Azacitidine for MDS and CMML

Emma St. Martin and Mrinal M. Patnaik

Division of Hematology, Department of Internal Medicine, Mayo Clinic, Rochester, MN, USA

E-mail: patnaik.mrinal@mayo.edu

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TITLE	Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the Cancer and Leukemia Group B
AUTHORS	Silverman LR, Demakos EP, Peterson BL, *et al.*
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DNA methyltransferase (DNMT) inhibitors such as azacitidine and decitabine inhibit DNA methyltransferase, an enzyme that regulates DNA methylation and gene expression. These agents were initially developed in the 1980s as epigenetic modifiers to upregulate fetal hemoglobin in β-thalassemia and sickle cell disease. Although those early studies did not advance, they laid the groundwork for exploring DNMT inhibitors in myelodysplastic syndromes (MDS), hematologic malignancies characterized by aberrant DNA methylation. Building on encouraging phase I and II studies assessing the safety and efficacy of azacitidine in MDS,[1] the phase III CALGB 9221 trial randomized patients with MDS to either azacitidine 75 mg/m² given subcutaneously for 7 days every 4 weeks, or best supportive care. The results were striking: 60% of patients receiving azacitidine demonstrated hematologic improvements (complete response, 7%; partial response, 16%; improvement, 37%), compared with only 5% in the best supportive care arm (P<0.001). Furthermore, the median time to leukemic transformation or death was significantly prolonged in the azacitidine arm at 21 months *versus* 13 months in the best supportive care arm, along with improvements in quality-of-life measures. This study represented the first instance in which a therapy for MDS demonstrated not only sustained improvement in cytopenias but also altered the course of the disease. This trial led to the U.S. Food and Drug Administration (FDA) approval of azacitidine for the treatment of MDS (May 19, 2004), and over two decades later, DNMT inhibitors

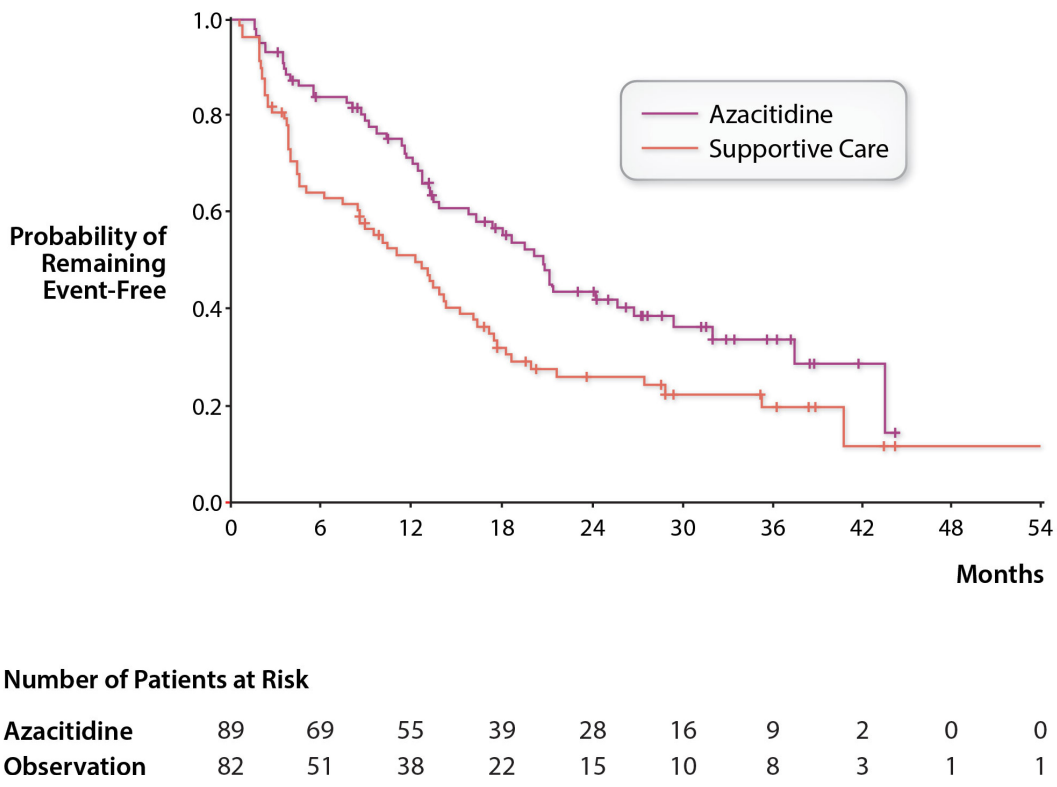

Figure 1. Time to acute myeloid leukemia transformation or death in patients with myelodyplastic syndrome receiving azacitidine *versus* best supportive care in the CALGB 9221 trial.[2] Figure adapted , with permission, from figure 3 in the paper by Silverman LR *et al.*[2]

remain foundational in the treatment of MDS and related hematologic malignancies. The subsequent AZA-001 trial,[3] which confirmed the overall survival benefit of azacitidine in high-risk MDS, and a phase III study of decitabine in MDS[4] reinforced the therapeutic effects of this class of agents. More recently, the VIALE-A study[5] demonstrated that azacitidine, when combined with the BCL-2 inhibitor venetoclax, significantly improved survival in older or medically unfit patients with acute myeloid leukemia. Interestingly, despite these successes, no subsequent trial has fully replicated the survival outcomes reported in the MDS CALGB 9221 and AZA-001 studies. Real-world studies of DNMT inhibitors in MDS show median overall survivals closer to 15 months, with consistent improvements in leukemia-free survival.

