



CORRESPONDENCE

Effectiveness of azacitidine for the treatment of higher-risk myelodysplastic syndromes in daily practice: the authors' reply

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There is an increasing interest on the effectiveness of azacitidine for the treatment of higher-risk myelodysplastic syndromes (MDS) outside clinical trials. We recently reported the lack of effect of this drug in an unselected population of 821 patients.¹ In response to our work, Dinmohamed *et al.*² have performed a similar retrospective analysis of a cohort including 121 patients with higher-risk MDS included in the Dutch registry and treated with either chemotherapy, azacitidine or best supportive care (BSC). Both studies are aimed to analyze the potential effect of the different treatment alternatives on overall survival (OS) in large population-based registries of higher-risk MDS patients. A common finding in both series is the lack of a survival advantage of azacitidine compared with intensive chemotherapy.

However, in contrast to our results, azacitidine-treated patients in the Dutch study showed an OS 9.3 months longer than those who received BSC. This difference was statistically significant in those patients who were classified as responders. Interestingly, and resembling our findings, the subgroup of patients with chromosome 7 abnormalities were the subgroup of patients with an apparently more pronounced benefit. The readership of *Leukemia* should be aware that there are some relevant methodological differences between both studies that could explain their different results.

First, the comparison between treatment alternatives used different statistical tests. The impact of treatment with azacitidine on outcomes was studied by considering this variable as a time-dependent covariate in our study but not in the Dutch series, which used the classical Kaplan–Meier actuarial survival method. We feel that the use of the time of starting treatment as starting point in survival curves for azacitidine- and BSC-treated cohorts

introduces a bias against the BSC cohort because some patients who were candidates for receiving azacitidine and died before being treated with azacitidine are in fact, by Kaplan–Meier method, considered BSC-treated patients. In this sense, in the Dutch report the median time from diagnosis to the onset of therapy was 7 days in the BSC group as compared with 33 days in the azacitidine group ($P < 0.001$). Moreover, some patients receiving azacitidine have been diagnosed up to 5 years before, in contrast to a maximum delay of 102 days in the BSC group. This suggests that those patients with a lower probability of survival or with worse predictors of response to either chemotherapy or azacitidine were assigned to the BSC group. In fact, patients in the BSC arm in the Dutch report showed more comorbidities and a lower percentage of good-risk cytogenetics ($P = 0.007$ and 0.002 , respectively). To establish whether differences in statistical methodology are the main cause of the discrepant results between both reports, we would be grateful if our Dutch colleagues could perform a time-dependent analysis of the effect of azacitidine treatment. As can be seen in Figure 1, when an incorrect Kaplan–Meier survival analysis is used, azacitidine treatment seems to be clearly beneficial.

A second critical difference between the Spanish and Dutch series concerns the lower than expected OS in Dutch patients receiving BSC. These patients showed a median OS of only 7.3 months compared with 11 months in the GESMD (Grupo Español de Síndromes Mielodisplásicos) registry. As the baseline characteristics in the two studies were closely similar, this striking difference could be due to a different intensity of the supportive care that could have a significant impact on OS. Interestingly, median survival in azacitidine-treated patients who did not show any response to the drug was 12.3 months. This survival is much closer to our BSC group and to the control group of the AZA-AML-001 trial (11.5 months).³ As the management of the patients included in a clinical trial is strictly protocolized according to the

