Correspondence

To the editor:

Long-term outcome of higher-risk MDS patients treated with azacitidine: an update of the GFM compassionate program cohort

We previously reported that peripheral blasts, performance status (PS), red blood cell (RBC) transfusion requirement, and International Prognostic Scoring System (IPSS) cytogenetic risk independently predicted inferior overall survival (OS) in 282 consecutive IPSS high- and intermediate-2–risk myelodysplastic syndromes (MDS) patients treated with azacitidine (AZA).1 These 4 criteria could be integrated in a 3-group prognostic score that significantly discriminated between high-, intermediate-, and low-risk groups, with median OS of 6.1, 15.0 months, and not reached, respectively. This prognostic score was validated in the AZA arm of the AZA-001 trial2 and in 2 smaller cohorts.3,4 Median follow-up of the 3 validation cohorts was 21, 8, and 15 months, respectively, and 26 months in our initial report. We report here an update of our cohort as of November 1, 2011, made to assess the long-term outcome of patients with favorable risk in our proposed prognostic score and to determine the characteristics of long-term survivors.

In the updated analysis, with a median follow-up of 41.3 months, 54 of the 282 patients were still alive and the median number of AZA cycles received was 6 (range 1-53). Median OS was 13.5 months, and the 3-year estimate of OS was 17.5% (95% confidence interval [CI]: 12.6%-22.4%). Sixteen of the 30 patients in the favorable risk group were still alive and median OS of this group was reached at 32.1 months. Our proposed prognostic score remained highly valid (Figure 1; log-rank test: P < 10⁻⁴). Censoring at the time of allogeneic stem cell transplantation did not affect those results.

Thirty-four patients (M/F: 20/14), with a median age of 69 years (range 42-86) had an OS of at least 3 years after AZA onset. At AZA onset, their World Health Organization diagnosis was refractory cytopenia with multilineage dysplasia, refractory anemia with excess blasts (RAEB)–1, RAEB-2, and AML with 20%-30% blasts in 1, 6, 21, and 6 cases, respectively. Four of them had therapy-related MDS. PS was < 2 in 30 cases (88%). Cytogenetic risk was low, intermediate, high, and not available in 18 cases (53%; all with normal karyotype), 8 cases (24%), 7 cases (21%: 3 with isolated monosomy 7 and 4 with complex abnormalities), and 1 case (2%). Only 22 of the 34 patients (64%) had responded to AZA according to International Working Group 2006 criteria,5 including 7 (21%) complete responses (CR), 1 (3%) partial response (PR), 4 (12%) marrow CR, and 10 (29%) stable disease with hematologic improvement. Three years after AZA onset, 6 (18%) of the 34 patients were still receiving AZA, 8 (24%) had been allografted, and 15 (44%) had received other treatments including intensive chemotherapy (n = 2), low-dose chemotherapy (n = 2), investigational drugs (n = 6), or decitabine (n = 5).

Altogether this updated report indicates that long-term survival with AZA in higher-risk MDS can be predicted using our daily-practice scoring system. Long-term survival can be achieved even in some of the patients with poor risk features including therapy-related cases, cases with 20%-30% blasts or with high-risk karyotype, and some patients who do not achieve CR or PR. However, for the majority of patients, long-term outcome remains poor, prompting the investigation of second-line therapies.

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Figure 1. Updated Kaplan-Meier estimates of overall survival (OS) of our previously reported cohort of 282 higher-risk myelodysplastic syndromes (MDS) patients treated with azacitidine, with a median follow-up of 41.3 months. (A) Global cohort (n = 282).1 (B) Cohort according to our risk stratification: low (n = 30, median OS: 32.1 month); intermediate (int; n = 191, median OS: 15.0 months); high (n = 48, median OS: 6.1 month; log-rank test: P < 10⁻⁴).
To the editor:

Development of myeloproliferative disease in 12/15-lipoxygenase deficiency

We read with interest the report by Kinder and colleagues at the Wistar Institute along with their related studies showing that 12/15-lipoxygenase (LOX)–deficiency in (C57BL/6, N11) mice leads to severe myeloproliferative disease (MPD). Moderate splenomegaly with 100% penetrance was observed at 10-12 weeks, with profound blood leukocytosis and basophilia. The defect was characterized as loss of hematopoietic stem cell function, with reductions in lymphocytes, monocytes, and eosinophils. Furthermore, mortality was enhanced to approximately 25% by 12 months. As the moribund, and were considered in blast crisis, with grossly enlarged spleens at up to 6-fold normal size (mean 0.6 g). Strikingly, up to 15% of 10- to 12-week-old animals became frankly malignant, and were considered in blast crisis, with grossly enlarged spleens at up to 6-fold normal size (mean 0.6 g). As the moribund, and were considered in blast crisis, with grossly enlarged spleens at up to 6-fold normal size (mean 0.6 g). Strikingly, up to 15% of 10- to 12-week-old animals became frankly malignant, and were considered in blast crisis, with grossly enlarged spleens at up to 6-fold normal size (mean 0.6 g).


The phenotype reported in the Wistar mice is consistent with MPD, with moribund mice showing features in keeping with myeloid blast transformation to acute myeloid leukemia (AML). Splenomegaly is a clinical feature of all MPDs. Basophilia is more associated with chronic myeloid leukemia (CML), although without Bcr-abl gene fusion, the 12/15-LOX–deficient mice would not be considered as true CML. To provide a tractable model for the
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