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Introduction

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Myelodysplastic syndromes (MDSs) and acute myelogenous leukemia (AML) comprise a closely linked continuum of malignant hematologic diseases. While MDS affects 15,000 new patients in the US each year,[1] and has an estimated worldwide annual incidence of anywhere from 3.5 to 12.6 per 100,000 people,[2] AML has an annual US incidence and prevalence of 12,000 and 50,000 cases, respectively.[3] Patients with MDS and AML are predominantly over 60 years of age and mortality is therefore high, and treatment options become more limited than for some other diseases.[4,5]

MDS involves multiple morphological and genetic changes within hematopoietic progenitors, resulting in excessive apoptosis and peripheral cytopenias characterized by anemia, neutropenia, and thrombocytopenia.[4–7] Overall, in 30% of patients with MDS the disease transforms to AML.[5] Complications include infection, bleeding, and a requirement for chronic transfusion, which leads to iron overload. Up to 50% of patients with MDS die from these complications, usually within 3–4 years of diagnosis.[8]

In both MDS and AML, strategies offering a cure are limited. In MDS, allogeneic stem cell transplantation has offered the prospect of cure, but only in a minority of younger patients with high-risk disease for whom sibling or volunteer unrelated donors are available. Nevertheless, the majority of patients are not able to receive transplants because of their age and other comorbid medical factors. In AML, high-dose chemotherapy strategies have offered promise; nonetheless, overall disease mortality remains high, with 15% patient survival at 3 years.[9] Subgroups with a poor prognosis in which there is preceding or associated dysplasia are particularly refractory to treatment. Furthermore, the majority of patients with AML are over 60 years of age[4,5] and, as mentioned already, are not good candidates for curative treatments and have shorter remissions than those patients who respond.[9]

Supportive care has been the empiric mainstay for the majority of MDS patients. This strategy has involved the administration of transfusions and the use of recombinant erythropoietin (e.g. epoetin alfa [Procrit®, Ortho Biotech Products, Bridgewater, NJ, USA, and Epogen®, Amgen, Inc., Thousand Oaks, CA, USA]) and myeloid growth factors such as filgrastim (recombinant human granulocyte-colony-stimulating factor [Neupogen®, Amgen, Inc., Thousand Oaks, CA, USA]). However, this approach helps to provide symptomatic treatment, rather than altering the inherent genetic defects that might produce long-term remissions and improvement in survival.

The pathology of MDS and AML appears to involve a malignant phenotype that gives rise to diverse and aberrant genetic and biological processes. It is with this understanding that treatment strategies should focus upon the pathobiology of the disease. The clinical and biological heterogeneity of these conditions that initially challenged therapeutic advancement is now creating tremendous interest in exploring how therapy may manipulate these processes at the genetic level in order to alter the natural course of these malignancies.

What is most exciting is the prospect that agents with the potential to reverse epigenetic changes in MDS–AML, such as inhibitors of the DNA methyltransferases (DNMTs), which catalyze DNA methylation, offer great promise in the management of these hematologic malignancies. Epigenetic alterations, consisting of heritable repression of transcription, in association with hypermethylation of involved gene promoters, appear to play a significant role in the development and progression of various cancers, including MDS. Genes inactivated by this process in MDS–AML and other cancers include those encoding $p15^{INK4b}$ and SOCS-1. These discoveries are providing tremendous insight into the molecular changes responsible for the initiation and maintenance of these conditions.[10] Epigenetic changes are

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Competing interests
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reversible, at least in cell-culture experiments, and inhibitors of DNA methylation appear to reactivate silenced tumor suppressor genes and restore their normal function. Furthermore, pharmacologic inhibition of DNA methylation appears to be synergistic with the inhibition of histone deacetylase, another critical player in the masking of regulatory genes. The therapeutic application of strategies using a combination of such inhibitors potentially provides new and effective options for clinicians and patients.

The 2004 FDA approval of the DNMT inhibitor azacitidine (Vidaza®, Pharmion, Boulder, CO, USA) in low- to high-risk MDS patients heralded a new era in cancer therapeutics, since this was the first agent approved based on the possibility of 'epigenetic therapy'. The Cancer and Leukemia Group B (CALGB) 9221 study with azacitidine provided a landmark publication in 2002,[11] showing favorable phase III experience in MDS. Decitabine (Dacogen™, SuperGen Inc., Dublin, CA, USA, and MGI Pharma Inc., Bloomington, MN, USA) is another DNMT inhibitor that is undergoing clinical and regulatory evaluation. This agent is currently in review by the FDA for MDS based upon phase II and III trials that have been recently presented at several major conferences. While the complete mechanisms underlying the clinical action of these drugs is not fully understood, both agents may exert their effects in part by reversing promoter methylation, allowing the expression of genes and concomitant differentiation and/or apoptosis of neoplastic cells.

This supplement was the result of a collective desire among a group of specialists with great interest in the potential that DNMT inhibitors offer in the area of hematologic malignancy. The goal of this publication is to review present knowledge and explore future directions. Opening the supplement is an overview of DNA methylation and gene silencing by Stephen Baylin, MD, of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins (Baltimore, MD, USA). This paper sets the stage for current review of the studies involving azacitidine and decitabine in MDS by Lewis Silverman, MD, from the Mount Sinai School of Medicine (New York, NY, USA) and Ghulam Mufti, DM, FRCP, FRCPath, of King's College London and King's College Hospital (London, UK). Both these authors and Jean-Pierre Issa, MD, of the MD Anderson Cancer Center (Houston, Texas, USA) examine some of the important clinical issues in MDS related to dose, duration, and patient selection in their respective articles. These papers provide pragmatic insights and raise important clinical questions requiring further exploration.

With respect to future directions, Steven Gore, MD, also of the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, reviews ongoing trials and new directions involving these agents with other strategies (i.e. histone deacetylase inhibitors), as part of treatment combinations for MDS that may enhance responses and long-term outcomes. Closing the supplement, Pierre Fenaux, MD, PhD, of Hôpital Avicenne (Bobigny, France) evaluates these agents' potential use beyond MDS by considering studies of the agents in the setting of AML.

These are exciting times in the management of hematologic malignancies. New avenues of research into the opportunities that DNMT inhibitors offer in MDS and AML are being explored. Azacitidine and decitabine are two agents that offer a long-awaited and feasible treatment option for MDS patients that is superior to best supportive care and directly affects the nature of the disease, long-term outcomes, and patients' quality of life. With the availability of these new agents, clinicians still need to fully appreciate some of the unique practical issues and questions associated with them: dosing, scheduling, duration of therapy, patient education, patient selection, and other treatments that use combination approaches. Furthermore, clinicians should be cautious about making direct comparisons between azacitidine and decitabine before head-to-head clinical studies are conducted.

Thus, while the present published research offers some answers, many questions remain. And so we find ourselves in the midst of an exciting journey with nothing less than the noblest of goals: realizing the optimal application of therapy with DNMT inhibitors in the interest of helping patients with hematologic malignancies to live longer and better.

As guest editors, we are honored to share the perspectives in this supplement, *Methylation inhibition and hematologic malignancies: present knowledge and future directions.*

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