

Haploidentical hematopoietic stem cell transplantation without total body irradiation for pediatric acute leukemia: a single-center experience

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Abstract: Hematopoietic stem cell transplantation (HSCT) is a promising method for therapy of pediatric patients with acute leukemia. However, less availability of matched donors limited its wide application. Recently, haploidentical HSCT has become a great resource. Here, we have retrospectively reported our experience of 20 pediatric patients with acute leukemia who underwent haploidentical HSCT without total body irradiation (TBI) myeloablative regimen in our center from November 2007 to June 2014. All the patients attained successful HSCT engraftment in terms of myeloid and platelet recovery. Thirteen patients developed grade I–IV acute graft-versus-host disease (a-GVHD). The incidence of grade I–II a-GVHD, grade III–IV a-GVHD, and chronic GVHD (c-GVHD) was 45%, 20%, and 25%, respectively. The mean myeloid and platelet recovery time was 13.20 ± 2.41 and 19.10 ± 8.37 days. The median follow-up time was 43.95 ± 29.26 months. During the follow-up, three patients died. The overall survival (OS) rate was 85%. The present study indicated that haploidentical HSCT without TBI myeloablative regimen significantly improved the OS rate of pediatric patients with acute leukemia.

Keywords: haploidentical, hematopoietic stem cell transplantation, myeloablative regimen, total body irradiation, acute leukemia, pediatric

Introduction

Acute leukemia (AL) is the most common malignancy in children. With the improvement in chemotherapy and risk stratification, children younger than 6 years show significantly better event-free survival – 83.7% in acute lymphoblastic leukemia¹ and 54% in acute myeloid leukemia.² The AL outcome has greatly improved in childhood in the past few decades. However, 15%–20% of the patients relapse, which is the most formidable challenge in leukemia treatment.³ Therefore, effective treatment strategies are imperative. Hematopoietic stem cell transplantation (HSCT) has been demonstrated to be safe and efficacious in children with AL.⁴ Transplantation from a human leukocyte antigen (HLA)-matched sibling is the ideal treatment for children with AL. However, the chance of availability of a matched donor is less than 25%.⁵ The availability of haploidentical donor has considerably widened the donor pool and many patients were assigned to haploidentical HSCT (haplo-HSCT).^{6,7} This method is now successfully utilized with myeloablative (MA) preparative regimen to achieve long-term survival compared to HLA-matched transplantation. Future directions will focus on optimizing conditioning regimens and enhancing graft-versus-leukemia effect. Limited data are available pertaining to haplo-HSCT without total body irradiation (TBI) regimens, particularly in the pediatric population. The aim of this single-center study was to

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review haplo-HSCT without TBI MA regimen for children with AL in our hospital.

Materials and methods

Patients

This retrospective study involved a total of 20 pediatric AL patients (13 males and seven females) who underwent haplo-HSCT between November 2007 and June 2014 in Beijing Children's Hospital. The patients were selected for our study according to our Children's Transplantation protocol, which was approved by the Health Department of Beijing City (Table 1). Patients with severe infection, organ failure, and sepsis were excluded. Twenty pediatric patients with a median age of 7.45 ± 3.61 years (range: 1–14 years) and a median weight of 28.32 ± 12.36 kg (range: 9.5–50 kg) were enrolled. This study was approved by the ethics and technological committees of the Beijing Children's Hospital. The patients and donors provided written informed consent for the protocol. None of the patients found an HLA-matched sibling or unrelated donors. Acute graft-versus-host disease (a-GVHD) was graded from I to IV. Chronic GVHD (c-GVHD) was defined as present or absent.

HLA typing and donors

All family members were tested for the degree of HLA match. HLA-A and HLA-B typing were performed by intermediate resolution techniques, while HLA-C typing were performed using high-resolution techniques. HLA typing was strictly analyzed for the donor and recipient. The donors were searched on the basis of best HLA match, killer immunoglobulin-like receptors genotype, and health

Table 1 Pediatric patients with acute leukemia indication for HSCT

The different CR status of pediatric patients with acute leukemia

CR1

- ALL with two courses of failure of induction treatment
- ALL with positive MRD after two courses of consolidation
- ALL with t (4;11) or *MLL* gene rearrangement
- ALL with t (9;22) or *BCR/ABL* fusion gene
- AML with poor-risk cytogenetics
- Mixed phenotype acute leukemia
- MDS-AML

CR2

- AL with positive MRD after two courses of consolidation

Beyond CR2

Abbreviations: HSCT, hematopoietic stem cell transplantation; AL, acute leukemia; AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CR, complete remission; MRD, minimal residual monitoring; MLL, mixed lineage leukemia; MDS, myelodysplastic syndromes.

status.^{8–10} We adopted granulocyte-colony stimulating factor (G-CSF)-mobilized bone marrow (BM) and peripheral blood stem cells (PBSCs) in haploidentical transplantation from family donors without in vitro T-cell depletion. The procedure was well tolerated by all donors, without any severe side effects. The father served as the donor for six of the patients, the mother for seven, the brother for one, and the sister for six.

