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Release date: February 10, 2022; Expiration date: February 10, 2023

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Myelodysplastic Syndromes
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Myelodysplastic Syndromes

Disclosure of Relevant Financial Relationships

None of the planners for this educational activity have relevant financial relationship(s) to disclose with ineligible companies whose primary business is producing, marketing, selling, reselling, or distributing healthcare products used by or on patients.

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Myelodysplastic Syndromes, Version 3.2022

Featured Updates to the NCCN Guidelines

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ABSTRACT

The NCCN Guidelines for Myelodysplastic Syndromes (MDS) provide recommendations for the evaluation, diagnosis, and management of patients with MDS based on a review of clinical evidence that has led to important advances in treatment or has yielded new information on biologic factors that may have prognostic significance in MDS. The multidisciplinary panel of MDS experts meets on an annual basis to update the recommendations. These NCCN Guidelines Insights focus on some of the updates for the 2022 version of the NCCN Guidelines, which include treatment recommendations both for lower-risk and higher-risk MDS, emerging therapies, supportive care recommendations, and genetic familial high-risk assessment for hereditary myeloid malignancy predisposition syndromes.

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**MANAGEMENT OF LOWER-RISK DISEASE
(IPSS-R VERY-LOW-, LOW-,
INTERMEDIATE-RISK DISEASE)^{o,p,q}**
TREATMENT

^o Presence of comorbidities should also be considered for evaluation of prognosis (See Comorbidity Indices in the Discussion).

^p Given its more accurate risk stratification, the IPSS-R categorization is preferred although the other systems also have good value. IPSS-R Intermediate patients may be managed as lower risk if their score is ≤ 3.5 vs. higher risk if score is > 3.5 . Pfeilstöcker M, et al. Blood 2016;128:902-910.

^q If the disease is initially managed as lower risk but fails to respond, move to higher risk management strategies.

^r See Supportive Care (MDS-7 and MDS-8).

^s Some studies have demonstrated clinical benefit with low doses of azacitidine or decitabine for lower-risk MDS. Jabbour E, et al. Blood 2017;130:1514-1522.

^t Oral decitabine and cedazuridine (DEC-C) could be a substitution for intravenous decitabine in patients with IPSS Intermediate-1 and above. (Garcia-Manero G, et al. Blood 2020;136:674-683).

^u Patients generally ≤ 60 y and with $\leq 5\%$ marrow blasts, or those with hypocellular marrows, PNH clone positivity, or STAT-3 mutant cytotoxic T-cell clones. IST includes equine ATG $\pm$ cyclosporin A $\pm$ eltrombopag. Additionally, for severe thrombocytopenia, eltrombopag alone could be considered.

^v Response should be evaluated based on IWG criteria: Cheson BD, et al. Blood 2006;108:419-425. Failure would be considered if no response within 3–6 mo.

^w For patients with severe or refractory thrombocytopenia, eltrombopag or romiplostim can be considered. Oliva EN, et al. Lancet Hematol 2017;4:e127-e136. Fenaux P, et al. Br J Haematol 2017;178:906-913. See Discussion.

^x IPSS Intermediate-1, IPSS-R Intermediate, and WPSS Intermediate patients with severe cytopenias would also be considered candidates for HCT. Matched sibling, unrelated donor, or alternative (haploidentical or cord blood when appropriate) donor, including standard and reduced-intensity preparative approaches, may be considered.

MDS-3

Overview

Myelodysplastic syndromes (MDS) encompass a group of myeloid clonal hemopathies with a relatively heterogeneous spectrum of presentation. Diagnosis and disease stratification are based on multiple factors, which may include clinical data, morphology of peripheral blood and bone marrow, fluorescence in situ hybridization, cytogenetics, flow cytometry, and next-generation sequencing myeloid mutation studies. The major clinical problems resulting from these disorders are morbidities caused by cytopenias and the potential for MDS to evolve into acute myeloid leukemia (AML). In addition, there are complications that may arise from chronic transfusions, treatment toxicity, and in some cases, secondary phenomena such as systemic inflammatory conditions.¹ The incidence rate of MDS is approximately 4.5 per 100,000 people per year in the general population.² MDS is rare among children, adolescents, and young adults. Accounting for 1.6% of patients diagnosed with MDS, individuals aged < 40 years have an incidence of 0.1 per 100,000 people per year. However, this incidence increases to 26.9 per 100,000 for those between age 70 and 79 years, and to 55.4 per 100,000 for those aged ≥ 80 years.² Management

of MDS is complicated by the generally advanced age of patients (median age, 77 years),³ the nonhematologic comorbidities commonly seen in this cohort, and the relative inability of older patients to tolerate certain intensive forms of therapy. Upon disease progression to AML, these patients experience lower response rates to standard therapy compared with patients with de novo AML.⁴

The MDS panel has proposed stratifying patients with clinically significant cytopenia(s) into 2 major risk groups: (1) patients with lower-risk MDS (ie, international prognostic scoring system [IPSS] low, intermediate-1 [int-1]; revised IPSS [IPSS-R] very low, low, intermediate; WHO prognostic scoring system [WPSS] very low, low, intermediate); and (2) patients with higher-risk MDS (ie, IPSS int-2, high; IPSS-R intermediate, high, very high; WPSS high, very high). Patients with IPSS-R intermediate risk may be managed as lower risk if their score is ≤ 3.5 versus higher risk if their score is > 3.5 .⁵ In addition, factors such as patient age, performance status, and presence of comorbidities have a major influence on the patient's ability to tolerate certain intensive treatments, and play a major role in selecting the optimal management strategy.

