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Original Article

A retrospective study comparing azacitidine with decitabine in Chinese patients with refractory anemia with excess blast based on two clinical trials in a single center

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Abstract: The aim of the present study was to conduct a retrospective analysis of efficacy and safety profiles of azacitidine (AZA) *versus.* decitabine (DAC) in Chinese patients with intermediate or higher-risk MDS, which was based on two clinical trials in a single center. A total of 40 included MDS patients diagnosed with refractory anemia with excess blast (RAEB) were from two independent clinic trials. Patients in each trial received either AZA (n = 19) or DAC (n = 21) respectively, and the effectiveness as well as the safety profile of the two drugs were compared. Patients treated with AZA showed a comparative efficacy to DAC group with regard to the overall response rate (73.7% *versus.* 76.2%, *P* = 0.86), overall survival (median: 19.3 *versus.* 20.8 months, *P* = 0.56), progression-free survival (median: 12.3 *versus.* 9.3 months, *P* = 0.43) and leukemia-free survival (median: 22.8 *versus.* 26.6 months, *P* = 0.62). Patients treated with DAC showed slightly higher incidence of severe hematological adverse events during the whole treatment. Comparing hematological AEs in each observation interval, a trend of higher percentage of neutropenia, leukopenia and anemia as well as treatment delays were seen during the first 6 cycles in the DAC group.

Keywords: Myelodysplastic syndromes, azacitidine, decitabine, comparison, toxicity

Introduction

Myelodysplastic Syndromes (MDS) are a clonal disorders of hematopoietic stem cells characterized by ineffective hematopoiesis in the bone marrow [1]. Patients with a higher-risk MDS are associated with increased risk of transforming to acute myeloid leukemia (AML), the primary goal of therapies in these patients is to alter the natural courses of the disease, while allogeneic stem-cell transplantation (allo-SCT) being the only curable arm [2, 3]. The DNA hypomethylating agents (HMAs) azacitidine (AZA) and decitabine (DAC) have been considered as the first-line therapies in treating higher-risk MDS in many areas. Several multi-center phase III clinical trials have compared either AZA or DAC with conventional arms including best supportive care (BSC), and both drugs showed significant overall survival (OS) benefit in patients with MDS [4-6]. This present study represented the first attempt to retrospectively compare the efficacy and safety profiles of AZA and DAC in Chinese MDS patients, which was based on two published clinical trials in a single center [7, 8].

Methods

Patients and treatment

A total of 40 patients were included and analyzed, all of them were diagnosed with MDS-REAB between November 2009 and December 2013. All eligible patients data were from the two clinical trials in Guangdong General Hospital, one was 'an open-label, phase-3b study of decitabine for treatment of myelodysplastic

syndrome in Chinese patients', and the other one was 'a multicenter, single-arm, open-label phase 2 study of azacitidine for treatment of Chinese patients with higher risk myelodysplastic syndromes' [7, 8]. Patients were diagnosed with intermediated or higher risk MDS-RAEB according to the 2008 WHO criteria and the revised International Prognostic Scoring System (IPSS-R) [9, 10]. All patients had received at least 2 cycles of HMA treatment courses.

Assessment of efficacy and safety

Outcomes of the two trials were compared with the following efficacy endpoints: overall response rate (ORR), overall survival (OS), progression-free survival (PFS), and leukemia-free survival (LFS). ORR includes the rate for complete response (CR), partial response (PR), marrow complete response (mCR) and hematological improvement (HI). Response to HMAs therapy was assessed according to the modified International Working Group (IWG 2006) response criteria [11]. The OS was defined as the time from the initiation of HMAs treatment to the date of death from any causes or to the last follow-up. The PFS were defined as the time from the initiation of HMAs medication to treatment failure, progression of diseases or death from any causes. The time period of AML transformation (PFS) was measured from the initiation time of HMAs treatment to the time with greater than 20% blasts in the bone marrow.

