Management of Myelodysplastic Syndromes: Emerging Therapies and Evidence-Based Practice

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Presenters' disclosures of conflicts of interest are found at the end of this article.

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Abstract

At JADPRO Live 2025, speakers discussed the latest safety and efficacy evidence behind recently approved therapies for myelodysplastic syndromes, implementing adverse event monitoring and management plans to support adherence and patient safety, and integrating current evidence into treatment decisions to reduce transfusion dependence and improve quality of life for patients with MDS.

Newly approved therapies are reshaping care for patients living with myelodysplastic syndromes (MDS). On October 25, 2025, at the Gaylord National in National Harbor, Maryland, **Kathryn E. Kennedy, MSN, APRN, ACNP-BC, AOCN,** outpatient hematology advanced practice provider at Vanderbilt University Medical Center, and **Olivia C. West, MSN, RN, AGACNP-BC,** inpatient APP manager also at Vanderbilt, provided oncology advanced practitioners with an overview of the disease and its treatment.

Myelodysplastic syndromes (MDS) are not one disease. "MDS is a heterogeneous group of disorders that include overlap with myeloproliferative neoplasms," explained Ms. West.

Myelodysplastic syndromes are defined as persistent cytopenias and less than 20% blasts in marrow or peripheral blood and either characteristic cytogenetic and/or molecular features and/or dysplastic morphology. It is a disease of older adults, with the median age of diagnosis about 70 years old and an annual incidence of 4 per 100,000 people.

CLASSIFICATION

Myelodysplastic syndromes exist along a continuum that includes clonal hematopoiesis of indeterminate potential (CHIP), clonal cytopenia of undetermined significance (CCUS), overt MDS, and progression to secondary acute myeloid leukemia (AML). As disease advances along this spectrum, clonality and blast burden increase.

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Recent updates to classification systems reflect the growing role of molecular data. The World Health Organization (WHO) 5th edition (2022) updated terminology to "myelodysplastic neoplasms" to emphasize the malignant nature of the disease. The International Consensus Classification (ICC) similarly incorporates new molecular and immunophenotypic insights.

"Both systems use 10% as the threshold for myelodysplasia in all cell lines," summarized Ms. Kennedy. There are distinctions in how blast percentages are handled for certain mutations and rearrangements, such as *KMT2A, MECOM, NUP98,* and *NPM1*. WHO classifies these abnormalities as AML regardless of blast count, whereas ICC applies a ≥ 10% blast threshold.

"But then the ICC goes on to say that less than 10% blast is generally rare and should be considered to represent "early stage" AML and treat it as AML," noted Ms. Kennedy. "So there's really no difference in practice."

RISK STRATIFICATION

"Why is risk stratification important?" asked Ms. West. "It's because individual clinical courses and outcomes are very variable within MDS."

Risk stratification helps clinicians determine expected overall survival, progression-free survival, and leukemia-free survival. It also helps determine treatment strategies and evaluate for the need for transplant.

The Revised International Prognostic Scoring System (IPSS-R) remains the standard tool, integrating cytogenetics, marrow blast percentage, hemoglobin, platelet count, and absolute neutrophil count to categorize patients from very low to very high risk. Higher-risk categories correlate with shorter overall survival and greater likelihood of leukemic transformation.

Building on this framework, the Molecular IPSS (IPSS-M) incorporates genomic profiling—accounting for high-impact mutations such as *TP53*, *ASXL1*, and *DNMT3A*—to refine prognostic estimates. While incorporation of IPSS-M into routine guidelines is still evolving, it has potential to enhance precision in risk assessment and, eventually, treatment selection.

Beyond disease biology, patient-related factors play a major role in outcomes. Tools used to quantify this burden include the Charlson Comorbidity Index, the Hematopoietic Cell Transplantation–Comorbidity Index (HCT-CI), and an MDS-specific comorbidity index.

"More than 50% of our patients present with at least one comorbid condition on diagnosis," noted Ms. West, emphasizing that comorbidities can significantly influence survival across risk groups. When used alongside disease-focused tools like IPSS-R, comorbidity indices provide a more complete picture of patient fitness, transplant candidacy, and expected outcomes.

TREATMENT PLANNING

Treatment planning in MDS starts with the question: does the patient have a clinically significant cytopenia? Not every patient requires immediate therapy; some can be monitored closely until cytopenias evolve or features develop such as excess blasts. Treatment selection is driven by IPSS-R risk, classification, age, performance status, comorbidities, patient preference, transplant candidacy, and later, response to therapy (Figure 1). Management includes options that range from monitoring and supportive care to low- and high-intensity therapy (including transplant), targeted agents, and clinical trials.

