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Decitabine improves overall survival in myelodysplastic syndromes-RAEB patients aged ≥60 years and has lower toxicities: Comparison with low-dose chemotherapy

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ABSTRACT

Decitabine and low-dose chemotherapy are common treatments for intermediate and high risk myelodysplastic syndromes (MDS). In this study, we retrospectively assessed the efficacy and toxicity of the two regimens for MDS-refractory anemia with excess blasts (MDS-RAEB) patients. A total of 112 patients with a diagnosis of MDS-RAEB are included. The overall response (OR) and complete remission (CR) rate was comparable between the two groups (OR: 64.1% vs. 66.7%, $p = 0.60$; CR: 23.4% vs. 31.3%, $p = 0.64$). The OR rates of 20 mg/m^2/day and 15 mg/m^2/day decitabine regimen were comparable (69.0% vs. 60.0%, $p = 0.46$). Overall survival (OS) did not differ significantly between the groups (20.7 vs. 13.5 months, $p = 0.17$). In a subgroup analysis that included only patients at ≥60 years of age, survival benefit of decitabine was apparent (20.6 vs. 10.0 months, $p = 0.03$). In hematological toxicities, the lowest count of platelet in the decitabine group was higher significantly. And, the incidence of Grade 3–4 infection in the decitabine group was lower significantly. Our results demonstrate that both decitabine and low-dose chemotherapy are effective for MDS-RAEB, but decitabine was safer. Decitabine might be a better choice for patients at ≥60 years of age.

1. Introduction

Myelodysplastic syndromes (MDS) are a group of clonal hematopoietic cell disorders, which are characterized by persistent cytopenias and ineffective hematopoiesis [1–3]. Approximately 30% patients with MDS will progress to acute myeloid leukemia (AML). For patients with intermediate and high risk MDS who are ineligible for hematopoietic stem cell transplantation, treatment with chemotherapeutic agents or hypomethylating agents is recommended [1,3–5]. Chemotherapeutic regimens, which are similar to that used for AML, might be through direct cytotoxicity effect. The regimens achieve approximately 50% complete remission (CR) rate [6–8]. However, high-intensity chemotherapy is associated with a great risk of morbidity and mortality [6–8]. To reduce the toxicities which is related to AML-like chemotherapy, low-intensity chemotherapy is adopted. Previous studies have demonstrated that low-dose chemotherapy is effective and tolerated in relapsed/refractory AML and intermediate and high risk MDS patients [9–13].

Decitabine (2′-deoxy-5-azacytidine) is the most widely used inhibitor of Deoxyribonucleic acid (DNA) methylation, which reactivates tumor suppressor genes by demethylating these genes. The regimen of 20 mg/m^2/day decitabine (for five days every four weeks) is widely used in intermediate and high risk MDS patients. Many studies have reported that the rate of CR and overall response (OR) is 10%–40% and 30%–70%, respectively [14–23]. Several dose-exploration trials found that decitabine of reduced dosage (15/m^2/day) could also achieve similar clinical response, and minimize course delay and therapy-related death [24–26]. Our study adopted two schedules of decitabine,

Abbreviations: MDS, myelodysplastic syndromes; RAEB, refractory anemia with excess blasts; AML, acute myeloid leukemia; CR, complete remission; DNA, deoxyribonucleic acid; OR, overall response; IA, idarubicin/cytarabine; AA, aclacinomycin/cytarabine; HA, homoharringtonine/cytarabine; CI, confidence interval; OS, overall survival; IWG, International Working Group; PR, partial remission; mCR, marrow CR; HI, hematologic improvement; SD, stable disease; NCI, National Cancer Institute; CTCAE v3.0, Common Terminology Criteria for Adverse Event version 3.0; WHO, World Health Organization; IQR, Inter-Quartile Range

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including 20 mg/m^2/day and 15 mg/m^2/day for five days.

