

Challenges in Myelodysplastic Syndromes: Raising Awareness and Promoting New Insight in Therapeutic Options

The long-standing obstacles to meaningful therapeutic developments for patients with myelodysplastic syndrome (MDS) were deeply rooted in the intrinsic features of the disease itself. MDS displays remarkable heterogeneity in clinical behavior, propensity for progression to acute myeloid leukemia (AML), hematologic features, and disease biology.¹⁻³ These challenges are compounded by the fact that historically, approximately 50% of patients succumb to complications of the disease within 3 to 4 years of diagnosis.⁴

Until recently, the capacity of treatments approved by the US Food and Drug Administration (FDA) to modify the natural history of disease remained in question. Management strategies that had convincing potential to extend survival for patients with MDS remained a reality for only the very small percentage of patients who were allograft candidates. Traditional chemotherapy rarely yielded durable remissions and carried with it an unacceptably high rate of toxicity and mortality. Reliance on supportive measures such as recombinant hematopoietic growth factors, platelet and red blood cell (RBC) transfusions, iron chelation, and antibiotics remained the backbone of care until the advent of the first FDA-approved active therapies.³

Today practitioners have several treatment alternatives that offer the prospect of durable responses that may extend survival with acceptable toxicity profiles. Lenalidomide (Revlimid®, Celgene Corp, Summit, New Jersey) results in transfusion independence and cytogenetic remission in the majority of lower-risk patients with chromosome 5q deletion. The methyltransferase inhibitors (MTIs) azacitidine (Vidaza®, Celgene Corp) and decitabine (Dacogen®, Eisai Inc, Woodcliff Lake, New Jersey) induce complete and partial responses, improve hematopoiesis, suppress leukemic potential, and prolong overall survival in the most challenging patient population, ie, those with higher-risk disease.^{5,6} This was most convincingly demonstrated in the results of the MDS-001 trial in which treatment with azacitidine at the FDA-approved dose and schedule significantly extended overall survival compared to the conventional care alternatives of induction chemotherapy, low-dose cytarabine, or supportive care alone (median survival, 24.4 vs 15 months; $P = .0001$) while nearly doubling 2-year survival rates in patients with intermediate-2 or high-risk disease, according to International Prognostic Scoring System (IPSS) criteria (50.8% vs 26.2%; $P < .0001$).⁶

The advent of these new treatments, novel doses and schedules, along with the emerging role of immunosuppressive therapy for a select subset of patients, provides a framework for clinicians to apply active management strategies. The inherent disease heterogeneity discussed above underscores the importance of distinguishing discriminatory features to properly tailor treatment selection and the goals of therapy. Treatment strategies should no longer focus solely on response rates, but rather on potentially prolonging time-to-leukemic transformation and extending overall survival. The MTI azacitidine has now positioned itself as a new reference for the management of patients with higher-risk disease and creates a new standard comparator for new agents.

This supplement to *Cancer Control*, titled *Myelodysplastic Syndromes: Present Status and New Avenues to Optimize Clinical Outcomes*, includes four articles from leading MDS experts who address the role of more recent data related to MDS diagnosis, classification, treatment, and application for the practicing hematologist.

Opening the issue is an article by Luca Malcovati, MD, and Stephen D. Nimer, MD, titled *Myelodysplastic Syndromes: Diagnosis and Staging*, in which the authors examine new considerations in the diagnosis and classification of MDS including the World Health Organization's classification-based prognostic scoring system (WPSS).

Next is an article by Ghulam J. Mufti, MB, DM, FRCP, FRCPATH, and Tara L. Chen, PharmD, titled *Changing the Treatment Paradigm in Myelodysplastic Syndromes*. They discuss how the primary treatment goal for many patients has now evolved to include extending survival and suppression of the disease's inherent propensity for progression through the use of an MTL. This sets the stage for the third article, titled *Treatment Strategies to Optimize Clinical Benefit in the Patient With Myelodysplastic Syndromes*. In this paper I review the current MDS treatment alternatives and strategies to optimize clinical benefit.

The final paper looks at what is on the horizon for management of MDS. In *Future Directions in Myelodysplastic Syndrome: Newer Agents and the Role of Combination Approaches*, Steven D. Gore, MD, and Evelyn R. Hermes-DeSantis, PharmD, BCPS, explore novel directions including promising new agents in the clinic and combination strategies under investigation.

This supplement reflects the cumulative efforts of many talented individuals without whom this publica-

tion would not have been possible. My sincere thanks to all the authors who contributed their time and knowledge and to Celgene Corp for its unrestricted educational grant to support this supplement. Finally, we extend our gratitude to John Horton, MB, ChB, the editor of *Cancer Control*, for his editorial review of these contributions and to the dedicated staff of *Cancer Control* for their coordination of this exciting issue.

The paradigm for the management of MDS continues to be redefined. Through this supplement, the contributors seek to raise awareness and facilitate discussion. We hope these perspectives will offer greater insight into not only the diagnosis and management of individuals with MDS, but also the powerful tools now available to modify disease potential and improve overall survival.

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