"Treatments are palliative and aimed at improving cytopenias, quality of life, and life expectancy," Ms. Kennedy said, "Except in the context of transplant, which is the only curative-intent option."

LOWER-RISK MDS

For lower-risk disease, (IPSS-R ≤ 3.5), there is an algorithm built around clinically significant anemia and biologic features, including del(5q), ring sideroblasts/SF3B1, and serum erythropoietin, to select therapy.

del(5q) (with limited additional abnormalities) steers clinicians toward lenalidomide, often with transfusion support as needed. Patients with increased ring sideroblasts (and no del(5q)) are candidates for luspatercept, again with transfusion support as appropriate. When SF3B1 is absent and ring sideroblasts are low, serum EPO helps decide between ESAs/luspatercept (EPO ≤ 500 mU/mL) and alternative strategies when EPO is higher. For hypoplastic MDS concern, the pathway shifts toward immunosuppression-style therapy (e.g., ATG/CSA with eltrombopag). For

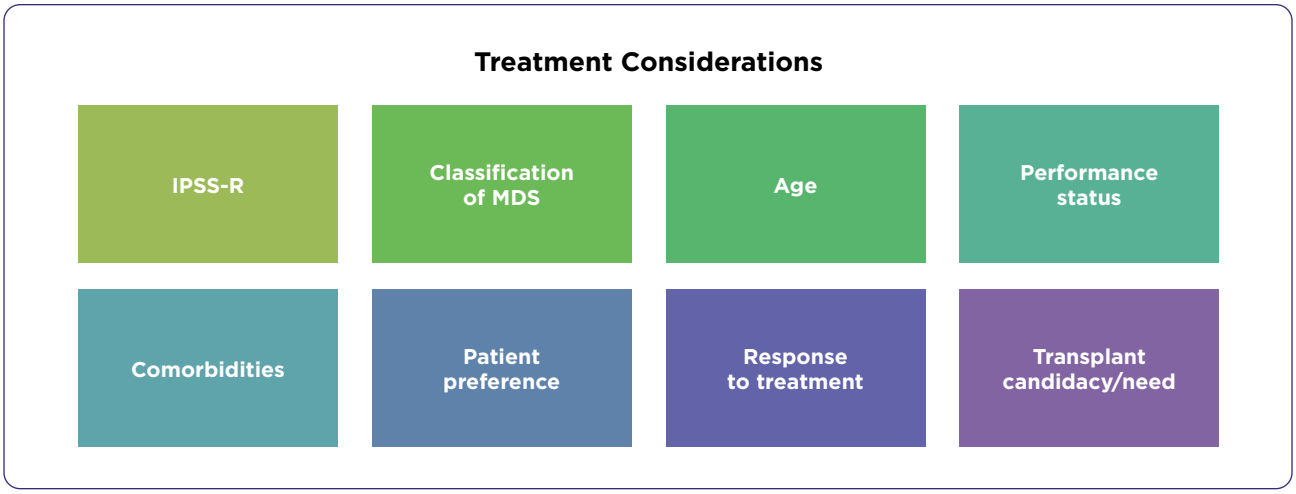

Figure 1. MDS treatment considerations.

significant cytopenias beyond anemia (neutropenia/thrombocytopenia), there are clinical trials, hypomethylating agents (HMAs), and, when thrombocytopenia is isolated, TPO agonists (eltrombopag or romiplostim).

When initial therapy fails, switching regimens, targeted therapy (e.g., IDH1), or incorporating newly approved options are considered.

Luspatercept

For ESA-naive, transfusion-dependent, lower-risk MDS, the COMMANDS phase III trial found that 59% of patients receiving luspatercept achieved transfusion independence vs. 31% receiving epoetin alfa (Platzbecker et al., 2023).

"Durability favored luspatercept in multiple measures," said Ms. Kennedy, with patients maintaining responses "approximately 1 year longer."

The regimen requires ongoing monitoring: luspatercept is started at 1 mg/kg subcutaneously every 3 weeks, with hemoglobin review before each dose and monitoring for thromboembolic symptoms and blood pressure. Hypertension (11.4%) is a notable adverse effect.

"We may need to partner with the PCP for better control of hypertension," noted Ms. Kennedy.

