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Intermediate dose cytarabine improves survival and relapse-free rate compared with standard-dose cytarabine as post-remission treatment for acute myeloid leukemia

A retrospection study

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Abstract

The exact dose of cytarabine still remain controversial for the management of patients with acute myeloid leukemia (AML) after complete remission (CR), but recent studies favor lower doses. This study aimed to investigate the toxic effects of single-intermediate dose (ID) cytarabine in patients with AML after achieving CR, compared with standard-dose cytarabine.

In this retrospective study, AML patients who achieved CR after consolidation therapy before enrollment between 07/2008 and 05/2019 were included. All patients were divided into single-ID cytarabine and standard-dose cytarabine. The Kaplan-Meier method was used to compare overall survival (OS) and relapse-free time (RFS). Cox regression models were used to assess factors independently associated with OS and RFS. The toxic side effects of hematology and non-hematology were observed.

52 patients were enrolled. There were 33 in ID group, 19 in Standard dose group. The 3-year RFS rate (40.4% vs 22.2%, $P = .031$) was better in the ID group than in the standard-dose group, while the 3-year OS rate was not different between the 2 groups (50.2% vs 27.8%, $P = .074$). Treatment stratage of ID cytarabine chemotherapy significantly improve the prognosis of AML regardless of patient age, risk grade, WBC count. There were no significant differences between the 2 groups in grade 3 to 4 bone marrow suppression, gastrointestinal symptoms, blood transfusion, infections.

Patients with AML receiving ID cytarabine showed better survival and similar toxicity profiles compared with patients who received standard-dose cytarabine.

Abbreviations: AEs = adverse effects, AML = acute myeloid leukemia, CR = complete remission, HD = high-dose, ID = intermediate dose, OS = overall survival, RFS = relapse-free time.

Keywords: acute myeloid leukemia, cytarabine, dose, prognosis, side effects, toxicity

1. Introduction

Acute myeloid leukemia (AML) is a collection of heterogeneous hematopoietic stem cell disorders characterized by incomplete maturation of blood cells and reduced production of normal hematopoietic elements.[1] AML is most common in elderly persons (more than half of the cases are in patients ≥65 years of age) and has a slightly higher incidence in males and in populations of European descent.[1] The estimated yearly incidence in the USA is 18,860 new cases, with 10,460 deaths.[2] In China, AML represents about 37% of leukemias, and the incidence is 1.35 per 100,000 individuals.[3] The likely risk factors for AML include exposure to ionizing radiation, drugs known to cause DNA damage (particularly alkylating agents and drugs targeting topoisomerase II), and myelodysplastic processes or chronic bone marrow stem cells disorders.[1,4]

With the continuous improvement of treatment methods and strategies, the remission rate of AML has obviously increased, reaching 60% to 80%, but there are still high recurrence and mortality rates.[5–7] In patients with AML, intermediate-dose (ID) and high-dose (HD) cytarabine chemotherapy in induction or consolidation enhancement regimen can significantly prolong the remission period of the patients and improve their prognosis.[5,8–10] The latest diagnosis and treatment guidelines from the Hematology

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Association of the Chinese Medical Association on AML[11] and the National Comprehensive Cancer Network[10] also recommend moderate- and large-dose HD cytarabine regimen for induction and consolidation therapy of AML. Nevertheless, HD cytarabine is associated with severe bone marrow suppression, greater risks of infection and hemorrhage, and increases the mortality rate related to treatment compared with loser-dose treatment.[10]

In relapsed/refractory AML, ID cytarabine has been associated with a complete remission (CR) rate of 18% to 19% and median overall survival (OS) of 6.1 to 6.3 months in the CLASSIC-1[12] and VALOR[13] trials. A study suggested that ID cytarabine led to lower CR rates than HD cytarabine for relapsed/refractory AML, but that this difference in CR did not translate into a significant difference in OS.[14] On the other hand, a network meta-analysis of patients with AML and complete remission indicated that HD cytarabine provided the maximal anti-relapse effect, but with a risk of grade 3-4 adverse effects (AEs) twice that of ID cytarabine.[15] For induction and consolidation therapy in patients (15–55 years of age) with AML, ID cytarabine improves relapse-free survival (RFS) and OS compared with standard-dose cytarabine.[16] A study showed that lower-dose cytarabine still achieved the maximum therapeutic effect, while HD cytarabine resulted in excess AEs.[17]

Hence, the exact dose of cytarabine still remains controversial. This retrospective study aimed to investigate the toxic and side effects of single-ID cytarabine in patients with AML after achieving complete remission, compared with standard-dose cytarabine.

