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ORIGINAL ARTICLE

Modified cladribine, cytarabine, and G-CSF as a salvage regimen in patients with relapsed/refractory acute myeloid leukemia: a bridge to myeloablative allogeneic hematopoietic stem cell transplantation

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Abstract

Patients with primary refractory or early relapsed acute myeloid leukemia (AML) have a dismal prognosis, and the treatment options for these patients are limited. The present study retrospectively examined the efficacy and toxicities of the combination of cladribine 5 mg/m^2 per day and intermediate-dose cytarabine 1 g/m^2 per day for 5 days and granulocyte colony–stimulating factor (G-CSF) as a salvage treatment in 36 patients with relapsed/refractory AML. Among these, 32 patients had de novo AML, and the remaining 4 patients had secondary AML. The median age for the study cohort was 45.8 years. According to the European LeukemiaNet prognostic index, 5 patients had favorable risk, 18 had intermediate risk, and 11 had poor risk. The complete remission was achieved in 58% of the patients with tolerable toxicities. Fifteen patients underwent stem cell transplantation later. Patients who underwent allogeneic hematopoietic stem cell transplantation had a significantly improved 1-year overall survival compared with those who did not (73% vs. 29%, $P < 0.001$). The results suggested that, as a salvage regimen, modified cladribine, cytarabine, and G-CSF were effective and well tolerated for patients with relapsed/refractory AML, especially for patients who underwent subsequent stem cell transplantation.

Keywords Acute myeloid leukemia · AML · Modified cladribine · Cytarabine and G-CSF · Refractory AML · Relapsed AML

Introduction

Despite the significant progress made in treating acute myeloid leukemia (AML) in the last decade, 20–40% of the patients still did not achieve complete remission (CR) with standard induction chemotherapy, and 50–70% of the patients in the first CR (CR1) may be expected to relapse [1, 2]. For patients relapsing after remission or with primary refractory disease, no standard salvage chemotherapy is available. About 25–50% of these patients receiving salvage chemotherapy achieved CR, and only 11% were still alive at 5 years [3, 4].

Allogeneic stem cell transplantation (ASCT), as the only potentially curative treatment, could significantly prolong the survival of patients with relapsed/refractory AML [5, 6]. However, ASCT was typically used in patients who responded to salvage chemotherapy. Therefore, a response to salvage treatment is essential for improving the overall survival (OS) of this group of patients.

Cladribine is a purine nucleoside analog with established clinical activity in AML. Moreover, it synergizes with cytarabine and may increase the synthesis of the triphosphate of cytarabine (ara-CTP), which is an active antileukemic metabolite of cytarabine [7–9].

In relapsed/refractory AML, the CLAG chemotherapy, consisting of cladribine, cytarabine, and G-CSF, was used as a reinduction therapy and resulted in 50% of CR and a median duration of 24 weeks for all patients and 36.1 weeks for those who achieved CR. However, 25% of patients died early [10]. These results were confirmed by subsequent studies evaluating CLAG chemotherapy in patients with refractory or early relapsed AML [11]. The CR rate was 50%, and the median OS was 34 weeks for all patients and 59 weeks for patients who

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achieved CR, but with 17% early death (ED). A higher dose of cytarabine (2000–3000 mg/m^2) increased toxicity without any improvement in efficacy [12, 13]. A large number of studies have indicated that cytarabine at doses > 1000 mg/m^2 should not be used in induction regimens [14]. Moreover, Joerger et al. found that the higher allelic frequency of the promoter polymorphism -C360G/-C201T in Asians than in Caucasians might predispose Asians to having more cytarabine-associated toxicities [15]. These results suggested that dose adjustment of cytarabine was needed in the CLAG regimen. Therefore, the dosage of cytarabine was decreased to 1000 mg/m^2 to reduce side effects for all Asian patients.

The main objective of the present retrospective study was to evaluate the efficacy and toxicity of the modified CLAG reinduction treatment in patients with relapsed/refractory AML and also the potential for subsequent hematopoietic stem cell transplantation (HSCT).