Severe (grade 3 or higher) hematological or non-hematological adverse events (AEs) occurred during HMAs treatment were evaluated according to the Common Toxicity Criteria of the National Cancer Institute, version 3.0 [12]. Baseline RBC transfusion-dependence (TD) was defined as receiving ≥ 1 U RBC transfusion within 56 days before the first HMAs dose. RBC transfusion-independence (TI) was defined as receiving no RBCs transfusion for at least a consecutive 56-day period during the HMAs treatment.

Statistical analysis

Statistical analysis was conducted by using SPSS 17.0 software. Continuous variables were compared using the Mann-Whitney *U* test or Student's *t* test for two independent samples. Categorical variables were compared using the Chi-square test or the Fisher's exact test. Survival analysis was conducted using the Kaplan-Meier method, and the differences were compared by employing the log-rank test. Statistical significance was set at $P < 0.05$ (2-sided). The hazard ratio (HR) and 95% confidence intervals (CIs) were estimated in comparison to a reference risk of 1.0.

Results

Patients and treatment

Of all analyzed patients, twenty-one patients (21/40, 52.5%) were treated with DAC while the other nineteen patients (19/40, 47.5%) with AZA. Baseline characteristics of the study population included sex, age, treatment cycles, peripheral blood cell count, WHO classification, cytogenetic risk group and IPSS-R risk group (**Table 1**). There was no significant difference concerning baseline characteristics between the two cohorts, while a higher proportion of RAEB-II was seen in the AZA group (89.5% *versus*. 66.7%, $P = 0.13$). Median treatment cycles were 12 (range, 2~26 cycles) in the AZA group and 7 (range, 3~21 cycles) in the DAC group ($P = 0.13$) (**Table 2**). Four patients (4/19, 21.1%) dropped the treatment in AZA group due to severe infection, while nine patients (9/21, 42.9%) did not finish 6 cycles of treatment in the DAC group (21.1% *versus*. 42.9%, $P = 0.14$). Among these nine patients in the DAC group, three patients dropped out due to severe infection, three patients died because of severe hemorrhage, and three patients transformed to AML, respectively.

Treatment response

Fourteen patients (14/19, 73.7%) who received AZA responded to the treatment: one CR (1/19, 4.8%); five mCR only (5/19, 26.3%); one HI only (1/19, 5.3%) and seven patients achieved both mCR and HI (7/19, 36.8%). Responses were seen in sixteen (16/21, 76.2%) patients in the DAC group: two CR (2/21, 9.5%); six mCR only (6/21, 28.6%); one HI only (1/21, 4.8%); and seven patients (7/21, 33.3%) achieved both mCR and HI. No significant difference was observed between the two groups ($P = 0.50$) according to the criteria [11]. The median number of treatment cycles needed to achieve patients' best response (BR) was 3 (range, 2~19 cycles) in the AZA group and 2 (range, 1~10 cycle) in the DAC group ($P = 0.14$). The

Table 1. Baseline characteristics of the azacitidine and decitabine cohorts

	Azacitidine group (n = 19)	Decitabine group (n = 21)	*P* value
Sex, n (%)			0.53
Male	9 (47.4%)	13 (61.9%)	
Female	10 (52.6%)	8 (38.1%)	
Median age (years)	61 (38~73)	63 (33~79)	0.94
Treatment cycles	12 (2~26)	7 (3~21)	0.13
Hemoglobin (g/L)	70 (50~114)	68 (42~98)	0.43
Leukocyte count (10^9/L)	2.3 (0.88~11.75)	2.4 (1.13~4.68)	0.14
Platelet count (10^9/L)	68 (11~353)	53.6 (5~336)	0.66
Neutrophil count (10^9/L)	0.93 (0.27~9.64)	0.86 (0.23~3.44)	0.29
WHO classification, n (%)			0.13
RAEB-1	2 (10.5%)	7 (33.3%)	
RAEB-2	17 (89.5%)	14 (66.7%)	
Cytogenetic risk group, n (%)			-
Normal	10 (53.4%)	11 (53.4%)	
Good	2 (10.5%)	4 (19.0%)	
Intermediate	2 (10.5%)	4 (19.0%)	
Poor	1 (5.3%)	1 (4.8%)	
Very poor	2 (10.5%)	0	
Unassessable	2 (14.3%)	1 (4.8%)	
IPSS-R risk group, n (%)			1.00
Intermediate	6 (31.6%)	7 (33.3%)	
High	8 (42.1%)	10 (47.6%)	
Very high	5 (26.3%)	4 (19.0%)	

