key words: Donor-derived, CD19-directed chimeric antigen receptor modified T (CAR-T), chronic graft-versus-host disease

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is an effective method for the treatment of refractory and relapsed acute lymphoblastic leukaemia (R / R-ALL) in children, but relapse after transplantation is still the main reason for treatment failure. Chimeric antigen modified T (CAR-T) cell therapy has a strong ability to clear leukemic cells and is associated with a high remission rate in R/R B-ALL[1-2]. CAR-T cell sources can be autogenous or donor. It can be difficult to collect enough T lymphocytes for children with a high leukaemia burden or relapse after transplantation. CAR-T cells from a donor can overcome this problem but carry the risk of graft-versus-host disease (GVHD) after infusion. We describe two cases of chronic GVHD (cGVHD) secondary to donor-derived CAR-T therapy.

Cases description

Patient 1: A 17-year-old boy was diagnosed with acute lymphocytic leukaemia (B cell). Chemotherapy was stopped per protocol in December 2016, and continuous complete remission (CR) of bone marrow was observed during the treatment. Unfortunately, minimal residual disease (MRD) increased to 0.18% at 3 months after discontinuation. Morphology suggested relapse with testicular leukaemia, and two courses each of consolidation and shelter treatment were completed. The infiltration of testis improved, and MRD continued to turn negative after treatment. On October 4, 2017, we completed a matched-sibling donor HSCT (sister donor, human leucocyte antigen (HLA) 10/10). There was no GVHD expression after transplantation, and cyclosporine was gradually reduced from 2 months after transplantation. MRD was 1.67% at 5 months after transplantation. Two weeks later, bone marrow morphology and MRD were 6% and 4.65%, respectively. A comprehensive evaluation and diagnostic workup showed R/R-ALL with an indication for CAR-T cell treatment. On May 1, 2018, donor-derived CAR-T cells were infused(Table.1).

A total of 12.6×10^6/kg CAR-T cells were infused and evaluated as cytokine release syndrome (CRS)grade II. At + 14 days, bone marrow was in CR, with MRD <0.01%; + 21 days, rashes of upper limbs, face, and back appeared, and acute GVHD (aGVHD) was considered. After methylprednisolone (0.5 mg/kg.d) for 2 weeks, and the rash gradually subsided. At +52 days, the rash appeared again, body-wide (Fig. 1A), and methylprednisolone (1 mg/kg.d) was added again. At the same time, basiliximab was given for symptomatic treatment, and the rash gradually subsided, but with pigmentation. At +76 days, liver damage was indicated (ALT 603 IU/L; R-GGT 305 IU/L), and in addition to continued methylprednisolone, sirolimus and ursodeoxycholic acid were added so that the liver damage would gradually recover. At +93 days, there was repeated persistent oral ulcer (Fig. 1B), a clinical diagnosis of cGVHD, so oral immunosuppressant treatment was continued, and oral care was strengthened. At +110 days, the patient developed signs of bronchiolitis obliterans syndrome[3-4] (BOS; Fig. 1C–E). We tried to use the FAM (fluticasone, azithromycin, and montelukast) regimen [5], mesenchymal stem cells (MSCs) (once every 2 weeks, four units each time, four times total), low-dose ruxolitinib (10 mg, once a day), and prednisone (0.25 mg/kg.d), which was gradually reduced to 5 mg prednisone for maintenance. At this writing, there was no significant wheezing attack or chest tightness during 20 months after CAR-T. Chest CT and lung function were improved, and the primary disease evaluation always showed CR.

Patient 2: A 5-year-old boy was diagnosed with B-ALL (pre-B) after intermittent lower extremity pain and left eyelid oedema for half a year. Genetics analysis was positive for E2A-PBX1 and chromosome 46, XY, t (1,19) (q21; p13). After induction of chemotherapy with the VPDL regimen (vincristine + prednisolone + daunorubicin + L-asparaginase), the bone marrow showed remission, immune residue turned negative, and E2A-PBX1 dropped to 0.02%. Regular chemotherapy was administered, and maintenance treatment began on February 6, 2017. In October 2017, the bone puncture was re-evaluated because of systemic bone pain. Results indicated that the tumour cells could not be controlled, and MRD continued to be positive. On December 7 and 8, 2017, auto CAR-T cells were retransmitted. The bone marrow showed CR, and MRD turned negative. On February 28, 2018, haploid HSCT (father donor, HLA 6/10) was performed. At 3 months after transplantation, bone puncture showed 8% immature lymphocytes and 1.02% MRD, indicating another relapse. The father gave peripheral blood for the preparation of CD19 CAR-T, and then Flu/CTX pretreatment was administered. On June 8 and June 13, 2018, donor-derived CAR-T cells were retransmitted (Table 1).

