ORIGINAL ARTICLE

Effect of allogeneic hematopoietic stem cell transplantation from matched siblings or unrelated donors during the first complete remission in patients with cytogenetically normal acute myeloid leukemia

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Abstract

We retrospectively examined the impact of hematopoietic stem cell transplantation (HSCT) during the first complete remission (CR1) in 81 patients with cytogenetically normal acute myeloid leukemia (CN-AML). Eligible patients were divided into three subgroups: HSCT recipients with allogeneic sibling or matched unrelated donors (MUD) (allogeneic HSCT, $n = 47$), recipients of autologous HSCT ($n = 12$), and patients receiving chemotherapy alone ($n = 22$). We examined factors associated with overall survival (OS) in these patients, focusing particularly on the effect of allogeneic HSCT. Comparing to those receiving chemotherapy alone, patients in the allogeneic HSCT group had significantly better OS, which was independent of the presence of comorbidities. Furthermore, patients who received allogeneic sibling HSCT had the best OS and disease-free survival (DFS). Patients who received MUD HSCT also had significant advantage in DFS but not in OS, when compared with patients in the chemotherapy group. The study results suggest that patients with CN-AML in CR1 who are eligible for HSCT may have a survival benefit from HSCT, especially the allogeneic HSCT. We suggest that future studies employ molecular classification of AML to better define the benefits of HSCT during CR1 in patients with CN-AML.

Key words AML; Cytogenetics; Prognosis; Survival; Transplantation

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Acute myeloid leukemia (AML) is a heterogeneous group of diseases, and its different subtypes are associated with different pathologies and clinical courses. Thus, it is necessary to properly classify AML cases to accurately assess the prognosis and determine the best treatment. Cytogenetics is the most important prognostic factor in AML, and it has played a major role in risk stratification and treatment selection in the past two decades (1–5). Current consensus recommends that patients with good-risk AML in their first complete remission (CR1) undergo intensive consolidation chemotherapy, with autologous hematopoietic stem cell transplantation (HSCT) as an acceptable alternative (6). Allogeneic HSCT is recommended for patients with poor-risk AML in CR1 (6). However, for patients with intermediate-risk AML in CR1, there remains debates on the most appropriate postremission therapy (6).

Nevertheless, allogeneic sibling HSCT has been considered the most effective treatment modality to reduce the risk of AML relapse. Despite advances in HSCT procedures and supportive care, the benefit of allogeneic HSCT is often offset by its high rate of transplant-

related mortality (TRM) (7). In addition, only about 30% of patients with AML had HLA-matched family members (8). In Taiwan, about 60% of all HSCT recipients received grafts from allogeneic siblings or matched unrelated donors (MUDs) (9). Grafts from MUDs accounted for about 25% of grafts, and there has been an increasing use of MUDs in Taiwan (10). With the development of high-resolution HLA typing, the outcome of HSCT with MUDs may approach that with matched sibling donors (11).

Cytogenetically normal AML (CN-AML), which accounts for about half of the AML cases, is generally classified as intermediate-risk. The role of allogeneic HSCT in patients with CN-AML during CR1 has not yet been established (9, 12, 13). Numerous studies have suggested a benefit of allogeneic sibling HSCT for CN-AML, but there were no randomized trials to support this argument (4, 6, 14–17). Moreover, prospective trials that examined the role of allogeneic HSCT during CR1 of patients with AML in all cytogenetic risk groups all adopted autologous HSCT as the control (4, 6, 14, 15, 17–22). Some studies have grouped patients with MUD HSCT and those receiving autologous HSCT into a so-called 'no-donor group', making it difficult to compare the effect of autologous and MUD HSCT in AML during CR1 (6, 16, 22). Other studies have grouped allogeneic sibling and MUD HSCT together (17). In addition, there is limited data on the effect of HSCT during CR1 of patients with CN-AML from Asia.

In this study, we assessed the impact of HSCT during CR1 in Taiwanese patients with CN-AML. We focused on the effect of HSCT from matched siblings or unrelated donors by conducting a subgroup survival analysis among the different types of HSCT (autologous, allogeneic sibling, or matched-unrelated). Moreover, we examined factors (including type of HSCT) associated with overall survival (OS) in these patients with CN-AML.