2. Methods

2.1. Study design and patients

This retrospective study included 52 patients treated between 07/2008 and 05/2019 at Hematology department, Lu'an Hospital Affiliated to Anhui Medical University. The patients were identified using the hospital's administrative database. The study was approved by the ethics committee of Lu'an Hospital Affiliated to Anhui Medical University. The requirement for individual consent was waived by the committee.

The inclusion criteria were:

(1) cytogenetic low and medium risk[10]; ECOG $\leq$2; and
(2) CR was achieved after 1 to 2 courses of induction therapy.

The patients were divided according to the dose of cytarabine they received: single-ID cytarabine and standard-dose cytarabine.

2.2. Treatment

In the ID group, the patients were treated with single-ID cytarabine (1-2 g/m^2, q 12 h, d1-3) for consolidation therapy, with 2-4 courses of treatment. The control group received standard-dose cytarabine (100–200 mg/m^2/d, d1-7), demethoxydaunorubicin (8–12 mg/m^2/d, d1-3), daunorubicin (IA) (40-60 mg/m^2/d, d1-3), homoharringtonine (HA) (2–4 mg/m^2/d, d1-3), and mitoxantrone (MA) (8–12 mg/m^2/d, d1-3) for alternating chemotherapy,[11] for 4–6 courses. After completing the above treatment, the drugs were withdrawn for observation.

2.3. Supportive and symptomatic treatment

During chemotherapy, all patients were treated with Belle Koushuang and 5% sodium bicarbonate gargle to maintain oral hygiene. A diluted iodophor or potassium permanganate hip bath was used to prevent perianal infection. In the ID group, tobramycin and dexamethasone eye drops were added to prevent keratitis. During the period of bone marrow suppression, component blood transfusion was given (erythrocyte transfusion when hemoglobin <60 g/L or hematocrit <20%; apheresis platelet transfusion if the platelet count $\leq 10 \times 10^9$/L or $\leq 30 \times 10^9$/L with obvious hemorrhage). For patients with neutrophils $\leq 1 \times 10^9$/L, antibiotic prevention, bedside isolation, and/or 100-grade aseptic laminar flow bed were used.

2.4. Observational indicators

Clinical symptoms, physical signs, blood routine, and bone marrow image changes were recorded. Liver and kidney function, electrolyte, C-reactive protein, and procalcitonin were monitored before, during, and after consolidation treatment. Electrocardiogram, chest radiograph, and chest CT were performed when necessary. The use of blood products and antibiotics was examined. Relapse was defined as the presence of at least 1 of the following conditions: reappearance of leukemic blasts in peripheral blood, recurrence of >5% blasts in bone marrow, and appearance of extramedullary leukemia. Relapse-free survival (RFS) was defined as the time from CR to disease recurrence or before hematopoietic stem cell transplantation. Overall survival (OS) was defined as the time interval from the date of remission to the date of last follow-up or before hematopoietic stem cell transplantation or death. The 3-year OS rate, RFS rate, and median OS and RFS were evaluated. The time to neutrophils recovering to $>1.0 \times 10^9$/L and platelets recovering to $>50 \times 10^9$/L was set as endpoint to record toxicity of hematology. The toxic and side effects of chemotherapy were evaluated according to the WHO Adverse Reaction Classification Criteria.[18]

2.5. Statistical analysis

SPSS 19.0 (IBM, Armonk, NY) and R3.2.2 were used for statistical analysis. The continuous data were presented as means $\pm$ standard deviations and analyzed using Student *t*-test (normal distribution according to the Kolmogorov-Smirnov test) or the rank-sum test (skewed distribution). The categorical data were presented as n (%) and analyzed using the chi-square test. The Kaplan-Meier survival method was used for survival analysis, and the log-rank test was used for inter-group comparison, and the Cox regression analysis was used for the multivariable analysis. The cumulative recurrence rate was calculated using the R software competition risk model. Two-sided *P*-values <.05 were considered statistically significant.

