Increasing aclarubicin dosage of the conventional CAG (low-dose cytarabine and aclarubicin in combination with granulocyte colony-stimulating factor) regimen is more efficacious as a salvage therapy than CAG for relapsed/refractory acute myeloid leukemia

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Abstract

The efficacy and safety of a modified CAG (low-dose cytarabine and aclarubicin in combination with granulocyte colony-stimulating factor) regimen with an increased aclarubicin dosage [high-dose (HD)-CAG] were observed in 145 patients with relapsed/refractory (R/R) acute myeloid leukemia (AML) and compared to the results of 172 patients treated with a conventional CAG regimen. The HD-CAG regimen showed both a higher complete remission (CR) rate (60.7% vs. 46.5%, $P=0.013$) and overall response (OR) rate (74.5% vs. 63.4%, $P=0.039$) than CAG. For patients aged <60 years, HD-CAG manifested an efficacy advantage over the CAG regimen (62.6% vs. 47.4%, $P=0.015$). The 4-year overall survival (OS) rate was $30.3\% \pm 13.2\%$ with a median survival time of 19.0 ± 5.4 months for patients re-induced with the HD-CAG regimen, which showed no significant difference compared to the CAG regimen (with a 4-year OS rate of $18.2\% \pm 5.3\%$ and a median survival time of 16.0 ± 3.6 months, $P=0.485$). The main adverse effect was myelosuppression; platelet recovery over $50 \times 10^9/L$ was extended by the HD-CAG regimen (15 days vs. 10 days of the CAG regimen, $P=0.003$), which was tolerable and manageable. HD-CAG can safely improve efficacy compared to the CAG regimen and thus serves as an alternative treatment for R/R AML.

Keywords: Acute myeloid leukemia; CAG protocol; Relapse; Refractory; Salvage therapy

1. Introduction

Despite the considerable advances that have been made in the treatment of acute myeloid leukemia (AML) in recent decades, only one third of cases (except for acute promyelocytic leukemia) are cured [1], and most suffer relapse or primary refractory (R/R). For these patients, the probability of achieving complete remission (CR) becomes lower, indicating an extremely challenging prognosis. Establishing regimens to achieve CR and then administering allogeneic hematopoietic stem cell transplantation (allo-HSCT) are both of importance for long-term survival [2]. The therapeutic options for re-induction include a second chemotherapy course identical to the first, dose escalation and a total therapy change. However, there is no standard regimen for R/R AML patients after conventional chemotherapy.

The utilization of anthracycline is considered to be indispensable by most study groups. A regimen containing granulocyte colony-stimulating factor (G-CSF) priming the combination of low-dose cytarabine (Ara-C) and aclarubicin, termed the CAG regimen, was first reported by a Japanese group in 1995 [3]. Over the next 20 years, the CAG regimen demonstrated significant benefits for AML and myelodysplastic syndrome (MDS) [4, 5]. For R/R AML patients, the CAG regimen induces a relatively higher CR rate [6-8]. Ideally, the salvage chemotherapy should induce a high remission rate with an acceptable toxicity profile and allow more patients to proceed to allo-HSCT, which is the only curative option for R/R AML. Efforts were made to improve the efficacy of the CAG regimen among institutions, including increasing the aclarubicin dosage [9] and combining it with etoposide, mitoxantrone and clofarabine [10-12].

We have found that increasing the aclarubicin dosage in the CAG regimen shows high efficacy and tolerable toxicity [9]. By enrolling a relatively large number of patients, we retrospectively investigated the clinical efficacy and safety of aclarubicin dosage increases with the CAG regimen, that is, a high-dose CAG regimen (HD-CAG regimen) compared with a conventional CAG regimen at our center.

