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Original Article

Long-term efficacy of haploidentical hematopoietic stem cell transplantation in the treatment of pediatric acute leukemia

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ABSTRACT

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the optimal treatment for pediatric patients with high-risk or intermediate-acute myeloid leukemia. Immunotherapies, such as CAR-T cellular therapy, have been rapidly developed, especially for refractory acute lymphoblastic leukemia. However, they are relatively expensive, limiting their widespread use. For patients lacking matched sibling donors, haploidentical donors are an option. This study analyzed the clinical outcomes of 119 pediatric acute leukemia patients who underwent haploidentical HSCT (n=68) or human leukocyte antigen (HLA)-matched HSCT (n=51). The 2-year overall survival (OS) and leukemia-free survival (LFS) in the haploidentical HSCT group were similar to those in the HLA-matched HSCT group (77.6% *vs.* 88.6%, P=0.076; 55.6% *vs.* 52.9%, P=0.497). The 3-year probability of total chronic graft-versus-host disease (GVHD) was 21.4% and 34.1% in the haploidentical and HLA-matched HSCT groups, respectively (P=0.526). Analysis of the 3-year cumulative recurrence rate suggested no significant difference between the haploidentical HSCT group and HLA-matched HSCT group (cumulative incidence, 32.7% *vs.* 31.2%, P=0.801). The cumulative incidence of acute GVHD, non-relapse mortality (NRM), and graft-versus-host relapse-free survival (GRFS) were similar in both groups. There was no difference in transplantation-related toxicity (TRT) in terms of infection, hepatic dysfunction, oral mucositis, and engraftment syndrome between the haploidentical HSCT and HLA-matched HSCT groups. The study suggests that haploidentical HSCT shows comparable OS, LFS, and GRFS to HLA-matched HSCT in pediatric patients with acceptable complications, and can therefore be recommended as an effective alternative for this population.

Keywords: pediatric acute leukemia, haploidentical donor transplantation, HLA-matched donor transplantation

INTRODUCTION

The survival rate of pediatric acute myeloid leukemia (PAML) patients has not exceeded 70% despite more intensive chemotherapy and better supportive care[1]. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a standard treatment option for patients with intermediate-risk or high-risk karyotype PAML[2], and is mainly performed on pediatric patients with high-risk factors, including

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high-risk genetic characteristics with consolidation or high-risk factors after persistent or recurrent minimal residual disease (MRD)[3]. The development of immunotherapies such as CAR-T-cellular therapy supports the significance of these immunotherapies in combination with allo-HSCT, especially for refractory acute lymphoblastic leukemia (ALL), pre-HSCT or MRD+ ALL post-HSCT[4–5]. However, these new immunotherapy modalities are relatively expensive, limiting their widespread use. Notably, immunotherapies do not completely eliminate the need for HSCT in patients with relapsed or refractory ALL. Therefore, allo-HSCT is mainly used for pediatric leukemia with a high risk of relapse and for consolidation of remission of relapsed or refractory disease.

The number of HLA-matched donors has been insufficient to meet the increasing need for allo-HSCT. However, haploidentical immediate family members could become donors. To overcome the HLA barrier and induce immune tolerance in haploidentical HSCT, several developments have been made, such as T-cell depletion (TCD), unmanipulated grafts with granulocyte colony-stimulating factor (G-CSF) plus anti-thymocyte globulin (ATG)-based regimens, and PT-Cy-based regimens[6]. In this study, we retrospectively analyzed the efficacy of haploidentical HSCT and HLA-matched HSCT in pediatric leukemia with allo-HSCT at Xinqiao Hospital from 2013 to 2020.