Conditioning regimens

In the haplo-HSCT, 14 patients underwent a preconditioning regimen intravenously with fludarabine (25 mg/m²/day, on days -14, -13, -12, -11, and -10), busulfan (Bu) (0.8–1 mg/kg four times per day, on days -9, -8, -7, and -6), and cyclophosphamide (Cy) (50 mg/kg/day on days -5, -4, -3, and -2). Five patients underwent intravenous preconditioning regimen with Bu (0.8–1 mg/kg four times per day, on days -8, -7, and -6), cytosine arabinoside (Ara-C) (4 g/m²/day, on days -10 and -9), Cy (50 mg/kg/day, on days -5 and -4), and oral semustine (MeCCNU) (250 mg/m²/day, on day -3). One patient underwent preconditioning regimen with intravenous Bu (0.8–1 mg/kg four times per day, on days -9, -8, -7, and -6) and intravenous Cy (50 mg/kg/day, on days -5, -4, -3, and -2). All patients were not treated by TBI before BM transplantation. The conditioning regimens of leukemia patients are summarized in Table 2.

Collection of hematopoietic stem cells

The donors were primed with G-CSF injected subcutaneously at a dose of 5 µg/kg/day for 5 consecutive days. On the sixth day, BM cells and PBSCs were harvested. The target mononuclear cell count was above 3×10^8 cells/kg of the recipient's weight. PBSCs were collected using a blood cell separator (COBE Spectra LRS, Ceridian BCT, Inc., Lakewood, CO, USA) from a total blood volume of 150–200 mL/kg. In case of ABO major blood group compatibility, fresh and unmanipulated BM and PBSCs were immediately infused into the recipient after collection. However, in case of ABO major blood group incompatibility, the red cells were removed from the stem cells by density gradient sedimentation with Hesperan according to the manufacturer's instructions (B. Braun Medical Inc., Irvine, CA, USA). The surface markers of the graft cells were determined with monoclonal antibodies specific for CD34 using flow cytometry.

Graft-versus-host disease prophylaxis

Eleven patients were treated with cyclosporine A (CsA) plus methotrexate (MTX) together with anti-human thymocyte globulin (ATG; Lymphoglobuline; Genzyme Imtix-SangStat,

Table 2 Patient transplantation profile

Case	Sex	Age (years)	Weight (kg)	Diagnosis	Relationship	HLA match	Conditioning regimen
1	Female	13	50	AML-CR2	Father	4/6	Ara-C+Bu+Cy+MeCCNU
2	Female	7	26	AML-CR1	Mother	5/10	Flu+Bu+Cy
3	Male	6	22	AML-CR2	Sister	3/6	Flu+Bu+Cy
4	Female	10	26	AML-CR1	Father	5/6	Ara-C+Bu+Cy+MeCCNU
5	Male	6	23.5	AML-CR1	Father	5/6	Flu+Bu+Cy
6	Male	5	20	AML-CR2	Sister	3/6	Flu+Bu+Cy
7	Female	7	24	AML-CR1	Brother	4/6	Flu+Bu+Cy
8	Male	10	47	AML-CR1	Father	4/6	Ara-C+Bu+Cy+MeCCNU
9	Female	2	11.5	AML-CR1	Mother	3/6	Ara-C+Bu+Cy+MeCCNU
10	Male	5	26.4	ALL-CR2	Sister	5/10	Ara-C+Bu+Cy+MeCCNU
11	Female	1	9.5	ALL-CR1	Mother	5/6	Flu+Bu+Cy
12	Male	9	33	ALL-CR1	Mother	3/6	Flu+Bu+Cy
13	Male	10	29	ALL-CR2	Mother	3/6	Flu+Bu+Cy
14	Male	8	22	ALL-CR1	Sister	4/6	Flu+Bu+Cy
15	Male	7	23	ALL-CR1	Father	3/6	Flu+Bu+Cy
16	Female	12	43	ALL-CR1	Mother	3/6	Bu+Cy
17	Male	7	27	ALL-CR1	Sister	5/6	Flu+Bu+Cy
18	Male	1	13.5	ALL-CR1	Sister	5/6	Flu+Bu+Cy
19	Male	14	55	ALL-CR2	Father	6/6	Flu+Bu+Cy
20	Male	9	35	ALL-CR2	Mother	3/6	Flu+Bu+Cy

Abbreviations: AML, acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CR, complete remission; HLA, human leukocyte antigen; Flu, fludarabine; Bu, busulfan; Cy, cyclophosphamide; Ara-C, cytosine arabinoside; MeCCNU, semustine.

