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Unmanipulated Haploidentical Hematopoietic Stem Cell Transplantation in First Complete Remission Can Abrogate the Poor Outcomes of Children with Acute Myeloid Leukemia Resistant to the First Course of Induction Chemotherapy

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A B S T R A C T

Allogeneic hematopoietic stem cell transplantation (HSCT) is an important therapy option for children with acute myeloid leukemia (AML) resistant to the first course of induction chemotherapy (IC_{1st}). We aimed to identify the efficacy of unmanipulated haploidentical HSCT (haplo-HSCT) in children with AML in the first complete remission and whether children resistant (IC_{1st}-resistant; n = 38) or sensitive (IC_{1st}-sensitive; n = 59) to the IC_{1st} can achieve comparable outcomes. The cumulative incidence of grades III to IV acute graft-versus-host disease (GVHD) and severe chronic GVHD was .0% versus 20.1% ($P = .038$) and 21.7% versus 13.2% ($P = .238$), respectively, for the IC_{1st}-resistant and IC_{1st}-sensitive groups. The 3-year cumulative incidence of relapse and nonrelapse mortality was 22.2% versus 7.6% ($P = .061$) and 5.3% versus 10.8% ($P = .364$), respectively, for the IC_{1st}-resistant and IC_{1st}-sensitive groups. The 3-year probability of overall survival and disease-free survival was 76.3% versus 83.0% ($P = .657$) and 72.5% versus 81.6% ($P = .396$), respectively, for the IC_{1st}-resistant and IC_{1st}-sensitive groups. Multivariate analysis failed to show significant differences in survival rates between the groups. Thus, our results show that unmanipulated haplo-HSCT may overcome the poor prognostic significance of IC_{1st}-resistance in children with AML, and it is valid as a postremission treatment for children with IC_{1st}-resistant AML lacking an HLA-matched donor.

INTRODUCTION

Children with high-risk acute myeloid leukemia (AML) have poor outcomes, although novel and effective reinduction options are available, and allogeneic hematopoietic stem cell transplantation (allo-HSCT) is still a necessary and effective therapy for children with high-risk AML [1]. Resistance to the first course of induction chemotherapy (IC_{1st}-resistance) is 1 high-risk factor associated with a poor outcome. In the AML-BFM 98 trial, patients with more than 5% blasts at day 15 had a 5-year disease-free survival (DFS) rate of only 29% if no donor was available and using chemotherapy alone [2]. Wheatley et al. [3] reported that children with AML who were IC_{1st}-resistant had a high early relapse rate of 49% in the first year even if they did achieve complete remission (CR). Thus, it is generally accepted that patients with IC_{1st}-resistant AML harbor leukemia cells that are primarily resistant to cytotoxic agents, and allo-HSCT is a necessary postremission treatment [4].

Although a healthy HLA-identical sibling donor (ISD) is preferred, such a donor is unavailable for many children with AML who present for HSCT. An HLA- matched unrelated donor (URD) is also an option, but the donor pools of the Unrelated Donor Program are still relatively small; thus, it may take a long time to find a suitable donor, and some children with IC_{1st}-resistant AML might relapse while waiting for the HSCT. Wareham et al. [5] observed that the clinical outcome of poor-response pediatric AML was good on using early HSCT. Thus, a haploidentical related donor is a suitable alternative source of hematopoietic stem cells. The use of haplo-HSCT has several advantages, such as the relatively short time

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associated with finding a suitable donor and the more substantial immunologic reactions against leukemia cells. Much progress has been made in the use of haplo-HSCT, and an increasing number of children have achieved long-term survival after haplo-HSCT [6]. Liu et al. [7,8] reported that the outcomes of the unmanipulated haplo-HSCT for children with acute leukemia showed benefits that were similar to those of ISD HSCT. However, the sample size of children with IC_{1st}-resistant AML was small in these studies. In addition, few studies had identified the efficacy of haplo-HSCT as postremission therapy for IC_{1st}-resistant AML children in first CR (CR1).