MATERIALS AND METHODS

Patients

The present study included 119 pediatric patients who underwent haploidentical HSCT or HLA-matched HSCT at the Xinqiao Hospital (Chongqing, China) from January 2013 to December 2020. All patients met the following criteria: (1) age ≤18 years at diagnosis; (2) diagnosis of high-risk or relapsed ALL or intermediate- and high-risk karyotype PAML based on NCCN Clinical Practice Guideline[2–3]; (3) in complete remission (CR); (4) haploidentical or HLA-matched HSCT; (5) peripheral blood (PB) or bone marrow (BM) or both as sources of stem cells; (6) no severe organ dysfunction or active infection; (7) an Eastern Cooperative Oncology Group (ECOG) score of 0–2. The exclusion criteria were as follows: (1) disease duration <1 year or >18 years; (2) Ph^+ lymphoblastic leukemia or acute promyelocytic leukemia (APL); (3) uncontrolled infection or organ dysfunction. The last follow-up date was December 30, 2021. Informed consent was obtained from the included patients according to the Helsinki Declaration. The project protocol was approved by the Xinqiao Hospital Ethics Committee.

Donors and stem cell mobilization and collection

The mobilization of peripheral blood stem cells (PBSCs) was performed according to our previous study[7]. Mobilized marrow and blood stem cells were used as grafts in the haploidentical HSCT group as the rates of engraftment of BM combined with PB were significantly higher than those of PB transplantation alone. The total number of CD 34+ cells in PB and BM was detected by flow cytometry analysis, and was at least $>4\times10^6$/kg in recipients. Fresh and treated BM and PBSCs were infused into recipients on the day of collection. Red blood cells (RBCs) and plasma were removed from the cells by density gradient sedimentation when the ABO major blood group was incompatible. BM cells did not require T-cell depletion *in vitro*.

Pretreatment regimens and GVHD prophylaxis

The pretreatment regimens were implemented as follows. Patients with identical-sibling donors were treated with busulfan (BU) and cyclophosphamide (CY); patients with HLA-identical unrelated HSCT received BU + CY + antithymocyte globulin (ATG, Sanofi, SangStat, Lyon, France); and patients with HLA-haploidentical relative HSCT were treated with semustine, arabinosylcytosine (Ara-c), BU, and CY.

The patients who received HLA-matched HSCT were treated post-transplantation with mycophenolate mofetil (MMF), cyclosporin A (CsA), and methotrexate (MTX). A total of 15 mg/kg MMF (Roche Pharmaceutical, Ltd., Switzerland) was administered orally every 12 hours from day 1 to day 30. Continuous intravenous CsA (2.5 mg/kg/day) was administered starting on day 1 and was continued until the patient was able to tolerate oral medication. MTX (15 mg/m^2) was administered intravenously on day 1, and 10 mg/m^2 MTX was administered on days 3 and 6. The patients who received haploidentical HSCT were treated with ATG, MMF, tacrolimus (FK506), and MTX. In addition to the standard treatment with ATG, MMF was administered from day 7 to day 90. Continuous intravenous FK506 (0.03 mg/kg/day) was started on day 7, and it was replaced with oral medication. A total of 15 mg/m^2 MTX was administered on day 1, and 10 mg/m^2 MTX was administered on days 3, 6, and 11.

Definitions and assessments

The primary endpoint was LFS. Secondary

endpoints included OS, engraftment, GVHD, NRM, TRT, and GRFS. Currently, LFS was defined as survival without evidence of relapse at any time post-transplantation. OS was defined as the time from transplantation to death for any reason or the last contact date. According to the tumor burden, disease relapse can be classified as hematologic relapse, cytogenetic relapse, and/or molecular recurrence. Recurrence can also be divided into intramedullary relapse, extramedullary relapse, or both[8]. The day of neutrophil engraftment was defined as the first 3 days with an absolute neutrophil count of 0.5×10^9/L after stem cell infusion. The day of platelet engraftment was defined as the first 7 days with a platelet count of 20×10^9/L without platelet transfusion. Recipient GVHD diagnosis, staging, and organ specificity were determined according to the 2014 National Institutes of Health's (NIH) Consensus Criteria[9]. NRM was defined as death after HSCT without disease progression or recurrence. TRT was defined following the standard criteria established by the National Cancer Institute. GRFS events were defined as the first event of grade Ⅲ–Ⅳ acute GVHD, extensive cGVHD, relapse, or death from any other causes[10]. CR was defined as BM blasts at ≤5.0%. CR1 was defined as the first complete remission[11]. CR2 was defined as the second complete remission.