2. Materials and methods

2.1 Patients and eligibility

Hospitalized patients with R/R AML were eligible (patients with acute promyelocytic leukemia were excluded). All diagnoses were confirmed by central bone marrow (BM) cytology examination and immunophenotyping, as well as cytogenetic and molecular analyses according to the World Health Organization (WHO) classification criteria. Based on chromosomal and mutation analyses, the patients were classified into three distinct prognostic categories: better-risk, intermediate-risk and poor-risk according to National Comprehensive Cancer Network (NCCN) guideline version 1.2014 for AML. Basically, better-risk refers to t (16; 16)/ inv (16) / t (8; 21) / t (15; 17) cytogenetic changes, normal cytogenetics with the NPM1 mutation, and normal cytogenetics with an isolated biallelic CEBPA mutation in the absence of FLT3-ITD. Intermediate-risk includes normal / +8 alone / t (9; 11) / other non-defined cytogenetics and molecular abnormalities including t (8; 21)/ inv16 / t (16; 16) with a c-KIT mutation. Poor-risk was defined as complex (≥ 3 clonal chromosomal abnormalities) /monosomal karyotype / -5 / 5q- / -7/ 7q-/11q23/ inv(3)/ t(3; 3)/ t(6;9)/ t (9;22) and normal cytogenetics with an FLT3-ITD mutation.

Any evidence of AML in the peripheral blood and BM, as well as extramedullary disease, was defined as relapse. Refractory AML was defined as not achieving CR after 2 courses of standard daunorubicin plus Ara-C (DA) (45 mg/m²/day daunorubicin on days 1-3 and 100 mg/m²/day cytarabine on days 1-7) or an equivalent anthracycline-based induction regimen. Multiple relapse (≥ 2) and MDS transformed (MDS-t) AML were also considered as refractory AML [13]. No exclusion was made on the basis of performance status; cardiac, pulmonary, hepatic or renal function; or concomitant active infection.

The selection of re-induction regimens was determined by the treating physicians. This study was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University and the Second People's Hospital of Huai'an and was conducted in accordance with the Declaration of Helsinki. All patients gave written informed consent.

2.2 Treatment and supportive care

The conventional CAG regimen consisted of 10 mg/m² Ara-C injected subcutaneously every 12 h on days 1-14, 5-7 mg/m² aclarubicin injected intravenously daily on days 1-8, and 200 µg/m² G-CSF administered subcutaneously on days 1-14. G-CSF was first administered immediately before the first injection of Ara-C and was ceased 12 h before the last injection of Ara-C. G-CSF was administered subcutaneously unless the white blood cell (WBC) count was $\geq 20 \times 10^9/L$. In patients treated with the HD-CAG regimen, 5-7 mg/m²/day aclarubicin was prolonged from 8 days to 14 days. Ara-C and G-CSF were administered as mentioned above.

Blood cell counting was performed daily. Liver and kidney function were monitored every week. If the hemoglobin and platelet counts dropped below 60 g/L and $20 \times 10^9/L$, respectively, blood transfusion was administered. Appropriate antibiotics were utilized according to the drug sensitivity test when symptoms of infection appeared.

Consolidation therapy varied among patients due to patient FAB subtype, age, and systemic status. Basically, allo-HSCT was strongly recommended as the primary choice if the condition was eligible after CR. For those who did not receive allo-HSCT, the younger patients (<60 years) were treated with high-dose Ara-C (HD-Ara-C)/ intermediate dose Ara-C (ID-Ara-C)/ fludarabine plus Ara-C (FA)/ daunorubicin plus Ara-C (DA)/ idarubicin plus Ara-C (IA)/ mitoxantrone plus Ara-C (MA)/ homoharringtonine plus Ara-C (HA) and the CAG regimen, while the older patients (≥ 60 years) were treated with the DA/IA/HA/MA/CAG regimen.

2.3 Evaluation of efficacy and toxicity

CR was defined as $\leq 5\%$ BM blasts with a neutrophil count of more than $1.5 \times 10^9/L$, a platelet count of more than $100 \times 10^9/L$, and no evidence of circulating or extramedullary leukemic cells. Partial remission (PR) was defined as $>5\%$ blasts but $<15\%$ in the BM. OR was defined as CR plus PR. BM aspiration was carried out within 4 weeks after therapy.

