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10-year retrospective study on 5-azacitidine, 5-day 100mg/m² schedule, as monotherapy for MDS and MDS/MPN (AZA-CHUV study)

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Introduction

Azacitidine (AZA), is a hypomethylating agent used as first line treatment for high-risk myelodysplastic neoplasms (MDS) and sometimes myelodysplastic/myeloproliferative (MDS/MPN) neoplasms. Validated dosage is 75 mg/m², subcutaneously over 7 days every 28 days. Alternative schedules have been tested, but none showed superiority. We conducted a retrospective analysis of an alternative AZA monotherapy dosing of 100 mg/m² administered over 5 consecutive days every 28 days in patients with high-risk MDS and MDS/MPN. Primary endpoint was the efficacy, and secondary endpoints were median overall survival (mOS), progression-free survival (PFS), and toxicities.

Methods

All patients who received AZA monotherapy as a first or subsequent line of treatment for MDS or MDS/MPN between 2008 and 2018, were screened. The follow-up continued until the end of 2023. Statistics were performed with R (v 4.2.0; CRAN project); using the package 'survival' for analysis and the package 'survminer' for the drawing of survival curves. Kaplan–Meier estimator to report the survival probability and a Cox regression to calculate hazard ratios (HR) were used. Median follow-up was calculated using the reverse Kaplan–Meier (KM) method. A Log-rank statistical test was applied to assess significance when comparing KM estimates. Univariate Cox regression analysis was performed to assess the predictive value of best response on OS. A Wald statistical test was applied to assess significance. Diagnoses were classified according to WHO 2016 classification, and the best response was evaluated using IWG 2006 MDS response criteria.

Results

Among 68 patients, 51 had MDS and 17 MDS/MPN. Five patients were re-exposed to AZA after allogeneic stem cell transplantation (HSCT), accounting for 74 documented responses. AZA was used as first-line in 50 patients. Median age was 66 years (range: 25-92) and M:F was 46/68. The median follow-up time was 98.6 months.

Sixteen patients presented complete responses (CR) (16/74, 22%) and 30 partial responses (PR) (30/74, 41%) (table 1). The median time to best response was longer for patients who responded to treatment while refractoriness was already apparent earlier (CR = 6.9 months, PR = 3.65 months, stable disease (SD) = 2.9 months, progressive disease (PD) = 2.6 months). Best response was significantly linked to OS, with patients without CR presenting an HR for death of 2.86 (95%CI: [1.21–6.76]), 3.36(95%CI: [1.33–8.5]), and 8.31(95%CI: [3.2–21.7]) for PR, SD, and PD, respectively.

Median OS was 22.5 months (95% CI: 17.2-47.3) and PFS 18.2 months (95% CI: 13.7-31.5) (Figure 1). HSCT was significantly associated with better mOS and PFS. Grade 3/4 hematotoxicity, mostly neutropenias, was present in 41% of patients with most patients presenting G3 neutropenias.

Table 1. Responses

Responses, N (%)	
ORR	46/74 (62.1%)
CR	16/74 (21.6%)
PR	30/74 (40.5%)
SD	15/74 (20.2%)
PD	13/74 (17.5%)

By subgroup

	MDS other	MDS-EB II	t-MDS	CMML, MDS/MPN NOS
ORR	13 (65%)	10 (52.6%)	8 (50%)	14 (73.6%)
CR	6 (30%)	4 (21%)	0	6 (31.5%)
PR	7 (35%)	6 (31.5%)	8 (50%)	8 (42.1%)
SD	2 (10%)	7 (36.8%)	5 (31.2%)	1 (5.2%)
PD	4 (20%)	2 (10.5%)	3 (18.7%)	4 (21%)

Abbreviations: CMML=chronic myelomonocytic leukemia, CR=complete remission, EB=excess blast, MDS=myelodysplastic neoplasm, MPN=myeloproliferative neoplasm, NOS=non otherwise specified, ORR=overall response rate, PD=progressive disease, PR=partial remission, SD=stable disease, t-MDS=therapy related MDS

