JBUON 2021; 26(1): 159-165
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
Email: editorial_office@jbuon.com

ORIGINAL ARTICLE

Effect of Anti-CD19 chimeric antigen receptor T cell therapy in children with relapsed or refractory acute B-lymphocytic leukemia and its prognosis

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Summary

Purpose: *To explore the efficacy of chimeric antigen receptor (CAR)-T cell therapy in children with relapsed or refractory acute B-lymphocytic leukemia (B-ALL) and the influencing factors for their prognosis.*

Methods: *A retrospective analysis was performed on the clinical data of 46 children with relapsed or refractory B-ALL, who were admitted to and treated in our hospital from January 2015 to October 2017, and the remission and post-infusion adverse reactions were observed in all the children. Besides, the survival of the children was followed up and recorded, and the influencing factors for the prognosis were identified by univariate and multivariate Cox regression analyses.*

Results: *A total of 35 children achieved morphologic complete remission. Cytokine release syndrome (CRS) occurred in 41 out of 46 children, consisting of 37 (80.4%) cases of grade I-II CRS and 4 (8.7%) cases of grade III-IV CRS. The concentrations of serum interleukin (IL)-6, interferon-γ (IFN-γ), ferritin and C-reactive protein (CRP) obviously rose during CRS, and their peak values in the patients with grade III-IV CRS were notably higher than those in grade I-II CRS patients. The 3-year overall survival (OS) and event-free survival (EFS) rates were 28.3% and 13.0%, respectively. The results also showed that tumor burden ≥5% prior to CAR-T cell therapy [hazard ratio (HR)= 3.496, 95% confidence interval (CI)= 1.448-9.891] and non-combination with hematopoietic stem cell transplant (HSCT) therapy [HR =0.890, 95% CI= 0.543-0.904] were the independent risk factors for the prognosis of the children.*

Conclusions: *Anti-cluster of classification (CD) 19 CAR-T cell therapy is safe and effective against relapsed or refractory B-ALL in children. Reducing the tumor burden before infusion of CAR-T cells and combined with HSCT after infusion are the independent factors for improving the prognosis of the children.*

Key words: *chimeric antigen receptor, CD19, leukemia, lymphoid, children, relapsed, refractory*

Introduction

Acute lymphocytic leukemia (ALL) is one of the most common childhood malignant hematological diseases. The long-term disease-free survival rate of ALL in children has exceeded 85% as chemotherapeutic drugs and regimens have been improved, but ALL is still refractory or recurrent in 10-15% of the children, and the prognosis remains fairly poor, usually with a mean survival of

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Received: 08/10/2020; Accepted: 12/11/2020

no more than 1 year [1-3]. Immunotherapy for the relapsed and refractory leukemia has become the hotspot of research in recent years.

Chimeric antigen receptor (CAR)-T cells are genetically engineered T lymphocytes that express the binding sites for the specific antibodies and specifically identify and kill tumor cells in a non-major histocompatibility complex-restricted manner [4,5]. In recent years, it has been growingly reported that CAR-T cell therapy produces substantial efficacy against relapsed or refractory ALL, with a complete remission (CR) rate of 90% in children and adult patients [6,7]. The present study retrospectively analyzed the children with relapsed or refractory B-ALL, who were treated in our hospital and summarized disease features, chemotherapy efficacy and the influencing factors for prognosis, so as to offer a potent basis for the treatment of children.

Methods

Subjects of study

The clinical data of 46 children with relapsed or refractory B-ALL, who were admitted to and treated in our hospital from January 2015 to October 2017, were collected. The children were firstly diagnosed with E2A-PBX1-positive B-ALL at the age ≤16 years old based on the morphology, immunology, cytogenetics and molecular biology classification with reference to the *Standard for the Diagnosis and Curative Effect of Hematopathy.* Among the 46 children, there were 31 cases of bone marrow morphology recurrence after regular chemotherapy, including 3 cases of accompanied testicular or central nervous system recurrence, 6 cases of molecular biology recurrence after regular chemotherapy, 4 cases of recurrence after allogeneic hematopoietic stem cell transplant (HSCT) and 5 cases of refractory B-ALL. This study was approved by the Ethics Committee of the First Hospital of Xi'an Jiaotong University. Signed written informed consents were obtained from all participants before the study.

