Management of cytokine release syndrome after chimeric antigen T-cell therapy for paediatric relapsed/refractory acute lymphoblastic leukaemia: a case report

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Case report

The event-free survival rate of standard risk/low-risk childhood acute lymphoblastic leukaemia (ALL) is approaching 90%, but there remains around 10% to 15% of children who suffer relapse.[1] Early relapse of ALL or refractory ALL has a very poor prognosis, even with haematopoietic stem cell transplantation. In recent years, chimeric antigen receptor T-cell (CAR-T) therapy has offered a promising treatment for relapsed/refractory ALL.[2] At present, CAR-T therapy is not available for ALL patients in Hong Kong. Cytokine release syndrome (CRS) is one of the most challenging complications following CAR-T therapy. We report our experience of four children prescribed CAR-T therapy for relapsed/refractory B-cell ALL.

Between June 2018 and March 2019, four children with relapsed/refractory CD19+ B-cell ALL (aged 1-17 years at first relapse) received CAR-T CD19 therapy at a haematology centre in Shanghai, China. Patients 1, 2, and 3 received autologous CAR-T cell products and patient 4 received allogeneic CAR-T cell products. The patients returned to Hong Kong within 12 hours of CAR-T cell infusion and were cared for at our centre. Their clinical progress and outcome are shown in Tables 1 and 2.

All patients experienced bone marrow relapses shortly following haematopoietic stem cell transplantation or had refractory leukaemic disease before receiving CAR-T therapy (Table 1). Three patients had a high leukaemic disease burden (>75% blast in bone marrow) prior to CAR-T therapy. For presentation of cytokine release syndrome (CRS), the first 10 days was the peak onset time, from 6 hours to 9 days following CAR-T cell infusion. The most common presenting symptoms were high fever with temperature >39°C, tachycardia, hypotension, and desaturation. As clinical differentiation from sepsis was difficult, all patients received empirical broad-spectrum antibiotics. Patients were managed with oxygen supplementation via a nasal cannula or high-flow oxygen when there was desaturation. Inotropic support in the intensive care unit was provided in the presence of hypotension. No child required invasive ventilatory support. Systemic steroid was prescribed only to patient 4 who had grade 3 CRS. No patient developed neurotoxicity and all were discharged from the intensive care unit.

Three patients (patients 1, 3, and 4) succumbed to disease relapse 2 to 8 months after CAR-T therapy. One patient (patient 2) remained disease-free for 9 months after CAR-T therapy with satisfactory Lansky performance score.

Discussion

Chimeric antigen receptor T-cell therapy is a promising novel therapeutic option for relapsed and refractory CD19+ B-cell ALL in children and young adults.[2] Cytokine release syndrome and neurotoxicity are the two most severe complications of CAR-T therapy. This has been reported to occur any time in the first 2 weeks after infusion of CAR-T cells. Up to 45% to 91% of patients develop CRS including serious CRS in 8.3% to 43% of cases.[3] The ASBMT (American Society for Blood and Marrow Transplantation) consensus grading system for CRS is based on the assessment of three vital signs: temperature, blood pressure, and oxygen saturation. Patients with fever (temperature >38°C) alone constitute grade 1 CRS; patients with fever and hypotension without the need for a vasopressor are considered grade 2; patients with fever, hypotension requiring vasopressor and/or hypoxia requiring oxygen supplementation are grade 3. In grade 4 CRS, patients have fever with

TABLE 1. Demographics of patients prescribed CAR-T therapy for ALL

Patient	Sex	Age at diagnosis of ALL (years)	Diagnosis	Risk group at diagnosis	Age at first relapse (years)	Salvage therapy before CAR-T therapy	Indication for CAR-T therapy
1	M	2.1	CD19+ B-ALL	IR	2.8	Chemotherapy* / 1st BM relapse and salvage with chemotherapy† / unrelated cord blood HSCT	2nd BM relapse at 2 months post-HSCT, salvage with 6-mercaptopurine / methotrexate / cytarabine / vincristine; 3rd relapse at 4 months later then decided for CAR-T therapy
2	M	1.8	CD19+ B-ALL	IR	2.7	Chemotherapy* / 1st BM relapse and salvage with chemotherapy† / blinatumomab / unrelated cord blood HSCT	2nd BM relapse at 4 months post-HSCT then for CAR-T therapy
3	M	0.8	CD19+ B-ALL	IR	1.5	Chemotherapy* / 1st BM relapse and treated with blinatumomab / unrelated cord blood HSCT	2nd BM relapse at 2 months post-HSCT, salvage with steroid / vincristine; 3rd relapse at 3 months later then for CAR-T therapy
4	M	15.5	CD19+ B-ALL	IR	17.0	Chemotherapy* / 1st BM relapse and salvage with chemotherapy†	2nd BM relapse after clofarabine / etoposide / cyclophosphamide then for CAR-T therapy

Abbreviations: B-ALL = B-cell acute lymphoblastic leukaemia; BM = bone marrow; CAR-T = chimeric antigen receptor T-cell; HSCT = haematopoietic stem cell transplantation; IR = intermediate risk

* Treated with Chinese Children's Cancer Group childhood acute lymphoblastic leukaemia 2015 study group (CCCG-ALL-2015) protocol

† Treated with Hong Kong Paediatric Haematology and Oncology Study Group ALL Relapse 2007 Protocol

