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Azacitidine versus decitabine in patients with refractory anemia with excess blast—Results of multicenter study

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ABSTRACT

The present study aimed to compare the efficacy and safety of azacitidine and decitabine in patients with myelodysplastic syndrome (MDS). A total of 88 patients diagnosed with refractory anemia with excess blast (RAEB) treated with azacitidine ($n = 57$) or decitabine ($n = 31$) were evaluated. Comparisons between azacitidine and decitabine groups were performed in the whole cohort, and in a 1:1 propensity score-matched cohort in order to reduce the simple selection bias. Patients who received azacitidine or decitabine had comparable overall response rates in both the unmatched (49.1% vs. 64.5%, $p = 0.166$) and the propensity-matched cohorts (52% vs. 68%, $p = 0.248$). The cumulative incidence of AML transformation at one year was comparable between azacitidine and decitabine in the unmatched (24.0% vs. 31.3%, $p = 0.26$) and in the propensity-matched cohorts (18.7% vs. 31.5%, $p = 0.11$). There was no difference in terms of transfusion requirement, febrile neutropenia episodes or the need for antifungal use during the treatment cycles in the propensity-matched cohort. The median overall survival was 20.4 months for azacitidine and 16.8 months for decitabine ($p = 0.59$). Finally, we found that at least a four-cycle treatment with any HMA was a favorable factor. In conclusion, both azacitidine and decitabine have similar efficacy and toxicity profiles in the treatment of MDS-RAEB.

1. Introduction

Refractory anemia with excess blast (RAEB) is a type of myelodysplastic syndrome (MDS) with 5–19% myeloblasts in the bone marrow. RAEB type 1 (RAEB-1) and type 2 (RAEB-2) together constitute about 40% of all MDS cases, and they have a shorter survival rate as well as a high risk of acute myeloid leukemia (AML) transformation [1]. Available treatment options for patients with MDS-RAEB include hypomethylating agents (HMAs), AML-like chemotherapy, and allogeneic stem-cell transplantation (allo-SCT) [2]. Although allo-SCT is the only curative treatment modality, most patients are not eligible for intensive therapy because of their advanced age and comorbidities. Currently, the HMAs, azacitidine and decitabine, are the standard of care in a large majority of patients with MDS-RAEB [2].

The antineoplastic effects of HMAs are attributed to being the result of HMAs' ability to promote the hypomethylation of DNA. The demethylation of DNA by these agents leads to the restoration of cancer-suppressing functions and normal gene differentiation and proliferation [3,4]. After phosphorylation by different kinases, decitabine is incorporated into DNA and acts by inhibiting DNA methyltransferase that causes hypomethylation and subsequent cell death [4]. Azacitidine also exerts a direct cytotoxic effect on abnormal hematopoietic cells in the bone marrow and inhibits protein synthesis as a result of incorporation into RNA [5,6]. Although azacitidine is a more potent inhibitor of DNA methylation and proliferation of leukemic cells than decitabine, these agents have

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different effects on the genes as well as different clinical activities [5,7–9].

Several phase II trials have demonstrated the efficacy and safety of azacitidine and decitabine in patients with MDS [10–15]. Thereafter, in many phase III trials, comparing azacitidine or decitabine with conventional care regimens or the best supportive care has shown that HMAs are effective with inconsistent results [16–19]. The AZA-001 study remains the only prospective randomized trial showing a survival advantage of azacitidine in higher-risk MDS patients [18]. On the other hand, Kantarjian showed that decitabine can increase the time to AML transformation [17]. In a few meta-analyses comparing decitabine and azacitidine for the treatment of MDS, slightly different results were reported [20–22]. Even though both agents showed higher response rates, only azacitidine alone showed an advantage in terms of overall survival.

In 2013, two retrospective comparative analyses between azacitidine and decitabine have been reported [23,24]. Among subgroups, survival was significantly higher with azacitidine. In terms of overall survival, the inferior outcome of decitabine should be interpreted with caution for a variety of reasons, due to the lack of a prospective randomized head-to-head study. Therefore, in routine clinical practice, there is still an unresolved question: which of the HMAs, azacitidine or decitabine, should be started for a patient with MDS.

The aim of our retrospective study was to compare the response rates (RR), overall survival (OS), and cumulative incidences of AML transformation at one year, as well as the hematologic toxicity and transfusion requirement of azacitidine and decitabine in patients diagnosed with MDS RAEB types 1 and 2.

2. Methods

2.1. Patients

Data from a total of 92 patients with previously untreated MDS, who were treated by HMAs between April 2007 and July 2015, were collected from six Turkish centers. Patients with refractory anemia with excess blast-I or II, who had at least International Prognostic Scoring System (IPSS) intermediate-1 risk disease, were included in the final analyses. These patients should have data about the date of the diagnosis, the date of the first dose of HMA, the date of death, the date of AML transformation, the date of last contact, the status of survival and AML transformation, the response to HMA, and the number of HMA cycles the patients received. Exclusion criteria for the final analyses included patients with low-risk MDS or chronic myelomonocytic leukemia or MDS with bone marrow fibrosis as well as those who did not fulfill the abovementioned minimum criteria.