Patients and methods

Study cohort

A retrospective analysis of 36 patients with relapsed/refractory AML treated with the modified CLAG regimen consisted of cladribine (5 mg/m^2 per day, infused 2 h for 5 days), cytarabine (1000 mg/m^2 per day, infused 4 h for 5 days), and G-CSF (5 μg/kg) beginning the day before chemotherapy and continuing daily until neutrophil recovery was performed at the Yinzhou Hospital Affiliated to Medical School of Ningbo University and The First Affiliated Hospital, Zhejiang University School of Medicine, from January 2015 to January 2018. AML was defined according to the criteria of the World Health Organization [16]. The cytogenetic categories were defined according to the standard International System for Human Cytogenetic Nomenclature criteria [17]. The three-risk group classification (favorable, intermediate, and adverse) was made according to the European LeukemiaNet (ELN) prognostic index [17]. Refractory AML was defined in this study as the persistence of greater than 40% bone marrow (BM) blasts after one cycle of induction chemotherapy or a failure to achieve CR after two cycles of induction chemotherapy. Relapsed AML was defined as patients having > 5% blasts in the BM after achieving CR. Written informed consent was obtained from all patients. The study was approved by the ethics committee of Yinzhou Hospital Affiliated to Medical School of Ningbo University and The First Affiliated Hospital, Zhejiang University School of Medicine.

Treatment

Patients with relapsed/refractory AML were given cladribine 5 mg/m^2 for 2 h intravenously (IV) daily on days 1–5, cytarabine 1 g/m^2 IV for 4 h daily on days 1–5, and G-CSF 5 μg/kg subcutaneously daily on the day before chemotherapy and continuing daily until neutrophil recovery. BM examination was performed on days 28–45 of induction to assess for remission. Patients who achieved partial remission (PR) or CR could continue with the same induction regimen for a second course. After completing none to two consolidation courses, patients who were still in CR or PR were recommended for ASCT based on the availability of a suitable donor and at the discretion of the treating physician, whereas those without a donor were offered autologous HSCT or maintenance therapy.

Response criteria and evaluation

The response was evaluated using BM 28–45 days after the start of modified CLAG. CR was defined as < 5% marrow blasts in BM and normal peripheral count. PR was defined as 5–25% marrow blasts in BM, or a 50% or better decrease in BM blasts, or BM blasts < 5%, but with the presence of Auer rods. Nonremission (NR) was defined when these criteria were not satisfied. ED was defined as death from any cause within 30 days of completion of modified CLAG treatment. Adverse events were assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

Statistical analysis

The study design was a retrospective review, and all patients were analyzed. Patients and their disease were summarized using descriptive statistics. OS was calculated from the first day of modified CLAG administration until death from any cause or time of the last follow-up. The binary data were assessed using the Fisher test. The survival curves of patients were estimated using the Kaplan–Meier method and compared using the log-rank test. Ninety-five percent confidence intervals were calculated using Cox models. A multivariate analysis was performed using Cox regression models for OS. All statistical tests were two sided, with a P value less than 0.05 considered statistically significant. All analyses were performed using SPSS version 22.0 (SPSS Inc., IL, USA).

Results

Patient demographics

A total of 36 patients with relapsed/refractory (14 relapsed and 22 primary refractory to chemotherapy) AML were treated with modified CLAG. The median follow-up time was 10.5 months (range, 1.3–33.3 months). The main clinical and biological characteristics are shown in Table 1. The median age was 45.8 years (range, 21.5–67.9). The sex ratio

Table 1 Characteristics of patients at the time of salvage therapy

Patients (*n*)	36
Sex ratio (male/female), *n*	(20/16), 1.3
Median age, years (range)	45.8 (21.5–67.9)
> 60 years, *n* (%)	6 (1317)
Cytogenetics, *n* (%)	
Favorable	3 (8)
Intermediate	23 (64)
Unfavorable	8 (22)
Not available	2 (6)
FLT3-ITD status, *n* (%)	
ITD	10 (28)
Wild type	21 (58)
Not available	5 (14)
NPM1 status, *n* (%)	
Mutated	9 (25)
Wild type	22 (61)
Not available	5 (14)
Prognosis index, *n* (%)	
Favorable	5 (14)
Intermediate	18 (50)
Unfavorable (25)	11 (31)
Not available	2 (6)
AML type, *n* (%)	
Primary AML	32 (89)
Secondary AML	4 (11)
Disease status, *n* (%)	
Primary refractoriness	22 (61)
Relapse	14 (39)

(male/female) was 1.3. Patients with primary relapsed/refractory AML accounted for 89% of cases, while 11% had secondary AML evolving from myelodysplastic syndrome (three patients) or related to therapy (1 patient). Cytogenetic features were available in 34 patients. Three patients had favorable-risk, 23 had intermediate-risk, and 8 had unfavorable-risk cytogenetics. Further, 18 patients (50%) displayed a normal karyotype. By adding nucleophosmin gene (NPM1), FMS-like tyrosine kinase 3 gene (FLT3) internal tandem duplication (ITD), biallelic mutated CCAAT/enhancer-binding protein-α (CEBPA), and tumor protein p53 (TP53 status), 5 had favorable, 18 had intermediate, and 11 had unfavorable prognostic index according to the ELN.