Treatment methods

The patients were pre-treated 1-2 weeks prior to the infusion of CAR-T cells. Specifically, cyclophosphamide was administered at 250 mg/m^2/d on d 1-3, busulfan at 0.8 mg/kg/time, q 6h on d 1-3 or fludarabine at 25 mg/m^2/d on d 1-3. Besides, etoposide and (or) doxorubicin were selectively given at 150 mg/m^2/d on d 1-3 and 30 mg/m^2/d on d 1, respectively, based on the tumor burden and proliferation rate. At 10-14 d before the infusion, T lymphocytes were collected from donor or autologous peripheral blood, transfected with the CAR structure fragments [anti-cluster of classification (CD) 19 scFv/CD28/CD137/CD27/iCasp9] via lentivirus vectors and amplified *in vitro.* Prior to the infusion of CAR-T cells, calcium gluconate was routinely infused to prevent hypersensitivity. The cells were infused at (0.60-10.64)×10^6/kg body weight once, including the CAR-T cells at (0.30-18.72)×10^6/kg body weight determined via polymerase chain reaction (PCR).

Observation indicators

After the infusion of CAR-T cells, the CAR-T cells were counted weekly. The morphology of bone marrows was reexamined via smear assay, and minimal residual disease (MRD) was detected via flow cytometry 1 week after the number of CAR-T cells began to decline. Afterwards, the review was performed once every 3 months, during which the peripheral blood count was reviewed once a week and the morphology of bone marrows and immune residues were reexamined when recurrence was suspected. The morphologic complete remission of bone marrows and MRD lower than the pre-infusion baseline level at any time after CAR-T cell therapy as well as no progressive extramedullary disease were defined as response to treatment, whereas the morphologic incomplete remission of bone marrows, MRD higher than the pre-infusion baseline level or progressive extramedullary disease as no response to treatment.

Cytokine release syndrome (CRS) was diagnosed and treated as follows: A certain degree of cytokinemia has an anti-tumor effect, but excessively powerful cytokine storms results in severe life-threating consequences. CRS was diagnosed based on the 2014 revised grading criteria for CRS [8, 9]. Besides, it was treated by monitoring the vital signs such as body temperature, blood pressure and blood oxygen, and the levels of the cytokines including tumor necrosis factor-α (TNF-α), interleukin (IL)-2, IL-6 and C-reactive protein (CRP) with reference to the three-level treatment principle, so as to perform CAR-T cell therapy safely and effectively [10].

Karyotype analysis was conducted on 10 bone marrow metaphase cells at least for each patient using the R-banding technique by the direct method or 24 h culture method. Moreover, immunotyping and MRD monitoring were carried out using FACSCalibur flow cytometer (Becton Dickinson, USA), and the surface antigens of tumor cells were detected using indirect immunofluorescence assay and a set of monoclonal antibodies. The sensitivity for the MRD test was 10^{-4}. Additionally, 43 ALL-associated fusion genes were detected using multiplex nested PCR, and real-time quantitative PCR was performed at the sensitivity of 10^{-4} to determine the copy number of E2A-PBXI fusion genes.

Common clinical adverse reactions were graded based on the Common Terminology Criteria for Adverse Events version 5.0 of the United States Department of Health and Human Services. The recurrence and survival of children were followed up and recorded until December 2019. Event-free survival (EFS) refers to the duration from the definite diagnosis to the occurrence of events or the ending date of follow-up, while overall survival (OS) to the period from the definite diagnosis to death or the ending date of follow-up.

Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were

presented as mean ± standard deviation, and the comparisons between two groups were made using t-test. Enumeration data were expressed by percentage (%) and compared using x^2 test or Fisher's exact test. The survival curves were plotted using the Kaplan-Meier method, and the log-rank test was conducted to compare survival between two groups. Besides, the influencing factors for the long-term survival of children were analyzed using multivariate Cox proportional-hazard regression model. P<0.05 suggested statistically significant difference.

Results

Remission in children after treatment

After infusion of CAR-T cells, bone marrows were routinely monitored. Based on the results, there were 35 children with morphologic complete remission, including 33 cases of MRD-negative remission, and their MRD level was lower than that before treatment, with a response rate of 76.1%. The time to response was at 7-28 d after the infusion, during which the maximum treatment response was achieved in 29 out of 35 children (82.9%) 7-14 d after the infusion. Among all the children with response to treatment (n=35), 17 MRD-negative patients underwent HSCT 31-90 d after the infusion of CAR-T cells, and the other 18 patients were ad-

Table 1. Demographics and general clinical data of all studied children

Parameters	*Cases n (%)*
Gender	
Male	26 (56.5)
Female	20 (43.5)
Age (years)	
<8	24 (52.2)
≥8	22 (47.8)
Disease condition	
Refractory	5 (10.9)
Molecular biological relapse	6 (13.0)
Relapse after chemotherapy	31 (67.4)
Relapse after HSCT	4 (8.7)
Molecular biological and genetic features	
BCR-ABL (+)	2 (4.3)
MLL Rearrangement	1 (2.2)
IKZF1 mutation	4 (8.7)
TEL-AML1 (+)	5 (10.9)
Complex chromosome abnormalities	3 (6.5)
Tumor load before CAR-T cells infusion	
<5%	29 (63.0)
≥5%	17 (37.0)

HSCT: hematopoietic stem cell transplantation; CAR-T: chimeric antigen receptors T cells