WHO, the world health organization; RAEB, refractory anemia with excess blast; IPSS-R, revised International Prognostic Scoring System.

duration of BR were 6.2 months (range: 1.0~11.9 months) in the AZA group and 3.5 months (range: 1.2~23.2 months) in the DAC group (*P* = 0.61). Similar incidence of death and transformation to AML were seen (**Table 2**).

Survival analysis

With a median follow-up of 19.3 months of the entire 40 patients, three patients were still alive at the last follow-up in each group, respectively. The median OS was 19.3 months (95% CI 7.21-31.39) in the AZA group and 20.8 months (95% CI 9.59-32.02) in the DAC group; no significant difference was observed between the two groups (HR 1.23; 95% CI 0.61-2.48; log-rank test, *P* = 0.56) (**Figure 1A**). Median PFS was 12.3 months (95% CI, 9.31-15.29) in the AZA group *versus.* 9.3 months (95% CI, 6.72-11.88) in the DAC group (HR 0.77; 95% CI 0.40-1.48; log-rank test, *P* = 0.43) (**Figure 1B**). As for AML transformation, the median LFS in the AZA group was 22.8 (95% CI, 21.67-23.94) *versus.* 26.6 months (95% CI NR) in the DAC group (HR 1.27; 95% CI 0.49-3.31; log-rank test, P = 0.62) (**Figure 1C**).

It was reported that the number of HMAs cycles laid an impact on patients' survival, thus we conducted a cycle-related survival analysis to confirm this notion. When separately comparing OS, PFS, LFS according to whether patients received no less than 2, 4 or 6 HMA cycles, similar survival was observed (**Table 3**). Patients who received no less than 4 cycles of HMAs (no matter which drug) showed a remarkably superior survival compared to those who didn't receive 4 cycles of HMAs (HR: 3.120; 95% CI 1.375-7.077, *P* = 0.04) (Figure S1A). Similar superior OS was also found in patients who responded to HMAs (including CR, PR, mCR, HI or multiple response). A median OS of 24.5 months (95% CI: 15.375-33.625) were seen in the responders' group *versus.* 9.3 months (95% CI: 1.831-16.769) in the non-responders group (HR 2.516; 95% CI 1.237-5.116; *P* = 0.03) (Figure S1B).

Safety and toxicities

During the first 12 months of treatment, four patients (4/19, 21.1%) died in the AZA group, six patients (6/21, 28.6%) died in the DAC group (*P* = 0.58). The mortality at 24 months was 10/19 (52.6%) in the AZA group *versus.* 11/21 (52.4%) in the DAC group (*P* = 0.99); the cumulative mortality of the two cohorts were 84.2% (16/19) in the AZA and 85.7% (18/21) in the DAC respectively, mainly attributed to AML (42.1% in the AZA group *versus.* 38.1%); severe infections (21.1% in the AZA group *versus.* 23.8%) and hemorrhage (15.8% in the AZA group *versus.* 14.3%).