A total of 13.3 x 10^6/kg CAR-T cells were infused and evaluated as CRS grade I. There was no obvious GVHD manifestation. At +28 days, we evaluated the continuous remission state of the bone marrow. At +3 months, this patient also received a clinical diagnosis of BOS. Prednisone (2 mg/kg) was given combined with the FAM regimen. At +4 months, chest CT showed resolution of mediastinal emphysema, wheezing was improved, lung function still showed moderate obstruction of ventilation function, and prednisone was gradually reduced to small dose maintenance. At +6 months, wheezing was reported, while lung function was not improved, and imatinib treatment was increased. Finally, lung symptoms were controlled, and lung function was improved. At this writing, 18 months after CAR-T, the patient's condition was stable and in complete remission from leukaemia (Table I).

3. Discussion

GVHD is a clinicopathological syndrome caused by the mismatch of HLA recognized by donor-derived T cells through T cell receptor $\alpha\beta$, thus attacking the organs and tissues of patients[6]. CAR-T therapy involves using genetic engineering technology to make allogeneic T cells specific to tumour antigens, such as CD19, rather than to all cells. Moreover, CAR-T cell therapy involves a small number of cells, which in theory induces a low rate of GVHD. However, in clinical application, we found that both haploid and non-haploid donor-derived CAR-T cell therapy can induce GVHD, and the reasons need to be further explored.

Here we describe two cases, one involving a matched-sibling donor (patient 1) and the other a haploid donor (patient 2).The incidence of GVHD after haploid transplantation is higher than with matched-sibling donor and unrelated donor transplantation[6]. Whether CAR-T from a haploid donor is more likely to induce GVHD and cause safety concerns is an important question. The incidence of GVHD after CAR-T infusion is lower than with donor leukocyte infusion and seems to be related to the tumour load. If the tumour load is low, the incidence of GVHD also is low[7-10,12,13].At present, there is no relevant research on cGVHD after CAR-T cell therapy, only limited clinical data from some samples.

We report here that two patients had different degrees of cGVHD after donor-derived CAR-T treatment. The most serious was lung involvement. The clinical diagnosis was BOS, which mainly manifested as shortness of breath after active, intractable cough, imaging findings of gas retention, and pulmonary function suggesting obstructive pulmonary disease with restricted ventilation. Studies have shown that the mortality rate with BOS after transplantation can be as high as 80%, and the main causes of death are respiratory failure and severe infection [11]. In theory, secondary BOS after CAR-T would be similar to that after transplantation. We actively intervened in these two cases at an early stage, including strengthening immunosuppressant, FAM regimen, TKI, and auxiliary cell therapy. Fortunately, the dyspnoea and lung function of the two children were significantly improved and recovered. They were in a state of continuous remission without a second transplant.

Donor-derived CAR-T cell therapy adds to the toolkit clinicians can use to prevent recurrence after transplantation and provides an effective treatment option for patients. However, there is a real risk of GVHD caused by donor-derived CAR-T. How to increase and extend the effect of CAR-T treatment while reducing the incidence and mortality of GVHD are being explored. In the near future, more effective and lasting off-the-shelf CAR-T products are anticipated.

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Disclosure Statement

The authors have no conflicts of interest to declare

Statement of Ethics

This clinical treatment program was approved by the Ethics Review Committee of Shanghai Children's Hospital.

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Author Contributions

Kai Chen and Yifei Cheng participated in the entire management and treatment for the cases, reviewed the relevant literature on the topic, and drafted and revised the manuscript. Na Zhang and Jiashi Zhu collected

the data. Min Xia, Jingbo Shao, Hong Li, and Lanying Gao conducted the research. Xiaojun Huang and Hui Jiang directed the entire treatment process and reviewed and revised the manuscript.