Figure 1

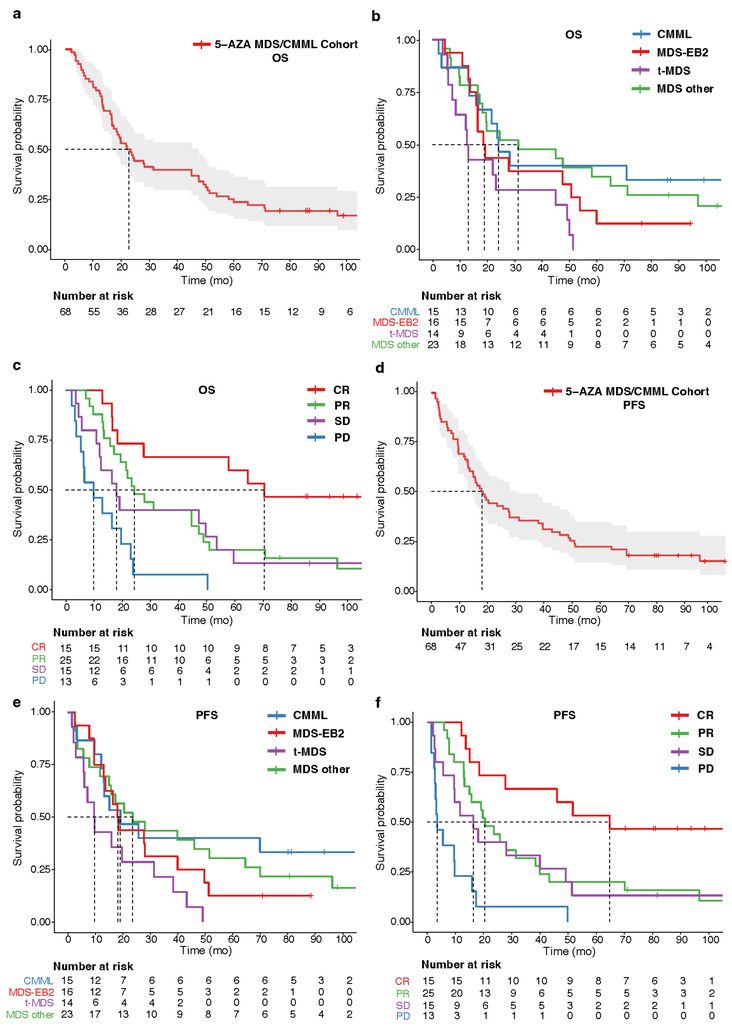

Figure 1. a. Cohort OS **b.** OS comparison between CMML, MDS-EB2, t-MDS, and remaining MDS categories (i.e. MDS other) according to WHO 2016. The mOS of CMML, MDS-EB2, t-MDS, and MDS other was 24.0 (95% CI: 16.6-NA), 18.8 (95% CI: 15.8-59.7), 12.8 (95% CI: 8.4-49.7) and 31.2 months (95% CI: 18.1-96.5), respectively. **c.** OS comparison between patients who achieved either a CR, PR, SD, or PD according to IWG 2006 MDS response criteria. The mOS of CR, PR, SD, and PD other was 70.6 (95% CI: 27.7-NA), 24.4 (95% CI: 19.5-49.0), 18.1 (95% CI: 12.1-59.7) and 9.9 months (95% CI: 5.4-NA), respectively. **d.** Cohort PFS **e.** PFS comparison between CMML, MDS-EB2, t-MDS, and remaining MDS categories (i.e. MDS other) according to WHO 2016. The mPFS of CMML, MDS-EB2, t-MDS, and MDS other was 19.1 (95% CI: 13.0-NA), 18.3 (95% CI: 13.0-51.4), 9.6 (95% CI: 5.9-43.4) and 23.6 months (95% CI: 15.0-70.2), respectively. **f.** PFS comparison between the patient groups who achieved either a CR, PR, SD, or PD according to IWG 2006 MDS response criteria. The mPFS of CR, PR, SD, and PD other was 64.7 (95% CI: 27.7-NA), 20.5 (95% CI: 15.0-40.0), 16.4 (95% CI: 9.5-51.4) and 3.5 months (95% CI: 2.7-NA), respectively.

Conclusions: Five-day AZA treatment schedule at 100 mg/m² seems to be equally efficacious as the standard 7-day schedule. CR and PR rates as well as OS were similar to AZA-001 historic study results. This schedule is more suitable for ambulatory settings, as it avoids weekends and enhances the quality of life by reducing the number of treatment days per month.