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Original Article

The prognostic factors and efficacy of induction chemotherapy in elderly patients with acute myeloid leukemia

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Abstract: Background and objective: Acute myeloid leukemia (AML) is the most common form of hematological malignancy in adults. We aimed to investigate the efficacy of different treatment measures and prognostic factors for elderly patients with AML. Methods: The clinical data of 65 newly diagnosed elderly patients with AML were retrospectively analyzed. Among them, 45 patients received induction chemotherapy including standard cytarabine regimen (n = 21) and low dose cytarabine regimen (n = 24), and 20 patients received palliative treatment. The efficacy and prognosis were compared between the groups. Results: There were no statistical differences in complete remission, overall survival and the 6-month disease-free survival rates between standard cytarabine group and low dose cytarabine group (P = 0.675, P = 0.775, P = 0.751, respectively). Significant difference in median overall survival and overall survival rate were detected (P < 0.001, P = 0.031, respectively), but no significant difference in early death rate (P = 0.238) was found between induction chemotherapy group and palliative treatment group. Multivariate analysis showed that the white blood cells count ≥ 100.0 × 10^9/L was associated with early death. Conclusions: The induction chemotherapy did not increase the early mortality. The low dose cytarabine regimen can be used as the first-line choice for elderly acute myeloid leukemia patients who are not suitable for intensive chemotherapy.

Keywords: Acute myeloid leukemia, elderly, treatment, prognosis

Introduction

Acute myeloid leukemia (AML) is the most common form of hematological malignancy in adults. AML is a disease of elderly at diagnosis with a median age of 65-70 years old [1, 2]. However, due to the many unique factors in the elderly patients with AML [3, 4], the treatment response rate was only about 45%; the 5-year survival rate was approximately 10%; and the early mortality rate was as high as 30% [5, 6].

Currently, the optimum treatment for elderly patients with AML remains controversial. According to the Chinese AML treatment guidelines, the standard treatment of "3+7" regimen with low remission rate was still recommended for induction therapy in elderly AML. However, a recent analysis has reported that the low-dose cytarabine (LD-AraC) regimen may have the potential advantages in treating elderly AML [7]. With the optimization of palliative support treatment, the chemotherapy regimens and consolidation therapy strategies have not been unified. However, several studies have suggested that elderly patients with AML who receive any therapy have a better outcome than patients who receive supportive care alone [2].

In this study, we retrospectively analyzed the clinical data of elderly patients with AML and explored the efficacy of induction chemotherapy in elderly patients with AML, as well as analyzed the prognostic factors for elderly AML, hoping to provide a basis for the choice of optimal treatment strategies.

Table 1. Baseline clinical characteristics according to treatment group

Variables	Standard AraC group	LD-AraC group	Palliative treatment	*P*
Age (year)	63.67 ± 1.79	67.25 ± 5.18	73.80 ± 6.02	< 0.001
Gender (n)				
Male	10	13	12	0.729
Female	11	11	8	
Prior MDS				
Yes	20	19	18	0.244
No	1	5	2	
PS (ECOG score)				
0-2	20	21	10	< 0.001
≥ 3	0	3	10	
WBC count (× 10^9/L)	28.58 ± 37.58	51.54 ± 82.41	63.93 ± 104.92	0.357
Hb (g/L)	80.9 ± 14.84	70.83 ± 21.8	68.3 ± 19.1	0.083
PLT (× 10^9/L)	34.24 ± 24.89	38.58 ± 47.14	52.45 ± 57.72	0.409
LDH (IU/L)	359 ± 353.25	556.17 ± 470.6	562 ± 568.37	0.285
Alb (g/L)	33.19 ± 3.25	33.01 ± 3.44	33.36 ± 3.52	0.650
ALT (IU/L)	35.6 ± 17.9	34.9 ± 30.2	26.3 ± 22.8	0.401
Creatinine (umol/L)	90.3 ± 28.4	107.4 ± 71.1	75.4 ± 21.2	0.093
BM blast (%)	78.5 ± 17.1	69 ± 21.8	71.4 ± 23.9	0.312
CD34				
Positive	14	12	16	0.114
Negative	7	12	4	
CD117				
Positive	14	10	10	0.207
Negative	7	14	10	
Lymphoblastic antigen				
Positive	10	5	10	0.081
Negative	11	19	10	
Cytogenetic				
Favorable/Intermediate risk	19	16	15	0.085
Unfavorable risk	4	8	5	

Abbreviations: AraC: cytarabine, LD-AraC: low-dose cytarabine, MDS: myelodysplastic syndrome, PS: performance status, ECOG: Eastern Cooperative Oncology Group, WBC: white blood cells, Hb: hemoglobin, PLT: platelet, LDH: lactate dehydrogenase, Alb: albumin, ALT: alanine aminotransferase, BM: bone marrow.