2.2. Study design

This is a retrospective study in which all data were recorded from patients' chart files and/or electronic medical records. The institutional ethic committee of Akdeniz University approved the study (*approval no.* 70904504/22). Permissions obtained from all participating institutions for data use were presented to the institutional ethic committee.

2.3. Baseline definitions

The MDS risk category was assessed according to the original IPSS [25]. The Revised-IPSS (R-IPSS) and the World Health Organization (WHO) Prognostic Scoring System (WPSS) were also used for risk stratification [26,27]. Centers were requested to reclassify the patients with MDS into subgroups based upon the WHO classification if they had any patients who had previously been classified according to the French-American-British (FAB) classification. [28,29]. Secondary or therapy-related MDS was defined as MDS that had developed after previous chemotherapy, radiotherapy, or any other medications. Cytogenetic data were categorized as follows: favorable, normal, −Y, del(5q), del(20q); unfavorable, complex (>3 cytogenetic abnormalities) and del(7q); and intermediate, all other abnormalities [25]. Standard G-banding and/or fluorescence in situ hybridization (FISH) were used to determine cytogenetic abnormalities, if any.

Other data collected included the results of cytogenetic analyses, hemoglobin level, leukocyte, neutrophil, monocyte and platelet counts, and bone marrow blast percentage at the time of diagnosis. Performance status was determined using the Eastern Cooperative Oncology Group (ECOG) score [30]. An ECOG score which was two or greater was defined as "poor performance status". At least two units of red blood cell suspension or one units or more platelet suspension transfusion per cycle was defined as "high transfusion need".

Azacitidine was administered at a subcutaneous dose of 75 mg/m^2 daily for 7 days every four weeks. Doses corresponding to weekend days were postponed to the first days of the next week. Decitabine was administered in two different schemas. In two patients who received decitabine before June 2010, 15 mg/m^2 by continuous IV infusion over 3 h, repeated every 8 h for 3 days (135 mg/m2 per cycle) every six weeks was administered. By June 2010, decitabine was given 20 mg/m^2 by continuous IV infusion over 1 h repeated daily for 5 days (100 mg/m2 per cycle) every four weeks.

2.4. Outcomes

The primary objective of this study was to evaluate hematologic response. The hematologic response was evaluated according to modified International Working Group (IWG) 2006 MDS criteria [31]. The overall response rate (ORR) was estimated as the proportion of patients with any response including a complete response (CR), marrow CR (mCR) with or without hematologic improvement, a partial response (PR), or just any hematologic improvement (HI) at all. Hematologic improvement was assessed with respect to neutrophils, erythrocytes, and platelets, as recommended previously [31].

The study's secondary aims were to determine the overall survival (OS), the cumulative incidence of AML transformation, the cause-specific death, and adverse events including erythrocyte and platelet transfusion needs, febrile neutropenia episodes, and the need for antifungal use during the treatment cycles.

2.5. Statistical analyses

Demographic variables were expressed descriptively. Data distribution was assessed using the Shapiro-Wilks normality test, and normally continuous distributed data were compared by the Student's *t*-test. Skewed data comparisons were performed using the Wilcoxon rank-sum test, and Chi-square or Fisher exact tests were used for the comparison of categorical variables, where appropriate.

Using the Kaplan-Meier method, the OS was estimated as the time that elapsed between the first dose of HMA and either death from any cause or last contact. The survival outcomes in groups were compared by the log-rank test. The hazard ratio (HR) and 95% confidence intervals (CIs) were estimated in comparison to a reference risk of 1.0. The cumulative incidence of AML transformation was estimated as the time elapsed from the first dose of HMA until AML transformation or last contact, using death as a competing risk. The cumulative incidence of cause-specific death was calculated as the time elapsed between the first dose of HMA and

death or last contact, using the AML transformation as a competing risk. Comparisons of cumulative incidences were performed using Gray's test. The subhazard ratios (SHR) and 95% CIs were estimated in comparison to a reference risk of 1.0 for cumulative incidence estimations.

Comparisons between the azacitidine and decitabine groups were first performed in the whole cohort. Then we created a 1:1 propensity score-matched cohort using the nearest neighbor method with no replacement in order to reduce the simple selection bias [32]. To calculate the propensity score, we performed a logistic regression analysis that included the following variables: age, gender, WHO subgroup, bone marrow blast percentage, number of HMA cycles, ECOG performance status, IPSS, WPSS, and IPSS-R risk scores. A total of 25 pairs were selected after propensity matching with a median 4.96% bias.

Backward stepwise multivariable analyses were performed using multivariate logistic regression analyses for the response rates, Cox's proportional hazard regression model for OS, and Fine–Gray proportional hazard regression for competing risks. Baseline variables that had an impact on clinical outcomes with a *p*-value of ≤0.10 in univariate analyses were included in the multivariate analyses. P-values of <0.05 were considered significant.

