Original Article

Efficacy of high-dose cytarabine and aclarubicin in combination with G-CSF regimen compared to intermediate/high-dose cytarabine and standard-dose cytarabine induction regimen for non-remission acute myeloid leukemia

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Abstract

BACKGROUND: Acute myeloid leukemia (AML) patients with non-remission (NR) after the first cycle of standard induction chemotherapy remain a challenge owing to poor response and tolerance to re-induction regimen. We retrospectively evaluated the efficacy and safety of three regimens in AML patients refractory to the first course of standard induction regimen.
MATERIALS AND METHODS: The three regimens consisted of (1) High-dose cytarabine, aclarubicin and granulocyte colony-stimulating factor (HD-CAG) regimen ($n = 44$); (2) intermediate/high-dose cytarabine (I/HDAC) regimen ($n = 30$); and (3) standard-dose cytarabine (SDAC) combination regimen that was identical to the first course of standard induction regimen ($n = 27$).
RESULTS: Results indicated that after the second course, the overall response (OR), i.e., complete remission [CR]+partial remission [PR]) rates in HD-CAG was higher than in the I/HDAC group (84.1% vs. 56.7%, P = 0.009), whereas the CR rates among 3 groups were not statistically different ($P = 0.541$). Meanwhile, the proportion of subjects reporting certain adverse effects in the HD-CAG group was lower than the I/HDAC or SDAC groups. There were no significant differences in overall survival (OS) and disease-free survival (DFS) rates among the 3 groups ($P = 0.881$ and $P = 0.872$, respectively).
CONCLUSION: Our preliminary results indicate that HD-CAG regimen may represent a better alternative option for AML patients with NR after the first course of standard induction chemotherapy.

Key Words: Acute myeloid leukemia, high-dose CAG, induction remission, non-remission, re-induction regimen

Introduction

The standard anthracycline-plus-cytarabine induction regimen (3 days of anthracycline and 7 days of cytarabine [Ara-C], namely "3+7") can enable 60–80% of younger adults and 40–50% of older patients with *de novo* acute myeloid leukemia (AML, excluding acute promyelocytic leukemia) achieve complete remission (CR). However, a significant proportion of AML patients exhibit non-remission (NR) after the first cycle of "3+7" regimen.[1] Unfortunately, there is no standard re-induction regimen for AML patients refractory to "3+7" regimen. According to NCCN Guidelines Version 2.2012 for AML, high-dose cytarabine (HDAC) alone or standard-dose cytarabine (SDAC) with idarubicin or daunorubicin are recommended if patients performance allows these regimens.[2] In fact, I/HDAC regimens were reported to result in a CR rate of 39.1–83%, yet followed by severe myelosuppression and related infection.[3,4] Meanwhile, SDAC combination regimens were utilized by other treatment groups, whereas the CR rate ranged from 31.1% to 60% in these AML patients.[5]

In 1995, a Japanese group first reported CAG (low-dose cytarabine and aclarubicin and granulocyte-colony-stimulating factor [G-CSF]) regimen for AML treatment.[6] Subsequently, this regimen was widely applied in Japan and China. Recently, a meta-analysis of CAG regimen treatment for 814 new and relapsed/refractory AML patients showed that the overall CR rate of a similar CAG regimen was higher than non-CAG regimens.[7] However, it should be noted that non-CAG regimens and the dosage of aclarubicin of the CAG regimen were varied in the study. Therefore, it is difficult to ascertain whether the inherent variation may influence the results. Therefore, efforts should be made to clarify the exact regimens being compared and explore some CAG-modified strategies. More recently, our clinical center found that increasing the aclarubicin dose in conventional CAG regimen (namely high-dose CAG [HD-CAG]) can improve CR rate of relapsed/refractory AML patients than conventional CAG regimen, with tolerable toxicity.[8,9] Herein, we performed a retrospective study to evaluate the effectiveness and tolerability of HD-CAG, I/HDAC, and SDAC regimens in these AML patients unresponsive to the first cycle of "3+7" regimen.