In addition, although previous studies demonstrated that allo-HSCT was superior to chemotherapy in the treatment of pediatric AML [9,10], whether IC_{1st}-resistant AML CR1 children can achieve outcomes comparable with those of children sensitive to the first course of induction chemotherapy (IC_{1st}-sensitive) after allo-HSCT is still unclear. Bunin et al. [11] reported that the 5-year probability rate of DFS was only 12% for IC_{1st}-resistant children who underwent URD HSCT. This was significantly worse than those who underwent HSCT in the second CR (45%); however, patients who received an HSCT in the CR1 were excluded in this study. Burke et al. [12] observed that URD or ISD HSCT in the CR1 can abrogate the poor outcomes associated with high-risk pediatric AML; however, only 10 IC_{1st}-resistant patients were enrolled in the high-risk group. In addition, there was no studies concerning whether IC_{1st}-resistance affects the outcomes of AML children receiving unmanipulated haplo-HSCT.

Thus, we retrospectively analyzed the clinical outcomes of children with IC_{1st}-resistant AML who underwent unmanipulated haplo-HSCT in the CR1. We also want to investigate whether IC_{1st}-resistant AML children can achieve outcomes comparable with those of IC_{1st}-sensitive AML children after haplo-HSCT.

METHODS

Patients

Eligible patients were aged ≤ 18 years at the time of transplantation; received haplo-HSCT between January 1, 2009 and December 31, 2015; and had intermediate- and high-risk AML in the CR1. Patients received a haplo-HSCT and met at least 1 of the following criteria: (1) AML defined as with an intermediate or poor cytogenetic risk or with a *FLT3-ITD* lacking *NPM1* mutation, (2) AML-t(8;21) or AML-inv(16) not achieving major molecular remission after the second consolidation therapy or those exhibiting the loss of major molecular remission within 6 months of achieving major molecular remission [13,14], and (3) IC_{1st}-resistant AML. We enrolled 97 consecutive children who received a haplo-HSCT from a family donor at the Peking University Institute of Hematology (PUIH). Children with IC_{1st}-resistant AML were enrolled in the IC_{1st}-resistant group (n = 38) and other children in the IC_{1st}-sensitive group (n = 59) (Table 1). The endpoint of the last follow-up was May 31, 2016. Informed consent was obtained from all patients' guardians. The study protocol was approved by the ethics committee of the Peking University People's Hospital and Anhui Provincial Hospital. Thirty-one children were previously reported by Liu et al. [8].

Chemotherapy before Transplantation

Induction chemotherapy regimens included IA(E) (idarubicin, cytarabine, and/or etoposide), DA(E) (daunorubicin, cytarabine, and/or etoposide), MA(E) (mitoxantrone, cytarabine, and/or etoposide), HAA (homoharringtonine, cytarabine, and aclacinomycin), HA, HAD, AA, and CAG (cytarabine, aclacinomycin, and granulocyte colony-stimulating factor [G-CSF]). Patients received induction chemotherapy according to doctors' experience and patients' intension. The initial induction chemotherapy regimens were comparable between IC_{1st}-resistant and IC_{1st}-sensitive groups (Supplementary Table 1). The most major consolidation chemotherapy regimen was high-dose cytarabine, and other consolidation chemotherapy regimens, including IA(E), DA(E), MA(E), or HA(A), were given in turn. Patients who did not achieve CR after induction received reinduction chemotherapy, and the reinduction chemotherapy regimens before CR included IA(E) (n = 10), HAA/HA/HAD (n = 10), DA(E) (n = 6), FLAG (fludarabine, cytarabine, and G-CSF, n = 5), CAG (n = 3), high-dose cytarabine (n = 2), and MA(E) (n = 2). Patients received reinduction chemotherapy also according to doctors' experience and patients' intension. Prophylaxis of central nervous system leukemia consisted of intrathecal chemotherapy with methotrexate (MTX), cytarabine, and dexamethasone for at least 1 dose during induction chemotherapy and consolidation chemotherapy. The detailed chemotherapy schedule is shown in Supplementary Data.