Patients and methods

Study population

This retrospective study was approved by the Institutional Review Board of Taipei Veterans General Hospital. We reviewed the records of patients with newly diagnosed AML who were admitted to our institute between January 2000 and December 2008. We screened patients with CN-AML aged ≤60 yrs who were potential candidates for HSCT. Patients included in our study were those with CN-AML who achieved CR1 after induction chemotherapy. Patients who underwent HSCT at CR2 (second complete remission) or non-myeloablative or cord blood HSCT were excluded. Patients were then divided into three subgroups according to their postremission therapy: (i) allogeneic HSCT, (ii) autologous HSCT, and (iii) chemotherapy alone. The rationale for this classification is based on the results of a major study by the Finnish Leukaemia Group (23). The choice of postremission treatment strategy was generally made on an individual basis and the availability of a donor. Each patient made the final decision after being adequately informed about the risks and benefits of different treatments. All patients who underwent MUD HSCT were matched at the allele level at HLA-A, B, DR loci (6/6 match) through high-resolution DNA typing. For all enrolled patients, we examined factors that were potentially associated with OS, including age at diagnosis, gender, *de novo* or secondary AML, comorbidities at diagnosis [defined according to the HSCT-specific comorbidity index, HSCT-CI (24)], extramedullary disease at diagnosis, initial white blood cell count (WBC), platelet count, lactate dehydrogenase (LDH), cycles of chemotherapy, and time to CR1.

Induction and consolidation chemotherapy

Induction regimens consisted of a combination of intravenous (IV) cytarabine (100–200 mg/m^2/d for 7 d) and either idarubicin (10 mg/m^2/d) or daunorubicin (45 mg/m^2/d) for 3 d. Consolidation regimens consisted of at least one cycle of IV high-dose cytarabine (3000 mg/m^2 every 12 h on days 1, 3, and 5). Other consolidation regimens included a combination of IV cytarabine (100 mg/m^2/d) for 5 d and either idarubicin (10 mg/m^2/d) or daunorubicin (45 mg/m^2/d) for 2 d.

Transplantation procedures

The decisions on HSCT are discussed thoroughly in our department monthly by hematology experts. All recipients of allogeneic HSCT were cared in a single room with positive air pressure and high-efficiency particulate air filtration. Conditioning regimens consisted of cyclophosphamide (60 mg/kg/d intravenously for 2 d) plus either total body irradiation (12 Gy in six fractions) or busulfan (1 mg/kg per os or 0.8 mg/kg intravenously four times a day for 4 d). Patients who underwent allogeneic HSCT received either bone marrow (BM) or peripheral blood stem cells (PBSC) from a matched sibling or unrelated donors. Graft-versus-host disease (GVHD) prophylaxis regimens consisted of a combination of cyclosporine (CsA) and methotrexate. Antithymocyte globulin (ATG) (Thymoglobulin; Genzyme, Cambridge, MA, USA) at doses of 6–15 mg/kg (in 3–4 d) or ATG-Fresenius (Fresenius-Biotech, Graefelfing, Germany) at doses of 40 mg/kg (in 4 d) was administered to recipients of MUD HSCT. Management of acute GVHD depended on corticosteroids according to the severity of acute

GVHD. In general, Grade II or higher grade of acute GVHD was treated with intravenous methylprednisolone at 1 mg/kg/d in divided doses, which were then gradually tapered according to patient response. For patients who responded unfavorably or were refractory to standard doses of corticosteroids, higher doses of corticosteroids or combinations of various immunosuppressives such as ATG, tacrolimus, or cyclosporine were administered under the clinicians' discretion. Regarding complications of HSCT, TRM in the current study was defined as death of any cause within 100 d after the HSCT (TRM <100 d), whereas non-relapse mortality (NRM) was defined as mortality not directly associated with relapse or progression of the original disease.

Statistical methods

The molecular methods for analyses of gene abnormalities (e.g. FLT3-ITD, FLT3/TKD, and NPM1 mutations) were not available in our institute until 2007. Thus, most patients (86.4%) in this study cohort were not assayed for these molecular markers. The correlations of variables among the three subgroups were analyzed by the Chi-square or the Mann–Whitney tests as appropriate. Time to CR1 was calculated from the day of AML diagnosis to the day of the first morphologic complete remission (25). Survival endpoints were OS and disease-free survival (DFS), as defined by the standard criteria (25). OS was measured from the date of diagnosis to the date of death or last follow-up; DFS was measured from the date of CR to the date of relapse, death, or last follow-up. OS since HSCT was measured from the date of HSCT to the date of death or last follow-up. Survival was estimated using the Kaplan–Meier method, and the log-rank test was used to compare survival curves among variables. The Cox proportional hazards model was used in univariate and multivariate analyses to determine the influence of variables on OS. Variables with $P < 0.10$ in univariate analysis were included in the multivariate analysis. A P value <0.05 in two-tailed tests was considered statistically significant. SPSS software (version 13.00; SPSS, Chicago, IL, USA) was used for all statistical analyses.

