Correspondence

To the editor:

Low-dose decitabine and high-risk MDS

Kantarjian et al1 present their randomized study of 3 schedules of low-dose decitabine in patients with higher-risk myelodysplastic syndrome/chronic monomyelocytic leukemia (MDS/CMML) reporting a high complete remission (CR) rate. This comprehensive clinical trial along with its biologic correlates represents a significant addition to the therapeutic choices available for patients with MDS. For the clinician to make an informed decision about the use of decitabine versus azacitidine, it would be helpful if the authors address the following issues that were left rather ambiguous.

The title of the report suggests that all patients in the study should have met the criteria of higher-risk MDS or CMML; however, 24% of patients had less than 5% blasts and 33% were in the International Prognostic Scoring System (IPSS) intermediate-1 (Int-1) prognostic group, suggesting that these patients were actually lower risk.

The IPSS score is missing for 39 patients. Did any of them have low-risk disease?

The use of several response criteria is confusing. In summary, the authors have not used acute myeloid leukemia International Working Group (AML IWG) criteria or modified MDS IWG criteria, but a third set of their own, where CR is defined as lasting at least 4 weeks. Since 4 authors reassessed the response of every patient based on the modified MDS IWG criteria, why not just report those results?

While effectively producing a high CR rate, there appears to be a high toxicity associated even with this low-dose schedule of decitabine, resulting in a 64% incidence of hospitalization. This seems to be more toxic than azacitidine.

The conclusion of p15 data is that there is no correlation between expression of p15 and its methylation pattern, yet there is a relationship between expression and outcome, CR patients having higher expression. What does this high expression mean since it is not related to methylation? Is this gene being expressed while it is hypermethylated?

Peripheral blood mononuclear cells (PBMC) were used for the measurement of p15 methylation and expression. PBMCs are predominantly lymphocytes that are not generally a part of the MDS clone. The authors explain the use of PB versus bone marrow (BM) on the basis of the results published by Aoki et al,2 where BM/PB compartments yielded similar results. However, Aoki et al compared p15 methylation/expression in the granulocytic fraction of PB and compared that with BMNCs. Therefore, the results of Kantarjian et al’s use of PBMCs may be confounded by the presence of lymphocytes.

While clarification of these points may help hematologists with clinical decisions, the fact remains that this study demonstrates a very important point: low-dose decitabine is a viable treatment option for high-risk MDS.

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References


Response:

Results of a randomized study of 3 schedules of low-dose decitabine in higher-risk myelodysplastic syndrome and chronic myelomonocytic leukemia

In reply to the comments of Raza and Galili regarding our recent publication,1 we provide the following clarifications.

This study included patients with higher-risk MDS (or poorer prognosis) by virtue of several factors: (1) 61% had failed prior therapy for MDS and were referred to our center for other options; (2) 32% had secondary MDS; and (3) 56% had chromosomal abnormalities. No patient in a low-risk IPSS group was included. Although 23 of 95 patients had blasts lower than 5%, they still had higher-risk MDS by the presence of at least 2 to 3 cytopenias (score 0.5) and/or adverse chromosomal abnormalities (scores 0.5 or 1.0), thus having IPSS scores of 0.5 to 1.5 (ie, IPSS risk groups Int-1 or worse). IPSS Int-1 was present in only 19 of 95 patients. The experience from our institution is that MDS Int-1 shows a median survival of only 1.2 years.2 This is likely because patients referred to a tertiary center like ours have adverse features that prompted the referral or progressed on other therapies.

The IPSS risk was “not applicable” in 39 of 95 patients (Table 1) because they had secondary MDS (n = 30; usually worse) or CMML with leukocytosis (n = 9). Both are excluded from the IPSS classification. Importantly, 61% of our patients had failed prior therapies. The IPSS classification applies to newly diagnosed primary untreated MDS (only 65% [88% of 816 had prior minimal therapy in the original IPSS study), and patients with prior therapies have usually a worse prognosis.2 However, we still elected to present them by IPSS risk to allow for comparative analyses.