**MANAGEMENT OF LOWER-RISK DISEASE
(IPSS-R VERY-LOW-, LOW-,
INTERMEDIATE-RISK DISEASE)^{o,p,q}**
TREATMENT

See footnotes on page MDS-5A.

^z Recommended initial dose is: 10 mg/day for 21 out of 28 days or 28 days monthly for 2–4 months to assess response (See Discussion). Alternative option to lenalidomide may include an initial trial of ESAs in patients with serum EPO ≤500 mU/mL. Use caution for patients with low platelet and neutrophil counts; consider modifying lenalidomide dose. Sekeres MA, et al. J Clin Oncol 2008;26:5943–5949. Patients with monosomy 7 are an exception and should be treated in the higher prognostic risk category (see MDS-6).

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MDS-5

Management of Lower-Risk MDS

During the annual meeting to update the NCCN Guidelines for MDS in 2022, the panel revisited the recommendation for oral decitabine and cedazuridine, which was previously included as a footnote, and agreed to add this recommendation directly in the algorithm (see MDS-3 and MDS-5, page 108 and above, respectively). As the clinical study documenting bioequivalence for this combination enrolled patients with IPSS int-1 and above, the panel decided to specify the prognostic risk category in a footnote: “Oral decitabine and cedazuridine could be a substitution for intravenous decitabine in patients with IPSS int-1 and above” (see MDS-3 and MDS-5A, pages 108 and 110, respectively).⁶

Furthermore, the panel discussed the addition of eltrombopag to immunosuppressive therapy (IST) for patients with lower-risk MDS, and voted to modify a footnote (see MDS-3, page 108). In the setting of clinically relevant thrombocytopenia or neutropenia, IST is recommended as an option that is useful in certain circumstances for select patients (generally those aged ≤60 years and with ≤5% marrow blasts, or those with hypocellular marrows, paroxysmal nocturnal hemoglobinuria [PNH] clone

positivity, or STAT-3–mutant cytotoxic T-cell clones). IST includes equine ATG, with or without cyclosporin A, and with or without eltrombopag. A phase I/II trial examined the combination of IST with eltrombopag, a thrombopoietin (TPO) agonist also known as a TPO mimetic, in patients with aplastic anemia (not MDS).⁷ Three cohorts were used that differed by the schedule for the start of treatment and the duration of treatment. The most common grade ≥3 adverse event attributed to eltrombopag was an abnormality in a liver test (18%), specifically transaminase elevation and/or hyperbilirubinemia. The complete hematologic response and overall response rate (ORR) for the combined cohorts at 6 months, when compared with a historical cohort of 102 patients who were treated with IST, were 39% (95% CI, 29%–49%) versus 10% and 87% (95% CI, 80%–94%) versus 66%, respectively. The rate of clonal evolution was not increased in patients who received eltrombopag compared with a historical cohort at the 2-year time point. A phase II trial with patients with aplastic anemia reported an ORR of 76% in those receiving the combination treatment compared with 71% in those treated with IST only.⁸ The complete remission rate, median time to response, and survival rate at 2 years were

