Predicting outcome of patients with myelodysplastic syndromes after failure of azacitidine: validation of the North American MDS consortium scoring system

The management of myelodysplastic syndromes (MDS) has been greatly modified by the introduction of hypomethylating agents (HMA) at the turn of the century. Azacitidine (AZA) and decitabine are able to trigger hematological responses in MDS patients, and both prolong the time to progression to acute myeloid leukemia.[1,2] Azacitidine was shown to prolong overall survival of higher-risk MDS patients in the setting of a phase III clinical trial.[1] Despite these improvements, we know that HMA are temporary measures, as only 40% of patients experience response and virtually all patients who stay on treatment will progress. Our group has demonstrated, in several publications,[3-5] that the outcome of patients with AZA failure have a dismal outcome, with the median OS ranging from 3.4 months for secondary AML, 5.6 months for higher-risk MDS, and 16.7 months for so called lower-risk MDS. Many investigations are currently ongoing in order to better understand the underlying biology and to try to improve the management of these patients. Defining variables that may influence outcome after HMA failure appears to be an important issue. In a recent publication from the North American MDS consortium,[6] Nazha *et al*. defined a score of 6 variables (including age, ECOG PS, bone marrow blast counts, cytogenetics, platelet counts, and RBC transfusion-dependency, see *Online supplementary Table S1* for details) which seems to discriminate the outcome of MDS patients with HMA failure more efficiently than the revised IPSS,[7] or other prognostic models. In Nazha *et al*.'s model, the patients were classified into a low-risk group (score below 2.5, median OS 11 months) and a high-risk group (score 2.5 and above, median OS 4.5 months). This score was not validated independently and we decided to apply it to our original datasets.

Briefly, we included all GFM patients with MDS (including RAEB-T) treated with at least one cycle of AZA. Patients may have stopped AZA due to the lack of efficacy, progression, or tolerance issues. As a result of the retrospective nature of our cohort there was some missing data, and we considered in our analysis only those patients with 0 or 1 piece of missing information to determine the score. For patients with 1 missing value, we arbitrarily chose to consider the "worst case scenario". For example a 75 year old patient (1pt) with very high-risk cytogenetics (1pt) and MDS which had evolved into leukemia at the time of failure (0.75 pt) was considered as high-risk whatever the platelet count may be (minimum score= 2.75). Conversely, a 60 year old patient (0 pts), with RCMD (0 pts), normal karyotype (0pts), and isolated transfusion dependent anemia (0.75 pts for RBC TD, 0 for platelets) was considered low-risk whatever might be their ECOG PS (maximum score= 1.75). Patients with not enough information were pooled into a third group. Survival analysis was performed using a Kaplan-Meier estimate and OS was defined by the time interval between the time of documentation of AZA failure to the time of last follow-up or death. GraphPad 6 software was used for the analysis and the figure.

A group of 223 patients were classified as low-risk or high-risk per Nazha *et al*.'s score, with 82 and 141 patients in each group, respectively. The median age was 69 years and the cohort included 150 males and 73 females. Only 3% of the patients had low-risk MDS at the initiation of AZA. 32 patients (16%) had very high-risk cytogenetics according to the revised IPSS.[7] The median number of AZA cycles administered was 6, with a range of 1 to 41. Seventy-nine patients (35%) received other treatments prior to AZA (48 growth factors, 21 chemotherapy, 10 other). Seventy-five patients (34%) responded to AZA prior to failure. The median OS of the whole cohort calculated from the date of failure was 7 months. As shown in Figure 1A, the median overall survival was 13 months for patients with a low-risk score and 5 months for patients with a high-risk score (P<0.001). The results were similar if we limit the analysis to the patients without any missing data, with a median OS of 16 months and 4 months, respectively (P<0.001). The unclassified patients (n=172) had a median survival of 6 months.

