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Acute myeloid leukemia relapse after allogeneic hematopoietic stem cell transplantation: a retrospective study from a single institution

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Abstract

Objective: The outcomes of patients with acute myeloid leukemia (AML) who relapse after allogeneic hematopoietic stem cell transplantation (allo-HSCT) are poor. However, the risk factors for relapse in this context remain unclear.

Methods: We retrospectively assessed 84 consecutive adult AML patients who underwent allo-HSCT and achieved complete remission (CR). These patients were dichotomized into non-relapse (n = 58) and relapse (n = 26) groups, and the cumulative relapse rates and associated risk factors were examined. We also examined the treatments for and outcomes of patients with AML relapse after allo-HSCT.

Results: Non-CR status before allo-HSCT and high-risk cytogenetics were significant risk factors for AML relapse in univariate analysis, and non-CR status was also identified as a risk factor in multivariate analysis. The cumulative AML relapse rates after allo-HSCT were significantly higher

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in patients with non-CR (70.0%) compared with patients with CR (25.6%). Only 2 of the 26 relapsed patients remained alive on the study-censored day.
Conclusions: Non-CR status before allo-HSCT was a significant risk factor for AML relapse after allo-HSCT. Patients with AML relapse after allo-HSCT had poor outcomes due to a lack of response to salvage remission-induction chemotherapy or treatment-related adverse events.

Keywords
Acute myeloid leukemia, allogeneic hematopoietic stem cell transplantation, relapse, complete remission, cytogenetics, risk factor

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Introduction

The incidence of acute myeloid leukemia (AML) is approximately 1.3 per 100,000 people, making it the most common type of leukemia in adults.[1] Clonal expansion of immature myeloid blasts due to abnormal proliferation and differentiation of hematopoietic stem cells is the primary pathophysiology of AML. The World Health Organization AML diagnostic criteria include myeloblasts accounting for more than 20% of nucleated cells from either peripheral blood or bone marrow.[2] The achievement of complete remission (CR) via remission-induction chemotherapy followed by consolidation chemotherapy is the standard of care for chemotherapy-eligible AML patients.

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is recommended for AML patients with intermediate- or high-risk cytogenetics or genetic mutations after achieving CR. However, although allo-HSCT is associated with improved overall survival (OS),[3] AML relapse occurs in nearly 50% of allo-HSCT recipients in a registry setting, indicating poor outcomes.[4] Some factors have been associated with AML relapse after allo-HSCT. A previous study showed that disease status beyond the first CR at the point of allo-HSCT and without chronic graft versus host disease (GVHD) increased the risk of relapse in pediatric acute leukemia patients.[5]

Treatment for relapsed AML after allo-HSCT varies and may depend on disease- and patient-related characteristics; nevertheless, the outcomes remain poor in most cases.[6] Although high-dose cytarabine followed by donor leukocyte infusion resulted in a CR rate of 47%, the estimated 2-year OS rate was only 19%.[7] Novel agents do not always improve survival. Although some patients with relapsed AML may benefit from salvage azacitidine, this treatment is not recommended for AML or myelodysplastic syndrome relapse after allo-HSCT.[8] Salvage use of venetoclax-based therapy may be another option for relapsed AML after allo-HSCT[9]; however, more evidence is needed to determine its efficacy. A second allo-HSCT is a key treatment for relapsed AML after allo-HSCT. Notably, a second allo-HSCT in CR, an interval of >6 months between first allo-HSCT and relapse, and using a matched sibling donor for the first allo-HSCT have been associated with better outcomes in patients undergoing second allo-HSCT.[10]

The characteristics of adult patients with AML relapse after allo-HSCT vary among populations. In addition, patient outcomes differ depending on the type of relapse

treatment used. The present study aimed to identify risk factors associated with AML relapse in adult patients undergoing allo-HSCT at our institution. We examined the relapse patterns, treatments, and outcomes of adult AML patients undergoing allo-HSCT.

