blood advances

TO THE EDITOR:

Azacitidine maintenance after allogeneic hematopoietic cell transplantation for MDS and AML

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Allogeneic hematopoietic cell transplantation (alloHCT) is standard-of-care therapy for patients with myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML) and is potentially curative. Disease relapse remains the most common reason for transplant failure, motivating the search for pharmacological adjuvant therapy that may supplement the immunotherapeutic action of the graft-versus-leukemia effect.[1] Observational series and single-arm trials have evaluated azacitidine post-alloHCT for such a "maintenance" role,[2-8] but high-quality randomized evidence of the efficacy of this approach is lacking. Oran et al recently reported the results of a phase 3 randomized controlled trial (RCT) that was conducted to test the hypothesis that maintenance azacitidine in high-risk MDS and AML patients in complete remission after alloHCT would improve 3-year relapse-free survival.[9] Although the investigators are to be congratulated for conducting an RCT on this important clinical question, we believe that multiple issues require further discussion and clarification.

There appear to be several discrepancies in the data presented in Table 2 of their study. In the azacitidine column, a total of 97 patients are listed within the "disease status" sections, whereas the column header and the main text state that only 87 patients started the first cycle of azacitidine. In addition, the combined percentages associated with AML patient numbers in the azacitidine column exceeds 100%. There also appears to be a typographical error in the observation column of Table 2, with n = 93 patients listed in the header (vs the n = 94 patients described in the text and accounted for in the table).

Once this table has been corrected, would the investigators comment on the implications for the balance between the 2 arms and agree to provide a patient-level disease characteristics therapy-received and outcomes data spreadsheet as supplemental material? This would add important information to this article and allow exploratory post hoc analysis focusing, for example, on the AML patients transplanted in complete remission. It will also be important to understand, for example, how many AML patients were classified as "high risk" in first complete remission based on pretreatment surrogates of disease biology (complex or adverse risk cytogenetics, *FLT3* mutation) vs those with demonstrated failure (ie, second complete remission) or evolution from (therapy-related) prior treatment before being able to begin to generalize from these results. Similarly, the relapse-free survival expectation of MDS patients (26% of this cohort) after alloHCT differs substantially from AML patients with active disease at the time of alloHCT, confounding interpretation.

The eligibility criterion requirement to be in complete remission after transplant, with enrollment possible 40 to 100 days post-alloHCT, contributed to the >75% screen failure rate of that study (>748 patients screened; reasons for 520 of the 561 recorded screen failures are listed in Table 1 of the study by Oran et al).[9] Compared with the 87 patients who received azacitidine post-alloHCT as part of that study, another 62 of the screened patients did so outside that clinical trial, including 26 for the indication of

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"minimal" (ie, measurable) residual disease (MRD),[10-12] representing a clear source of potential bias. Although oral azacitidine (CC-486) improved survival for MRD-positive and MRD-negative patients in a nontransplant maintenance setting,[13] information on all of the MRD testing performed in this post-alloHCT study would have been important, particularly because MRD results available to the treating physicians may have influenced decisions regarding participation on this trial. Indeed, such results have previously formed the basis of trials of azacitidine use post-alloHCT in a preemptive MRD-directed role.[14,15]

Despite an enrollment upper age limit of 75 years, only 32 patients (17.7%) received reduced intensity conditioning on this trial. Although the randomized BMT-CTN 0901 study showed that myeloablative conditioning is preferred when tolerable in the myeloid malignancies (particularly for AML) in those 65 years of age or younger,[16,17] the benefit of such intensification is particularly important in those with MRD.[18,19] Patients ineligible for myeloablative conditioning and with detectable MRD pre-alloHCT may be more likely to benefit from posttransplant interventions, such as maintenance therapy.[2] The role of maintenance in that particularly high-risk population is not answered by this study, but it may be by a future double-blind phase 3 RCT that will stratify by conditioning intensity, age, and donor type (NCT04173533). This upcoming study (AMADEUS) will also address concerns regarding the dose, schedule, and duration of therapy by including treatment with oral azacitidine (CC-486) or placebo for 14 days of every 28-day cycle, as previously evaluated,[3] rather than the dose used in that study, which had already been shown to be challenging when given for a prolonged period for this indication.[5] Additionally, some patients may have been classified in the Oran et al trial as being high risk because of the presence of an *FLT3* mutation. Targeted maintenance therapy with tyrosine kinase inhibitors, for such patients as reported[20-23] and currently under investigation in the BMT-CTN 1506 RCT (NCT02997202), may be preferable to hypomethylating agents. Finally, presumably some patients initiated azacitidine while still receiving posttransplant immunosuppression; the impact of this combination and the generalizability of such findings in an era of posttransplantation cyclophosphamide are unclear.[24]

In summary, although the authors are to be congratulated on the publication of this RCT, the data as presented do not provide definitive evidence for the role of azacitidine maintenance after alloHCT for MDS and AML. However, this study does make clear that such a hypomethylating agent–based maintenance approach, even if later shown to be effective, would serve only a subset of those undergoing alloHCT for these diseases because of the exclusion of those with comorbidity, such as acute graft-versus-host disease and persistent cytopenia (more patients were excluded than enrolled). Future work will test azacitidine alone and in combination with other agents as maintenance, perhaps compared with genetically targeted or immunotherapy approaches, which may be preferable for some disease subtypes. Hopefully, these will be placebo-controlled randomized trials with comprehensive genomic risk classification and integrated MRD assessments to directly quantify any antileukemic efficacy of this maintenance approach to post-alloHCT relapse prevention. Stratification for conditioning intensity, age, and disease risk group will also be important in such trials, along perhaps with other factors, such as immunosuppressive approach used, donor type, and prior receipt of the maintenance agent. In the meantime, we look forward to amended, and more granular, data being made available from this trial.

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