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Clinical Characteristics and Optimal Therapy of Acute Myeloid Leukemia with Myelodysplasia-related-changes: A Retrospective Analysis in a Cohort of Chinese Patients

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Abstract

Objective: This study aimed to investigate the clinical characteristics of acute myeloid leukemia with myelodysplasia-related-changes (AML-MRC) according to the 2016 WHO classification and the preferred therapy of patients with AML-MRC and aged 60-75 years.

Materials and Methods: We retrospectively analyzed the differences of clinical data between 190 patients with AML-MRC and 667 patients with AML not otherwise specified (AML-NOS). And we compared different therapeutic regimens among patients with AML-MRC and aged 60-75 years.

Results: Compared with AML-NOS, patients with AML-MRC had significantly different clinical characteristics as well as worse overall survival (OS) (9.2 vs 13.6 months; $p<0.001$) and complete remission (CR) rate (65.3% vs 76.2%; $p=0.005$). Multivariate analysis performed in the whole group (patients with AML-MRC and AML-NOS) showed that AML-MRC was the independent prognostic factor

(p=0.002). Additional multivariate analysis performed in 190 patients with AML-MRC indicated that age (p<0.001) and LDH (p=0.031) were independent prognostic factors. Compared with IA/DA regimen [idarubin and cytarabine (IA) or daunorubicin and cytarabine (DA)], DAC+CAG regimen [decitabine and half-dose CAG regimen (cytarabine, aclarubicin and granulocyte colony-stimulating factor)] was associated with better OS (4.5 vs 6.2 months; p=0.021) in patients aged 60-75 years and categorized into unfavorable-risk group.
Conclusion: AML-MRC exhibited worse clinical outcome compared with AML-NOS. Compared with IA/DA regimen, DAC+CAG regimen was the optimal choice for patients with AML-MRC in unfavorable-risk group and aged 60-75 years.
Keywords: Acute Myeloid Leukemia with Myelodysplasia-related-changes, Clinical Characteristics, Therapy

Introduction

Acute myeloid leukemia with myelodysplasia-related-changes (AML-MRC) is a distinct entity first defined by the World Health Organization (WHO) in 2008 [1].The 2016 WHO classification revised the MDS-related cytogenetic abnormalities: del (9q) were removed and patients with mutated NPM1 or biallelic CEBPA were recategorized as recurrent genetic abnormalities [2]. According to recent studies, AML-MRC exhibited worse prognosis, including lower complete remission (CR) rate and shorter overall survival (OS) compared with AML-NOS [3-5]. Although IA/DA regimen [idarubin and cytarabine (IA) or daunorubicin and cytarabine (DA)] and DAC+CAG regimen [decitabine and half-dose CAG regimen (cytarabine, aclarubicin and granulocyte colony-stimulating factor)] were often the prior selections for chemotherapy, no particular therapy has yet been found to have therapeutic advantages, especially in patients older than 60 years and not eligible for allogeneic hematopoietic stem cell transplantation (allo-HSCT). We retrospectively investigated 190 patients with AML-MRC admitted in our hospital and compared it with AML-NOS to have better understanding of its clinical and biological features and we compared IA/DA and DAC+CAG regimen in patients aged 60-75 years to find out the optimal therapy.

Material and Methods

Patients

Our study was performed based on a cohort of 857 patients with complete data regarding baseline characteristics and treatment outcomes admitted in our hospital between August 2010 and September 2019. These patients were reevaluated as AML-NOS or AML-MRC according to the 2016 WHO classification of myeloid neoplasms and acute leukemia [2], strictly excluding cases with therapy-related myeloid neoplasms and AML with recurrent genetic abnormalities including mutated NPM1 and biallelic CEBPA. Patients who underwent allo-HSCT were also excluded. Clinical and laboratory data were searched in electronic medical records. Follow-up information was obtained in electronic record or by contacting family members and was initialized from the day of diagnosis

to October 1st 2020 or the day of death. All subjects provided informed consent in compliance with the Declaration of Helsinki.

