Chapter e160: Myelodysplastic Syndromes

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KEY CONCEPTS

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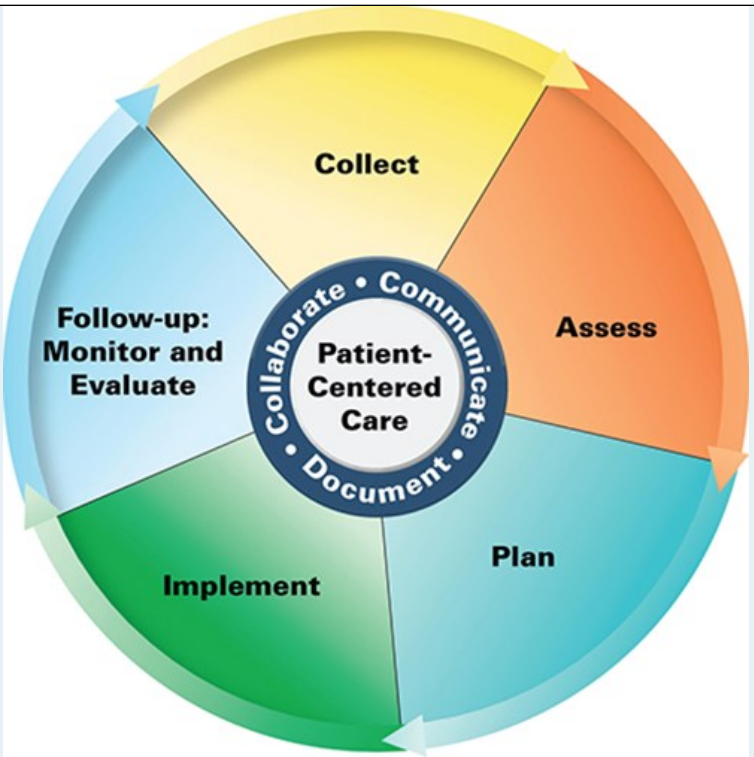
1. Myelodysplastic syndromes (MDS) primarily affect older adults.
2. The exact cause of MDS is unknown and is probably multifactorial. MDS have been associated with host-specific characteristics, environmental, lifestyle, and therapeutic exposures.
3. Genomic instability drives MDS development and progression. The clonal population of cells manifested as MDS results from enhanced self-renewal of a hematopoietic stem cell or acquisition of self-renewal in a progenitor cell, increased proliferative capacity in the abnormal clone, impaired cell differentiation, evasion of immune regulation, and antiapoptotic mechanisms in the disease-sustaining cell.
4. Most patients with MDS present with fatigue, infection, bleeding/bruising, lethargy, or other symptoms related to cytopenias.
5. The prognosis of patients with MDS depends on the biology of the MDS and host characteristics. Overall survival time ranges from a few months to several years and is most accurately estimated with the International Prognostic Scoring System—Revised (IPSS-R).
6. The goals of therapy for MDS are to change the natural history of the disease, reduce the number of red blood cell transfusions, and improve quality of life.
7. Lenalidomide should be considered for patients with MDS that harbor a del(5q) clone and is particularly beneficial in those with symptomatic anemia.
8. Patients with lower-risk MDS and symptomatic anemia who have a serum erythropoietin level ≤500 mU/mL (U/L) are suitable candidates for an erythropoiesis stimulating agent with or without growth factor support.
9. A subset of lower-risk MDS patients respond well to antithymocyte globulin (ie, immunosuppressive therapy), which is most effective in patients who have a hypocellular marrow, MDS that expresses HLA DR15 with trisomy 8 as the sole cytogenetic abnormality, refractory anemia, and younger than 60 years.
10. Further evaluation is required to determine the optimal hypomethylating agent treatment regimen.
11. Allogeneic hematopoietic stem cell transplantation offers potentially curative therapy to patients with MDS who have a donor and are healthy enough for the procedure.

PATIENT CARE PROCESS

Patient Care Process for Myelodysplastic Syndromes



Collect

- Patient chief complaint (eg, fatigue, easy bruising)
- Patient characteristics (eg, age, sex, pregnant, weight)
- Patient medical history (personal including blood transfusion history, sexual history, reproductive history including whether the patient is still menstruating and has her uterus (if female), and family history minimum of 3 generations)
- Social history (eg, tobacco/ethanol use), employment status, and history
- Current medications including over-the-counter aspirin/nonsteroidal anti-inflammatory drug use, herbal products, dietary supplements, and prior chemotherapy, radiotherapy, or granulocyte colony-stimulating factor
- Full review of systems (objective data)
    - Blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight
    - Labs including complete blood count with differential, peripheral blood smear, reticulocyte count, serum vitamin B_{12}, RBC folate and copper, HIV, TSH, ferritin, iron, TIBC, LDH
    - Bone marrow biopsy procedure: morphologic evaluation, karyotyping, consider molecular genetic evaluation for TP53, ASXL1, etc.
    - Serum erythropoietin level (for lower risk MDS)

Assess

- Karyotype, cytogenetics as well as any identified somatic mutation, degree of cytopenias, and percentage of blasts
- Determine the WHO subtype of MDS according to the 2016 guidelines and the IPSS-R category of risk
- Determine if molecularly guided therapy (ie, deletion 5q) and lenalidomide or immunosuppressive therapy (for patients who are ≤60 years old,

shorter duration of red cell transfusion dependence, over-representation of the class II histocompatibility antigen DR15 [HLADR15], <5% blasts, and normal cytogenetics) is indicated

- Based on a review of systems, determine if symptoms related to anemia are present; patient-specific factors (eg, performance status and ability to tolerate treatment); and eligibility for allogeneic HSCT

Plan*

- Develop a treatment plan based on risk category (lower risk vs higher risk), cytogenetics and eligibility for allogeneic HSCT
- Monitoring parameters including efficacy (eg, CBC with differential, history, physical examination) and safety (eg, sign and symptoms of toxicities or complications); frequency and timing of follow-up should be individualized
- Patient education (eg, purpose of treatment, treatment schedule (cycles, days), safe handling, reproduction and sexual precautions, administration, adverse drug reactions and their management)
- Review self-monitoring plan for the need to call the cancer care team or proceed to the nearest emergency department as well as home management of adverse drug reactions and complications where possible

Implement*

- Provide patient education regarding all elements of the treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up (eg, infusion appointments where applicable, blood count evaluation, chemistries, history, and physical examination)

Follow-up: Monitor and Evaluate*

- For patients on chemotherapy, evaluations should occur with each cycle
- Restoration of hematopoiesis as evidenced by normalization in CBC with differential
- Evaluate for signs and symptoms of anemia, bleeding, or infection
- Morphologic, cytogenetic, and molecular normalization in bone marrow biopsy sample evaluations
- Patient adherence to treatment plan based on multiple sources of information

****Collaborate with patient, caregivers, and other healthcare professionals.***

BEYOND THE BOOK

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Name of drug	Target	Dosing	Top 3 counseling points
Lenalidomide			
Antithymocyte globulin (equine)			
Cyclosporine			
Azacitidine			
Decitabine			
Decitabine + Cedazuridine			
Venetoclax			

INTRODUCTION

Myelodysplastic syndromes (MDS) are a heterogeneous group of myeloid stem cell disorders that are clonal in nature and characterized by ineffective hematopoiesis with morphologic dysplasia in hematopoietic cells and peripheral cytopenias.[1] About one-third of patients with MDS will have a disease course that progresses to acute myeloid leukemia (AML). The diagnostic criteria for MDS is the presence of bone marrow dysplasia in at least 10% of cells in one or more of three major bone marrow lineages. Additionally, a diagnosis of MDS can be achieved if 5% to 19% blasts or an MDS-associated karyotype is noted in the bone marrow.[1-3] The clinical course of patients with MDS varies from a slowly progressing, indolent disease, to more aggressive disease characterized by excess bone marrow blasts and rapid progression to AML.[2,3]

Our understanding of the molecular biology behind MDS has advanced in recent years, but few targeted treatments have been approved in MDS. Aberrations in epigenetic regulator genes, spliceosome component pathways, DNA damage response genes, and genes regulating transcription factors have redefined the molecular landscape in MDS.[4] Chromosomal abnormalities have been incorporated into prognostic models predicting survival and leukemic transformation.[2,3] Several agents exist to treat MDS, and are generally selected based on severity of disease and prognostic factors.[2] Despite progress in disease classification, identification of over 40 recurrently mutated genes, improvement in risk stratification, and development of new treatment options in the past two decades, few personalized treatment options are available.

EPIDEMIOLOGY

1 MDS primarily affects older adults with a median age at diagnosis of 76 years and a slight male predominance (ie, male-to-female ratio of about 1.75 to 1).[2] An estimated 3 to 12 cases of MDS are diagnosed per 100,000 persons/year.[5] The risk of MDS increases with age, most commonly occurring in the seventh and eighth decade of life.[2,5] It is difficult to accurately determine the prevalence of MDS but recent reports suggest that the prevalence of MDS has been grossly underestimated and as many as 60,000 people with MDS live in the United States.[2] Many experts predict that the incidence of MDS will increase as the population of the United States ages and clinicians become more aware of MDS.

ETIOLOGY

2 The exact cause of MDS is unknown and is probably multifactorial. MDS have been associated with host-specific characteristics, lifestyle,

environmental, and therapeutic exposures (medical treatments or radiation).[6,7] A small proportion of the MDS population has a genetic predisposition.[6,7] Several well-characterized inherited syndromes can increase the risk of developing MDS or acute leukemia.[7] For example, telomere biology disorders, bone marrow failure syndromes (eg, Fanconi anemia, Shwachman-Diamond syndrome, dyskeratosis congenita), which often manifest in childhood, and Down syndrome. In addition, familial MDS/Acute Leukemia predisposition syndromes as the most common presenting feature have been recognized. Familial genetic information may have implications on the treatment of MDS, for example, if allogeneic hematopoietic stem cell transplant is indicated.

Another host characteristic associated with an increased risk of developing MDS is senescence. With age, an individual's hematopoietic stem cell (HSC) population has a reduced capacity for self-renewal. In addition, HSCs become more clonal in nature as one ages and have a bias toward myeloid cells. Clonal hematopoiesis of indeterminate potential (CHIP) occurs when hematopoietic stem/progenitor cells divide and accumulate recurrent somatic mutations that generally do not affect function and are common in MDS and AML.[8] These myeloid clones may contain disease causing or epigenetic changes that increase an individual's risk of developing MDS. Modifiable host risk factors for MDS include smoking and obesity.[2] Lastly, chronic immune stimulation or therapy to manage infectious and autoimmune diseases in a given host increases the risk for development of MDS.

Environmental exposure to agricultural chemicals (eg, pesticide) has been associated with an increased risk of developing MDS.[9] MDS have also been linked in a dose-dependent relationship to ionizing radiation in atomic bomb survivors in Japan and have been reported in workers in the Chernobyl nuclear accident.[10] Further, occupational exposures to hair dyes, cereal dust, exhaust gases, diesel fuel, and industrial solvents (including benzene and toluene) have been associated with the development of MDS.

Therapy-related myeloid neoplasms (TR-MN) are designated by the World Health Organization as a distinct subgroup.[1] TR-MNs can be further divided into therapy-related MDS or AML (t-MDS or t-AML1). About 10% to 20% of all cases of MDS and acute leukemia are attributed to therapies such as radiation, chemotherapy, or both. Patients who receive intensive chemotherapy regimens have an increased risk of TR-MNs that is 4.7-fold higher than the general population.[2] Since 1975, there has been a noted increase in the risk of TR-MNs after treatment for non-Hodgkin lymphoma over time. In contrast, a decreased risk of developing TR-MNs over time has been observed after therapy for multiple myeloma and ovarian cancer since 1975. In addition, newly observed risk in patients with sarcoma, cervical, prostate, esophageal, endometrial, and possibly anal cancers have emerged. Trends in risk for developing TR-MNs have coincided with treatment patterns for a given malignancy.[10] For example, melphalan was once used routinely to treat multiple myeloma but has fallen out of favor. The risk for developing t-MDS increases with age, higher doses of chemotherapy or radiation, longer duration of exposure, and exposure to both chemotherapy and radiation.[2] Chromosomal abnormalities are found in about 90% of t-MDS compared with 50% to 60% of *de novo* MDS.[11] t-MDS has an increased risk of progression to AML and a poorer prognosis than *de novo* MDS.

Several chemotherapeutic agents have been associated with t-MDS (Table e160-1). The contribution of a specific agent is difficult to assess because patients are usually exposed to multiple agents, often in combination with radiation. The most frequently reported classes of chemotherapeutic agents associated with t-MDS are alkylating agents and topoisomerase II inhibitors.[12]

TABLE e160-1

Therapies Associated with Therapy-Related Myelodysplastic Syndromes

Alkylating Agents	Topoisomerase II Inhibitors	Miscellaneous
Busulfan	Dactinomycin	Azathioprine
Carmustine	Daunorubicin	Carboplatin
Chlorambucil	Doxorubicin	Cladribine
Cyclophosphamide	Epirubicin	Cisplatin
Dacarbazine	Etoposide	Docetaxel
Ifosfamide	Idarubicin	Fludarabine
Lomustine	Mitoxantrone	Iodine-131 tositumomab
Mechlorethamine	Teniposide	Mercaptopurine
Melphalan		Methotrexate
		Mycophenolate
		Paclitaxel
Mitomycin		Vinblastine
Procarbazine		
Temozolomide		Vincristine
Thiotepa		Vindesine
		Yttrium-90 ibritumomab tiuxetan

Data from References 12-16.

The role of alkylating agents in the development of t-MDS is well established in patients with cancer and those receiving high cumulative doses of alkylating agents for autoimmune disorders such as rheumatoid arthritis.[12] The latency period between exposure to alkylating agents and the development of t-MDS is about 4 to 7 years. Characteristic chromosomal abnormalities in t-MDS associated with alkylating agents include deletions on chromosomes 5 and 7.