Herein, the scoring system developed by the consortium was able to discriminate the potential outcome of

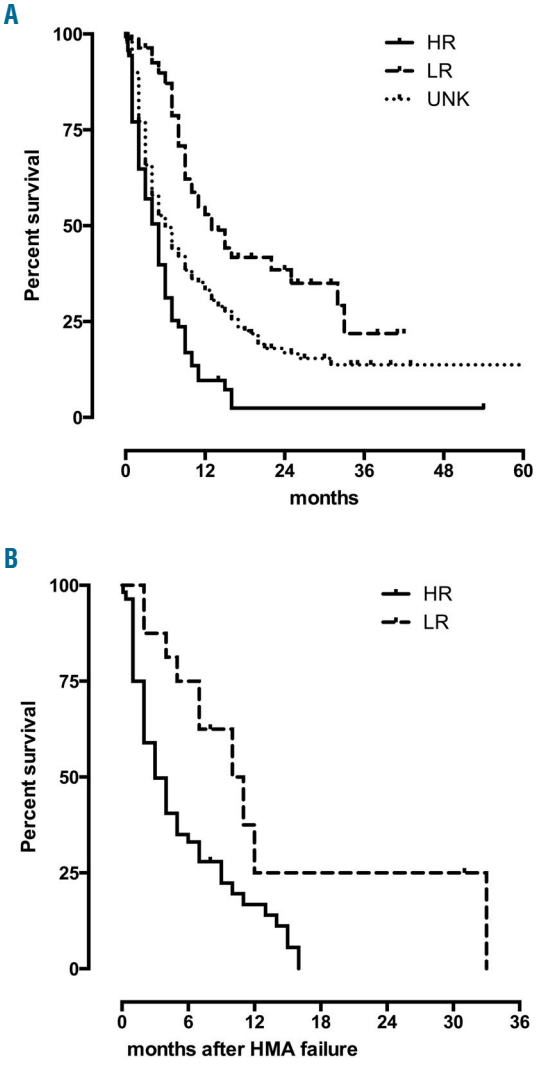

Figure 1 A. Kaplan-Meir estimate of the survival of MDS patients with HMA failure classified according to MDS consortium HMA failure score. B. Subset analysis for patients treated with best supportive care. Survival is expressed in months and is defined from the time of HMA failure to last follow-up or death. HR: high-risk; LR: low-risk; UNK: unknown; HMA: hypomethylating agents; MDS: myelodysplastic syndrome.

MDS patients after failure of AZA. The observed survival of the 2 groups in our analysis were consistent with the findings presented by Nazha *et al*. on behalf of the North American MDS consortium. Interestingly, advanced age and adverse cytogenetics were two variables also associated with outcome in our initial publication.[3] A potential concern is the heterogeneity of the treatments after failure of AZA. From our experience, we know that outcome is significantly influenced by the availability of treatment options, with a median OS ranging from 4 months for patients treated with best supportive care to 18 months for allotransplanted patients.[3] Obviously, the choice of treatment is partially dependent on the clinical presentation at the time of HMA failure, and this is captured by the variables included in the present scoring system. For example, 14 out of the 64 patients (22%) in the low-risk group with available treatment information went on to have allogeneic transplantation, while only 3 out of 61 (5%) in the high-risk group were allotransplanted. So, an important next step will be to try to validate the score in a large cohort of homogeneously treated patients. In our cohort, if we focus on the subgroup of patients treated with BSC (n=74), we were able to show a difference of survival between high-risk and low-risk patients (3m *vs.* 10.5m respectively, *P*=0.006, see Figure 1B). However, in actively treated patients, the numbers of patients in each treatment group were too small to provide a really meaningful analysis.

In conclusion, this scoring system may represent a valuable tool to help risk stratification of the patients with HMA failure. However, additional data, specifically in actively treated patients, will be warranted to confirm its applicability for future analyses and clinical trials.

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Acknowledgments: the authors would like to thank the investigators and teams of the centers of the Groupe Francophone des Myelodysplasies.

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doi:10.3324/haematol.2016.150714

Key words: melodysplastic syndromes, acute myeloid leukemia, cytogenics and molecular genetics, stem cell transplantation, hypomethylating agents.

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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