Statistical analysis

Demographic characteristics and relevant clinical data were analyzed and compared between the haploidentical HSCT and HLA-matched HSCT groups by chi-square or Fisher's exact tests for categorical variables and by the Mann–Whitney U test for continuous variables. The probabilities of OS, LFS and GRFS were estimated using the Kaplan–Meier method. GVHD, disease relapse, and NRM rates were estimated using cumulative incidence analysis. All reported *P* values were based on two-sided hypothesis tests, and values of $P<0.05$ were considered statistically significant. Data analyses were primarily conducted with the SPSS software package 22.0.

RESULTS

Characteristics of patients and donors

A total of 119 pediatric leukemia patients (75 male and 44 female patients) received allo-HSCT. The median patient age was 10 years. There were 95 high-risk patients. Most patients achieved CR1 status, and the median age of the donors was 31 years. There were 56 parent donors in the haploidentical HSCT group and 14 identical-sibling donors and 35 unrelated donors in the HLA-matched HSCT group. There was no statistically significant difference between the haploidentical HSCT and HLA-matched HSCT groups in terms of the median age of donors, gender, and recipient disease status at the time of transplantation (***Table 1***).

Engraftment

All 119 patients received continuous neutrophil and platelet implantation, with 100% donor chimerism in their DNA fingerprints. Compared to the HLA-matched HSCT group infused with PBSCs, the haploidentical HSCT group was additionally infused with BM allografts. The median times of neutrophil engraftment and platelet engraftment were similar in both groups.

GVHD and TRT

The incidence of acute graft-versus-host disease (aGHVD) in the two groups was not significantly different (38.2% *vs.* 23.5%, $P=0.061$, ***Fig. 1A***). At day +100, the incidence of grade Ⅱ–Ⅳ aGVHD was 36.7% and 23.5% in the haploidentical HSCT and HLA-matched HSCT groups, respectively ($P=0.119$). Only one case of grade Ⅳ aGVHD occurred in the haploidentical HSCT group.

Among the cases with organ involvement, there were 7 cases (10.7%) in the skin, 5 cases (7.7%) in the liver, 2 cases (3.1%) in the eyes, and 3 cases (4.6%) in the mouth of the haploidentical HSCT group and 5 cases (13.7%) in the skin, 10 cases (19.6%) in the liver, 1 case (1.9%) in the eyes, 2 cases (3.9%) in the mouth, and 1 case (1.9%) in the lungs of the HLA-matched HSCT group. The 3-year cumulative incidence of chronic GVHD (cGVHD) was 21.4% in the haploidentical HSCT group and 34.1% in the HLA-matched HSCT group ($P=0.526$, ***Fig. 1B***). The 3-year cumulative incidence of severe cGVHD was 6.8% and 5.6% in the haploidentical HSCT and HLA-matched HSCT groups, respectively ($P=0.644$, ***Fig. 1C***).

TRT showed no significant difference between the haploidentical HSCT and HLA-matched HSCT groups. Fever was the most common TRT in all patients who received HSCT. Of the 119 patients with fever, 36 patients were diagnosed with bloodstream infections. Bacterial infections occurred in 2 cases in each of the two groups. In addition, 25 cases of viral infections occurred in the haploidentical HSCT group, while 9 cases were detected in the HLA-matched HSCT group ($P=0.067$). Other TRTs observed in HSCT mainly included hepatic dysfunction, oral mucositis, and engraftment syndrome. The incidence of hepatic insufficiency was 47.1% and 54.9% in the

