Impact of two azacitidine administration schedules in myelodysplastic syndromes

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Introduction

Myelodysplastic syndromes (MDS) are a rare group of diseases manifesting as progressive cytopenias and carrying a risk of progression to acute myeloid leukemia (AML). Apart from transplantation, only azacitidine demonstrated survival benefit in a randomized phase 3 study(1). According to that study, the approved regimen is 75 mg/m^2/day for 7 consecutive days, imposing a logistic challenge for outpatient weekend administration. Therefore, over 80% of patients treated in US community-based practices received either less than 7 days or 7 days with breaks(2). Although the European label restricts the use to higher-risk MDS (according to the landmark trial setting), the largest retrospective study(3) and the only randomized trial(4) comparing alternative regimens of azacitidine to avoid weekend administration were performed in lower-risk cohorts. Additionally, most studies addressing the use of a 5-day schedule, used a reduced dose of azacitidine (5x75 mg/m^2) rather than dividing the approved dose per cycle (7x75 mg/m^2) by 5 days. This second approach was evaluated only in a small sample of MDS patients (N=24)(5). The existing evidence may not adequately inform practice in the most common higher-risk setting without weekend administration.

Objectives

Our aim was to compare full-dose azacitidine administration (7x75 mg/m^2) in 5 days (AZA 5) versus 7 days with a weekend break (AZA 5+2) regarding overall survival (OS, primary outcome), AML-free survival (AMLFS), probability of infections and transfusion burden.

Methods

We performed a single-center, retrospective cohort study including MDS patients treated at our center between 01/01/2010 and the 12/31/2021. Patients were identified through hospital prescription registry. Of the 103 patients identified, 1 patient was excluded because azacitidine was used post-transplant, and 2 patients had no record of azacitidine schedule. We evaluated 100 patients for overall survival (primary outcome) and a subsample of 49 patients for secondary outcomes. Kaplan-Meier analysis and Cox proportional hazards models were used for survival analyses. Linear and logistic regressions were applied for univariate and multivariate assessment, as appropriate.

References

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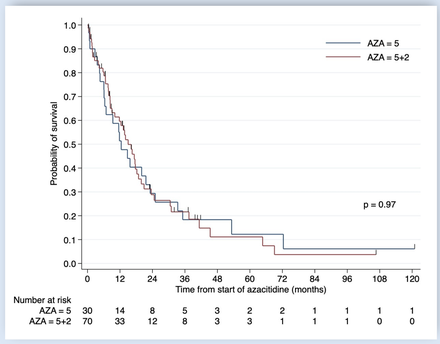
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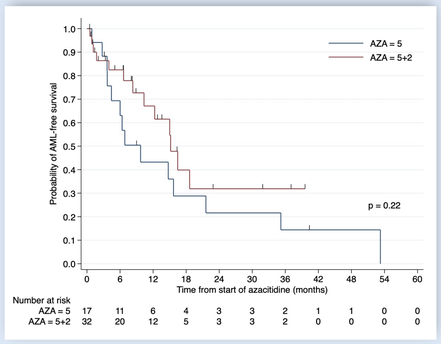
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Results

Groups were well balanced regarding sex, performance status, WHO classification, risk according to the International Prognostic Scoring System Revised, marrow cellularity, dysplastic lineages, baseline blood counts, use of antiviral/antifungal prophylaxis, granulocyte colony stimulating factor (G-CSF), erythropoiesis-stimulating agents (ESA), iron chelation, days from diagnosis, number of cycles and dose of azacitidine per cycle. The age difference was marginally non-significant (p= 0.0508): median age of 76 years (AZA 5) *versus* 71 years (AZA 5+2).



Overall survival according to administration schedule. Censored observations are marked with 'I'.



AML-free survival according to administration schedule. Censored observations are marked with 'I'.

Infection Rate = 1.38 infections per patient-year.

Schedules could not predict the proportion of infections

(OR 1.51, 95% CI 0.35–6.56; p= 0.58)

controlling for use of antiviral and antifungal prophylaxis, G-CSF and baseline neutrophil count.

Kaplan-Meier survival estimates and hazard ratios from multivariate Cox proportional hazards models

	1-year survival estimates		Hazard Ratio (95% confidence interval)	p-value
	AZA 5	AZA 5+2		
OS (N=100)	0.51 (95% CI 0.32–0.68)	0.60 (95% CI 0.46–0.71)	0.95 (0.57–1.56)[a]	0.83
AMLFS (N=49)	0.43 (95% CI 0.19–0.65)	0.67 (95% CI 0.44–0.82)	1.70 (0.70–4.14)[b]	0.24

[a] Model adjusted for age and sex. N=100 (AZA 5: N=30; AZA 5+2: N=70).
[b] Model adjusted for age, sex and ECOG performance status. N=49 (AZA 5: N=17; AZA 5+2: N=32).

Multivariate linear regression to predict red blood cell (RBC) and platelet transfusion burden according to azacitidine schedule

	Coefficient for AZA 5 (vs AZA 5+2)	95% Confidence Interval	p-value
Packed RBC per month (N=43)	0.08	-0.68 – 0.84	0.83
Platelet units per month (N=43)	0.09	-0.68 – 0.85	0.82

Models adjusted for baseline values, ESA use and dose of azacitidine per cycle.
Patients who underwent hematopoietic stem cell transplantation were excluded from these analyses (N=6).

Full-dose azacitidine (7x75 mg/m^2) can be administered both in 5 days and in 7 days with a weekend break with no significant difference in survival, infection or transfusional outcomes.