The results were reported by the modified MDS IWG criteria, which require durability of complete or partial responses for at least 4 weeks, but of hematologic improvements for at least 8 weeks.3
As was pointed out, the CR rate was 34% by the modified IWG criteria and 40% in the best schedule (5-day intravenous). This compares favorably with prior experiences with decitabine and 5-azacitidine (CR rates, 6%-20%). Also, decitabine was less toxic than 5-azacitidine in relation to nausea/vomiting and local skin reactions (pain and induration in 5%-10% of patients on 5-azacitidine). The incidence of 65% of hospitalization is cumulative. As one delivers more courses of effective therapy, the probability of a 1-time hospitalization would be more likely after multiple courses than after 1 or 2 courses. In the summary briefing of the Food and Drug Administration (FDA) by Kaminskas et al., the incidence of serious adverse events (mostly febrile episodes and hospitalizations) was 60%, similar to our experience. Thus, short of directly comparative trials, the current studies suggest that at the current dose schedules, decitabine and 5-azacitidine are probably equally myelosuppressive.

The paper makes no comments on the relationship between p15 methylation and expression. In fact, analysis of the data shows that samples in which p15 methylation was greater than 15% had 6-fold lower expression of p15 than unmethylated samples, exactly as expected (deltaCT compared with GAPDH, $-21.7$ in the methylated group, and $-19.2$ in the unmethylated group; $P < .001$). No patients with a high degree of methylation had high levels of expression. However, a low degree of methylation was not necessarily predictive of high-level expression, suggesting that factors other than methylation are also associated with p15 down-regulation in MDS. It is interesting to note that few patients in this study had high levels of p15 methylation. Thus, the p15 induction by decitabine observed came from both p15 hypomethylation-related and -unrelated epigenetic effects. It is also well known that DNA methylation inhibitors can affect gene expression independent of promoter methylation.

We agree that the results we observed may be confounded by the presence of lymphocytes. Unfortunately, no sorted samples are available from these patients to address this issue experimentally. Unpublished data from our laboratory (Y.O. and J-P.I., 2006) showing a high degree of correlation between methylation in unsorted peripheral blood mononuclear cells and unsorted bone marrow mononuclear cells suggest that variable contamination with nonmalignant lymphocytes is unlikely to be significant. This issue clearly should be tested in future studies.

We hope this clarifies the points raised. Based on our experience, decitabine appears to be the most active anti-MDS single agent. Further experience with single-agent decitabine and with decitabine combinations may hopefully improve prognosis in MDS and CMML.

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References

To the editor:

Recovery of spermatogenesis after total-body irradiation

We read with interest the paper by Rovo et al., who studied spermatogenesis in 39 long-term survivors after abllogenic stem cell transplantation (allo-SCT). Eleven patients had recovery of spermatogenesis. The authors found that a younger age (<25 years) and a non-total-body irradiation (TBI)–based conditioning regimen (CR) were independent factors predicting active sperm production after allo-SCT.

At our institution, male patients gave written consent to be enrolled in a long-term posttransplantation follow-up study, including annual semen analysis (SA). Of the 74 patients enrolled in the study, 40 were male, and 35 underwent a SA. The indication for allo-SCT was chronic myelogenous leukemia (CML; 25 patients), myelodysplastic syndrome (MDS; 5 patients), acute myelogenous leukemia (AML; 3 patients), acute lymphoblastic leukemia (ALL; 1 patient), and chronic lymphocytic leukemia (CLL; 1 patient). Median follow-up after transplantation was 6 years (range, 3-13 years). Most (33) patients (median age, 38 years; range, 17-56 years) received a fractionated TBI (12-13.6 Gy)–based myeloablative stem cell transplantation (MST); 2 patients (aged 39 and 40 years) received a non-TBI nonmyeloablative stem cell transplantation (NST). Follicle-stimulating hormone (FSH) levels ranged from 6 to 46 U/L (median, 19 U/L; reference range, 2-15 U/L), and free testosterone levels ranged from 0.18738 to 0.82586 μM (5.4-23.8 ng/dL) (median, 0.449365 μM [12.95 ng/dL]; reference range, 0.3123-1.041 μM [9-30 ng/dL]) in all patients except for 1, who was treated with a testosterone patch. SA and morphology were assessed as described previously. Five (14.3%) patients showed evidence of sperm production (3 [9%] MST recipients and the 2 NST recipients; Table 1). Sperm production was associated with younger age at transplantation (<30 years old; $P = .04$), and a follow-up of 7 years or more (3 of 5 vs 0 of 28; $P = .002$) in MST recipients. Both NST recipients had spermatogenesis and the highest sperm counts, despite their older age. We did not find a relationship with disease type ($P = .874$), acute graft-versus-host
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