Results

Patient characteristics and OS of subgroups

We finally enrolled 81 patients, including 47 (58%) patients in the allogeneic HSCT group, 12 (14.8%) in the autologous HSCT group, and 22 (27.2%) in the chemotherapy alone group. The median age was 42.2 yrs (range: 16–60). The median length of follow-up was 31.2 months (range: 3.2–124.3). Most patients (76/81, 93.8%) had *de novo* AML. Table 1 summarizes the general characteristics of the three groups of patients. More than 90% of patients in HSCT groups received ≤3 cycles of consolidative chemotherapy, while all patients in chemotherapy alone group received at least three cycles of consolidative chemotherapy. This may reflect the different consolidative strategies between HSCT and non-HSCT groups.

The actuarial 5-yr OS rate for all 81 patients was 58.8% [95% confidence interval (CI): 46.6–71%].

Table 1 General characteristics of enrolled patients according to allogeneic, autologous HSCT, and chemotherapy alone

Factors	Allogeneic HSCT, *N* = 47 (%)	Autologous HSCT, *N* = 12 (%)	Chemotherapy alone, *N* = 22 (%)
Age, yrs[1]	37.9 (16–60)	45.5 (16–60)	44.7 (16–59)
Gender			
Male	20 (42.6)	9 (75.0)	14 (63.6)
Female	27 (57.4)	3 (25.0)	8 (36.4)
De novo AML	45 (95.7)	12 (100)	19 (86.4)
Comorbidities			
None	38 (80.9)	8 (66.7)	13 (59.1)
At least 1	9 (19.1)	4 (33.3)	9 (40.9)
HSCT-CI[1,2]	2 (1–3)	1 (1–2)	1 (1–2)
EM involvement			
No	43 (91.5)	12 (100)	22 (100)
Yes	4 (8.5)	0 (0)	0 (0)
Cycle of induction			
1 cycle	31 (66.0)	7 (58.3)	13 (59.1)
>1 cycles	16 (34.0)	5 (41.7)	9 (40.9)
Time to CR1			
≤30 d	15 (31.9)	4 (33.3)	5 (22.7)
>30 d	32 (68.1)	8 (66.7)	17 (77.3)
Cycles of consolidation[1]	2 (2–5)	3 (2–4)	3 (3–4)
2 cycles	26 (55.3)	4 (33.3)	0 (0)
3 cycles	17 (36.2)	7 (58.3)	13 (59.1)
≥4 cycles	4 (8.5)	1 (8.4)	9 (40.9)
HiDAC based	36 (76.6)	12 (100)	18 (81.8)
1 cycle	22 (46.8)	8 (66.7)	5 (22.7)
2 cycles	12 (25.5)	3 (25.0)	10 (45.5)
3 cycles	2 (4.3)	1 (8.3)	2 (9.1)
4 cycles	0 (0)	0 (0)	1 (4.5)
WBC ($\times 10^9$/L)			
<100	42 (89.4)	12 (100)	18 (81.8)
≥100	5 (10.6)	0 (0)	4 (18.2)
Platelet ($\times 10^9$/L)			
<20	42 (89.4)	11 (91.7)	17 (77.3)
≥20	5 (10.6)	1 (8.3)	5 (22.7)
LDH			
≤2X ULN	27 (57.4)	9 (75.0)	10 (47.6)
>2X ULN	20 (42.6)	3 (25.0)	11 (52.4)

AML, acute myeloid leukemia; CR1, first complete remission; EM, extramedullary; HiDAC, high-dose cytarabine; HSCT-CI, hematopoietic stem cell transplantation comorbidities index; LDH, lactate dehydrogenase; ULN, upper limit of normal; WBC, white blood cells.
[1]Data were expressed as median (range).
[2]Defined according to the HSCT-specific comorbidity index (24) and data were shown only for patients with comorbidities .