Thus far, only very few studies have compared the efficacy and toxicity of decitabine and low-dose chemotherapy in MDS. Wu et al. [14] demonstrated both regimens were effective in higher risk MDS patients. There have been no prospective trials comparing the clinical effects. It remains unclear that whether the efficacy and safety of decitabine is comparable with that of low-dose chemotherapy for MDS-refractory anemia with excess blasts (RAEB) patients. In this study, we retrospectively assessed the efficacy and toxicity of the decitabine and low-dose chemotherapy regimens in patients with MDS-RAEB.

2. Methods

2.1. Patients

This study was approved by the Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University. For this type of study (retrospective data analysis), formal consent is not required. The study included all patients with MDS-RAEB (RAEB-1 and RAEB-2) based on the 2008 WHO classification [27], receiving low-dose chemotherapy regimens, including idarubicin/cytarabine (IA), aclacinomycin/cytarabine (AA) and homoharringtonine/cytarabine (HA), or decitabine regimen during a period from January 2011 to December 2016. Cases with one or more of the following conditions were excluded from data analysis: (1) secondary MDS; (2) having previously received chemotherapy or any demethylating agent; (3) severe comorbid cardiac, pulmonary, neurologic, or metabolic diseases; (4) malignant tumors; (5) impaired hepatic (serum total bilirubin level $\geq 2 \times$ upper normal limit) or renal (serum creatinine $\geq 2 \times$ upper normal limit) function prior to treatment.

2.2. Treatment regimens

The low-dose IA regimen consisted of intravenous infusion of idarubicin (6–8 mg/m^2/day, d1–3) and cytarabine (100 mg/m^2/day, d1–7). The maximum dosage of idarubicin was 10 mg/day for 3 consecutive days. The low-dose AA regimen consisted of intravenous infusion of aclacinomycin (20 mg/day, d1–4, or 10 mg/day, d1–8) and cytarabine (10 mg/m^2, q12h, d1–14). The low-dose HA regimen consisted of intravenous infusion of homoharringtonine (2 mg/day, d1–7) and cytarabine (10 mg/m^2, q12h, d1–14). Decitabine was delivered at a dose of 20 mg/m^2/day or 15 mg/m^2/day via intravenous infusion over 1 h for 5 consecutive days. G-CSF was administered (150 μg twice a day) when neutrophil count was lower than 1×10^9/L, and discontinued when neutrophil count elevated to 2×10^9/L. Treatment cycle was repeated every four or six weeks unless upon myelosuppression. Supportive care, including standard antiemetic, blood transfusion and antimicrobial therapy, were given at the physician's discretion.

2.3. Follow-up

The last follow-up was conducted on May 2017. The median follow-up was 16.2 months with 95% confidence interval (CI) of 4.1–28.3 months. The overall survival (OS) was defined as the period from the day of treatment to the day of death regardless of the cause, or the day of hematopoietic stem cell transplantation. Data were censored at the last follow-up.

2.4. Evaluation of treatment response and toxicity

Treatment response was assessed using modified International Working Group (IWG) 2006 response criteria [28], and categorized to CR, partial remission (PR), marrow CR (mCR), hematologic improvement (HI), stable disease (SD), and treatment failure. OR included CR, PR, mCR and HI. The extent and duration of severe bone marrow suppression was evaluated using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event version 3.0 (CTCAE v3.0) [29]. Given the fact that the majority of the patients had pre-treatment neutropenia or thrombocytopenia, we documented duration of grade 3–4 hematologic toxicity in the CR patients during treatment.

2.5. DNA sequencing

Bone marrow mononuclear cells were used to sequence 6 MDS-related genes, including 3 epigenetic regulatory genes (DNMT3A, IDH1, IDH2) and 3 splicing factor genes (SF3B1, SRSF2, and U2AF1). DNA segments that were sequenced were: exon 17/18 of DNMT3A (NM_175629.2) [30], exon 4 of IDH1 (NM_001282387.1) [31], exon 11 of IDH2 (NM_002168.3) [30], exon 13–16 of SF3B1 (NG_032903.2) [32,33], exon 1 of SRSF2 (NM_003016.4) [34], and exon 2/6 of U2AF1 (NM_001025203.1) [34].