Adverse events were monitored using a WHO score [14]. Hematological and

non-hematological toxicity were observed and recorded by evaluating the blood cell count, biochemical parameters and other related laboratory examinations.

2.4 Statistical analysis

Patients who died within 8 weeks after the start of re-induction chemotherapy were considered as early deaths (ED), and the duration of overall survival (OS) was calculated from the re-induction treatment to the date of the last follow-up or death, regardless of the reason of death. The difference between patient subsets was analyzed by the Chi-squared test for categorical variables and by the t-test or Kruskal-Wallis exact test for continuous variables. Survival data were analyzed by means of the log-rank test, and survival curves were made using the Kaplan-Meier method. Cox logistic analysis was applied to identify significantly independent factors for OS. All of the data were analyzed with SPSS 16.0 software (SPSS, Inc, Chicago, IL, USA). All *P* values were 2-sided and were considered significant when <0.05 .

3. Results

3.1 Characteristics of the patients

From February 2007 to September 2014, we sequentially recruited 317 patients who were diagnosed with R/R AML and had undergone CAG-based re-induction therapy in the First Affiliated Hospital of Soochow University and the Second People's Hospital of Huai'an City. Among these patients, 172 patients were treated with a conventional CAG regimen (Group A) and 145 patients (previously reported 37 patients [9] were also included) with the HD-CAG regimen (Group B). The clinical characteristics of the patients are summarized in Table 1. No significant differences were found for gender, age, FAB subtype, blood cell count before re-induction, cytogenetic risk classification, disease status and post-induction therapy between Group A and Group B. The median duration of first CR for relapsed patients was

7.5 months (Group A) and 7 months (Group B), with no significant difference detected. After the CAG-based re-induction therapies, 37 patients in Group A and 43 patients in Group B received allo-HSCT as a further treatment.

3.2 Treatment response

After one course of therapy, 80 of 172 patients in Group A and 88 of 145 patients in Group B achieved CR, with a CR rate of 46.5% and 60.7%, respectively. Significantly different CR rates between Group A and Group B were revealed ($P=0.013$) (Table 2). There were 109 patients in Group A and 108 patients in Group B achieving OR, yielding OR rates of 63.4% and 74.5%, respectively, with higher OR rates in Group B than Group A ($P=0.039$).

Patients aged <60 years accounted for the majority of the two groups, and for these younger patients, those in Group B (77/123, 62.6%) acquired a higher CR rate compared to Group A (74/156, 47.4%) ($P=0.015$) while showing a similar OR rate when compared to Group A (73.2% vs. 65.4%, $P=0.193$). As for elderly patients aged ≥ 60 years, re-induction with different CAG regimens showed no significant difference for CR rate (40.0% of Group A vs. 50.0% of Group B, $P=0.738$) or OR rate (81.8% vs. 53.3%, $P=0.080$).

A relatively larger portion of relapsed AML patients in Group B achieved CR (59.3% vs. 42.6% of Group A), but no significance was detected ($P=0.112$). The difference in OR rate was also found to be insignificant (57.4% of Group A vs. 74.1% of Group B, $P=0.094$). In addition, no significance for CR/ OR rates was observed in refractory AML patients between groups, with CR rates of 48.0% for Group A and 56.0% for Group B ($P=0.271$) and OR rates of 65.6% for Group A and 72.5% for Group B ($P=0.302$). Further analysis of relapsed and refractory AML to different re-induction regimens was carried out. A comparable CR rate (42.6% vs. 48.0%, $P=0.608$) and OR rate (57.4% vs. 65.6%, $P=0.376$) for relapsed and refractory AML, respectively, in Group A were revealed. A similar result was found for relapsed and refractory AML in Group B, with a respective CR rate of 59.3% vs. 56.0% ($P=0.731$) and an OR rate of 74.1% vs. 72.5% ($P=0.839$), suggesting no difference between regimens in terms of efficacy against R/R AML. Moreover, subgroups of risk level assumed a similar response to different CAG treatment protocols, as shown in Table 2. Although

relatively higher CR/OR rates in different risk groups were found in Group B, there was no significant difference compared with Group A.