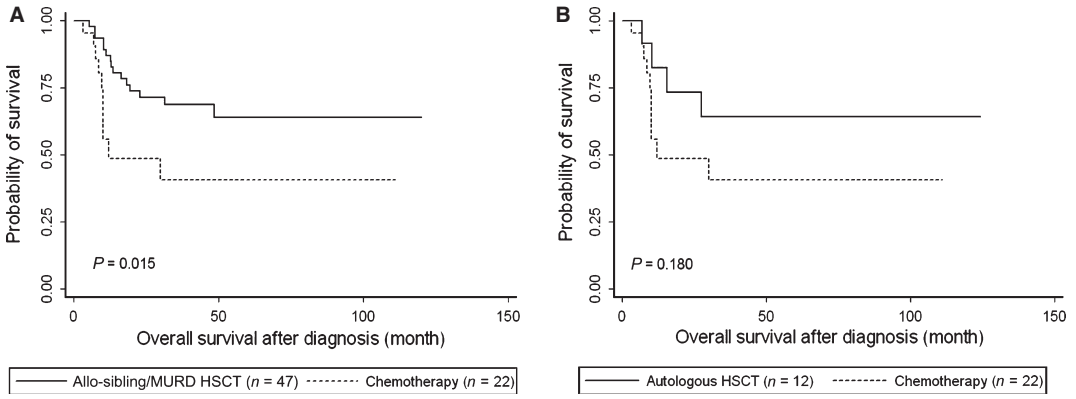

Figure 1 (A) Overall survival curves for patients in the allo-sibling/matched unrelated donors HSCT group (n = 47) and the chemotherapy alone group (n = 22; P = 0.015). Abbreviations in this and subsequent figure legends: HSCT, hematopoietic stem cell transplantation; Allo, allogeneic; MURD, matched unrelated donor; OS, overall survival. (B) Overall survival curves for patients in the autologous HSCT group (n = 12) and the chemotherapy alone group (n = 22; P = 0.180).

Figure 1 shows the OS curves of the three subgroups and illustrates the survival advantage of patients undergoing allogeneic HSCT over non-HSCT patients. Comparing to patients receiving chemotherapy alone, patients who underwent allogeneic HSCT had significantly better OS (P = 0.015, Fig. 1A), whereas no significantly better OS was found in patients who underwent autologous HSCT (P = 0.180, Fig. 1B).

Effect of allogeneic HSCT during CR1

In these 81 patients, we further determined whether the benefit of allogeneic HSCT on OS was independent of other potential factors associated with OS. Results from the univariate analysis indicated that the presence of at least one comorbidity (vs. none) and allogeneic HSCT (compared to chemotherapy alone) both had a P value <0.1, indicating an association with OS (Table 2). After adjusting for comorbidities, the multivariate Cox proportional hazard analysis indicated that allogeneic HSCT remained as a significant independent factor associated with better OS (Table 2). Compared to the chemotherapy alone group, the allogeneic HSCT group showed a decreased HR of 0.43 (95% CI: 0.19–0.99; P = 0.047), whereas the autologous HSCT group, albeit with a decreased HR, was not an independent factor associated with better OS (Table 2). Furthermore, because allogeneic HSCT and comorbidities apparently impacted survival outcome in opposite directions (Table 2), we depicted cumulative hazard curves starting from the day of HSCT in recipients of allogeneic HSCT with or without comobidities. As shown in Fig. 2, the hazard curve of recipients with at least one comorbidity not only arises steeper within the first year (12 months) after HSCT but also reaches a plateau faster (12 months vs. 45 months after HSCT), suggesting that the presence of comorbidities poses a great and early impact on survival during the first year after HSCT.

Comparison of characteristics, transplant complications, and outcome between recipients of allogeneic sibling HSCT or MUD HSCT