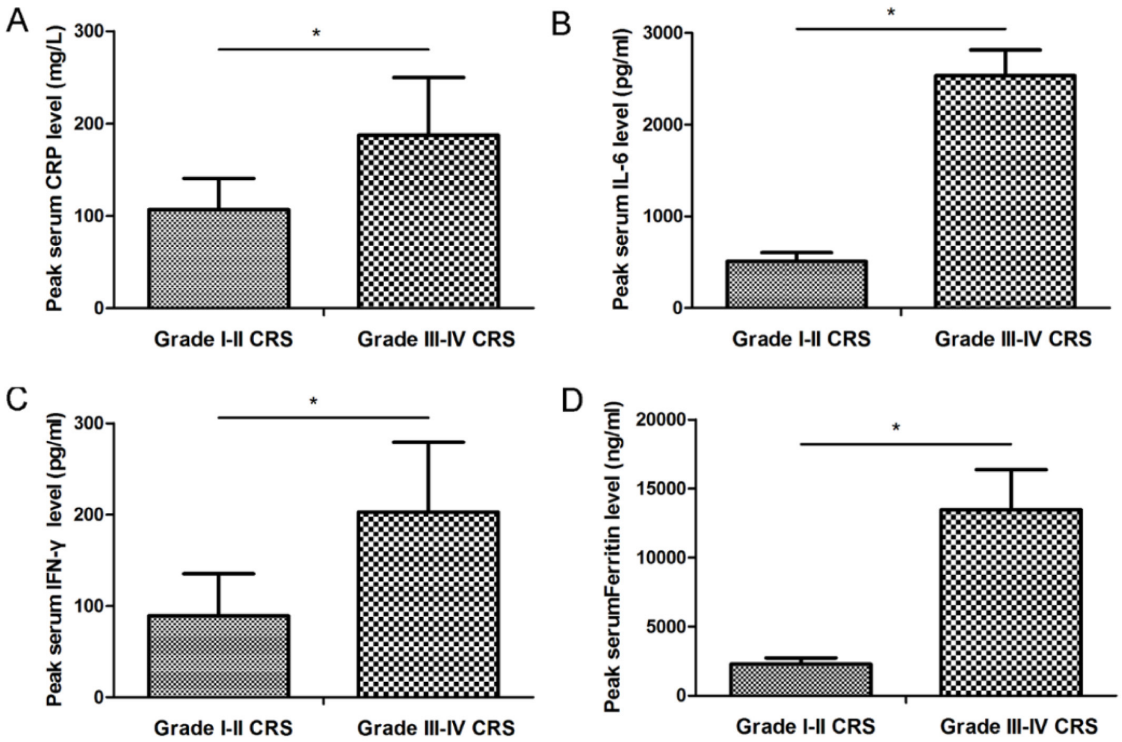

Figure 1. Comparison of serum peak levels of CRP **(A)**, IL-6 **(B)**, IFN-γ **(C)** and Ferritin **(D)** of children with relapsed or refractory ALL after CAR-T cells infusion. The serum peak levels of CRP **(A)**, IL-6 **(B)**, IFN-γ **(C)** and Ferritin **(D)** of relapsed or refractory ALL children with Grade III-IV cytokine-release syndrome (CRS) were significantly higher than those of children with Grade I-II CRS (*p<0.001).

Table 2. Comparison of adverse reactions of children with relapsed or refractory ALL

Parameters	*Cases* *n (%)*	*Grade I-II* *n (%)*	*Grade III-IV* *n (%)*
Cytokine-release syndrome	41 (89.1)	37 (80.4)	4 (8.7)
B cell exhaustion	38 (82.6)	33 (71.7)	5 (10.9)
Fever	37 (80.4)	34 (73.9)	3 (6.5)
Headache	11 (23.9)	11 (23.9)	0 (0)
Nausea and vomiting	7 (15.2)	7 (15.2)	0 (0)
Neurotoxicity	10 (21.7)	9 (19.6)	1 (2.2)
Hypertension or hypotension	9 (19.6)	8 (17.4)	1 (2.2)
Arrhythmia	4 (8.7)	4 (8.7)	0 (0)
DIC	2 (4.3)	2 (4.3)	0 (0)
Elevated aminotransferase	3 (6.5)	2 (4.3)	1 (2.2)

DIC: Disseminated intravascular coagulation

ditionally treated with the chemotherapeutic drugs or traditional Chinese medicines after the CAR-T cells *in vivo* disappeared, with a median duration of 81 d at the MRD-negative status (Table 1).

Incidence of adverse reactions in children

Among the 46 children, there were 41 cases of different grades of CRS, including 37 (80.4%) cases of grade I-II CRS and 4 (8.7%) cases of grade III-IV CRS. The median time to the onset of CRS was at 6 d (1-10 d) after the infusion, and the median duration was 7 d (2-13 d). Diverse types of fever, the most common clinical manifestation, had an incidence rate of 80.4%, occurred 1-12 d after the infusion, and lasted for several hours to more than 10 d. Other manifestations of CRS included hypodynamia, changes in blood pressure, arrhythmia, gastrointestinal reactions, edema, serous effusion and coagulation abnormalities. Besides, the concentrations of serum cytokines IL-2, IL-6, IL-10, interferon-γ (IFN-γ), TNF-α, ferritin and CRP were determined in all the children with CRS. The results revealed that the concentrations of IL-6, IFN-γ, ferritin and CRP were evidently raised in CRS, and reached substantially higher peaks in grade III-IV CRS patients than those in grade I-II CRS patients ($p<0.001$, Figure 1). Since the CRS in most children was reversible, its symptoms were mitigated only through supportive care, and in addition to the supportive care, tocilizumab therapy, instead of glucocorticoid therapy, was performed in 4 cases of grade III-IV CRS, relieving the CRS symptoms.