Patients and methods

Patients

A total of 65 patients with AML who were aged 60 years or older were admitted to our hospital from January 2009 to December 2016. AML was defined as myeloblasts ≥ 20% in the marrow or peripheral blood which was based on the WHO classification criteria [8]. All the patients were newly diagnosed or secondary to myelodysplastic syndrome, with performance status (PS) score < 3, no liver and kidney injury, and normal cardiac function were selected as subjects. Relapsed refractory leukemia, acute promyelocytic leukemia and blastic phase of chronic myeloid leukemia were excluded.

The data were collected retrospectively including age, sex, history of myelodysplastic syndrome (MDS), FAB type, comorbidities, PS, white blood cells (WBC), platelet (PLT), hemoglobin (Hb), lactate dehydrogenase (LDH), bone marrow (BM) blasts, chromosome karyotype, immunophenotypic and so on. PS scores were scored according to the Eastern Cooperative Oncology Group (ECOG) score system. For cytogenetic risk-stratification, the karyotypes were divided into three subgroups (favorable risk, intermediate risk, unfavorable risk) according

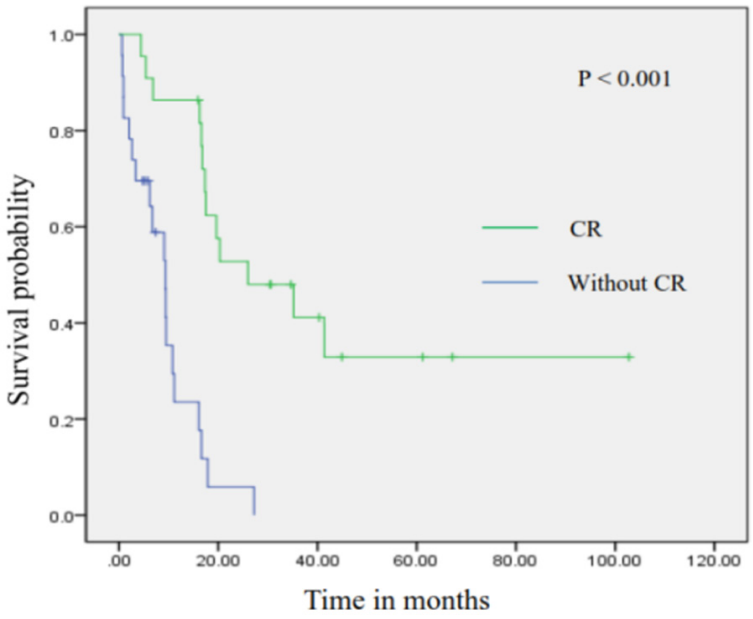

Figure 1. Overall survival of elderly patients with AML stratified by remission status.

to the National Comprehensive Cancer Network (NCCN) guidelines. All participants provided written informed consent. This study was approved by the ethics committee of the First People's Hospital of Lianyungang, and was conducted in accordance with the Ethics Committee guide-lines and the principles of the Declaration of Helsinki.

Treatments

Forty-five patients were treated by induction chemotherapy. 21 (32.3%) patients received standard cytarabine (AraC) regimen and 24 (36.9%) patients received LD-AraC regimen. The remaining 20 (30.8%) patients received palliative treatment. The standard AraC regimen include DA, MA, HA and IA regimen, comprising daunorubicin (30-45 mg/m^2), mitoxantrone (5 mg/m^2) or idarubicin (8-10 mg/m^2) for 3 days plus AraC (100 mg/m^2) for 7 days. LD-AraC regimen was consisted of CAG, HAG regimen comprising aclarubicin (10 mg/d) for 4 to 8 days or homoharringtonine (1 mg/m^2) for 1 to 7 days plus a low dose of AraC (15-20 mg/m^2 every 12 hours) for 1 to 14 days and granulocyte colony-stimulating factor (G-CSF) (300 μg/d) for 14 days. Patients with complete remission (CR) after induction chemotherapy were given consolidation chemotherapy regimen according to the protocol design. Palliative treatment includes components of blood transfusion, cytoreductive treatment with hydroxyurea and other best supportive care (BSC).