2.6. Statistical analysis

Statistical analysis was conducted using the SPSS 22.0 software (SPSS Inc.; Chicago, IL, USA). The baseline characteristics and toxicities were compared using the Mann-Whitney U test for two independent samples. Categorical variables were analyzed with the Chi-square test or the Fisher's exact test. Survival curves were constructed by the Kaplan–Meier method and compared by the log-rank test. Statistical significance was set at $p < 0.05$ (2-sided).

3. Results

3.1. Patient characteristics

A total of 760 patients were included. 648 were ineligible; 112 were included in data analyses (Fig. 1). Among them 64 received decitabine therapy ($n = 29$ for 20 mg/m^2/day decitabine; $n = 35$ for 15 mg/m^2/day decitabine), and 48 patients received low-dose chemotherapy ($n = 12$ for IA; $n = 18$ for AA; $n = 18$ for HA). Patient baseline characteristics were generally comparable between the two groups, except for age, neutrophil count, and World Health Organization (WHO) classification (Table 1). The median age was 62 and 56 years old in the decitabine group and chemotherapy group, respectively ($p = 0.001$). The neutrophil count and the percentage of RAEB-2 in the chemotherapy group was higher than that in the decitabine group (neutrophil count: 1.2×10^9/L in the chemotherapy group vs. 0.8×10^9/L in the decitabine group, $p = 0.003$; the percentage of RAEB-2: 62.5% vs. 39.1%, $p = 0.02$). Mutation status of splicing factor or epigenetic regulatory genes was also comparable (Table 2).

3.2. Treatment response

In the overall analysis, the rate of CR and OR was 26.8% and 65.2%, respectively. The CR and OR rate was comparable between the decitabine and chemotherapy group (CR: 23.4% vs. 31.3%, $p = 0.64$; OR: 64.1% vs. 66.7%, $p = 0.60$) (Table 3). The OR rate of 20 mg/m^2/day and 15 mg/m^2/day decitabine regimen was 69.0% (20/29) and 60.0% (21/35) ($p = 0.46$), respectively. The OR rate of the low-dose chemotherapy regimens, including IA, AA, HA, was 75.0% (9/12), 72.2% (13/18), and 55.6% (10/18), respectively. The median number of cycle to achieving best response was 2 (Inter-Quartile Range, IQR: 1–3) for decitabine and 1 (IQR: 1–2) for chemotherapy. The OR rate of the first cycle in the chemotherapy group was higher than that in the decitabine group (65.1% vs. 29.3%, $p = 0.002$). However, the OR rate of the third cycle between the two groups was reversed (3.1% in the chemotherapy group vs. 22.0% in the decitabine group, $p = 0.05$). There were no significant difference in the OR rate between the two groups based on age, WHO classification, karyotypes (Table 4) and gene mutation.