Materials and Methods

Patients

In total, 101 hospitalized AML patients (excluding acute promyelocytic leukemia) were analyzed from October 2006 to September 2015 in our center and Haikou Municipal People's Hospital. All subjects had the following characteristics: (1) newly diagnosed AML *de novo* with cytogenetic and/or molecular results; (2) refractory to

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the first course of "3+7" regimen (excluding CR or partial remission (PR); (3) the second protocol had to be HD-CAG, I/HDAC, or SDAC regimen; (4) performance status of 0-3 according to the Eastern Cooperative Oncology Group and without severe function damage of vital organ (cardiac, hepatic, and renal). (5) All subjects were younger than 60 years.

Diagnosis

The AML was confirmed by bone marrow (BM) morphologic, immunophenotypic, cytogenetic, and/or molecular analyses according to the World Health Organization 2008 classification criteria.[2] The risk status was according to cytogenetics and molecular genetic abnormalities according to NCCN guidelines Version 2.2012 for AML.[10] All patients were classified as 3 grades: better-risk including t(8;21), and inv(16) or t(16;16)), normal cytogenetics with the *NPM1* mutation, and normal cytogenetics with an isolated biallelic *CEBPA* mutation in absence of *FLT3-ITD*; intermediate-risk referring to normal cytogenetics, +8, t(9;11) and other non-defined, and t(8;21)/inv16/t(16;16) with *c-KIT* mutation; and poor-risk defined as complex ≥3 clonal chromosomal abnormalities, -5/5q-, -7/7q-, 11q23 - non t(9;11), inv(3)/t(3;3), t(6;9), t(9;22), and normal cytogenetics with *FLT3-ITD* mutation.

Treatment protocols

According to past NCCN guidelines, the recommended AML re-induction therapy after standard-dose cytarabine for patients age <60 year is HDAC alone or SDAC. I/HDAC-based regimens included Ara-C 1–3 g/m^2 every 12 h for 4 days. For regimens combining IDAC with anthracyclines (idarubicin/pirarubicin) or non-anthracyclines (mitoxantrone/etoposide), Ara-C was 1–2 g/m^2 every 12 h for 4 days. Fludarabine, Ara-C and G-CSF (FLAG) regimen (fludarabine 35 mg/m^2 infused intravenously daily from day 1 to 5, Ara-C 2 g/m^2 infused intravenously daily from day 1 to 5, and G-CSF administered subcutaneously at a dose of 200 μg/m^2/d from days 0 to 5 unless patient WBC count was ≥20 × 10^9/L). SDAC combination regimens: combining Ara-C with anthracyclines (daunorubicin/idarubicin) or non-anthracyclines (mitoxantrone/homoharringtonine); the dose of Ara-C in all these regimens was 100–200 mg/m^2/day for 7 days.

As for other alternatives, it is best to meet the following three criteria: (i) is less toxic than HDAC; (ii) avoids leukemia resistance due to previous SDAC exposure; and (iii) improves the effect of conventional CAG. From this, we evaluated the effect of the HD-CAG regimen as follows: HD-CAG regimen (Ara-C [Actavis Italy S.p.A] 10 mg/m^2 injected subcutaneously every 12 h for 14 days, aclarubicin [Yangzhou Pharmaceutical Co., Ltd, China] 5-7 mg/m^2/day infused intravenously for 14 days, G-CSF [Qilu Pharmaceutical Co., Ltd, China] 200 μg/m^2/d administered subcutaneously for 14 days, unless patient WBC count was ≥20 × 10^9/L, the administration of G-CSF was postponed, and reused when patient WBC count returned to <20 × 10^9/L. G-CSF was first administered before the first subcutaneous injection of Ara-C and was stopped 12 h before the last dose of Ara-C.

The choice of re-induction regimen was according to the treating physician's discretion depending the patient's age, comorbidities, and preferences. Chemotherapy-related supportive care was implemented as previously described.[9] CR patients received consolidation therapy. If a suitably matched donor was found, the eligible patients underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT). Without a matched donor, the patients with intermediate/poor-risk status were recommended for haploidentical related-donor HSCT. If patients did not accept HSCT, subsequent consolidation chemotherapy was arranged on time including I/HDAC regimens. Patients with poor performance status were treated with SDAC or low-intensity therapy (subcutaneous Ara-C, 5-azacytidine, and decitabine). The flow diagram is indicated in Figure 1.