Topoisomerase II inhibitors, including the epipodophyllotoxins (etoposide and teniposide), anthracyclines (daunorubicin, doxorubicin, epirubicin, idarubicin), and the anthracenedione mitoxantrone, are also associated with t-MDS.[12] t-MDS associated with topoisomerase II inhibitors typically occur a median of 2 to 3 years after exposure, and patients are more likely to present with AML at diagnosis. Chromosomal abnormalities often found in patients with t-MDS associated with topoisomerase II inhibitors include balanced translocations involving the *MLL* gene 11q23 and 21q22.

Y-ibritumomab tiuxetan is a monoclonal antibody linked to a radioactive isotope (ie, radioimmunoconjugate). Another agent, iodine-131

tositumomab, is no longer commercially available. These radioimmunoconjugates deliver radiation to the antibody-bound targeted cell and to neighboring cells through a "cross-fire" effect. TR-MNs are reported to occur in 5% to 10% of patients exposed to iodine-131 tositumomab and in 1% to 5% of patients exposed to Y-ibritumomab tiuxetan.[13-15] About 8% of patients receiving myeloablative doses of ibritumomab tiuxetan as part of their conditioning regimen before hematopoietic stem cell transplantation (HSCT) developed TR-MNs, similar to the rate in patients receiving myeloablative chemotherapy-based conditioning regimens.[14] Radioimmunoconjugates are primarily used to treat non-Hodgkin lymphoma, a patient population likely to receive other therapies associated with t-MDS, including alkylating agents, anthracyclines, and radiation. Therefore, it is difficult to determine the additional risk for TR-MNs due solely to exposure to one of these agents.

Two systematic reviews have been conducted to evaluate the impact of granulocyte colony-stimulating factors used during treatment of adults with solid tumors and lymphoma on all-cause mortality and secondary malignancies.[17,18] Both of these studies reported reduced all-cause mortality in patients treated with granulocyte colony-stimulating factors, likely as a result of increased ability to use dose-dense chemotherapy. However, both systematic reviews showed an increased risk of secondary malignancies including t-MDS. It is not clear whether the increased risk of secondary malignancies was due to either the use of granulocyte colony-stimulating factor or dose-dense chemotherapy. In contrast, clonal evolution was not observed in aplastic anemia patients treated with granulocyte colony-stimulating factors.[18] Benefit-to-risk evaluation continues to be important when the use of granulocyte colony-stimulating factors is considered.

Patients undergoing autologous HSCT are at increased risk for the development of t-MDS. Conditioning regimens given before HSCT usually include high doses of alkylating agents or etoposide, sometimes in combination with total body irradiation. As many as 8% to 20% of patients with non-Hodgkin lymphoma treated with autologous HSCT will develop t-MDS within 10 years of transplantation.[19,20] Risk factors for development of t-MDS after autologous HSCT include antecedent conventional chemotherapy, prior radiation therapy, low stem cell dose, older age at time of transplant, and use of total body irradiation in the conditioning regimen.[19,20]

PATHOPHYSIOLOGY

Knowledge of normal hematopoiesis is needed to understand the pathophysiology of MDS (see Chapter e106 for a more detailed description of hematopoiesis). Diverse pathophysiology underlying MDS causes heterogeneity in clinical presentation, pattern of disease progression, and response to therapy. Further, the pathogenesis of MDS has not been fully elucidated.[2] Progressive bone marrow failure is characteristic of patients with MDS and is the result of ineffective hematopoiesis. In addition to peripheral blood cytopenias, the terminally differentiated cells that are produced may have functional defects. Neutrophils may have reduced bactericidal and fungicidal activity despite a normal quantity.[21] Platelets may be normal in quantity but have impaired activation, secretion, and aggregation.[22] It may seem odd that MDS is a clonal disease with a phenotype that includes cytopenias, but impairment of terminal differentiation and increased apoptosis explain this phenomenon.

A multistep model for the pathogenesis of MDS has been proposed and the disease can arise via multiple different pathways.[2] Recurrent somatic mutations drive MDS development and progression. The clonal population of cells manifested as MDS results from enhanced self-renewal of an HSC or acquisition of self-renewal in a progenitor cell, increased proliferative capacity in the abnormal clone, impaired cell differentiation, evasion of immune regulation, and antiapoptotic mechanisms in the disease-sustaining cell. The abnormal clone proliferates or evades apoptosis because of genomic instability and abnormalities in cytokines and the bone marrow stroma. These changes create a dysplastic, clonal population of cells in a milieu unable to support normal hematopoiesis.

Genomic Instability

MDS is clonal in nature and is preceded by the acquisition and expansion of genetic alterations. The diagnosis of MDS is not based on a defining mutation or single inciting genetic alteration but a genomic fingerprint is emerging. Chromosomal abnormalities, most often genomic losses and gains, are detected by cytogenetic analysis in approximately 45% of patients with *de novo* MDS and remain one of the strongest determinants of prognosis.[2] Multiple cytogenetic abnormalities that correlate with the clinical course of MDS were incorporated in the original International Prognostic Scoring System (IPSS) classification and prognostic assessment, including 5q or 20q deletions and chromosome 7 abnormalities.[2] The International Prognostic Scoring System—Revised [IPSS-R] includes several additional cytogenetic abnormalities that correlate with the clinical course of MDS such as trisomy 8 or 19, 12p, or 11q deletions, and double abnormalities.[3] Deletions on chromosome 5q occur in up to 12% of patients and are of particular

interest because multiple genes involved in hematopoiesis are located there.[11] In addition, MDS with 5q deletions as the sole genetic aberration is recognized as a distinct subtype of MDS with a favorable prognosis and a high likelihood of response to lenalidomide.[1,11,23]

Emerging data about somatic mutations found in MDS have the potential to allow clinicians to provide personalized therapy.[24] The most frequently mutated MDS genes (>5%) are *SF3B1, TET2, ASXL1, SRSF2, DNMT3A, RUNX1, U2AF1, ZRSR2, STAG2, TP53, NRAS*, and *EZH2*.[4] Some of these mutations are associated with prognosis, including *SF3B1* (more favorable prognosis) and *ASXL1, SRSF2, DNMT3A, RUNX1, U2AF1, ZRSR2, TP53, NRAS*, and *EZH2* (poor prognosis).[2,24] Frequently mutated genes in MDS suggest a disease of disordered spliceosome function and epigenetic regulation.

Somatic mutations occur in five major categories: RNA splicing, DNA methylation, histone modification, activated cell signaling, and myeloid transcription factors. At least 90% of patients with MDS will harbor at least one somatic mutation from a set of about 40 recurrently mutated MDS genes.[2] Furthermore, some somatic mutations are associated with prognosis and they can be used to better understand the clonal architecture of MDS. Unfortunately, a similar spectrum of somatic mutations can be seen in older patients without dysplasia. Therefore, DNA sequencing cannot completely replace morphologic evaluation for the diagnosis of MDS at this time.

Mutations within components of the spliceosome, the unit within eukaryotic nuclei that splices introns from pre-mRNA, occur in up to 60% of cases and are the most common recurrent lesions in MDS.[4,24] Splicing mutations are associated with ring sideroblast morphology, lower-grade disease, and better prognosis.[24] The splicing mutation *SF3B1* is the most common spliceosome alteration in MDS.

The splicing factors and epigenetic modifiers *DNMT3A* and *TET2* tend to be mutated early in the evolution of MDS.[2] The term *epigenetics* refers to mechanisms that regulate the expression of DNA without affecting its sequence. Epigenetic changes, including DNA methylation (*TET2, DNMT3*) and histone modification (*ASXL1, EZH2*) among many others, have been identified in numerous malignancies but are of particular importance in MDS.[24]

DNA methylation is the best described and most common epigenetic marker. In the mammalian genome, only cytosine located 5′ to a guanosine (CpG) can be methylated (CpG pair). Clusters of CpG pairs, known as *CpG islands*, are near the promoter regions for many genes. These regions are unmethylated in normal cells, allowing for standard DNA expression to occur. Increased methylation (hypermethylation) of *CpG* islands occurs via DNA methyltransferases and is associated with aberrant gene silencing, which may lead to further genetic instability and cell cycle dysfunction. Demethylation (hypomethylation), regulated by *TET2*, may lead to reexpression of previously silenced genes.[24] Hypermethylation and gene silencing have been identified in patients with MDS, and azacitidine and decitabine reverse this process.[25]

Histone modification is another significant epigenetic marker in MDS. Histones coil with DNA to form tightly wound complexes called chromatin. Posttranslational modifications of histones, by acetylation, methylation, and ubiquitination can alter the structure of chromatin creating opportunities for gene suppression or expression, depending on the structural change of the chromatin. *ASXL1*, an epigenetic regulator of chromatin modification, has been identified as the third most commonly mutated gene in MDS, occurring in 15% to 25% of MDS patients and is independently associated with worse overall survival.[24] Histone hypoacetylation has been documented in malignant cells and several histone deacetylase inhibitors have been studied in patients with MDS as monotherapy, in combination with hypomethylating agents or with low-dose cytarabine in an attempt to promote histone acetylation and expression of previously suppressed tumor suppressor genes.[26-29]

Genes that encode for proteins involved in cell signaling cascades can be mutated in MDS, although this is more frequently observed in AML.[2] The pathways impacted are those that often promote cell proliferation. Many of these mutations affect the cell through the MAPK pathway (ie, NRAS, KRAS, NF1, and PTPN11). When these mutations occur in MDS, they typically arise late in disease evolution. Mutations in NRAS are associated with a poor prognosis in MDS.[2]

Transcription regulation genes can be mutated in MDS. Examples include *TP53, RUNX1, GATA2*, and *MECOM*.[2] *TP53* mutations occur in about 5% of MDS cases and in greater than 30% of TR-MNs. *TP53* mutations can adversely affect the prognosis in all subtypes of MDS.[4] *TP53* mutations are generally associated with low platelet levels, high blast count, prior exposure to chemotherapy, and complex cytogenetics.[2]

Some studies suggest that *TP53* mutations may sensitize cancer cells to hypomethylating agents like decitabine. In a study of 84 patients with AML or MDS, response rates after 10-day courses of decitabine were significantly higher among patients with mutated *TP53* when compared with wild-type *TP53*.[29] The authors concluded that 10-day courses of decitabine for AML or MDS in patients who had mutations in *TP53* had better responses.

However, other experts disagreed with this conclusion citing other studies that found no difference in response rates to decitabine when comparing *TP53* mutated disease to wild-type *TP53* disease.[30]

Bone Marrow Microenvironment and Immune System Dysregulation

The myelodysplastic clone is associated with cellular dysfunction, including excess secretion of cytokines, defective differentiation, genomic instability, and reduced response to regulatory cytokines.[2] Bone marrow cells often have a paradoxically high rate of cellular division and are generally normocellular or hypercellular for age. Apoptosis, or programmed cell death, is increased leading to the futile cycling of precursor cells and impaired production of mature peripheral blood cells. Overproduction of proapoptotic and inflammatory cytokines and vascular endothelial growth factor may contribute to this process.[2] Bone marrow stromal cells from MDS patients show decreased ability to support normal hematopoietic cell function.

Patients with MDS frequently have evidence of immune dysregulation, such as impaired immune surveillance and autoimmune reactions. Cytopenias can be related to an autoimmune T-cell–mediated response. A subset of MDS patients characterized by younger age, refractory anemia of short duration, a hypocellular bone marrow, trisomy 8 as the sole cytogenetic abnormality, and expression of human leukocyte antigen (HLA) haplotype DR15 have a high likelihood of response to immunosuppressive therapy.[2] Cyclosporine and antithymocyte globulin may induce durable responses in this subgroup of patients, confirming the role of immune dysregulation. Whether B-cells and T-cells are a part of the MDS clonal population or a secondary reaction after the development of the malignant clone is unclear.

CLASSIFICATION AND PROGNOSIS

Different strategies to identify phenotypes of MDS based on the heterogeneous biology observed within the disease have evolved over time. The French-American-British (FAB) classification established subgroups of MDS based on morphology of bone marrow aspirates and peripheral blood blast percentage. The FAB classification system was replaced in 2008 by the WHO classification system, which also incorporates whether dysplasia or cytopenias affect a single-cell lineage or multiple myeloid cell lines and cytogenetics.[31] A revision of the WHO classification was published in 2016 with changes to simplify classification and define the role of molecular genetic testing (Table e160-2).[1]

TABLE e160-2

2016 World Health Organization Classification of Myelodysplastic Syndrome

Classification	Blood[a]	Bone Marrow
MDS with single lineage dysplasia	• 1-2 cytopenia(s) • No or rare blasts (<1%)	• 1 dysplastic lineage • <5% blasts • <15% ringed sideroblasts
MDS with multilineage dysplasia	• 1-3 cytopenia(s) • No or rare blasts (<1%)	• Dysplasia in 2-3 myeloid cell lines • <15% ringed sideroblasts • <5% blasts
MDS with ringed sideroblasts (single or multilineage dysplasia)	• 1-3 cytopenia(s) • No or rare blasts (<1%)	• Dysplasia in 1-3 myeloid cell lines • <5% blasts • +15% ringed sideroblasts
MDS with isolated del(5q)	• 1-2 cytopenia(s) • No or rare blasts (<1%)	• 1-3 dysplastic lineages • <5% blasts • Del(5q) alone or with 1 additional abnormality except −7 or del(7q)
MDS with excess blasts	• 1-3 cytopenia(s) • 2%-19% blasts • ± Auer rods	• 0-3 dysplastic lineages • 5%-19% blasts • ± Auer rods
MDS, unclassifiable	• 1-3 cytopenias • <1% blasts	• 0-3 dysplastic lineages • 0 or <15% ringed sideroblasts • <5% blasts MDS defining karyotype

[a]Cytopenias are defined as hemoglobin <10 g/dL (100 g/L; 6.21 mmol/L), platelet count <100 × 10^9/L (100,000/mm^3), and absolute neutrophil count <1.8 × 10^9/L (1,800/mm^3).

Data from Reference 1.

