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EDITORIAL

Improving Outcomes in High-Risk Myelodysplasia: Festina Lente

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The myelodysplastic syndromes (MDS) represent a compendious group of clonal hematopoietic disorders characterized by ineffective hematopoiesis resulting in peripheral blood cytopenias and a significant risk of transformation to acute myeloid leukemia (AML). The degree of cytopenia, blast percentage, and presentation karyotype permit identification of patients with high-risk MDS whose outcome is particularly poor. Targeted mutational analysis has transformed our understanding of the pathogenesis of MDS and, at the same time, provided the tools for preliminary analyses of clonal structure. Acquired abnormalities in classes of genes determining chromatin structure, including mutations in *DNMT3A*, *TET2*, *IDH1*, and *IDH2* (which influence CpG island methylation status) and *EZH2* and *ASZL1* (which contribute to the control of histone acetylation) are commonly observed in MDS and likely contribute to disease pathogenesis.[1]

Currently, the only curative treatment in MDS is allogeneic stem-cell transplantation. Over the last decade, pharmacologic reversal of acquired abnormalities in chromatin structure has emerged as a plausible therapeutic strategy in a range of hematologic malignancies, notably AML and MDS, where inhibitors of DNA methyltransferase (DNMT) and histone deacetylase enzymes have demonstrated activity in preclinical models.[2] Indeed, the most important therapeutic advance in the treatment of adult higher-risk MDS, particularly in older patients ineligible for intensive chemotherapy or allogeneic stem-cell transplantation, has been the demonstration that the DNMT inhibitors azacitidine (AZA) and decitabine can produce either complete remission (CR) or a hematologic improvement in a significant number of patients.[3,4] Furthermore, in a prospective randomized trial, AZA was shown to improve overall survival (OS), thereby representing the first pharmacologic agent to alter the natural history of high-risk MDS.[5] Importantly, recent prospective trials have also demonstrated improved OS after AZA therapy in older adults with AML who are not eligible for intensive chemotherapy.[6] The current subcutaneous mode of administration of AZA is inconvenient and sometimes painful, but the recent development of a relatively well-tolerated formulation, CC486, with augmented pharmacokinetics promises to transform the ease of administration of an agent that has now become the standard of care in older patients with high-risk MDS.[7] Of interest, CC486 also demonstrates clinical activity in patients who have experienced treatment failure with subcutaneous AZA, suggesting that the more prolonged exposure to AZA delivered by CC486 can result in clinical responses in patients resistant to AZA.

It remains the case, however, that only a minority of patients treated with AZA achieve a bone marrow CR or CRi (characterized by a reduction in bone marrow blast percentage to $< 5\%$ without complete peripheral count recovery), and disease progression remains inevitable. Consequently, the last decade has witnessed an active search for novel agents with the capacity to both improve response rates and prolong survival in AZA-treated patients. In preclinical models, the combination of AZA with histone deacetylase inhibitors, such as sodium valproate, etinostat, and vorinostat, markedly increases antitumor activity.[2] Indeed, two early-phase studies of combined AZA and vorinostat administration seemed encouraging, with CR rates reported between 50% and 70%.[8,9] An alternative strategy that has shown promising results in early-phase trials is combination with the immunomodulatory drug lenalidomide.[10] Consequently, the prospective randomized trial by Sekeres et al[11] reported in the article that accompanies this editorial, which demonstrated no increase in either overall response rate or survival in patients with high-risk MDS treated with either combination compared with AZA monotherapy, is important and consistent with recent studies showing no benefit of combining AZA with entinostat or pracinostat.[12,13] Why might this meticulously conducted trial have failed to replicate the encouraging results of previous early-phase trials using both drug combinations? Such disparities are most commonly attributed to potential selection bias in early-phase trials, and it is therefore important to note that in this study, the demographic and molecular characteristics of the trial population appear representative of a typical population of patients with high-risk MDS. Alternatively, it is possible that the additional toxicity observed with the experimental combination arms resulted in either underdosing of AZA or premature cessation of combination therapy, and this possibility is supported by the trend toward improved survival in the vorinostat arm despite increased toxicity.