Evaluation of efficacy and toxicity

CR was defined as BM blasts <5%, without blasts with Auer rods, the absence of extra-medullary disease, neutrophil count >1.0 × 10^9/L, and a platelet count >100 × 10^9/L. PR was defined as the decrease of BM blasts to 5%-20% in the BM aspirate and normalization of blood counts. Overall response (OR) included CR and PR. NR was defined as not achieving CR or PR after chemotherapy.[10] Refractory to the first course of standard induction chemotherapy was defined as a failure to achieve CR or PR after this regimen. Adverse events were evaluated by the WHO score.[11] Hematological and non-hematological toxicity was observed and recorded by monitoring hemogram, biochemical parameters, and conducting other related auxiliary examinations.

Statistical analysis

Data were analyzed by SPSS19.0. The independence of the categorical parameters among patient subsets was calculated using the chi-squared test. The distribution of the continuous variables was estimated using the Kruskal-Wallis test. The

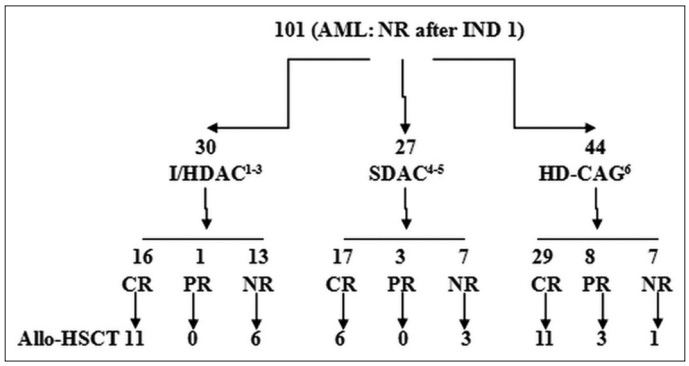

Figure 1: Treatment scheme of the 101 patients in this study. AML, acute myeloid leukemia; Allo-HSCT, allogeneic hematopoietic stem cell transplantation; IND1, initial standard anthracycline-plus-cytarabine induction chemotherapy; CR, complete remission; PR, Partial remission; NR, Non-remission; 1: HDAC (high-dose cytarabine); 2: IDAC+M/IDA/VP16/THP (intermediate-dose cytarabine plus mitoxantrone/idarubicin/etoposide/pirarubicin); 3: FLAG (fludarabine, cytarabine, and G-CSF); 4: DA/IA (daunorubicin plus cytarabine/idarubicin plus cytarabine); 5: MA/HA (mitoxantrone plus cytarabine/homoharringtonine plus cytarabine); 6: HD-CAG (high-dose cytarabine and aclarubicin in combination with G-SCF regimen)

overall survival (OS) was measured from the date of AML diagnosis to death regardless of any cause, and the surviving patients were followed-up to the conclusion of this study or date of the last contact. The disease-free survival (DFS) was measured from the CR to relapse or death during CR. The Kaplan-Meier analysis was used to analyze OS and DFS rates. Statistical results ($P < 0.05$) were considered significant.

Results

Characteristics of patients and disease

In total, 101 AML patients refractory to the first cycle of standard induction chemotherapy were enrolled in this study. Among them, 44 patients were treated with HD-CAG regimen, 30 patients treated with I/HDAC regimens (HDAC, $n = 4$; IDAC, $n = 4$; IDAC+M, $n = 3$; IDAC+IDA/VP16/THP, $n = 3$; and FLAG, $n = 16$), and 27 treated patients with SDAC regimens (DA, $n = 1$; IA, $n = 12$; MA, $n = 8$; and HA, $n = 6$) [Figure 1]. The respective characteristics of patients are summarized in Table 1. There were no significant differences found for age, gender, FAB subtype, risk status, and WBC count onset. The proportion of allo-HSCT among active treatment patients was not different among the 3 groups [Table 1].