FOOTNOTES

- ^o Presence of comorbidities should also be considered for evaluation of prognosis (See Comorbidity Indices in the Discussion).
- ^p Given its more accurate risk stratification, the IPSS-R categorization is preferred although the other systems also have good value. IPSS-R Intermediate patients may be managed as lower risk if their score is ≤ 3.5 vs. higher risk if score is > 3.5 . Pfeilstöcker M, et al. *Blood* 2016;128:902-910.
- ^q If the disease is initially managed as lower risk but fails to respond, move to higher risk management strategies.
- ^r See Supportive Care (MDS-7 and MDS-8).
- ^t Oral decitabine and cedazuridine (DEC-C) could be a substitution for intravenous decitabine in patients with IPSS Intermediate-1 and above. (Garcia-Manero G, et al. *Blood* 2020;136:674-683).
- ^v Response should be evaluated based on IWG criteria: Cheson BD, et al. *Blood* 2006;108:419-425. Failure would be considered if no response within 3–6 mo.
- ^x IPSS Intermediate-1, IPSS-R Intermediate, and WPSS Intermediate patients with severe cytopenias would also be considered candidates for HCT. Matched sibling, unrelated donor, or alternative (haploidentical or cord blood when appropriate) donor, including standard and reduced-intensity preparative approaches, may be considered.
- ^y Refers predominantly to lower-risk IPSS-R and IPSS patients.
- ^z Recommended initial dose is: 10 mg/day for 21 out of 28 days or 28 days monthly for 2–4 months to assess response (See Discussion). Alternative option to lenalidomide may include an initial trial of ESAs in patients with serum EPO ≤ 500 mU/mL. Use caution for patients with low platelet and neutrophil counts; consider modifying lenalidomide dose. Sekeres MA, et al. *J Clin Oncol* 2008;26:5943-5949. Patients with monosomy 7 are an exception and should be treated in the higher prognostic risk category (see MDS-6).
- ^{aa} At some institutions, darbepoetin alfa has been administered using doses up to 500 mcg every other week.
- ^{bb} Data have demonstrated the effectiveness of luspatercept for treating the anemia of ring sideroblastic (RS) lower-risk MDS patients. Fenaux P, et al. *N Engl J Med* 2020;382:140-151. For lower-risk MDS patients lacking RS treated with luspatercept, encouraging albeit limited data have emerged (36% HI-E in 44 patients) in abstract form [Platzbecker U, et al. *Clin Lymphoma Myeloma Leuk* 2020;20:S319-320 Abstract MDS-191]. However, FDA approval has not yet occurred for use of the drug for RS negative patients. We recommend such patients enter clinical trials for use of luspatercept.
- ^{cc} Target hemoglobin range 10 to 12 g/dL; not to exceed 12 g/dL.
- ^{dd} Lack of 1.5 gm/dL rise in hemoglobin or lack of a decrease in RBC transfusion requirement by 3 to 6 months of treatment.
- ^{ee} Lack of 1.5 gm/dL rise in hemoglobin or lack of a decrease in RBC transfusion requirement by 6 to 8 weeks of treatment.
- ^{ff} Lenalidomide 10 mg daily if ANC > 0.5 , platelets $> 50,000$; Toma A, et al. *Leukemia* 2016;30:897-905.
- ^{gg} Patients generally ≤ 60 y and with $\leq 5\%$ marrow blasts, or those with hypocellular marrows, PNH clone positivity, or STAT-3 mutant cytotoxic T-cell clones. IST includes equine ATG $\pm$ cyclosporin A $\pm$ eltrombopag (category 2B for eltrombopag combinations).
- ^{hh} Patients lack features listed in footnote gg.
- ⁱⁱ See dosing of hematopoietic cytokines. (MDS-4)
- ^{jj} Emerging data are demonstrating effectiveness of ivosidenib and enasidenib for MDS patients with *IDH1/2* mutations (Medeiros BC, et al. *Leukemia* 2017;31:272-281).

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MDS-5A

similar in both groups. Concerns for potential proliferation of leukemic blasts in response to exogenous TPO have been raised in earlier in vitro studies, particularly for high-risk MDS.^{9,10} Results from ongoing clinical trials with TPO mimetics will help elucidate the risks for leukemic transformations in patients with MDS. It should be noted that eltrombopag is not currently approved for use in patients with MDS. The panel voted to add eltrombopag as a treatment option in combination with ATG, with or without cyclosporin A, for patients with symptomatic anemia with no del(5q), with or without other cytogenetic abnormalities, with ring sideroblasts $< 15\%$ (or ring sideroblasts $< 5\%$ with an *SF3B1* mutation), serum erythropoietin > 500 mU/mL, and good probability to respond to IST (see MDS-5 and MDS-5A, page 109 and above, respectively). Eltrombopag combinations are category 2B recommendations.

Following a panel vote, eltrombopag was added as a treatment option for patients with lower-risk MDS with certain cytopenias (see MDS-3, page 108). The panel updated a footnote to include that eltrombopag alone could be considered for severe thrombocytopenia. A phase II study enrolled patients with low-risk or IPSS int-1 risk MDS with severe thrombocytopenia who were randomized 2:1 to receive eltrombopag or

placebo.¹¹ At the time of the interim analysis, in the intention-to-treat population, 47% of patients receiving eltrombopag demonstrated a platelet response, as opposed to 3% of patients in the placebo group ($P < .0001$; odds ratio, 27.1 [95% CI, 3.5–211.9; $P = .0017$]), and 46% of patients in the eltrombopag arm had grade 3/4 adverse events compared with 16% in the placebo group ($P = .0053$). Fewer bleeding events were reported in the eltrombopag arm compared with the placebo arm (14% vs 42%, respectively; $P = .0025$). Results from another phase II trial determined that eltrombopag monotherapy in patients with lower-risk MDS with cytopenia, including anemia, thrombocytopenia, or neutropenia, led to a 44% rate of hematologic response at 16 to 20 weeks.¹² A few patients acquired chromosomal abnormalities. A study by Fan et al¹³ found that 50% of patients with moderate aplastic anemia or unilineage cytopenias (platelet count $< 30 \times 10^9/L$ or dependence on platelet transfusions or hemoglobin count < 8.5 g/dL or dependence on RBC transfusions) treated with eltrombopag achieved a clinically meaningful response at 16 to 20 weeks. Of 34 patients, 2 acquired cytogenetic abnormalities.