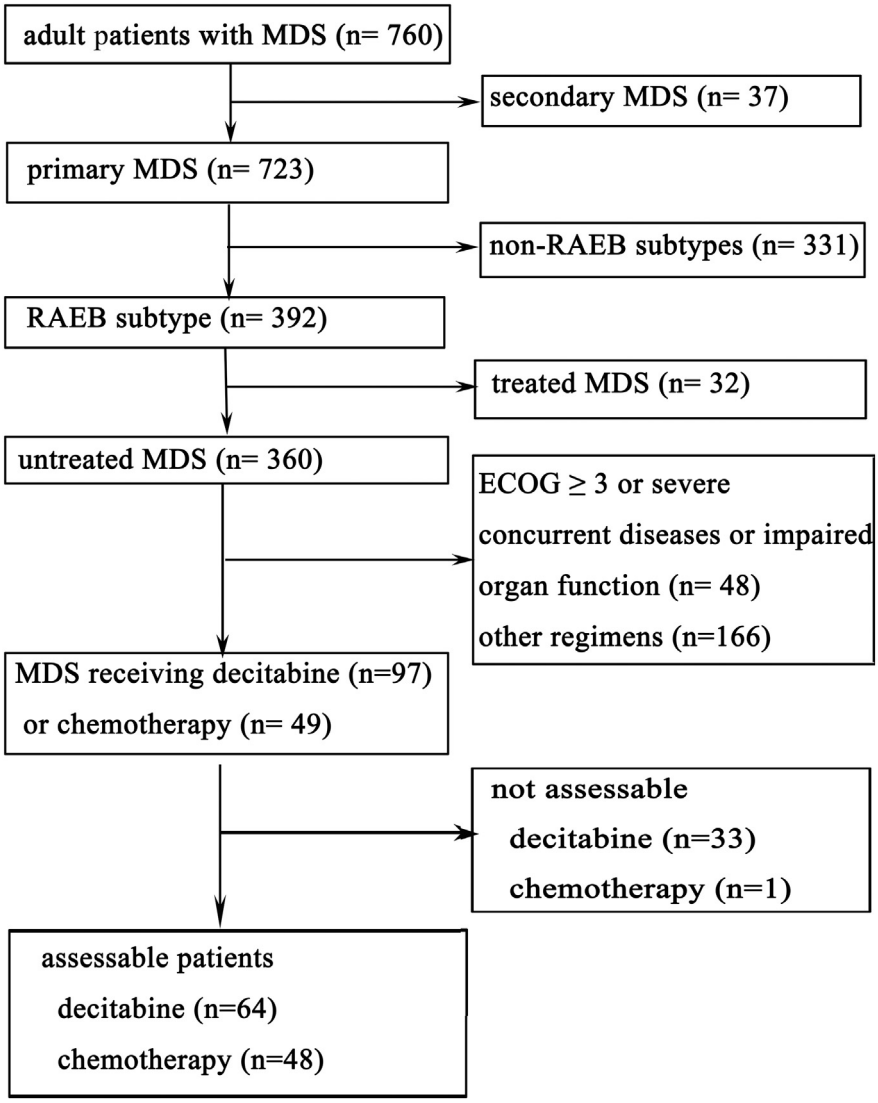

Fig. 1. Flow diagram of selecting patients with MDS in this study.

3.3. Patient survival

Of the 112 subjects, 10 were lost to follow-up (5 cases in each group). OS was not significantly different between the two groups (20.7 months with 95% CI of 16.0–25.4 months in the decitabine group vs. 13.5 months with 95% CI of 8.6–18.4 months in the chemotherapy group, $p = 0.17$) (Fig. 2). A subgroup analysis based on age revealed an association of decitabine with longer OS (20.6 months with 95% CI of 12.7–28.5 months vs. 10.0 months with 95% CI of 7.2–12.8 months, $p = 0.03$) in subjects at ≥60 years of age (Fig. 3B). A Subgroup analysis based on WHO classification, karyotypes, neutrophil count, as well as gene mutation, suggested OS were comparable between the two groups.

3.4. Toxicities

In terms of hematological toxicities, the lowest platelet count differed significantly between decitabine and chemotherapy group (10 vs. 5×10^9/L, $p = 0.001$), but the lowest neutrophil count did not (0.2 vs. 0×10^9/L, $p = 0.12$). The duration of grade 3/4 neutropenia and thrombocytopenia was not different significantly between the two groups (Table 5). In non-hematological toxicities, the incidence of infection (56.3% vs. 77.1%, $p = 0.02$) in the decitabine group was lower than that in the chemotherapy group (Table 5). No patient in each group died within four weeks from the beginning of treatment.

4. Discussion

There have been many clinical studies that suggest the five-day decitabine regimen is an effective treatment for intermediate and high risk MDS [14–23]. Meanwhile, low-dose chemotherapy is also proved to be effective and tolerated in MDS and AML patients [9–13]. In this study, we retrospectively compared the efficacy and toxicity of the two regimens in MDS-RAEB patients. The CR and OR rate in our study were similar to that reported in the papers (CR rate: 30%–55%; OR rate: 50%–70%) [9–14,35]. The response rate was comparable between the two groups, suggesting that they are both effective in MDS-RAEB patients, which is consistent with the results of previous study [14]. However, these studies had limitation with small sample size and retrospective analysis. Therefore, large-sample prospective clinical trials are required for further verification.