Lyon, France) and mycophenolate mofetil (MMF) to prevent the occurrence of GVHD. Four patients were treated with CsA plus MTX and ATG. Three patients were treated with CsA plus MTX and anti-lymphocyte immunoglobulin (ALG). One patient was treated with CsA plus MTX and one with CsA plus ALG. CsA at a daily dose of 2.5 mg/kg was injected intravenously twice a day from day 10 before transplantation and administered orally until the recovery of digestion function. The whole blood CsA concentration level was monitored twice a week using fluorescence polarization immunoassay, and the dosage was maintained at 150–250 ng/mL. In the absence of the evidence of GVHD after 100 days, the CsA dosage was gradually reduced and discontinued at ~180 days. If GVHD was observed, then CsA was continued. MTX was injected intravenously at a dose of 15 mg/m² on day 1 and at a dose of 10 mg/m² on days 3, 6, and 11 after transplantation. ATG (Genzyme Imtix-SangStat) was injected intravenously at a daily dose of 3.5 mg/kg/day, from days -6, -5, -4, -3, and -2 before transplantation. ALG (Lymphoglobuline; Genzyme Imtix-SangStat) was injected intravenously at a daily dose of 30 mg/kg/day, from pre-transplantation days -6, -5, -4, -3, and -2. MMF was orally administered at a daily dose of 0.25 g twice a day, from day 0 before transplantation, and was subsequently reduced from day 30 after transplantation. If GVHD failed to occur, the administration of MMF was terminated 90 days

post-transplantation. The onset and grades of a-GVHD and c-GVHD were assessed according to published consensus criteria.^{11,12} The characteristics of the pediatric leukemia patients after haplo-HSCT are shown in Table 3.

Evaluation of engraftment and chimeras

Hematopoietic stem cell engraftment was defined as an absolute peripheral myeloid count $\geq 0.5 \times 10^9/L$ for 3 consecutive days. Platelet recovery was defined as a platelet count $\geq 20 \times 10^9/L$ without transfusion support for 7 consecutive days.⁷ Hematopoietic chimeras were identified by HLA typing, blood type analysis, or sex chromosome determination. The chimeras were assessed by short tandem repeat polymerase chain reaction (STR-PCR). Immune reconstruction was evaluated by observation of the lymphocyte subsets at 3, 6, 12, and 18 months after transplantation.

Supportive care

All patients were nursed in separate rooms with laminar air flow until hematopoietic stem cell engraftment. Oral antibiotics including sulfamethoxazole and voriconazole were administered for infections with *Pneumocystis* and fungal infections. Intestinal prophylaxis drugs were orally administered along with systemic aseptic treatment. Acyclovir was administered as prophylaxis from day 0 for 10 days. Intravenous human immunoglobulin at a dosage of 400 mg/kg was infused once

Table 3 Graft characteristics and current status

Case	Myeloid recovery	Platelet recovery	Chimerism	a-GVHD	c-GVHD	Relapse	Status/cause of death	Follow-up (months)
1	+13	+19	Mixed	Yes	No	No	Died/lymphoproliferative	3
2	+14	+16	Donor	Yes	Yes	No	Alive in remission	20
3	+16	+45	Donor	Yes	No	No	Alive in remission	20
4	+16	+18	Donor	Yes	No	No	Alive in remission	21
5	+13	+16	Donor	No	No	No	Alive in remission	70
6	+12	+14	Donor	Yes	Yes	Yes	Died/relapse	11
7	+13	+16	Donor	No	No	No	Alive in remission	52
8	+15	+10	Donor	Yes	No	No	Alive in remission	38
9	+10	+10	Donor	Yes	No	No	Alive in remission	36
10	+11	+18	Donor	Yes	No	Yes	Alive/relapse	11
11	+11	+25	Donor	Yes	No	No	Alive in remission	24
12	+18	+27	Donor	No	No	No	Alive in remission	81
13	+10	+17	Donor	Yes	Yes	No	Alive in remission	72
14	+14	+14	Donor	No	No	Yes	Died/relapse	17
15	+11	+14	Donor	Yes	Yes	No	Alive in remission	84
16	+12	+17	Donor	No	No	No	Alive in remission	89
17	+14	+18	Donor	No	No	No	Alive in remission	61
18	+11	+18	Donor	No	No	No	Alive in remission	56
19	+18	+35	Donor	Yes	Yes	No	Alive in remission	23
20	+12	+15	Donor	Yes	No	No	Alive in remission	90