Evaluation of therapy

Therapeutic evaluation including CR rate, disease-free survival (DFS) rate and early mortality were defined according to the 2003 revised International Working Group response criteria [9]. CR was defined as blasts < 5% in bone marrow, and neutrophils > 1.0 × 10^9/L and PLT > 100.0 × 10^9/L in peripheral blood. Early death was defined as death occurring within 4 weeks after diagnosis [6]. Overall survival (OS) was measured from the date of diagnosis until the date of death or the last follow-up (December 31, 2017). DFS was measured from the date of CR until the date of death or the first relapse.

Statistical analysis

All statistical analyses were carried out using the SPSS 20.0 statistical package. Differences in the patient characteristics between groups were calculated by the Student's *t*-test, one-way analysis of variance (for continuous variables) and χ^2 test (for categorical variables). OS was estimated using Kaplan-Meier analysis, and log-rank analysis was used to evaluate differences in survival between groups. A multivariate prognostic analysis was performed using COX proportional hazards model to calculate survival hazard ratios, and logistic regression was used to analyze the risk factors for early mortality. Statistical significance was set at a *P* value < 0.05.

Results

Patient characteristics

The 65 patients had a median age of 67 years (range, 60-83 years); 35 (53.8%) were male and 30 (46.2%) were female. According to FAB and the 2008 WHO classification, patients were classified as follows: 14 (21.5%) cases of

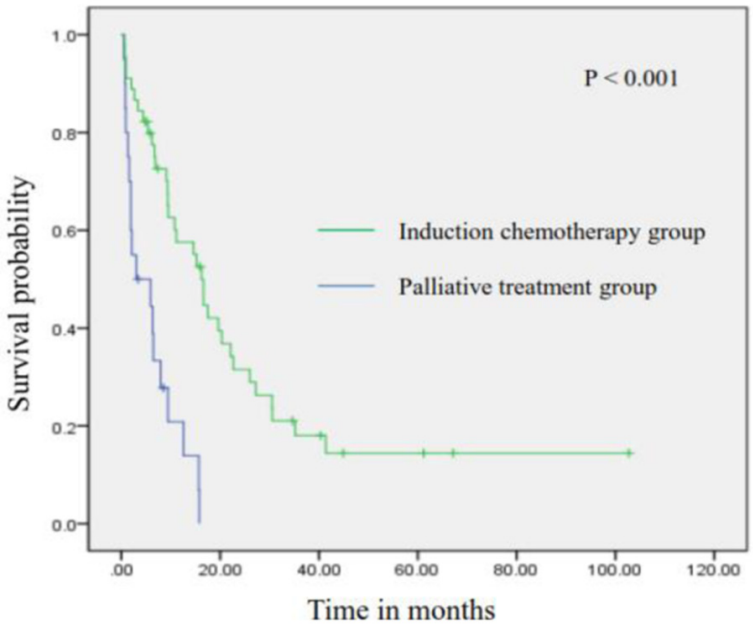

Figure 2. Overall survival of elderly patients with AML according to the treatment status.

Table 2. Univariate analysis of prognosis in elderly patients with AML

Variables	n	Median OS (month)	χ^2	P
Age (year)				
60-70	40	16.6	13.423	0.001
≥ 70	25	5.9		
Gender				
Male	35	9.4	0.930	0.335
Female	30	9.5		
Prior MDS				
Yes	11	7.9	0.007	0.931
No	54	9.4		
PS (ECOG score)				
0-2	50	15.7	11.795	0.001
≥ 3	15	5.9		
WBC count (× 10^9/L)				
< 100	52	15.7	17.737	0.001
≥ 100	13	1.5		
Hb (g/L)				
≤ 70	26	9.4	1.448	0.229
> 70	39	11.1		
PLT (× 10^9/L)				
< 20	20	9.4	0.151	0.697
≥ 20	45	9.5		
LDH level/normal				
< 2-fold	42	12.6	7.635	0.006
≥ 2-fold	23	5.4		

M_1, 21 (32.3%) cases of M_2, 5 (7.7%) cases of M_4, 14 (21.5%) cases of M_5, 3 (4.6%) cases of M_6 and 8 (12.3%) cases of undifferentiated type. At the time of diagnosis, 13 patients (20%) had an ECOG PS ≥ 3, while the other patients had ECOG PS < 3. The baseline characteristics of all patients at the time of diagnosis are summarized in **Table 1**. Among of 11 (16.9%) patients who had a history of MDS, 4 converted to M_2, 2 to M_6, 1 to M_1, 1 to M_4 and 1 to M_5, respectively.

