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Research paper

Haploidentical allogeneic hematopoietic stem cell transplantation compared to matched unrelated transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia

Bin Gu[a,b,c], Xiaojin Wu[a,b,c], Guanghua Chen[a,b,c], Xiao Ma[a,b,c], Zhengming Jin[a,b,c], Xiaowen Tang[a,b,c], Yue Han[a,b,c], Chengcheng Fu[a,b,c], Huiying Qiu[a,b,c], Aining Sun[a,b,c], Depei Wu[a,b,c,*]

[a] Jiangsu Institute of Hematology, The First Affiliated Hospital of Soochow University, 188 Shizi Street, Suzhou 215006, China
[b] Collaborative Innovation Center of Hematology, Soochow University, 188 Shizi Street, Suzhou 215006, China
[c] Suzhou Institute of Blood and Marrow Transplantation, 188 Shizi Street, Suzhou 215006, China

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ABSTRACT

To investigate the effect of haploidentical allogeneic hematopoietic stem cell transplantation (Haplo-HCT) in Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL), the outcome of 58 patients with Ph+ ALL who received Haplo-HCT (n = 42) or matched unrelated donor transplantation (MUD-HCT) (n = 16) during the same period were analyzed retrospectively. All patients received a tyrosine kinase inhibitor (TKI)-based regimen before transplantation, and TKI was resumed primarily after transplantation. At the 3-year follow-up, the overall survival (OS), leukemia-free survival (LFS), the cumulative incidence of relapse (CIR), and non-relapse mortality (NRM) rates in Haplo-HCT group were 69.1, 64.3, 19.0, and 14.3%, respectively, without significant differences from that of MUD-HCT. Haplo-HCT was not related to higher incidences of severe acute graft-versus-host disease (GvHD) (17.6 ± 5.2% vs. 20.0 ± 10.0%, P = 0.603) or chronic GvHD (19.5 ± 7.1% vs. 13.3 ± 8.6%, P = 0.637) as compared to MUD-HCT. Multivariate analysis showed that chronic GvHD was associated with lower relapse rate in Haplo-HCT group. Haplo-HCT is a promising choice for improving the long-term survival in Ph+ ALL patients.

1. Introduction

The application of tyrosine kinase inhibitors (TKIs) for Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) as conventional chemotherapy improved the complete remission rate and overall survival [1,2]. However, relapse through BCR/ABL mutations or other mechanisms continues to be the main factor for treatment failure [2,3]. Allogeneic hematopoietic stem cell transplantation (allo-HCT) remains the cure of Ph+ ALL [4,5]. The efficacy of matched related donor and matched unrelated donor allo-HCT (MUD-HCT) have been confirmed [6,7]. The haploidentical allogeneic hematopoietic stem cell transplantation (Haplo-HCT) has been attempted for more than two decades. Previous studies demonstrated that non-T-cell depleted Haplo-HSCT could achieve a promising long-term survival in patients without increased transplantation-related mortality [8–10]. Therefore, in the absence of HLA-matched donor, Haplo-HCT could be the first choice of therapy in patients with Ph+ ALL. Objectively, Haplo-HCT presents several advantages over MUD-HCT, such as opportunities for patients who need an urgent transplantation, convenient availability of bone marrow and/or peripheral blood stem cells, donor lymphocyte infusion (DLI) if necessary, cost-effectiveness, and the probability for each patient to finding at least one haploidentical donor. However, the adverse data about the inferior outcome of Haplo-HCT has also been exposed including a high rate of severe graft-versus-host disease (GvHD) [11]. Due to the heterogeneity of patients and different transplantation systems, the benefit of Haplo-HCT in Ph+ ALL is yet controversial.

Hitherto, a large-scale study on the outcome of haplo-HCT for the treatment of Ph+ ALL was limited. In the present study, we summarized the outcomes of patients who accepted Haplo-HCT for the treatment of Ph+ ALL and compared to that of MUD-HCT during the same period in the first affiliated hospital of Soochow University in

* Corresponding author at: Jiangsu Institute of Hematology, The First Affiliated Hospital of Soochow University, Collaborative Innovation Center of Hematology, Soochow University, Suzhou Institute of Blood and Marrow Transplantation, 188 Shizi Street, Suzhou 215006, China.
E-mail address: wudepei@medmail.com.cn (D. Wu).

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Table 1
Clinical characteristics of the patients.

Characteristic	Haplo-HCT	MUD-HCT	P
No. of patients	42	16	
Median age,years(range)	26(9–50)	24(9–47)	0.416
Patient gender			0.308
male	30	14	
female	12	2	
WBC count	46.4(1.0–523.5)	67.0(2.2–220.1)	0.097
Disease status			0.092
CR1	34	16	
CR2	8	0	
BCR/ABL before HCT			0.951
positive	18	7	
negtive	24	9	
Conditioning			0.123
mBU/CY	40	13	
TBI/CY	2	3	
Donor gender			1.000
male	22	9	
female	20	7	
pTKIs			0.595
yes	19	6	
No	23	10	
BCR/ABL mutation			0.71
positive	8	2	
negative	34	14	

CR: complete remission; HCT: hematopoietic stem cell transplantation; pTKIs: prophylaxis and preemptive tyrosine kinase inhibitors.

China.

