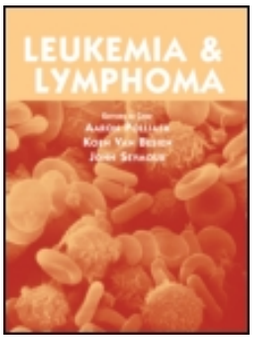

Leukemia & Lymphoma

ISSN: 1042-8194 (Print) 1029-2403 (Online) Journal homepage: informahealthcare.com/journals/ilal20

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To cite this article: Raphael Itzykson & Pierre Fenaux (2012) Predicting the outcome of patients with higher-risk myelodysplastic syndrome treated with hypomethylating agents, Leukemia & Lymphoma, 53:5, 760-762, DOI: 10.3109/10428194.2011.651618

To link to this article: https://doi.org/10.3109/10428194.2011.651618

Leukemia & Lymphoma, May 2012; 53(5): 760–762

ISSN: 1042-8194 print / 1029-2403 online
DOI: 10.3109/10428194.2011.651618

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COMMENTARY

Predicting the outcome of patients with higher-risk myelodysplastic syndrome treated with hypomethylating agents

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The hypomethylating agents (HMAs) azacitidine (AZA) and decitabine (DAC) improve long-term outcomes of higher-risk (International Prognostic Scoring System [IPSS] intermediate-2 or high) myelodysplastic syndrome (MDS) [1,2] and are now the reference frontline therapy of higher-risk MDS not eligible for allogeneic stem cell transplant [1]. Notably, in a phase III randomized trial, AZA significantly prolonged overall survival (OS) compared to conventional care regimens in all cytogenetic subgroups. In that trial, azacitidine was not only superior to best supportive care, but also to low-dose AraC (LDAC) [1,3], while there were too few patients eligible for intensive chemotherapy for adequate comparison to AZA. These results, however, do not necessarily mean that all patients have the same benefit of treatment with azacitidine. Many clinical and biological studies have thus tried to determine which subgroups of patients with MDS may benefit most from azanucleotides, not only for prognostic purposes, but also to obtain insights into the mode of action of hypomethylating agents.

These studies focused on two different outcomes: response to azacitidine, and longer-term endpoints, mainly OS. The endpoint analyzed is of importance, as response may not be a perfect surrogate marker of survival in the setting of HMA therapy, where survival improvements can be observed despite limited complete and partial response rates [4,5].

Prior to the report by Breccia *et al*. in this issue, all studies addressing the prediction of response to HMA had found limited prognostic value of routine parameters. A pooled analysis of decitabine phase II studies and a retrospective series of patients with mostly lower-risk MDS treated with azacitidine failed to identify factors predictive of response [6,7]. In the M. D. Anderson series, only prior therapy and longer MDS duration predicted inferior complete response (CR) rates [8], while shorter MDS duration prior to treatment appeared detrimental in a large prospective trial of DAC [2]. In the French compassionate named-patient program that included 282 patients with higher-risk disease, only normal karyotype, bone marrow blasts $<15\%$ and absence of previous exposure to LDAC predicted slightly superior response rates, and with only moderate statistical significance [4].

In contrast, it appears easier to predict OS following AZA therapy using the same routine parameters. Using our 282 patient cohort, we proposed a three-category risk score prognostic classification based on independent prognostic factors for OS identified by multivariate analysis, which included performance status ≥ 2, IPSS cytogenetic risk, presence of peripheral blasts and red blood cell (RBC) transfusion dependency ≥ 4 RBC units/8 weeks. This score identified two groups with an extreme prognosis: 11% of patients had a median survival not reached after more than 2 years of median follow-up, another 18% had a very poor prognosis, with a median OS of 6 months, while the bulk of the cohort (71%) had an intermediate outcome, with a median OS of 15 months [4]. This score was validated in the more selected population randomized to the AZA arm of the AZA-001 trial, where the proportion of patients with low, intermediate and high risk disease according to this classification was 15%, 75% and 10%, respectively.