Table 3 summarizes the characteristics between recipients of allogeneic sibling HSCT and MUD HSCT. As shown in Table 3, the baseline characteristics were in general comparable between these two subgroups. However, there was a significant difference with regard to the HSCT graft source (Table 3). In addition, there seemed to be a trend toward more cycles of consolidative chemotherapy in recipients of MUD HSCT: 66.7% of patients in the MUD HSCT group had three or more cycles of consolidative chemotherapy, but the figure was only 31% in the allogeneic sibling HSCT group. Regarding transplant complications, there were no significant differences between groups in terms of acute or chronic GVHD, TRM within 100 d, or overall mortality (Table 3). Moreover, there was no survival difference with regard to OS since HSCT between groups (P = 0.724, Fig. 3). These analyses implicated that the effect of MUD HSCT may be comparable to that of allogeneic HSCT in patients with CN-AML. However, when analyzing the impact of GVHD in the whole allogeneic HSCT group (n = 47), three patients (3/47, 6.4%) who developed severe (grade 3–4) acute GVHD died within 100 d. In addition, there were eight patients (8/47, 17.0%) who developed extensive chronic GVHD, where two of them died of relapsed leukemia, one died of intractable thrombocytopenia related to severe chronic GVHD, and three died of other causes (one hepatitis B reactivation, one CMV pneumonia, and one septic meningitis). Looking into the two patients who survived, one

Table 2 Univariate and multivariate analyses of HSCT factors associated with overall survival (n = 81)

	Univariate[1]			Multivariate[2]		
Factors	HR	95% CI	*P* value	HR	95% CI	*P* value
Age, per 10-yr increment	1.30	0.94–1.78	0.109	–	–	–
Gender						
Male	1.00	–	–			
Female	0.58	0.28–1.24	0.160	–	–	–
De novo AML	1.00	–	–			
Others	1.51	0.36–6.38	0.574	–	–	–
HSCT-CI						
0	1.00	–	–	1.00	–	–
≥1	3.50	1.67–7.31	0.001*	3.27	1.55–6.90	0.002*
EM involvement						
None	1.00	–	–			
Yes	0.05	0.00–33.81	0.358	–	–	–
WBC ($\times 10^9$/L)						
<100	1.00	–	–			
≥100	1.69	0.64–4.43	0.286	–	–	–
Platelet ($\times 10^9$/L)						
≥20	1.00	–	–			
<20	0.77	0.23–2.54	0.667	–	–	–
LDH						
≤2X ULN	1.00	–	–			
>2X ULN	1.81	0.86–3.82	0.117	–	–	–
Induction regimen						
1 cycle	1.00	–	–	–	–	–
>1 cycles	1.25	0.60–2.62	0.556			
Time to CR1						
≤30 d	1.00	–	–	–	–	–
>30 d	2.07	0.79–5.44	0.138			
Postremission therapy						
Chemotherapy alone	1.00	–	–	1.00	–	–
Autologous	0.40	0.13–1.30	0.129	0.42	0.13–1.35	0.143
Allogeneic	0.38	0.17–0.85	0.019*	0.43	0.19–0.99	0.047*

AML, acute myeloid leukemia; CI, confidence interval; CR1, first complete remission; EM, extramedullary; HR, hazard ratio; HSCT-CI, hematopoietic stem cell transplantation comorbidities index; LDH, lactate dehydrogenase; ULN, upper limit of normal; WBC, white blood cells.
*$P < 0.05$.
[1]Univariate Cox proportional hazard model.
[2]Multivariate Cox proportional hazard model.

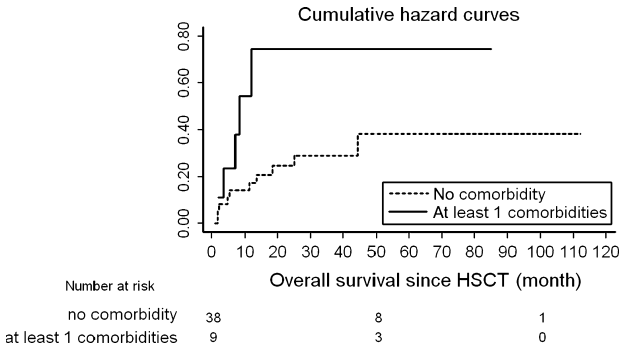

Figure 2 Cumulative hazard curves starting from the day of hematopoietic stem cell transplantation (HSCT) in recipients of allogeneic HSCT with or without comobidities. Numbers of patients at risk were labeled beneath the plot.

has been completely tapered off immunosuppressant for more than 2 yrs, and the other still needs a minimal maintenance of mycophenolate on 250 mg/d.

