



Allogeneic Hematopoietic Stem Cell Transplantation could be as an Effective Salvage Modality for Relapsed Acute Myeloid Leukemia with t(8;21)

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Abstract

Objective: Acute Myeloid Leukemia (AML) with translocation of chromosome 8 and 21 [t(8;21) (q22;q22)] is known to have a favorable prognosis. Once relapse occurred, allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT) is recommended for Complete Remission (CR) patients after salvage chemotherapies. Allo-HSCT might be as a salvage strategy for patients without achieving morphological CR.

Methods: We performed a retrospective study on 21 relapsed AML patient (13 with molecular relapse and 8 with morphological relapse) with t(8;21) treated with allo-HSCT at our center from August 2016 to January 2021.

Results: The median time of follow-up was 15 (5 to 47) months. Nineteen from twenty-one patients achieved full donor chimerism at 30 days after transplantation. All eight patient with morphological relapse got molecular CR, while eleven from thirteen patients with molecular relapse achieved molecular CR. The 2-year Cumulative Incidences of Relapse (CIR) and Non-Relapse Mortality (NRM) for all patients were 19.0% and 20.4%, respectively. The 2-year CIRs were 7.7% and 37.5% in molecular and morphological relapse groups (p=0.1001), respectively. The 2-year NRM were 11.1% vs. 40.0% (p=0.1585) without statistical significance. The 2-year probability of Overall Survival (OS) were similar between the molecular and the morphological relapse group (74.1% vs. 60.0%, p=0.3789), while the 2-year probability of Relapse-Free Survival (RFS) was 80.8% and 37.5% (p=0.04), respectively.

Conclusion: Allo-HSCT has yielded encouraging results in this study focusing on relapsed AML with t(8;21) translocation and could be as an effective salvage modality for morphological relapsed patients.

Keywords: t(8;21) (q22;q22); Allogeneic hematopoietic stem cell transplantation; Acute myeloid leukemia; Relapse

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Received Date: 08 May 2021

Accepted Date: 04 Jun 2021

Published Date: 08 Jun 2021

Citation:

Li T, Cai Y, Yang J, Wan L, Huang C, Qiu H, et al. Allogeneic Hematopoietic Stem Cell Transplantation could be as an Effective Salvage Modality for Relapsed Acute Myeloid Leukemia with t(8;21). *Clin Oncol*. 2021; 6: 1820.

ISSN: 2474-1663

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Introduction

Acute Myeloid Leukemia (AML) is one of the most common adult hematopoietic malignancies and the AML with translocation of chromosome 8 and 21 [t(8;21) (q22;q22)] accounts for about 10%, which is known to have a favorable prognosis [1]. The translocation results in fusion gene of RUNX1 (AML1) and RUNX1T1 (ETO) [2]. Standard induction chemotherapy and high-dose cytarabine consolidation therapy can prolong the remission duration in about 50% patients with RUNX1-RUNX1T1 fusion gene [3,4]. However, it was reported that high risk factors, such as older age, complex karyotype and the failure to achieve Complete Remission (CR) after induction, had increased the relapse rate and reduced the overall survival after the chemotherapy [5].

Allogeneic Hematopoietic Stem Cell Transplantation (allo-HSCT) is a post-remission modality with lowering the relapse incidence and improving the overall survival due to the high-dose chemotherapy and/or radiotherapy conditioning and Graft-Versus-Leukemia (GVL) effects [6], but it is not recommended for the first CR (CR1) patients with t(8;21) [7]. For the relapsed patients, allo-HSCT is recommended after the subsequent CR with salvage chemotherapy [8]. However,

many relapsed patients could not achieve CR, especially molecular remission (CR) even after intensive salvage chemotherapies. Allo-HSCT is an effective salvage strategy for AML patients with active disease and prolonged the long-term survival [9]. Therefore, we performed a retrospective study to evaluate the effects of all-HSCT as a salvage modality for relapsed AML patients with t(8;21) in our center.