3. Results

3.1. Clinical and demographic characteristics

The data from a total of 92 patients were collected from six centers. However, four patients were excluded from the final analyses. One received azacitidine for lower-risk MDS, and decitabine was used for chronic myelomonocytic leukemia in one patient. Two patients who had received azacitidine had incomplete data.

Finally, a total of 88 patients were included in the study. All patients were either red blood cell- or platelet transfusion-dependent. Fifty-seven patients (64.8%) received azacitidine, while 31 patients were decitabine users. The median age was 69 (60–73) years for the entire population. Sixty patients (68.2%) were male. Almost half of the patients had MDS-RAEB-2 disease (53.4%) and a poor ECOG performance status (51.1%). Most patients (87.5%) completed a minimum of four cycles of any HMA. The azacitidine group consisted of more males (75.4% vs. 54.8% for the decitabine group, p = 0.047). Other variables, including the HMA cycles received, were similar between the groups. Two patients in azacitidine, and one in decitabine group had therapy-related MDS, which was caused by previous chemotherapies used for non-hematologic malignancies (Table 1).

The propensity-matched cohort consisted of a total of 50 patients, 25 patients in each group. Their basal clinical and demographic features were comparable (Table 1).

3.2. Efficacy of HMAs

The ORRs were 49.1% and 64.5% for azacitidine and decitabine, respectively (p = 0.166). Azacitidine provided CR or mCR in 28.1% and HI in 21.0% of 57 patients. The CR or mCR and HI rates, which were comparable to those in the azacitidine group, were 38.7% and 25.8%, respectively, for 31 decitabine users (p = 0.375, Table 2). The median follow-up time in the azacitidine and decitabine groups was 13.2 (7.0–23.8) months and 13.3 (6.1–16.8) months, respectively (p = 0.50). The median OS was 20.4 (9.8–not reached) months for patients who received azacitidine, while the median OS for decitabine-users was 16.8 (13.3–34.8) months (p = 0.59, Table 3, Fig. 1A). The cumulative incidence of AML transformation at one year was comparable between the azacitidine and decitabine groups (24.0% vs. 31.3%, p = 0.26, Table 3, Fig. 2A). Efficacy

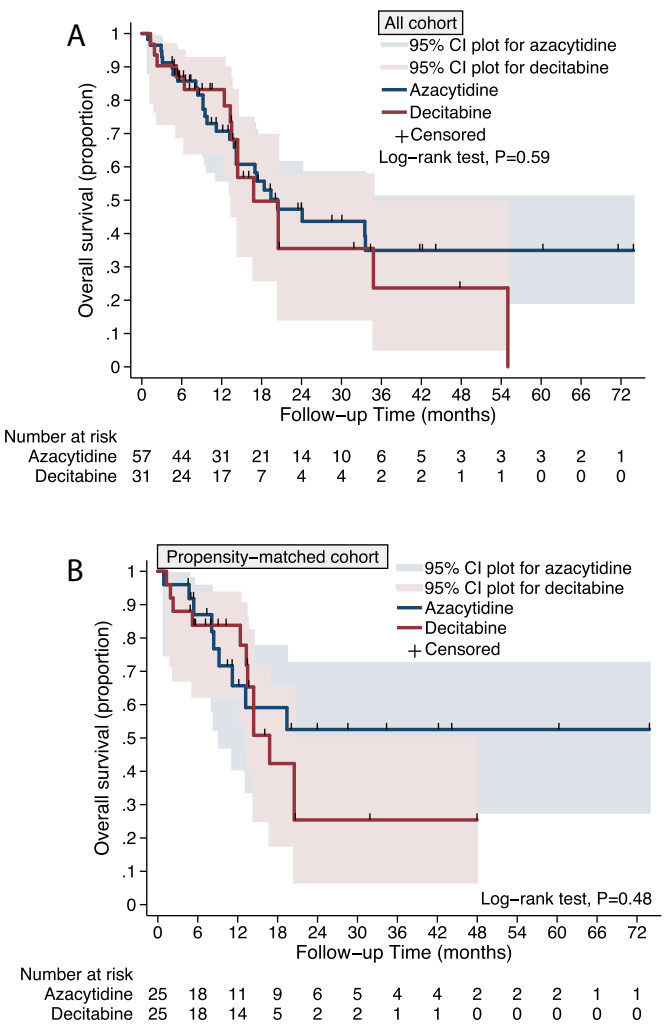

Fig. 1. Overall survival by the hypomethylating agents in the overall cohort (A) and in the propensity score-matched cohort (B).

parameters were also similar in the azacitidine and decitabine groups in the propensity-matched cohort (Table 3, Figs. 1B and 2B).