Table 2. Treatment response in the two HMA groups

Response by IWG 2006 criteria	Azacitidine group (n = 19)	Decitabine group (n = 21)	*P* value
CR	1 (5.3%)	2 (9.5%)	-
mCR only	5 (26.3%)	6 (28.6%)	-
HI only	1 (5.3%)	1 (4.8%)	-
mCR+HI	7 (36.8%)	7 (33.3)	-
SD	3 (15.8%)	4 (19.0%)	-
Treatment failure	2 (10.5%)	1 (4.8%)	-
ORR (CR+PR+mCR+HI)	14 (73.7%)	16 (76.2%)	0.86
Cumulative incidence of ORR			
At 2nd cycle	5 (26.3%)	8 (38.1%)	0.43
At 4th cycle	11 (57.9%)	14 (66.7%)	0.57
At 6th cycle	13 (68.4%)	15 (71.4%)	0.84
First BR (best response) cycle	3 (2~19)	2 (1~10)	0.14
Duration of response			
Duration of BR (months)	6.2 (1.0~11.9)	3.5 (1.2~23.2)	0.61
Duration of CR (months)	10.8 (10.8)	5.2 (1.2~9.3)	-
Duration of mCR (months)	3.8 (1.0~30.1)	2.6 (1.7~23.9)	0.43
Duration of HI (months)	6.0 (1.0~30.1)	9.4 (2.1~23.2)	0.13
12-months incidence of AML transformation (%)	2 (10.5%)	4 (19.0%)	0.67
24-months incidence of AML transformation (%)	7 (36.8%)	7 (33.3%)	0.82
Cumulative incidence of AML transformation (%)	8 (42.1%)	8 (38.1%)	0.80
12-months incidence of death (%)	4 (21.1%)	6 (28.6%)	0.58
24-months incidence of death (%)	10 (52.6%)	11 (52.4%)	0.99
Cumulative incidence of death (%)	16 (84.2%)	18 (85.7%)	0.89

CR, complete response; mCR, marrow complete response; HI, hematological improvement; SD, stable disease; ORR, overall response rate; AML, acute myeloid leukemia.

Severe hematological and non-hematological AEs were screened. In general, patients treated with DAC showed slightly higher incidence of neutropenia (85.7% in the DAC group *versus.* 73.7%, *P* = 0.44) and leukopenia episodes (85.7% in the DAC group *versus.* 78.9%, *P* = 0.69) during the whole treatment; higher incidence of severe anemia was also observed in the DAC group (76.2% *versus.* 52.6%, *P* = 0.12); incidence of thrombocytopenia remained similar between the two cohorts (**Table 4**).

When evenly separating the first 8 HMAs cycles into 4 observation intervals, patients treated with DAC showed higher incidence of neutropenia episodes during the first 6 HMAs cycles, however, no significant difference was observed (**Figure 2A**, **2B**); likewise, higher incidence of severe anemia episodes was observed in the DAC group during the first 8 cycles (**Figure 2C**); the percentage of RBC-TI patients was similar during the whole treatment (**Figure 2D**). On the other hand, these curves of mentioned AEs or RBC-TI patients remained similar in the shape as HMAs treatment went on, indicating analogous pharmacological and toxicological effects between these two regimens.

Toleration to HMAs was also analyzed by means of comparing the incidence of treatment delays, which were attributed to the drug-related toxicities: 12.5%-26.3% cycles were delayed during the AZA treatment, while the incidence of treatment delays in the DAC group was 18.8%-29.6%. When analyzed HMAs treatment beyond the 6th cycle, patients received DAC exhibited a significant higher rate of treatment delays (21/71 *versus.* 25/144, *P* = 0.04) (**Figure 2E**).