2. Patients and methods

2.1. Patients

We retrospectively analyzed 58 cases of Ph+ ALL during the period from Jan 2012 to Aug 2015 at our center. The clinical characteristics of the patients are summarized in Table 1. Ph+ ALL was diagnosed according to the criteria set by the World Health Organization. All patients provided written informed consent before the treatment that was approved by the Hospital Ethics Committee. 42 cases underwent Haplo-HCT and 16 cases accepted MUD-HCT. HLA-A, −B, −C, −DQB1, and −DRB1 typing of the recipients and donors was examined by high-resolution DNA typing techniques through polymerase chain reaction (PCR) before transplantation.

2.2. TKIs and BCR/ABL monitoring

All patients received Imatinib and routine chemotherapy as first-line induction and consolidation treatment. 50/58 patients were in the first complete remission (CR1) without BCR/ABL mutation before transplantation. Eight patients achieved the second complete remission (CR2) by the application of Dasatinib or Ponatinib and underwent Haplo-HCT as essential. BCR/ABL fusion transcripts were monitored by real-time quantitative PCR before and after allo-HCT. The mutations in the BCR/ABL kinase domain were further analyzed by direct sequencing if the BCR/ABL transcripts were increasing. The T315I mutation was detected in 6 patients from the Haplo-HCT group. TKIs were resumed in case the absolute neutrophil counts in the peripheral blood of the patients were $> 1.0 \times 10^9$/L lacking granulocyte colony-stimulating factor (G-CSF), and the platelet count was $> 50.0 \times 10^9$/L without infusion, irrespective of the levels of BCR-ABL transcript, or the BCR/ABL fusion gene was detected again. TKIs administered when BCR/ABL transcripts were negative and defined as prophylactic TKIs, and those used when the transcripts were positive without hematologic relapse were defined as preemptive TKIs. TKIs were administered as salvage therapy to patients with leukemia recurrence of hematology. Nineteen patients received prophylactic and preemptive TKIs after transplantation. Three patients with existing T315I mutation pre-transplant received Ponatinib prophylaxis. Two patients accepted salvage Ponatinib combined with DLI after transplantation. The TKIs were chosen according to the type of BCR/ABL mutation [12], and the doses of TKIs depend on the patients' tolerance and/or the attending physicians' experience.

2.3. Conditioning regimen and GvHD prophylaxis

We defined a modified BU/CY conditioning regime (mBU/CY) as follows: cytarabine 2 g/m2/12 h (on days −10 and − 9), busulfan (Bu) 0.8 mg/kg/6 h (on days −8 to −6), cyclophosphamide (Cy) 1.8 g/m2 (on days −5 and −4), and semustine 250 mg/m2 (on day −3). The TBI/CY regime was defined using total body irradiation (TBI; 12 Gy, lung shielding at 8 Gy) substituted for Bu and cytarabine started on day −7. GvHD prophylaxis consisted of continuous cyclosporine infusion at 3 mg/kg/day starting on day −10, mycophenolate mofetil 1.0 g/day from days −10 to +30, short-term methotrexate administered on days +1, +3, +6, and +11 at a dosage of 15, 10, 10, and 10 mg/m2, respectively, and rabbit antithymocyte globulin (ATG; Genzyme, Cambridge, MA) 2.5 mg/kg/d (on days −5 to −2). We tapered the immunosuppressive agents if there was no indication of aGvHD and/or BCR/ABL was detected at the earliest. GvHD was diagnosed and graded according to the consensus criteria [13,14]. Acute GvHD (aGvHD) equal or more than grade II was treated with methylprednisolone 2 mg/kg/day as the first-line treatment, and patients who developed steroid-refractory aGvHD were treated with tacrolimus (Astellas, Japan), anti-CD25 monoclonal antibodies (Novartis Pharma, Ltd., Switzerland), anti-TNFα monoclonal antibodies (Cilag AG, Switzerland), and/or mesenchymal stem cells.

2.4. Stem cells

Bone marrow (BM) and peripheral blood (PB) stem cells were collected from the donors in the Haplo-HCT group and PB stem cells from the MUD-HCT group. G-CSF (Filgrastim, Kirin Pharma Co., Ltd., Japan) 10 μg/kg/day was administered to the donors for 5 days in order to mobilize the stem cells. In the Haplo-HCT, BM stem cells were harvested from day 4, and the PB stem cells were collected on day 5 and continued if the number of cells was not sufficient. In the MUD-HCT, only PB stem cells were harvested. The objective was to collect at least $(6–8) \times 10^8$ and 2×10^6 mononuclear cells (MNCs) and $CD34^+$ cells, respectively, per kg of the patient's weight.

2.5. Treatment efficacy definitions

Neutrophil recovery was defined by the absolute neutrophil count $> 0.5 \times 10^9$/L for 3 consecutive days and platelet recovery as $> 20 \times 10^9$/L without transfusion. The overall survival (OS) was defined as the probability of survival after transplantation. Patients were censored at the final follow-up. Leukemia free survival (LFS) was calculated from the time of transplantation until relapse or death. Non-relapse mortality (NRM) was defined as death during remission. Relapse was defined as > 5% recurrence of lymphoblasts in the bone marrow or any lymphoblast in PB or extramedullary infiltration.

2.6. Statistical analysis

Patients' characteristics were compared using chi-square or Fisher's exact tests for categorical variables and the Mann–Whitney test for continuous variables. The probabilities of OS and LFS were estimated by the Kaplan–Meier method and compared using the log-rank test. GvHD, relapse, and NRM rates were assessed using the cumulative

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