Patients and Methods

Patients

The reporting of this study conformed to the STROBE guidelines for reporting observational studies.[11] We retrospectively reviewed the medical records of consecutive AML patients aged $\geq$20 years who underwent allo-HSCT at Taichung Veterans General Hospital between February 2010 and May 2020. The censored day of data analysis was 31 May 2021. We confirmed CR status by bone marrow examination on day 30 after allo-HSCT.

To evaluate the risk factors for AML relapse after allo-HSCT, we divided the study cohort into non-relapse and relapse groups. Data collection for this retrospective study started in 2010 when data on *FLT3* and *NPM1* mutation statuses were incomplete, and we therefore used the 2008 revision of the World Health Organization classification in the current study.[2] The Institutional Review Board of Taichung Veterans General Hospital approved this retrospective study on 1 July 2021 under the current version of the Declaration of Helsinki (CE21224A). The need for informed consent was waived because of the retrospective nature of the study. All patient details were de-identified.

Definitions and outcome measures

We defined AML relapse as myeloblasts accounting for >5% of nucleated cells in either the bone marrow or peripheral blood. Extramedullary relapse was defined as clinical evidence of histological relapse observed exclusively at extramedullary sites. We defined AML as the cause of death if leukemic cells were present in either the peripheral blood or bone marrow at the time of death. Re-induction therapy was considered as the cause of death in patients who died of complications during remission-induction therapy without evidence of residual leukemia. Regarding the severity of GVHD, acute and chronic GVHD were graded according to the National Comprehensive Cancer Network, Version 2.2020.[12]

For the analysis of follow-up time, the starting day (day 0) was the day of allogeneic hematopoietic stem cell infusion and the end day was the day of death from any cause or 31 May 2021, whichever came first. Cumulative incidence was calculated from day 0 to the day of AML relapse.

Statistical analysis

Continuous variables were analyzed by Mann–Whitney U tests and categorical variables by χ^2 or Fisher's exact tests, as appropriate. Risk factors associated with AML relapse after allo-HSCT were identified using a Cox proportional hazards model and quantified as hazard ratios (HRs) with accompanying 95% confidence intervals (CIs). Patient characteristics, age (in 1-year intervals), disease status before allo-HSCT, cytogenetic risk at AML diagnosis, donor type, conditioning regimen intensity, anti-thymoglobulin (ATG) administration, and GVHD status were included as potential risk factors in univariate analysis. Factors that were significant in univariate analyses were included in the multivariate analysis. The Fine–Gray test was used to compare cumulative relapse rates between groups and to eliminate potential competing risks. All the analyses were conducted using IBM SPSS Statistics

for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). The results were considered statistically significant at $P < 0.05$.

Results

We retrospectively reviewed the medical records of 86 consecutive patients with AML. Two patients with AML relapse within 30 days after transplantation were excluded after bone marrow examination on day 30 after allo-HSCT. Data for 84 patients were therefore included in the analysis. We evaluated cytogenetic risk using the 2017 European Leukemia Network criteria.[13] Only nine (10.7%) patients in our cohort harbored favorable cytogenetics at the diagnosis of AML. Donor types were heterogeneous. Most (48/84; 57.1%) patients were conditioned using myeloablative regimens (Table 1).

Patient demographics in non-relapse and relapse groups

To evaluate the risk factors for AML relapse after allo-HSCT, we divided the study cohort into non-relapse (n = 58) and relapse (n = 26) groups. Patients in the two groups had similar demographic and clinical characteristics. However, significantly more patients in the non-relapse group underwent allo-HSCT in CR1 (75.9% vs. 53.8%, $P = 0.013$) and a significantly higher proportion of patients in the non-relapse group had low-risk cytogenetics compared with the relapse group (75.8% vs. 50.0%, $P = 0.043$) (Table 1).