3.3 Adverse effects

The most common adverse effect was myelosuppression. The incidence of grade 3 or 4 hematological toxicity was similar among groups, with 90.1% (155/172) in Group A and 92.4% (134/145) in Group B ($P=0.553$). The respective median duration of neutropenia (neutrophils $<0.5 \times 10^9/L$) was 7 days and 9 days for each group, respectively ($P=0.066$). As for the median time of platelet recovery over $50 \times 10^9/L$, Group B showed an extended platelet recovery duration compared with Group A (15 days vs. 10 days, $P=0.003$). However, the incidence of grade 3 or 4 hemorrhage was comparable between groups, with 1 patient in Group A and 4 patients in Group B (0.6% vs. 2.8%, $P=0.183$). Grade 3 or 4 infectious toxicity was not different between groups, with an incidence of 4.1% in Group A and 7.6% in Group B ($P=0.225$). In addition, the ED rates between groups were low and showed no significant difference, as shown in Table 3.

Non-hematological side effects were mild. Only 3 patients in Group A and 1 patient in Group B developed grade 1 or 2 cardiac dysfunction. Transient laboratory evidence of self-limiting grade 1 or 2 hepatic dysfunction was observed in 23 patients in Group A and 20 patients in Group B. Renal dysfunction during re-induction seldom occurred, and only 2 patients with grade 1 or 2 renal dysfunction in Group B were noted. Grade 3 or 4 gastrointestinal side effects were rarely observed, owing to the prophylactic antiemetic drug administration. No significant difference in the above side effects was revealed, as shown in Table 3. All adverse effects were resolved quickly with supportive treatment.

3.4 Survival

The terminal point of the follow-up period was September 30th, 2014, and the median follow-up period duration in Group A and Group B was 8 months (range, 1-86 months) and 5 months (range 1-53 months), respectively. A relatively higher 4-year OS rate in Group B was

revealed, as compared to Group A ($30.3\% \pm 13.2\%$ vs. $18.2\% \pm 5.3\%$), with a median survival time of 19.0 ± 5.4 months (16.0 ± 3.6 months of Group A), but no significant difference was obtained ($P=0.485$) (Fig. 1). By multivariate analysis, among the potential factors influencing OS between Group A and Group B, disease status ($P=0.026$), re-induction efficacy ($P=5.695E-7$) and post-induction therapy ($P=1.617E-6$) were revealed as independent factors, but the different re-induction groups did not show any significance for OS ($P=0.526$) (Table 4).

For patients aged <60 years in Group B, the median survival time was 19.0 ± 6.6 months and the 4-year OS rate was $32.7\% \pm 14.1\%$, which manifested no statistical advantage over Group A, with a median survival time of 21.0 ± 3.8 months and a 4-year OS rate of $16.3\% \pm 5.8\%$ ($P=0.098$) (Fig. 2A). As for patients aged ≥ 60 years, a median survival time of 8.0 ± 1.9 months with a 2-year OS rate of $13.3\% \pm 8.6\%$ and a median survival time of 10.0 ± 6.2 months with a 2-year OS rate of $19.8\% \pm 17.3\%$ for Group A and Group B were obtained, respectively, although no significant difference was revealed ($P=0.595$) (Fig. 2B).

Among patients administered allo-HSCT after achieving CR, there was a trend showing that Group B obtained a higher 4-year OS rate ($75.5\% \pm 9.0\%$) than Group A ($32.9\% \pm 12.0\%$), but no significant difference was detected ($P=0.200$) (Fig. 3A). Moreover, patients who were consolidated with chemotherapy after re-induction therapy in each group showed a similar OS outcome, which manifested as a median survival time of 10.0 ± 1.5 months with a 3-year OS rate of $7.6\% \pm 4.0\%$ for Group A and a median survival time of 10.0 ± 1.3 months with a 3-year OS rate of $11.3\% \pm 9.0\%$ for Group B ($P=0.962$) (Fig. 3B).