Studies from western countries and Asia also reported that median course to response for patients treated with decitabine monotherapy was two or later [16–23]. In this study, the median course was one in the chemotherapy group and two in the decitabine group. The OR rate at cycle 1was 65.6% and 29.3% ($p = 0.002$), respectively. However, the OR rate at cycle 3 was reversed between the two groups (3.1% vs.

Table 1
Baseline characteristics.

	Chemotherapy (n = 48)	Decitabine (n = 64)	p value
Sex, male/female	25/23	43/21	0.11
Median age, (IQR; years)	56 (40–63)	62 (55–70)	0.001*
Neutrophil count, (IQR; $\times 10^9$/L)	1.2 (0.6–2.8)	0.8 (0.5–1.3)	0.003*
Hemoglobin level, (IQR; g/L)	74 (64–88)	73 (56–87)	0.36
Platelet count, (IQR; $\times 10^9$/L)	50 (33–87)	41 (19–85)	0.15
WHO classification, RAEB-1/RAEB-2	18/30	39/25	0.02*
Cytogenetic risk, n (%)			0.80
Favorable	29 (60.4%)	38 (59.3%)	
Intermediate	7 (14.6%)	8 (12.5%)	
Unfavorable	6 (12.5%)	12 (18.8%)	
Unknown	6 (12.5%)	6 (9.4%)	
IPSS risk, n (%)			0.51
Intermediate-1	14 (29.2%)	27 (42.2%)	
Intermediate-2	19 (39.6%)	23 (35.9%)	
High	9 (18.7%)	8 (12.5%)	
Unknown	6 (12.5%)	6 (9.4%)	
IPSS-R risk, n (%)			0.70
Low	0	1 (1.6%)	
Intermediate	9 (18.8%)	7 (10.9%)	
High	18 (37.5%)	27 (42.1%)	
Very high	15 (31.3%)	23 (35.9%)	
Unknown	6 (12.5%)	6 (9.4%)	

IQR = Inter-Quartile Range, WHO = World Health Organization, RAEB = refractory anemia with excess blasts, IPSS = international prognostic scoring system, IPSS – R = IPSS – revised.
* $p < 0.05$.

Table 2
Gene mutation status.

	Chemotherapy (n = 48)	Decitabine (n = 64)	p value
Gene mutation status, n (%)			
Mutated (≥1 gene)	12/30 (40.0%)	25/50 (50.0%)	0.39
Splicing factor gene mutation status, n (%)			
Mutated (≥1 gene)	8/30 (26.7%)	18/50 (36.0%)	0.39
SF3B1 mutation	1/26 (3.8%)	2/37 (5.4%)	> 0.99
U2AF1 mutation	3/30 (10.0%)	9/41 (22.0%)	0.18
SRSF2 mutation	4/29 (13.8%)	7/44 (15.9%)	> 0.99
Epigenetic regulatory gene mutation status, n (%)			
Mutated (≥1 gene)	4/30 (13.3%)	10/50 (20.0%)	0.45
IDH1 mutation	1/30 (3.3%)	5/45 (11.1%)	0.39
IDH2 mutation	2/30 (6.6%)	4/47 (8.5%)	> 0.99
DNMT3A mutation	3/30 (10.0%)	4/46 (8.7%)	> 0.99

Table 3
Treatment response.

	Chemotherapy (n = 48)	Decitabine (n = 64)	p value
OR	32 (66.7%)	41 (64.1%)	0.60
CR	15 (31.3%)	15 (23.4%)	0.64
PR	0	2 (5.0%)	0.50
mCR/HI	17 (35.4%)	24 (37.5%)	0.56
SD	12 (25.0%)	16 (25.0%)	0.46
Failure	4 (8.3%)	7 (10.9%)	> 0.99
Median cycles to best response (IQR)	1 (1–2)	2 (1–3)	0.002*
OR rate at cycle 1	21 (65.6%)	12 (29.3%)	0.002*
OR rate at cycle 2	10 (31.3%)	19 (46.3%)	0.19
OR rate at cycle 3	1 (3.1%)	9 (22.0%)	0.05

OR = overall response, CR = complete remission, PR = partial remission, mCR = marrow CR, HI = hematologic improvement, SD = stable disease, IQR = Inter-Quartile Range.
* $p < 0.05$.