5 Models to predict overall survival and risk of transformation to AML continue to be developed and refined as new information about the genetic basis of MDS evolves. Based on an observational study of mostly untreated MDS patients, the IPSS was developed to identify factors that would predict the progression of MDS.[2] Multivariate analyses identified four prognostic factors: cytogenetic abnormalities, percentage of bone marrow blasts, age, and number of cytopenias. Using these four factors, researchers were able to stratify patients into four risk groups that correlated with overall survival, which ranged from a few months to several years (Table e160-3).

TABLE e160-3

International Prognostic Scoring System for Myelodysplastic Syndromes

	Score Value				
Prognostic Variable	**0**	**0.5**	**1**	**1.5**	**2**
Bone marrow blasts (%)	5	5-10	—	11-20	21-30
Karyotype	Good	Intermediate	Poor		
Cytopenia	0 or 1	2 or 3			
Cytopenia: Absolute neutrophil count <1,800 cells/mm^3 (1.8×10^9/L) Hemoglobin <10 g/dL (100 g/L; 6.21 mmol/L) Platelet count <100,000 cells/mm^3 (100×10^9/L)					
Karyotype: Good: normal, isolated 5q deletion, isolated 20q deletion, Intermediate: any other abnormalities Poor: trisomy 7, complex or >3					
Score	**Risk Group**	**Median Survival (years)**			
0	Low	5.7			
0.5-1	Intermediate-1	3.5			
1.5-2.0	Intermediate-2	1.2			
≥2.5	High	0.4			

Data from Reference 2.

The IPSS-R was developed after analysis of more than 7,000 patients whose disease had not been treated with disease-altering therapy (Table e160-4).[3] This model differs from the IPSS in that it identifies five risk categories by incorporating different groupings for marrow blast percentage value and depth of cytopenias. This expands the cytogenetic risk groups from three to five and includes a number of less common cytogenetic abnormalities. Patient age, performance status, serum ferritin, and lactate dehydrogenase levels were additional significant predictors for survival, but not for AML transformation.

TABLE e160-4

International Prognostic Scoring System—Revised for Myelodysplastic Syndromes

Prognostic Variable	0	0.5	1	1.5	2	3	4
Cytogenetics*	Very good		Good		Intermediate	Poor	Very poor
Bone marrow blast (%)	≤2		>2-<5		5-10	>10	
Hemoglobin (g/dL)	≥10 (100 g/L; 6.21 mmol/L)		8-<10 (80-100 g/L; 4.97-6.21 mmol/L)	<8 (80 g/L; 4.97 mmol/L)			
Platelets (cells/mm^3)	≥100,000 (100 × 10^9/L)	50,000-<100,000 (50-<100 × 10^9/L)	<50,000 (50 × 10^9/L)				
Absolute neutrophil count (cells/mm^3)	≥800 (0.8 × 10^9/L)	<800 (0.8 × 10^9/L)					

*Karyotype: Very good: Y, del(11q).
Good: normal, del(5q), del(12p), del(20q), double including del(5q).
Intermediate: del(7q), +8, +19, i(17q), any other single or double independent clones.Poor: 7, inv(3)/t(3q)/del(3q), double, including 7/del(7q); complex: three abnormalities.Very poor: complex: >3 abnormalities.

Score	Risk Group	Median Survival (years)
≤1.5	Very low	8.8
>1.5-3	Low	5.3
>3-4.5	Intermediate	3
>4.5-6	High	1.6
>6	Very high	0.8

Data from Reference 3.

Recent reports have demonstrated that recurrent somatic gene mutations predict prognosis independent of the IPSS score, and their incorporation into a risk classification scheme does enhance the model.[2,32] About half of patients with MDS have normal cytogenetics. After the full spectrum of somatic mutations in MDS has been defined, prognostic scoring systems will need to incorporate relevant molecular features.

The IPSS and the IPSS-R are prognostic systems applied at diagnosis and the systems most widely used in clinical trials. However, patients with MDS can have disease biology that changes over time. Some of these changes may impact risk. Two prognostic systems have been developed that are more dynamic (ie, they can be applied beyond the time of diagnosis) are the World Health Organization Prognostic Scoring System (WPSS) and the global MD Anderson Cancer Center (MDACC) lower risk prognostic scoring system.

The WPSS was created in 2007. Part of its original criteria included whether the MDS patient was transfusion-dependent or not, and some experts thought this criterion was too subjective. In 2011, the WPSS was revised to address the criticism by adding hemoglobin thresholds of 11 g/dL (110 g/L; 6.83 mmol/L) in males and 9 g/dL (90 g/L; 5.59 mmol/L) in females.[2] The WPSS system classifies patients into five-risk groups with different survival and probability of leukemic evolution. The WPSS was compared to the IPSS-R.[33] The two prognostic systems were in agreement with discrepancies mainly occurring in early stage disease. Further, the WPSS placed more weight on degree of anemia when compared with the IPSS-R.[33] It is anticipated that the addition of somatic mutation data to WPSS and the IPSS-R will improve their accuracy and clinical utility.

Low-risk MDS patients have significant biological variability that may not be adequately considered in current prognostic systems. The MD Anderson Cancer Center developed the lower-risk scoring system for MDS.[33] In that system, MDS patients with low-risk disease had a more unfavorable prognosis within this risk group if they had unfavorable cytogenetics, age ≥60 years old, anemia, low platelet counts, or ≥4% blasts.[33] While this is a validated prognosis classification system, it is not widely used in clinical practice.

CLINICAL PRESENTATION

CLINICAL PRESENTATION: Myelodysplastic Syndromes

General

- Patients with MDS may develop isolated anemia (hemoglobin less than 11 g/dL [110 g/L; less than 6.83 mmol/L]), neutropenia (less than 1,500 cells/mm^3 [1.5×10^9/L]), or thrombocytopenia (less than 100,000 cells/mm^3 [100×10^9/L]) or multiple peripheral cytopenias
- Patients may be asymptomatic, with cytopenia(s) discovered on complete blood count with differential
- A thorough transfusion history should be obtained upon diagnosis of MDS

Symptoms

- If symptomatic, the patient may report fatigue, lethargy, malaise, palpitations, dyspnea on exertion, exercise intolerance, or other symptoms associated with hypoxia secondary to anemia
- Patients may have symptoms of infection, including cough or dysuria
- Patients may present with complaints of easy bruising or bleeding

Signs

- Pallor, tachycardia, or tachypnea related to anemia
- Fever, chills, rigors caused by infection and immune dysfunction
- Petechiae, bruising, epistaxis, gingival bleeding, excessive vaginal bleeding, bruising, or hematuria caused by thrombocytopenia

Laboratory Tests

- Complete blood count with differential
- Anemia often is macrocytic or normocytic with a low reticulocyte index
- Serum vitamin B_{12}, red blood cell (RBC) folate, and copper levels
- Testing for the human immunodeficiency virus (HIV)
- Serum thyroid-stimulating hormone

- Serum erythropoietin (EPO) level
- Serum ferritin, iron, and total iron-binding capacity
- Peripheral blood smear
- Lactate dehydrogenase level

Other Diagnostic Tests

- Bone marrow biopsy and aspirate: morphologic examination, cytochemical staining, immunophenotyping, and cytogenetics (chromosome analysis)
- Consider MDS-relevant molecular genetics testing

Criteria for Diagnosis

- Stable cytopenia for at least 6 months (2 months if accompanied by a specific karyotype associated with MDS or bilineage dysplasia)
- Exclusion of other causes of cytopenia or dysplasia
- One of the following:
  1. Dysplasia (more than 10% in one or more of three major bone marrow lineages)
  2. Blast cell count of 5% to 19%
  3. Specific MDS-associated karyotype (eg, del(5q), del(20q), +8, or del(7q))

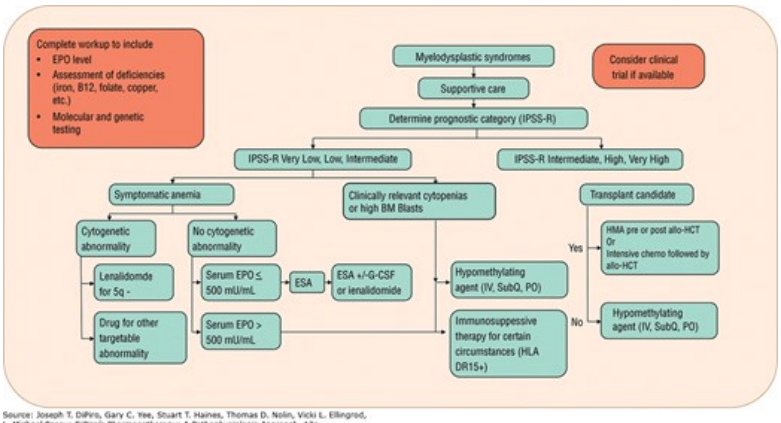
Data from Reference 34.

TREATMENT

Treatment of MDS has rapidly evolved during the past two decades following discoveries in disease biology, new research that predicts the natural history of the disease and response to a given therapy, and new treatment strategies such as molecularly guided therapy and lenalidomide (see Fig. e160-1).[2]

FIGURE e160-1

Myelodysplastic syndrome treatment algorithm. (HMA, hypomethylating agent; HCT, hematopoietic cell transplant.)



Treatment of MDS uses a risk-adapted approach that considers disease- and host-related factors. Patients are classified as lower-risk or higher-risk based on a prognostic system, such as the IPSS-R. In addition, host factors should be considered. Clinicians should recognize that the clinical course of MDS is not stable. The MDS may progress and patient comorbidities or symptoms may change; either of these changes may necessitate a change in treatment strategy. In general, therapy for MDS is palliative and the only curative treatment available is allogeneic HSCT. Enrollment in a suitable clinical trial is always a viable approach.

6 Overall goals of therapy for MDS are to (1) change the natural history of the disease (ie, delay disease progression), (2) reduce the number of RBC transfusions, and (3) improve quality of life.[34] These goals of treatment may vary with disease-related factors and patient factors including age, organ function, performance status, patient preference, and presence of symptoms related to myelodysplasia. When selecting treatment for MDS, the clinician should carefully consider comorbidities. Patients with extensive, life-limiting comorbidities or who are asymptomatic at diagnosis may warrant supportive care alone. Careful interpretation is necessary when comparing the results of clinical trials in MDS to determine treatment because baseline patient characteristics, prognostic scores, and response criteria vary widely. All patients with MDS should receive supportive care, including clinical monitoring, psychosocial support, and quality-of-life assessment.

Lower-Risk MDS Patients

The primary goal of therapy is hematologic improvement for lower-risk patients (IPSS low-, intermediate-1 risk; or IPSS-R very low, low, and intermediate; or WPSS very low, low, and intermediate).[2] Pharmacotherapy to treat lower-risk MDS includes immunomodulating agents, erythropoiesis-stimulating agents (ESAs) with or without growth factor support, immunosuppressive therapy, and hypomethylating agents.

Immunomodulating Agents

7 Lenalidomide is an analog of thalidomide and selectively suppresses del(5q) clones by inducing ubiquitination of the haplodeficient casein kinase 1A1 (CK1α), resulting in CKα1 degradation and erythroid growth arrest.[35] CKα1 is a kinase that is located on chromosome arm 5q. Cells that are haplodeficient, or deletion 5q, are more susceptible to this degradation process. Thus, lenalidomide should be considered in patients with MDS that harbors a del(5q) clone. Thalidomide and lenalidomide are immunomodulating drugs, frequently referred to as *IMiDs*. Thalidomide was discovered to possess anti-inflammatory, antiangiogenic, and antiapoptotic properties, prompting its investigation as a potential treatment for MDS. Initial response rates were encouraging, but low complete response rates and high rates of discontinuation because of intolerable adverse drug reactions have limited thalidomide's use in MDS.

Lenalidomide is structurally similar to thalidomide but offers a distinct safety profile and potentially enhanced therapeutic effects. Compared with thalidomide, lenalidomide causes less fluid retention, peripheral neuropathy, thrombosis, and constipation but more frequently induces neutropenia and thrombocytopenia. Pruritus, rash, diarrhea, and hypothyroidism have been reported with lenalidomide use but seldom require treatment discontinuation. Lenalidomide undergoes substantial renal elimination, and dose reduction in patients with renal insufficiency is recommended to decrease the likelihood of significant bone marrow suppression. Treatment-emergent thrombocytopenia and neutropenia during lenalidomide therapy are associated with response in low-risk MDS patients.[36] Careful consideration is necessary before reducing the dose or holding lenalidomide treatment in low-risk MDS patients who develop myelosuppression. Lenalidomide is a known teratogen. As such, its manufacturer has limited distribution of lenalidomide according to its FDA-approved risk evaluation and mitigation strategy (REMS).