Morphology analysis

Morphology analyses of 857 patients were confirmed by at least two morphological experts. Peripheral blood and bone marrow smears were stained using Wright-Gimesa method. Cytochemistry was performed using myeloperoxidase (MPO), non-specific esterase, sodium fluoride inhibition tests and periodic acid Schiff (PAS). Dyserythropoiesis was confirmed when there were erythroid precursors showing megaloblastic nuclei, karyorrhexis, nuclear fragments or multinucleation. Dysgranulopoiesis was characterized as polymorphonuclear neutrophils with agranular or hypogranular cytoplasm or with hyposegmented nuclei (pseudo Pelger-Hüet anomaly). Dysmegakaryopoiesis was defined as micromegakaryocytes, multiple separated nuclei or monolobed nuclei in megakaryocytes of all sizes. Patients were categorized as AML with multilineage dysplasia (AML-MLD) when the presence of dysplasia in ≥ 50% cells in at least two cell lineages. All cases fulfilled the 2016 WHO criterion: there were at least 20% blasts in the peripheral blood or bone marrow.

Molecular mutation analysis:

Molecular mutation analyses including CEBPA, NPM1, ASXL1, RUNX1 and Flt3-ITD and so on were obtained in the whole group. Before May 2016, it was performed by polymerase chain reaction, which was replaced by high throughput sequencing afterwards.

Cytogenetic analysis

Cytogenetic information was obtained in all patients. Chromosome karyotype detection of bone marrow cells was performed by short time culture and G-banding methods. Patients were categorized into intermediate-risk group or poor-risk group based on cytogenetics and molecular mutation reported in 2017 European Leukemia Net (ELN) criteria [6]. According to the 2016 WHO criteria [2], when ≥ 20% peripheral blood or bone marrow blasts were present and prior therapy had been excluded, cytogenetic abnormalities sufficient to diagnose AML-MRC were as follows：1) complex karyotype; 2) unbalanced abnormalities: -7/del(7q), del(5q)/t(5q), i(17q)/t(17p), -13/del(13q), del(11q), del(12p)/t(12p), idic(X)(q13); 3) balanced abnormalities: t(11;16), t(3;21), t(1;3), t(2;11), t(5;12), t(5;7).

Therapy

According to treatment regimens, patients with AML-MRC aged 60-75 years (n=99) were divided into three groups, including IA/DA group (n=43), DAC+CAG group (n=49) and supportive group (n=7). Patients in IA/DA group were treated with IA (idarubicin 10-12mg/m^2 d1-3, Ara-C 100-200mg/m^2 d1-7) or DA (daunomycin 45-60mg/m^2 d1-3, Ara-C 100-200mg/m^2 d1-7). Patients in DAC+CAG group received decitabine (20mg/m^2, d1-5), Aclarubicin (10-14mg/m^2, d4-7), Ara-C (10mg/m^2 q12h d4-10) and Granulocyte colony-stimulating factor (5μg/Kg, d4-10 or d4 until white blood cell count was more than 30×10^9/L). In the supportive group, patients received hydroxyurea to inhibit the proliferation of

leukemia cells or just supportive care such as transfusions of blood products when necessary and anti-infection therapy when patients had symptoms of infection.

Statistical analysis

OS was defined as the time from diagnosis to death or the last follow-up. Comparison of quantitative data was performed using t-test or Mann-Whitney U test. Comparison of categorical variables was performed by χ^2 or Fisher's exact tests. Kaplan-Meier methods and log-rank test were used for survival analysis based on OS. Cox multivariate analysis was used to examine the prognostic factors of AML patients and confirm which of them was the independent factor. $P<0.05$ was considered statistically significant. All Statistical calculations were finished by SPSS 24.0.

Results

Risk status of the whole group

The information of risk status was based on the revised 2017 ELN criteria [6]. Since patients with mutated NPM1 or biallelic mutation of CEBPA were recategorized as recurrent genetic abnormalities [2], there was no patient assigned to the favorable-risk group. In the whole cohort (n=857), 689 cases (80.4%) were assigned to the intermediate-risk group, accounting for the largest proportion and the remaining 168 cases (19.6%) were classified as unfavorable-risk group. Just as we expected, compared with unfavorable-risk group, the intermediate-risk group had better OS (13.4 vs 6.8 months; $p<0.001$) and CR rate (76.5% vs 59.5%; $p<0.001$).

Sub-classification of patients with AML-MRC

Among 857 patients, 190 patients (22.2%) were diagnosed as AML-MRC according to 2016 WHO classification [2]. There were 7 different sub-classifications in AML-MRC patients. Most cases diagnosed as AML-MRC for meeting only one criterion: 38 patients (20%) presented solely MLD, 108 patients (56.8%) showed MDS-related cytogenetics and 11 patients (5.8%) had prior history of MDS or MDS/MPN. And 32 patients (16.8%) met two criteria: 14 (7.4%) of them had MDS-related cytogenetics ad prior history of MDS or MDS/MPN, 14 (7.4%) cases showed MLD and MDS-related cytogenetics, 4 (2.1%) cases had MLD and history of MDS or MDS/MPN. Only 1 case (0.5%) had a combination of all these three criteria.