4. Discussion

Regardless of the extent to which knowledge of AML has increased in recent years, R/R AML is considered the most important adverse prognostic factor and remains a challenge in clinical strategies due to the poor response to chemotherapy and short survival time of patients [15, 16]. The CAG regimen, which has become popular in China for the treatment of MDS and AML patients, offers an alternative approach and is reported to provide a CR rate

of 44.4%-60.1% for R/R AML [4, 8]. However, the remaining 50% of patients do not benefit from the conventional CAG regimen. Therefore, efforts to modify the CAG regimen should continue, specifically focused on increasing the CR rate and extending the survival time for R/R AML patients.

Aclarubicin, the anthracene nucleus antibiotic, is a cell cycle nonspecific anticancer drug. In the CAG regimen, this drug plays a role in inducing apoptosis of blast cells by directly intercalating into DNA base pairs and preventing mRNA formation [17, 18]. We suspected that increasing the routine dosage of aclarubicin might potentially improve the response of R/R AML patients, and our preliminary report suggested a good efficacy and safety profile after enrolling 37 patients [9]. In the present study, we analyzed the efficacy of a modified CAG regimen by increasing the aclarubicin dosage and made a comparison with the conventional CAG regimen; to our knowledge, this study represents the largest series reported for R/R AML. The CR rates of the CAG (46.5%) and HD-CAG (60.7%) regimens were comparable to those previously reported [8, 9], and the HD-CAG regimen showed an efficacy advantage over the conventional regimen. HD-CAG also displayed better efficacy than other intensive salvage therapies, such as HD-Ara-C with a reported CR rate of 32% [19] and FLAG with a CR rate of 48% [20], although the clinical settings of each trial were not directly comparable. Impressively, the HD-CAG regimen manifested a selectively better response in younger patients, yielding a CR rate of 62.6% and an OR rate of 73.2%. On the other hand, for elderly patients aged ≥ 60 years, a similar response was obtained regardless of whether the aclarubicin dosage was increased or not. These data indicated that HD-CAG had a better therapeutic effect on R/R AML, especially for younger patients. This result carries important implications, as more R/R AML patients can achieve CR and have the opportunity to proceed to allo-HSCT, which represents the only curative option. Nevertheless, for elderly R/R AML patients, HD-CAG still showed no efficacy improvement, which could be attributed to the extremely difficult treatment of R/R AML in the elderly and the relative small number of these patients in our study. Although we obtained a higher efficacy with CAG regimens for difficult-to-treat subgroups (with a CR rate of 40.0% for the CAG regimen and 50.0% for the HD-CAG regimen) compared to previous studies using the FLAG regimen (ranging from 30%-36%) [21, 22], a direct comparison could not be made. Efforts to identify

subgroups based on treatment benefit are underway; however, in our study, no priority for the HD-CAG regimen was revealed among different risk groups.

According to current research, G-CSF promotes cells in the G0 phase into the proliferative phase through interactions with the G-CSF receptor (G-CSFR), which enhances the effect of Ara-C and anthracyclines in leukemia cells. Some preliminary results from our experiment in ALL cell lines exhibited G-CSFR expression on the cell surface [23], and we speculate that a similar mechanism may contribute to the effect of the CAG protocol on R/R AML. In addition, the HD-CAG regimen increases the aclarubicin concentration in the blood circulation and heightens the apoptotic effect in leukemic cells, which may account for its good response in R/R AML patients. Further mechanistic studies are required to elucidate this effect.