3.3. Predictors of efficacy

In the univariate simple logistic regression analyses, those performed in the whole cohort— younger age (<65 years), female gender, and having at least four cycles of any HMA—were associated with a better ORR (OR: 3.00, 95% CI: 1.20–7.47, p = 0.018; OR: 3.67, 95% CI: 1.36–9.92, p = 0.011; and OR: 6.67, 95% CI: 1.35–33.02, p = 0.02, respectively). In the final multivariate logistic regression analysis with backward selection, female gender and more than four cycles of HMA were the only independent predictors of ORR (OR: 3.94, 95% CI: 1.37–11.32, p = 0.011; and OR: 7.40, 95% CI: 1.39–39.44, p = 0.019, respectively) (Supplemental Table 1).

Several variables such as older age (HR: 1.76, 95% CI: 0.92–3.35, p = 0.087), MDS-RAEB-2 (HR: 1.96, 95% CI: 1.04–3.68, p = 0.037), having fewer than four cycles (HR: 4.14, 95% CI: 1.96–8.74, p < 0.001), a higher IPSS score (HR: 1.69, 95% CI: 1.00–2.88, p = 0.051), a higher IPSS-R score (HR: 2.99, 95% CI: 1.88–4.76, p < 0.001), a higher WPSS score (HR: 2.01, 95% CI: 1.27–3.20, p = 0.03), and a higher blast count (≥10%) (HR: 1.89, 95% CI: 0.99–3.62, p = 0.053) were included in the multivariate Cox proportional hazard model to find the predictors of OS. Only a higher IPSS-R score (HR: 2.99, 95% CI: 1.85–4.81, p < 0.001) and fewer than

Table 1
Baseline characteristics.

Variables	Unmatched cohort (n = 88)			Propensity-matched cohort (n = 50)		
	AZA (n = 57)	DEC (n = 31)	*P*	AZA (n = 25)	DEC (n = 25)	*P*
Age at diagnosis, years						
Median (IQR)	69 (60–74)	65 (61–72)	0.421	70 (66–74)	65 (62–73)	0.312
≥65, n (%)	37 (64.9)	17 (54.8)	0.354	19 (76.0)	15 (60.0)	0.225
Gender, n (%)						
Male	43 (75.4)	17 (54.8)	0.047	16 (64.0)	17 (68.0)	0.765
WHO subtype, n (%						
RAEB-1	29 (50.9)	12 (38.7)	0.274	12 (48.0)	10 (40.0)	0.569
RAEB-2	28 (49.1)	19 (61.3)		13 (52.0)	15 (60.0)	
Treatment cycles						
Median (IQR)	4 (4–7)	4 (4–6)	0.152	4 (4–6)	4 (4–6)	0.944
≥4, n (%)	50 (87.7)	27 (87.1)	1.000	22 (88.0)	22 (88.0)	1.000
ECOG score, n (%)						
≥2	29 (50.9)	16 (51.6)	0.947	15 (60.0)	11 (44.0)	0.258
IPSS risk category, n (%)						
Intermediate-1	22 (38.6)	15 (48.4)	0.715	12 (48.0)	11 (44.0)	0.828
Intermediate-2	29 (50.9)	14 (45.2)		12 (48.0)	12 (48.0)	
High	6 (10.5)	2 (6.4)		1 (4.0)	2 (8.0)	
IPSS-R risk category, n (%)						
Intermediate	20 (35.1)	11 (35.5)	0.300	10 (40.0)	9 (36.0)	0.951
High	20 (35.1)	15 (48.4)		10 (40.0)	11 (44.0)	
Very high	17 (29.8)	5 (16.1)		5 (20.0)	5 (20.0)	
WPSS risk category, n (%)						
Intermediate	15 (26.3)	9 (29.1)	0.911	7 (28.0)	7 (28.0)	0.725
High	30 (52.6)	17 (54.8)		15 (60.0)	13 (52.0)	
Very high	12 (21.1)	5 (16.1)		3 (12.0)	5 (20.0)	
Cytogenetics, n (%)						
Favorable	32 (56.1)	20 (64.5)	0.782	16 (64.0)	15 (60.0)	0.909
Intermediate	8 (14.0)	2 (6.5)		3 (12.0)	2 (8.0)	
Unfavorable	12 (21.1)	6 (19.3)		4 (16.0)	5 (20.0)	
Not evaluable	5 (8.8)	3 (9.7)		2 (8.0)	3 (12.0)	
Bone marrow blast percentage, n (%)						
Median (IQR)	10 (8–12)	10 (6–12)	0.860	10 (8–12)	10 (7–12)	0.831
Etiology						
De novo	55 (96.5)	30 (96.8)	1.000	24 (96.0)	24 (96.0)	1.000
Secondary	2 (3.5)	1 (3.2)		1 (4.0)	1 (4.0)	

AZA denotes azacytidine; DEC, decitabine; IQR, interquartile range; WHO, the World health Organization; RAEB, refractory anemia with excess blast; ECOG, the Eastern Cooperative Oncology Group; IPSS, the International Prognostic Scoring System; IPSS-R, Revised International Prognostic Scoring System; and WPSS, the World Health Organization Prognostic Scoring System.