Analyses of OS and DFS in subgroups of HSCT and non-HSCT controls

Table 4 summarizes the actuarial 5-yr OS rates and 3-yr DFS rates for each subgroup of HSCT, compared to the chemotherapy alone group. As shown in Table 4, patients who received allogeneic sibling HSCT had significantly better OS and DFS, compared to patients receiving chemotherapy alone. Patients undergoing MUD HSCT had similar OS but better DFS than that of patients in the chemotherapy alone group. Moreover,

Table 3 Comparison of characteristics between recipients of allogeneic sibling HSCT or MUD HSCT

Factors	Allogeneic sibling HSCT, *N* = 29 (%)	MUD HSCT, *N* = 18 (%)	*P* value[1]
Age, yrs[2]	38.9 (16–60)	37.1 (16–60)	0.196
Gender			
Male	12 (41.4)	8 (44.4)	1.000
Female	17 (58.6)	10 (55.6)	
De novo AML	27 (93.1)	18 (100)	0.517
Comorbidities			
At least 1	6 (20.7)	3 (16.7)	1.000
None	23 (79.3)	15 (83.3)	
Cycle of induction			
1 cycle	19 (65.5)	12 (66.7)	1.000
>1 cycles	10 (34.5)	6 (33.3)	
Time to CR1 (d)			
≤30 d	8 (27.6)	7 (38.9)	0.627
>30 d	21 (72.4)	11 (61.1)	
Cycle of consolidation			
2 cycles	20 (69.0)	6 (33.3)	0.055
3 cycles	7 (24.1)	10 (55.6)	
≥4 cycles	2 (6.9)	2 (11.1)	
HiDAC based	20 (69.0)	16 (88.9)	0.164
1 cycle	11 (37.9)	11 (61.1)	
2 cycles	8 (27.6)	4 (22.2)	
3 cycles	1 (3.5)	1 (5.6)	
HSC source			
BM	5 (17.2)	9 (50)	0.039*
PB	24 (82.8)	9 (50)	
aGvHD			
None	21 (72.4)	10 (55.6)	0.399
Grade 1–2	7 (24.1)	6 (33.3)	
Grade 3–4	1 (3.5)	2 (11.1)	
cGvHD			
None	15 (51.7)	9 (50.0)	0.987
Limited	9 (31.0)	6 (33.3)	
Extensive	5 (17.3)	3 (16.7)	
TRM,<100 d			
No	27 (93.1)	14 (77.8)	0.185
Yes	2 (6.9)	4 (22.2)	
Overall mortality			
Alive	19 (65.6)	12 (66.7)	0.413
NRM	5 (17.2)	5 (27.8)	
Relapse mortality	5 (17.2)	1 (5.5)	

aGvHD, acute graft-versus-host disease; AML, acute myeloid leukemia; BM, bone marrow; cGvHD, chronic graft-versus-host disease; CR1, first complete remission; HiDAC, high-dose cytarabine; HSC, hematopoietic stem cell; HSCT, hematopoietic stem cell transplantation; NRM, non-relapse mortality; PB, peripheral blood; TRM, transplantation related mortality; MUD, matched unrelated donors.
*$P < 0.05$.
[1]Fisher's exact test or chi-square test as appropriate.
[2]Data were expressed as median (range).

when grouping together recipients of allogeneic sibling and MUD HSCT (allogeneic), there were also significant survival benefits in OS and DFS, compared to patients receiving chemotherapy alone. In contrast to patients who underwent allogeneic sibling or MUD HSCT, patients who underwent autologous HSCT had no significant survival benefit over chemotherapy alone group with regard to OS and DFS.

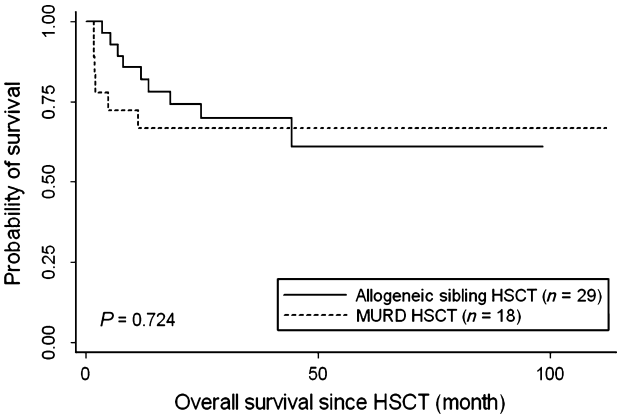

Figure 3 Overall survival curves since the date of hematopoietic stem cell transplantation (HSCT) for patients in the allo-sibling HSCT group and the matched unrelated donors HSCT group ($P = 0.724$).