The baseline data of the three groups according to the induction chemotherapy are shown in **Table 1**. The age of standard AraC group, LD-AraC group and palliative treatment group were 63.67 ± 1.79, 67.25 ± 5.18 and 73.80 ± 6.02, respectively ($P < 0.001$). The palliative treatment group had a higher median age than the other two groups. Furthermore, the palliative treatment group had a higher proportion of poor PS ($P < 0.001$). There was no significant difference in the baseline data between the two groups receiving induction chemotherapy and palliative treatment in terms of gender, history of MDS, FAB classification, and pre-treatment laboratory tests ($P > 0.05$).

Comparison of the efficacy of different induction chemotherapy regimens

The CR rate in the standard AraC regimen group and LD-AraC regimen group was 52.4% (11/21) and 41.7% (10/24), respectively. There was no significant difference between the two groups ($\chi^2 = 0.176$, $P = 0.675$). The 6-month DFS rates in the two groups were 38.1% (8/21) and 29.2% (7/24), with no significant difference ($\chi^2 = 0.100$, $P = 0.751$). The median OS was 17.9 (0.6-67.2) months and 16.1 (0.87-102.77) months, respectively. There was also no significant difference between the

Alb				
Normal	55	9.5	0.018	0.895
< Normal	10	7.9		
ALT				
Normal	52	12.6	6.807	0.009
> Normal	13	6.2		
Creatinine				
Normal	56	12.6	7.128	0.008
> Normal	9	5.4		
BM blast (%)				
< 50	27	15.7	0.087	0.768
≥ 50	38	6.8		
CD34				
Positive	42	11.1	0.118	0.731
Negative	23	9.4		
CD117				
Positive	35	15.7	2.287	0.130
Negative	30	9.1		
Lymphoblastic antigen				
Positive	25	9.3	0.280	0.596
Negative	40	11.1		
Cytogenetic				
Favorable/Intermediate risk	48	11.1	9.236	0.002
Unfavorable risk	17	2.6		
Induction regimen				
Standard Ara-C regimen	21	17.9		
LD-AraC regimen	24	16.1	24.508	0.001
Without induction regimen	20	3		

Abbreviations: MDS: myelodysplastic syndrome, PS: performance status, ECOG: Eastern Cooperative Oncology Group, WBC: white blood cells, Hb: hemoglobin, PLT: platelet, LDH: lactate dehydrogenase, Alb: albumin, ALT: alanine aminotransferase, BM: bone marrow, LD-AraC: low-dose cytarabine.

two groups (χ^2 = 1.171, P = 0.229). The early mortality rates in both groups were 9.5% (2/21) and 8.3% (2/24), respectively, also with no significant difference (χ^2 = 0.02, P = 0.889).

The median survival for patients with CR was 25.9 (4.2-102.77) months and for patients who never achieved CR was 9.3 (0.6-27.2) months. The median survival of patients with CR was significantly longer than that of patients without CR achievement (χ^2 = 21.024, P < 0.001, **Figure 1**).

Comparison of efficacy between chemotherapy and palliative treatment groups

The median OS was 16.27 (0.6-102.77) months and 3 (0.53-15.77) months in the induction chemotherapy group and the palliative treatment group, respectively. The median OS of induction chemotherapy group was significantly longer than that of palliative treatment group (χ^2 = 19.386, P < 0.001, **Figure 2**).

The early death rate was 8.9% (4/45) in induction chemotherapy and 20% (4/20) in palliative treatment group, respectively. The early death rate did not significantly differ between the two groups (χ^2 = 1.584, P = 0.238). The OS rates of the induction chemotherapy group and palliative treatment group were 28.9% (13/45) and 5% (1/20), respectively. Significant difference (χ^2 = 4.676, P = 0.031) in OS was detected between the two groups.