3. Results

3.1. Basic clinical data of patients

The clinical data of 52 AML patients who entered consolidation therapy after initial remission are detailed in Table 1. The median age was 53 (range, 22–73) years, and the median white blood cell count was 12.4 (range, 0.7–111.6) $\times 10^9$/L at the onset of disease in the 33 patients in the single-ID group, including 15 males and 18 females. The median age was 56 (range, 26–74) years, and the median white blood cell count was 6.5 (range, 1.2–135.1) $\times 10^9$/L at the onset of disease in the 19 patients in the standard-dose group, including 10 males and nine females. According to the FAB classification criteria, there were 1 M_1 case, 22 M_2, 4 M_4, 5 M_5, and 1 M_6 in the ID group, and 12 M_2 cases, and 7 M_5 in the

Table 1

Clinical data of the 155 patients with acute myeloid leukaemia.

Clinical feature	Intermediate dose group, n = 33	Standard dose group, n = 19	*P* value
Sex, n, Male/female	15/18	10/9	.25
Age, yr, Median (range)	53 (22–73)	56 (26–74)	.23
WBC $\times 10^9$/L, Mean ± SD	25.3 ± 42.5	22.8 ± 36.8	.52
Course of CR			
One period of treatment, n	22	11	.17
Two periods of treatment, n	11	8	
Number of courses of consolidation, Median (range)	5 (3–7)	7 (6–8)	.19

CR = complete response, WBC = white blood cells.

standard-dose group. There were no significant differences in risk stratification ($P = .22$). There were no significant differences between the 2 groups in sex, age, white blood cells at onset, and the number of courses of induction chemotherapy (all $P > .05$).

3.2. Survival analysis

The median follow-up was 18 (range, 4.4–117) months. The 3-year OS rate was not different between the 2 groups (50.2% vs 27.8%, $P = .07$) (Fig. 1A). The 3-year RFS rate in the ID group was higher than in the standard-dose group (40.4% vs 22.2%, $P = .031$) (Fig. 1B). The 3-year recurrence rate in the ID group was lower than in the standard-dose group (53% vs 77.8%, $P = .010$) (Fig. 1C).

Using multivariate regression we showed that the treatment stratage of ID cytarabine chemotherapy significantly improve the prognosis of AML, regardless of patient age, risk grade, WBC count (Table 2).

3.3. Hematological and non-hematological toxicity

For grade 3 to 4 hematological toxicity, all patients in follow up were evaluated by indicators for neutrophil and platelet recovery (Table 3). There were no significant differences in the median number of days for neutrophil and platelet recovery between the 2 groups.

All patients showed different degrees of nausea, vomiting, and other reactions during chemotherapy, mostly of grade 1-2, and could tolerate such symptoms after symptomatic treatment. There were no significant differences between the 2 groups ($P = .35$). There were no significant differences in liver function damage between the 2 groups ($P = .18$). There were 19 cases of respiratory tract infections in the ID group and 15 in the standard-dose group ($P = .79$). There were no significant differences between the 2 groups for the use of antibiotics ($P = .89$). There were no significant differences in the transfusion of blood products between the 2 groups ($P = .93$) (Table 3).