Table 1 **Characteristics of patients with acute leukemia following allo-HSCT**

Characteristics	Haploidentical HSCT	HLA-matched HSCT	*P*
Number of patients	68	51	-
Median age (years, range)	9 (1–18)	11 (2–18)	0.963
Sex of recipients [*n* (%)]			0.956
Male	43 (63.2)	32 (62.7)	
Female	25 (36.8)	19 (37.3)	
Diagnosis [*n* (%)]			0.672
B-ALL	18 (26.5)	17 (33.3)	
T-ALL	12 (17.6)	7 (13.7)	
AML	38 (55.9)	27 (52.9)	
Disease status at transplantation [*n* (%)]			0.745
CR1	53 (77.9)	41 (80.4)	
≥ CR2	15 (22.1)	10 (19.6)	
Positive MRD [*n* (%)]	10 (14.7)	6 (11.8)	0.642
Median cycles of prior chemotherapy (*n*, range)			
ALL	5 (2–15)	4 (2–15)	0.414
AML	5 (2–11)	4 (2–7)	0.094
Median time from diagnosis to transplant (months, range)	6 (3–43)	4 (3–27)	0.709
Donor-recipient relationship [*n* (%)]			NA
Father-child	49 (72.1)	2 (3.9)	
Mother-child	7 (10.3)	0	
Sibling-sibling	9 (13.2)	14 (27.5)	
Other	3 (4.4)	35 (68.6)	
Donor-recipient sex matched grafts [*n* (%)]			0.336
Female-female	5 (7.4)	6 (11.8)	
Female-male	11 (16.2)	14 (27.5)	
Male-female	20 (29.4)	12 (23.5)	
Male-male	32 (47.1)	19 (37.3)	
ABO matched grafts [*n* (%)]			0.984
Matched	35 (51.5)	26 (51.0)	
Major mismatched	16 (23.5)	12 (23.5)	
Minor mismatched	12 (17.6)	10 (19.6)	
Major-minor mismatched	5 (7.4)	3 (5.9)	
Donor gender [*n* (%)]			0.065
Male	52 (76.5)	31 (60.8)	
Female	16 (23.5)	20 (39.2)	
Median age (years, range)	32 (11–49)	31 (8–46)	0.932
Cell composition in grafts (median, range)			
Infused nuclear cells, 10^8/kg	11.65 (3.36–27.45)	10.00 (1.52–25.27)	0.543
Infused CD34+ cells, 10^6/kg	7.62 (0.55–20.61)	7.10 (1.21–31.60)	0.866

Allo-HSCT: allogeneic hematopoietic stem cell transplantation; HSCT: hematopoietic stem cell transplantation; ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; CR1: the first complete remission; CR2: the second complete remission; MRD: minimal residual disease.

haploidentical and HLA-matched HSCT groups, respectively. Approximately 10% of the patients presented with oral mucositis. Engraftment syndrome occurred in one patient with haploidentical HSCT and in two patients with HLA-matched HSCT. No secondary malignancy was reported in any of the survivors.

Relapse and NRM

There were 27 and 26 patients in the haploidentical HSCT and HLA-matched HSCT groups, respectively, with 43 hematological relapses (haploidentical HSCT, *n*=18; HLA-matched HSCT, *n*=25) and 10 extramedullary relapses (haploidentical HSCT, *n*=9; HLA-matched HSCT, *n*=1). Among them, there were 8 cases of central nervous system recurrence (haploidentical HSCT, *n*=7; HLA-matched HSCT, *n*=1), and the 3-year recurrence rate in the HLA-matched HSCT group was higher than that in the haploidentical HSCT group without significant difference (32.7% *vs.* 31.2%, *P*=0.801, ***Fig. 1D***). There were 14 and 6 patient deaths in the haploidentical HSCT and HLA-matched HSCT groups, respectively. Recurrence was the leading

cause of death (haploidentical HSCT, *n*=11; HLA-matched HSCT, *n*=6). The 3-year cumulative rate of NRM in the HLA-matched HSCT group was 0.0%, while the 3-year cumulative NRM rate in the haploidentical HSCT group was 4.4% (*P*=0.585). The nonrecurrent causes of death were infections (*n*=2) and cerebrovascular diseases (*n*=1).