Lenalidomide has been evaluated in several clinical trials. An uncontrolled trial of lenalidomide in 43 MDS patients reported a 56% overall response rate and 62% rate of transfusion independence. Patients with a clonal deletion of chromosome 5q had a 83% complete response rate.[37] A subsequent phase II trial of patients with 5q deletion and transfusion-dependent anemia evaluated lenalidomide 10 mg orally once daily. Cytogenetic remission was seen in 45% of patients with 67% achieving transfusion independence.[23] The median time-to-response was 4 weeks. The results of this pivotal trial led to FDA approval of lenalidomide for the treatment of low-risk MDS in patients with a 5q deletion. Nearly 8 years later, long-term follow-up of patients enrolled in these phase II trials shows longer survival for those who achieved transfusion independence for at least 8 weeks as compared with nonresponders.[37]

A phase III randomized, placebo-controlled study of lenalidomide in low- and intermediate-1-risk MDS patients with a deletion 5q compared the efficacy and safety of lenalidomide 10 mg daily for 21 of 28 days or 5 mg daily with placebo in transfusion-dependent patients with a primary endpoint of transfusion independence for at least 26 consecutive weeks.[38] Transfusion independence was significantly improved in both the lenalidomide 10-

and 5-mg groups, 56% and 43%, respectively, versus placebo at 6%. The lenalidomide 10-mg group showed significantly better transfusion independence for patients with baseline erythropoietin (EPO) levels greater than 500 mU/mL (U/L). Cytogenetic remission was achieved in 50% and 25% of the patients treated with lenalidomide 10 and 5 mg, respectively. Overall survival was not significantly different between groups, although this may reflect the crossover of more than 80% of placebo patients beginning at week 16. Patients with either isolated deletion 5q or a single additional cytogenetic abnormality were less likely to progress to AML at 24% and 21%, respectively, versus the 47% rate of progression observed in patients with two or more additional abnormalities. Further subgroup analyses showed that patients who achieved transfusion independence for greater than 182 days had an improvement in overall survival for lenalidomide-treated patients at either dose level.[2,34]

Lenalidomide has also been studied in a phase II trial of 214 patients with lower-risk MDS without 5q deletions. Transfusion independence was achieved in 26% of patients who received lenalidomide after a median of 4.8 weeks, and 43% had hematologic improvement by IWG criteria.[39] The response rate to lenalidomide is lower in patients with higher-risk MDS and those without a 5q deletion but the drug may still be considered for patients who do not respond to initial therapy.[34]

Lenalidomide may be used to restore or increase response to EPO.[40] A phase III trial randomized 195 patients to receive either lenalidomide + EPO or lenalidomide alone to determine if lenalidomide can restore hemoglobin response to EPO. All patients had either EPO refractory or a low probability of benefit from EPO, lower risk, non-deletion 5q MDS.[41,42] After four cycles of treatment, the major erythroid response rate was significantly higher in the combination arm than in the monotherapy arm. Major erythroid response was largely defined as transfusion independence and sustained rise in hemoglobin. The responses to the combination treatment were durable with a median duration of 23.8 months.

Lenalidomide may be associated with secondary malignancies. Evaluation of patients from two clinical trials treated with lenalidomide and who had del(5q) low- or intermediate-1-risk MDS were compared to outcomes with a registry-based cohort of untreated patients with RBC transfusion-dependent patients with del(5q) low- or intermediate-1-risk MDS. The 2-year overall survival probabilities were 89.9% in the lenalidomide cohort versus 74.4% in the untreated MDS cohort. The risk of AML progression was similar in both cohorts. The authors concluded that lenalidomide treatment does not increase the risk of AML progression, but instead provides a possible survival benefit in RBC transfusion-dependent patients with del(5q) low- or intermediate-1-risk MDS.[2,34]

About 5% of MDS exhibits mutations in isocitrate dehydrogenase (IDH1 and IDH2).[34] Oral IDH1 and IDH2 inhibitors are available for the treatment of acute leukemias, and work by decreasing intracellular levels of 2-hydroxygluterate to induce cell differentiation and decrease numbers of malignant cells.[43] Studies are ongoing to evaluate the activity of IDH1 and IDH2 inhibitors for MDS, particularly in the combination setting. Therapy selection based on specific mutations is becoming more prevalent in the treatment of all malignancies.

Growth Factors

As the goal of therapy for lower-risk MDS is hematologic improvement, treatment is based on transfusion needs. Patients without symptoms of anemia are typically observed, but further investigation is warranted if symptoms of anemia are present (ie, indicating a possible transfusion need). The serum EPO level can determine whether or not a patient is a candidate for ESAs. For example, patients with lower-risk MDS and symptomatic anemia who have a serum EPO level ≤500 mU/mL (U/L) are likely candidates for an ESA with or without growth factor support.[34]

EPO is a protein produced by the kidney in response to hypoxia that stimulates the proliferation and differentiation of erythroid cells. Anemic patients with MDS may have either a lower than expected endogenous serum EPO level relative to the degree of anemia present or an elevated EPO level. The mechanism of action of recombinant ESAs in MDS is not clear, but exogenous EPO may stimulate a normal clone of cells that is unresponsive to low endogenous levels of EPO, stimulate a dysplastic clone to differentiate that is less responsive to endogenous EPO, or induce apoptosis. An immunomodulatory effect of EPO, G-CSF, or GM-CSF has been proposed.

Unlike some solid tumors, no detrimental effects on overall survival or progression to leukemia attributed to the use of ESAs have been noted in patients with MDS.[44] Treatment with ESAs alone results in hematologic improvement and transfusion independence in low- and intermediate-1-risk patients. Two meta-analyses have evaluated the efficacy of ESAs in MDS. The first analysis, which included 2,106 patients from 59 studies reported between 1990 and 2005, found a hemoglobin response of about 30% based on the definition of hemoglobin response in the original publication.[45] A subsequent meta-analysis of studies reported from 1990 to 2006 that used International Working Group (IWG) criteria to define erythroid response (an

increase in hemoglobin of 2 g/dL [20 g/L; 1.24 mmol/L] or transfusion independence). This report included 30 studies with 925 patients with MDS and found an overall erythroid response rate of 58% in patients receiving ESAs.[46] The latter report also suggests that EPO and darbepoetin can be used interchangeably for the management of MDS based on similar response rates achieved. The higher response rate compared with the previous meta-analysis likely reflects the inclusion of a higher proportion of patients most likely to respond to ESAs.

Patients with lower-risk MDS who have a serum EPO level less than 500 mU/mL (U/L) and a history of receiving fewer than 2 Units of RBC transfusions per month have the best chance of responding to ESAs.[34] The EPO doses required to achieve a response in MDS are higher than those used to treat renal causes of anemia, in the range from 40,000 to 60,000 Units subcutaneously 2 to 3 times/week. Darbepoetin doses ranging from 100 to 300 µg subcutaneously weekly or every other week have also been used for MDS management.[46] Doses should be titrated up or down, as clinically indicated, to achieve a hemoglobin level of 10 to 12 g/dL (100-120 g/L; 6.21-7.45 mmol/L).[34] Additionally, patients should receive at least 8 weeks of therapy before doses are adjusted or before patients are considered nonresponders because response to ESAs in MDS can be delayed.[34] The median response duration for ESAs in MDS is 1 to 2 years, and the ESA should be discontinued if there is no benefit or the response wanes.

Several trials report that the addition of G-CSF to ESAs improves hematologic response. A large phase III randomized controlled trial of ESAs in MDS compared EPO with or without G-CSF to best supportive care in 110 patients.[47] At 4 months, 34% of patients receiving EPO had an erythroid response by IWG 2006 criteria compared with 5.8% of patients receiving placebo. A total of 47% of patients had a major erythroid response when EPO doses were escalated or filgrastim was added. Patients with refractory anemia with ringed sideroblasts (RARS) were most likely to respond to the addition of filgrastim. No difference in overall survival or leukemic evolution was observed between patients receiving EPO compared with best supportive care after a median follow-up period of 5.8 years, but the study was not powered to determine differences in these outcomes.

A subsequent phase II study treated 99 patients with darbepoetin alfa 500 µg every 2 weeks subcutaneously for 12 weeks; nonresponders at 12 weeks continued the same darbepoetin regimen with the addition of filgrastim 300 µg twice weekly for an additional 12 weeks.[48] At 12 weeks, 48% of patients had a response according to IWG 2006 criteria, improving to 56% at 24 weeks after 40 of the nonresponders had filgrastim added to darbepoetin.

A meta-analysis of 15 published trials was performed to compare the erythroid response in patients who received EPO as a single agent with those who received EPO plus G-CSF or GM-CSF.[34,46] The overall erythroid response was 49%, 50.6%, and 64.5% for patients who received standard EPO (30,000-40,000 Units/week), standard EPO plus G-CSF or GM-CSF, or high-dose EPO (60,000-80,000 Units/week), respectively. The authors concluded that higher doses of single-agent EPO are more effective than standard doses alone or in combination with G-CSF or GM-CSF. However, a significantly higher proportion of transfusion-dependent patients were enrolled in the trials of combination therapy compared with the other two treatment groups which could have negatively impacted the outcomes.

Some, but not all, studies have shown that patients who respond to ESAs have improved quality of life. Although EPO, with or without G-CSF, does not improve overall survival, it does not shorten overall survival or time-to-development of leukemia and may decrease the need for RBC transfusions and improve quality of life. ESA therapy is well tolerated, and the National Comprehensive Cancer Network (NCCN) guideline recommends a trial in lower-risk patients who have a serum EPO level less than 500 mU/mL (U/L) and a limited transfusion history to target a hemoglobin of 10 to 12 g/dL (100-120 g/L; 6.21-7.45 mmol/L).[34]

Luspatercept is a novel erythroid maturation agent that was recently FDA-approved for anemia due to MDS with ring sideroblasts or myelodysplastic/myeloproliferative neoplasms with ring sideroblasts and thrombocytosis. This includes patients with very low to intermediate risk MDS. Luspatercept is indicated for patients who have failed ESAs and require two or more RBC transfusions over an 8-week period.[49] Luspatercept binds to endogenous transforming growth factor-beta (TGF-β) ligands, which reduces SMAD2 and SMAD3 signaling, and ultimately increases differentiation and proliferation of RBC precursors. In the MEDALIST phase III, double-blind, randomized trial, patients received either luspatercept subcutaneously every 3 weeks or placebo. Dosing of this agent started at 1 mg/kg subcutaneously every 3 weeks for two doses, and if minimal response, the dose can be increased every two cycles (6 weeks) to a maximum dose of 1.75 mg/kg. Transfusion independence was achieved in 38% of the study group versus 13% in the placebo group. The drug was generally well tolerated, with fatigue, diarrhea, asthenia, nausea, and dizziness most commonly reported. The incidence of adverse drug reactions decreased over time.[49]

Thrombopoietin is a hormone synthesized in the liver and secreted into the systemic circulation, where it binds to thrombopoietin receptors on stem cells, progenitor cells, and platelets, resulting in increased platelet production. Romiplostim and eltrombopag are novel drugs that stimulate the thrombopoietin receptor similar to endogenous thrombopoietin. Both agents are FDA-approved for patients with chronic idiopathic

thrombocytopenic purpura and eltrombopag is also indicated for use in chronic hepatitis C–associated thrombocytopenia and severe aplastic anemia.

A randomized, placebo-controlled trial of romiplostim to manage thrombocytopenia in MDS was stopped early in 2011 because of safety concerns regarding the potential for transient increases in blast cell counts and the risk for progression to AML; 6% of romiplostim patients developed progression to AML compared with 2.4% of placebo patients.[50] A warning about the risk for progression from MDS to AML, potential for an increase in blast percentage without progression to AML, and a limitation of use noting romiplostim is not indicated for use in MDS were subsequently included in the romiplostim label. Only 56 of a planned 250 patients completed the 58-week study; longer follow-up shows no difference in the risk for progression to AML or overall survival. The study design limits the ability to detect a true risk for progression to AML to romiplostim.

A multicenter phase I/II trial evaluated the safety and tolerability of eltrombopag for the treatment of thrombocytopenia in adult patients with advanced MDS, sAML, or *de novo* AML.[51] Patients were randomized to once daily eltrombopag or placebo. In total, 98 patients participated in the study. Drug-related adverse drug reactions of grade 3 or higher were reported in 9% of participants in the eltrombopag arm versus 12% in the placebo arm. Increases in the percentage of peripheral blasts did not differ significantly between groups. The NCCN guidelines recommend a TPO agent only in MDS patients with severe thrombocytopenia.[34] Further studies of TPO agents investigating the risk of progression to AML and the benefit in patients with MDS are warranted.

Immunosuppressive Therapy

9 A subset of lower-risk MDS patients respond well to immunosuppressive agents. Immunosuppressive agents that modulate effector T-cells, including antithymocyte globulin (ATG), cyclosporine, and corticosteroids have been evaluated in patients who have hypoplastic MDS with a disease pathobiology similar to aplastic anemia. The National Institutes of Health has developed an algorithm to predict response to immunosuppressive therapy based on age younger than 60 years, hypocellular marrow, refractory anemia of short duration, trisomy 8 as the sole cytogenetic abnormality, and HLA DR15 positive expression.[31] ATG, with or without cyclosporine, has been investigated primarily in patients with intermediate-1-risk and low-risk MDS. Treatment with ATG may not be beneficial for all patients because of the potential for infectious complications and serum sickness. Most studies have used equine ATG at a dose of 40 mg/kg/day IV for 4 consecutive days with corticosteroids to prevent serum sickness complications.[31,52] A retrospective evaluation of patients enrolled in clinical trials at the National Institutes of Health demonstrated that the combination of equine ATG and cyclosporine was associated with response to therapy compared with either agent administered alone.[53] Responses generally occur within 4 months, and about one-third of previously transfusion-dependent patients achieve durable transfusion independence.[31,52] Rabbit ATG has also been evaluated in daily doses ranging from 2.5 to 3.75 mg/kg/day administered IV for 4 to 5 consecutive days.[54-56] Response rates are similar and treatment with either horse or rabbit ATG is reasonable.

A survival benefit from therapy with ATG has not been demonstrated, despite clinical trials of various regimens including both formulations plus cyclosporine or corticosteroids, with or without hematopoietic growth factor support. A phase III randomized controlled trial compared equine ATG and cyclosporine versus best supportive care in all IPSS risk categories.[57] At 6 months, 29% of patients achieved a hematologic response in the immunosuppressive therapy arm compared with 9% of those receiving best supportive care, but no difference was seen in overall, leukemia-free, or 2-year transformation-free survival. Notably, these patients were not evaluated for HLA DR15, and nearly 25% of patients in each group had undetermined risk, intermediate-2-risk, or high-risk IPSS.

Hypomethylating Agents (HMA)

Azacitidine and decitabine are nucleoside analogs structurally similar to cytosine and capable of being incorporated into DNA in place of cytosine. When these agents incorporate into DNA, substitution of carbon for nitrogen at the 5′ position prevents methylation by DNA methyltransferase. As a result, DNA methylation is decreased, and genes previously silenced by aberrant hypermethylation are activated. In vitro studies have confirmed that these agents can promote the reexpression of previously silenced genes.[24] The activity of both agents is concentration and time dependent, and trials are ongoing to evaluate the optimal dose, route, schedule, and duration of therapy.