Table 2
Comparison of treatment responses and adverse events.

Variables	Unmatched cohort (n = 88)			Propensity-matched cohort (n = 50)		
	AZA (n = 57)	DEC (n = 31)	*P*	AZA (n = 25)	DEC (n = 25)	*P*
Response by modified IWG, n (%)						
Overall response rate	28 (49.1)	20 (64.5)	0.166	13 (52.0)	17 (68.0)	0.248
CR + mCR with or without HI[a]	16 (28.1)	12 (38.7)	0.375	8 (32.0)	10 (40.0)	0.508
PR	0	0		0	0	
HI only	12 (21.0)	8 (25.8)		5 (20.0)	7 (28.0)	
No response	29 (50.9)	11 (35.5)		12 (48.0)	8 (32.0)	
Transfusion need[b]						
RBCs						
Median (IQR), units per cycle	2.0 (0.3–3.4)	1.6 (0.5–3.0)	0.790	2.0 (0–3.3)	1.5 (0.5–2.8)	0.914
≥2 units per cycle, n (%)[c]	27 (51.9)	11 (36.7)	0.182	12 (52.2)	8 (33.3)	0.192
Platelets						
Median (IQR), units per cycle	0 (0–1.6)	0.7 (0–3.3)	0.150	0 (0–1.5)	0.6 (0–3.3)	0.108
≥1 units per cycles, n (%)[d]	17 (32.7)	13 (41.9)	0.396	6 (26.1)	9 (36.0)	0.459
Febrile neutropenia during the cycles, n (%)[e]	29 (50.9)	9 (29.0)	0.048	12 (48.0)	6 (24.0)	0.077
Need for antifungal treatment, n (%)	8 (14.0)	5 (16.1)	0.791	4 (16.0)	3 (12.0)	1.000

AZA denotes azacytidine; DEC, decitabine; IQR, interquartile range; CR, complete response; mCR, marrow CR; HI, hematologic improvement; PR, partial response; and RBCs, red blood cells.

[a] The proportions of CR and mCR were not estimated separately.
[b] All patients were either RBC or platelet transfusion dependent.
[c] Data were available in a total of 82 and 45 patients in unmatched and propensity-matched cohorts, respectively.
[d] Data were available in a total of 83 and 46 patients in unmatched and propensity-matched cohorts, respectively.
[e] It represents the patients who experienced febrile neutropenia episode(s) during the HMA cycles.

four cycles of HMA (HR: 4.00, 95% CI: 1.84–8.68, p < 0.001) were associated with a worse OS (Supplemental Table 2).

MDS-RAEB-2 (SHR: 3.02, 95% CI: 1.56–5.83, p = 0.001), a higher IPSS score (SHR: 2.03, 95% CI: 1.19–3.46, p = 0.01), a higher IPSS-R score (SHR: 1.62, 95% CI: 1.06–2.46, p = 0.024), and a higher WPSS

Table 3
Survival data.

Variables	Unmatched cohort (n = 88)			Propensity-matched cohort (n = 50)		
	AZA (n = 57)	DEC (n = 31)	*P*	AZA (n = 25)	DEC (n = 25)	*P*
Overall survival (OS)						
Hazard ratio (95% CI)	Reference	1.19 (0.63–2.24)	0.59	Reference	1.37 (0.57–3.26)	0.48
Median (IQR), months	20.4 (9.8-NR)	16.8 (13.3–34.8)		NR (9.2-NR)	16.8 (13.3-NR)	
Cumulative incidence of AML transformation						
Subhazard ratio (95% CI)	Reference	1.44 (0.76–2.75)	0.26	Reference	2.06 (0.84–5.05)	0.11
12-months, %	24.0	31.3		18.7	31.5	
Cumulative incidence cause-specific death						
Subhazard ratio (95% CI)	Reference	0.86 (0.30–2.46)	0.77	Reference	0.83 (0.25–2.68)	0.75
3-months, %	7.0	6.5		4.0	8.0	
12-months, %	18.7	9.8		27.3	12.2	
Follow-up, months, median (IQR)	13.2 (7.0–23.8)	13.3 (6.1–16.8)	0.50	11.0 (5.4–23.8)	13.3 (5.5–15.9)	0.80

AZA denotes azacytidine; DEC, decitabine; IQR, interquartile range; IQR denotes interquartile range; AML, acute myeloid leukemia; HR, hazard ratio; 95% CI, 95% confidential interval.