Discussion

Reported by other published works comparing AZA and DAC, both drugs showed comparable efficacy in treating MDS patients [13-15], while different survival exist between the two HMAs concerning to some special subgroups. There was a superior overall survival for AZA among patients with more than 65 years old (*P* =

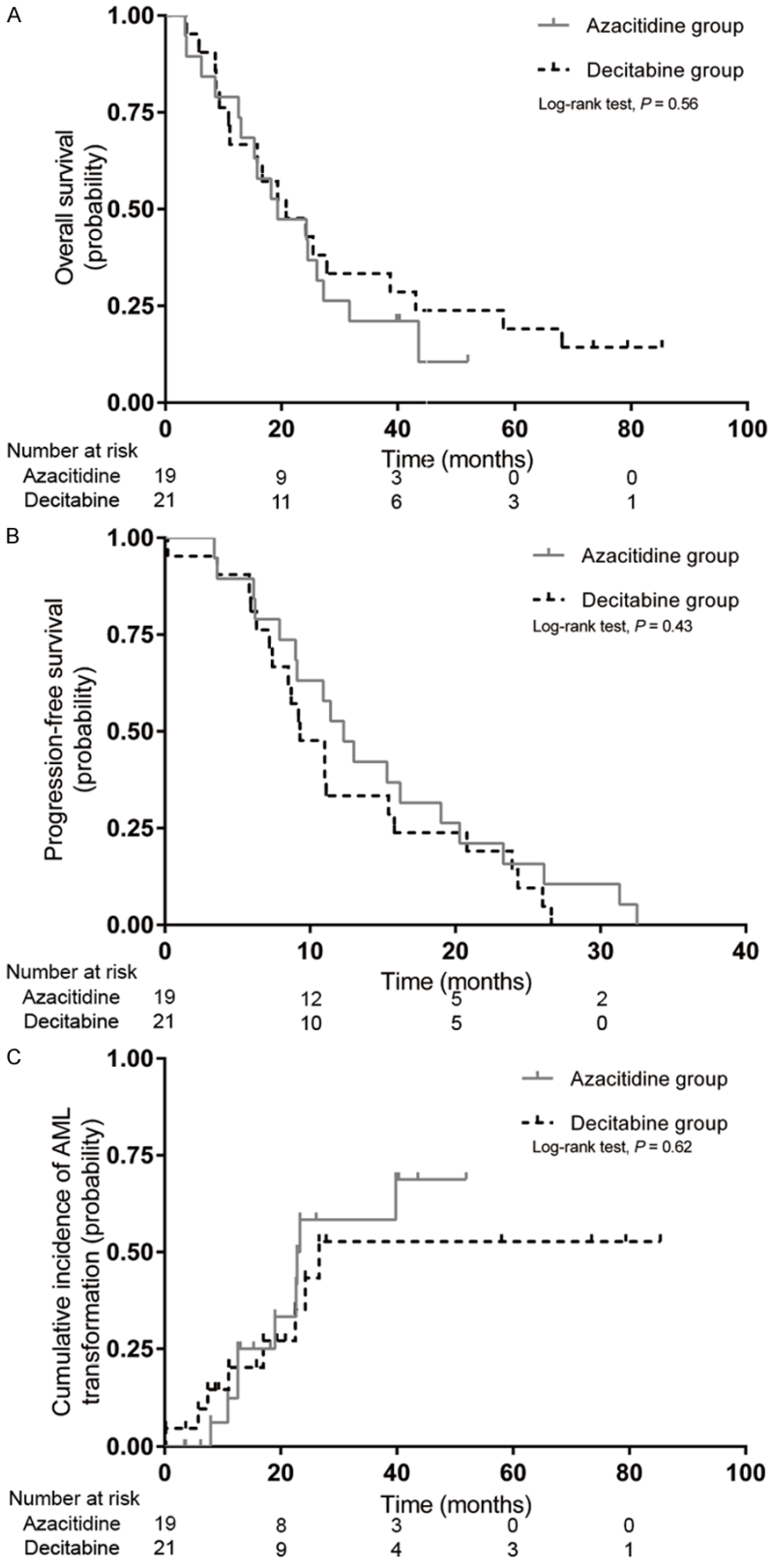

Figure 1. Analysis of the efficacy endpoints. A. Overall survival (OS) by hypomethylating agents (HMAs) in the two groups. B. Progression-free survival (PFS) by HMAs in the two groups. C. Leukemia-free survival (LFS) by HMAs in the two groups.