Clinical Characteristics of AML-MRC

After comparing 190 patients with AML-MRC and 667 patients with AML-NOS, we really found many differences between these two groups (Table1). Patients with AML-MRC had significantly higher age ($p< 0.001$), lower Hb ($p< 0.001$), lower WBC ($p< 0.001$) and higher male: female ratio ($p=0.006$) than AML-NOS group, while no significant differences were detected in terms of platelet ($p=0.462$) and LDH ($p=0.139$). As to clinical outcomes, compared with AML-NOS, AML-MRC had significantly lower CR rate (65.3% vs 76.2%; $p=0.005$) and worse OS (9.2 vs 13.6 months; $p < 0.001$) (Figure 1). Moreover, in the intermediate-risk group, OS of AML-MRC was still worse than AML-NOS (9.5 vs 13.9 months; $p=0.011$).

Univariate analysis and Multivariate analysis

Univariate analysis was performed in the whole cohort of 857 AML patients in terms of age, WBC, Hb, plt, history of MDS or MDS/MPN, MDS-related cytogenetic abnormalities, MLD, LDH and MRC. It was found that age ($p<0.001$),

WBC (p<0.001), history of MDS or MDS/MPN (p=0.009), MDS-related cytogenetic abnormalities (p<0.001), MLD (p=0.002), LDH (p<0.001), and MRC (p<0.001) were prognostic factors for OS. Subsequent multivariate analysis indicated that among these factors age (HR=2.774; p<0.001)、LDH (HR=1.788; p<0.001) and MRC (HR=0.653; p=0.002) were independent prognostic factors (Table2).
In 190 patients with AML-MRC, univariate analysis suggested that LDH (p=0.031) and age (p<0.001) were prognostic factors, while WBC, Hb, plt, history of MDS or MDS/MPN, MDS-related cytogenetic abnormalities and MLD were not relatedo prognosis. Multivariate analysis showed that both age (HR=0.447; p<0.001) and LDH (HR=1.604; p=0.032) were independent prognostic factors for AML-MRC (Table3).

Treatment analysis of patients with AML-MRC and aged 60-75 years

There were 99 patients aged 60-75 years in AML-MRC, which can be categorized as intermediate-risk group (n=46) and unfavorable -risk group (n=53) based on the 2017 ELN criteria. We analysed the efficacy of different treatment regimens in each group. In intermediate-risk group, no significant difference was found between IA/DA group and DAC+CAG group with respect to CR rate (60% vs 63.6%, p=0.808) and OS (6 vs 6.5 months, p=0.272). However, in the unfavorable-risk group, the OS of DAC+CAG group was significantly better than IA/DA group (6.2 vs 4.5 months; p=0.021). The CR rate of DAC+CAG group was higher than IA/DA group, but the difference had no statistical significance (59.3% vs 52.2%; p=0.406).

Discussion

AML-MLD was first proposed in 2001 WHO classification of myeloid neoplasms and acute leukemia and was classified as a separate category [7]. The concept was renamed as “AML-MRC” in the 2008 WHO classification [1] and myelodysplasia-related cytogenetic abnormalities as well as prior history of MDS or MDS/MPN were added as additional criteria for its recognition. Although the newly revised 2016 WHO classification has made some modifications, AML-MRC still includes these three categories [2], which were considered associated with poor prognosis.
We analyzed the clinical features, and prognosis of 857 AML patients including 190 patients with AML-MRC and 667 patients with AML-NOS based on the 2016 WHO classification of AML [2]. Significant biological differences were found between AML-NOS and AML-MRC concerning age (p< 0.001), Hb (p< 0.001), WBC (p< 0.001) and so on. Compared with AML-NOS, AML-MRC had significantly shorter OS (9.2 vs 13.6 months; p< 0.001) and CR rate (65.3% vs 76.2%; p=0.005), similar to recent studies [3-5]. However, Raynier et al [8] suggested that the worse prognosis of AML-MRC was probably due to the unfavorable cytogenetics which were categorized as MDS-related cytogenetics because they assessed the prognosis of AML-NOS and AML-MRC in intermediate risk group and found no difference between both groups in OS and Relapse-free survival (RFS). On the contrary, the study of Weinberg et al [5] showed that AML-MRC had worse OS and CR rate even after excluding patients with unfavorable cytogenetics. To figure out it, we carried out a similar research as Raynier’s and got the opposite result that among patients with intermediate risk group, OS of AML-

MRC were still significantly worse than AML-NOS (9.5 vs 13.9 months; p=0.011). Moreover, our multivariate analysis showed that MRC was an independent prognostic factor after adjusted by age and MDS-related cytogenetics, in coincidence with the study of Weinberg et al [5]. The results described above supported the WHO classification separating these two categories.