The panel received an external request to consider the inclusion of luspatercept-aamt as a treatment option

MANAGEMENT OF HIGHER-RISK DISEASE
 (IPSS-R INTERMEDIATE-, HIGH-, VERY-HIGH-RISK DISEASE)^{o,p}

See footnotes on page MDS-6A.

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MDS-6

for patients with anemia and lower-risk MDS without ring sideroblasts. After a thorough discussion, the panel did not recommend luspatercept-aamt for such patients because the data are only available in abstract format¹⁴ and the drug is not FDA-approved for this indication. The panel updated a footnote to highlight the emerging data on luspatercept-aamt for this group of patients and recommends such patients enroll in a clinical trial for the use of this agent (see MDS-5A, opposite page).

The panel members also discussed imetelstat, a telomerase inhibitor. Given that it is not FDA-approved, a decision was made to include information about imetelstat in the discussion section rather than in the algorithm. In a phase II trial comprising 57 patients with lower-risk MDS that had relapsed or was refractory to erythropoiesis-stimulating agents (ESAs) and who were RBC transfusion-dependent, treatment with imetelstat resulted in 37% and 23% rates of RBC transfusion independence (TI) at 8 and 24 weeks, respectively.¹⁵ At the same time points, RBC-TI rates of 42% and 29%, respectively, were observed in a subgroup of 38 patients without del(5q) and who were not previously treated with a hypomethylating agent (HMA) or lenalidomide. The median

duration for TI was 65 weeks for the overall group compared with 86 weeks in the subgroup. Hematologic improvement, in terms of erythroid response per the International Working Group 2006 response criteria, was achieved in 65% of patients in the overall group and 68% of patients in the subgroup. Overall, the most common grade ≥3 hematologic adverse events were neutropenia (60%), thrombocytopenia (54%), and anemia (19%). At 5%, the most common grade ≥3 nonhematologic adverse events were back pain, increased alanine aminotransferase, increased aspartate aminotransferase, and bronchitis.

Management of Higher-Risk MDS

The panel included the combination of oral decitabine and cedazuridine directly in the algorithm for patients with higher-risk MDS and noted that the combined oral formulation could be a substitution for intravenous decitabine in patients with IPSS int-1 and above (see MDS-6 and MDS-6A, above and page 112, respectively).⁶ The panel also discussed recommendations for the management of higher-risk MDS and debated the merits of emerging therapies, such as the combination of venetoclax and HMAs, and noted that published phase III data

FOOTNOTES

- ^o Presence of comorbidities should also be considered for evaluation of prognosis (See Comorbidity Indices in the Discussion).
- ^p Given its more accurate risk stratification, the IPSS-R categorization is preferred although the other systems also have good value. IPSS-R Intermediate patients may be managed as lower risk if their score is ≤ 3.5 vs. higher risk if score is > 3.5 . Pfeilstöcker M, et al. *Blood* 2016;128:902-910.
- ^r See Supportive Care (MDS-7 and MDS-8).
- ^t Oral decitabine and cedazuridine (DEC-C) could be a substitution for intravenous decitabine in patients with IPSS Intermediate-1 and above. (Garcia-Manero G, et al. *Blood* 2020;136:674-683).
- ^v Response should be evaluated based on IWG criteria: Cheson BD, et al. *Blood* 2006;108:419-425. Failure would be considered if no response within 3–6 mo.
- ^{kk} Based on age, performance status, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver, patients may be taken immediately to transplant or bridging therapy can be used to decrease marrow blasts to an acceptable level prior to transplant.
- ^{ll} Allogeneic HCT from the most suitable donor (HLA-matched sibling or unrelated donor, HLA-haploidentical family member or cord blood). [Early referral for transplant evaluation is recommended to allow moving to transplant efficiently](#). Pre-transplant debulking therapy to reduce marrow blasts to $< 5\%$ with the goal of reducing post-transplant relapse (see footnote nn and Discussion) is recommended, although the optimum strategy (azacitidine, decitabine, induction-type chemotherapy) has not been determined. To reduce the disease burden pre-transplant is particularly important in patients who will receive a reduced-intensity conditioning regimen (Festuccia M, et al. *Biol Blood Marrow Transplant* 2016;22:1227-1233). At some centers, failure to achieve $< 5\%$ blasts with cytoreduction should not preclude from proceeding to transplant, as these patients appeared to derive survival benefit from transplant (Nakamura R, et al. *ASH Annual Meeting 2020:Abstract 75*. Schroeder T, et al. *Biol Blood Marrow Transplant* 2019;25:1550-1559). Strategies for patients with specific mutations are under investigation. Patients with TP53 mutations, particularly biallelic, have a poor prognosis even with transplantation. These cases should be discussed with a transplant physician and patients should be enrolled in a clinical trial whenever possible.
- ^{mm} High-intensity chemotherapy: Clinical trials with investigational therapy (preferred); or standard induction therapy if investigational protocol is unavailable or if it is used as a bridge to HCT.
- ⁿⁿ Some emerging data have shown efficacy of novel agents, including venetoclax in combination with hypomethylating agents or targeted IDH1/2 inhibitors for cytoreduction for patients with high-risk MDS (DiNardo C, et al. *N Engl J Med* 2018;378:2386-2398) who have HMA-refractory disease. When used as cytoreduction for MDS in combination with HMA, venetoclax has been effectively given in monthly courses of 14 days (Garcia JS, et al. *ASH Annual Meeting 2020:Abstract 656*). Repeat of marrow evaluation after 1–2 cycles is important to clarify recovery of hematopoiesis and potential requirement for further therapy. Clinical trials are preferred. (See Discussion).
- ^{oo} While the response rates are similar for both drugs, survival benefit from a phase III randomized trial is reported for azacitidine and not for decitabine. Azacitidine or decitabine therapy should be continued for at least 4–6 cycles to assess response to these agents. In patients who have clinical benefit, continue treatment with the hypomethylating agent as maintenance therapy.
- ^{pp} Consider second transplant or donor lymphocyte infusion immuno-based therapy for appropriate patients who had a prolonged remission after first transplant.