Efficiency

The overall CR rate was 58%: 64% in refractory and 50% in relapsed AML ($P = 0.418$). The patients in the ELN favorable-risk ($n = 5$), intermediate-risk ($n = 18$), unfavorable-risk ($n = 11$), and not available ($n = 2$) groups had a CR rate of 80%, 56%, 55%, and 50%, respectively. The median OS was 10.8 months (95% CI, 6.0–15.7 months) (Fig. 1a). Two-year OS was 22% (95% CI, 15–30%). Patients in ELN poor-risk category had a similar duration of OS compared with those with favorable or intermediate risk (poor = 15.2 months with 95% CI, 0.9–29.5; favorable or intermediate = 10.8 months with 95% CI, 6.7–14.9%; $P = 0.242$) (Fig. 1b). No significant differences in OS were found between the relapsed (median OS 8.4 months; 95% CI, 0.9–15.9) and refractory (median OS 11.1 months; 95% CI, 6.5–15.7; $P = 0.322$) groups (Fig. 1c). Also, no significant differences in OS were observed on the FLT3 status (median OS for FLT3 wild type, 12.0 months; 95% CI, 4.8–19.2; and median OS for ITD, 8.7 months; 95% CI, 6.2–11.2; $P = 0.355$) (Fig. 1d). However, OS significantly improved in patients who achieved CR (median OS, 16.9 months; 95% CI, 9.6–24.2) compared with those who did not (median OS, 5.1 months; 95% CI, 3.3–6.9; $P < 0.001$) (Fig. 1e). Also, OS significantly improved in younger patients (median OS, 12.0 months; 95% CI, 8.7–15.3) compared with those older than 60 years (median OS, 5.1 months; 95% CI, 3.3–6.9; $P = 0.027$) (Fig. 1f).

Safety

The 36 treated patients developed grade 3–4 neutropenia, thrombocytopenia, and anemia. The median duration of neutropenia < 500/m^2 was 11 days (range, 4–32), and the median duration of thrombocytopenia < 20,000/m^2 was 13 days (range, 8–34). Neutropenia and thrombocytopenia contributed to significant rates of documented infection (64%) and severe bleeding (8%). The most frequently observed nonhematologic side effects (all grade 2 or lower) included diarrhea, mucositis, nausea, periorbital edema, constipation, pericardial effusion, and angina. Only one patient developed grade 3 cardiac insufficiency who was known to have preexisting cardiac disease, and this might not be related to the regimen. Significant hepatic or renal toxicities or treatment-related mortality (TRM) was not noted in the patients. The nonhematologic and hematologic toxicity during salvage therapy is summarized in Table 2.

Allogeneic hematopoietic stem cell transplantation

Overall, 21 patients did not undergo allo-HSCT: 13 of them did not achieve CR, 3 were not considered fit enough, while no donor was identified for the remaining 5 patients. Further, 15 (42%) patients underwent allo-HSCT after achieving adequate disease control; 7 (64%) of 11 patients were in ELN poor-risk category prior to transplant. The patient characteristics at the time of allo-HSCT are summarized in Table 3. The median age was 46.2 years. Moreover, 14 patients achieved CR and 1 achieved PR prior to transplant. Four patients underwent HLA-matched sibling donor (MSD) transplantation, two underwent HLA-matched unrelated donor (URD) transplantation, and nine underwent haploidentical-related donor (HRD) HSCT. Six