Risk factors for AML relapse after allo-HSCT

Univariate analysis identified non-CR status before allo-HSCT (HR: 5.04, 95% CI: 2.08–12.20, $P < 0.001$) and high-risk cytogenetics (HR: 2.95, 95% CI: 1.04–8.35, $P = 0.042$) as factors significantly associated with the risk of AML relapse after allo-HSCT. However, age (HR: 1.00, 95% CI: 0.97–1.03), sex (HR: 1.71, 95% CI: 0.78–3.78), *de novo* or secondary AML (HR: 1.26, 95% CI: 0.52–3.01), ATG administration (HR: 0.93, 95% CI: 0.37–2.31), regimen intensity (HR: 1.04, 95% CI: 0.48–2.26), and chronic GVHD (HR: 0.04, 95% CI: 0.00–4.19) were not significantly associated with AML relapse. Multivariate analysis revealed that non-CR status before allo-HSCT (HR: 3.69, 95% CI: 1.10–12.39, $P = 0.035$) significantly increased the risk of AML relapse after allo-HSCT (Table 2).

Cumulative incidence rates of AML relapse after allo-HSCT

The overall cumulative incidence rate of AML relapse after allo-HSCT was 32.9% (Figure 1). Cumulative relapse rates were compared between patients transplanted at CR (n = 73) and non-CR (n = 10) status, and between patients with high-risk (n = 11) and low-risk cytogenetics (n = 57) at AML diagnosis. The cumulative AML relapse rate after allo-HSCT was significantly higher in non-CR compared with CR patients (70.0% and 25.6%, respectively; $P = 0.002$) (Figure 2a). The cumulative relapse rate after allo-HSCT was also higher in patients with high-risk compared with low-risk cytogenetics (47.7% and 24.7%, respectively), but the difference was not significant (Figure 2b).

Treatments and outcomes of relapsed AML after allo-HSCT

Most patients had bone marrow relapse, but extramedullary relapse occurred in 15.4% (4/26) of patients. Three of 26 relapsed patients received palliative care only. Among patients who received intent-to-cure therapy (n = 23), chemotherapy re-induction was the most common

Table 1. Clinical characteristics of patients in the non-relapse and relapse groups.

	All patients (n = 84)		Non-relapse group (n = 58)		Relapse group (n = 26)		P-value
Age, years, median (range)	47.0	(20–73)	47.5	(22–73)	46.5	(20–68)	0.642[§]
Sex, n (%)							0.238[¶]
Male	42	(50.0%)	32	(55.2%)	10	(38.5%)	
Female	42	(50.0%)	26	(44.8%)	16	(61.5%)	
Diagnosis, n (%)							0.249[¶]
De novo AML	64	(76.2%)	46	(79.3%)	18	(69.2%)	
Secondary AML	19	(22.6%)	12	(20.7%)	7	(26.9%)	
Unknown	1	(1.2%)	0	(0.0%)	1	(3.8%)	
Disease status, n (%)							0.013[¶]
CR1	58	(69.0%)	44	(75.9%)	14	(53.8%)	
>CR1	15	(17.9%)	11	(19.0%)	4	(15.4%)	
Non-CR	10	(11.9%)	3	(5.2%)	7	(26.9%)	
Unknown	1	(1.2%)	0	(0.0%)	1	(3.8%)	
Cytogenetic risk, n (%)*							0.043[¶]
Favorable	9	(10.7%)	9	(15.5%)	0	(0.0%)	
Intermediate	48	(57.1%)	35	(60.3%)	13	(50.0%)	
Poor	11	(13.1%)	6	(10.3%)	5	(19.2%)	
Unknown	16	(19.0%)	8	(13.8%)	8	(30.8%)	
Donor type, n (%)							0.568[¶]
MSD	30	(35.7%)	22	(37.9%)	8	(30.8%)	
MUD	17	(20.2%)	9	(15.5%)	8	(30.8%)	
MMUD	11	(13.1%)	8	(13.8%)	3	(11.5%)	
Haploidentical donor	25	(29.8%)	18	(31.0%)	7	(26.9%)	
Unknown	1	(1.2%)	1	(1.7%)	0	(0.0%)	
Conditioning regimen, n (%)							0.865[¶]
Myeloablative	48	(57.1%)	34	(58.6%)	14	(53.8%)	
Reduced intensity	36	(42.9%)	24	(41.4%)	12	(46.2%)	
Acute GVHD, n (%)							0.632[¶]
No	36	(42.9%)	23	(39.7%)	13	(50.0%)	
Grade I–II	35	(41.7%)	25	(43.1%)	10	(38.5%)	
Grade III–IV	13	(15.5%)	10	(17.2%)	3	(11.5%)	
Chronic GVHD, n (%)							0.051[f]
No	75	(89.3%)	49	(84.5%)	26	(100.0%)	
Yes	9	(10.7%)	9	(15.5%)	0	(0.0%)	
Leukocytes >50,000/μL	24	(32.4%)	15	(28.8%)	9	(40.9%)	0.458[¶]
Follow-up, months, median (range)	16.4	(1.1–133.9)	35.6	(1.3–133.9)	5.4	(1.1–51.5)	<0.001[§]