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MDS-6A

for this combination are not available. There are also limited data for the use of targeted drugs such as IDH inhibitors for patients with MDS. As overexpression of the B-cell lymphoma 2 (BCL-2) protein has been linked to disease progression in MDS, studies are ongoing to investigate the efficacy and safety of venetoclax, a BCL-2 inhibitor, in patients with MDS either first-line or refractory or resistant to HMAs.^{16–18} Preliminary results from a phase Ib study investigating the combination of venetoclax and azacitidine (AzaC) for 14 days in a 28-day cycle in up-front higher-risk MDS (IPSS int-2 or high) resulted in an ORR, median overall survival (OS), median progression-free survival, and median duration of response of 77%, not reached (95% CI, 16.2 months–not estimable), 17.5 months (14.5 months–not estimable), and 14.8 months (95% CI, 12.9 months–not estimable), respectively.¹⁷ The most frequent grade ≥ 3 adverse events were neutropenia (51%), febrile neutropenia (46%), and thrombocytopenia (30%). In a study exploring venetoclax as a salvage agent alone or in combination, preliminary results showed an ORR of 7% with venetoclax alone compared with 50% with venetoclax/AzaC.¹⁸ The panel updated a footnote to mention that emerging data have shown the

efficacy of venetoclax in combination with HMAs or targeted IDH1/2 inhibitors for cytoreduction in patients with high-risk MDS^{17,19} refractory to HMAs (see MDS-6A, above). When used as cytoreduction for MDS in combination with an HMA, venetoclax has been effectively given for 14 days in monthly courses.¹⁷ Repeating the bone marrow evaluation after 1 to 2 cycles is important to clarify the recovery of hematopoiesis and potential requirement for further therapy.¹⁷ Clinical trials are preferred (eg, ClinicalTrials.com identifier: NCT04401748).

Mutations in the *IDH1* or *IDH2* genes occur in approximately 4% to 12% of patients with MDS.^{20–22} Ongoing clinical trials are investigating the efficacy of targeted IDH1/2 inhibitors in patients with MDS (NCT03503409, NCT03471260, and NCT03744390). A phase I trial evaluating the efficacy and safety of ivosidenib in patients with AML or MDS with an *IDH1* mutation¹⁹ found that of 12 patients with MDS, 11 had an overall response, 5 of whom achieved complete remission. A phase I/II trial evaluating the efficacy and safety of enasidenib, an inhibitor of the mutant IDH2 protein, found a 53% ORR (95% CI, 28%–77%), a median OS of 16.9 months (95% CI, 1.5–32.3 months), and a median duration of response of 9.2 months