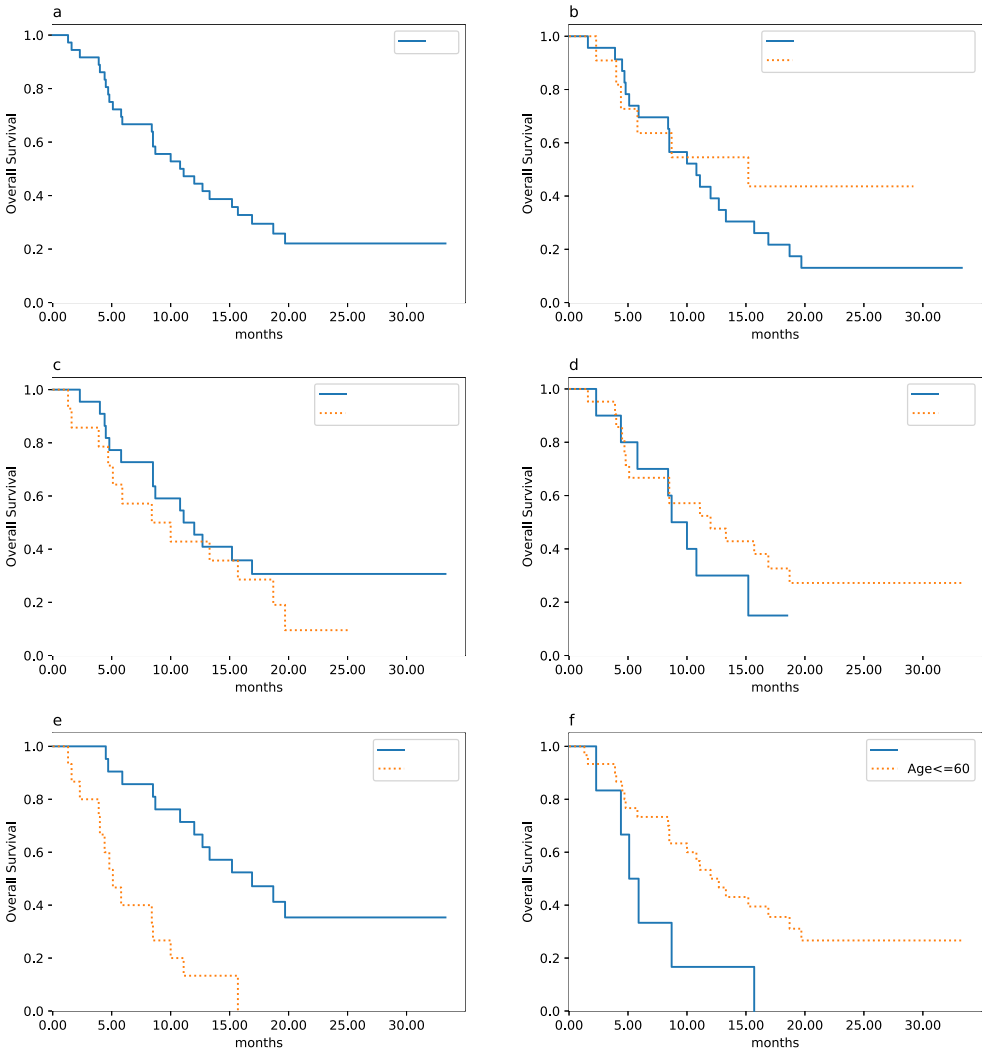

Fig. 1 Overall survival. Kaplan–Meier representation of overall survival. **a** Of all patients in the cohort. **b** Comparing patients according to European LeukemiaNet stratification as ELN poor risk and favorable or intermediate risk. **c** Comparing refractory and relapsed AML. **d** According to FLT3 status. **e** According to the complete remission status after salvage therapy. **f** Comparing patients younger and older than 60 years. *CR* complete remission, *ITD* internal tandem duplication, *WT* wild type

patients experienced grade 3–4 acute graft-versus-host disease, while four patients relapsed after allo-HSCT.

OS was significantly higher in the allo-HSCT group than in those without allo-HSCT ($P < 0.001$) (Fig. 2). One-year OS after allo-HSCT was 73% (95% CI, 61–84%) versus 29% (95% CI, 19–39%) in the absence of allo-HSCT. Two patients died consecutively of grade 4 graft-versus-host disease (GVHD) after allo-HSCT.

In the multivariate analysis, in a model including the age (> 60 years), allo-HSCT, refractory AML, and achievement of CR after modified CLAG, only the performance of allo-HSCT after modified CLAG predicted patient outcome with a hazard ratio (HR) of 4.266 (95% CI, 1.482–12.282; $P = 0.007$) (Table 4).

