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CORRESPONDENCE

Effectiveness of azacitidine for the treatment of higher-risk myelodysplastic syndromes in daily practice: results from the Dutch population-based PHAROS MDS registry

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We read with interest the recent article by Bernal *et al.*[1] on the effectiveness of azacitidine for the treatment of higher-risk myelodysplastic syndromes (HR-MDS), based on registration of patients by hematologists in selected hospitals in Spain. That study provided valuable findings complementary to that obtained from clinical trials, which generally includes selected patient populations. The main finding of their study was that there was no beneficial effect of azacitidine. Their patient population included a heterogeneous group of patients with HR-MDS, chronic myelomonocytic leukemia and acute myeloid leukemia (AML) with 20–30% blasts, which may limit the generalizability of the study results to a population with exclusively HR-MDS.

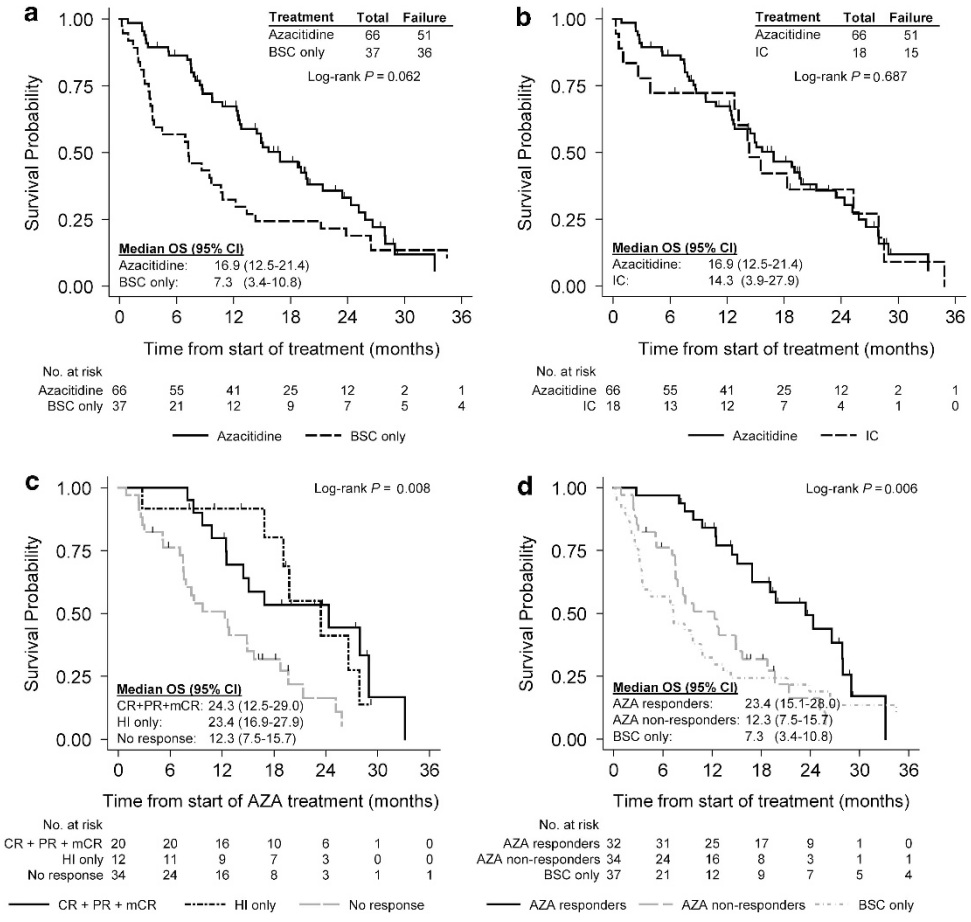

Figure 1. Overall survival of patients with HR-MDS treated with azacitidine compared with patients with HR-MDS receiving (**a**) BSC only or (**b**) intensive chemotherapy. (**c**) OS of patients with HR-MDS treated with azacitidine according to the type of response (**d**) compared with patients with HR-MDS receiving BSC only. In **d**, patients who responded to azacitidine were grouped as those who achieved a CR, PR, marrow CR or HI with or without SD. In that same Figure, as well as in **c**, non-responders were defined as patients without a bone marrow evaluation and lacking a HI, SD without HI or progressive disease. Hematological remission and improvement were based on International Working Group 2006 criteria for MDS. OS was measured with the Kaplan–Meier method as the time from treatment to death or last follow-up, and compared with the log-rank test. AZA, azacitidine; BSC, best supportive care; CI, confidence interval; CR, complete remission; HI, hematologic improvement; HR-MDS, higher-risk myelodysplastic syndromes; IC, intensive chemotherapy; OS, overall survival; PR, partial remission; SD, stable disease.