SUPPORTIVE CARE†

- **Pre-transplant**
 - ▶ Transplant and non-transplant patients should receive support.
 - ▶ Transfusion products should be irradiated with 25 Gy or per institution standard.
 - ▶ Patients with ≥5% marrow blasts who are candidates for reduced-intensity conditioning (RIC) are encouraged to receive "debulking" therapy with HMA or induction chemotherapy. Transplantation should be carried out as long as patients are responding; it should not be delayed until the response is lost.
- **Clinical monitoring**
 - ▶ Psychosocial support (See NCCN Guidelines for Survivorship)
 - ▶ Quality-of-life assessment
 - ▶ Transfusions^{¶¶}:
 - ◊ RBC transfusions (CMV-safe) are recommended for symptomatic anemia, and platelet transfusions are recommended for thrombocytopenic bleeding. However, they should not be used routinely in patients with thrombocytopenia in the absence of bleeding unless platelet count <10,000/mcL. Irradiated products are suggested for transplant candidates.
 - ▶ Antibiotics are recommended for bacterial infections, but no routine prophylaxis is recommended except in patients with recurrent infections.
- Aminocaproic acid or other antifibrinolytic agents may be considered for bleeding refractory to platelet transfusions or profound thrombocytopenia.
- **Iron chelation:**
 - ▶ If >20 to 30 RBC transfusions have been received, consider daily chelation with deferoxamine subcutaneously or deferasirox orally to decrease iron overload, particularly for patients who have lower-risk MDS or who are potential transplant candidates (LOW/INT-1). For patients with serum ferritin levels >2500 ng/mL, aim to decrease ferritin levels to <1000 ng/mL.^{††} (See Discussion). Patients with low creatinine clearance (<40 mL/min) should not be treated with deferasirox or deferoxamine.

† See NCCN Guidelines for Supportive Care.

¶¶ Avoid transfusions for arbitrary hemoglobin thresholds in the absence of symptoms of active coronary disease, heart failure, or stroke. In situations where transfusions are necessary, transfuse the minimum units necessary to relieve symptoms of anemia or to return the patient to a safe hemoglobin level. Hicks L, et al. Blood 2013;122:3879-3883.

†† Clinical trials in MDS are currently ongoing with oral chelating agents.

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MDS-7

(95% CI, 1.0 month–not reached) in patients with MDS with an *IDH2* mutation.²³ Hyperbilirubinemia (35%), pneumonia (29%), and thrombocytopenia (24%) were the most frequent grade 3/4 treatment-emergent adverse occurrences. A phase II study in patients with higher-risk *IDH2*-mutated MDS/chronic myelomonocytic leukemia or low-blast AML determined an ORR, complete remission rate, and hematologic improvement rate of 84%, 24%, and 8%, respectively, in patients with no prior HMA treatment, compared with 43%, 24%, and 10%, respectively, in patients with disease that progressed or was refractory to HMA treatment.²⁴ Frequent treatment-related grade 3/4 adverse occurrences reported in the combination arm included neutropenia (64%), thrombocytopenia (28%), and anemia (8%), as opposed to 10%, 0%, and 5%, respectively, in the monotherapy arm.

HMAs are listed as treatment options for patients with higher-risk MDS who are not eligible for transplant or as a bridge to transplant. In 2021, the panel completed the stratification of systemic therapy recommendations for patients with higher-risk MDS (see MDS-6, page 111). AzaC is listed as "preferred," while decitabine and the combination of oral decitabine and cedazuridine are listed as "other recommended regimens," both for

nontransplant candidates as well as for individuals with MDS that relapsed after allogeneic hematopoietic cell transplant or did not respond. Clinical trial is also an option for these patients. Although the response rates for AzaC and decitabine are similar, survival benefit from one phase III randomized trial has been reported for AzaC²⁵ and not for decitabine.

The panel also discussed the recent data regarding allogeneic hematopoietic cell transplant (HCT) versus continued HMA therapy for treating patients with higher-risk MDS, indicating a survival advantage for patients who underwent transplantation.²⁶ These data have since been published.²⁷ At 3 years, an intention-to-treat analysis revealed that the adjusted OS rate in patients aged 50 to 75 years was 47.9% (95% CI, 41.3%–54.1%) and 26.6% (95% CI, 18.4%–35.6%; *P*=.0001) for those in the donor arm (expected to undergo reduced-intensity conditioning HCT, *n*=260) and the no-donor arm (expected to receive HMA therapy or best supportive care, *n*=124), respectively. In addition, at the same time point, the leukemia-free survival rate was 35.8% (95% CI, 29.8%–41.8%) versus 20.6% (95% CI, 13.3%–29.1%; *P*=.003), respectively. Subgroup analyses showed no differences in outcomes by age ≤65 versus

SUPPORTIVE CARE^r

- **Cytokines:**
 - ▶ **EPO: See Anemia Pathway (MDS-4)**
 - ◊ EPO refers to the following agents: epoetin alfa and epoetin alfa-epbx.
 - ▶ **G-CSF:**
 - ◊ G-CSF refers to the following agents: filgrastim^{ss} and tbo-filgrastim. Not recommended for routine infection prophylaxis.
 - ◊ Consider use in neutropenic patients with recurrent or resistant infections.
 - ◊ Combine with EPO for anemia when indicated. See Anemia Pathway (MDS-4).
 - ◊ Platelet count should be monitored.
- **Clinically significant thrombocytopenia**
 - ▶ In patients with lower-risk MDS who have severe or life-threatening thrombocytopenia, consider treatment with a thrombopoietin-receptor agonist.^{tt}
- **Post-transplant**
 - ▶ Patients should receive antibiotic prophylaxis at least as long as they are on immunosuppressive therapy.
 - ▶ Detailed recommendations are provided in the Guidelines generated by the American Society of Transplantation and Cellular Therapy (ASTCT, formerly ASBMT). See NCCN Guidelines for Hematopoietic Cell Transplantation (HCT).