Patients and Methods

Patients

Twenty-one AML patients with t(8;21) underwent allo-HSCT from August 2016 to January 2021 in our center and were enrolled into the respective study. All patients were diagnosed with conventional cytomorphology and cytogenetics and/or a qualitative Polymerase Chain Reaction (PCR) assay (RUNX1-RUNX1T1 transcripts). The median age of the cohort patients was 31 (range: 15 to 54) years old. Thirteen patients were in molecular relapse and eight in morphological relapse status at transplantation, respectively. All the morphological relapsed patients received salvage chemotherapy and the disease could not be controlled. Five molecular relapsed patients still remained Minimal Residual Disease (MRD) positive after intensive salvage chemotherapies and finally received transplantation, while the others did not receive any therapy before transplantation. There were no significant differences in the clinical features between the molecular and morphological relapse groups, except the level of RUNX1-RUNX1T1 fusion gene and the percentage of bone marrow blasts. The level of fusion gene and the percentage of bone marrow blasts were significantly higher in the morphological relapse group than that in the molecular relapse group ($p < 0.0001$, respectively) (Table 1). All patients provided written informed consent for the

Table 1: Characteristic of patients.

Characteristics	Total(n=21)	Molecular relapse (n=13)	Morphological relapse (n=8)	P value
Gender(male/female)	15/6	8/5	7/1	0.2205
Age [median (range), year]	31 (15 to 54)	31 (16 to 53)	26.5 (15 to 54)	0.5042
Bone marrow blasts at HSCT	0.5% (0.0% to 1.5%)	0.0% (0.0% to 1.5%)	48.0% (16.5% to 89.0%)	<0.0001
AE before allo-HSCT [median (range)]	1.04% (0.04% to 238.30%)	0.45% (0.04% to 1.21%)	122.26% (74.32% to 238.30%)	<0.0001
AE at 2 weeks after HSCT (pos./neg.)	6/15	3/10	3/5	0.5022
AE at 4 weeks after HSCT (pos./neg.)	3/18	3/10	0/8	0.1570
Gender of Donors (male/female)	17/4	11/2	6/2	0.6077
Age of Donors [median, (range), year]	44 (12 to 61)	43 (12 to 61)	44 (14 to 50)	0.5241
Type of Donors				0.4914
Matched donors	10 (47.6%)	7 (53.8%)	3 (37.5%)	
Haploidentical donors	11 (52.4%)	6 (46.2%)	5 (62.5%)	
Blood type of Donors				0.9670
Matched	13 (61.9%)	8 (61.5%)	5 (62.5%)	
Unmatched	8 (38.1%)	5 (38.5%)	3 (37.5%)	
Conditioning regimens				0.7894
RIC	6 (28.6%)	4 (30.8%)	2 (25.0%)	
MAC	15 (71.4%)	9 (69.2%)	6 (75.0%)	
MNC ($\times 10^9$ /kg)	18.45 (6.64 to 31.35)	18.92 (6.44 to 31.35)	14.39 (9.92 to 26.26)	0.4162
CD34+ cells ($\times 10^6$ /kg)	9.86 (3.69 to 14.26)	8.89 (3.69 to 14.26)	10.64 (7.25 to 13.45)	0.0599
CD3+ cells ($\times 10^9$ /kg)	3.40 (1.72 to 8.00)	3.25 (2.00 to 8.00)	3.65 (1.72 to 5.22)	0.5773
Follow to up time [median (range), month]	15 (5 to 47)	15 (5 to 31)	17.5 (7 to 47)	0.2143

AE: AML1 to ETO (RUNX1/RUNX1T1); HLA: Human Leukocyte Antigen; HSCT: Hematopoietic Stem Cell Transplantation; MAC: Myeloablative Conditioning; RIC: Reduced Intensity Conditioning; MNC: Mononuclear Cell; pos.: Positive; neg.: Negative

transplant.