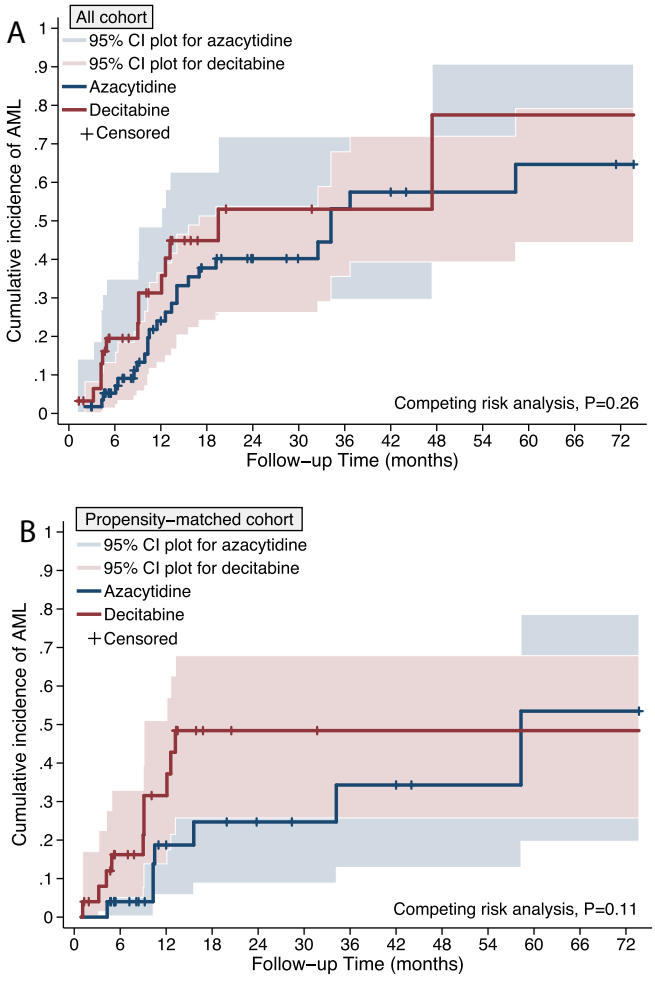

Fig. 2. Cumulative incidence of acute myeloid leukemia (AML) transformation in the overall cohort (A) and in the propensity score-matched cohort (B).

score (SHR: 2.12, 95% CI: 1.32–3.40, p = 0.002) were associated with a higher cumulative incidence of AML in univariate competing risk analyses. However, multivariate analysis was not performed due to a high colinearity between the variables.

The type of HMA had no impact on the efficacy parameters in the univariate analyses. P-values achieved in univariate analyses did not meet the criterion to be included in the multivariate analysis

3.4. Adverse event profiles of HMAs

Red blood cell and platelet transfusion needs were comparable in the azacitidine and decitabine groups in both the whole and the propensity-matched cohorts. Febrile neutropenia episodes were more common in azacitidine users (50.9% vs. 29.0%, p = 0.048, Table 2). Although a febrile neutropenia episode had a higher tendency to occur in the azacitidine group, no significant relationship was observed in the propensity-matched cohort (48% vs. 24%, p = 0.077, Table 2). Both HMAs had caused a similar rate of antifungal need (14.0% vs. 16.1%, p = 0.791 in the whole cohort and 16% vs. 12%, p = 1.00 in the propensity-matched cohort, Table 2).

We also analyzed the cumulative incidence of cause-specific death transformation in order to compare the potentially treatment-related early deaths within the first three months. The cumulative incidence of early death was 7% and 6.5% in the azacitidine and decitabine groups, respectively (p = 0.77, Table 3, Fig. 3A). No differences were observed in the propensity-matched cohort (Table 3, Fig. 3B).

3.5. Predictors of adverse events

MDS-RAEB-2 (OR: 2.78, 95% CI: 1.13–6.83, p = 0.026), a higher WPSS score (OR: 2.32, 95% CI: 1.15–4.73, p = 0.019), a higher IPSS-R score (OR: 2.68, 95% CI: 1.40–5.12, p = 0.003), a poor (score ≥2) ECOG performance status (OR: 3.90, 95% CI: 1.54–9.85, p = 0.004), and receiving fewer than four cycles (OR: 15.36, 95% CI: 1.86–126.67, p = 0.011) were the potential predictors of RBC transfusion need in univariate simple logistic regression analyses. Multivariate logistic regression analysis revealed that a poor (score ≥2) ECOG performance status (OR: 4.17, 95% CI: 1.53–11.34, p = 0.005) and a higher IPSS-R score (OR: 2.79, 95% CI: 1.41–5.53, p = 0.003) were the only independent predictors of high (≥2U per cycle) RBC transfusion need (Supplemental Table 3).

Older age (≥65 years) (OR: 2.28, 95% CI: 0.86–6.02, p = 0.098), fewer than four cycles of HMA (OR: 10.93, 95% CI: 2.18–54.91, p = 0.004), a poor ECOG performance status (OR: 5.01, 95% CI: 1.82–13.74, p = 0.002), and a higher IPSS-R score (OR: 1.83, 95% CI: 0.98–3.40, p = 0.056) had a tendency to be related to a high platelet transfusion need. In multivariate analysis, a poor ECOG performance status (OR: 4.15, 95% CI: 1.44–11.93, p = 0.008) and fewer than four cycles of HMA (OR: 8.34, 95% CI: 1.56–44.47, p = 0.013) were associated with a high platelet transfusion need (Supplemental Table 4).