^r See NCCN Guidelines for Supportive Care.^{ss} An FDA-approved biosimilar is an appropriate substitute for filgrastim.^{tt} Giagounidis A, et al. Cancer 2014;120:1838-1846. Platzbecker U, et al. Lancet Haematol 2015;2:e417-e426. Oliva EN, et al. Lancet Haematol 2017;4:e127-e136.

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MDS-8

>65 years. Another study examined retrospectively the outcomes of patients with high-risk MDS or secondary AML who underwent transplantation without prior cytoreductive therapy (n=67) compared with those who received cytoreductive therapy in the form of induction chemotherapy (n=64) or HMAs (n=34) prior to transplantation.²⁸ Patients had a blast count of $\geq 5\%$ in the bone marrow. Reduced-intensity conditioning was applied before stem cell infusion in 68% of patients. Compared with the other groups, a higher percentage of patients in the HMA group (85%) were treated with a reduced-intensity conditioning regimen, which is likely due to the difference in age. Multivariate analyses revealed that the type of pretransplant treatment did not impact OS, relapse-free survival (RFS), and nonrelapse mortality. However, cytogenetics, reduced-intensity conditioning, and use of an unrelated donor were found to be predictors of negative outcomes. At 5 years, there was no difference in OS (61%, 50%, and 45%, respectively; $P=.116$) and RFS (38%, 41%, and 38%, respectively; $P=.926$) between the 3 groups. OS ($P=.971$) and RFS ($P=.883$) were similar in patients with blasts $<10\%$ or $\geq 10\%$ in the bone marrow who underwent transplantation without prior cytoreductive therapy.

Based on the positive results of the donor versus no-donor analysis,^{26,27} a footnote was amended to clarify that early referral to transplant is recommended to allow moving to transplant efficiently (see MDS-6A, page 112). Pretransplant debulking therapy to reduce marrow blasts to $<5\%$ blasts with the goal of reducing posttransplant relapse is recommended, although the optimum strategy has not been determined. Reducing the disease burden pretransplant is particularly important in patients who will receive a reduced-intensity conditioning regimen.²⁹ At some centers, failure to achieve $<5\%$ blasts with cytoreduction did not preclude from proceeding to transplant, as these patients appeared to derive survival benefit from transplant.^{27,28}

An argument in favor of pretransplant cytoreduction was provided by Festuccia et al,²⁹ who showed that the presence of minimal identifiable disease (MID) prior to transplantation in patients with MDS or AML arising from MDS impacted prognosis following transplantation. Among patients who were MID-positive by cytogenetics, irrespective of positivity by flow cytometry, the overall mortality risk was higher in those who underwent low-intensity conditioning compared with those who underwent high-intensity conditioning. However, in patients with an

GENETIC FAMILIAL HIGH-RISK ASSESSMENT: HEREDITARY MYELOID MALIGNANCY PREDISPOSITION SYNDROMES

4. Post-test counseling done when the test results are disclosed

- Discuss results and associated medical risks.
- Interpret results in context of patient's presentation.
- Discuss recommended medical management.
- Discuss and offer assistance with information and testing at-risk family members.
- Discuss available resources such as high-risk clinics, disease-specific support groups, and research studies.
- For patients of reproductive age, advise about options for prenatal diagnosis and assisted reproduction, including pre-implantation genetic diagnosis.
- Consider carrier status implications of certain autosomal recessive disorders.

5. Limitations of the proposed approach

- The current criteria are focused mainly on known genetic predisposition syndromes to MDS or AML. The proposed age threshold of 50 years at the time of diagnosis is arbitrary and conditions known to be diagnosed at older ages (*DDX41*) with predisposition to MDS or AML due to germline may be missed. Additionally, there are certainly genetic aberrations predisposing to the development of myeloid neoplasms that have not yet been identified and as such, some patients may not fit the aforementioned criteria. Any clinical suspicion of a hereditary condition not included in these guidelines may still warrant a referral to an institution with expertise in the field.

6. Surveillance

- Individuals who fulfill the clinical diagnostic criteria for a myeloid neoplasm with a germline predisposition should undergo surveillance, even if the pathogenic genetic variant is undetermined.
- Individuals with a deleterious or likely deleterious genetic variant associated with a germline predisposition should undergo surveillance, regardless of clinical presentation.

⁶ Wong JC, Bryant V, Lamprecht T, et al. Germline *SAMD9* and *SAMD9L* mutations are associated with extensive genetic evolution and diverse hematologic outcomes. *JCI Insight* 2018;3:e121086.

⁷ Tesi B, Davidsson J, Voss M, et al. Gain-of-function *SAMD9L* mutations cause a syndrome of cytopenia, immunodeficiency, MDS, and neurological symptoms. *Blood* 2017;129:2266-2279.