0.017) [13]; Patients with more than one-year MDS duration showed a significant better survival in the AZA group than DAC [14]. Meta-analysis also found that AZA provided a survival benefit on MDS patients than DAC [16, 17].

In accordance with former real-world studies rather than meta-analysis, results from our study revealed a comparable efficacy between AZA and DAC regarding to ORR (73.7% *versus.* 76.2%), OS (19.3 *versus.* 20.8 months), PFS (12.3 *versus.* 9.3 months) and time to AML transformation (22.8 *versus.* 26.6 months) in Chinese MDS-RAEB patients, while patients who received DAC showed a slightly longer HI duration (6.0 *versus.* 9.4 months, P = 0.13). Meanwhile, our retrospective analysis also confirmed the previously reported findings that a better OS goes for patients who received longer HMA treatment and patients who responded to HMAs (Figure S1A, S1B).

There are divergences in the toxicity profiles of the two HMAs. According to a phase II study conducted comparison between DAC and AZA in USA, both AZA and DAC were well tolerated in MDS/MPN patients [18]. Researches from Korean had reported strong myelosuppression in both AZA and DAC, and higher probability for MDS patient who received DAC to undergo hematological AEs or bleeding episodes [13, 14]. In another report conducted in Turkey, higher proba-

Table 3. Survival endpoints of two HMAs in general group and subgroups

Patients	Overall survival (OS, months)			Progression-free survival (PFS, months)			Leukemia-free survival (LFS, months)		
	AZA group	Decitabine group	*P* value (HR; 95% CI)	AZA group	Decitabine group	*P* value (HR; 95% CI)	AZA group	Decitabine group	*P* value (HR; 95% CI)
Overall	19.3 (n = 19)	20.8 (n = 21)	0.56 (1.23; 0.61-2.48)	12.3 (n = 19)	9.3 (n = 21)	0.43 (0.77; 0.40-1.48)	22.8 (n = 19)	26.6 (n = 21)	0.62 (1.27; 0.49-3.31)
Received 4 cycles	24.3 (n = 16)	24.2 (n = 17)	0.76 (1.13; 0.52-2.45)	13.0 (n = 16)	11.0 (n = 17)	0.45 (0.76; 0.37-1.56)	23.3 (n = 16)	26.6 (n = 17)	0.77 (1.16; 0.42-3.22)
Received 6 cycles	24.5 (n = 15)	38.7 (n = 11)	0.26 (1.73; 0.67-4.45)	15.3 (n = 15)	15.4 (n = 11)	0.70 (0.85; 0.38-1.92)	23.3 (n = 15)	26.6 (n = 11)	0.58 (1.37; 0.45-4.20)

AZA, azacitidine; DAC, decitabine; HR, hazard ratio; 95% CI, 95% confidential interval.

Table 4. Severe (grade 3 or higher) hematological or non-hematological adverse events of two HMAs

	AZA group (n = 19)			DAC group (n = 21)			*P* value of total
	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total	
Hematological AEs							
Anemia	8	2	10 (52.6%)	5	11	16 (76.2%)	0.12
Leukopenia	7	8	15 (78.9%)	8	10	18 (85.7%)	0.69
Neutropenia	3	11	14 (73.7%)	1	17	18 (85.7%)	0.44
Thrombocytopenia	6	7	13 (68.4%)	3	12	15 (71.4%)	0.84
Non-hematological AEs							
Febrile neutropenia	2	0	2 (10.5%)	2	0	2 (9.5%)	1.00
Pneumonia	5	3	8 (42.1%)	7	2	9 (42.9%)	0.96
Peripheral infection	4	0	4 (21.0%)	4	1	5 (23.8%)	1.00
Upper respiratory tract infection	4	1	6 (31.6%)	2	2	4 (19.0%)	0.36
Hemorrhage	1	1	3 (15.8%)	3	0	3 (14.3%)	1.00

AZA, azacitidine; DAC, decitabine; AE, adverse events.