The CALGB 9221 and AZA-001 trials also led to the FDA approval of azacitidine for chronic myelomonocytic leukemia (CMML). In CALGB 9221, only seven patients with CMML received azacitdine, while seven received best supportive care. Most patients in both studies had myelodysplastic-CMML and thus far, there is limited evidence supporting the use of DNMT inhibitors in myeloproliferative-CMML (white blood cell count ≥13.0x10^9/L). Indeed, the recent DACOTA study[6] found that decitabine conferred no event-free survival benefit over hydroxyurea in myeloproliferative-CMML.

Ultimately, the legacy of CALGB 9221 lies in its validation of epigenetic modulation as a viable therapeutic strategy in myeloid neoplasms. Moreover, it inspired the development of additional drugs in this space with a focus on optimizing delivery and tolerability of DNMT inhibitors. Newer second-generation, oral formulations of DNMT inhibitors promise to further improve patients' quality of life, treatment adherence, and access to care.

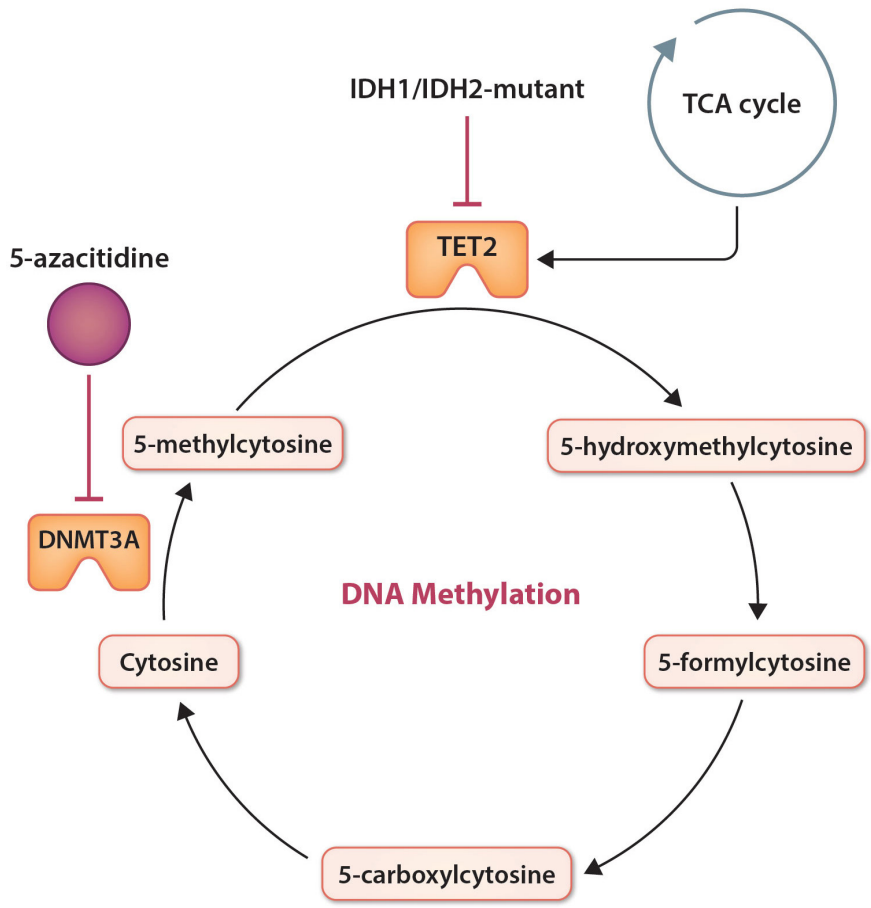

Figure 2. Impact of 5-azaciditine on DNA methylation via inhibition of DNMT3A, which converts cytosine to 5-methylcytosine. DNMT3A: DNA methyltranserase 3 alpha; IDH: isocitrate dehydrogenase; TET2: Tet methylcytosine dioxygenase 2; TCA: tricarboxylic acid.

Disclosures

MMP has received research support from Kura Oncology, Stem Line Pharmaceuticals, Polaris, Epigenetix and Solutherapeutics. He has also served on advisory boards for GSK, SOBI and AstraZeneca. EM has no conflicts of interest to disclose.

Contributions

Both authors contributed to this paper.

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