Imetelstat

Imetelstat is a first-in-class telomerase inhibitor supported by IMerge phase III results in lower-risk, ESA-refractory, transfusion-dependent disease (excluding del(5q) and without prior lenalidomide/HMA; Platzbecker et al., 2024). 39.8% of patients achieved ≥ 8 weeks of RBC transfusion independence vs. 15% on placebo, with a median duration of response of 80 weeks. Dosing is 7.1 mg/kg IV every 4 weeks (administered over 2 hours) with premedication, weekly CBCs initially, and close liver test monitoring early in therapy, with dose delays/reductions for grade 3 to 4 cytopenias.

"We had new or worsening grade 3 or 4 thrombocytopenia in 65% and neutropenia in 72% of patients," noted Ms. Kennedy.

Cytopenias were reversible in about 58% of the patients. Infusion-related reactions occurred in 8%, with severe adverse events uncommon.

Ivosidenib

For patients with IDH1-mutated MDS, ivosidenib produced a CR+PR rate of 38.9%, with durable remissions and acquisition/maintenance of transfusion independence in a substantial portion of transfusion-dependent patients. There is a boxed warning for differentiation syndrome

"I want to point out prolonged QT interval was observed," noted Ms. Kennedy. There is no guidance on EKG frequency, so it can vary by provider.

HIGHER-RISK MDS

For higher-risk disease (IPSS-R >3.5), "The first step is to determine if the patient is a candidate for a transplant," said Ms. West. However, transplant

is not feasible for many patients: "As the median diagnosis is 70, this puts our patients at the higher end of what a lot of centers are comfortable with transplanting," said Ms. West. Finding a related donor can also be difficult for older patients.

Hypomethylating Agents

HMAs are the mainstay of higher-risk therapy. Expanding formulation options can better match treatment to patient goals and logistics.

"We have different options, which is exciting because it gives patients the opportunity to utilize different formats of medications that would be best suited to their goals," said Ms. West.

Common regimens are IV decitabine, oral decitabine/cedazuridine, and IV/subcutaneous azacitidine. Treatment duration should not be cut short prematurely.

"Generally speaking with HMA, we're going to do at least four to six cycles without a lack of response before we stop. Median time to response is two to three cycles," noted Ms. West.

"If the patient is not a transplant candidate, typically the mainstay of therapy is an HMA +/- another agent depending on the patient and disease specifics," said Ms. West. These include azacitidine plus venetoclax, decitabine plus venetoclax, oral decitabine/cedazuridine plus venetoclax, or azacitidine and ivosidenib or olutasidenib if the disease is IDH1 mutated.

Olutasidenib

Olutasidenib for patients with IDH1-mutated MDS can be used in combination with HMA or as monotherapy, including in relapsed/refractory and post-transplant settings. It carries a boxed warning for differentiation syndrome and also is high risk for hepatotoxicity," which requires frequent early lab monitoring.

HMA and Venetoclax

"Venetoclax is a potent, selective, orally bioavailable BCL-2 inhibitor which has a synergistic effect when combined with hypomethylating agents," said Ms. West.

The VERONA trial examined HMA plus venetoclax. The phase 1b trial showed a median overall response rate of 80% and overall survival of 26 months (Garcia et al., 2025). However, the phase III trial failed to demonstrate that overall survival benefit of venetoclax plus azacitidine versus placebo plus azacitidine in higher-risk patients. Response rates were higher in the combination group, particularly with patients with greater than 5% blasts (AbbVie et al., 2025). This has also not changed the current FDA approvals or the current NCCN guidelines and HMA plus VEN is still commonly used.

QUALITY OF LIFE

"Quality of life is only included as an outcome in about 50% of studies. However, patients prioritize it as #1," noted Ms. West (Seghers et al., 2022). "Patients typically say that quality of life is more important than overall survival, progression-free survival, side effects, treatment response."

Transfusion burden is a factor in quality of life: "Patients are typically spending about 8 hours just in the chair to get a unit of blood," said Ms. Kennedy. Add travel and waiting, and transfusions become a day-long, quality of life–limiting event.

"MDS is a life-changing diagnosis," Ms. West stressed, particularly for higher-risk disease that can progress faster and require escalating supportive care. Better health-related quality of life has been correlated with improved survival in patients with MDS.

"Therefore, the goal of new and novel MDS therapies should be to improve anemia while reducing the frequency of red cell transfusions," stated Ms. Kennedy. ●

Disclosure

Ms. Kennedy has served as a consultant for Geron. Ms. West has no relevant financial relationships to disclose.

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