Before and after the infusion of CAR-T cells, the proportion of CD19-positive B lymphocytes in the peripheral blood and bone marrows was determined by flow cytometry in 38 children. A decline

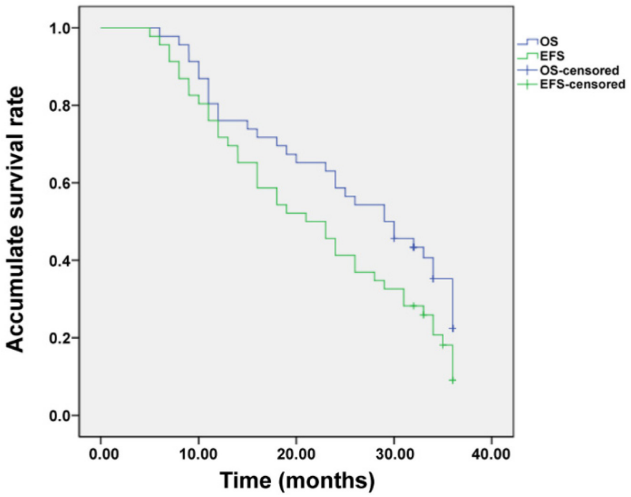

Figure 2. Kaplan-Meier survival curves of relapsed or refractory ALL children. Shown are the overall survival rate and event-free survival rate of the studied children

in the proportion of the peripheral blood CD19-positive B lymphocytes was detected in 31 cases 4-30 d after the infusion, including 16 cases of complete disappearance of CD19-positive B lymphocytes. Moreover, the proportion of bone marrow CD19-positive B lymphocytes were distinctly decreased in 34 cases after the infusion, including 18 cases of complete disappearance of CD19-positive B lymphocytes.

After the infusion of CAR-T cells, 10 children presented symptoms of neurotoxicity, including dizziness, lethargy, dysphoria, delirium and convulsions, among whom there were 9 cases of grade I-II neurotoxicity and 1 case of grade III-IV neurotoxicity. The above symptoms appeared 4-15 d after the infusion of CAR-T cells, lasted for 1-5 d and resolved after symptomatic treatment. Table 2 describes the specific adverse reactions.

Recurrence and survival of children

A total of 9 out of 35 children with response to the infusion of CAR-T cells re-underwent CAR-T cell therapy. At the end, 5 patients died and 2 patients survived after achieving CR again. Besides, HSCT was performed in 23 out of 35 children. Then, 13 patients experienced recurrence and 10 patients were in sustaining remission. Finally, 11 patients died, including 3 deaths of HSCT-associated complications, 2 patients survived after receiving anti-CD19 CAR-T cell therapy again, 2 patients survived after chemotherapy and 8 survived with no disease. The remaining 5 out of 35 children received non-chemotherapy medications and then experienced recurrence. Finally, 4 patients died and 1 patient survived. Among the 11 children with no response to the infusion of CAR-T cells, 9 patients died, 1 achieved CR through receiving infusion of anti-CD19 CAR-T cells and survived after HSCT, and 1 survived after chemotherapy combined with HSCT therapy. At the end of follow-up, the median follow-up time was 28.2 months, and the 3-year OS and EFS rates were 28.3% and 13.0%, respectively. The survival curves of patients were plotted using the Kaplan-Meier method (Figure 2).

