Leukemia insights

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This month's Leukemia Insights newsletter—by Alex Bataller, M.D., Ph.D., and Guillermo Garcia-Manero, M.D., offers an in-depth look at our approach to managing myelodysplastic syndrome (MDS) and provides details on ongoing clinical trials. Discover more about our Leukemia Program.

An update on the myelodysplastic syndromes program at MD Anderson

The Myelodysplastic Syndrome (MDS) program at MD Anderson Cancer Center is the largest of its kind in the world. Each year, we evaluate approximately 450 new patients with MDS. The reasons for these referrals include diagnostic confirmation, treatment planning, and evaluation for allogeneic stem cell transplantation (alloSCT). A substantial number of referred patients participate in clinical trials, which aim to provide access to innovative therapies that we hope will soon become standard-of-care treatments.

Patients are cared for by a multidisciplinary team that includes leukemia physicians, hematopathologists, stem cell transplant specialists, pharmacists, advanced practice providers, and research nurses. In addition to clinical care, the MDS program conducts extensive translational and basic research, with findings regularly published in high-impact, peer-reviewed journals.

In recent years, our understanding of MDS has grown exponentially, leading to the approval of several novel therapies: the erythropoiesis promoter luspatercept, the telomerase inhibitor imetelstat, and the oral hypomethylating agent (HMA) decitabine/cedazuridine1. MD Anderson played a leading role in the clinical trials that supported the approvals of luspatercept and decitabine/cedazuridine, underscoring the importance of referring patients to our center for participation in clinical research.

Despite this progress, the prognosis for many patients with MDS remains poor, and there is an ongoing need for more effective treatments. Below, we provide an overview of our approach to managing MDS and a list of active clinical trials. Notably, several clinical trials are underway for related conditions, including chronic myelomonocytic leukemia (CMML), clonal hematopoiesis of indeterminate potential (CHIP) and clonal cytopenia of undetermined significance (CCUS), which will be discussed in future reports.

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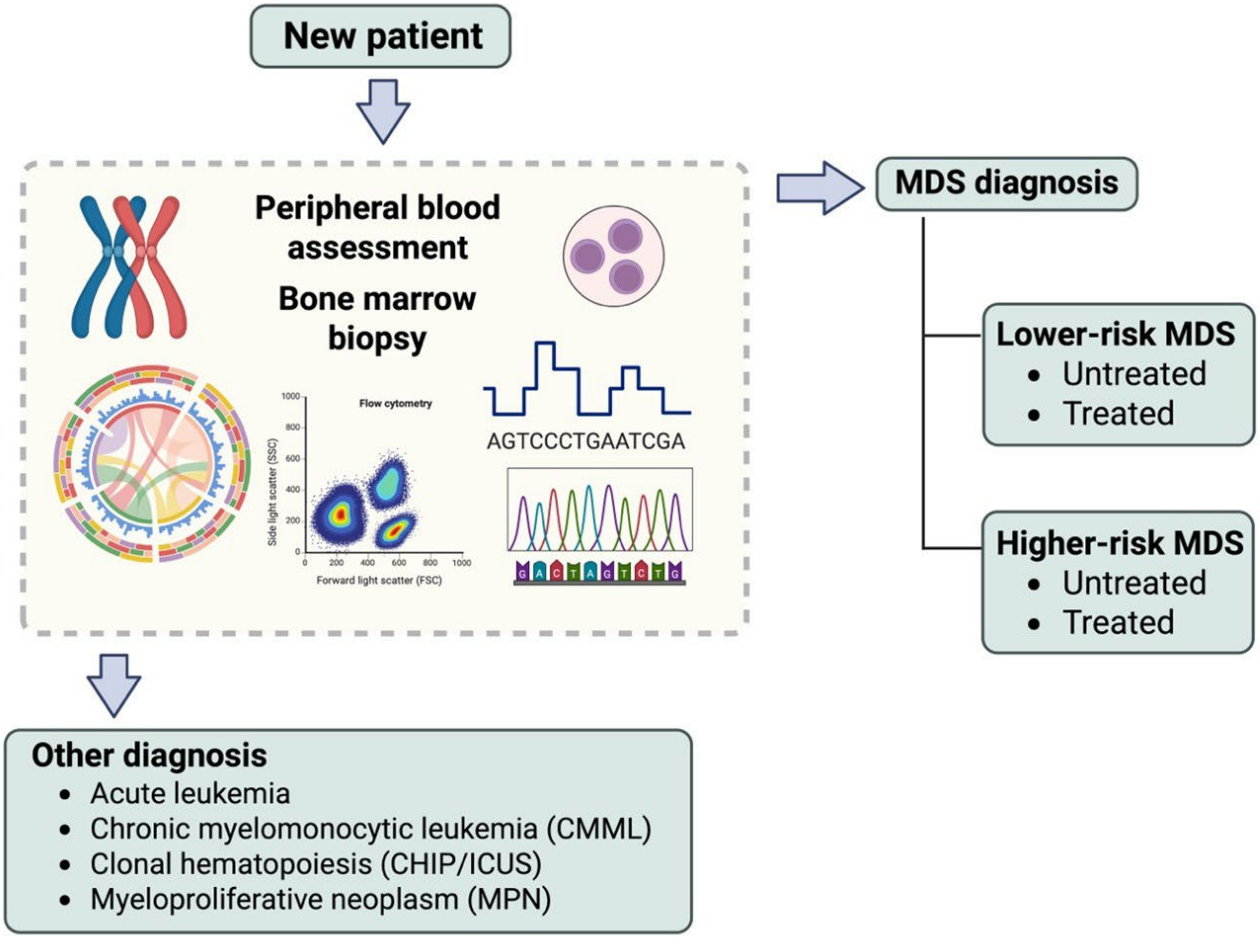
Conceptual framework for the management of myelodysplastic syndromes