OS, LFS, and GRFS

The median follow-up period after HSCT in survivors was 36.4 months (range: 2.3–80.3 months) in the haploidentical HSCT group and 29.4 months (range: 2.4–100.5 months) in the HLA-matched HSCT group (*P*=0.658). The 2-year OS and LFS rates were not significantly different between the groups. The 2-year OS rates were 77.6% and 88.6% (*P*=0.076) (***Fig. 2A***), and the 2-year LFS rates were 55.6% and 52.9% (*P*=0.497), respectively (***Fig. 2B***). In addition, the 3-year cumulative GRFS rates were 41.2% and 33.3% (*P*=0.288) in the haploidentical

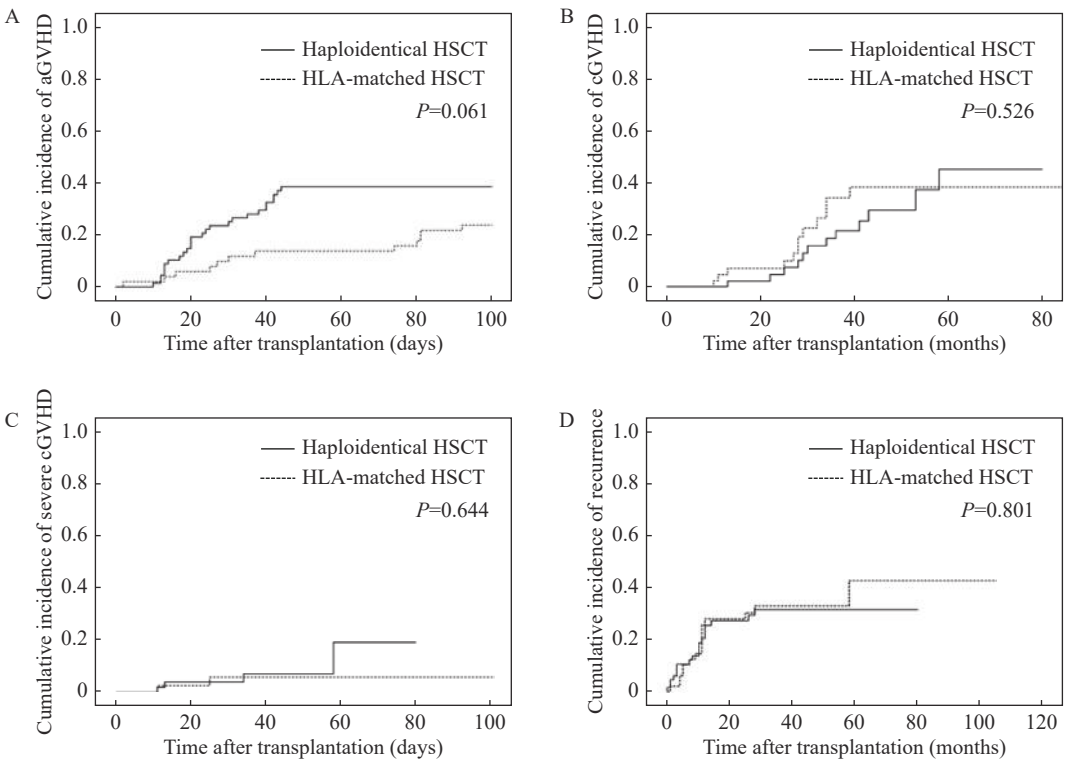

Fig. 1 **Cumulative incidence of GVHD and recurrence in haploidentical HSCT and HLA-matched HSCT.** A: Cumulative incidence of aGVHD. B: Cumulative incidence of cGVHD. C: Cumulative incidence of severe cGVHD. D: Cumulative incidence of recurrence. GVHD: graft-versus-host disease; aGVHD: acute graft-versus-host disease; cGVHD: chronic graft-versus-host disease; HSCT: hematopoietic stem cell transplantation; HLA: human leukocyte antigen.