Analysis of prognostic factors affecting the survival of the studied children

sex, age, disease status, tumor burden before CAR-T cell therapy, number of infused CAR-T cells and combination with HSCT therapy were subjected to univariate analysis of the influence on the 3-year OS and EFS of patients. According to the results, the long-term OS and EFS were shorter in the children who were under the age of 8 years, expe-

Table 3. Analysis of predictors for 3-year overall survival (OS) rate and event-free survival (EFS) rate in children with relapsed or refractory ALL

Parameters	*Cases (n=46)*	*3-year OS rate*		*3-year EFS rate*	
	n (%)	*%*	*p value*	*%*	*p value*
Gender			0.312		0.690
Male	26 (56.5)	23.1		11.5	
Female	20 (43.5)	35.0		15.0	
Age (years)			0.012		0.040
<8	24 (52.2)	16.7		8.3	
≥8	22 (47.8)	40.9		18.2	
Disease status			0.001		0.010
Relapse	35 (38.2)	14.3		8.6	
No Relapse	11 (61.8)	72.7		27.3	
Tumor load before CAR-T cells infusion			0.039		0.038
<5%	29 (63.0)	34.5		17.2	
≥5%	17 (37.0)	17.6		5.9	
Number of infused CAR-T cells			0.541		0.882
$<5\times10^5$/kg	24 (52.2)	25.0		12.5	
$\geq5\times10^5$/kg	22 (47.8)	31.8		13.6	
Combined HSCT			0.041		0.048
Yes	23 (50)	39.1		17.4	
No	23 (50)	17.4		8.7	

ALL: acute lymphoblastic leukemia; HSCT: hematopoietic stem cell transplantation; CAR-T: chimeric antigen receptors T cells

Table 4. Multivariate Cox regression analysis of predictors for relapsed or refractory ALL children

Parameters	*HR*	*95% CI*	*p value*
Age (≥8 years)	1.116	0.789-1.565	0.394
Disease relapse	1.097	0.882-1.293	0.527
Tumor load before CAR-T cells infusion ≥5%	3.496	1.448-9.891	0.014
Combined HSCT	0.890	0.543-0.904	0.025

ALL: acute lymphoblastic leukemia; HSCT: hematopoietic stem cell transplantation; CAR-T: chimeric antigen receptors T cells; CR: complete remission; HR: hazard ratio; CI: confidence interval

rienced recurrence, had tumor burden ≥5% before CAR-T cell therapy and did not receive the combined HSCT therapy (p=0.012, p<0.001, p=0.039, p=0.041, p=0.040, p=0.010, p=0.038 and p=0.048), but the sex and number of the infused CAR-T cells were not obviously correlated with the 3-year OS and EFS (p>0.05) (Table 3).

The four factors (age, disease status, tumor burden before CAR-T cell therapy and combination with HSCT therapy) were included into the multivariate Cox regression analysis. According to the results, the tumor burden ≥5% prior to CAR-T cell therapy [hazard ratio (HR)= 3.496, 95% confident interval (CI)= 1.448-9.891, p=0.014] and non-combination with HSCT [HR= 0.890, 95% CI= 0.543-0.904, p=0.025] were independent risk factors for the prognosis of the children (Table 4).

Discussion

Previous clinical studies have demonstrated that the relapsed or refractory ALL has an extremely poor prognosis, and its median survival tends not to be longer than 6 months [11]. UKALL12/ECOG 2993 study included 609 patients with relapsed ALL of all subtypes and over 90% of them died of recurrence in the subsequent follow-up, with the 5-year survival rate not exceeding 10% [12]. Constant efforts have been made to explore the treatment regimens of relapsed or refractory leukemia in the medical field, and anti-CD19 CAR-T cell therapy represents one of the hotspots of research in recent years.