In univariate simple logistic regression analyses, male gender (OR: 2.50, 95% CI: 0.95–6.55, p = 0.062), MDS-RAEB-2 (OR: 2.99,

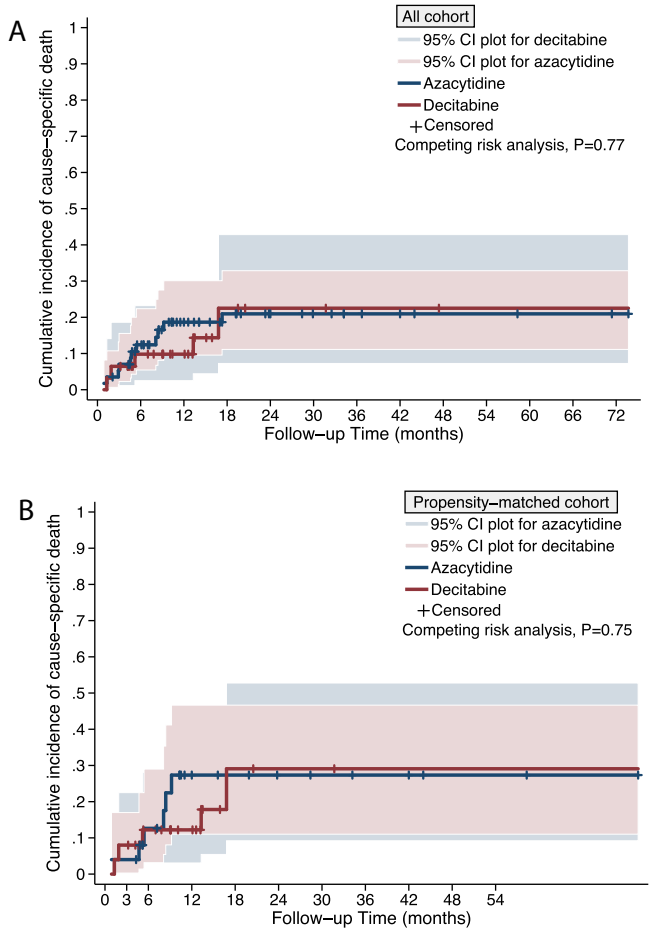

Fig. 3. Cumulative incidence of cause-specific death in the overall cohort (A) and in the propensity score-matched cohort (B).

95% CI: 1.23–7.25, p = 0.015), fewer than four cycles of HMA (OR: 17.50, 95% CI: 2.13–143.97, p = 0.008), a poor ECOG performance status (OR: 2.88, 95% CI: 1.20–6.93, p = 0.018), a higher IPSS risk (OR: 2.16, 95% CI: 1.07–4.38, p = 0.031), a higher IPSS-R risk (OR: 2.47, 95% CI: 1.35–4.50, p = 0.003), a higher WPSS risk (OR: 1.87, 95% CI: 0.97–3.58, p = 0.06), and azacitidine use (OR: 2.53, 95% CI: 0.99–6.44, p = 0.051) seemed to be related to febrile neutropenia episodes. After multivariate analyses, MDS-RAEB-2 disease (OR: 5.31, 95% CI: 1.81–15.60, p = 0.002), fewer than four cycles of HMA (OR: 30.60, 95% CI: 3.27–286.10, p = 0.003), and azacitidine use (OR: 4.19, 95% CI: 1.34–13.10, p = 0.014) were the only predictors of febrile neutropenic episodes (Supplemental Table 5).

Finally, having fewer than four cycles of HMA (OR: 9.91, 95% CI: 3.34–29.40, p < 0.001) was the only independent predictor of cumulative incidence of death not caused by AML.

4. Discussion

The introduction of epigenetic therapy such as azacitidine and decitabine has produced a substantial improvement in the treatment of patients with higher-risk MDS [33]. Therefore, these FDA-approved agents are currently the preferred treatment options for the treatment of higher-risk MDS patients who are ineligible for intensive therapy. Although both drugs have a similar mechanism of action of hypomethylating DNA, their activities with respect to cell viability, protein synthesis, cell cycle, and gene expression have been reported as different from each other [5]. Furthermore, an improvement of the T-cell repertoire in patients with MDS has been reported with azacitidine, and a variable response in patients with MDS by hENT1 and DCK genes has been reported with decitabine [34,35]. Recently, the MDS Clinical Research Consortium (MDS CRC) reported a differential response to hypomethylating agents based on sex [36]. Comparative analyses regarding the efficacy and safety of azacitidine and decitabine are very limited [23,24]. Currently, an important unanswered question is the choice of HMAs for a patient with the specific subgroup of MDS.