In this issue, Breccia and colleagues further validate this prognostic score in a series of 60 patients from the Italian compassionate use program of azacitidine, most of whom (85%) had IPSS intermediate-2 risk disease. According to the French prognostic azacitidine system, 20%, 63% and 17% of patients belonged to the low, intermediate and high risk groups, respectively. In the Breccia *et al*. series, not only was OS predicted by the French prognostic system (with median OS of 21, 15 and 11 months, respectively), but so was the overall response rate, with rates of 50%, 24% and 0%, respectively [9]. This prognostic score has also been recently validated in an independent Dutch cohort [10].

Can such scores based on routine clinical and hematological parameters improve clinical practice, regarding treatment decisions in individual patients, and the design of clinical trials? They may help for patients in the 'low' risk group, who had almost exclusively refractory anemia

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This commentary accompanies an article to be published in *Leukemia & Lymphoma*. Please refer to the table of contents of the print issue in which this commentary appears.

with excess blasts type 2 (RAEB-2; or low-blast-count acute myeloid leukemia/refractory anemia with excess blasts in transformation [AML/RAEB-T]), normal karyotype and good performance status, and were thus, in the absence of major comorbidities, potential candidates for intensive chemotherapy (IC). It would therefore be interesting to determine whether AZA is superior to IC in this subgroup. More individually, if these patients respond to AZA and are suitable for allogeneic transplant, whether the transplant should be performed after response achievement or delayed until after disease recurrence would also have to be determined. This issue is currently being addressed by decision model studies [11].

In contrast, patients with a high risk score, because of their poor prognosis with AZA alone, could be candidates for alternative first-line investigational therapies, which would, however, generally have to be associated with limited myelosuppression given their usual poor general condition. Currently, these alternative options are mainly studied in patients relapsing or failing hypomethylating therapy [12].

Clinical scores for AZA efficacy such as the French example could also be used to compare different clinical trials including apparently similar patient populations according to standard IPSS criteria.

It is nevertheless important to further improve prognostic factors of response to HMA. Other clinical parameters, including early platelet count increase [10] and evaluation of comorbidities [13], could be useful. However, much is expected from ongoing research on biomarkers of the efficacy of HMA, both for selecting patients a priori, and for treatment monitoring. Global methylation levels or the methylation status of a few gene promoters (including that of the tumor suppressor *CDKN2B* that encodes p15/INK4B, a regulator of the cell cycle) appear insufficient [14,15]. Integrating the methylation level of several genes in a "methylation signature" seems more promising, but requires validation in independent laboratories [16]. Promising results from studies of gene or microRNA (such as mir-29b, which regulates DNA methyltransferase [DNMT] expression) levels have also been reported, but again await independent confirmation [17–19]. Importantly, mutations in genes with epigenetic function have been reported in MDS (see [20] for a review). These include *TET2* and *DNMT3* that directly regulate DNA methylation, the *IDH1/2* genes that affect TET2 functionality [21], and the *EZH2*, *UTX* and *ASXL1* genes that regulate histone modifications which dynamically interplay with DNA methylation to regulate gene expression. Mutations in these genes may affect the response to hypomethylating agents. We reported in 86 patients with higher-risk MDS treated with azacitidine that *TET2* mutation (found in 13% of them) was associated with twice the overall response rate of patients with wild-type *TET2*, independent of cytogenetics, although this increased response rate did not translate into superior survival in this small cohort [22]. These results have received a recent confirmation from early reports that further extend this favorable prognostic value for response to *ASXL1*, *DNTM3A* and possibly *EZH2* mutations [23–25]. A similar trend, though not statistically significant (43% vs. 28% of response for mutated and wild-type *TET2*, respectively, $p = 0.17$), was noted in a cohort of patients with advanced chronic myelomonocytic leukemia (CMML) prospectively treated with decitabine [18].

Ongoing efforts to determine which patients benefit most from current hypomethylating therapy and to discover biomarkers of these agents will likely help to refine therapeutic strategies, including the evaluation of combinations between HMA and other drugs, and treatment monitoring to detect impending relapse.

Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

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