Abbreviations: a-GVHD, acute graft-versus-host disease; c-GVHD, chronic graft-versus-host disease.

per week from transplantation +2 day until hematopoietic recovery. Hepatic veno-occlusive disease was prevented with low-molecular-weight heparin calcium. G-CSF at a dosage of 5 µg/kg/day was administered from post-transplantation day 5 until myeloid engraftment. Patients were monitored twice weekly for cytomegalovirus (CMV) antigenemia with real-time quantitative polymerase chain reaction. Patients with CMV viremia received therapy with foscarnet sodium at a daily dose of 100–160 mg/kg until CMV was eradicated. Epstein–Barr virus (EBV) pathogenesis was monitored twice weekly with real-time quantitative polymerase chain reaction. Ganciclovir was administered if EBV viremia was persistently positive with any of the symptoms, such as fever or enlargement of the lymph nodes. Minimal residual disease was evaluated by fluorescence in situ hybridization and flow cytometry. All the blood products were irradiated before infusion.

Statistical analysis

The day of the stem cell transfusion was counted as day 0, and all the intervals were calculated based on this date. Descriptive statistics were provided for baseline patient characteristics. Retrospective measures of the cumulative incidence, such as a-GVHD, c-GVHD, and transplantation-related mortality, were used to evaluate the outcome. The probabilities of overall survival (OS) were estimated by Kaplan–Meier method. All statistical analyses were performed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA).

Results

GVHD and infection

The median follow-up time was 43.95±29.26 months (ranging from 3 to 90 months). Thirteen patients developed grade I–IV a-GVHD, including four cases of grade III–IV a-GVHD. The cumulative incidence of a-GVHD was 65%. The rate of occurrence of grade I–II a-GVHD was 45%, grade III–IV a-GVHD was 20%, and c-GVHD was 25%. The CMV infection rate on days +100 was 55% (11/20).

Hematologic reconstitution and engraftment

All pediatric patients achieved successful hematological recovery after transplantation. The median time to reach a myeloid count $\geq 0.50 \times 10^9/L$ was 13.20±2.41 days and a platelet count $\geq 20 \times 10^9/L$ was 19.10±8.37 days. The grafts contained a median of CD34+ cells of $(11.72 \pm 8.65) \times 10^6/kg$ body weight (range: 3.35–39.44×10⁶). The grafts contained a median of total nucleated cells of $(17.99 \pm 6.06) \times 10^8/kg$ body weight (range: 7.42–30.1×10⁸). The pediatric leukemia patients' hematologic reconstitution and engraftment are shown in Table 3.

Relapse and survival

All pediatric patients achieved complete remission before transplantation. Evidence for engraftment 30 days post-transplantation revealed that the hematopoietic stem cells from donors survived well in recipients. Two acute

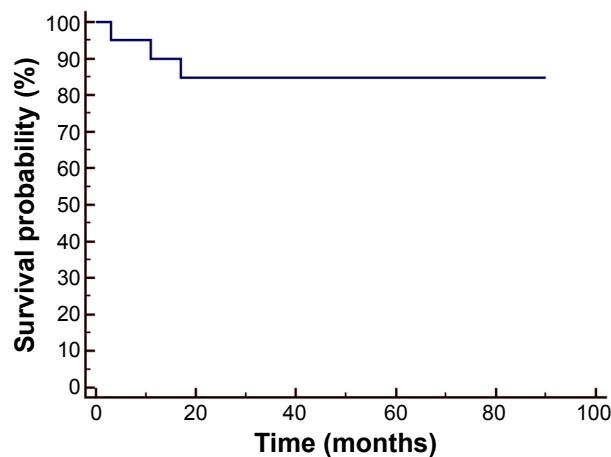


Figure 1 The Kaplan–Meier curves of overall survival (OS).

Note: This figure shows the survival probability (%) of haplo-HSCT patients for 100 months (n=20).

Abbreviation: haplo-HSCT, haploidentical hematopoietic stem cell transplantation.

lymphoblastic leukemia and one acute myeloid leukemia patients showed relapse. The relapsed patients were treated with donor lymphocyte infusion and immunosuppressant therapy simultaneously. The Kaplan–Meier curves depicting OS are shown in Figure 1. Three patients died during the follow-up time after transplantation. The OS rate was 85%.