This real-world study was designed to compare the efficacy and safety of azacitidine and decitabine in patients with MDS-RAEB. In our study, both azacitidine and decitabine showed similar efficacy and toxicity profiles in the treatment of MDS-RAEB in both unmatched and propensity-matched cohorts. Although the type of HMA had no impact on efficacy parameters in univariate and multivariate analyses, female gender and undergoing more than four cycles of HMA were the only independent predictors of ORR, while a higher IPSS-R score and fewer than four cycles of HMA were associated with a worse OS in multivariate analysis. Similarly, Lee et al. found no significant differences between the two regimens regarding ORR (44% for azacitidine vs. 52% for decitabine), OS (26 vs. 22.9 months), EFS (7.7 vs. 7.0 months), and the rate of leukemic transformation (16% vs. 22% at one year) in the overall and the propensity-matched cohorts. Inferior survival with decitabine was reported in elderly patients (>65 years) (p = 0.017) in the propensity-matched cohorts [23]. Furthermore, Lee et al. found that the two regimens did not differ significantly in terms of clinical response and overall response. In patients whose MDS duration exceeded one year or who had a poor performance status, survival was significantly better in the azacitidine group [24]. Our findings are inconsistent with the retrospective comparative analysis between azacitidine and decitabine in which the OS for azacitidine was found to be longer than decitabine in some subgroups [23,24]. These differences may be due to baseline characteristics, methodological differences, and the number of cycles of HMAs. Additionally, compared with the retrospective studies, [23,24,37], this present study only included the RAEB subtype of MDS. Lee YG reported that both azacitidine and decitabine were given for a median of 5 courses (interquartile range, 4–8 courses), on the other hand Lee JH reported that the median number of courses as 5 (interquartile range, 1–48) for azacitidine and 4 (interquartile range, 1–26) for decitabine [23,24]. In the present study, the median number of courses for azacitidine was 4 (range, 4–7) and for decitabine was also 4 (range, 4–6). We found that at least a 4-cycle treatment with any HMA was a favorable factor. Similarly, Cabrero et al. found that HMA interruption should be avoided once a sustained response has been achieved [37].

Gurion et al. and Kumar et al. found a significant survival benefit for azacitidine in an indirect comparison of azacitidine versus decitabine in two different meta-analyses [20,21]. Recently, Mixue Xie et al. reported that overall response rates for azacitidine were significantly higher in a meta-analysis including eleven trials with a total of 1392 patients with MDS. Also, azacitidine, but not decitabine, significantly improved overall survival (hazard ratio [HR], 0.69; 95% CI, 0.54–0.87) and time to acute myeloid leukemia transformation (HR, 0.51; 95% CI, 0.35–0.74) [22]. This advantage of azacitidine over decitabine was observed especially in elderly patients (>75 years) or in those with high risk [22]. Contrary to these results, more recently, MDS CRC reported a marginally better OS with decitabine than with azacitidine (p = 0.043), (median OS of 18.7 months vs. 16.3 months, respectively); also, female patients treated with decitabine had a much better OS than female patients treated with azacitidine (p = 0.0014), with a median OS of 21.2 months (95% CI 16.1–27.9) versus 13.1 months (95% CI 10.7–15.9), respectively [36]. Zeidan et al. found no significant differences in OS between azacitidine and decitabine in a large cohort of older high-risk MDS patients treated with HMAs [38]. Interestingly, they reported a significantly shorter OS with azacitidine in real-world

clinical practice compared to results from randomized trials (11 vs. 24.5 months, respectively).

Lee et al. reported more grade 3 or 4 cytopenia (87% vs. 67%, respectively) and infectious episodes in the decitabine group (15.7 cytopenia episodes per 100 cycles vs. 11.8 infectious episodes per 100 cycles) [23]. Likewise, Lee et al. found that grade 3 or higher neutropenia occurred more frequently with the decitabine group (79.6% vs. 72.2%) [24]. On the other hand, in a meta-analysis, Xie et al. found no differences between these two drugs regarding red blood cell transfusion-independent rates and grade 3 or 4 hematologic toxicity [22]. Similarly, in our study, there was no difference in terms of transfusion requirement and febrile neutropenia episodes in the propensity-matched cohort. In a subgroup analysis, there were no difference in terms of toxicity profiles in patients who are at least 65 years or older.

Our multicenter study is limited due to its retrospective design. Also, patients were not randomly assigned to treatment. The choice of HMAs was made according to the treating physician's preference, and the duration of the treatment was related to repayment terms in Turkey. On the other hand, our study population was homogeneous regarding the subtype of MDS, with an acceptable sample size. The MDS-RAEB subtype, which accounts for 40% of MDS patients, was comparatively analyzed for the first time with respect to the two drugs.

In conclusion, both azacitidine and decitabine have similar efficacy and toxicity profiles in the treatment of MDS RAEB. Until head–to–head comparisons in prospective randomized studies are conducted, the current source of available data will derive from meta-analyses that consist either of the indirect comparison of treatment arms or retrospective analyses with inevitable biases. Finally, comparative analyses between azacitidine and decitabine in particular subgroups of MDS are needed.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.leukres.2016.04.003.

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