[§]Mann–Whitney U test. [¶]χ^2 test. [f]Fisher's exact test.

AML: acute myeloid leukemia; CR: complete remission; MSD: matched sibling donor; MUD: matched unrelated donor; MMUD: mismatched unrelated donor; GVHD: graft versus host disease.

*According to 2017 European Leukemia Network recommendation.

Age determined at the time of allogeneic hematopoietic stem cell infusion; leukocyte count and disease status determined at the time of diagnosis.

therapeutic strategy, accounting for 82.6% (19/23) of cases (Supplemental Table 1). Two of the four patients with extramedullary relapse received radiotherapy. The overall CR rate was 43.5% (10/23). Notably, the CR rates of patients relapsing within and after 6 months were 33.3% (4/12) and 54.5% (6/11), respectively.

Table 2. Risk factors associated with acute myeloid leukemia relapse after allogeneic hematopoietic stem cell transplantation.

	Univariate			Multivariate		
Characteristic	HR	95% CI	P-value	HR	95% CI	P-value
Age	1.00	(0.97–1.03)	0.963			
Sex (female vs. male)	1.71	(0.78–3.78)	0.181			
Diagnosis						
Secondary vs. *de novo* AML	1.26	(0.52–3.01)	0.607			
Disease status						
Non-CR vs. CR	5.04	(2.08–12.20)	<0.001	3.69	(1.10–12.39)	0.035
Cytogenetic risk*						
High risk vs. non-high risk	2.95	(1.04–8.35)	0.042	2.14	(0.70–6.60)	0.184
Donor type						
MUD vs. MSD	2.51	(0.94–6.71)	0.066			
MMUD vs. MSD	1.06	(0.28–4.00)	0.931			
Haploidentical vs. MSD	1.06	(0.38–2.93)	0.909			
ATG (yes vs. no)	0.93	(0.37–2.31)	0.869			
Condition intensity						
Reduced intensity vs. myeloablative	1.04	(0.48–2.26)	0.916			
Acute GVHD						
Grade I–II vs. no GVHD	0.63	(0.28–1.44)	0.275			
Grade III–IV vs. no GVHD	1.12	(0.32–3.96)	0.862			
Chronic GVHD (yes vs. no)	0.04	(0.00–4.19)	0.173			
Leukocytes >50,000/μL (yes vs. no)	1.75	(0.74–4.10)	0.200			

AML: acute myeloid leukemia; CR: complete remission; MSD: matched sibling donor; MUD: matched unrelated donor; MMUD: mismatched unrelated donor; ATG: anti-thymoglobulin; GVHD: graft versus host disease; HR: hazard ratio; CI: confidence interval.