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Figure Legends

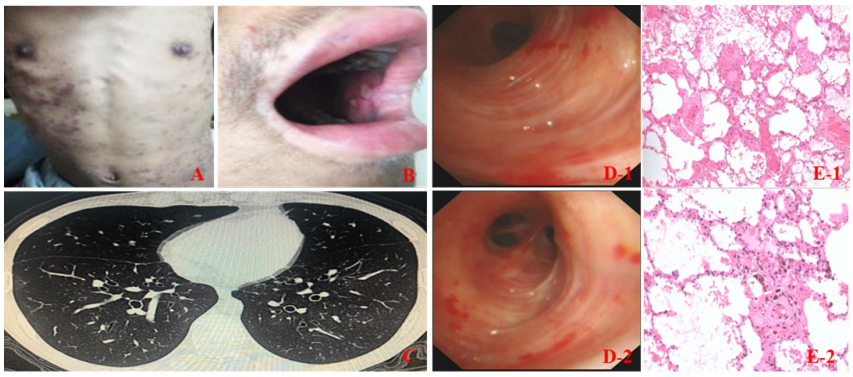

FIGURE. 1 Clinical manifestations and related examination of Patient 1. A. Scattered rash after CAR-T treatment. B. Recurrent oral ulcer. C. Chest CT showed local emphysema and local bronchiectasis. D. Fishbone-like changes were seen in bronchial mucosa, and bronchiectasis was considered; E-1 (×40) E-2 (×100). Only vascular tissue was found in the suspected small airway structure, which was considered to be accompanied by bronchioles, with slight hyperplasia and degeneration of fibrous tissue.

TABLE 1. Clinical characteristics of donor-derived CAR-T therapy after transplantation and relevant literature reports

Patient	Sex	Age	Diagnosis	Status	Blast% before CART	MRD before CART	Chemotherapy	CART type	Donor type	CART (*10^6/kg)	CRS	MRD (%) after CAR-T	MR (%) af- ter CAI T
1	M	17y	R/R B-ALL	Relapse af- ter transplantation	6%	4.65%	Flu+CTX	DD	MSD	12.6	Grade 2	CR	CR

Patient	Sex	Age	Diagnosis	Status	Blast% before CART	MRD before CART	Chemotherapy	CART type	Donor type	CART (*10^6/kg)	CRS	MRD (%) after CAR-T	MR (%) after CA T
2	M	5y	R/R B-ALL	Relapse after transplantation	8%	1.02%	Flu+CTX	DD	HRD	13.3	Grade 1	CR	CR

Author / publication time	Author / publication time	Cases	status before CAR-T treatment	status before CAR-T treatment	status before CAR-T treatment	Type of transplantation	Type of transplantation	CART type	Transfusion cell count	Transfusion cell count	CRS (case)	CRS (case)	GVI (cas
Cruz et al(2013)[12]	Cruz et al(2013)[12]	4	2 cases relapsed, 2 cases MRD (+)	2 cases relapsed, 2 cases MRD (+)	2 cases relapsed, 2 cases MRD (+)	MUD/MSD	MUD/MSD	DD	3.15×10^7	3.13×10^7	1.13×10^8	0	0
Brudno et al(2016)[13]	Brudno et al(2016)[13]	6	2 cases recurred and 3 cases progressed	2 cases recurred and 3 cases progressed	2 cases recurred and 3 cases progressed	MUD/MSD	MUD/MSD	DD	5×10^6~10×10^6	5×10^6~10×10^6	5×10^6	0	0
Kebriaei et al(2016)[7]	Kebriaei et al(2016)[7]	9	Preventive re-infusion within 6~12 weeks after transplantation	Preventive re-infusion within 6~12 weeks after transplantation	Preventive re-infusion within 6~12 weeks after transplantation	HRD	HRD	DD	1×10^6~5×10^6	1×10^6~5×10^8		2	2

Patient	Sex	Age	Diagnosis	Status	Blast% before CART	MRD before CART	Chemotherapy	CART type	Donor type	CART (*10^6/kg)	CRS	MRD (%) after CAR-T	MRD (%) after CAR-T
Kebriaei et al(2016)[7]	Kebriaei et al(2016)[7]	8	Preventive re-infusion within 6~12 weeks after transplantation	Preventive re-infusion within 6~12 weeks after transplantation	Preventive re-infusion within 6~12 weeks after transplantation	MSD	MSD	DD	1×10^{6}~5×10^{6}	1×10^{8}~5×10^{8}	1	1	
chen et al(2017)[8]	chen et al(2017)[8]	6	Hematological recurrence	Hematological recurrence	Hematological recurrence	HRD	HRD	DD	6.3×10^{7}~2.6×10^{8}	2.6×10^{8}~3.6×10^{8}	3	3	
Cheng et al(2019)[9]	Cheng et al(2019)[9]	6	MRD(+)	MRD(+)	MRD(+)	HRD	HRD	DD	2×10^{7}~3.26×10^{7}	3.26×10^{8}~3.66×10^{8}	0	0	

R/R, refractory/relapse; Flu, fludarabine; CTX, cyclophosphamide; DD, donor-derived; MUD,matched-unrelated donor;MSD, matched-sibling donor; HRD, haploidentical related donor; CRS, cytokine release syndrome; MRD, minimal residual disease; CR, complete remission.

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