Annals of Hematology (2019) 98:2833–2836
https://doi.org/10.1007/s00277-019-03840-6

LETTER TO THE EDITOR

Secondary haploidentical hematopoietic stem cell transplantation in patients with relapse or graft failure after initial hematopoietic stem cell transplantation

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Received: 4 May 2019 / Accepted: 31 October 2019 / Published online: 18 November 2019

Dear Editor,

The prognosis of patients with malignant hematological diseases relapse or graft failure after hematopoietic stem cell transplantation (HSCT) is poor, and optimal salvage therapy is limited. Secondary allogeneic hematopoietic stem cell transplantation (HSCT2) is an effective salvage option for patients in whom primary hematopoietic stem cell transplantation (HSCT1) has failed. Most published studies have reported favorable effects of HSCT2 from an HLA related or unrelated donor [1–4]. Given that only approximately 30% of patients have a matched sibling donor or unrelated donor, transplantation from a related haploidentical donor (HID) is an effective option with acceptable outcomes [5]. Here, we reported our experience using HID-HSCT for the treatment of 24 patients with disease relapse or graft failure after HSCT1.

Twenty-four patients, including 19 males and 5 females, were diagnosed with acute myeloid leukemia (n = 10), non-Hodgkin's lymphoma (n = 6), marrow failure (n = 3), acute lymphoblastic leukemia (n = 2), myelodysplastic syndromes (n = 2), and Hodgkin's lymphoma (n = 1) at the Affiliated Hospital of Soochow University between September 2010 and March 2018. The median age of the patients at the first and second transplants were 29 (4–56 years) and 30 years (4–56 years), respectively. For HSCT1, 17 (70.8%) patients received autologous stem cell transplants (ASCT) and 7 (29.2%) patients received allogeneic stem cell transplants (allo-SCT). There were 20 patients (83.3%) who relapsed and 4 patients (16.7%) with graft failure after HSCT1 in the total cohort. The median time between the two transplants was 288 days (range 44–2199 days). For HSCT2, only 1 patient received the same donor. Disease status before HSCT2 was described as active in 14 patients (58.3%), complete remission (CR) in 6 patients (25%), and graft failure in 4 patients (16.7%). The 24 patients' and donors' characteristics for HSCT2 were summarized in Table 1.

During HSCT2, there were 22 patients who received the GIAC protocol (the Beijing protocol) with TBI/Cy or BuCy [6]. TBI/Cy was administered to 9 patients and consisted of TBI (12 Gy on days − 8 to − 6), IV CTX 1.8 g/m^2/d from day − 4 to day − 3, and oral semustine 250 mg/m^2/d on day − 9. Bu/Cy was administered to 13 patients and consisted of IV Ara-c 2 g/m^2/d on days − 9 to − 8, IV Bu 3.2 mg/kg/d from day − 7 to day − 5, IV CTX 1.8 g/m^2/d from day − 4 to − 3, and oral semustine 250 mg/m^2/d on day − 10. One patient received Flu/Bu, which consisted of IV Bu 3.2 mg/kg/d on days − 7 to − 5 and IV Flu 30 mg/m^2/day from day − 6 to day − 2. Additionally, 1 patient received a Flu/Cy conditioning regimen (Flu 35 mg/d from day − 5 to day − 1 and IV CTX 1.2 g/d on day − 1) for graft failure with the same donor. For GVHD prophylaxis, anti-thymocyte globulin (ATG) (10 mg/kg on days − 5 to 2), cyclosporine A (CSA) (3 mg/kg/d daily), methotrexate (MTX) (15 mg/m^2 on day 1 after transplantation and 10 mg/m^2 on days 3, 6, and 11) and mycophenolate mofetil (MMF) (0.5 g/12 h daily) were used in patients during HSCT2. Twenty patients received stem cells combined with peripheral blood (PB) and bone marrow (BM) with a median 11.61 × 10^8/kg (5.00–21.26) mononuclear cells and 4.17 × 10^6/kg (1.90–6.89) CD34+ cells, while 2 patients received only PB stem cells with median 8.35 × 10^8/kg mononuclear cells and 3.15 × 10^6/kg CD34+ cells, and the