Discussion

Long-term survival is difficult to achieve with conventional chemotherapy for patients with high-risk leukemia.¹³ HSCT is regarded as the most effective curative therapy for such kinds of patients. An HLA-identical sibling donor, which has optimal 10/10 match (HLA-A, -B, -C, -DRB1, and -DQB1),^{5,6} is the first choice for HSCT treatment. However, sibling HLA-identical donor has become rare due to birth control in the Chinese population. Therefore, haplo-HSCT has become an option for AL patients without an appropriate HLA-identical or an immediate donor. However, haploidentical transplantation was associated with the high rate of GVHD and non-engraftment.¹⁴ A number of strategies have led to improved haplo-HSCT outcomes and decreased complications. The high number of CD34+ cell implants led to faster hematopoietic recovery and reduced incidence of GVHD.^{15,16} Transplantation of G-CSF-mobilized BM and peripheral blood for hematopoietic recovery and the occurrence of a-GVHD in haplo-HSCT are associated with great benefits.¹⁷ The outcome of haplo-HSCT with G-CSF-mobilized PBSCs grafts without T-cell depletion for hematologic diseases is similar to HLA-identical matched donor HSCT.¹⁸ Owing to these advantages, we decided to use haploidentical stem cells as a graft source for patients with no suitable HLA-identical sibling or unrelated donor

in our center. To achieve great outcome, all donors were administrated with G-CSF and treated with CsA plus MTX, ATG, or ALG. Our results indicated that all the patients obtained successful myeloid and platelet recovery. The mean myeloid and platelet recovery time was 13.20 ± 2.41 and 19.10 ± 8.37 days, respectively. Thirteen patients developed grade I–IV a-GVHD, with a cumulative incidence of 65.0%. The incidence of grade I–II a-GVHD, grade III–IV a-GVHD, and c-GVHD was 45%, 20%, and 25%, respectively. The OS rate was 85%. Haplo-HSCT requires more intensive preparative regimen to overcome the HLA mismatch barrier. MA preparative regimen plays a critical role in facilitating engraftment of full haplotype-mismatched donor hematopoietic stem cell and in preventing relapse. TBI MA preparative regimen eliminates leukemic cells in residual sites such as the central nervous system. Therefore, TBI regimen reduces relapse and transplantation-related mortality. However, the TBI preparative regimen increases transplantation-related toxicity and mortality, which indirectly influences the long-term survival rate of patients undergoing transplantation.¹⁹ TBI preparative regimen also is associated with radiation-related adverse effects such as decreased fertility, asymptomatic alterations in pulmonary function, cataracts, diarrhea, and thyroid dysfunction.^{20–23} The use of TBI preparative regimen in young children is controversial, as children are expected to lead a long life of high quality. Therefore, MA preparative regimens without TBI are expected to minimize the toxicities of irradiation. All the patients who underwent MA preparative regimen without TBI before haplo-HSCT in our center were free from central nervous system complications. Fourteen patients were administered with fludarabine, Bu, and Cy; five patients were treated with TBI plus high-dose Ara-C, MeCCNU, Bu, and Cy as precondition regimen; only one patient was treated with Bu plus Cy; and five patients were treated with high-dose Ara-C, Semustine (MeCCNU), Bu, and Cy as precondition regimen. These protocols greatly reduced the incidence of GVHD with minimal complication. Only one patient had early toxicity and died from lymphoproliferative disease. The CMV infection rate on days +100 was 55% (11/20). Hemorrhagic cystitis was found in two cases and no veno-occlusive disease was observed, which frequently occurred after HSCT. GVHD was the common complication. The GVHD clinical manifestation was relatively low in our study, since MA regimen without TBI reduces the toxicities of irradiation. Further, steroid and other immune inhibitor usage for GVHD treatment also reduced its clinical morbidity. Two patients died of original disease relapse.

To prevent disease relapse, we utilized a few methods for detecting disease. First, we monitored minimal residual

disease by PCR method. Second, we treated the Philadelphia chromosome-positive leukemia patients with imatinib to prevent molecular recurrence before and after transplantation. Third, we applied prophylactic donor lymphocyte infusion, which was helpful in decreasing the relapse rates in high-risk AL patients following transplantation.

Conclusion

The present study demonstrated that most pediatric patients with AL can tolerate haplo-HSCT without TBI MA regimen with long-term disease-free survival. This protocol provided a great benefit for leukemia patients without available identical-matched donors.

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Author contributions

HY Zheng and MQ Qin designed and guided the study. MQ Qin, B Wang, GH Zhu, SD Li, K Wang, W Lin, and X Zhou enrolled patient and collected clinical data. YS Mu and J Yang collected and interpreted data. YS Mu wrote the paper. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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