To complement and extend their observations in a more homogenous population, including all patients within a well-defined area, we conducted a retrospective, population-based cohort study to assess the effectiveness of azacitidine compared with best supportive care (BSC) only and intensive chemotherapy (IC) for the treatment of transplant-ineligible patients with exclusively HR-MDS in the Netherlands.

We selected 121 (azacitidine, $n = 66$; BSC only, $n = 37$; and IC, $n = 18$) over 18-year-old transplant-ineligible HR-MDS patients diagnosed between 2008 and 2011 from the Dutch **P**opulation-based **HA**ematological **R**egistry for **O**bservational **S**tudies (PHAROS) in MDS (see Supplementary Figure S1 for patient flow and Supplementary Table S1 for patient characteristics). We exclusively selected World Health Organization-defined MDS patients with intermediate-2 or high-risk on the International Prognostic Scoring System, which is an approved indication for treatment with azacitidine. Central review of diagnostic specimens was not possible due to the retrospective nature of this study. The PHAROS MDS registry is a true population-based registry, which relies on the nationwide Netherlands Cancer Registry (NCR) for case ascertainment; its coverage is therefore identical to the NCR (see Supplementary Figure S2 for study design). The validity and completeness of the NCR were previously reported.[2–4] Details about the registries and treatment definitions are provided in the Supplementary Information. The study was approved by the Ethics Committee of the Erasmus University Medical Center.

Azacitidine and IC were, respectively, given for a median (range) of 8.5 (1–26) and 2 (1–3) cycles, and BSC only for a median of 4.2 (0–30.5) months. After a median (range) follow-up of 14.6 (0.3–68.9) months, median overall survival (OS) was 16.9, 7.3 and 14.3 months for patients receiving azacitidine, BSC only and IC, respectively (Figures 1a and b). By multivariate Cox regression analysis, treatment with azacitidine relative to BSC only (hazard ratio (HR) = 0.61; $P = 0.039$), and good- ($P = 0.009$) and intermediate-risk cytogenetics ($P = 0.003$) were significantly associated with better survival, whereas hemoglobin < 10 g/dl ($P = 0.008$) exhibited the opposite association (Supplementary Table S2). Although survival was similar with either azacitidine or IC (Figure 1b; HR = 0.88; $P = 0.699$; Supplementary Table S2), patients receiving IC spend substantial more days hospitalized than azacitidine-treated patients (median days, 71 vs 2.5; $P < 0.001$; Table 1). Of note, in line with previous reports,[1,5] patients with -7/del(7q) abnormalities seem to benefit significantly from azacitidine compared with BSC only and IC (median OS 21.4 vs 3.9 months; $P = 0.019$; Supplementary Figure S3).

The proportion of patients achieving hematological remission based on International Working Group 2006 criteria for MDS was 30, 0 and 67% for patients receiving azacitidine, BSC only and IC, respectively (Table 1). The corresponding estimates for hematological improvement were 39, 0 and 39%, respectively (Table 1). As for leukemic transformation in the overall series, the corresponding estimates were 51, 35 and 39%, respectively ($P = 0.231$). The proportion of relapse was similar between patients receiving azacitidine or IC (Table 1).

The median (range) time to best response with azacitidine was 5 (1–12) cycles (Supplementary Table S3). Patients who responded to azacitidine received a median (range) of 13.5 (3–26) cycles, whereas non-responders received 5 (1–18) cycles (Supplementary Table S3). Median OS was significantly higher in responders compared with non-responders ($P = 0.002$; Figures 1c and d). Survival was similar between non-responding azacitidine-treated patients and patients who received BSC only ($P = 0.682$; Figure 1d).