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Table 1 The clinical characteristics of 24 patients with HID-HSCT2

Patient	Number
Median age at HSCT1 (range)	29 (4–56) years
Sex	
Male	19
female	5
Underlying disease	
AML	10
Lymphoma	7
Bonemarrow failure	3
ALL	2
MDS	2
Donor for HSCT1	
Autologus	17
Cord blood	2
HLA-matched	3
Haploidentical	1
HLA-9/10matched unrelated donor (URD)	1
Median age at HSCT2 (range)	35 (16–55)years
ABO-match	13
Sex-match (donor/recipient)	
Female–female	3
Female–male	7
Male–male	8
Male–female	6
Median time from HSCT1 to HSCT2 (range)	288 (44–2199) days
Disease status at HSCT2	
CR/active/graft failure	6
Active	14
Graft failure	4
Conditioning for HSCT2	
Bu/CY	13
TBI/CY	9
RIC	2
Stem cells source for HSCT2	
B+P+U	15
B+P	5
B/P+U	2
B/P	2
Infused $CD34^+$cells/kg	4.17(1.9-6.89)* 10^6
Infused MNC/kg	11.61(5.0-21.26)*10^8

* *HSCT*, hematopoiectic stem cell transplantation; *AML*, acute myeloid leukemia; *ALL*, acute lymphoid leukemia; *MDS*, myelodysplastic syndrome; *RIC*, reduce-intensity conditioning; *CR*, complete remission; *B*, bone marrow; *P*, peripheral blood; *U*, umbilical cord blood

remaining 2 patients received BM stem cells with median 7.52 × 10^8/kg mononuclear cells and 3.81 × 10^6/kg CD34+ cells.

One patient passed away at day 2 from status epilepticus. The other 23 patients were demonstrated neutrophil engraftment, defined as neutrophil granulocytes > 0.5 × 10^9/L, with a median of 12 days (11–16 days), and platelet engraftment, defined as platelets > 20 × 10^9/L, was achieved in 16 patients (16/23, 67%) with a median of 17 days (11–37 days). Ten patients (41.6%) developed acute GVHD and the median day of onset of aGVHD was 39 days (23–81 days). The distributions of different grade aGVHD were as following: grade 1–2 aGVHD (n = 7), grade 3 aGVHD (n = 2), and grade 4 aGVHD (n = 1). Six patients suffered from only skin GVHD; 1 patient suffered from both intestinal and skin GVHD; and 2 patients suffered from skin, liver and intestinal GVHD. Chronic GVHD was observed in 6 patients by the end of the study period and was characterized as limited in 5 patients and extensive in 1 patient. Hemorhagic cystitis (HC) occurred in 7 patients (29.2%), and veno-occlusive disease (VOD) occurred in 2 (8.3%) patients. Eighteen (75%) patients were documented with infectious complications. Briefly, 5 patients acquired bacterial infections at a median of 38 days (Staphylococcus species, n = 2; Pseudomonas species, n = 1; and *Escherichia coli*, n = 2). Fungal infections affected 3 patients (12.5%). Ten patients had CMV reactivation, while 1 patient was diagnosed with CMV interstitial pneumonia and another patient was diagnosed with CMV encephalitis. Two cases were diagnosed with EBV reactivation, and 1 case with HSV reactivation.