Donors

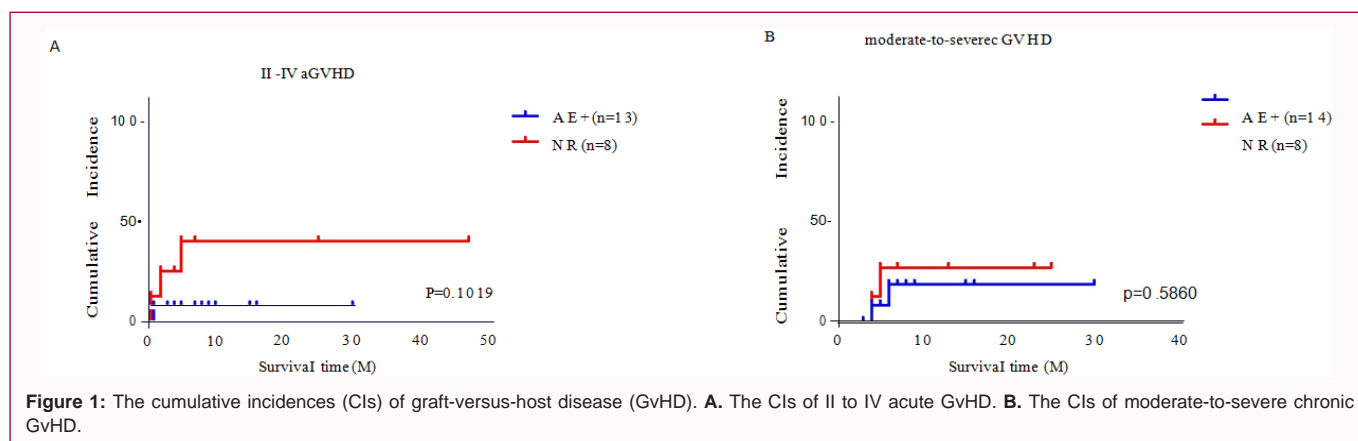
Sixteen and five patients received related and unrelated donor transplantation, respectively. Two patients underwent primary graft failure, and received the second transplantation with haploidentical donors. Human Leukocyte Antigen (HLA) matched intensity was defined according to the matched number of HLA-A, -B, -C, -DRB1 and -DQB1 locus at high-resolution level. More than 8/10 HLA locus matched between related/unrelated donor and recipient was defined as HLA matched and at least 3 loci mismatched between familiarly donor and recipient as HLA haplo-matched [10]. Five donors (23.8%) were from HLA-matched sibling, 5 (23.8%) from HLA-matched unrelated donors, and 11 (52.4%) from haploidentical donors. The Peripheral Blood Stem Cell (PBSC) grafts for all patients were mobilized with granulocyte colony-stimulating factor (G-CSF, 7.5 to 10 μ g/(kg. d)) for 5 days. The target value for CD34+ cells is a minimum of 4×10^6 /kg of recipient's weight in HLA matched donors and 8×10^6 /kg of recipient's weight in haploidentical related donors.

Conditioning regimens

Reduced-intensity conditioning (RIC) was given to the patients above 55 years old (≥ 55 years) or HSCT comorbidity index above 2 (HCT-CI >2), while Myeloablative Conditioning Regimens (MACs) were designed for patients below 55 years old (<55 years) or HCT-CI ≤ 2 . Fifteen patients received myeloablative conditioning (MAC, 71.4%), while six patients were prescribed with reduced intensity conditioning (RIC, 28.6%). The MAC regimen was based on busulphan (Bu), cytarabine (Ara-C) and fludarabine (Flu): Bu 3.2 mg/(kg. d) for 4 days, Flu 30 mg/(m^2 . d) and Ara-C 1 to 2 g/(m^2 .d) for 5 days. The RIC regimen was based on Bu 3.2 mg/(kg. d) for 2 days

Table 2: Outcomes of patients in two groups.

Variable	Molecular relapse median (range, %)	Morphological relapse median (range, %)	Total median (range, %)	P value
2 to year OS	74.1 (28.9 to 93.0)	60.0 (19.5 to 75.2)	68.4 (38.8 to 85.8)	0.3789
2 to year RFS	80.8 (41.0 to 95.0)	37.5 (8.7 to 67.4)	62.9 (36.6 to 80.7)	0.04
2 to year CIR	7.7 (0.0 to 69.7)	37.5 (4.6 to 73.1)	19.0 (1.2 to 53.7)	0.1001
2 to year NRM	11.1 (0.0 to 73.4)	40.0 (2.4 to 79.8)	20.4 (0.7 to 60.2)	0.1585
180 today CIs of II to IV aGVHD	7.7 (0.0 to 69.7)	40.0 (5.3 to 75.1)	20.0 (1.3 to 55.0)	0.1019
2 to year CIs of moderate to severe cGVHD	18.5 (0.2 to 66.0)	27.1 (0.5 to 72.6)	22.1 (1.5 to 57.3)	0.586



and Total Body Irradiation (TBI) 3 Gy on day-1. The dose of Flu and Ara-C was the same as that in the MAC regimen.