Table 4
Subgroup analysis.

	Chemotherapy (n = 48)	Decitabine (n = 64)
Age (yr)		
< 60	17/31 (54.8%)	16/27 (59.3%)
≥60	15/17 (88.2%)	25/37 (67.6%)
WHO classification		
RAEB-1	13/18 (72.2%)	25/39 (64.1%)
RAEB-2	19/30 (63.3%)	16/25 (64.0%)
Karyotype		
Favorable	21/29 (72.4%)	23/38 (82.1%)
Non-favorable	8/13 (61.5%)	16/20 (80.0%)

Non-favorable karyotypes include intermediate and unfavorable karyotypes.
yr = year, WHO = World Health Organization, RAEB = refractory anemia with excess blasts.

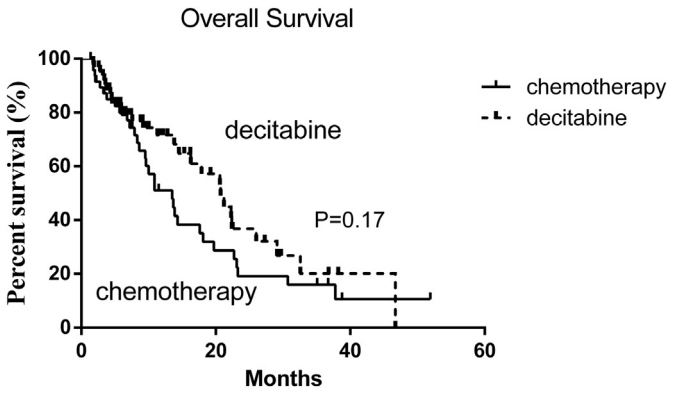

Fig. 2. Overall survival (OS) in the two groups: decitabine vs. chemotherapy.

22.0%, $p = 0.05$). The results demonstrated patients could react faster to low-dose chemotherapy than to decitabine. Besides, the OR rate in the current study was not significantly different between 20 mg/m^2/day and 15 mg/m^2/day decitabine regimen. Yang et al. [25] examined DNA methylation in patients with hematologic malignancies treated with decitabine, and found the degree of DNA hypomethylation was comparable between 15 mg/m^2/day and 20 mg/m^2/day decitabine regimens. In a retrospective study, Li et al. [24] demonstrated MDS patients with intermediate and high risk treated with decitabine of reduced dosage (15 mg/m^2/day for five days) had similar OR rate and decreased toxicities compared with previous studies. Therefore, low dose of decitabine regimen (15 mg/m^2/day) is also optimal for patients with intermediate and high risk MDS.

In our study, the percentage of patients older than 60 years in decitabine group (37/64, 57.8%) was higher than that in the chemotherapy group (17/48, 35.4%), and the percentage of RAEB-2 between the two groups was reversed (decitabine: 25/64, 39.1%; chemotherapy: 30/48, 62.5%). However, a longer OS (20.6 months) was achieved by a subgroup analysis in the current study in the decitabine group, which included higher number of patients at ≥60 years of age. This finding suggested that patients at ≥60 years of age could benefit more from decitabine treatment, which could be attributed to decreased toxicities. Previous studies suggested that decitabine is a better choice for MDS patients with poor karyotypes [14,36–38]. The current study showed prolonged OS with decitabine treatment (16.3 months) in patients with non-favorable karyotypes, compared with chemotherapy (13.5 months). Although such a difference was not statistically significant ($p = 0.12$), it showed the tendency that MDS-RAEB patients with non-favorable karyotypes, which were treated with decitabine, could achieve survival benefit.