The median time-to-response with DNA hypomethylating agents is 3 to 4 months.[2] Long-term follow-up of high-risk MDS patients who responded to azacitidine therapy reported the median time-to-first response was two cycles, and 91% of responding patients achieved their first response within six cycles. The first response was the best response in 52% of patients; the remaining 48% did not achieve their best response until a median of three

additional cycles beyond their first response.[34] Experts recommend continuing therapy until evidence of disease progression or unacceptable toxicity even in patients who only achieve stable disease.[2,34]

The primary dose-limiting toxicity of both azacitidine and decitabine is myelosuppression, including leukopenia, granulocytopenia, and thrombocytopenia. Febrile neutropenia and other infectious complications have been reported with azacitidine and decitabine.[58,59] Nausea and vomiting may occur and antiemetic prophylaxis is recommended. Azacitidine-induced erythema at the site of subcutaneous injection may occur and can be minimized with the use of cold compresses. Rare hepatotoxicity is reported after either azacitidine or decitabine. Hypomethylating agents should be used cautiously in patients with an estimated glomerular filtration rate of less than or equal to 29 mL/min/1.73 m^2. Pharmacokinetics of a single cycle in this population do not demonstrate significant variability in area-under-the-curve or maximum observed plasma concentration, but cumulative dosing may increase the risk of grade 3 or 4 myelosuppression, necessitating cycle delays and dose reductions.

It remains unclear if the degree of DNA methylation at baseline or the level of demethylation response predicts success and survival after treatment. Higher levels of methylation correlate with shorter median overall survival and progression-free survival. The degree of methylation at baseline did not predict response to decitabine. Mutations in *TET2* likely affect the global methylation level, but changes in methylation status as a result of treatment have not yet been evaluated.[60] Methylation levels are not routinely incorporated into clinical decision making for MDS therapy at this time.

Azacitidine activity in MDS has been evaluated in a phase III, multicenter, randomized trial of patients with any classification of MDS based on FAB criteria.[59] Patients in lower-risk categories of MDS, including refractory anemia and RARS, were required to meet additional criteria for significant bone marrow dysfunction. A total of 191 patients were randomized to treatment with either supportive care alone or supportive care plus azacitidine 75 mg/m^2 subcutaneously once daily for 7 days, repeated every 28 days. Hematopoietic growth factor support was not permitted. Responses based on Cancer and Leukemia Group B criteria occurred in 60% of patients in the azacitidine group compared with 5% in the supportive care alone group. Almost half of the patients previously transfusion dependent who received azacitidine became transfusion independent. Although the rate of progression to AML was significantly lower with azacitidine compared with supportive care alone, azacitidine did not significantly improve overall survival. A quality-of-life analysis identified a significant advantage for azacitidine therapy compared with supportive care alone, including improvements in physical functioning, fatigue, dyspnea, psychosocial distress, and affect.[61]

Decitabine was also evaluated in a multicenter, randomized phase III trial of patients diagnosed with MDS by FAB criteria.[58] Patients were required to have an IPSS risk of intermediate-1 or greater and two-thirds of patients had intermediate-2- or high-risk MDS. A total of 170 patients were randomized to either supportive care alone or supportive care plus treatment with decitabine 15 mg/m^2 by IV infusion every 8 hours for 3 days repeated every 6 weeks. In contrast to the azacitidine trial, hematopoietic growth factor support was allowed. The overall response rate by IWG criteria was 17% in the decitabine group compared with 0% in the supportive care group. Thirteen percent of patients who received decitabine experienced hematologic improvement compared with 7% who received supportive care alone. Time-to-progression to AML or overall survival was not significantly different between groups. The patients with known clonal abnormalities at baseline who underwent follow-up cytogenetic evaluation were noted to have a complete cytogenetic response of 35% with decitabine compared with 10% in the supportive care arm. Decitabine also improved quality-of-life measures, including global health status, fatigue, and dyspnea.

Azacitidine dosing strategies have been evaluated in a trial of 151 lower-risk MDS patients.[62] Patients were randomized to receive azacitidine 5-2-2 (75 mg/m^2/day subcutaneously for 5 days followed by 2 days of rest [to account for a weekend] followed by azacitidine 75 mg/m^2/day subcutaneously for 2 more days) versus azacitidine 5-2-5 (50 mg/m^2/day subcutaneously for 5 days followed by 2 days of rest [to account for a weekend] followed by azacitidine 50 mg/m^2/day subcutaneously for 5 more days) versus azacytidine 5 (75 mg/m^2/day subcutaneously for 5 days); all strategies were administered every 4 weeks for six cycles. Hematologic improvement was noted in 44%, 45%, and 56%, respectively. Further, RBC transfusion independence was observed in 50%, 55%, and 64%, respectively. The authors concluded that all three dosing strategies for azacitidine had similar outcomes to standard FDA-approved dosing.

To understand dosing strategies in low-risk MDS further, one study evaluated low-dose azacitidine versus low-dose decitabine.[63] In that study, azacitidine 75 mg/m^2 was administered intravenously or subcutaneously every 24 hours for 3 days. Decitabine 20 mg/m^2 was administered IV every 24 hours for 3 days. Cycles for each agent were every 28 days. Overall response and cytogenetic response rates were higher for decitabine as compared with azacitidine. No significant difference in event-free survival was observed.

Higher-Risk MDS Patients

The primary goal of pharmacotherapy in higher-risk MDS is to change the natural history of MDS. DNA hypomethylating agents may prolong overall survival, but allogeneic HSCT remains the only curative option for patients. Because most patients with MDS are not candidates for HSCT, less-toxic therapeutic modalities are being evaluated to improve quality of life and disease-free survival.

Immunomodulating Agents

The activity of lenalidomide in low-risk MDS patients prompted its evaluation in patients with higher-risk MDS with 5q deletion. A phase II trial of lenalidomide in patients with higher-risk MDS with a 5q deletion and other cytogenetic abnormalities reported responses by IWG 2006 criteria in 27% of patients. Significant myelosuppression was reported and most patients required hospitalization.[64] Patients with thrombocytopenia or additional cytogenetic complexity progressed rapidly despite lenalidomide therapy.

Hypomethylating Agents

Azacitidine has been evaluated in patients with higher-risk MDS. In a randomized controlled trial of 191 patients with MDS, azacitidine 75 mg/m^2/day subcutaneously for 7 days in 28 day cycles was compared to supportive care. The median time-to-leukemic transformation or death was 21 months for azacitidine versus 13 months for supportive care. Transformation to AML occurred as the first event in 15% of those receiving azacitidine compared with 38% receiving supportive care.[59] Data analysis, which removed the cross-over effect of the trial, determined an additional 18 months for azacitidine versus 11 months for supportive care. A subsequent analysis combined the results of three clinical trials of azacitidine in MDS and used WHO diagnostic criteria and IPSS prognostication.[65] These trials tested azacitidine 75 mg/m^2/day administered either intravenously or subcutaneously daily every 28 days. The overall response was 60%. The median number of cycles to first response was three and 90% of responses were observed by cycle 6. Azacitidine did not increase the risk of infection or bleeding.

An open-label, randomized, phase III study compared azacitidine with a conventional care regimen in patients with higher-risk MDS.[2,34] Before randomization, treating physicians selected supportive care alone, low-dose cytarabine, or AML-type induction as the conventional care regimen for a given patient if randomized to the conventional care arm. Of the 340 patients receiving treatment, 175 received azacitidine, 102 received best supportive care, 44 received low-dose cytarabine, and 19 received AML-type induction. At 2 years, 51% of azacitidine patients were alive compared with 26% of patients who received a conventional care regimen, and median overall survival was prolonged by 9 months. This is the only randomized controlled study to demonstrate that therapy improves overall survival in MDS.

In an attempt to better define which patients are most likely to respond to azacitidine, Itzykson and colleagues identified four factors that independently predicted overall survival in a cohort of 282 higher-risk MDS patients who received azacitidine for a median of six cycles in a compassionate use study.[2,34] Each factor was assigned a score: performance status greater than or equal to 2 (1 point), intermediate- and poor-risk cytogenetics (1 and 2 points, respectively), presence of circulating blasts (1 point), and RBC transfusion dependency of at least 4 Units within 8 weeks (1 point). Median overall survival was not reached in the low-risk (0 point), 15 months in intermediate-risk (1-3 points), and 6.1 months in high-risk (4-5 points) patients. This prognostic scoring system was independently validated in the azacitidine cohort of another study.

Decitabine has also been compared with best supportive care in a phase III trial of 233 intermediate- or high-risk MDS patients older than 60 years who were ineligible for intensive chemotherapy.[66] Decitabine was more active than best supportive care, with a complete and partial response rate of 13% and 6%, respectively, versus 0% for best supportive care. Median progression-free survival was significantly improved with decitabine compared with supportive care at 6.6 months versus 3 months, respectively. Progression to AML at 1 year was significantly reduced with decitabine to 22% versus 33% in the best supportive care arm. However, unlike the trial with azacitidine, no overall survival benefit was observed. Decitabine did improve quality-of-life measures of fatigue and physical functioning. Another phase III trial evaluated decitabine versus best supportive care and demonstrated a response rate of 17% versus 0%, but this trial used decitabine 15 mg/m^2/day intravenously every 8 hours for 3 days as part of 6-week cycles.[58] This dose differs from the FDA-approved dose.

These pivotal trials for azacitidine and decitabine led to the approval of both agents for the treatment of patients with MDS. However, the FDA-approved administration schedules for decitabine were inconvenient for many cancer centers whose outpatient clinics were not open extended hours or on weekends, necessitating hospitalizations. A more convenient regimen for decitabine (20 mg/m^2 by intravenous infusion daily for 5 consecutive

days every 4 weeks) demonstrated similar response rates and adverse events to the traditional regimen.[67] In early 2010, the FDA granted approval for this alternative dosing regimen.

Oral decitabine with cedazuridine was FDA-approved for use in MDS in July 2020. Hypomethylating agents, specifically decitabine and azacitidine, are rapidly inactivated by cytidine deaminase in the gastrointestinal tract when given orally. Cedazuridine inhibits cytidine deaminase and allows for increased decitabine exposure with the oral route.[68] In a phase II cross-over trial, the oral formulation of decitabine 35 mg with cedazuridine 100 mg daily for 5 days was compared with standard-dose decitabine 20 mg/m^2 intravenously daily for 5 days each of a 28-day cycle (note the flat-dose of the oral formulation, rather than BSA or weight-based dosing). Patients had intermediate 1 or 2, or high-risk MDS by the IPSS. This trial demonstrated similar pharmacokinetic and pharmacodynamic outcomes with the oral and intravenous approaches. Clinical responses were observed in 60% of the 80 study patients, including a complete response rate of 21%. Cedazuridine/decitabine tablets should not be taken within 2 hours before or after food, and premedication with an antiemetic is recommended.[69] The current NCCN guidelines list oral decitabine and cedazuridine as a substitute for intravenous decitabine, regardless of MDS prognostic category.[34]

Despite some activity with both hypomethylating agents used separately, sequencing decitabine after azacitidine failure is not effective. A retrospective study evaluated 25 MDS and AML patients with disease progression or lack of response to azacitidine who went on to receive decitabine.[2,34] Five patients demonstrated stable disease with decitabine but no patient achieved a response. Thus, higher-risk MDS patients who fail hypomethylating therapy may require an alternative therapeutic intervention with a different mechanism of action or participate in a clinical trial.

Preliminary results of an oral azacitidine formulation given for 14 or 21 days have been published. The extended dosing strategy results in sustained demethylation throughout the entire treatment cycle. An ongoing phase III trial of oral azacytidine in lower-risk MDS with significant cytopenias should provide more definitive information on its place in therapy.[70]

Another strategy for patients with treatment-naïve high-risk MDS is the combination of azacitadine and venetoclax. Venetoclax is an oral B-cell lymphoma (BCL-2) inhibitor.[71] BCL-2 is an anti-apoptotic protein that mediates tumor cell survival and is overexpressed in several hematologic malignancies. Although new to the MDS landscape, venetoclax has demonstrated activity in chronic lymphocytic leukemia, acute leukemias, and lymphomas. An ongoing open-label, phase Ib trial provided venetoclax at escalating doses for 14 days and azacitidine 75 mg/m^2/day administered subcutaneously or intravenously days 1 through 7 of each 28-day cycle to patients with high-risk MDS. The overall response rate was 77%, with 42% complete responses. Median duration of response was 14.8 months and progression-free survival was 17.5 months in the 57 patients treated. The incidence of toxicities was high with >grade 3 events in nearly all patients, specifically neutropenia, febrile neutropenia, and thrombocytopenia. These early results compare favorably to single-agent hypomethylating agents, although the combination has not been compared to the standard of care.

10 The lack of a durable survival benefit with existing therapies and the inability to offer HSCT in many patients has led to clinical trials of combination therapy with hypomethylating agents. A phase II/III trial randomized patients with higher-risk MDS and CMML to azacitidine alone, azacitidine plus lenalidomide, and azacitidine plus vorinostat.[72] In this study of 277 patients, the overall response rate was similar (38%, 49%, and 27% for azacitidine, azacitidine plus lenalidomide, and azacitidine plus vorinostat, respectively). The risk of serious adverse events was similar, but patients receiving azacitidine and another drug were more likely to require protocol-based dose modifications. Interestingly, mutations in DNMT3A were associated with a higher overall response rate while SRSF2 mutations were associated with a lower overall response rate. Patients with fewer mutations had a longer duration of response. Further evaluation is required to determine the optimal hypomethylating agent treatment regimen and therapeutic options in higher-risk MDS after hypomethylating agent resistance develops.

Intensive Chemotherapy

Patients with higher-risk MDS may be candidates for intensive chemotherapy with AML-type induction combination chemotherapy regimens. AML-induction combination therapy includes anthracyclines and cytarabine and is described in detail in Chapter 157. This type of intensive chemotherapy in MDS patients is often less successful than *de novo* AML, with complete remission rates of 40% to 60%, a median duration of response of only 10 to 12 months, and a longer period of aplasia.[34] Treatment-related mortality in younger patients with current supportive care measures, including antibiotic and hematopoietic growth factor support, is less than 10%.[2] Patients younger than 55 years who have a favorable karyotype and good performance status are most likely to benefit, but this approach cures fewer than 15% of patients. Intensive chemotherapy can be used as a bridge to allogeneic HSCT to reduce tumor burden and control disease while a suitable donor is found and a referral is made to a transplant center.