TABLE 2. Presentation and management of CRS after CAR-T therapy

Patient	Delay of onset of CRS after CAR-T therapy	Presentation	Grading of CRS	Highest interleukin-6 level (<3.1 pg/mL)	Management of CRS	Intensive care needed	Outcome
1	6 Hours after infusion	Fever (39°C), tachycardia (HR=160 beats/min), desaturation (SaO2 85%)	Grade 2	357 (Day 1 of CAR-T)	Empirical antibiotics, 1 dose of tocilizumab given at 7 hours from onset CRS, oxygen supplement	Yes Inotrope - Oxygen + Ventilator -	CRS subsided, no neurotoxicity, died at 2 months post–CAR-T due to relapse and septicaemia
2	9 Days	Fever (39°C), tachycardia, headache, transaminitis	Grade 1	-	Empirical antibiotics, 2 doses of tocilizumab	Yes Inotrope - Oxygen - Ventilator -	CRS subsided, no neurotoxicity, in remission at 9 months post–CAR-T; Lansky performance score 90
3	9 Days	Fever (39°C), tachycardia, desaturation (SaO2 88%) with oxygen supplement	Grade 2	3929 (Day 9 of CAR-T)	Empirical antibiotics, 1 dose of tocilizumab, oxygen supplement	Yes Inotrope - Oxygen + Ventilator -	CRS subsided, no neurotoxicity, in remission until 5 months post–CAR-T, died at 8 months post–CAR-T therapy owing to relapse; Lansky performance score 70-80 at disease-free period
4*	3 Hours after infusion	Fever (39.5°C), hypotension, chills, rigor, desaturation (SaO2 80%) with oxygen supplement, oliguria	Grade 3	9746 (Day 1 of CAR-T)	Empirical antibiotics 2 doses of tocilizumab, given 1 day from onset CRS, methylprednisolone for 2 days, inotropes	Yes Inotrope + High-flow oxygen + Ventilator -	CRS subsided, no neurotoxicity, died at 2.5 months post–CAR-T owing to relapse and septicaemia

Abbreviations: CAR-T = chimeric antigen receptor T-cell; CRS = cytokine release syndrome; HR = heart rate; SaO2 = oxygen saturation

* Received allogeneic CAR-T therapy

hypotension requiring multiple vasopressors and positive pressure ventilation.[4]

In recent years many centres in Western countries and mainland China have started to provide CAR-T therapy, either as part of a clinical trial or as standard treatment using commercial CAR-T cell products. The treatment will soon be introduced in Hong Kong so local experience of managing CRS will be of interest to our readers.

Cytokine release syndrome is a systemic

inflammatory response that can be triggered by a variety of factors such as infection and certain drugs. The term "cytokine release syndrome" was first used in the early 1990s when the anti–T-cell antibody muromonab-CD3 (OKT3) was introduced as an immunosuppressive treatment for solid organ transplantation. Recently, with the success of the newer T-cell-engaging immunotherapy, namely blinatumomab, there has been a refocus on CRS since it represents one of the most frequent serious complications.[5] The clinical features of CRS sometimes overlap with those of haemophagocytic lymphohistiocytosis or macrophage activation syndrome.[6] In our cohort, the peak onset was observed in the first 10 days following CAR-T therapy. A high disease burden prior to CAR-T therapy may be associated with severe CRS. Close monitoring and early intervention are key for successful control of CRS. Remaining alert for this condition and timely institution of monoclonal antibody against interleukin-6 receptor (tocilizumab 8 mg/kg; 12 mg/kg if body weight <30 kg), or adding systemic steroid in severe cases together with intensive cardiorespiratory support is the recommended treatment for CRS.[3,4] Institutes are advised to have tocilizumab readily available prior to commencement of CAR-T therapy since timely control of CRS by this agent is vital to prevent progression of cytokine storm. The mortality of CRS has now been much reduced with clinicians acquiring more experience in managing complications. Vigorous respiratory and circulatory support in an intensive care unit is also essential.[7] Gardner et al[3] reported that early intervention with tocilizumab and/or systemic steroid in patients with early signs of CRS did not negatively impact the anti-tumour potency of CD19 CAR-T therapy.

Our treatment outcome seems inferior to that reported in the literature in which 3-month remission rate was 81%; 73% at 6 months and 50% at 12 months.[2] In our cohort, two patients (50%) remained in disease remission at 3 months whereas only one (25%) was in remission 9 months post–CAR-T therapy. However, the case number is small and comprised of patients with multiple relapses, three of whom developed relapse after haematopoietic stem cell transplantation and one who had very refractory disease. These patients are well known to be a group with one of the worst prognoses and most individuals do not survive long-term.

Some centres utilise CAR-T therapy as a bridge before transplantation as consolidative therapy for relapsed or refractory ALL. Unfortunately, in our four patients, three were at a very early post-transplant stage and would be unable to tolerate a second transplant. In other case scenarios, namely those with chemorefractory ALL, CAR-T therapy may play a role in bridging prior to hematopoietic stem cell transplantation. Recent clinical trials have adopted alternative CAR-T therapy strategies such as bispecific or sequential CAR-T therapy that may have a more potent anti-leukaemic effect.[8]

In conclusion, early recognition of CRS and early intervention with vigorous cardiopulmonary support and timely initiation of anti–interleukin-6 receptor therapy can achieve good control of CRS. Chimeric antigen receptor T-cell therapy is now offered as a new salvage therapy for patients with relapsed/refractory CD19+ B-acute lymphoblastic leukaemia.

Author contributions

Concept or design: BS Li, CK Li.
Acquisition of data: FWT Cheng, GKS Lam, G Joynt, KL Hon.
Analysis or interpretation of data: FWT Cheng.
Drafting of the manuscript: FWT Cheng.
Critical revision of the manuscript for important intellectual content: CK Li.

Conflicts of interest

As an editor of the journal, KL Hon was not involved in the peer review process. The other authors have disclosed no conflicts of interest.

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Ethics approval

The patient was treated in accordance with the tenets of the Declaration of Helsinki. The patient provided written informed consent for all treatments and procedures.

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