Table 4 Subgroup analysis of actuarial 5-yr OS rate and 3-yr DFS rate for subtypes of HSCT, compared with chemotherapy alone

Types of HSCT	5-yr OS rate (%)	3-yr DFS rate (%)
Autologous vs. chemotherapy	64 vs. 41	50 vs. 32
Allogeneic sibling vs. chemotherapy	62 vs. 41*	68 vs. 32*
Allogeneic MUD vs. chemotherapy	67 vs. 41	61 vs. 32*
Allogeneic[1] vs. chemotherapy	64 vs. 41*	65 vs. 32*

DFS, disease-free survival; HSCT, hematopoietic stem cell transplantation; MUD, matched unrelated donors; OS, overall survival.
*$P < 0.05$ by log-rank test.
[1]Calculated as grouping allogeneic sibling and MUD together.

Postrelapse survival and effect of salvage treatments

To examine the effect of salvage treatments after leukemic relapse, we analyzed postrelapse survival in patients who relapsed from postremission therapy according to their salvage treatments (divided into HSCT containing and non-HSCT containing) (Fig. 4). A total of 24 (29.6%) patients experienced leukemic relapse, and all of them received at least one type of salvage treatments. Types of salvage treatments included a second allogeneic sibling or MUD HSCT, cytarabine-combination chemotherapy regimens [fludarabine, cytarabine, and granulocyte colony stimulating factor (FLAG), mitoxantrone, etoposide, and cytarabine (MEC), or others], and gemtuzumab ozogamicin.

Figure 4 demonstrates that there was no significant postrelapse survival difference between patients receiving

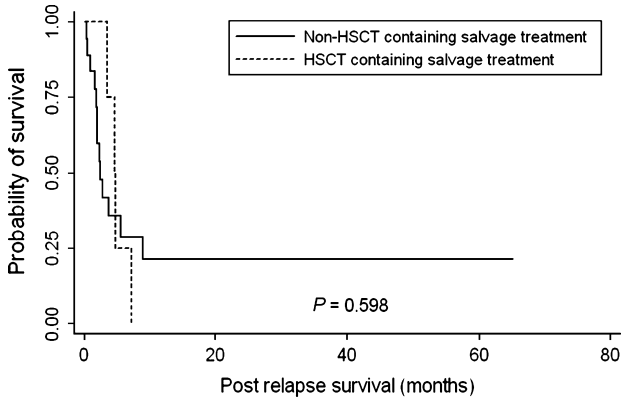

Figure 4 Postrelapse survival curves according to salvage therapy [hematopoietic stem cell transplantation (HSCT) containing vs. non-HSCT containing, $P = 0.598$].

HSCT or non-HSCT containing salvage treatments. These results indicated that the survival advantage found in patients in the postremission allogeneic HSCT group (Fig. 1) might not be explained by the effects of postrelapse salvage treatments.

Discussion

In this study, we retrospectively analyzed 81 patients with CN-AML to determine the role of allogeneic HSCT at CR1. In an attempt to reduce the limitations of our retrospective design, we enrolled patients from a single institution who received similar treatments. The results of the current study support the view that allogeneic sibling HSCT should be considered for postremission treatment in patients with CN-AML who achieved CR1, and that MUD may be a suitable alternative to allogeneic HSCT (Fig. 3 and Table 4). Autologous HSCT did not differ from chemotherapy alone with regard to OS and DFS, suggesting this treatment is less beneficial. In addition, we found that comorbidities at diagnosis and allogeneic HSCT were independent factors associated with OS in patients with CN-AML at CR1, who were potential HSCT candidates.