With a median follow-up time of 416 days (range 3–2607 days), 16 patients (66.7%) were deceased by the time of follow-up. Causes of death were as follows: relapse (n = 6), infectious complications (n = 6; 4 with severe pulmonary infection, 1 with infective shock, and 1 from CMV reactivation viral encephalitis), VOD (n = 1) and cerebral hemorrhage (n = 3). The cumulative incidence of non-relapse mortality (NRM) was 30% by 1 year after HSCT2. The probability of 2-year progression-free survival (PFS) was 37.5%, and 2-year OS was 46% for HSCT2. It should be noted that there were 17 patients who received ASCT and 7 patients who received allo-HSCT in the first HSCT, while no significant differences in 2-year PFS (29% vs. 35%, P = 0.467) and OS (43% vs. 48%, P = 0.449) were observed between allo-SCT and ASCT groups.

Earlier reports have analyzed the outcomes of HSCT2 with a matched related donor (MRD), which has a reported 2-year OS of 39–60% and 1-year relapse-free survival (RFS) of 38% in MRD transplants [2–4]. Additionally, Christopeit et al. [4] reported that the estimated 2-year OS was 20 ± 6% for matched Unrelated Donor (URD) in HSCT2. Accordingly, patients receiving HSCT2 from MRDs and URDs for acute leukemia relapse after HSCT1 could be rescued. However, clinical outcomes for secondary HID-HSCT are unclear. Tischer et al. [5] reported that 20 patients with secondary HID-HSCT following post-transplant CY (PTCY) GVHD prophylaxis experienced 45% 1-year OS, 33% RFS and 36% NRM. It should be noted that HID-HSCT is the main type of allogenic HSCT in China, and nearly 99% of HID-HSCT cases have followed the Beijing protocol [5]. To our knowledge, there were no cohort reports on secondary HID-

HSCT with the Beijing protocol. In the present study, the overall outcomes in our cohort were encouraging with 2-year OS and PFS of 46% and 33%, respectively (Fig. 1). Moreover, the observed 1-year NRM was 29%, which was better than the secondary HID-HSCT with PTCY protocol. We believe that this study could help in exploring the role of secondary HID-HSCT in clinical practice.

The cumulative incidence of engraftment was 96%, which was similar to the 85–100% of patients who have received haploidentical HSCT with PTCY [7, 8]. Notably, the median time to neutrophil and platelet engraftment were 12 days and 17 days, respectively, compared with 15–29 days and 24–31 days after HSCT2 using HLA-identical donors [5, 9]. The rapid engraftment was consistent with a previous report with an ATG-based protocol. Infection was the most frequent life-threatening complication and the major factor for early mortality. In this study, bacterial infections were observed in 20.8% of patients. Interestingly, compared with 25–30% of patients who received haploidentical HSCT with PTCY [5, 8], fungal infections were only observed in three (12.5%) patients from our cohort, which was possibly due to the rapid neutrophil engraftment. However, the incidence of CMV reactivation or infection was higher in our study than in other reports with the PTCY protocol in HSCT (42% vs. 23-38%) [5, 8, 9]. We speculated that the use of ATG was associated with delayed immune reconstitution and increased infectious complications, particularly viral reactivations of CMV.

In addition, the effectiveness of ATG-based regimens in modulating severe aGVHD and cGVHD was comparable to other conditioning regimens. Our results showed that 12.5% of the patients developed grade III–IV aGVHD, mostly involving the skin and intestines, which was comparable to the 12–29% incidence after PTCY or RIC conditioning in HSCT2 [1, 7, 8]. Hemorhagic cystitis occurred in 29% of all patients. Veno-occlusive disease (VOD) only occurred in 2 patients (8%), whereas the rate reported in patients undergoing HSCT2 was 21% from the same matched related donor or after Myeloablative (MA) conditioning [2, 10]. We suspected that the significant difference observed was due to different characteristics between eastern and western populations. Another reason might be the high rate of patients with ASCT in HSCT1 in this study.

In conclusion, HID-HSCT with the Beijing protocol was a feasible and valuable option for salvage HSCT2 in patients with malignant hematological diseases.