*According to 2017 European Leukemia Network recommendation.

Four patients received second allo-HSCT. However, only 2 of the 26 relapsed patients were still alive on the study-censored day. AML was the most common cause of death, accounting for 57.7% (15/26) of cases. Re-induction-related deaths occurred in six patients (Table 3).

Discussion

This study found that non-CR status before allo-HSCT and high-risk cytogenetics at diagnosis were significant risk factors associated with AML relapse after allo-HSCT. Furthermore, AML patients undergoing allo-HSCT at non-CR status had a significantly higher risk of relapse than those transplanted at CR status, and only 2 of the 26 relapsed patients remained alive on the study-censored day, regardless of the relapse pattern and therapeutic strategies used.

Relapse remains a critical issue in patients with AML after allo-HSCT. The current study showed a relapse rate of 31.0% (26/84) in a real-life setting. This was similar to the relapse rate reported by Yuda et al.,[14] who found an estimated relapse rate of 37.5% in this patient group. Furthermore, Yuda et al.[14] also demonstrated that 16.4% of relapses occurred at isolated extramedullary sites, consistent with the present findings.

Although systemic salvage re-induction chemotherapy was the primary therapy in

the current study (80.8% of relapsed patients, 21/26), most AML patients who relapse after allo-HSCT either fail to achieve durable remission or experience chemotherapy toxicity.[15] In the present study, 18 of 23 patients undergoing intent-to-cure treatments for relapse eventually died of AML or re-induction-associated toxicities. Novel agents may provide alternative treatments for this patient group, such as mutation-targeting therapies in patients with *FLT3* and *IDH1/2* mutations.[6] However, the ability of mutation-targeting therapies to improve OS in AML patients who relapse after allo-HSCT remains unclear. The present study did not involve FLT3 or IDH1/2 inhibitors for relapsed AML because of a lack of availability of these mutation-targeting therapies. Venetoclax-based regimens represent another potential therapeutic strategy, and one patient in the present study (patient No. 18) achieved CR after receiving venetoclax with low-dose cytarabine.[16] A retrospective study by Aldoss et al.[17] also demonstrated that 30%, 21%, and 12% of relapsed and refractory AML patients achieved CR, CR with incomplete blood count recovery, and a morphological leukemia-free state after treatment, respectively, after treatment with a combination of venetoclax and hypomethylating agents. However, more evidence is required to validate the role of venetoclax-based treatments in patients with AML relapse after allo-HSCT.

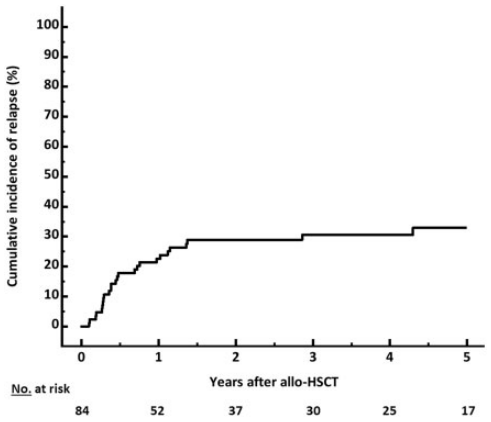

Figure 1. Cumulative incidence rates of acute myeloid leukemia (AML) recurrence after allogeneic hematopoietic stem cell transplantation (allo-HSCT). The overall cumulative incidence rate of AML relapse after allo-HSCT was 32.9%.