On the assumption that therapeutic decision making should be informed by Einstein's apocryphal observation that the definition of insanity is doing the same thing over and over again and expecting different results, it is perhaps important now to consider what alternative strategies might improve the clinical activity of AZA with regard to both increasing CR rate and prolonging OS. Rational construction of novel AZA-based combinations is hampered by our failure to fully understand both how AZA exerts its antitumor effect and the cellular basis of disease relapse in this clinical setting. Studies correlating upregulation of key cell cycle

regulators, such as *CDKN1A*, with AZA's activity in both in vitro and animal models of AML implicate induction of G1/S cell cycle arrest as one of the mechanisms of AZA-induced antitumor activity. These observations provide a rationale for combining AZA with inhibitors that target G2 checkpoint kinases, such as Wee1, Chk1, or ATR. Combination with other agents that exert a p53-independent mechanism of killing is also of interest, and it is noteworthy that in preliminary studies, coadministration of AZA with the *Bcl-2* inhibitor venetoclax has been reported to produce CR rates of up to 70% in newly diagnosed patients with high-risk MDS and AML.[14]

The major cause of treatment failure in AZA-treated patients is the almost-universal occurrence of disease resistance; consequently, strategies with the capacity to maintain bone marrow responses are required. The occurrence at relapse of subclones present at only a low frequency at diagnosis in AZA-treated patients supports the implementation of a sequential therapeutic strategy using targeted agents such as *FLT3ITD*, *IDH1*, or *IDH2* inhibitors in combination with AZA,[15] potentially on the basis of sequential analysis of clonal structure. At the same time, immunophenotypic characterization of the stem/progenitor cell compartments containing leukemic stem cells permits serial quantitation of leukemic stem/progenitors during therapy.[16] A current but largely untested hypothesis is that this population serves as a reservoir of disease resistance, which, if confirmed, raises the possibility of both using serial quantitation of this population as a biomarker of response to novel AZA-based combinations and highlights the importance of developing novel drug or antibody treatment strategies with the potential to target residual leukemic stem/progenitor cells.

A major factor limiting the effective use of AZA in clinical practice is the challenge of identifying the patients likely to obtain a major clinical benefit at the start of treatment, either in terms of CR acquisition or improved survival. A notable feature of the article by Sekeres et al[11] is the prospective correlation of clinical response with the results of next-generation sequencing of 40 candidate myeloid genes. In previous retrospective analyses, mutations in *DNMT3A* have been shown to correlate with an increased likelihood of achieving a clinical response to AZA, although this has not been consistently observed.[17] It is therefore of considerable interest that this observation was replicated in this prospective study because just as retrospective phase I/II trials can yield unreproducible clinical observations, the same may also apply to the previous, mostly retrospective, analyses of the molecular predictors of response to AZA-based therapy. Just as importantly, this prospective evaluation provides a template for integrating mutational profiling into future trials of AZA-based combination therapy.

More generally, the increasing molecular stratification of diseases previously considered homogeneous clinical entities, such as MDS and AML, coupled with the tsunami of emergent novel therapies, poses profound questions about the scale and capacity of the translational infrastructure that will be required if we are to rapidly assess an exponentially increasing number of promising novel drug, antibody, and cellular therapies in ever-decreasing genetically defined disease populations. What is increasingly clear is that our current reliance on both trial designs and translational infrastructures that may have been fit for purpose in 2007 when the therapeutic cupboard was bare threatens to disadvantage patients, academia, and the pharmaceutical sector in the next decade. Although the precise models that will be required to realize the therapeutic promise of the next decade will be nuanced according to factors such as disease incidence, molecular stratification, and therapeutic opportunities, certain common principles can be predicted to apply. At the heart of accelerated trial delivery is the establishment of resourced trial networks with a sufficient density of patients to allow the rapid assessment of a range of novel therapies as developed so effectively in stem-cell transplantation and planned for antibiotic trials.[18,19] Such networks should be appropriately resourced and incentivised to reward rapid trial development with enhanced pharmacovigilance allowing trial delivery to regulatory standard, removing the current inefficient split between commercial and academic studies. Finally, integration of next-generation sequencing, studies of measurable residual disease and candidate biomarkers, where possible in real time, must be ensured so that both discovery science and trial delivery have the opportunity to impact clinical care as swiftly as possible.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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