Response to re-induction regimens

Despite no differences in CR rate among the 3 groups being found, there were overall significant differences in OR rate ($P = 0.032$) [Table 1]. Specifically, the OR rate of HD-CAG group was higher than I/HDAC group

Table 1: Clinical characteristics of patients in the 3 groups

Characteristic	I/HDAC (*n*=30)	SDAC (*n*=27)	HD-CAG (*n*=44)	*P*
At new diagnosis				
Median age (years, range)	40 (16-53)	40 (19-59)	32 (16-60)	0.233
Gender, *n* (%)				0.781
Male	17 (56.7)	17 (63.0)	24 (54.5)	
Female	13 (43.3)	10 (37.0)	20 (45.5)	
WBC onset ($\times 10^9$/L)				0.643
Median (range)	17.18 (1.9-168)	20.6 (1.6--225.4)	22.2 (1.9-200)	
FAB subtypes, *n* (%)				0.638
M1	2 (6.7)	4 (14.8)	5 (11.4)	
M2	13 (43.3)	9 (33.3)	15 (34.1)	
M4	8 (26.7)	4 (14.8)	9 (20.5)	
M5	6 (20.0)	6 (22.2)	13 (29.5)	
other	1 (3.3)	4 (14.8)	2 (4.5)	
Risk status, *n* (%)				0.909
Better-risk	4 (15.4)	3 (11.5)	8 (18.2)	
Intermediate-risk	18 (69.2)	20 (76.9)	29 (65.9)	
Poor-risk	4 (15.4)	3 (11.5)	7 (15.9)	
After second induction				
CR rate, *n* (%)	16 (53.3)	17 (63.0)	29 (65.9)	0.541
OR rate, *n* (%)	17 (56.7)	20 (74.1)	37 (84.1)	0.032
	17 (56.7)	20 (74.1)		0.169
	17 (56.7)		37 (84.1)	0.009
		20 (74.1)	37 (84.1)	0.303
WBC decrease, *n* (%)				0.590
Grade 1 or 2	0 (0)	0 (0)	1 (2.9)	
Grade 3 or 4	12 (100)	12 (100)	34 (97.1)	
PLT decrease, *n* (%)				0.590
Grade 1 or 2	0 (0)	0 (0)	1 (2.9)	
Grade 3 or 4	12 (100)	12 (100)	34 (97.1)	
Time of WBC <0.5×10^9/L				0.140
Median (range)	16 (10-27)	15 (0-24)	12 (3-25)	
Time of PLT <50×10^9/L				0.820
Median (range)	16 (7-23)	14 (7-27)	16 (0-30)	
Infection rate, *n* (%)				0.051
Lung	9 (36.0)	12 (54.5)	10 (22.7)	
Sepsis	3 (12.0)	1 (4.5)	1 (2.3)	
Febrile neutropenia	7 (28.0)	4 (18.2)	16 (36.4)	
Other organs	3 (12.0)	3 (13.6)	7 (15.9)	
No infection	3 (12.0)	2 (9.1)	10 (22.7)	
Allo-HSCT, *n* (%)	17 (60.7)	9 (34.6)	15 (36.6)	0.082

Allo-HSCT=Allogeneic hematopoietic stem cell transplantation; HD-CAG=High-dose cytarabine and aclarubicin in combination with G-SCF regimen; I/HDAC=Intermediate/high-dose cytarabine; SDAC=Standard-dose cytarabine induction regimen; WBC=White blood cell count; FAB=French-American-British; M=Myeloid; CR=Complete remission; OR=Overall remission; PLT=Platelet

(84.1% vs. 56.7%, $P = 0.009$). Moreover, there were no significant differences in OR rates between SDAC and I/HDAC or HD-CAG group ($P = 0.169$ and $P = 0.303$, respectively).