Prophylaxis of graft-versus-host disease (GVHD) and infection

The GVHD prophylaxis regimen included Cyclosporine A (CsA), short-term Methotrexate (MTX) and Mycophenolate Mofetil (MMF) for HLA-matched sibling HSCT (MSD-HSCT), while rabbit anti-thymocyte globulin (ATG, 5 mg/kg) was added besides CsA, short-term MTX and MMF for matched unrelated HSCT (MUD-HSCT). ATG (10 mg/kg) combined with CsA, short-term MTX and MMF or low dose ATG plus low dose cyclophosphamide Post-Transplant (Low dose ATG/PTCy) combined with CsA and MMF were for Haploidentical Related Donor (HRD) transplantation. CsA was dosed intravenously starting on day-7 to achieve a target trough level of 200 to 300 ng/ml. Intravenous methotrexate was delivered on days + 1, + 3, and + 6 after graft infusion.

MMF was given for 30 days with a dose of 15mg/kg twice for MSD and three times a day for MUD and Haplo-HSCT. The details of low dose ATG/PTCy based regimen was in reference [11]. The diagnosis and classification of acute GVHD (aGVHD) and chronic GVHD (cGVHD) were performed as described in reference [12].

All patients received G-CSF since day + 5 until neutrophil recovery. Levofloxacin and acyclovir were given from the beginning of conditioning regimens to neutrophil recovery. Posaconazole was given from the day of conditioning until 1 month after engraftment [13].

Chimerism monitoring

Quantitative chimerism monitoring was performed by Short-Tandem Repeat-based (STR) PCR techniques on CD3-positive T cell population from bone marrow or by Fluorescent *In Situ* Hybridization (FISH) for patients with sex-mismatched donors at regular intervals

for every 4 weeks after transplant at first 6 months [14,15]. Mixed T cell chimerism was defined as between 5% and 94% recipient cells and Complete Donor Chimerism (CDC) was defined as the presence of more than 95% donor chimerism at all measured time points [16].

Engraftment, MRD Monitoring and Definitions

Neutrophil engraftment time is the day when the Absolute Neutrophil Count (ANC) $\geq 0.5 \times 10^9/L$ for 3 consecutive days after transplantation without G-CSF. Platelet engraftment was defined as the first day of 7 consecutive days with platelet counts of $>20 \times 10^9/L$ without platelet transfusion. Graft failure was defined as the failure of neutrophil engraftment on day 28 following transplantation (primary graft failure), or loss of donor chimerism after initial engraftment with $\geq 95\%$ recipient cells at any time, not due to relapsed disease (secondary graft failure) [17].

RUNX1/RUNX1T1 fusion gene provides an ideal target for monitoring the MRD [18]. MRD was monitored using Real-time Quantitative reverse transcriptase-Polymerase Chain Reaction (RQ-PCR) to quantify the level of RUNX1/RUNX1T1 transcripts and the qualification was expressed as the percentage of the fusion to control transcript levels. Molecular relapse was defined as MRD positive after MRD negative with transcript level $>0.001\%$ for two consecutive times within one month [19]. CR was defined as the absence of leukemia symptoms, $<5\%$ bone marrow blasts, no Auer rods and the absence of extramedullary disease. Morphological relapse was defined as the reappearance of leukemia cells in the peripheral blood or the recurrence of $\geq 5\%$ bone marrow blasts or the appearance of extramedullary leukemia infiltrates [20].

Statistical Analysis

Overall survival (OS) was defined as the time from the first day of transplantation to death as a result of any cause. Relapse Free

Survival (RFS) was measured from the date when the relapse or death whichever occurred first. Cumulative Incidences of Relapse (CIR) were defined as the time from the first day of transplantation to relapse or non-relapse mortality. Non-Relapse Mortality (NRM) was defined as death as a result of any cause other than relapse. Cumulative incidences of GVHD were defined as the time from the first day of transplantation to II to IV aGVHD or moderate-to-severe cGVHD. Cox proportional hazards regression model and survival analysis were calculated using SPSS software. The probabilities of OS and RFS were estimated with the Kaplan-Meier method and compared using the log-rank test. The Cumulative Incidence of Relapse (CIR) and Non-Relapse Mortality (NRM) were estimated in the competing risks framework. All outcomes were treated as time-to-event endpoints. Log-rank analyses were performed to compare the impact of various prognostic variables. Grouped variables were compared by X² and continuous variables were compared using the Mann-Whitney U test. $p < 0.05$ was considered to be significant.