Analysis of prognostic factors

When using univariate analysis to evaluate the prognostic value, the following factors were significant for prognosis (P < 0.05): age, ECOG PS score ≥ 3, WBC ≥ 100.0 × 10^9/L, serum LDH level/normal ≥ 2-fold, elevated ALT levels, creatinine levels, chromosome karyotype, whether or not to receive induction chemotherapy. The results were shown in **Table 2**.

In multivariate analysis, the factors including WBC count ≥ 100.0 × 10^9/L (HR = 2.873, 95% CI: 1.383-5.968, P = 0.005), ECOG PS score ≥ 3 (HR = 2.066, 95% CI: 1.051-4.059, P = 0.035), unfavorable karyotypes (HR = 2.465, 95% CI: 1.355-4.485, P = 0.003) and whether or not received induction chemotherapy (HR = 0.329, 95% CI: 0.157-0.689, P = 0.003) were confirmed to be independent risk factors for prognosis of elderly patients with AML (**Table 3**; **Figure 3**).

Analysis of early death factors

The main causes of early death in patients receiving chemotherapy and palliative treatment were cerebral hemorrhage, septic shock and severe pulmonary infection. Univariate analysis showed that WBC count, serum LDH level/normal ≥ 2-fold, elevated ALT levels were the risk factors for early death in elderly AML

Table 3. Multivariate analysis of prognosis in elderly patients with AML by COX proportional hazards model

Parameters	B (Coefficient)	SE	Wald	*P*	HR	95% CI
ECOG PS ≥ 3	0.725	0.345	4.430	0.035	2.066	1.051-4.059
WBC ≥ 100.0 × 10^9/L	1.055	0.373	8.004	0.005	2.873	1.383-5.968
Unfavorable cytogenetic	0.902	0.305	8.724	0.003	2.465	1.355-4.485
Whether or not induction chemotherapy	-1.111	0.377	8.677	0.003	0.329	0.157-0.689

Abbreviations: ECOG: Eastern Cooperative Oncology Group, WBC: white blood cells, SE: standard error, HR: hazard rate, CI: confidence interval.