In recent years, several gene mutations have been identified among MDS patients. The most frequently mutated genes include *SF3B1*,

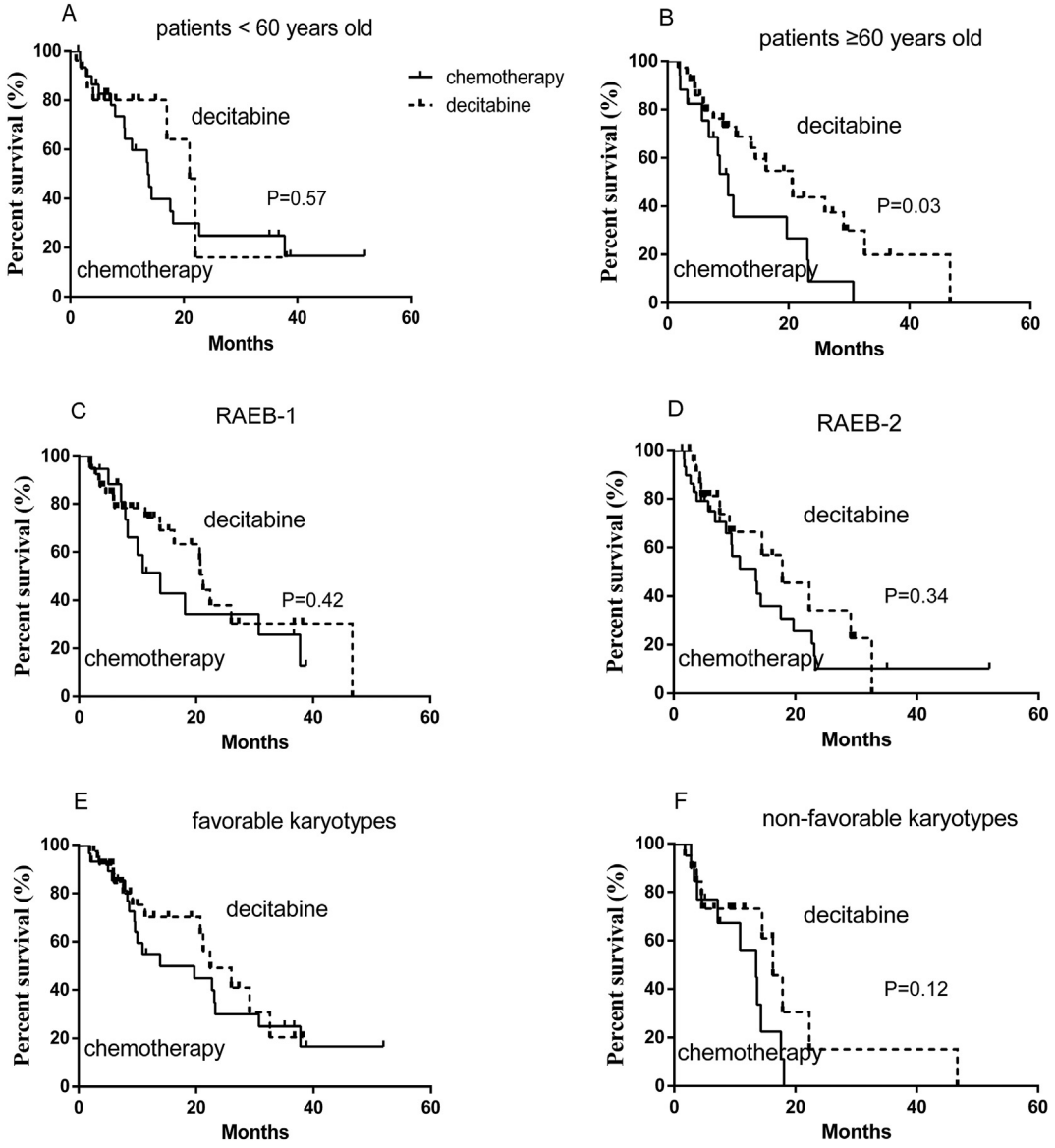

Fig. 3. Kaplan-Meier survival analysis: the results of subgroup analysis. (A) Patients < 60 years old, (B) patients ≥60 years old, (C) RAEB-1, (D) RAEB-2, (E) favorable karyotypes and (F) non-favorable karyotypes.