Results

Engraftment

All the patients received G-CSF mobilized PBSC graft with mononuclear cells (MNCs) $18.45 (6.44 \text{ to } 31.35) \times 10^8/\text{kg}$, CD34+ cells $9.86 (3.69\text{-}14.26) \times 10^6/\text{kg}$ and CD3+ cells $3.40 (1.72\text{-}8.00) \times 10^8/\text{kg}$. The median MNC, CD34+ cell and CD3+ cell numbers in molecular relapse group were $18.92 (6.44 \text{ to } 31.35) \times 10^8/\text{kg}$, $8.89 (3.69 \text{ to } 14.26) \times 10^6/\text{kg}$ and $3.25 (2.00 \text{ to } 8.00) \times 10^8/\text{kg}$, respectively, while in the morphological relapsed patients, were $14.39 (9.92 \text{ to } 26.26) \times 10^8/\text{kg}$, $10.64 (7.25\text{-}13.45) \times 10^6/\text{kg}$ and $3.65 (1.72 \text{ to } 5.22) \times 10^8/\text{kg}$, respectively. The CD34+ cell number in morphological relapse group was higher than that in molecular group, but not significant ($P=0.0599$). The median time for neutrophil engraftment was 14 days (range 11 to 18) for patients in molecular relapse group, and 12.5 days (range 10 to 15) in morphological relapse group ($P=0.1998$).

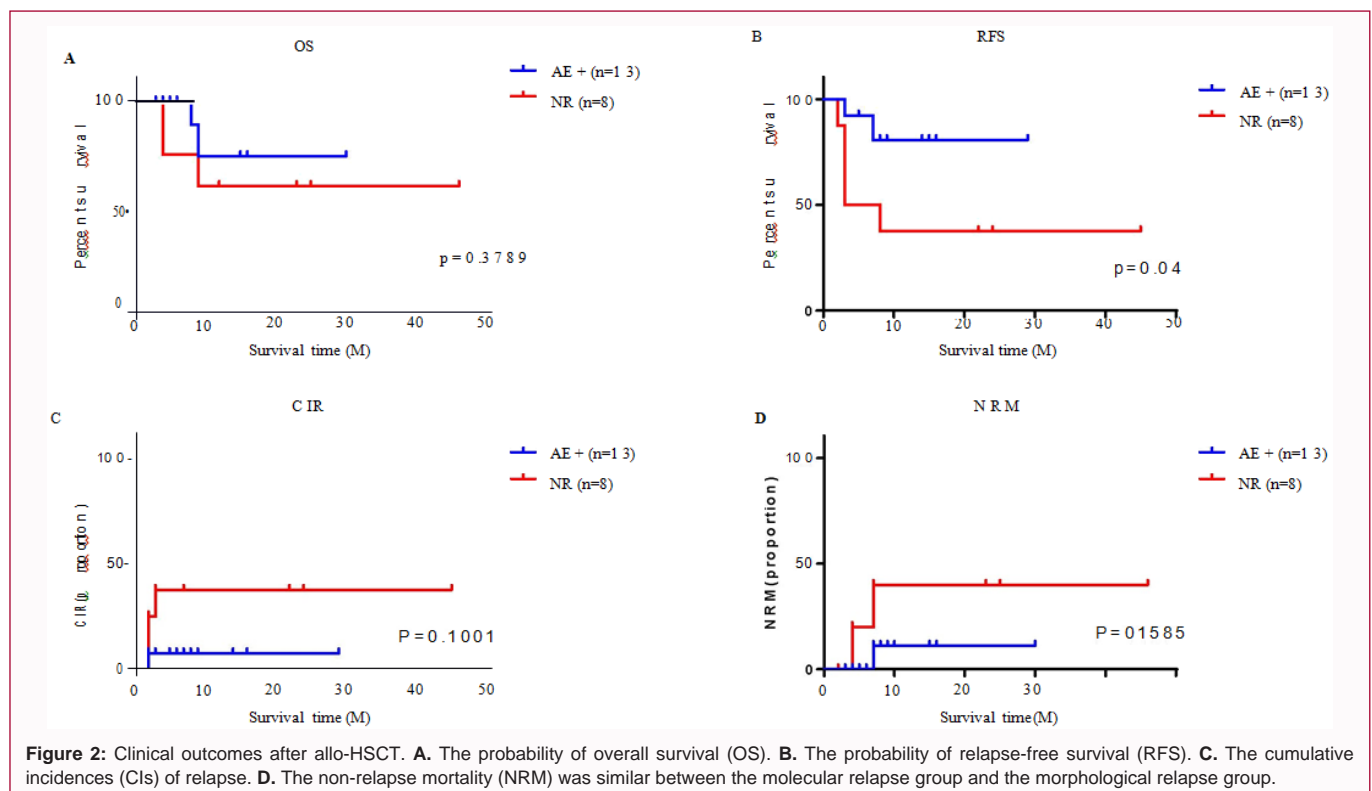
Moreover, the median time of platelet engraftment for patients in molecular and morphological relapse groups were observed in 15 days (range 11 to 25) and 13 days (range 10 to 15), respectively ($P=0.0581$). 19/21 (90.5%) patients achieved full donor chimerism at days 30 after transplantation. One patient in each group developed primary graft failure and both patients received haplo-HSCT from their father; one was 62-year-old and another 45-year-old. The two patients received second transplantation with non-myeloablative conditioning including fludarabine ($30\text{mg}/\text{m}^2/\text{d}$ for 5 days), ATG ($2.5 \text{ mg}/\text{kg}/\text{d}$ for 4 days) and TBI (3 Gy on day-1), and both successfully engrafted.