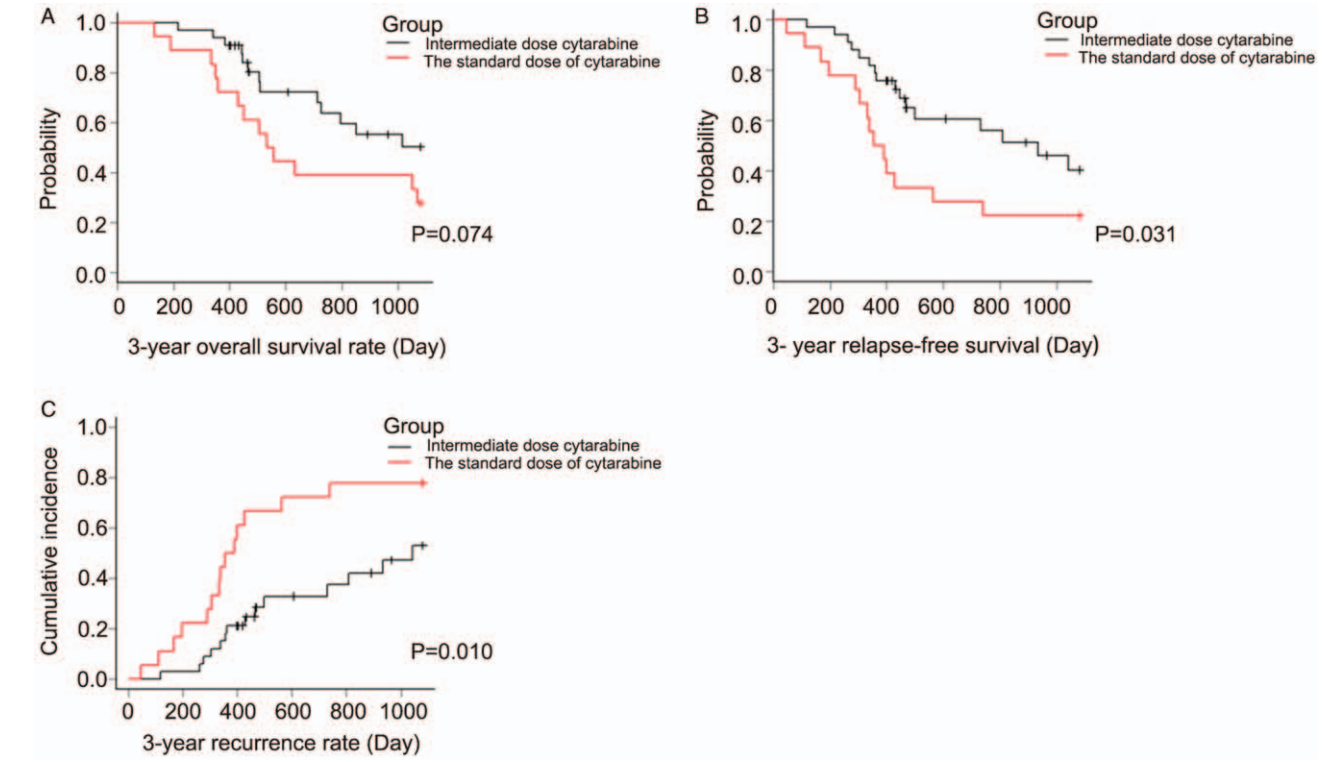

Figure 1. Outcome comparison of the two different treatment strategies at endpoint of 3 year in AML patients with PR after consolidation therapy. A = 3-year overall survival comparison, B = 3-year relapse-free survival comparison, C = 3-year recurrence rate comparison.

Table 2

Multivarivate analysis by Cox Regression for survival and relapse-free of 3 year.

Variable	HR	95% CI	*P* value
3-year survival			
Age	1.012	0.996–1.071	.079
Treatment strategy (Standard dose)	2.302	1.009–5.255	.048
Risk grade	1.033	0.3291–2.412	.82
WBC count	0.891	0.997–1.027	.126
3-year relapse-free survival			
Age	1.01	0.973–1.048	.604
Treatment strategy (Standard dose)	2.23	1.055–4.715	.036
Risk grade	0.968	0.362–2.594	.949
WBC count	1.002	0.987–1.108	.759

ID = intermediate-dose, WBC = white blood cells.

4. Discussion

The exact dose of cytarabine still remains controversial for the management of patients with AML after CR, but recent studies favor lower doses. This retrospective study aimed to investigate the toxic effects of single-ID cytarabine in patients with AML after achieving CR, compared with standard-dose cytarabine. The results suggest that patients with AML receiving ID cytarabine showed better survival and similar toxicity profiles compared with patients who received standard-dose cytarabine.

Cytarabine is a pyrimidine antimetabolic drug that acts by inhibiting the DNA polymerase and mainly acts in cells in the S phase. It has no cross-resistance with other types of antimetabolic drugs. ID and HD cytarabine can increase the level of the active compound Ara-CTP and enhance the ability to inhibit DNA synthesis. The ratio of the drug inside and outside the cells is close to 1:1, and it can pass through the blood-brain barrier and blood-testis barrier to maintain effective drug concentrations. Compared with standard-dose cytarabine, ID and HD cytarabine can significantly induce AML cell cycle arrest in the G0/G1 phase and exert an anti-AML effect through cell apoptosis,[19] but at the cost of higher toxicity, which limits the safety of HD cytarabine in patients over 50–60 years old.[20]

At present, the best single dose and chemotherapy course of Ara-C are still controversial.[17,21,22] ID cytarabine has no clear definition in terms of dose and dose rate. Some authors suggested that the dose range of ID cytarabine is 1.0–1.5 g/m^2, 2 times per day, while other authors suggest that ID cytarabine is 1-2 g/m^2, 2 times per day.[17,21,22] The exact definition of ID cytarabine will have to be clarified.