As described above, many well-known adverse factors were observed in AML-MRC such as older age, unfavorable cytogenetics and multidrug resistance phenotype, which lead to its unsatisfied therapeutic response and survival. Young patients in good physical condition are offered intensive chemotherapy followed by allo-HSCT. However, the optimal chemotherapy regimen of patients older than 60 years and not eligible for allo-HCST has always been controversial. The standard 3+7 regimen, IA or DA, is the most common induction therapy, while CAG regimen is another common choice and is often combined with decitabine. However the comparison of IA/DA regimen and DAC+CAG regimen in AML-MRC aged 60-75 years has rarely been reported. In our study, no significant difference was found between two regimens (OS: 6 vs 6.5 months, p=0.272; CR rate: 60% vs 63.6%, p=0.808) in intermediate-risk group (Figure 2). But in poor-risk group, the OS of DAC+CAG regimen was significantly longer than the IA/DA regimen (6.2 vs 4.5 months; p=0.021) (Figure 3). Therefore, we propose the DAC+CAG regimen should be the preferred choice for AML-MRC patients categorized to poor-risk group and aged 60-75 years.

Decitabine, a DNA-hypomethylating agent (HMA), can induce differentiation and apoptosis of leukemic blasts and activate the silenced tumor suppressor gene (TSG) which was impaired by the disorder of DNA methylation [9-11]. Recent studies have proved that decitabine was well tolerated and could improve the response rate and OS in older AML patients when used as a single agent [12-13]. And when combined with other chemotherapy regimens such as CAG, IA, HAA (Homoharringtonine, cytarabine, aclarubicin) and so on, decitabine could significantly enhance the therapeutic efficacy [14-16]. In 2016, Welch et al [17] enrolled 84 patients with AML or MDS in a single-institution trail of decitabine. The result showed that the response of DAC was higher among patients in unfavorable-risk group than patients in intermediate-risk or favorable-risk cytogenetic group (67% vs 34%, p<0.001) and there was no statistical difference of OS between these two groups (11.6 vs 10 months, p=0.29). Similar findings were also showed by other researchers [18-20]. These researches offered a possible explanation for our result that patients in unfavorable-risk group benefited most from DAC+CAG regimen. Further researches will be required to find out the inmost mechanism of the better efficacy of DAC among patients in unfavorable-risk group.

Despite the efficacy of conventional chemotherapy, the survival of AML patients remains unsatisfactory. Over the decades, efforts made by researchers have led to minor improvement in the outcome of AML patients until the presence of several new therapies offered something fresh in the landscape of AML therapy. CPX-351, a liposomal formulation of cytarabine and daunorubicin, was approved by the US Food and Drug Administration (FDA) in 2017 for the treatment of newly diagnosed

therapy-related AML (tAML) or AML-MRC based on a phase III clinical trial named CLTR0310-301 [21]. In this clinical trial, CPX-351 showed better OS (9.56 vs 5.85 months, p=0.003), better EFS (2.53 vs 1.31 months, p=0.021) and higher CR rate (37.3% vs 25.6%, p=0.016) compared with standard 3+7 regimen in patients 60-75 years of age with newly diagnosed tAML or AML-MRC and was found to be safe and well-tolerated [22-24]. Venetoclax, a selective inhibitor of the antiapoptotic protein B-cell lymphoma 2 (BCL-2), can lead to rapid initiation of apoptosis in leukemia cells [25]. When combined with low-dose cytarabine (LDAC) or HMA, venetoclax demonstrated significant improvement of CR rate and OS compared with single-agent LDAC or HMA in AML patients ineligible for intensive chemotherapy, which was proved by several multicenter clinical trails [26-28]. Based on these results, current guidelines recommended this combination as standard therapy for older and unfit patients [29]. In addition to more researches on new therapies, future eforts should be focused on reducing therapeutic toxicities for a wider utilization and improving the OS of AML patients through different therapies combinations.

Study Limitations

There are several limitations in our study. All data were collected in a retrospective manner and the scale of the cohort was small when analysed the optimal choice for patients with AML-MRC in unfavorable-risk group and aged 60-75 years.