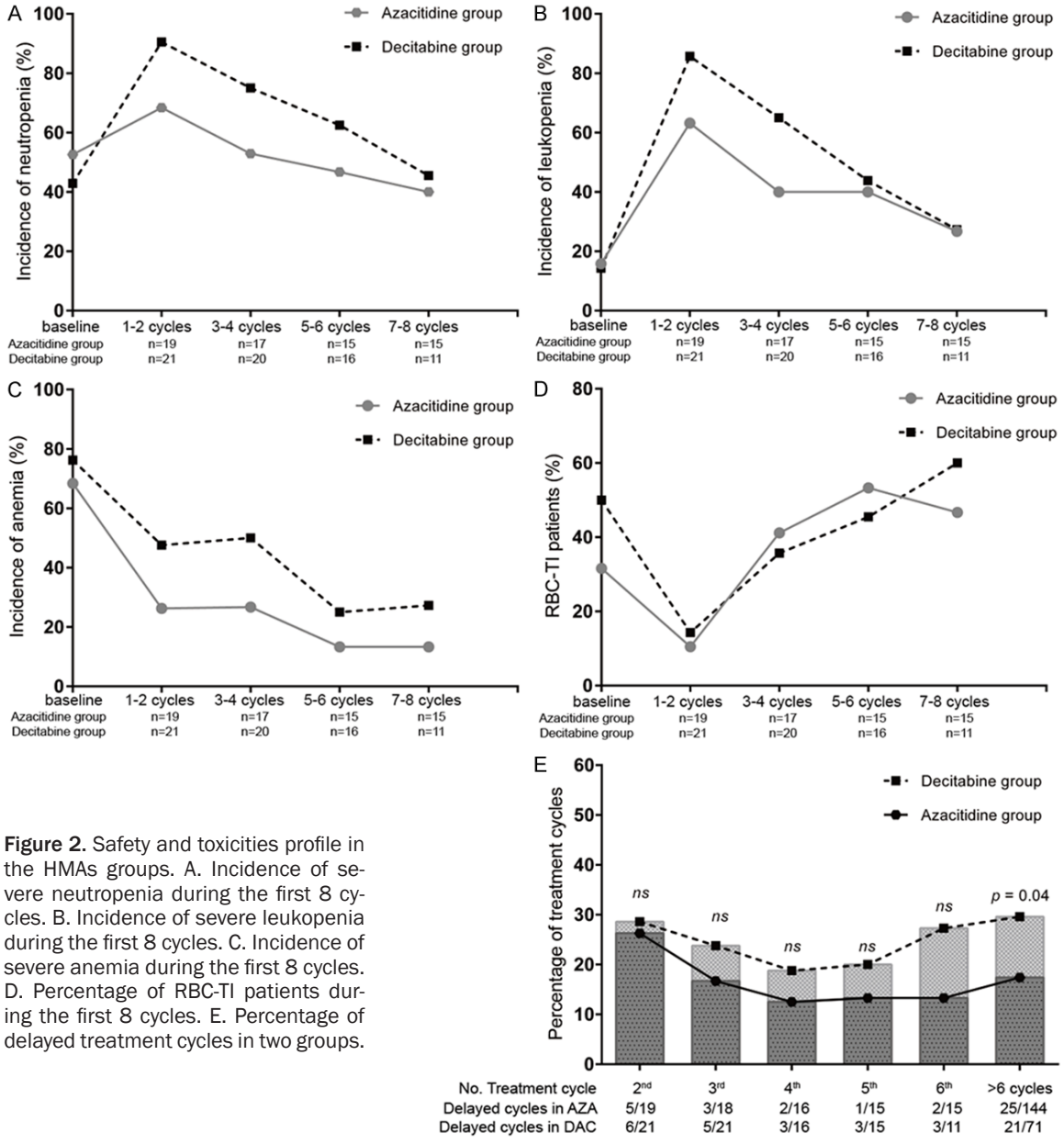

Figure 2. Safety and toxicities profile in the HMAs groups. A. Incidence of severe neutropenia during the first 8 cycles. B. Incidence of severe leukopenia during the first 8 cycles. C. Incidence of severe anemia during the first 8 cycles. D. Percentage of RBC-TI patients during the first 8 cycles. E. Percentage of delayed treatment cycles in two groups.