Table 5
Toxicities.

	Chemotherapy (n = 48)	Decitabine (n = 64)	p value
Lowest neutrophil count	0 (0–0.2)	0.2 (0–0.5)	0.12
Lowest platelet count	5 (3–7)	10 (8–15)	0.001*
Median duration of neutropenia in CR patients (IQR; days)	15 (11 − 22)	16 (0–27)	0.95
Median duration of thrombocytopenia in CR patients (IQR; days)	22 (13–28)	17 (0–26)	0.35
Infection	37 (77.1%)	36 (56.3%)	0.02*
Hemorrhage	11 (22.9%)	6 (9.4%)	0.05
Cardiac	0	1 (1.6%)	> 0.99
Hepatic	0	0	> 0.99
Renal	0	0	> 0.99

* $p < 0.05$; CR = complete remission, IQR = Inter-Quartile Range; neutropenia is defined as $< 1 \times 10^9$/L; thrombocytopenia is defined as $< 50 \times 10^9$/L.

U2AF1, *SRSF2*, *ZRSR2*, *TET2*, *DNMT3A*, *EZH2*, *ASXL1*, *RUNX1*, *TP53*, *STAG2*, *CBL*, and *NRAS*. Only *SF3B1* mutation has been associated with a more favorable prognosis in several, but not all studies [39–41]. Other mutated genes, including *U2AF1*, *SRSF2*, *DNMT3A*, *IDH1/2*, *SETBP1* and *CBL*, have been associated with poor survival and progression to AML [39,42–48]. In several studies, gene mutations also affect the response rate [49,50]. Itzykson et al. [49] found that patients with mutated *TET2* had an 82% response rate to azacitidine compared to 45% of patients with wildtype *TET2*. However, response duration and OS were comparable in the two groups. Bejar et al. [50] also demonstrated *TET2* mutation was only associated with better response rate to DNA hypomethylating agents. In the current study, we examined the mutational status of the 3 epigenetic regulatory genes (*IDH1/2* and *DNMT3A*) and the 3 splicing factor genes (*SF3B1*, *SRSF2*, and *U2AF1*) in 112 MDS-RAEB patients. Among patients harboring mutated splicing factor genes or epigenetic regulatory genes, OS and response rate were not significantly affected between the decitabine and chemotherapy group. However, it had limitations with small sample size and only six genes sequenced. Other mutated genes, which also affected the response and survival, were not sequenced. Further clinical trials are required to

verify the results.

AML-type chemotherapy increases early-phase mortality (5%–20%) and decreases long-term survival [7,23]. In addition, most of intermediate- and high-risk MDS patients are elderly with diminished function reserve. Therefore, chemotherapy regimens in the current study were modified (decreased dosage). These regimens contributed to zero therapy-related death within first four weeks. The lowest count of platelet (10 vs. 5×10^9/L, $p = 0.001$) and neutrophil (0 vs. 0.2×10^9/L, $p = 0.12$) in the decitabine group was higher than that in the chemotherapy group. Besides, the incidence of Grade 3–4 infection (56.3% vs. 77.1%, $p = 0.02$) in the decitabine group was lower significantly. These results suggested that decitabine treatment was safer than low-dose chemotherapy in MDS-RAEB patients.

In brief, this study show that both decitabine and low-dose chemotherapy are effective for MDS-RAEB patients. The benefit of survival is most apparent in patients at ≥60 years of age. And decitabine treatment is safer because of lower incidence of toxicities. These results need to be validated by multi-center, double-blind, and controlled clinical trials.

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Conflict of interest

The authors have no conflicts of interest. The funding sources had no involvement in study design; collection, analysis and interpretation of data; as well as in the decision to submit the article for publication.

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HT and LY designed the study. LY and HT wrote the manuscript. YL analyzed and arranged the data. HY, LY, XZ, CM and YL performed the gene mutation analysis. WX, LM, XY, JW, YL and JJ provided patient samples and data. HT guided the project design and article modification. We sincerely thank the sample donors and clinical investigators who participated in this study.

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