Conclusion

In conclusion, AML-MRC is associated with worse prognosis compared with AML-NOS and shows independent prognostic effect. DAC+CAG regimen may be preferred for patients aged 60-75 years and classified as unfavorable-risk group.

Ethics Committee Approval: The study was approved by the Ethics Committee of Qingdao University Medical College Affiliated Yantai Yuhuangding Hospital.

Informed Consent: Informed Consent was obtained from all participants included in the study.

Conflict of interest: No conflict of interest was declared by the authors.

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Authorship Contributions

Concept: L.W., J.X., X.C; Design: L.W., J.X., X.C; Data Collection or Processing: L.W., J.W., L.A.; Analysis or interpretation: L.W., J.X., L.A; Literature Search: L.W., J.X., J.W., L.A., Y.L., X.C., L.L; Writing: L.W., J.X., J.W., L.A., Y.L., X.C, L.L.

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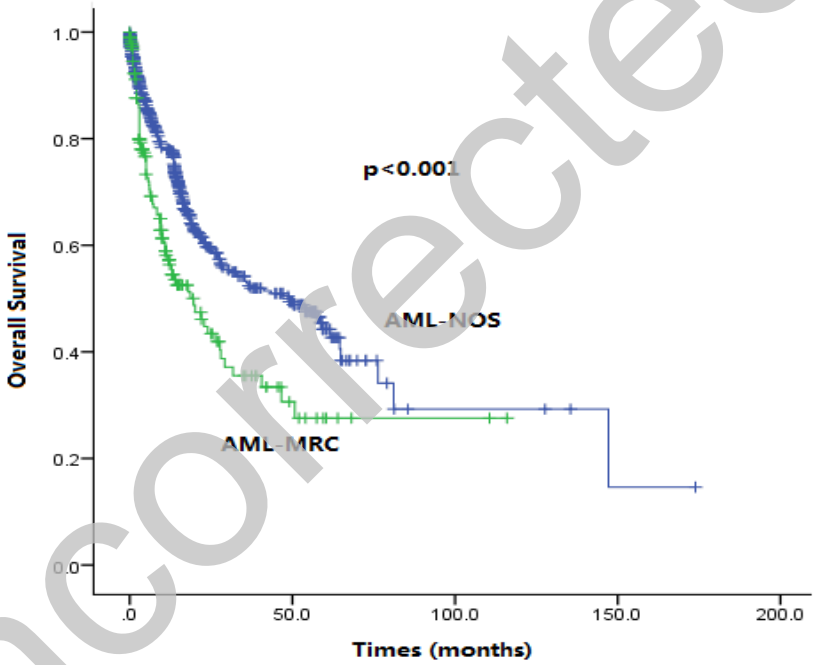

Figure1. Kaplan-Meier survival rates. Overall survival for patients with AML-MRC and AML-NOS.

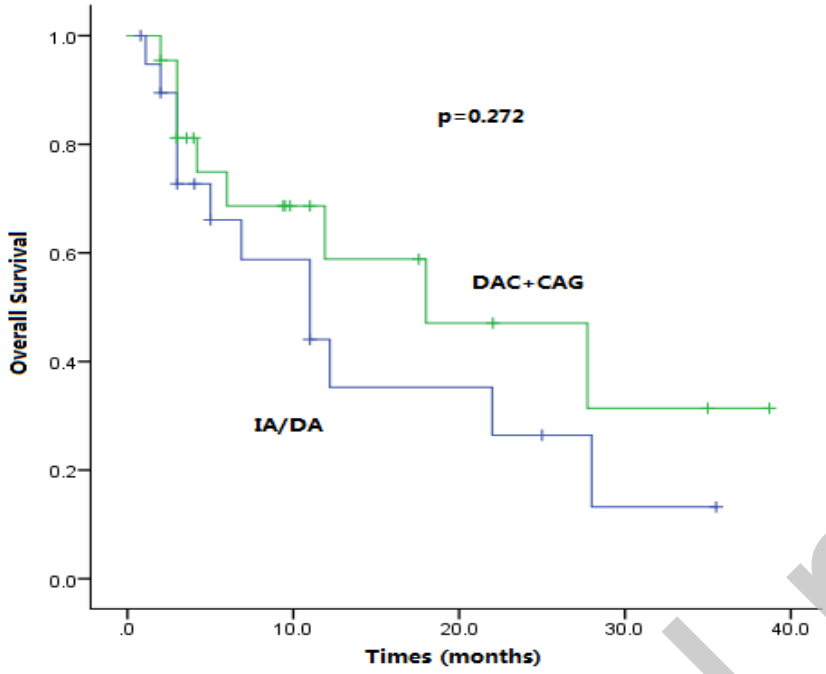

Figure 2. Kaplan-Meier survival rates. Overall survival for IA/DA regimen and DAC+CAG regimen in patients with AML-MRC in intermediate-risk group and aged 60-75 years.