Myelosuppression was ubiquitous in all re-induction regimens. Although relatively shorter median duration of neutropenia (neutrophils $<0.5 \times 10^9$/L) was found in the HD-CAG group, there were no significant differences among the 3 groups ($P = 0.140$). The median duration of thrombocytopenia (PLTs $<50 \times 10^9$/L) was similar among the 3 groups. There was also no statistically significant differences in incidence of grade 3–4 leukopenia and thrombocytopenia among the 3 groups ($P = 0.590$ and $P = 0.590$, respectively). During neutropenia, infection was common, but there was no difference in the various types of infections ($P = 0.051$) among the groups. Non-hematological side effects were mild, and two events of severe complications were reported in the I/HDAC group: grade 4 hepatic dysfunction, from which the patient quickly recovered following intensifying supportive treatment and a pneumonia that resulted in a fatality.

Survival

In the HD-CAG group ($n = 44$), 41 patients received subsequent treatment, including allo-HSCT ($n = 15$; 11 achieving CR, 3 achieving PR, and 1 achieving NR), auto-HSCT (2 achieving CR), and chemotherapy ($n = 24$). In the I/HDAG group ($n = 30$), 28 patients received subsequent treatment, including allo-HSCT ($n = 17$; 11 achieving CR and 6 achieving NR) and chemotherapy ($n = 11$). In the SDAC group ($n = 27$), 25 patients received subsequent treatment, including allo-HSCT ($n = 9$; 6 achieving CR, 3 achieving NR), auto-HSCT (1 achieving CR), and chemotherapy ($n = 15$) [Figure 1]. In the HD-CAG, I/HDAC, and SDAC groups, the OS rates at 24 months were 39.9% ± 9.3%, 45.2% ± 13.4%, and 35.4% ± 12.5%, whereas the respective DFS rates at 24 months were 53.6% ± 11.1%, 53.6% ± 16.9%, and 55.9% ± 13.7%. There was no differences in OS [$P = 0.881$, Figure 2a], and DFS rates [$P = 0.872$; Figure 2b] were observed among the 3 groups.

Discussion

Reasonable choice of re-induction regimen for these AML patients with failure of "3+7" standard inductive chemotherapy has important clinical implications because it is closely related to subsequent therapeutic options and prognosis. Despite better tolerance of CAG than I/HDAC and SDAC, approximately 40–50% of patients do not achieve CR. Thus, some modified CAG regimens have been explored including combination with decitabine, Fms-like tyrosine kinase 3 inhibitor, or by increasing the dose of aclarubicin.[8,12,13]

In this study, we enrolled 101 eligible AML patients refractory to the first cycle of "3+7" regimen to compare the efficacy and safety of HD-CAG, I/HDAC, and SDAC regimens. Overall statistic analysis on OR rate revealed significant differences among the 3 groups ($P = 0.032$). Furthermore, by Chi-square segmentation, the results indicated that the OR rate of HD-CAG regimen was significantly higher than the I/HDAC regimen ($P = 0.009$), whereas the OR rate of SDAC regimen group was not significant when compared with either HD-CAG or I/HDAC. Moreover, the CR rate was not statistically different among the 3 groups. It is not difficult to infer from the above results that HD-CAG regimen gets a higher percentage of patients achieving PR than I/HDAC and SDAC regimens, which may alleviate the burden of residual leukemia and related complications, and improve patient tolerability as early as possible to proceed to allo-HSCT. These results suggest that HD-CAG regimen for the second cycle can achieve higher OR rate and should also be considered as an alternative.

During re-induction chemotherapy with intensive salvage regimens, severe adverse effects have been reported to occur. Our study suggested that the dose escalation of aclarubicin on CAG regimen basis did not increase treatment-related mortality. The white blood cell count (WBC) and platelet (PLT) recovery time to more than 0.5×10^9/L and 50×10^9/L was shorter in HD-CAG group than the other 2 groups probably because of G-CSF administration and the lower dose of anti-cancer agents. There were no differences in grade 1-2 and grade 3-4 leucopenia and thrombocytopenia among the 3 groups. These patients had a similar proportion on the incidence of infection among the 3 groups. All patients received blood transfusion support according to blood cell count evaluation. Except for severe complications (which included an early death) in the I/HDAC group, non-hematological toxicity was acceptable among the 3 groups, and routine