CAR-T cell therapy, a novel cellular immunotherapy, enables the genetically engineered T cells to express tumor-specific CAR and combines the antigen-antibody binding mechanism with killing effect of T cells to specifically kill tumors, during which some CAR-T cells are transformed into memory cells with the anti-tumor effect, thereby preventing cancer recurrence. CD19 is only expressed in mature B lymphocytes and B lymphocyte precursor cells in normal tissues. According to the statistics, more than 95% of B lymphocytic leukemia cells express CD19, so B-ALL can be treated via constructing the CAR-T cells specifically identifying CD19 [13,14]. Maude et al [15] treated 30 children and adult ALL patients with the anti-CD19 CAR-T cell therapy, and found that there were 27 cases of CR, with a CR duration of 24 months, a 6-month disease-free survival rate of 67% and an OS rate of 78%. Brentjens et al [16] treated 5 adult patients with relapsed B-ALL with anti-CD19 CAR-T cell therapy, and found that they achieved MRD-negative molecular biology remission, with the CR lasting as long as 18 months after undergoing allogeneic HSTC. Moreover, the tumor cells in 1 case of recurrence after treatment persistently expressed CD19 and were sensitive to the 2nd generation anti-CD19 CAR-T cytotoxicity, thereby adding the benefits of the infusion of CAR-T cells. In 2014, Davila et al [17] used the 2nd generation anti-CD19 CAR-T cells to treat 16 cases of relapsed or refractory B-ALL, including Ph (+) high-risk patients and patients with recurrence after allogeneic HSTC, and the overall CR rate reached 88% after treatment. Grupp's research team reported that 36 out of 39 children with relapsed or refractory ALL achieved CR after CTL019 therapy and that 70% of the patients with response to treatment were still in remission after 6 months, with enriched and amplified CAR-T cells *in vivo* and a survival time of more than 2 years [18].

In the present study, it was found that the children infused with CAR-T cells exhibited a response rate of 76.1% to the treatment, slightly lower than that previously reported, probably because different CAR structures activate CTL cells to different extents. Almost all patients receiving the CAR-T cell therapy will experience CRS, the most common comorbidity of the therapy, but the incidence rate of severe CRS (hypotension and respiratory failure) is only 27% [18]. CAR-T cells cause the release of massive cytokines, such as IL-1, IL-6, IL-12 and IFN-γ, while killing large numbers of tumor cells, resulting in discomforts such as headache, tachycardia, hypotension, and shortness of breath, and acute respiratory distress syndrome and multiple organ failure and even death in severe cases. The treatment with glucocorticoids and IL-6 antagonists can lower the mortality rate of CRS, but glucocorticoids can not only inhibit inflammatory responses, but also weaken the anti-tumor activity of CAR-T cells [19, 20]. It has been generally held that the severity of CRS is positively correlated with the tumor burden before infusion. In this study, the incidence rates of CRS, grade III-IV CRS and neurotoxicity in children were 89.1%, 8.7% and 21.7%, respectively, which are lower than those in previous studies, probably due to the lower tumor burden before the infusion in the children in the present study. The incidence rate of adverse reactions was relatively low and there were no deaths due to treatment in this study. These results corroborate the safety of CAR-T cell therapy and indicate that adequate pretreatment chemotherapy is supposed to be performed before CAR-T cell therapy to decrease tumor burden. The pretreatment chemotherapy regimens can be individualized based on the conditions of children.

According to the follow-up results, the 3-year OS and EFS rates of the children were 28.3% and

13.0%, respectively. Besides, the findings of this study revealed that the tumor burden ≥5% before CAR-T cell therapy and non-combination with HSCT therapy were independent risk factors for the prognosis of children. Therefore, it now remains a relatively reasonable option for CAR-T cell therapy first to remove MRD by CAR-T cell therapy and then conduct elective HSCT for children with relapsed or refractory B-ALL.

In this retrospective study, the number of the enrolled children was limited, the follow-up content was not comprehensive enough, and the influences of the CAR-T cell therapy before HSCT on the complications during the later HSCT and long-term prognosis need to be further explored. Therefore, multi-center large-scale prospective randomized studies remain to be designed more rigorously in the future to verify the conclusion of the present study.

Conclusions

Anti-CD19 CAR-T cell therapy is safe and effective in the treatment of relapsed or refractory B-ALL in children. Reducing the tumor burden before infusion of CAR-T cells and combining with HSCT after infusion are independent factors for improving the prognosis of the children.

Conflict of interests

The authors declare no conflict of interests.

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