This study intended to evaluate the toxic and side effects and therapeutic effects of ID and standard-dose cytarabine combined with anthracyclines. There were no significant differences in hematological and non-hematological toxicity between the ID and standard-dose groups, which indicates that this dose of cytarabine is relatively safe and does not increase treatment-related toxic and side effects. The most important differences in toxicity reported in the literature are between ID and HD cytarabine.[14,15,17] Wei et al.[16] showed that neutrophil and platelet recovery was still longer with ID than standard-dose cytarabine, but that the other AEs were similar. The differences might be due to the study populations, selection criteria, and composition of the regimens.

The AML96 study included 933 adult patients with primary or secondary AML aged 15–60 years old. Patients with CR were randomized to receive the HDAC regimen (ie, cytarabine 3 g/m^2, 2 times/d, d1-6, with a cumulative dose of 36 g/m^2) or the IDAC regimen (ie, cytarabine 1 g/m^2, 2 times/d, d1-6, with a cumulative dose of 12 g/m^2) for 1 course of consolidation chemotherapy.[22] Their results showed that the 5-year OS (56% vs 45%) and RFS (48% vs 41%) rates of the 2 groups were similar ($P = .12$ and $P = .32$), but the time required for blood cell recovery in the HDAC group was longer than in the IDAC group (24 vs 18 days, $P = .004$), and the number of erythrocyte transfusions required in the HDAC group was higher than in the IDAC group (8 vs 6, $P = .030$).[22] Therefore, compared with the HDAC regimen, the IDAC regimen displayed the same curative effect, but with a faster hematopoietic function recovery.[22] Another study showed that lower-dose cytarabine achieves a maximum therapeutic effect.[17] On the other hand, a network meta-analysis of patients with AML and complete remission indicated that HD cytarabine provided the maximal anti-relapse effect, with a hazard rate of 0.87 (95% confidence interval: 0.79-0.97) favoring HD over ID cytarabine.[15] In this study, 2-year OS and 2- and 3-year RFS and recurrences rates were all better in the ID group than in the standard-dose group. This is supported by previous studies.[14,16,17,23–26]

This study has limitations. Due to the limitations of the patient's economic status and hospital conditions, the number of cases in this study is small, but there are good results. Large-scale studies can be carried out by means of multi-center cooperation in the later period. It was a small single-center retrospective study. Differences in chemotherapy regimens preclude direct comparisons with other trials and studies. The retrospective nature of the study limited the data to those contained in the charts. No comparison with HD cytarabine could be made since this regimen is not used at our center.

Table 3

Grade 3-4 hematological toxicity and non-hematological toxicity.

Group	Intermediate dose group, n = 33	Standard dose group, n = 19	*P* value
Grade 3-4 hematological toxicity			
Neutrophil recovery time (d), Mean ± SD	15.5 ± 5.9	14 ± 2.4	.16
Minimum neutrophil time (d), Mean ± SD	10 ± 5.8	9 ± 1.9	.09
Duration of neutrophil deficiency (d), Mean ± SD	7.8 ± 10.7	7 ± 2	.90
Platelet recovery time (d), Mean ± SD	16 ± 5.3	14.5 ± 1.5	.29
Minimum platelet time (d), Mean ± SD	10.3 ± 2.2	9.4 ± 1.6	.47
Duration of thrombocytopenia (d), Mean ± SD	9.5 ± 7.5	9 ± 2.1	.36
Non-hematological toxicity			
Adverse gastrointestinal reactions, n	31	16	.51
Blood transfusion, n	24	11	.43
Infection occurs, n	25	14	.87

In conclusion, patients with AML receiving ID cytarabine showed better survival and similar toxicity profiles compared with patients who received standard-dose cytarabine. The ID regimen should probably be favored over the standard-dose regimen.

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