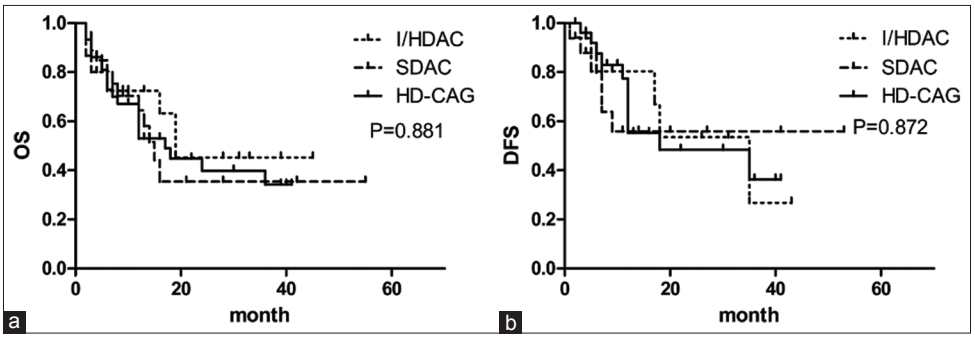

Figure 2: Effect of the three re-induction chemotherapy regimens on overall survival (a) and disease-free survival (b) in AML patient's refractory to initial induction therapy. HD-CAG, high-dose cytarabine, and aclarubicin in combination with G-SCF; I/HDAC, intermediate/high-dose cytarabine; and SDAC, standard-dose cytarabine induction

supportive therapy was able to prevent and resolve complications. Therefore, HD-CAG regimen not only achieved equivalent myelosuppression but also did not result in undue toxicity as compared with I/HDAC and SDAC regimens. Moreover, not all patients are ideal candidates for intensive chemotherapy because of poor performance status or comorbidities or personal wishes. Therefore, lower-intensity therapy is an important treatment option for some patients.[14]

Although older adults (>60 years) have been excluded at the time of enrollment, patients with 50–60 years were much more involved in the HD-CAG group, resulting in a lower allo-HSCT ratio in this cohort. Therefore, higher OR rate and lesser toxicities in this group did not translate into survival advantage. Of course, with the advances in conditioning regimens, supportive care, and multiple choice of donor sources, allo-HSCT can be safely performed in patients with higher age.[15,16] Therefore, achieving OR remains important for refractory AML patients. Although NCCN guidelines Version 2.2012 for AML recommended HDAC alone or SDAC combination regimen for NR AML patients,[2] our preliminary results suggest that HD-CAG regimen for the second cycle can achieve higher OR rate and should also be considered as an alternative, which is similar to another clinical study.[17]

The mechanisms of priming are probably because of the ability of G-CSF to transition leukemic cells from G0/G1 to S phase, sensitizing the other chemical agents to kill resting leukemia cells.[18,19] Low-dose Ara-C chiefly induces apoptosis of AML cells, rather than differentiation.[20]Aclarubicin is a less cardiotoxic oligosaccharide anthracycline and it does not only induce leukemic apoptosis by inhibiting DNA replication and RNA synthesis but it also targets multi-drug resistance gene.[21,22] More importantly, other studies reported that aclarubicin was still effective for daunorubicin-resistant AML patients and hepatoma cells.[23,24] However, mechanistic studies are required to elucidate this effect of HD-CAG regimen on AML patients.

There are some limitations in this study because it was not randomized, controlled, nor was it large-cohort design, therefore the diversity of post-reinduction treatment may have affected the evaluation of survival effect among the 3 groups. Nonetheless, our results suggested that the major advantage of HD-CAG regimen was in achieving a high OR rate than I/HDAC regimen rather than improving the survival directly.

Conclusion

In summary, HD-CAG regimen may improve OR rate than I/HDAC regimens for AML patients refractory to the first cycle of standard "3+7" regimen, particularly for older patients. As this was a pilot study, the efficacy of HD-CAG regimen in comparison to I/HDAC regimens in the NR AML patient population needs to be further confirmed in a larger, well-designed clinical trial in the future.

Ethical approval

This study was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University and Haikou Municipal People's Hospital. All patients provided written informed consent, and the study was conducted in line with the Declaration of Helsinki guidelines.

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Conflicts of interest

There are no conflicts of interest.

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