Hematopoietic Stem Cell Transplantation

11 Allogeneic HSCT offers potentially curative therapy to patients with MDS who have a suitable donor and are healthy enough for the procedure. With a median age of 76 years at the time of diagnosis, fewer than 5% of MDS patients are referred for allogeneic HSCT.[2,34] Two large retrospective studies indicate that recipient age alone should not be a contraindication to allogeneic HSCT.[73,74] About 30% to 50% of patients with MDS treated with allogeneic HSCT have prolonged disease-free survival.[73] However, 20% to 50% of patients succumb to treatment-related mortality, and many of the remaining patients experience relapse. Outcomes vary based on patient comorbidities, time from diagnosis to transplant, MDS subtype, percentage of bone marrow blasts at the time of HSCT, IPSS risk category, type of conditioning regimen administered before HSCT, and dose and source of stem cells infused.[73] Complications of allogeneic HSCT are described in greater detail in Chapter e163. An HLA-matched allogeneic HSCT is recommended if an appropriate donor is available. An autologous HSCT can be considered in the context of a clinical trial if an allogeneic donor is not available, complete remission is achieved with chemotherapy, and adequate stem cells can be collected.

Because of the high rate of treatment-related mortality in patients with MDS, allogeneic HSCT is not recommended for lower-risk MDS patients because these patients may have stable disease for several years, and early transplant may shorten overall survival. The International MDS Risk Assessment Workshop conducted a decision analysis based on clinical data from two international registries and a single center to identify the optimal time to recommend allogeneic HSCT for patients who have a donor and meet HSCT eligibility criteria.[2,34] The analysis showed that patients with low- and intermediate-1 IPSS risk scores should be closely observed and transplanted at the time of disease progression. Patients with intermediate-2 and high IPSS risk scores should be transplanted soon after diagnosis to confer the greatest benefit from allogeneic HSCT. This model was developed in 2003 and included patients younger than 60 years who had undergone HSCT primarily in the 1990s. It did not incorporate treatment with novel agents for MDS, the use of reduced-intensity conditioning (RIC), or all of the known prognostic factors available and thus may not apply to contemporary patients being evaluated for HSCT.

The WPSS may enhance the selection of patients likely to derive the most benefit from allogeneic HSCT. Based on recent retrospective data, patients with lower-risk disease have low rates of treatment-related mortality and relapse, and a 5-year overall survival rate of 80%.[75] Another retrospective series reported a 4-year overall survival rate of 52% in younger patients with lower-risk refractory anemia after allogeneic HSCT, remarkably similar to the median survival rate for untreated patients with refractory anemia.[2,34] The decision to proceed to allogeneic HSCT and optimal timing should be weighed carefully at diagnosis and subsequently at regular intervals for factors that might influence prognosis, such as degree of cytopenias, cytogenetic abnormalities, transfusion requirement, progression to a higher-risk category, donor availability, comorbidities, and availability of effective nontransplant therapies. Prospective studies comparing allogeneic HSCT with hypomethylating agents or best supportive care are ongoing.

It is difficult to compare the results from patients receiving RIC with myeloablative conditioning regimens because patients treated with RIC regimens tend to be older or have significant comorbid illnesses preventing them from receiving myeloablative conditioning regimens. However, a recent phase III prospective open-label randomized trial compared a busulfan-based RIC with myeloablative conditioning in patients with MDS or sAML.[76] Patients were stratified by donor, age, and blast count. The rate of engraftment and risk of acute and chronic graft-versus-host disease were comparable between both groups. Two-year relapse-free survival and overall survival were similar in the two groups. The selection of the conditioning regimen for HSCT in MDS patients should continue to be patient specific. The only curative therapy for MDS patients is allogeneic HSCT, but most patients lack a suitable donor, are not healthy enough to undergo this intensive therapy, or may not be referred for HSCT because of advanced biologic age despite adequate health and organ function.

Supportive Care

All patients with MDS should receive appropriate supportive care and be encouraged to participate in clinical trials to determine the role of different approaches in the management of MDS.[34] The NCCN guidelines recommend that patients with symptomatic anemia should receive leukoreduced RBC transfusions, and those with bleeding caused by thrombocytopenia or platelet counts below 10,000 cells/mm^3 (10×10^9/L) should receive platelet transfusions.[34] Hematopoietic growth factor support should be considered in patients with refractory, symptomatic cytopenias. Patients with evidence of infection should have an appropriate diagnostic evaluation based on history and physical examination followed by appropriate antimicrobial therapy. Routine antimicrobial or hematopoietic growth factor prophylaxis is not recommended in the absence of repeated infections. Iron chelation may be considered in lower-risk patients and candidates for allogeneic HSCT who have received more than 20 to 30 RBC transfusions in their lifetime

and are expected to continue to require transfusions.[34]

Infection

Patients with MDS may be neutropenic or have functional defects in neutrophils, predisposing them to infection.[21] In MDS, the most frequently isolated organisms are bacteria, and the most common sites of infection are the lungs, urinary tract, and bloodstream. Patients with evidence of infection should have appropriate diagnostic evaluation based on history and physical examination and then appropriate antimicrobial therapy. Neutropenic patients with evidence of infection or fever of unknown origin should receive empiric broad-spectrum, intravenous antibiotics.

Hematopoietic Growth Factors

Filgrastim (G-CSF) and sargramostim (granulocyte-macrophage colony-stimulating factor [GM-CSF]) are colony-stimulating factors that stimulate white blood cell production and may increase circulating neutrophils in 70% to 90% of patients, which may decrease the risk of infection.[77] These agents are not beneficial as chronic monotherapy because they do not reliably prevent infection and have no impact on survival. Filgrastim, sargramostim, or any biosimilar product should only be administered temporarily as monotherapy in the rare neutropenic MDS patient who develops recurrent severe infections. Pegfilgrastim, a long-acting myeloid growth factor, does not have a place in MDS treatment.[34]

Transfusions

Patients generally receive RBC transfusions when they develop signs or symptoms of anemia, including tachycardia, fatigue, or dyspnea, which generally occur when hemoglobin drops below 8 to 10 g/dL (80-100 g/L; 4.97-6.21 mmol/L).[34] Some clinicians use a transfusion threshold of 10 g/dL (100 g/L; 6.21 mmol/L) in patients with significant cardiovascular disease. Platelet transfusions are generally reserved for patients with evidence of bleeding to avoid alloimmunization from repeated platelet transfusions, which leads to refractoriness to donor platelets.

Iron Overload

RBC transfusions are associated with shortened leukemia-free and overall survival times in MDS.[2] It is unclear if this reflects disease severity or is a direct result of iron toxicity. MDS patients receiving RBC transfusions are at higher risk for infections, cardiac, hepatic, and endocrine dysfunction compared with nontransfused MDS patients or the general population without MDS.[78] The role of excess iron is unclear as anemia likely contributes to heart failure and neutropenia to infections.

Prospective clinical trials in MDS demonstrate that iron chelation is able to decrease markers of iron overload.[79-82] Six studies of over 700 patients with MDS receiving deferasirox for iron overload show improvement in hematologic parameters related to chelation with an increase in hemoglobin level ranging from 6% to 45%, an increase in platelet count from 13% to 61%, and in neutrophil count from 3% to 76%.[83] Eight observational studies have assessed the relationship between iron chelation and overall survival in about 1,500 patients with low-risk and intermediate-1-risk patients with MDS. A meta-analysis reported an improvement in overall survival of 61.2 months, with seven of eight studies reporting improvement in overall survival.[83] It is possible that patients who had a better prognosis were more likely to receive iron chelation, which would explain the association between improved survival time and iron chelation. In a cohort of Medicare beneficiaries with MDS, a longer duration of deferasirox use correlated with improved overall survival times, but deferasirox use was not associated with the risk of heart failure or endocrine or renal disease.[2,34] It is hypothesized that iron chelation may lower infection risk, improve the outcome of allogeneic HSCT, and delay leukemic transformation in patients with MDS. A randomized controlled trial comparing deferasirox with placebo in low- and intermediate-1-risk MDS patients with transfusional iron overload with a primary outcome of event-free survival is ongoing.

The potential toxicity, expense, and benefits of iron chelation should be carefully considered before initiating therapy. Deferasirox and deferoxamine are FDA-approved for use in patients with chronic iron overload caused by RBC transfusions. Deferiprone is FDA-approved for patients with transfusional iron overload secondary to thalassemia when current chelation therapy is inadequate. The prescribing information for deferiprone has a black box warning regarding agranulocytosis, which may lead to serious infection and death. The prescribing information for deferasirox has a black box warning describing renal and hepatic impairment and GI hemorrhage; fatalities were reported. These reactions were more frequently observed in patients with advanced age, high-risk MDS, underlying renal or hepatic impairment, or thrombocytopenia (less than 50,000 cells/mm^3 [50×10^9/L]).

Diarrhea may complicate therapy with deferasirox and recommendations for management have been published.

The NCCN guidelines recommend that iron chelation be initiated when greater than 20 RBC transfusions are administered or when serum ferritin levels exceed 2,500 ng/mL (µg/L; 5,620 pmol/L) in patients with lower-risk MDS who have an anticipated survival of at least 1 year or in patients proceeding to allogeneic HSCT.[34] For patients who start on iron chelation therapy due to an elevated ferritin, it is recommended to continue therapy until the ferritin level is <1,000 ng/mL [µg/L; 2,250 pmol/L]).[34] Patients receiving pharmacotherapy for iron chelation should be monitored for gastrointestinal and ocular toxicity, ototoxicity, renal and hepatic dysfunction, and complete blood counts in addition to markers of iron overload.

EVALUATION OF THERAPEUTIC OUTCOMES

Standardized response criteria in clinical trials of MDS enable clinicians to evaluate study outcomes, compare results from different trials, and tailor therapy according to patient or disease characteristics. The IWG for MDS guidelines for response criteria in MDS clinical trials categorize patient responses into categories that correlate with quality of life or morbidity.[2,34] Based on these criteria, the four treatment goals are to change the natural history of the disease, cytogenetic response, hematologic improvement, and improve quality of life. Changes in the WHO classification system and new therapies with novel mechanisms of action, time to response, and likelihood of treatment-related cytopenias have created a need for further refinement of these guidelines. Patients with MDS should have regular follow-up with a history, physical examination, and complete blood counts. The frequency of follow-up varies with the natural history of each patient from weekly to every 6 months.

CONCLUSION

MDS are a heterogeneous group of myeloid stem cell disorders, ranging widely in prognosis and type of treatment. A prognostic scoring system, IPSS-R, can be applied at the time of diagnosis to predict disease progression and treatment selection. Low-risk MDS treatments use monitoring, growth-factor support, hypomethylating agents, and other agents to improve cytopenias. Intermediate- and high-risk MDS have a higher risk of progressing to more aggressive forms, such as AML. Consequently, more aggressive treatment strategies can be considered in younger and more fit patients. Supportive care strategies must be considered in the optimal treatment of the patient with MDS. The need for blood transfusions is common in advanced or end-stage MDS, with the associated risk of iron overload secondary to the transfusions. Patients with MDS are at higher for infections from the disease or its treatment and infections must be treated promptly.

Treatments for MDS are evolving and incorporate more targeted therapies, including lenalidomide, BCL-2 inhibitors, and IDH mutation-directed therapies. Careful consideration of disease- and patient-specific characteristics will lead to more personalized therapies and optimal outcomes.

ABBREVIATIONS

AML	acute myeloid leukemia
sAML	secondary acute myeloid leukemia
ASXL1	additional sex combs like-1
ATG	antithymocyte globulin
CBC	complete blood count
DNA	deoxyribonucleic acid
DNMT3A	DNA-methyltransferase 3A
EPO	erythropoietin or epoetin alfa

ESA	erythropoiesis-stimulating agent
EZH2	enhancer of zest homolog 2
FAB	French-American-British
FDA	Food and Drug Administration
GATA2	GATA binding protein 2
G-CSF	granulocyte colony-stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
HMA	hypomethylating agent
HSCT	hematopoietic stem cell transplantation
IMiD	immunomodulating drug
IPSS	International Prognostic Scoring System
IPSS-R	International Prognostic Scoring System—Revised
IWG	International Working Group
KRAS	Kirsten rat sarcoma gene
LDH	lactate dehydrogenase
MAPK	mitogen-activated protein kinase
MDS	myelodysplastic syndromes
MECOM	MDS1 and EV11 complex locus protein
MLL	mixed lineage leukemia gene
NCCN	National Comprehensive Cancer Network
NF1	neurofibromatosis type 1 gene
NRAS	neuroblastoma rat sarcoma gene
PRBC	packed red blood cells
PTPN11	protein tyrosine phosphatase non-receptor type 11

RARS	refractory anemia with ringed sideroblasts
RIC	reduced-intensity conditioning
RBC	red blood cell
RNA	ribonucleic acid
mRNA	messenger ribonucleic acid
RUNX1	runt-related transcription factor 1 gene
SF3B1	splicing factor 3B subunit 1
SRSF2	serine and arginine rich splicing factor 2
STAG2	stromal antigen 2 gene
TET2	tet methylcytosine dioxygenase 2
TIBC	total iron binding capacity
t-AML	therapy-related AML
t-MDS	therapy-related MDS
TP53	tumor suppressor protein 53
TPO	thrombopoietin
TR-MN	therapy-related myeloid neoplasm
TSH	thyroid stimulating hormone
U2AF1	U2 small nuclear RNA auxiliary factor 1
WHO	World Health Organization
WPSS	World Health Organization Classification-based Scoring System
ZRSR2	zinc finger RNA binding motif serine/arginine risk 2 gene

REFERENCES

1. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the world health organization classification of myeloid neoplasms and acute leukemia. *Blood*. 2016;127:2391–2405. [PubMed: 27069254]

2. Cazzola M. Myelodysplastic syndromes. *NEJM.* 2020;383:1358–1374.

3. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood*. 2012;120:2454–

2465. [PubMed: 22740453]