Despite a better CR rate after HD-CAG treatment, the 4-year OS rates were similar between the two regimens. In addition, distinct age subgroups showed similar results, and most patients suffered relapse during the follow-up period. In a clinical trial conducted by Wierzbowska et al. [24] of 118 R/R AML patients, 70% relapsed or died within 4 years, suggesting a high relapse risk after the second CR and a poor outcome in the AML setting. A similar result was noted between patients administered allo-HSCT and chemotherapy consolidation subgroups. Indeed, most salvage therapies are intended to maximally “debulk” the disease burden prior to allo-HSCT; however, minimal residual disease (MRD) could represent the origin of secondary relapse after allo-HSCT, indicating a poor prognosis. Therefore, an MRD test may be prognostic of OS [25]. Our current results indicated that CAG and HD-CAG played a limited role in minimal residual leukemia. On the other hand, however, the median follow-up periods for both regimens were short (with 8 and 5 months for the CAG and HD-CAG regimens, respectively), which could have influenced the evaluation of OS and underestimated the benefit of the HD-CAG regimen. Therefore, continuous follow-up of patients is needed to explore the benefit of the HD-CAG regimen.

The attractive safety profile of HD-CAG, which showed tolerable and mostly reversible side effects, was also noted in our study. Despite the extended platelet recovery time after re-induction with the HD-CAG regimen, the incidence of grade 3 or 4 hematological toxicity and hemorrhage was similar between groups. We admitted all of our patients to a laminar airflow room during the re-induction cycle, and all patients received blood transfusion

support according to blood cell count evaluation. Non-hematological toxicity was acceptable, and routine supportive therapy was sufficient to control this issue. Therefore, the toxicity associated with the HD-CAG regimen was acceptable.

In summary, the results of our preliminary observations suggest that the HD-CAG regimen shows significant potential as salvage therapy for R/R AML, improves the efficacy of treatment (especially for younger patients) compared to the CAG regimen, and increases the opportunity for these patients to proceed to allo-HSCT. No statistically significant difference in the 4-year OS rate between groups was demonstrated, and the tolerability profile was acceptable. In conclusion, the HD-CAG regimen is expected to serve as a bridge between R/R AML and allo-HSCT. Comprehensive, large-cohort and head-to-head clinical trials and relevant mechanistic studies should be performed to gain a precise understanding of the HD-CAG regimen as a salvage treatment for R/R AML.

Disclosure Statement

We declare that we have no conflict of interest.

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Fig. 1

Fig. 2

Fig. 3

Figure legends:

Fig. 1 Cumulative rates of overall survival for patients treated with CAG-based regimens. No significant difference was detected between Group A and Group B ($P=0.485$).

Fig. 2 Cumulative rates of overall survival for distinct age subgroups treated with CAG-based regimens. **(A)**, patients aged <60 years ($P=0.098$); **(B)**, patients aged ≥60 years ($P=0.595$).

Fig. 3 Cumulative rates of overall survival for different consolidation therapy subgroups after achieving complete remission. **(A)**, allogeneic hematopoietic stem cell transplantation subgroups ($P=0.200$); **(B)**, chemotherapy consolidation subgroups ($P=0.962$).

Tables:

Table 1. Patients Characteristics

Characteristics	Group A ^a	Group B ^a	<i>P</i> value
Total number	172	145	
Age, n (%)			0.121
< 60 years	156 (90.7)	123 (84.8)	
≥ 60 years	16 (9.3)	22 (15.2)	
Median age (range)	40 (13-79)	42 (14-71)	
Sex, n (%)			0.822
Male	90 (52.3)	78 (53.8)	
Female	82 (47.7)	67 (46.2)	
FAB subtypes, n (%)			0.175
M0	5 (2.9)	3 (2.1)	
M1	21 (12.2)	14 (9.7)	
M2	63 (36.6)	55 (37.9)	
M4	31 (18.0)	29 (20.0)	
M5	29 (16.9)	33 (22.8)	
M6	10 (5.8)	9 (6.2)	
MDS-t ^b	13 (7.6)	2 (1.4)	
Blood cell count before re-induction			
WBC ^c (×10 ⁹ /L, mean ± SD)	3.4 ± 5.0	5.7 ± 6.3	0.067
PLT ^c (×10 ⁹ /L, mean ± SD)	56.0 ± 70.5	66.3 ± 60.7	0.475
HB ^c (×g/L, mean ± SD)	78.6 ± 18.4	83.0 ± 21.4	0.290
Cytogenetic risk group, n (%)			0.101
Low risk	32 (18.6)	18 (12.4)	
Intermediate risk	94 (54.7)	96 (66.2)	
High risk	46 (26.7)	31 (21.4)	
Disease status, n (%)			0.069
Relapse	47 (27.2)	54 (37.2)	
Refractory	125 (72.8)	91 (62.8)	
Duration of first complete remission, months (range)	7.5 (1–36)	7 (1–34)	0.831
Post-induction therapy, n (%)			0.119
Allo-HSCT ^d	37 (21.5)	43 (29.7)	
Chemotherapy	135 (78.5)	102 (79.3)	