Patients with myelodysplastic syndrome who come to MD Anderson Cancer Center undergo a bone marrow aspiration and biopsy to confirm and refine their diagnoses. Our hematopathologists, recognized as world experts in MDS diagnosis, provide essential insights into the microscopic morphology, chromosomal abnormalities, and mutations associated with each case.

In conjunction with blood count analysis, we assess disease risk using established international prognostic scoring systems, including the IPSS, IPSS-R, and IPSS-M. These prognostic tools allow us to stratify patients into two categories: lower-risk and higher-risk MDS2,3. Based on this classification—along with other key factors such as age, degree of cytopenias, and genetic profile—we develop a personalized treatment strategy for each patient (Figure 1).



Below we highlight some of the active clinical trials available for patients. We are constantly evaluating novel therapies to improve the treatment landscape of MDS.

Clinical trials for lower-risk MDS

Targeting inflammation in lower-risk MDS:

• **Canakinumab:** Our group has extensively characterized the role of altered innate immune signaling in MDS, with particular emphasis on the cytokine interleukin-1 (IL-1). Canakinumab, a potent IL-1 inhibitor currently approved for rare inflammatory disorders, is being investigated in this context. This study is especially important because the drug not only targets MDS pathology, but may also improve comorbid inflammatory conditions known to influence patient outcomes. Initial results, published last year in Nature Communications4, demonstrated that canakinumab is safe and active in specific patient subsets. The study is currently enrolling patients with earlier-stage disease.

• **R289:** Another strategy to modulate inflammation in lower-risk MDS involves targeting downstream regulators of innate immunity. We are recruiting patients with lower-risk MDS for a clinical trial evaluating R289, an oral inhibitor of interleukin-1 receptor–associated kinases (IRAK1 and IRAK4). These kinases play a key role in inflammatory pathway activation in lower-risk MDS.
• **DFV890:** We are also exploring novel approaches to correct immune dysregulation in lower-risk MDS. The inflammasome is a multiprotein intracellular complex that regulates innate immune activation and is known to be dysregulated in lower-risk MDS. DFV890 is an oral inhibitor of NLRP3, a key component of the inflammasome. Previous studies have shown DFV890 to be safe and well tolerated. We are enrolling patients with lower-risk MDS, including those previously treated, in an ongoing phase 2b clinical trial.