All patients with morphological relapse achieved molecular CR, while 2/13 patients with molecular relapse did not get molecular CR at one month after transplantation.

GVHD and infectious complications

One patient (grade II) in the molecular relapse group and three patients (2 with grade II and one with grade III) in morphological relapse group developed grade above II aGVHD with a 180-day Cumulative Incidence (CI) of 20.0% (95% CI 1.3% to 55.0%). The 180-day CIs of II to IV aGVHD in the molecular and morphological relapse groups were 7.7% (95% CI, 0.0% to 69.7%) and 40.0% (95% CI, 5.3% to 75.1%), respectively ($P=0.1019$) (Figure 1a, Table 2). In all 21 patients, 4 patients developed moderate cGVHD after 3 months (two patients in each group). The 2-year CI of moderate-to-severe cGVHD was 18.5% (95% CI, 0.2% to 66.0%) in the molecular relapse group and 27.1% (95% CI, 0.5% to 72.6%) in the morphological relapse group ($P=0.5860$) (Figure 1b, Table 2).

Four patients developed Cytomegalovirus (CMV) viremia after transplantation, two of which were accompanied with viral hemorrhagic cystitis. Four patients suffered from Epstein-Barr virus (EBV) viremia. Two patients suffered from pneumonia (One with aspergillus and bacterial infection, one with bacterial and CMV



infection). No patients died from infection complications.

Relapse, non-relapse mortality and survival analysis

The median time of follow-up was 15 (5 to 47) months. Four cases developed morphological relapse with a 2-year Cumulative Incidence of Relapse (CIR) of 19.0% (95% CI 1.2% to 53.7%) with a median relapse time of 4 months (range, 2 to 4 months) after transplantation, and two patients died. One patient was from the molecular relapse group and three from the morphological relapse group. The patient in the molecular relapse group maintained MRD positive and experienced extramedullary recurrence at 4 months and died at 9 months after transplantation. One patient from the morphological relapse group developed morphological relapse at 4 months after transplantation and only received palliative treatments and finally died. The other two patients in the morphological relapse group achieved CR with salvage chemotherapies after one month. One patient continued to be MRD negative and the other maintained MRD positive until the terminal of follow-up.