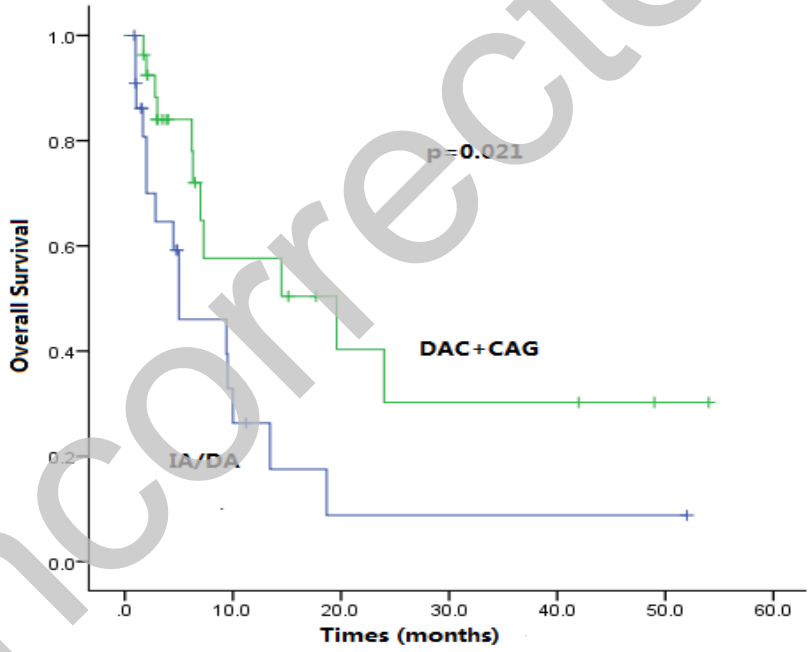

Figure 3. Kaplan-Meier survival rates. Overall survival for IA/DA regimen and DAC+CAG regimen in patients with AML-MRC in unfavorable-risk group and aged 60-75 years.

Table 1. Information of the whole cohort.			
Variable	AML-NOS	AML-MRC	p-value
No.	667	190	
Age (years, range)	50 (16-90)	61 (16-87)	<0.001
Male:female (ratio)	354: 313 (1.13: 1)	122: 68 (1.79: 1)	0.006
Hb (g/L, range)	81 (22-158)	71 (30-146)	<0.001
WBC ($X10^9$/L, range)	13.4 (2-720)	7.5 (0.3-375.9)	<0.001
Plt ($X10^9$/L, range)	46 (3-494)	44 (1-458)	0.462
LDH (IU)	336 (2-10168)	387 (86-5986)	0.139
OS (month, range)	13.6 (0-173.9)	9.2 (0-116)	<0.001
CR rate (%)	457/600 (76.2%)	109/167 (65.3%)	0.005
Risk status			
Intermediate	617/667 (92.5%)	72/190 (37.9%)	<0.001
Poor	50/667 (7.5%)	118/190 (62.1%)	<0.001

Table 2. Univariate and Multivariate analysis for OS of 864 AML patients			
Parameter	Univariate	Multivariate	
	P value	HR (95%CI)	P value
age≥60	<0.001	2.774 (2.166-3.54)	<0.001
WBC count	<0.001		0.064
Hb count	0.092		
Platelet count	0.483		
History of MDS or MDS/MPN	0.009		0.481
MDS-related cytogenetic changes	<0.001		0.323
Presence of MLD	0.002		0.681
LDH	<0.001	1.788(1.416-2.257)	<0.001
AML-MRC	<0.001	0.653(0.51-0.848)	0.002

Table 3. Univariate and Multivariate analysis for OS of 191 patients with AML-MRC			
Parameter	Univariate	Multivariate	
	P value	HR (95%CI)	P value
age≥60	<0.001	0.447(0.292-0.685)	<0.001
WBC count	0.21		
Hb count	0.426		
Platelet count	0.465		
History of MDS or MDS/MPN	0.481		
MDS-related cytogenetic changes	0.676		
Presence of MLD	0.441		
LDH	0.031	1.604 (1.041-2.471)	0.032