TGF-beta inhibition in lower-risk MDS

• **Luspatercept:** Inhibition of the TGF-beta pathway has proven effective in improving cytopenias in patients with lower-risk MDS, particularly those with SF3B1 mutations and ring sideroblasts5,6. We are currently conducting an open-label pilot study evaluating luspatercept in a variety of settings, including patients without ring sideroblasts and those who are not transfusion-dependent.
• **Elritercept:** Novel TGF-beta inhibitors are being developed for lower-risk MDS. We are l recruiting patients for a phase 3 clinical trial that randomizes individuals with lower-risk MDS to receive either placebo or the TGF-beta inhibitor elritercept.

Hypomethylating agents in lower-risk MDS

• **Oral azacitidine/cedazuridine:** Traditionally, HMAs have been administered intravenously or subcutaneously. Our group led the studies that resulted in the approval of oral decitabine combined with cedazuridine for MDS. Building on this progress, we are now enrolling patients in a multi-phase study evaluating oral azacitidine with cedazuridine.

• **Oral decitabine/cedazuridine:** To assess the safety and pharmacokinetics of oral HMAs in MDS, we are enrolling patients in two clinical trials of oral decitabine—one for patients with renal impairment and another for those with hepatic impairment.

Clinical trials for higher-risk MDS

Chemotherapy and hypomethylating agents:

• **Azacitidine and lisaftoclax:** We have previously reported encouraging results using HMAs with the BCL-2 inhibitor venetoclax in patients with higher-risk MDS7. Building on this experience, we are evaluating the next-generation BCL-2 inhibitor lisaftoclax (APG-2575) with azacitidine in the randomized phase 3 clinical trial GLORA-4.
• **CPX-351 and venetoclax:** CPX-351, a liposomal formulation of cytarabine and daunorubicin at a fixed molar ratio, is approved for the treatment of acute myeloid leukemia, particularly cases with myelodysplasia-related changes. We now are investigating the role of CPX-351 with venetoclax in patients with higher-risk MDS and CMML.

Immunotherapy:

• **Monoclonal antibodies:** In several ongoing clinical trials, we are evaluating the role of novel antibody-based therapies targeting MDS and leukemia cells. Among these, bexmarilimab (targeting Clever-1) and nadunolimab (targeting IL1RAP) are being actively investigated in patients with higher-risk MDS, both treatment-naïve and those who have failed prior therapies.

Other clinical trials of interest:

• Molecules that target various biological pathways, including RNA splicing and histone regulation, are also being investigated in patients with treated higher-risk MDS. Examples include CTX-712, (a CLK inhibitor), seclidemstat (an LSD1 inhibitor), and CA-4948 (an IRAK4 inhibitor).

Clinical trials with targeted therapy for MDS

• **IDH1/2 inhibitors:** Mutations in IDH1 and IDH2 occur in approximately 6% of patients with MDS8. IDH inhibitors have demonstrated safety and efficacy in related diseases such as acute myeloid leukemia (AML). Several clinical trials at our institution are currently evaluating different IDH1 and IDH2 inhibitors—ivosidenib, olutasidenib, and enasidenib—both as monotherapies and in combination with other agents for the treatment of both lower- and higher-risk MDS.

• **FLT3 inhibitors:** FLT3 mutations are uncommon in MDS, occurring in roughly 1% of patients. However, targeting FLT3 mutations with selective inhibitors has significantly improved outcomes in patients with AML. For this reason, despite their rarity in MDS, FLT3 inhibitors (quizartinib and gilteritinib) are also being investigated as potential therapeutic options in this setting.

In summary, outcomes for patients with MDS have improved with novel and innovative therapies. Nonetheless, significant challenges remain, particularly for patients who have failed standard-of-care treatments—such as erythropoiesis-stimulating agents or hypomethylating agents—where therapeutic options are limited and outcomes remain poor.

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