bility for patients who received AZA to get febrile neutropenia were seen compared to patients who received DAC [15].

Similar to Korean researchers, we found higher incidence of severe hematological AEs in the DAC group during the whole treatment: 76.2% *versus.* 47.6% for anemia ($P = 0.12$); 85.7% *versus.* 73.7% for neutropenia ($P = 0.44$); 85.7% *versus.* 78.9% for leukocytopenia ($P = 0.69$). Comparing hematological AEs in each observation interval, a trend of higher percentage of neutropenia, leukopenia and anemia were also seen during the first 6 cycles in the DAC group (**Figure 2A-C**). As the treatment went on, the highest peaks of neutropenia and leukopenia curves emerged at the 2nd cyle in both HMAs. Higher percentage of RBC-TI patients emerged at 2-8 cycles in both HMAs group (**Figure 2D**). These results implied that analogous pharmacological toxicities may exist between AZA and DAC, both drugs led to the myelosuppression at the early stage of treatment. After the 2nd cycle of HMAs, patients seemed to recovery from myelosuppression during next 5-8 cycles, while a higher trend of toxicities curves were seen in the DAC group. Higher incidence of cycles delays was required in DAC then in AZA arm before 6th cycle (**Figure 2E**).

In brief, the current retrospective study provides evidence for comparable efficacies of AZA and DAC in Chinese MDS patients. In accordance with studies conducted in Korea, both HMAs showed high hematological toxicities in Chinese MDS patients, we found remarkable lower incidence of hematological AEs and cycles delays in patients treated with AZA rather than DAC. Thus, prospective comparisons AZA with DAC in Chinese patients are needed in future.

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Disclosure of conflict of interest

None.

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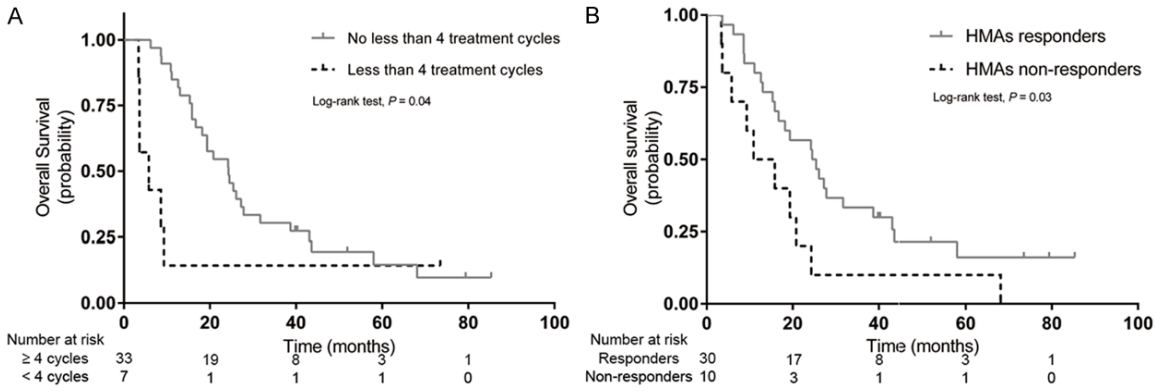

Figure S1. A. OS by HMAs in patients who received less than 4 cycles *versus.* patients received no less than 4 cycles. B. OS by HMAs in the responders (including CR, PR, mCR and HI) *versus.* non-responders.