^a Group A, CAG re-induction group;

Group B, high dose CAG regimen (HD-CAG) re-induction group;

^b MDS-t, myelodysplastic syndrome (MDS) transformed;^c WBC, white blood cell

PLT, platelet

HB, hemoglobin;

^d Allo-HSCT, allogenic hematopoietic stem cell transplantation.

Table 2. Responses after re-induction therapy of CAG-based regimens

Variable	Group A ^a	Group B ^a	<i>P</i> value
Total			
CR ^b , n (%)	80 (46.5) *	88 (60.7) *	0.013
OR ^b , n (%)	109 (63.4) *	108 (74.5) *	0.039
< 60 years			
CR, n (%)	74 (47.4) *	77 (62.6) *	0.015
OR, n (%)	102 (65.4)	90 (73.2)	0.193
≥ 60 years			
CR, n (%)	6 (40.0)	11 (50.0)	0.738
OR, n (%)	8 (53.3)	18 (81.8)	0.080
Relapse			
CR, n (%)	20 (42.6)	32 (59.3)	0.112
OR, n (%)	27 (57.4)	40 (74.1)	0.094
Refractory			
CR, n (%)	60 (48.0)	51 (56.0)	0.271
OR, n (%)	82 (65.6)	66 (72.5)	0.302
Low risk			
CR, n (%)	21 (65.6)	15 (83.3)	0.211
OR, n (%)	25 (78.1)	16 (88.9)	0.459
Intermediate risk			
CR, n (%)	44 (46.8)	57 (59.4)	0.110
OR, n (%)	58 (61.7)	70 (72.9)	0.122
High risk			
CR, n (%)	15 (32.6)	16 (51.6)	0.105
OR, n (%)	26 (56.5)	22 (71.0)	0.236

^a Group A, CAG regimen re-induction group;

Group B, high dose CAG regimen (HD-CAG) re-induction group;

^b CR, complete remission;

OR, overall response;

* indicates significant difference ($P < 0.05$) between groups.