Discussion

Despite the increasing availability of multiple chemotherapy combinations (cytarabine + mitoxantrone + etoposide or gemtuzumab, and cytarabine + purine analogue ± anthracycline) in patients with relapsed/refractory AML who achieve relatively high CR rates (44–59.4%), the prognosis of these patients is still very poor for most of these regimens that are not associated with substantial CR duration (4.9–9.8 months) or OS (6.2–8.7 months). Also, still no standard cytoreductive regimen exists [18]. Although it is currently unlikely to cure relapsed/refractory AML without allo-hematopoietic cell transplantation (HCT), an effective treatment regimen with less toxicities is urgently needed, which can be used as a bridge to ASCT, the only curative option for relapsed/refractory AML. The CLAG regimen is commonly used as a salvage chemotherapy regimen in patients with relapsed/refractory AML with a CR rate of 50% [10, 11]. The addition of mitoxantrone to the regimen (CLAG-M) resulted in increased CR rate when retrospectively compared with CLAG regimen (58% vs. 50%); however, 7% patients died early [19]. Because of a higher dose of cytarabine (2000–3000 mg/m^2) in induction therapy that increased toxicity without any improvement in efficacy, the modified CLAG regimen

Table 2 Nonhematologic and hematologic toxicity during salvage therapy

Nonhematological toxicity (CTCAE)	Grade 2 or lower, *n* (%)	Grade 3 or higher, *n* (%)
Lung infection	0	12 (33%)
Sepsis	0	3 (8%)
Skin infection	1 (3%)	1 (3%)
Soft tissue infection	1 (3%)	2 (6%)
Catheter-related infection	0	1 (3%)
Cholecystitis	0	1 (3%)
Gum infection	0	1 (3%)
Upper gastrointestinal hemorrhage	0	2 (6%)
Uterine hemorrhage	0	1 (3%)
Heart failure	0	1 (3%)
Diarrhea	3 (8%)	0
Mucositis	2 (6%)	0
Nausea	2 (6%)	0
Periorbital edema	1 (3%)	0
Constipation	1 (3%)	0
Pericardial effusion	1 (3%)	0
Angina	1 (3%)	0
Hematologic toxicity	Median	Range
Days for neutropenia < 500/m^2	11	4–32
Days for thrombocytopenia < 20,000/m^2	13	8–34

CTCAE Common Terminology Criteria for Adverse Events

was employed as an induction therapy and was supposed to reduce toxicity [12, 13].

The present retrospective study evaluated the use of modified CLAG regimen in patients with relapsed/refractory AML. Compared with patients included in previous studies who used the CLAG regimen as an induction therapy in relapsed/refractory AML [11], the patient population in this study was a similar-age (median age, 45.8 vs. 45 years), high-risk population (31% vs. 16–28% unfavorable cytogenetics or FLT3-ITD positive) with secondary AML (11% vs. 10%). The patients had a CR rate of 58% after salvage treatment (64% in refractory and 50% in relapsed AML), which was higher than the results obtained with the CLAG regimen [11]. This might be because the modified CLAG regimens at intermediate-dose levels of 1000 mg/m^2 were as effective as the CLAG regimens and well tolerated without any TRM associated with the salvage therapy. The TRM was 17–25% for the CLAG regimen [10, 11] and 9–20% for conventional chemotherapy agents [4, 20–22]. However, the number of patients in this study was small, and a selection bias in choosing candidates treated with the modified CLAG regimen could not be excluded. Such a bias might have contributed to the high CR rates observed in this analysis.

In addition to this encouraging response rate, the toxicity profile of modified CLAG regimen was generally well tolerated in the present study, and no patient experienced TRM. The improved standards of supportive care, reduced neutropenia associated with CLAG induction (11% vs. 17%) [11], initiation of salvage treatment at an earlier stage of the disease, and reduced dose of cytarabine might explain the benefits of modified CLAG regimen without any ED. The complications were severe but manageable. Mild nonhematological toxicity mainly included mucositis, nausea, and constipation, and only one patient developed grade 3 cardiac insufficiency who had preexisting cardiac disease (may not be modified CLAG associated), which was lower than that associated with the CLAG regimen observed in an analysis on 50 patients with primary resistant AML and 8 with early relapsed AML [11].

The results suggested that the modified CLAG regimen might be particularly useful for high-risk disease characteristics, especially as a bridge to HSCT. In this study, the survival of patients with ELN poor risk was at least as long as the survival of those with intermediate or favorable risk (median, 15.2 vs. 10.8 months; $P = 0.242$). The prolonged survival in these patients might be related to high CR rates (55%) for the modified CLAG regimen in patients with poor risk, and 64% of ELN poor-risk patients were able to undergo subsequent transplantation. Also, those with FLT3 wild type had a similar OS relative to patients with FLT3-ITD AML (median, 12.0 vs. 8.7; $P = 0.355$). Similar findings were seen in a series of 3324 adult patients with relapsed/refractory AML treated in the different trials [23]. In addition, Libura observed that cladribine could abolish the negative effect of FLT3-ITD on the survival of normal-karyotype patients with AML [24]. Additionally, the median survival of all patients was slightly better in the present study (10.8 months longer) compared with those with relapsed/refractory AML treated with the CLAG regimen