Protocols for the management of AML extramedullary relapse after allo-HSCT

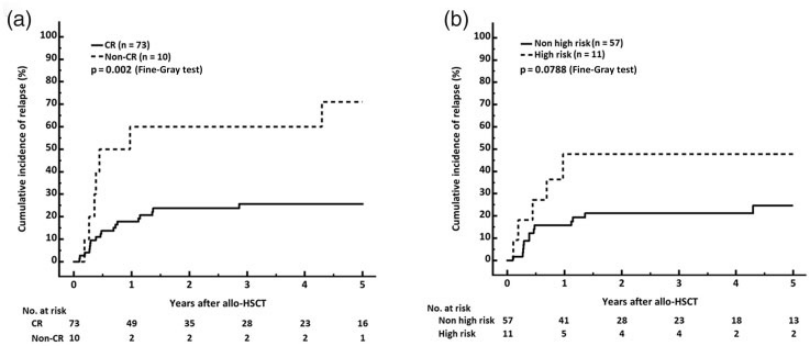

Figure 2. Cumulative incidence rates of relapse from the day of allogeneic hematopoietic stem cell infusion. (a) The cumulative incidence rates of acute myeloid leukemia (AML) relapse after allogeneic hematopoietic stem cell transplantation (allo-HSCT) in patients without (n = 10) and with complete remission (CR) (n = 73) were 70.0% and 25.6%, respectively (P = 0.002). (b) The corresponding values for patients with high-risk (n = 11) and low-risk (n = 57) cytogenetics were 47.7% and 24.7%, respectively (P = 0.079).

Table 3. Patients with acute myeloid leukemia relapse after allogeneic hematopoietic stem cell transplantation.

Patient number	Sex, age (years)	Relapse days	Relapse site	Treatment after relapse	Response to post-relapse treatment	Subsequent allo-HSCT	Current status	Days from relapse to death	Cause of death
1	(M, 49)	103	Bone marrow	C/T re-induction	Refractory	No	Death	59	AML
2	(M, 20)	372	Bone marrow	C/T re-induction	CR	Yes	Alive		
3	(F, 31)	70	Bone marrow	C/T re-induction	Refractory	No	Death	56	AML
4	(F, 27)	251	Breast	Radiotherapy	CR	No	Death	635	AML
5	(M, 62)	418	Chest wall	C/T re-induction	Not evaluated	No	Death	35	Induction death
6	(F, 53)	497	Bone marrow	C/T re-induction	Not evaluated	No	Death	11	Induction death
7	(M, 37)	96	Bone marrow	C/T re-induction	CR	Yes	Death	232	AML
8	(F, 24)	162	Bone marrow	C/T re-induction	Refractory	No	Death	64	AML
9	(F, 68)	130	Bone marrow	Re-induction with azacitidine	Refractory	No	Death	97	AML
10	(M, 67)	101	Bone marrow	C/T re-induction	CR	No	Death	316	AML
11	(F, 36)	140	Bone marrow	C/T re-induction	Refractory	No	Death	57	AML
12	(F, 46)	356	Bone marrow	C/T re-induction	Not evaluated	No	Death	56	Induction death
13	(F, 20)	408	Nasal sinus	C/T re-induction	CR	Yes	Death	272	EBV-related lymphoproliferative neoplasm
14	(F, 37)	98	Bone marrow	C/T re-induction	Not evaluated	No	Death	33	Induction death
15	(M, 45)	501	Bone marrow	C/T re-induction	CR	No	Death	358	AML
16	(M, 45)	174	Bone marrow	C/T re-induction	CR	Yes	Death	146	Infection
17	(F, 50)	139	Bone marrow	C/T re-induction	Refractory	No	Death	39	AML
18	(F, 50)	1569	Bone marrow	Re-induction with venetoclax	CR	No	Alive		
19	(F, 36)	1045	Bone marrow	C/T re-induction	Not evaluated	No	Death	26	Induction death
20	(M, 60)	107	Bone marrow	BSC	Nil	No	Death	103	AML
21	(F, 53)	275	Bone marrow	C/T re-induction	CR	No	Death	166	Infection
22	(F, 47)	67	Bone marrow	BSC	Nil	No	Death	8	AML
23	(M, 60)	264	Bone marrow	C/T re-induction	Not evaluated	No	Death	39	Induction death
24	(M, 27)	168	Myeloid sarcoma	Radiotherapy	CR	No	Death	217	AML
25	(F, 48)	35	Bone marrow	C/T re-induction	Refractory	No	Death	61	AML
26	(F, 65)	39	Bone marrow	BSC	Nil	No	Death	61	AML

AML: acute myeloid leukemia; allo-HSCT: allogeneic hematopoietic stem cell transplantation; M: male; F: female; C/T: chemotherapy; BSC: best supportive care; CR: complete remission; EBV: Epstein–Barr virus.