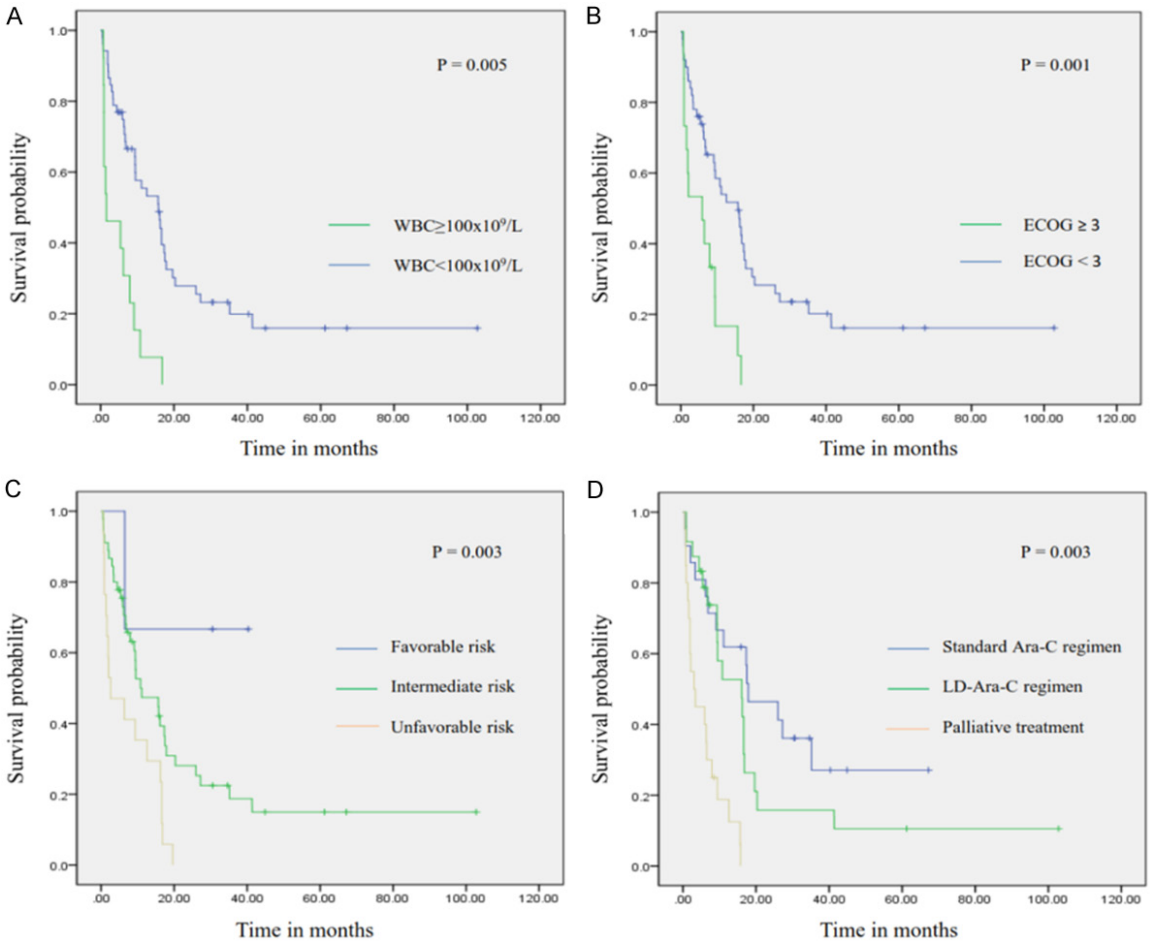

Figure 3. Overall survival stratified by different prognostic factors. A. OS stratified by WBC count. B. OS stratified by ECOG score. C. OS stratified by cytogenetic risk group. D. OS stratified by type of treatment.

Table 4. Univariate analysis of early death in elderly patients with AML

Variables	Early death (n)	χ^2	P
Age (year)			
60-70	3/40	2.062	0.151
≥ 70	5/25		
Gender			
Male	3/35	0.921	0.337
Female	5/30		

patients ($P < 0.05$, **Table 4**). In multivariate analysis, only the factor of WBC count ≥ 100.0 × 10^9/L (HR = 10.208, 95% CI: 2.031-51.313, $P = 0.005$) was associated with early death (**Table 5**).

Discussion

For elderly patients with AML, disease-specific factors including comorbidities, poor PS, poor organ function and unfavorable

Prior MDS			
Yes	1/11	0.158	0.691
No	7/54		
PS (ECOG score)			
0-2	4/50	3.270	0.071
≥ 3	4/15		
WBC count (× 10^9/L)			
< 100	3/52	9.698	0.002
≥ 100	5/13		
Hb (g/L)			
≤ 70	1/26	2.667	0.102
> 70	7/39		
PLT (× 10^9/L)			
< 20	2/20	0.138	0.710
≥ 20	6/45		
LDH level/normal			
< 2-fold	2/42	6.418	0.011
≥ 2-fold	6/23		
Alb			
Normal	8/55	1.559	0.212
< Normal	0/10		
ALT			
Normal	3/52	11.425	0.001
> Normal	5/13		
Creatinine			
Normal	6/56	0.850	0.356
> Normal	2/9		
BM blast (%)			
< 50	1/27	3.056	0.080
≥ 50	7/38		
CD34			
Positive	5/42	0.014	0.905
Negative	3/23		
CD117			
Positive	4/35	0.051	0.822
Negative	4/30		
Lymphoblastic antigen			
Positive	4/25	0.553	0.457
Negative	4/40		
Cytogenetic			
Favorable/Intermediate risk	4/48	2.587	0.108
Unfavorable risk	4/17		
Induction regimen			
Standard AraC regimen	2/21		
LD-AraC regimen	2/24	1.633	0.442
Without induction regimen	4/20		

Abbreviations: MDS: myelodysplastic syndrome, PS: performance status, ECOG: Eastern Cooperative Oncology Group, WBC: white blood cells, Hb: hemoglobin, PLT: platelet, LDH: lactate dehydrogenase, Alb: albumin, ALT: alanine aminotransferase, BM: bone marrow, LD-AraC: low-dose cytarabine.

cytogenetic contribute to the poorer outcomes [4, 10]. Previous reports confirmed that age, complex cytogenetic, treatment approach and other factors were poor prognostic factors for elderly with AML. The data of this study were consistent with those of previous reports [3, 5, 6]. Although intensive treatment strategies could improve CR rate in elderly AML patients, chemotherapy-related toxic and lethal adverse effects limit the widespread use of the intensive chemotherapy [11], and therefore present some challenges and uncertainties in the treatment of elderly patients with AML. Moreover, in China, fewer elderly AML patients had the opportunity to participate in clinical trials because of the poor PS and medical condition, especially in economically underdeveloped areas. Up to recently, a considerable number of elderly patients with AML had been chosen not to receive chemotherapy, but some studies showed that patients receiving any chemotherapy would have a better prognosis than those only receiving palliative treatment [2, 12].