Three patients in the morphological relapse groups presented with bone marrow blasts from 26.0% to 78.0% at transplantation and relapsed at 2 to 4 months after transplantation. Two of the three patients achieved CR with chemotherapy and were still alive. Although the CIRs were similar between the molecular and the morphological relapse groups, there was a trend with higher CIR in patients with morphological relapse. [CIR 7.7% (95% CI 0.0% to 69.7%) vs. 37.5% (95% CI 8.7% to 67.4%), respectively ($p=0.1001$, Figure 2c, Table 2). 2-year Non-Relapse Mortality (NRM) for all patients was 20.4% (95% CI 0.7% to 60.2%). One patient in each group died from aGVHD and one patient in the morphological relapse group died of Capillary Leak Syndrome (CLS). The NRMs in molecular and morphological relapse groups were 11.1% (95% CI 0.0% to 73.4%) and 40.0% (95% CI 2.4% to 79.8%), respectively ($p=0.1585$) (Figure 2d, Table 2).

The 2-year probability of Overall Survival (OS) and Relapse-Free Survival (RFS) were 68.4% (38.8% to 85.8%) and 62.9% (36.6% to 80.7%) for all patients, respectively. In the molecular and morphological relapse groups, the 2-year probability of OS were 74.1% (95% CI 28.9% to 93.0%) and 60.0% (95% CI 19.5% to 75.2%), respectively. ($p=0.3789$, Figure 2a, Table 2). The 2-year probability of RFS was 80.8% (95% CI 41.0% to 95.0%) in molecular relapse group, which was significantly higher than that of 37.5% (95% CI 8.7% to 67.4%) in morphological relapse group, ($p=0.0400$, Figure 2b, Table 2).

Discussion

Data from our retrospective study showed that the 2-year OS and RFS of relapsed patients with t(8;21) after allo-HSCT were 68.4% and 62.9%, especially for morphological relapsed patients with a probability of 2-year OS of 60.0%, which was similar to previous report on refractory t(8;21) AML patients (5-year OS 61%, RFS 40%) [21]. The results suggested that allo-HSCT has yielded encouraging results focusing on relapsed AML with RUNX1-RUNX1T1, and could be an optimized salvage strategy to improve the long-term survival.

The relapse rate of t(8;21) AML after standard chemotherapy was approximately 30% to 40% [22]. Fludarabine and cytarabine (FA) consolidation therapy could decrease the relapse rate of t(8;21) AML patients, especially those without c-kit mutations [23]. Kuwatsuka et al reported that the 3-year CIR of high-risk and refractory t(8;21) AML after transplantation was 38% [24]. According to our results, the 2-year CIR were 7.7% and 37.5% in the molecular relapse and

the morphological relapse group respectively without significant difference ($p=0.1001$). Even in patients with morphological relapse, the CIR was consistent with the previous reports, indicating allo-HSCT might overcome the poor outcomes of relapsed patients. On the other hand, morphological relapse patients were prone to relapse after transplantation. Although the 2-year RFS in morphological group was significantly lower than that in molecular group, the 2-year probability of OS was similar between two groups. That is because two of the three relapsed patients after transplantation achieved CR after salvage therapies and achieved durable remission. The median time of relapse was 4 months (range, 2 to 4 months) after transplantation. The early relapsed patients could maintain long-term remission after CR, which suggested the GVL effects of allo-HSCT to eradicate the residual leukemic cells.

In the molecular relapse group, NRM was 11.1%, which was comparable to the morphological relapse group (NRM 40.0%, $p=0.1518$). Two patients died from aGVHD and one patient died from CLS. The Shen's group reported that grade II to IV aGVHD and generalized cGVHD were the most important factors for survival [25]. According to our results, the 180-day CI of II to IV aGVHD and 2-year CI of moderate-to-severe cGVHD were 7.7% and 18.5% in the molecular relapse group, while 40% and 27.1% in the morphological relapse group. Although there was no significant difference in the incidences of aGVHD between two groups ($P=0.1019$), there was a trend with higher incidence of aGVHD in patients with morphological relapse. The difference of aGVHD might be significant with more patients in morphological group. The active leukemia status was positively correlated with the occurrence of aGVHD, but were not significantly associated with the development of chronic GVHD [26].

In summary, allo-HSCT could overcome the poor outcomes of relapsed patients. Although active disease status was prone to a higher relapse incidence after transplantation, the GVL effects could help patients with early relapse maintain long-term remission after CR. Therefore, our study indicated that allo-HSCT could be an optimized strategy to further improve the outcomes of relapsed AML patients with t(8;21).

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