Note:-Please delete Taiwan from affiliation and corresponding author country details.

remain unclear. Extramedullary relapse is a significant contributor to mortality risk after allo-HSCT for AML, with a 2-year OS rate after extramedullary relapse of only 12%.[18] However, a previous study showed that isolated extramedullary relapse was associated with a significantly better 6-month OS rate than bone marrow relapse (69% vs. 27%; $P < 0.01$), possibly because of the patient's responsiveness to local radiotherapy.[19] The present study revealed a comparable result. Among the four patients with extramedullary relapse in the present cohort, two patients who received local radiotherapy and one patient treated with systemic re-induction chemotherapy achieved CR, while the fourth patient experienced induction-related death. Although local radiotherapy may temporarily eliminate extramedullary relapse, these treatments are not well established. Nevertheless, only 2 of 23 relapsed patients undergoing intent-to-cure salvage therapies in the current study remained alive, suggesting an urgent need for new treatments for AML patients who relapse after allo-HSCT.

Several previous studies have addressed the risk factors associated with AML relapse after allo-HSCT. Non-CR status, high-risk cytogenetics, and specific molecular markers are among the disease-specific risks, while transplant-related factors include less-intense conditioning regimens, profound GVHD prophylaxis, and absence of chronic GVHD.[20] Our study showed that non-CR status and high-risk cytogenetics increased the risk of AML relapse, while the Fine–Gray test revealed that non-CR status before allo-HSCT, but not high-risk cytogenetics, significantly increased the cumulative incidence of AML relapse after allo-HSCT. ATG administration, reduced-intensity conditioning regimens, and chronic GVHD did not significantly increase the risk of AML relapse in the present study. This apparent discrepancy may be accounted for by the small sample size in the present study.

Methods of preventing AML relapse after allo-HSCT remain unclear. Minimal residual disease-triggered azacitidine maintenance for at least 1 year may be considered in high-risk AML cases after allo-HSCT.[21] Sorafenib maintenance for 24 months may also be considered in FLT3-ITD AML patients.[22] The role of other targeting agents and combination therapies with donor lymphocyte infusion are currently under investigation and may contribute to maintenance therapy options after allo-HSCT.[23] However, more evidence is required to establish effective strategies to prevent AML relapse after allo-HSCT.

This study had some limitations, including its small sample size and retrospective design. Moreover, this study did not account for the molecular risks of AML relapse because of a lack of relevant data. Further large, prospective, randomized-controlled studies are therefore required to validate the present findings.

Conclusion

The present study showed that non-CR status before allo-HSCT and high-risk cytogenetics at diagnosis may increase the risk of AML relapse after allo-HSCT. Furthermore, non-CR status was associated with a substantial increase in the cumulative incidence rate of AML relapse. The outcomes of patients with AML relapse after allo-HSCT remain poor, and most patients fail to respond to salvage remission-induction chemotherapy or die as a result of treatment-related adverse events. Further studies are therefore required to identify effective preventive or therapeutic strategies for AML relapse after allo-HSCT, especially in patients at high risk of relapse.

Declaration of conflicting interest

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Chieh-Lin Jerry Teng received an honorarium and consulting fees from Novartis, Roche, Takeda, Johnson & Johnson, Amgen, BMS Celgene, Kirin, AbbVie, and MSD. The other authors declare that they have no conflicts of interest.

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Supplemental material

Supplemental material for this article is available online.

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