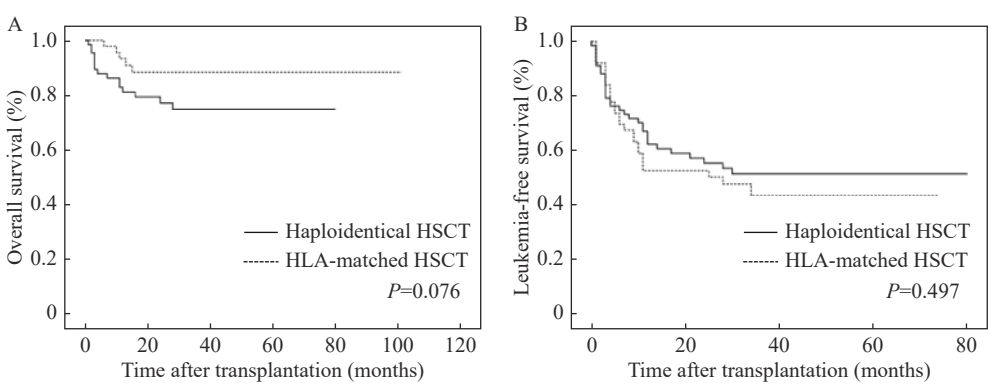

Fig. 2 **Kaplan-Meier estimates of outcomes in the haploidentical HSCT and HLA-matched HSCT.** A: Overall survival B: Leukemia-free survival. HSCT: hematopoietic stem cell transplantation; HLA: human leukocyte antigen.

HSCT and HLA-matched HSCT groups, respectively.

DISCUSSION

Allo-HSCT has been demonstrated to be effective and improve event-free survival in childhood acute leukemia. For high-risk patients in primary CR and most children with relapsed or refractory disease, allo-HSCT may be the only cure. The HLA system plays a central role in the immune response to pathogens, as well as in organ and allogenic HSCT[12]. However, sibling pairs have only an approximate 25% chance of inheriting the same HLA-compatible type, and matched unrelated donors have high cost and time constraints[13]. Haploidentical matched donors can enter the HSCT process faster due to their easy availability and may have a stronger graft versus-leukemia effect, especially in high-risk patients who are in urgent need of HSCT, thus reducing the cumulative recurrence rate after transplantation. Historically, the patients who received haploidentical HSCT faced numerous challenges, including a high incidence of graft failure, severe GVHD, delayed immune reconstitution, and delayed engraftment[14–16]. Removing T cells from grafts using *in vitro* and *in vivo* techniques significantly improved the outcomes of haploidentical transplants[17–18]. This was a retrospective study that reviewed the therapeutic effect of haploidentical HSCT for PAML.

A target CD34+ cell dose of 4–5×10^6 CD34+ cells/kg seemed most reasonable[19]. Higher cell doses were associated with faster engraftment, lower transplant-related mortality, and a reduced risk of relapse. CD34+ cell doses of >8×10^6/kg were associated with more rapid neutrophil engraftment, but also with the development of extensive chronic GVHD in previous research[20]. In our study, successful hematopoietic stem cell engraftment demonstrated to be associated with the use of applicable numbers of CD34+ cells. All patients in this study achieved hematopoietic recovery after transplantation. Consistent with other reports, there was no significant difference in neutrophil and platelet implantation in children treated with haploidentical HSCT compared with those treated with HLA-matched HSCT.

In terms of donors, younger donors were more likely to have a higher yield of CD34+ cells[21]. Younger donors had a much lower cumulative incidence of aGVHD than older donors, and donors <30 years old and male donors had less NRM and better survival than their older or female counterparts[22]. The reasons for this age influence were not elucidated, and it is speculated that the age influence may be related to the decrease in BM reserves with age and normal human aging, as mutations may impede PBSC mobilization and accumulation[23]. Huang *et al.* previously established the principle of donor selection in TCR Haplo-SCT mode based on ATG for GVHD prevention, and young, male, nonhereditary maternal antigen incompatible donors should be the optimal choice[22]. We observed that the donors were approximately 31 years of age and that there were more male donors in haploidentical HSCT.