4. Taylor J, Xiao W, Abdel-Wahab O. Diagnosis and classification of hematologic malignancies on the basis of genetics. *Blood*. 2017;130:410–423. [PubMed: 28600336]

5. National Cancer Institute SEER*Stat software [seer.cancer.gov/seerstat]; 2018.

6. Churpek JE, Pyrtel K, Kanchi KL, et al. Genomic analysis of germ line and somatic variants in familial myelodysplasia/acute myeloid leukemia. *Blood*. 2015;126:2484–2490. [PubMed: 26492932]

7. West AH, Godley LA, Churpek JE. Familial myelodysplastic syndrome/acute leukemia syndromes: A review and utility for translational investigations. *Ann N Y Acad Sci.* 2014;1310:111–118. [PubMed: 24467820]

8. Xie M, Lu C, Wang J, et al. Age-related mutations associated with clonal hematopoietic expansion and malignancies. *Nature Medicine*. 2014;20:1472–1478. [PubMed: 25326804]

9. Jin J, Yu M, Hu C, et al. Pesticide exposure as a risk factor for myelodysplastic syndromes: A meta- analysis based on 1,942 cases and 5,359 controls. *PLoS One*. 2014;9:e110850. [PubMed: 25335083]

10. Iwanaga M, Hsu WL, Soda M, et al. Risk of myelodysplastic syndromes in people exposed to ionizing radiation: A retrospective cohort study of nagasaki atomic bomb survivors. *J Clin Oncol.* 2011;29:428–434. [PubMed: 21149671]

11. Smith SM, Le Beau MM, Huo D, et al. Clinical-cytogenetic associations in 306 patients with therapy- related myelodysplasia and myeloid leukemia: The University of Chicago series. *Blood*. 2003;102:43–52. [PubMed: 12623843]

12. Armitage JO, Carbone PP, Connors JM, et al. Treatment-related myelodysplasia and acute leukemia in non-Hodgkin's lymphoma patients. *J Clin Oncol.* 2003;21:897–906. [PubMed: 12610191]

13. Bennett JM, Kaminski MS, Leonard JP, et al. Assessment of treatment-related myelodysplastic syndromes and acute myeloid leukemia in patients with non-Hodgkin lymphoma treated with tositumomab and iodine i131 tositumomab. *Blood*. 2005;105:4576–4582. [PubMed: 15731177]

14. Czuczman MS, Emmanouilides C, Darif M, et al. Treatment-related myelodysplastic syndrome and acute myelogenous leukemia in patients treated with ibritumomab tiuxetan radioimmunotherapy. *J Clin Oncol.* 2007;25:4285–4292. [PubMed: 17709799]

15. Guidetti A, Carlo-Stella C, Ruella M, et al. Myeloablative doses of yttrium-90-ibritumomab tiuxetan and the risk of secondary myelodysplasia/acute myelogenous leukemia. *Cancer*. 2011;117:5074–5084. [PubMed: 21567384]

16. Lyman GH, Dale DC, Wolff DA, et al. Acute myeloid leukemia or myelodysplastic syndrome in randomized controlled clinical trials of cancer chemotherapy with granulocyte colony-stimulating factor: A systematic review. *J Clin Oncol.* 2010;28:2914–2924. [PubMed: 20385991]

17. Lyman GH, Yau L, Nakov R, et al. Overall survival and risk of second malignancies with cancer chemotherapy and G-CSF support. *Ann Oncol.* 2018;29:1903–1910. [PubMed: 30099478]

18. Ding SX, Chen T, Wang T, et al. The risk of clonal evolution of granulocyte colony-stimulating factor for acquired aplastic anemia: A systematic review and meta-analysis. *Acta Haematol.* 2018;140:141–145. [PubMed: 30253387]

19. Metayer C, Curtis RE, Vose J, et al. Myelodysplastic syndrome and acute myeloid leukemia after autotransplantation for lymphoma: A multicenter case-control study. *Blood*. 2003;101:2015–2023. [PubMed: 12393427]

20. Milligan DW, Kochethu G, Dearden C, et al. High incidence of myelodysplasia and secondary leukaemia in the UK Medical Research Council pilot of autografting in chronic lymphocytic leukaemia. *Br J Haematol.* 2006;133:173–175. [PubMed: 16611308]

21. Fianchi L, Leone G, Posteraro B, et al. Impaired bactericidal and fungicidal activities of neutrophils in patients with myelodysplastic syndrome. *Leuk Res.* 2012;36:331–333. [PubMed: 22177732]

22. Vladareanu AM, Vasilache V, Bumbea H, et al. Platelet dysfunction in acute leukemias and myelodysplastic syndromes. *Rom J Intern Med.* 2011;49:93–96. [PubMed: 22026258]

23. List A, Dewald G, Bennett J, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N Engl J Med.* 2006;355:1456–1465. [PubMed: 17021321]

24. Itzykson R, Fenaux P. Epigenetics of myelodysplastic syndromes. *Leukemia*. 2014;28:497–506. [PubMed: 24247656]

25. Cashen A, Juckett M, Jumonville A, et al. Phase II study of the histone deacetylase inhibitor belinostat for the treatment of myelodysplastic syndrome. *Ann Hematol.* 2012;91:33–38. [PubMed: 21538061]

26. Raza A, Galili N, Smith SE, et al. A phase 2 randomized multicenter study of 2 extended dosing schedules of oral ezatiostat in low to intermediate-1 risk myelodysplastic syndrome. *Cancer*. 2012;118:2138–2147. [PubMed: 21887679]

27. Prebet T, Braun T, Beyne-Rauzy O, et al. Combination of vorinostat and low dose cytarabine for patients with azacitidine-refractory/relapsed high risk myelodysplastic syndromes. *Leuk Res.* 2014;38:29–33. [PubMed: 23953882]

28. Issa JP, Garcia-Manero G, Huang X, et al. Results of phase 2 randomized study of low-dose decitabine with or without valproic acid in patients with myelodysplastic syndrome and acute myelogenous leukemia. *Cancer*. 2015;121:556–561. [PubMed: 25336333]

29. Welch JS, Petti AA, Miller CA, et al. TP53 and decitabine in acute myeloid leukemia and myelodysplastic syndromes. *N Engl J Med.* 2016;375:2023–2036. [PubMed: 27959731]

30. Sauntharajah Y, Nakamura R, Wesley R, et al. A simple method to predict response to immunosuppressive therapy in patients with myelodysplastic syndrome. *Blood*. 2003;102:3025–3027. [PubMed: 12829603]

31. Bejar R, Stevenson KE, Caughey BA, et al. Validation of a prognostic model and the impact of mutations in patients with lower-risk myelodysplastic syndromes. *J Clin Oncol.* 2012;30:3376–3382. [PubMed: 22869879]

32. Malcovati L, Germing U, Kuendgen A, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. *J Clin Oncol.* 2007;25:3503–3510. [PubMed: 17687155]

33. Garcia-Manero G, Shan J, Faderl S, et al. A prognostic score for patients with lower risk myelodysplastic syndrome. *Leukemia*. 2008;22:538–543. [PubMed: 18079733]

34. National comprehensive cancer network clinical practice guidelines in oncology (NCCN guideline). National Comprehensive Cancer Network, Inc 2022;v3.2022. January 13, 2022.

35. Kronke J, Fink EC, Hollenbach PW, et al. Lenalidomide induces ubiquitination and degradation of CK1α in del(5q) MDS. *Nature*. 2015;523:183–188. [PubMed: 26131937]

36. List A, Kurtin S, Roe DJ, et al. Efficacy of lenalidomide in myelodysplastic syndromes. *N Engl J Med.* 2005;352:549–557. [PubMed: 15703420]

37. List AF, Bennett JM, Sekeres MA, et al. Extended survival and reduced risk of AML progression in erythroid-responsive lenalidomide-treated patients with lower-risk del(5q) MDS. *Leukemia*. 2015;29:2452. [PubMed: 26648407]

38. Fenaux P, Giagounidis A, Selleslag D, et al. A randomized phase 3 study of lenalidomide versus placebo in RBC transfusion-dependent patients with low-/intermediate-1-risk myelodysplastic syndromes with del5q. *Blood*. 2011;118:3765–3776. [PubMed: 21753188]

39. Raza A, Reeves JA, Feldman EJ, et al. Phase 2 study of lenalidomide in transfusion-dependent, low- risk, and intermediate-1 risk myelodysplastic syndromes with karyotypes other than deletion 5q. *Blood*. 2008;111:86–93. [PubMed: 17893227]

40. Komrokji RS, Lancet JE, Swern AS, et al. Combined treatment with lenalidomide and epoetin alfa in lower-risk patients with myelodysplastic syndrome. *Blood*. 2012;120:3419–3424. [PubMed: 22936658]

41. List AF, Sun Z, Verma A, et al. Lenalidomide-epoetin alfa versus lenalidomide monotherapy in myelodysplastic syndromes refractory to recombinant erythropoietin. *JCO.* 2021;39(9);1001–1009. doi: 10.1200/JCO.20.01691.

42. Sibon D, Cannas G, Baracco F, et al. Lenalidomide in lower-risk myelodysplastic syndromes with karyotypes other than deletion 5q and refractory to erythropoiesis-stimulating agents. *Br J Haematol.* 2012;156:619–625. [PubMed: 22211483]

43. Dinardo CD, Jabbour E, Ravandi F, et al. IDH1 and IDH2 mutations in myelodysplastic syndromes and role in disease progression. *Leukemia*. 2016;30:980–984. [PubMed: 26228814]

44. Bohlius J, Schmidlin K, Brillant C, et al. Recombinant human erythropoiesis-stimulating agents and mortality in patients with cancer: A meta-analysis of randomised trials. *Lancet*. 2009;373:1532–1542. [PubMed: 19410717]

45. Ross SD, Allen IE, Probst CA, et al. Efficacy and safety of erythropoiesis-stimulating proteins in myelodysplastic syndrome: A systematic review and meta-analysis. *Oncologist*. 2007;12:1264–1273. [PubMed: 17962620]

46. Moyo V, Lefebvre P, Duh MS, et al. Erythropoiesis-stimulating agents in the treatment of anemia in myelodysplastic syndromes: A meta-analysis. *Ann Hematol.* 2008;87:527–536. [PubMed: 18351340]

47. Greenberg PL, Sun Z, Miller KB, et al. Treatment of myelodysplastic syndrome patients with erythropoietin with or without granulocyte colony-stimulating factor: Results of a prospective randomized phase 3 trial by the Eastern Cooperative Oncology Group (e1996). *Blood*. 2009;114:2393–2400. [PubMed: 19564636]

48. Mundle S, Lefebvre P, Vekeman F, et al. An assessment of erythroid response to epoetin alpha as a single agent versus in combination with granulocyte- or granulocyte-macrophage-colony-stimulating factor in myelodysplastic syndromes using a meta-analysis approach. *Cancer*. 2009;115:706–715. [PubMed: 19152429]

49. Fenaux P, Platzbecker U, Mufti GJ, et al. Luspatercept in patients with lower-risk myelodysplastic syndromes. *N Engl J Med.* 2020;382(2):140–151. doi: 10.1056/NEJMoa1908892

50. Giagounidis A, Mufti GJ, Fenaux P, et al. Results of a randomized, double-blind study of romiplostim versus placebo in patients with low/intermediate-1-risk myelodysplastic syndrome and thrombocytopenia. *Cancer*. 2014;120:1838–1846. [PubMed: 24706489]

51. Platzbecker U, Wong RS, Verma A, et al. Safety and tolerability of eltrombopag versus placebo for treatment of thrombocytopenia in patients with advanced myelodysplastic syndromes or acute myeloid leukaemia: A multicentre, randomised, placebo-controlled, double-blind, phase 1/2 trial. *Lancet Haematol.* 2015;2:e417–e426. [PubMed: 26686043]

52. Sauntharajah Y, Nakamura R, Nam JM, et al. HLA-DR15 (DR2) is overrepresented in myelodysplastic syndrome and aplastic anemia and predicts a response to immunosuppression in myelodysplastic syndrome. *Blood*. 2002;100:1570–1574. [PubMed: 12176872]

53. Sloand EM, Wu CO, Greenberg P, et al. Factors affecting response and survival in patients with myelodysplasia treated with immunosuppressive therapy. *J Clin Oncol.* 2008;26:2505–2511. [PubMed: 18413642]

54. Garg R, Faderl S, Garcia-Manero G, et al. Phase II study of rabbit anti-thymocyte globulin, cyclosporine and granulocyte colony-stimulating factor in patients with aplastic anemia and myelodysplastic syndrome. *Leukemia*. 2009;23:1297–1302. [PubMed: 19242494]

55. Stadler M, Germing U, Kliche KO, et al. A prospective, randomised, phase II study of horse antithymocyte globulin vs rabbit antithymocyte globulin as immune-modulating therapy in patients with low-risk myelodysplastic syndromes. *Leukemia*. 2004;18:460–465. [PubMed: 14712285]

56. Komrokji RS, Mailloux AW, Chen DT, et al. A phase II multicenter rabbit anti-thymocyte globulin trial in patients with myelodysplastic syndromes identifying a novel model for response prediction. *Haematologica.* 2014;99:1176–1183. [PubMed: 24488560]

57. Passweg JR, Giagounidis AA, Simcock M, et al. Immunosuppressive therapy for patients with myelodysplastic syndrome: A prospective randomized multicenter phase III trial comparing antithymocyte globulin plus cyclosporine with best supportive care—SAKK 33/99. *J Clin Oncol.* 2011;29:303–309. [PubMed: 21149672]

58. Kantarjian H, Issa JP, Rosenfeld CS, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: Results of a phase III randomized study. *Cancer*. 2006;106:1794–1803. [PubMed: 16532500]

59. Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: A study of the Cancer and Leukemia Group B. *J Clin Oncol.* 2002;20:2429–2440. [PubMed: 12011120]

60. Yamazaki J, Taby R, Vasanthakumar A, et al. Effects of TET2 mutations on DNA methylation in chronic myelomonocytic leukemia. *Epigenetics*. 2012;7:201–207. [PubMed: 22395470]