Our result that allogeneic sibling HSCT was the best postremission treatment for patients with CN-AML at CR1 was in agreement with numerous previous studies (4, 6, 14–17). A recent meta-analysis by Koreth *et al.* (6) showed that allogeneic sibling HSCT during CR1 provided significant improvement in OS for patients with AML with intermediate-risk and poor-risk disease. However, only about 30% of patients with AML could find matched sibling donors; thus, it is important to expand the acceptable donor pool for patients with AML. With the use of high-resolution typing at HLA genetic loci, the outcomes of MUD HSCT may be similar to those by allogeneic sibling HSCT (8). Results from the subgroup analysis suggested that MUD HSCT might also be a suitable alternative to allogeneic HSCT because there was no difference in OS between patients receiving allo-sibling HSCT and MUD HSCT (as shown in Fig. 3). Possible explanations for the favorable outcome of MUD in the current study include the use of ATG to reduce the severity and incidence of GVHD and improved supportive care during HSCT (26, 27). The differences of characteristics between patients receiving allogeneic sibling HSCT and MUD HSCT were only found in cycles of consolidation and HSCT graft source (Table 3). Regarding cycles of consolidation, recipients of MUD HSCT may receive more cycles of consolidation chemotherapy because it generally takes more time for the process of matching an unrelated donor than matching a sibling in Taiwan. The fact that PBSC grafts were more often used in allogeneic sibling HSCT setting than in MUD HSCT setting probably reflects the preferential strategies in choosing graft types for the two HSCT types. As a principle, BM grafts were preferred for MUD HSCT at the Tzu-Chi Stem Cell Center, which is the largest MUD provider in Taiwan. Moreover, there was no difference in the incidence and severity of GVHD between the allo-sibling HSCT group and the MUD HSCT group, suggesting that there was no difference regarding the impact of GVHD on quality of life. However, one should be cautious that severe acute and chronic GVHD substantially impact the outcome of allogeneic HSCT despite current advanced GVHD prophylaxis and HSCT procedures. The influence of GVHD must be weighed carefully for every patient before performing allogeneic HSCT at CR1.

This study also provides valuable information on treatment of CN-AML in Asian population. A review of the literature indicates limited studies of HSCT in Asian patients with AML during CR1 (28, 29). Sakamaki *et al.* (28) reported the outcome of allogeneic HSCT during CR1 in a Japanese AML population, and the authors concluded that allogeneic sibling HSCT, compared with a no-donor group, improved survival in patients aged 36–50 yrs who had intermediate-risk or poor-risk disease. A more recent report of a Japanese population provided survival data of patients with intermediate-risk AML who underwent allogeneic sibling HSCT (3-yr OS rate of 69%) and autologous HSCT (3-yr OS rate of 74%). However, there was no comparison between these two treatment modalities (29). Our study, which enrolled only patients with CN-AML, also found a survival benefit in allogeneic sibling HSCT. When comparing with the Japan Adult Leukaemia Study Group report (28), there seem to be few ethnic differences between Asians and Westerners with regard to the impact of HSCT on survival (28).

Chen *et al.* (30, 31) studied prognostic factors in patients of different AML subtypes treated at our institute. They identified five factors associated with poor OS in elderly patients with *de novo* AML: (i) PS score of 2–4, (ii) presence of comorbidities, (iii) serum LDH level at least twofold above the upper limit of normal, (iv) extreme leukocytosis (leukocytes $\geq 100 \times 10^9$/L), and (v) marked thrombocytopenia (platelets $\leq 20 \times 10^9$/L). They also identified postremission HSCT and a WBC count index < 20 (WBC index = WBC × [% of marrow blasts/100]) as good independent prognostic factors for OS in patients with AML who had the M2 FAB subtype, t(8;21)(q22;q22). At our institute, this particular subgroup of patients had a prognosis similar to that of patients with CN-AML (31). In the current study focusing on patients with CN-AML at CR1 aged60 yrs or less, we identified the absence of comorbidities and postremission allogeneic HSCT as factors associated with better OS. Compared with the studies mentioned above, there are different prognostic factors associated with OS in different subpopulations, presumably because of the heterogeneous nature of AML. We believe that in addition to using clinical factors to predict prognosis, genetic testing and molecular prognostic markers may help to better elucidate the biology that underlies the heterogeneity of AML.

Subject to the retrospective design, selection bias turned out as a limitation of this study. In addition, the modest sample size of our study limited the statistical power of the comparisons. More importantly, owing to the relatively late introduction of new molecular prognostic markers (such as NPM1, c-kit, and FLT3 genes abnormalities) in our institute, few patients with molecular prognostic markers (15/81 patients) had favorable FLT-3/NPM status, where all of whom had FLT-3/NPM wild type. Moreover, we did not have data for patients with CN-AML at CR1 who directly underwent allogeneic HSCT without any consolidative chemotherapy.

In conclusion, our study suggests that allogeneic HSCT from a sibling donor or secondarily from MUD is the preferred postremission therapy at CR1 for patients with CN-AML who are eligible for HSCT. We suggest that future prospective trials examine the impact of HSCT on patients with CN-AML by using molecular markers to more completely characterize the disease of each patient.

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Conflict of interests

The authors declare no conflict of interest.

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