In this study, both the median OS and OS were better in elderly patients with AML receiving chemotherapy compared to palliative treatment only. Furthermore, early death rate was lower in elderly AML patients who received chemotherapy compared to palliation treatment alone. In a previous report [13], the median OS was 12.4, 11.5 and 2.6 months for elderly patients with AML receiving intensive chemotherapy, lower-intensity therapy or best supportive care (BSC), respectively. In this study, the median OS was 17.9 (0.6-67.2) months, 16.1 (0.87-102.77) months and 3 (0.53-15.77) months for standard AraC regimen group, LD-AraC regimen group and palliative treatment group, respectively. Our results were also similar to the results of several previous reports and indicated that the patients benefits from receiving chemotherapy as opposed to palliation treatment alone [14, 15].

The current induction remission chemotherapy strategy consisting of daunorubicin (60 mg/m^2) for 3 days plus AraC (100 mg/m^2) for 7 days has become standard regimen for fit, newly diagnosed, elderly AML patients (over 60 years old). The CR rate can reach 75%. However, due to ethnicity differ-

Table 5. Multivariate logistic regression analysis of early death in elderly patients with AML

Parameter	B (Coefficient)	SE	Wald	*P*	HR	95% CI
WBC ≥ 100.0 × 10^9/L	2.323	0.824	7.952	0.005	10.208	2.031-51.313

Abbreviations: WBC: white blood cells, SE: standard error, HR: hazard rate, CI: confidence interval.

ences between China and the West counties, regional epidemiology and economic differences, the dosage of daunorubicin in the domestic standard "3+7" regimen was less than 60 mg/m^2, so the CR rate also dropped. Several studies had shown that the CR rate was about 44-60% [16, 17]. In this study, we found CR rate of the standard dose of AraC regimen was 52.4%, which was similar to the results reported in the previous studies. The CR rate of LD-AraC regimen was 41.7%, although lower than the standard dose of AraC regimen, but with no statistical significance. Previous study compared the effects of BSC, LDAC and conventional induction chemotherapy. In comparison, our study has the similar results [12, 13].

Moreover, the early mortality and DFS in the LD-AraC regimen were not significantly different from the standard regimen and palliative treatment in this study. Therefore, the LD-AraC regimen has shown a promising clinic efficacy. Many studies demonstrated that the LD-AraC-based chemotherapy represented by CAG regimen might be an alternative and feasible chemotherapy in elderly AML [7, 18, 19]. In addition, another study showed that CAG regimen could significantly prolong the OS of elderly AML [20], but the results still need to be further confirmed in large-scale, sub-grouping, long-term follow-up clinical trials.

The results of this study also indicated that the WBC count ≥ 100 × 10^9/L, without induction chemotherapy, unfavorable cytogenetic changes were independent risk factors for poor prognosis in elderly AML patients, which was consistent with the previously studies [21, 22]. High WBC count represents a high tumor burden, suggesting a poor prognosis. The unfavorable karyotype and age, especially in patients ≥ 70 years old had been recognized as the most important prognosis factors [6, 13].

Older age, poor PS, and WBC count ≥ 100 × 10^9/L had been confirmed as the risk factors for early death in elderly AML patients. This study showed that only the high WBC count was the independent risk factor for early death. However, our study confirmed the result that chemotherapy did not increase early death compared to palliation treatment in elderly AML patients [16, 23, 24]. Therefore, the NCCN, European Leukemia Net (ELN), and European Society for Medical Oncology (ESMO) all recommended LD-AraC regimen as a possible treatments option [3].

But in the real elderly AML world, age was still a very important factor that troubled the doctors and patients for treatment choice. More importantly, the decision of doctors for specific patients should be based on the factors including the disease status, age, comorbidities, PS, and patient's economic conditions. They should not give up induction chemotherapy just because older age. Overall, this study showed that LD-AraC regimen was still a better treatment option for elderly AML patients who were not suitable for intensive chemotherapy regimen.

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Disclosure of conflict of interest

None.

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