Table 3 Characteristics of allografted patients after salvage therapy

Patients (*n*)	15
Sex ratio (M/F), *n*	(6/9), 0.67
Median age, years (range)	46.2 (21.5–60.7)
> 60 years, *n* (%)	2 (13)
TRM, *n* (%)	1 (7)
Death, *n* (%)	6 (40)
Primary refractoriness	11 (73)
Relapse	4 (27)
Donor, *n* (%)	
MSD	4 (27)
URD	2 (13)
HRD	9 (60)
Acute GVHD > grade 2, *n* (%)	6 (40)
Post-ASCT relapse, *n* (%)	4 (27)

ASCT allogeneic stem cell transplantation, *GVHD* graft-versus-host disease, *HRD* haploidentical related donor, *MSD* matched sibling donor, *TRM* treatment-related mortality, *URD* unrelated donor

(median, 34 weeks). These differences might be related to treatment with modified CLAG, which was associated with a higher rate of achieving CR compared with those treated with CLAG (58% vs. 50%) and a higher proportion of patients treated with modified CLAG undergoing subsequent HCT compared with those treated with CLAG (42% vs. 21%) [11].

These improved responses were achieved in patients with relapsed/refractory AML and correlated with the ultimate goal of reinduction to serve as a bridge to potentially curative HSCT. The outcomes for allo-HSCT for AML were superior when the marrow had a lower leukemia burden with a negative minimal residual disease (MRD) assessment before allogeneic HSCT [25, 26]. In the present study, 42% of all patients, after intensive salvage therapy with lower BM blast counts, were able to undergo transplantation, and 7 of 15 had ELN poor-risk disease. After 1 year, 73% of these patients

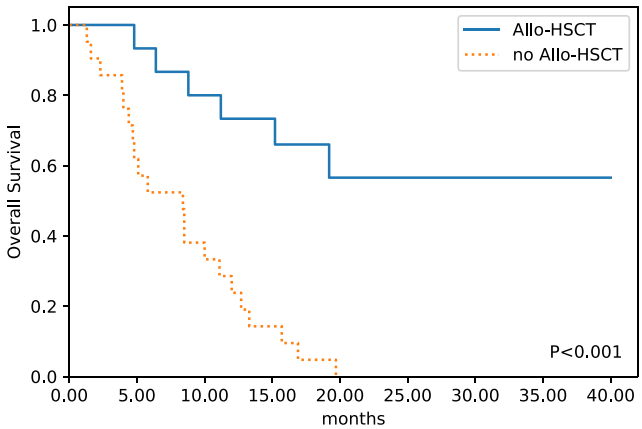

Fig. 2 Kaplan–Meier representation of overall survival comparing allografted patients versus non-allografted patients. *Allo-HSCT* allogeneic hematopoietic stem cell transplantation

Table 4 Multivariate analysis of risk factors of OS post-HSCT

Variable	Adjusted HR (95% CI)	*P* value
> 60 years vs. ≤ 60 years	0.706 (0.223–2.234)	0.554
CR vs. no CR	2.331 (0.844–6.433)	0.102
Primary refractoriness vs. relapse	0.763 (0.319–1.826)	0.544
allo-HSCT vs. non-allo-HSCT	4.266 (1.482–12.282)	0.007

CR complete remission, *allo-HSCT* allogeneic hematopoietic stem cell transplantation

survived, which was consistent with the literature data [27]. Allo-HSCT had a role in the treatment of relapsed/refractory AML either as a salvage therapy or as a subsequent therapy following CR2 achieved by salvage chemotherapy.

In the present study, no prognostic factors were identified except for allogeneic transplant in the multivariate analysis. For patients with ELN classification, FLT3 status, and age older than 60 years, the achievement of CR after modified CLAG treatment seemed to lose its prognostic value. Hence, allogeneic transplant was a prognostic factor in this subgroup of patients with relapsed/refractory AML. However, the present study was a retrospective study having several limitations such as a small number of patients and the high heterogeneity of patient characteristics.

In conclusion, the results of this study suggested that lower doses of Ara-C produced similar remission frequency as higher doses for relapsed/refractory AML in the Chinese population and could be used as a bridge to allo-HSCT, particularly in high-risk patients.

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Compliance with ethical standards

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

Ethical approval This study was conducted in accordance with the principles of the Declaration of Helsinki and approved by the ethics committee of the institution.

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