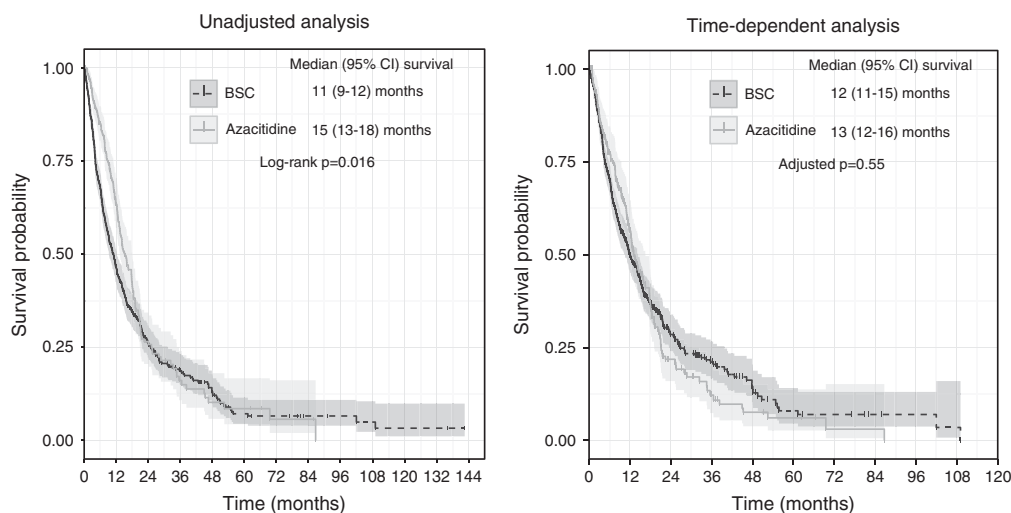


Figure 1. Survival curves of azacitidine treatment versus best supportive therapy (BSC, excluding chemotherapy). If a conventional Kaplan–Meier is used (left), there are significant differences between groups. However, when azacitidine is considered a time-dependent covariate (right), these differences disappear.

best available evidence, we can hypothesize that an optimal supportive care could have yielded a survival benefit similar to the one achieved in patients with no response to other treatments, including azacitidine. This contrasts with the hypothesis raised by Dinmohamed *et al.*,² suggesting that azacitidine could be beneficial even in the absence of a response to the drug according to the International Working Group (IWG) criteria. Although these two hypotheses are not mutually exclusive, the contribution of a carefully applied standard care to the OS cannot be underestimated.

Finally, the greater heterogeneity of the Spanish cohort, including cases of chronic myelomonocytic leukemia, other myeloproliferative neoplasms or acute myeloid leukemia (20–30% blasts), could also explain some of the differences with the Dutch study. However, a subgroup analysis restricted to only high-risk MDS patients did not show the superiority of azacitidine compared with conventional therapy.

In conclusion, we agree with Dinmohamed *et al.*,² on the clear need of population-based studies to confirm the findings of clinical trials in the real life setting. In addition, we remark the importance of an appropriate statistical analysis and of establishing a standardized clinical management for all the patients included in clinical trials, not only for those receiving the active drug under evaluation.

CONFLICT OF INTEREST

TB has served as advisory board member and consultant for Celgene and has received speaker fees. GS has received honoraria and research funding from Celgene,

Novartis and Amgen, and is on the advisory committee for Amgen, Böehringer-Ingelheim, Celgene, MerckSharp and Dohme, and Novartis. The Spanish Group on Myelodysplastic Syndromes is sponsored by Celgene and Novartis.

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REFERENCES

- 1 Bernal T, Martínez-Camblor P, Sánchez-García J, de Paz R, Luño E, Nomdedeu B *et al.* Effectiveness of azacitidine in unselected high-risk myelodysplastic syndromes: results from the Spanish registry. *Leukemia* 2015; **29**: 1875–1881.
- 2 Dinmohamed AG, van Norden Y, Visser O, Posthuma EF, Huijgens PC, Sonneveld P *et al.* Effectiveness of azacitidine for the treatment of higher-risk myelodysplastic syndromes in daily practice: results from the Dutch population-based PHAROS MDS registry. *Leukemia* 2015; **29**: 2449–2451.
- 3 Fenaux P, Mufti GJ, Hellström-Lindberg E, Santini V, Finelli C, Giagounidis A *et al.* Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol* 2009; **10**: 223–232.