Transplant Regimen

The major preconditioning treatment consisted of cytarabine (4 g/m^2/day, from days –10 to –9), busulfan (3.2 mg/kg/day administered intravenously on days –8 to –6), cyclophosphamide (1.8 g/m^2/day, from days –5 to –4), and semustine (250 mg/m^2, on day –3), along with rabbit antithymocyte globulin (Thymoglobulin; Imtix Sangstat, Lyon, France; 2.5 mg/kg/day, from days –5 to –2). All patients received cyclosporine A, mycophenolate mofetil, and short-term MTX for graft-versus-host disease (GVHD) prophylaxis. Cyclosporine A (2.5 mg/kg, every 12 hours i.v.) was used from day –9, of which the trough concentration was adjusted to 150 to 250 ng/mL. It was switched to oral administration when the patient's bowel function returned to normal. From day –9, .25 to .5 g of mycophenolate mofetil was administered orally every 12 hours and was then tapered to half until day +60 and discontinued thereafter. After graft infusion, a dose of 15 mg/m^2 MTX was administered intravenously on day +1 as well as a dose of 10 mg/m^2 on days +3, +6, and +11. All haplo-HSCT recipients received G-CSF–mobilized, fresh, and unmanipulated bone marrow cells plus peripheral blood stem cells. G-CSF (5 μg/kg per day, injected subcutaneously) was provided to all recipients from day 6 after transplantation until their WBC count exceeded 2×10^9 cells/L for 3 consecutive days [15,16]. Detection of the immunophenotype after transplantation was performed as previously reported [17].

Treatment of GVHD was in accordance with the common international criteria [18,19]. Acute GVHD (aGVHD) was treated with 1 to 2 mg/kg/day of methylprednisolone and resumption of full-dose cyclosporine A administration. Second- or third-line immunosuppressive therapy such as CD25 monoclonal antibody (Basiliximab; Novartis Pharma Stein AG, Basel, Switzerland), mycophenolate mofetil, tacrolimus, or MTX was given for steroid-refractory aGVHD. Moderate to severe chronic GVHD (cGVHD) was treated with 1 mg/kg/day prednisone and cyclosporine A was adjusted to maintain a blood concentration greater than 150 ng/mL. Second- or third-line immunosuppressive therapy such as mycophenolate mofetil, MTX, penicillamine, azathioprine, or tacrolimus was given for steroid-refractory cGVHD.

Patients were clinically managed according to PUIH standard guidelines including infection prophylaxis for *Pneumocystis carinii*, herpes viruses, and fungi. Patients received no cytomegalovirus (CMV)-specific prophylaxis, and real-time quantitative PCR was used to detect CMV-DNAemia in plasma. Preemptive therapy was instituted in patients with documented CMV-DNAemia [20]. After completion of the study treatment, bone marrow samples were analyzed at 1, 2, 3, 4.5, 6, 9, and 12 months after transplantation and at 6-month intervals thereafter for the monitoring of minimal residual disease (MRD). MRD targets were also regularly examined in the 2 weeks before the transplantation. MRD assessment consists of the PCR-based evaluation of expression levels of leukemia-related genes and determination of leukemia-associated immunophenotypic patterns with multiparameter flow cytometry (FCM).

Four children in the IC_{1st}-resistant group received prophylactic donor lymphocyte infusion (DLI) after transplantation; the protocol of prophylactic DLI was reported [21]. Preemptive DLI was given before hematologic relapse 2 months post-HSCT after a trial of immunosuppressant withdrawal. The detailed criteria for preemptive DLI administration included the following: (1) patients were scored as MRD-positive if they had 2 consecutive positive results using FCM or Wilms' tumor gene 1 (*WT1*) or were both FCM-positive and *WT1*-positive in a single sample within 1 year after transplantation [22], (2) had no uncontrolled GVHD or life-threatening infection, and (3) had donor availability and willingness. Patients with GVHD first received GVHD therapy. After GVHD was controlled, MRD testing was repeated, and those patients that remained MRD-positive received DLI [23]. The MRD monitoring and DLI regimen was as previously described [24].

When a hematologic relapse was diagnosed after HSCT, post-transplant immune suppression was immediately discontinued. If patients did not develop GVHD within 2 weeks and if patients agreed to receive targeted therapeutic DLI and their donors also agreed to undergo peripheral blood stem cell collection again, the patients would receive chemotherapy followed by DLI; otherwise, the patients would receive chemotherapy alone [25].

HLA Typing and Stem Cell Harvesting

At PUIH all donor–recipient pairs were typed at the HLA-A, -B, and -DR loci. HLA-A and HLA-B typing was performed by intermediate resolution DNA-typing, whereas HLA-DRB1 typing was performed by high-resolution DNA techniques. Each subject received a graft from a family member sharing 1 HLA haplotype with the recipient but differed to a variable degree for the