Calcium-regulated phosphatase inhibitors (tacrolimus/Tac and cyclosporine/CsA) were shown to inhibit T-cell proliferation and activation, and therefore were clinically used in combination with either MTX or MMF as standard prophylaxis for HLA-matched HSCT[24]. In our study, the 3-year cumulative cGVHD incidence was lower in the haploidentical HSCT group than in the HLA-matched HSCT group (21.4% *vs.* 34.1%). Our previous studies reported that the short-term Tac regimen (from −8 days to +30 days) for GVHD prophylaxis in patients undergoing haplo-HSCT was associated with a low incidence and mild severity of aGVHD[25]. ATG was used as part of transplant pretreatment to affect T-cell depletion *in vivo* with the aim of reducing both acute and chronic GVHD with varying success. Rabbit ATG was generally considered to deplete T cells more effectively and allow regulatory T cells (Tregs) to achieve greater expansion[26]. Zhou *et al.* reported that moderate doses (7.5 mg/kg) of ATG achieved a significant reduction in the incidence of moderate to severe aGVHD and viral infections without increasing mortality[27]. In accordance with the research, GVHD prophylaxis in haploidentical HSCT contained ATG and FK506.

The degree of toxicity manifested in HSCT varies depending on the type of transplantation procedure, pretreatment regimen, underlying disease, and patient comorbidities. Patients can develop pancytopenia, infection, gastrointestinal toxicity, and organ dysfunction. During this period, common infections are often associated with neutropenia and consist of gram-positive and gram-negative bacteria, cytomegalovirus, candidiasis, and invasive aspergillosis[28–29]. There was no difference in TRT between the haploidentical HSCT and HLA-matched HSCT groups due to the effectiveness of blood products, anti-infective drugs, and general supportive therapy, including hydration and parenteral or enteral nutrition.

Relapse of the underlying disease remains the most important cause of death throughout the post-transplant period[29]. In the present study, the

recurrence rate was 32.7% in the haploidentical HSCT group, which is higher than that in a recent study that enrolled 23 children with identical sibling donor-HSCT and 156 children in the haploidentical HSCT group with pediatric AML[11]. Mo *et al.* also reported a 2-year cumulative recurrence rate of 16.1% in haploidentical transplant[30]. The reason for the difference may be related to the sample size and patients' baseline characteristics. In addition, Peters *et al.* reported a cumulative relapse rate from 22% to 24% in patients transplanted with unrelated or sibling donors[31], which is comparable to the results of HLA-matched HSCT in our study.

A recent study showed that the 3-year disease-free survival (DFS) after allo-HSCT treatment was 47.4% and DFS could be used as an accurate indicator to evaluate the long-term success of allo-HSCT[32]. The results of a multicenter, large-sample study revealed that the mean 3-year expected DFS and OS of URD allo-HSCT for leukemia were approximately 67% and 71%, respectively[33]. Our study also found that the 2-year LFS and OS in the haploidentical HSCT group were similar to those in the HLA-matched HSCT group. This suggests that the efficacy of haploidentical HSCT and HLA-matched HSCT in the treatment of childhood leukemia is comparable and consistent with current findings reported in related studies.

In summary, there was no additional increase observed in GVHD after haploidentical HSCT treatment. Our findings suggest that haploidentical HSCT shows comparable OS, LFS, and GFRS to HLA-matched HSCT in pediatric patients with acceptable complications. In addition, haploidentical HSCT can be recommended as an effective alternative for this population, especially for those patients at a risk of rapid disease progression, whereas rapid access and transplant flexibility are advantages of haploidentical HSCT.

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