⁸ Trotter AM, Cavalcante de Andrade Silva M, Li Z, Godley LA. Somatic mutation panels: Time to clear their names. *Cancer Genet* 2019;235-236:84-92.

⁹ Alder JK, Hanumanthu VS, Strong MA, et al. Diagnostic utility of telomere length testing in a hospital-based setting. *Proc Natl Acad Sci USA* 2018;115:E2358-E2365.

¹⁰ Schratz KE, Haley L, Danoff SK, et al. Cancer spectrum and outcomes in the Mendelian short telomere syndromes. *Blood* 2020;135:1946-1956.

¹¹ Fargo JH, Kratz CP, Giri N, et al. Erythrocyte adenosine deaminase: diagnostic value for Diamond-Blackfan anaemia. *Br J Haematol* 2013;160:547-554.

MID-negative status, as determined by both cytogenetics and flow cytometry, the risk of mortality with low- and high-intensity conditioning regimens was similar. It is important to note that this study did not specifically examine outcomes in patients who proceeded to transplant without cytorreductive therapy. Among patients with an MID-positive status, as assessed by both cytogenetics and flow cytometry, the risk of relapse was higher in those who underwent low-intensity conditioning, as opposed to those who underwent high-intensity conditioning. As the MID classification can help identify patient subgroups that may have better outcomes with high- or low-intensity conditioning, the authors propose considering the presence of MID to help determine the intensity of the conditioning regimen for patients being considered for transplant.

Supportive Care

Supportive care is an important aspect of MDS management, which entails observation, clinical monitoring, psychosocial support, and quality-of-life (QoL) assessment. In the 2022 update, the panel included some new recommendations for the pretransplant and posttransplant settings (see MDS-7 and MDS-8, page 113 and opposite

page, respectively). Prior to transplant, transplant patients should receive support. Transfusion products should be irradiated with 25 Gy or per institution standard. Patients with $\geq 5\%$ marrow blasts who are candidates for reduced-intensity conditioning are encouraged to receive “debulking” therapy with an HMA or induction chemotherapy. Transplantation should be carried out as long as patients are experiencing response and should not be delayed until the response is lost. Posttransplantation, patients should receive antibiotic prophylaxis at least as long as they are on immunosuppressive therapy. Detailed recommendations are provided in the guidelines generated by the American Society of Transplantation and Cellular Therapy³⁰ and the NCCN Guidelines for Hematopoietic Cell Transplantation (available at NCCN.org).

Genetic Familial High-Risk Assessment: Hereditary Myeloid Malignancy Predisposition Syndromes

Molecular and genetic screening for hereditary hematologic malignancy predisposition is recommended in a subset of patients, particularly those aged <50 years. Diseases, syndromes, and mutations that may potentially be

associated include GATA2 deficiency syndrome, Shwachman-Diamond syndrome, short telomere syndromes, *DDX41* mutations (usually present at older ages), and others (see “Genetic/Familial High-Risk Assessment: Hereditary Myeloid Malignancy Predisposition Syndromes” and “Gene Mutations Associated with Hereditary Myeloid Malignancies” in the full algorithm at NCCN.org). This year, a subcommittee of the NCCN MDS Panel worked on updating recommendations for genetic familial high-risk assessment of hereditary myeloid malignancy predisposition syndromes. The subcommittee members discussed the new proposed content and panel members reviewed the content during the panel review process. The guidelines include information about pretest counseling prior to ordering testing, appropriate DNA source for germline genetic testing, consideration of the appropriate genetic testing methodologies and other diagnostic testing, and postcounseling performed when the test results are disclosed. In this update, limitations of the proposed approach were added to the recommendations, as well as recommendations about which patients should undergo surveillance, namely individuals who fulfill the clinical diagnostic criteria for a myeloid neoplasm with a germline predisposition (even if the pathogenic variant is undetermined), as well as individuals with a deleterious or likely deleterious genetic variant associated with a germline predisposition, regardless of

clinical presentation (see MDS-D 4 of 5, page 115). In the evaluation for suspected hereditary myeloid malignancy predisposition syndromes, the panel included individuals with aberrations of chromosome 7 and age <50 years among individuals for whom testing is recommended, and also updated allogeneic sibling donor to allogeneic related donor in this setting. The panel also included information about some newly added germline gene mutations that are associated with hereditary myeloid malignancies, more specifically *XPC^{delTG}*, *ERCC6L2*, and *LIG-4*.^{31–36}

Conclusions

The NCCN Guidelines for MDS are based on extensive evaluation of the reviewed risk-based data and indicate current approaches for managing patients with MDS. These NCCN Guidelines Insights highlight some of the updated recommendations, preference stratification, and emerging data on novel agents. Treatment options vary based on the risk category and clinical characteristics. Ongoing clinical trials are underway to investigate new therapeutic avenues, and the results of these trials may help inform the panel's recommendations.

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