Table 1. Treatment outcomes of patients with higher-risk MDS by treatment group

	Treatment group						P *value*[a]	
	Azacitidine (n = *66*)		*BSC only* (n = *37*)		*IC* (n = *18*)		*Azacitidine vs BSC only*	*Azacitidine vs IC*
	n	%	n	%	n	%		
Hospitalization (days)								
Median (range)	2.5 (0–53)		4 (0–86)		71 (3–150)		0.989	< 0.001
Hematological response								
Any hematological remission[b]	20	30	0		12	67	< 0.001	0.007
CR	8	12	0		7	39	–	–
PR	2	3	0		0		–	–
mCR	10	15	0		5	28	–	–
SD	8	12	0		0		–	–
PD	20	30	11	30	3	17	–	–
Not evaluated[c]	18	27	26	70	3	17	–	–
Hematological improvement[d]								
Any hematological improvement	26	39	0		7	39	< 0.001	1
Erythroid response	22	33	0		6	33	–	–
Platelet response	22	33	0		5	28	–	–
Neutrophil response	12	18	0		2	11	–	–
Overall response[e]	32	48	0		12	67	< 0.001	0.194
Relapse after CR, PR or mCR[f]	12	60	0		6	50	–	0.718
Relapse after HI[g]	17	65	0		4	57	–	0.686

Abbreviations: BSC, best supportive care; CR, complete remission; HI, hematologic improvement; IC, intensive chemotherapy; mCR, marrow CR; MDS, myelodysplastic syndromes; PD, progressive disease; PR, partial remission; SD, stable disease. [a]Characteristics of patients were compared with the Fisher's exact test for categorical variables, and the Kruskal–Wallis test for continuous variables. $P < 0.05$ indicated statistical significant differences. [b]Any hematological remission includes CR, PR or mCR. [c]In this patient subset, a bone marrow assessment was not performed. The decision to perform a bone marrow assessment was always at the discretion of the treating physician. [d]The proportion of patients achieving a hematological improvement was calculated for the entire patient group (that is, the intention to treat population). [e]Overall response includes patients who achieved CR, PR, mCR or HI with or without SD. [f]The proportion of relapse after CR, PR or mCR was calculated based on the number of patients who achieved a hematological remission. [g]The proportion of relapse after HI was calculated based on the number of patients who achieved a hematological improvement. Hematological response and improvement were assessed according to the International Working Group 2006 criteria for MDS.

In contrast to our study, the study by Bernal *et al.*[1] could not demonstrate any beneficial effect of azacitidine. Several possibilities can be considered to explain the differences. First, our patients received an increased number of azacitidine cycles than Spanish patients (median, 8.5 vs 6). As demonstrated in the AZA-001 trial,[5,6] long-term treatment with azacitidine (that is, $\geqslant 6$ treatment cycles) seems necessary to reach and maintain clinical benefit. Interestingly, our azacitidine-treated patients received a similar number of treatment cycles as patients in the AZA-001 trial[5] (median, 8.5 vs 9); still, our azacitidine-treated patients (85% managed in non-university hospitals) fared much worse (median OS, 16.9 vs 24.5 months), which might indicate patient selection in clinical trials. For example, azacitidine-treated patients in our study have comparatively unfavorable features than azacitidine-treated patients in the AZA-001 trial, such as more frequent poor-risk cytogenetics (44 vs 28%) and therapy-related MDS (18 vs 0%).[5] The incidence of these higher-risk features was similar between our study and the Spanish study.[1] Second, although information on response was lacking in the Spanish study, we show that patients who achieved a response to azacitidine seems to have better survival than non-responders.[1] As shown for azacitidine-treated patients in the AZA-001 trial,[7] achievement of a response seems to translate into a survival benefit relative to non-responders, although a response is not necessarily a prerequisite for clinical benefit. Together, our population-based data suggests that azacitidine might be a suitable treatment approach for elderly HR-MDS patients. Nevertheless, survival curves of azacitidine and BSC only converge at $\sim$2.5 years, which is not unexpected as azacitidine is a non-curative disease-modifying agent.

In agreement with the Spanish study, outcome with either azacitidine or IC was similar.[1] Such observation was recently noted among elderly AML patients in the AZA-AML-001 trial.[8] In addition, we show that patients receiving IC spend substantial more time hospitalized than azacitidine-treated patients. Collectively, azacitidine might be an alternative treatment approach for HR-MDS patients who are likely to tolerate and benefit from IC, but refrain from it and its related long-term hospitalization.

Well-established population-based studies with representative patient populations are useful to assess whether findings from clinical trials translate into benefits for patients in daily practice.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

AGD, AAvdL and MJ-L designed the study; AGD and OV collected the data; AGD analyzed the data; YvN provided advice on statistical analyses; AGD, YvN, OV, EFMP, PCH, PS, AAvdL and MJ-L interpreted the data, AGD wrote the manuscript; and all authors read, commented on, and approved the final version of the manuscript.

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Supplementary Information accompanies this paper on the Leukemia website (http://www.nature.com/leu)