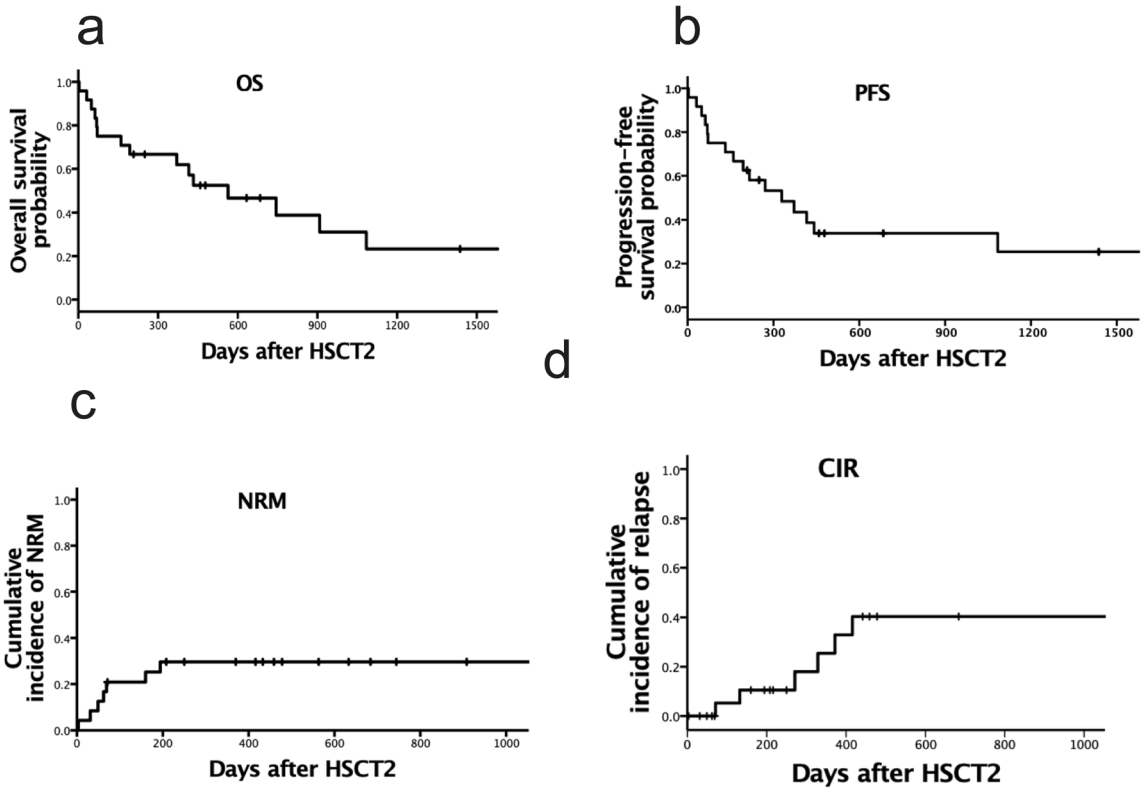

Fig 1 **a** Overall survival (OS), **b** progression-free survival (PFS), **c** cumulative incidence of non-relapse related mortality (NRM), **d** cumulative incidence of relapse (CIR) in secondary HID transplantation

Author's contributions Dr. Depei Wu and Yang Xu contributed to the conception of the study and manuscript revision. Chang Hou and Nan Chen contributed to collecting and performing data analysis and preparing the manuscript. Jia Chen and Yi Fan helped collect and perform data analysis and prepare the manuscript. Shuhui Jiang and Sifan Chen contributed to data analysis and manuscript revision.

Funding information This work has been supported by grants from The National Key Natural Science Foundation of China (81730003, 81870120), The Natural Science Foundation of Jiangsu Province (BK20171205), The Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD), The Innovation Capability Development Project of Jiangsu Province (no. BM2015004), and The National Key Research and Development Program (2016YFC0902800, 2017YFA0104500).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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