Table 3. Adverse effects after re-induction therapy of CAG-based regimens

Variable	Group A ^a	Group B ^a	P value
Grade 3 or 4 Hematopoietic toxicity, n (%)	155 (90.1)	134 (92.4)	0.553
Hematopoietic recovery			
Granulocytes > 0.5×10 ⁹ /L, median days, (range)	7 (0–24)	9 (0–27)	0.066
Platelets > 50×10 ⁹ /L, median days, (range)	10 (0–35) *	15 (0–36) *	0.003
Grade 1 or 2 infection, n (%)	70 (40.7)	55 (37.9)	0.646
Febrile neutropenia, n (%)	31 (18.0)	25 (17.2)	
URTI ^b , n (%)	13 (7.6)	9 (6.2)	
Anal infection, n (%)	7 (4.1)	5 (3.4)	
Pulmonary infections, n (%)	16 (9.3)	13 (9.0)	
Skin/ soft tissue, n (%)	2 (1.2)	3 (2.1)	
Parotid gland, n (%)	1 (0.6)	0 (0.0)	
Grade 3 or 4 infection, n (%)	7 (4.1)	11 (7.6)	0.225
Febrile neutropenia, n (%)	2 (1.2)	1 (0.7)	
Anal infection, n (%)	0 (0.0)	1 (0.7)	
Pulmonary infections, n (%)	2 (1.2)	6 (4.1)	
Septicemia, n (%)	2 (1.2)	1 (0.7)	
Skin/ soft tissue, n (%)	1 (0.6)	2 (1.4)	
Grade 1 or 2 hemorrhage, n (%)	3 (1.8)	2 (1.4)	1.000
Fundus oculi, n (%)	1 (0.6)	0 (0.0)	
Gingiva, n (%)	2 (1.2)	2 (1.4)	
Grade 3 or 4 hemorrhage, n (%)	1 (0.6)	4 (2.8)	0.183
Lung, n (%)	0 (0.0)	1 (0.7)	
Urinary tract, n (%)	1 (0.6)	2 (1.4)	
Cerebrum, n (%)	0 (0.0)	1 (0.7)	
Toxicity of heart, n (%)	3 (1.8)	1 (0.7)	0.752
Allorhythmia, n (%)	2 (1.2)	0 (0.0)	
Grade 1 or 2	2 (1.2)	1 (0.7)	
Grade 3 or 4	0 (0.0)	0 (0.0)	
Cardiac dysfunction, n (%)	1 (0.6)	0 (0.0)	
Grade 1 or 2	1 (0.6)	0 (0.0)	
Grade 3 or 4	0 (0.0)	0 (0.0)	
Toxicity of Liver, n (%)	23 (13.4)	20 (13.8)	0.913
Grade 1 or 2 liver dysfunction, n (%)	23 (13.4)	20 (13.8)	
Grade 3 or 4 liver dysfunction, n (%)	0 (0.0)	0 (0.0)	
Toxicity of Gastrointestinal tract, n (%)	11 (6.4)	10 (6.9)	1.000
Vomit, n (%)	8 (4.7)	5 (3.4)	
Grade 1 or 2	8 (4.7)	5 (3.4)	

Grade 3 or 4	0 (0.0)	0 (0.0)	
Stomatitis, n (%)	2 (1.2)	5 (3.4)	
Grade 1 or 2	2 (1.2)	5 (3.4)	
Grade 3 or 4	0 (0.0)	0 (0.0)	
Diarrhea, n (%)	1 (0.6)	0 (0.0)	
Grade 1 or 2	1 (0.6)	0 (0.0)	
Grade 3 or 4	0 (0.0)	0 (0.0)	
Toxicity of Renal, n (%)	0 (0.0)	2 (1.4)	0.177
Grade 1 or 2 renal dysfunction, n (%)	0 (0.0)	2 (1.4)	
Grade 3 or 4 renal dysfunction, n (%)	0 (0.0)	0 (0.0)	
Early death, n (%)	9 (5.2)	6 (4.1)	0.793

^a Group A, CAG regimen re-induction group;

Group B, high dose CAG regimen (HD-CAG) re-induction group;

^b URTI, upper respiratory tract infection;

* indicates significant difference ($P < 0.05$) between groups.

Table 4. Multivariate Cox logistic analysis^a of factors relating to overall survival

Variables	<i>P</i> value	Odds ratio	95% confidence interval
Group	0.526	0.773	0.348-1.713
Sex	0.188	0.769	0.520-1.137
Age	0.135	1.012	0.996-1.029
AML subtype	0.098	1.079	0.986-1.181
Disease status	0.026		
Relapse		0.642	0.434-0.950
Refractory		1	
Risk status	0.123	1.290	0.933-1.782
Reinduction efficacy	5.695E-7		
CR ^b		1	
Not CR		1.748	1.404-2.175
Post-induction therapy	1.617E-6		
Allo-HSCT ^c		0.307	0.189-0.497
Chemotherapy		1	

^a, Variables were selected and analyzed by enter method;

^b, CR, complete remission;

^c, Allo-HSCT, allogenic hematopoietic stem cell transplantation.