61. Kornblith AB, Herndon JE 2nd, Silverman LR, et al. Impact of azacytidine on the quality of life of patients with myelodysplastic syndrome treated in a randomized phase III trial: A Cancer and Leukemia Group B study. *J Clin Oncol.* 2002;20:2441–2452. [PubMed: 12011121]

62. Lyons RM, Cosgriff TM, Modi SS, et al. Hematologic response to three alternative dosing schedules of azacitidine in patients with myelodysplastic syndromes. *J Clin Oncol.* 2009;27:1850–1856. [PubMed: 19255328]

63. Jabbour E, Short NJ, Montalban-Bravo G, et al. Randomized phase 2 study of low-dose decitabine vs low-dose azacitidine in lower-risk MDS and MDS/MPN. *Blood*. 2017;130:1514–1522. [PubMed: 28774880]

64. Ades L, Boehrer S, Prebet T, et al. Efficacy and safety of lenalidomide in intermediate-2 or high-risk myelodysplastic syndromes with 5q deletion: Results of a phase 2 study. *Blood*. 2009;113:3947–3952. [PubMed: 18987358]

65. Silverman LR, McKenzie DR, Peterson BL, et al. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: Studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. *J Clin Oncol.* 2006;24:3895–3903. [PubMed: 16921040]

66. Lubbert M, Suciu S, Baila L, et al. Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: Final results of the randomized phase III study of the European Organisation for Research and Treatment of Cancer Leukemia Group and the German MDS Study Group. *J Clin Oncol.* 2011;29:1987–1996. [PubMed: 21483003]

67. Steensma DP, Baer MR, Slack JL, et al. Multicenter study of decitabine administered daily for 5 days every 4 weeks to adults with myelodysplastic syndromes: The alternative dosing for outpatient treatment (ADOPT) trial. *J Clin Oncol.* 2009;27:3842–3848. [PubMed: 19528372]

68. Garcia-Manero G, Griffiths EA, DP Steensma, et al. Oral cedazuridine/decitabine for MDS and CMML: A phase 2 pharmacokinetic/pharmacodynamic randomized crossover study. *Blood*. 2020;136(6):674–683. [PubMed: 32285126]

69. Inqovi PI, Otsuka Pharmaceutical Co., LTD. Japan. 7/2020

70. Garcia-Manero G, Almeida A, Giagounidis A, et al. Design and rationale of the QUAZAR lower-risk MDS (AZA-NDS-003) trial: A randomized phase 3 study of CC-486 (oral azacitidine) plus best supportive care vs placebo plus best supportive care in patients with IPSS lower-risk myelodysplastic syndromes and poor prognosis due to red blood cell transfusion-dependent anemia and thrombocytopenia. *BMC Hematol.* 2016;16:12. [PubMed: 27148452]

71. Garcia JS, Wei AH, Borate U. et al. Safety, efficacy, and patient-reported outcomes of venetoclax in combination with azacytidine for the treatment of patients with higher-risk myelodysplastic syndrome: A Phase Ib Study. *Blood.* 2020;136(suppl 1):55–57.

72. Sekeres MA, Othus M, List AF, et al. Randomized phase II study of azacitidine alone or in combination with lenalidomide or with vorinostat in higher-risk myelodysplastic syndromes and chronic myelomonocytic leukemia: North American Intergroup Study SWOG S1117. *J Clin Oncol.* 2017;35:2745–2753. [PubMed: 28486043]

73. Lim Z, Brand R, Martino R, et al. Allogeneic hematopoietic stem-cell transplantation for patients 50 years or older with myelodysplastic syndromes or secondary acute myeloid leukemia. *J Clin Oncol.* 2010;28:405–411. [PubMed: 20008642]

74. McClune BL, Weisdorf DJ, Pedersen TL, et al. Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. *J Clin Oncol.* 2010;28:1878–1887. [PubMed: 20212255]

75. Alessandrino EP, Della Porta MG, Bacigalupo A, et al. WHO classification and WPSS predict posttransplantation outcome in patients with myelodysplastic syndrome: A study from the Gruppo Italiano Trapianto di Midollo Osseo (GITMO). *Blood*. 2008;112:895–902. [PubMed: 18497321]

76. Kroger N, Iacobelli S, Franke GN, et al. Dose-reduced versus standard conditioning followed by allogeneic stem-cell transplantation for patients with myelodysplastic syndrome: A prospective randomized phase III study of the EBMT (RICMAC trial). *J Clin Oncol.* 2017;35:2157–2164. [PubMed: 28463633]

77. Greenberg P, Taylor K, Larson RA. Phase III randomized multicenter trial of G-CSF vs observation for myelodysplastic syndromes. *Blood*. 1993;82:1. [PubMed: 8324214]

78. Delea TE, Hagiwara M, Phatak PD. Retrospective study of the association between transfusion frequency and potential complications of iron overload in patients with myelodysplastic syndrome and other acquired hematopoietic disorders. *Curr Med Res Opin.* 2009;25:139–147. [PubMed: 19210147]

79. Cermak J, Jonasova A, Vondrakova J, et al. Efficacy and safety of administration of oral iron chelator deferiprone in patients with early myelodysplastic syndrome. *Hemoglobin*. 2011;35:217–227. [PubMed: 21599434]

80. Gattermann N, Jarisch A, Schlag R, et al. Deferasirox treatment of iron-overloaded chelation-naive and prechelated patients with myelodysplastic syndromes in medical practice: Results from the observational studies eXtend and eXjange. *Eur J Haematol.* 2012;88:260–268. [PubMed: 22023452]

81. Greenberg PL, Koller CA, Cabantchik ZI, et al. Prospective assessment of effects on iron-overload parameters of deferasirox therapy in patients with myelodysplastic syndromes. *Leuk Res.* 2010;34:1560–1565. [PubMed: 20615548]

82. List AF, Baer MR, Steensma DP, et al. Deferasirox reduces serum ferritin and labile plasma iron in RBC transfusion-dependent patients with myelodysplastic syndrome. *J Clin Oncol.* 2012;30:2134–2139. [PubMed: 22547607]

83. Mainous AG 3rd, Tanner RJ, Hulihan MM, et al. The impact of chelation therapy on survival in transfusional iron overload: A meta-analysis of myelodysplastic syndrome. *Br J Haematol.* 2014;167:720–723. [PubMed: 25048454]

SELF-ASSESSMENT QUESTIONS

1. Which of the following descriptions has the highest risk for developing MDS based on host characteristics?

   A. An 88-year-old man with a history of non-Hodgkin lymphoma treated with chemotherapy plus radiation

   B. A 21-year-old man with no significant past medical history

C. A 45-year-old woman with a history of rheumatoid arthritis

D. A 7-month-old infant

2. What is the dose-limiting toxicity of azacytidine and decitabine?

A. Nausea and vomiting

B. Mucositis

C. Myelosuppression

D. Hepatotoxicity

3. Significant opportunity exists for pharmacists to play a large role in the treatment of MDS patients. Given the median age of diagnosis for MDS, which medication-related problem is most likely to be indicated for resolution while providing pharmacist care services?

A. Breast feeding contraindications

B. Pregnancy considerations

C. Immunization status

D. Polypharmacy

4. Lenalidomide is associated with a risk evaluation and mitigation strategy (REMS). Why does lenalidomide have a REMS program in place?

A. Complex manufacturing processes

B. Oral chemotherapy

C. Teratogenic

D. Manufactured outside of the United States

5. JV is a 68-year-old male with lower-risk MDS who is being treated with lenalidomide. Unfortunately, JV contracted a gastrointestinal illness associated with significant emesis. JV became dehydrated and went to the emergency room. At the emergency room, his serum creatinine was noted to be elevated to 2.5 mg/dL (221 µmol/L). Which of the following is the most appropriate recommendation at this time?

A. Maintenance intravenous fluids

B. Hold lenalidomide

C. Ondansetron

D. Levofloxacin

6. Lenalidomide is targeted therapy that is most appropriate for which of the following bone marrow results?

A. Del(5q)

B. Normal cytogenetics

C. TP53

D. Complex cytogenetics

7. AK is a 71-year-old female with lower-risk MDS being treated with watch and wait strategy. AK becomes fatigued and her hematologist orders blood

work. Which of the following lab values is needed to proceed with ESA support?

A. Neutrophils <1,000 cells/mm^3 (1×10^9/L)

B. Platelets <50 cells/mm^3 (0.05×10^9/L)

C. EPO level <500 mU/mL (U/L)

D. Hemoglobin <8 g/dL (80 g/L; 4.97 mmol/L)

8. CH is a 57-year-old male with MDS, a hypocellular marrow, and refractory anemia of short duration. Which of the following bone marrow results should be present for the selection of immunosuppressive therapy to treat MDS?

A. TP53

B. Normal cytogenetics

C. Del(5q)

D. Trisomy 8 with HLADR15+

9. TK has lower-risk MDS and is being treated with ATG plus cyclosporine. On day 8, TK develops fever, rigors, and malaise. TK is started on antibiotics. Which of the following is the most appropriate additional recommendation to manage TK?

A. Prednisone

B. Filgrastim

C. Acetaminophen

D. Maintenance intravenous fluids

10. Both azacitidine and decitabine are FDA-approved therapies for MDS. Which of the following outcomes supports the use of azacitidine over decitabine despite the fact that no head-to-head clinical trials are available?

A. Overall response rate

B. Overall survival

C. Hazard rate

D. Complete response

11. Which of the following drug class are azacitidine and decitabine part of?

A. Immunomodulating agents

B. Erythropoietin stimulating agents

C. Anthracyclines

D. Hypomethylating agents

12. PB is a 76-year-old man being treated with azacitidine. His oncologist asks you whether or not a bone marrow biopsy should be scheduled when PB completes cycle 1. Which of the following is the best response to this inquiry?

A. A bone marrow biopsy should be scheduled after cycle 1.

B. A bone marrow biopsy is not necessary.

C. It takes 4 to 6 cycles to observe a response and a bone marrow biopsy should be scheduled after allowing time to respond.

D. A CBC with differential can be exclusively used to monitor PB's MDS.

13. Which of the following is the only potentially curative treatment modalities for MDS patients who are candidates for therapy?

A. Allogeneic hematopoietic stem cell transplantation

B. Chimeric antigen receptor T-cells

C. Donor lymphocyte infusion

D. Autologous hematopoietic stem cell transplantation

14. MG is a 74-year-old woman with high-risk MDS that is transfusion dependent. MG has a lifetime transfusion history of 25 PRBC transfusions. Her ferritin level is 3,000 ng/mL (µg/L; 6,740 pmol/L) and she presents with complaints of SOB. Which of the following is an appropriate supportive care consideration for MG?

A. Apheresis

B. Deferoxamine

C. Iron supplementation

D. Albuterol

15. Which of the following treatments is associated with MDS?

A. Doxorubicin

B. Cytarabine

C. Cetuximab

D. Vaccination

SELF-ASSESSMENT QUESTION-ANSWERS

1. **A.** An 88-year-old man with a history of non-Hodgkin lymphoma treatment treated with chemotherapy plus radiation because of his age and lymphoma treatments, which likely included an alkylating agent (cyclophosphamide) + topoisomerase II inhibitor (doxorubicin) as part of standard-of-care chemotherapy and radiation.

2. **C.** Myelosuppression is the dose-limiting toxicity of azacytidine and decitabine.

3. **D.** MDS is a disease of older adults with a median age at diagnosis of 76 years and a slight male predominance. Thus, the most likely medication-related problem is polypharmacy as older adults tend to have more comorbid conditions.

4. **C.** Lenalidomide is an analog of thalidomide, which was removed from the market in the mid-twentieth century after reports of teratogenicity. It was later reintroduced for treatment of HIV-related leprosy and later MDS with the implementation of a REMS to prevent teratogenic effects.

5. **B.** Lenalidomide is renally excreted and requires dose adjustment for kidney dysfunction. Given that JV is experiencing acute kidney injury and it is not known if this condition will worsen, the best course of action would be to hold lenalidomide.

6. **A.** Lenalidomide studies have shown positive outcomes in MDS with del(5q) as a targeted therapy. See the "Immunomodulating Agents" section

under the "Lower-Risk MDS Patients" section.

7. **C.** MDS patients with an erythropoietin level <500 mU/mL (U/L) had better outcomes with ESA support than those with higher levels in low-risk MDS without del(5q).

8. **D.** The National Institutes of Health has developed an algorithm to predict response to immunosuppressive therapy, and criteria include age younger than 60 years, hypocellular marrow, refractory anemia of short duration, **trisomy 8 as the sole cytogenetic abnormality, and HLA DR15 positive expression**. See the "Immunomodulating Agents" under the "Lower-Risk MDS Patients" section.

9. **A.** TK has nonspecific symptoms that could be related to infection and thus is on appropriate antibiotics. Given TK is already on antibiotics, and it is over 1 week status post treatment with ATG, TK could have symptoms of serum sickness and thus prednisone is appropriate.

10. **B.** Both azacitidine and decitabine have been demonstrated to provide benefits for the treatment of MDS. However, only azacitidine has been associated with improved overall survival.

11. **D.** Azacitidine and decitabine are hypomethylating agents with effectiveness in the treatment of both low-risk MDS and certain forms of high-risk MDS.

12. **C.** Hypomethylating agents work by acting on epigenetic factors related to MDS. Given this mechanism of action, their effect on cell kill takes time and so it is most appropriate to assess response to hypomethylating agents after multiple cycles of treatment, typically 4 to 6, 28-day cycles.

13. **A.** Most treatments for MDS are palliative and the only curative treatment for MDS is allogeneic hematopoietic stem cell transplantation. However, not all MDS patients will be candidates for this treatment modality.

14. **B.** MG has symptoms that have been associated with iron overload, a lifetime transfusion history of 25 PRBC transfusions, and her ferritin level is elevated above 2,500 ng/mL (µg/L; 5620 pmol/L). She should be started on deferoxamine.

15. **A.** Doxorubicin is a topoisomerase II inhibitor and these agents have been associated with TR-MDS.