CHAPTER 140 Myelodysplastic Syndromes

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KEY CONCEPTS

1. Myelodysplastic syndromes (MDSs) are primarily a disease of the elderly, with a median age at diagnosis between 60 and 75 years.
2. MDS are associated with environmental, occupational, and therapeutic exposures to chemicals or radiation.
3. The manifestations of MDS are due to a combination of immune dysregulation and genomic instability, which creates a dysplastic, clonal population of cells in a milieu unable to support normal hematopoiesis.
4. Most patients with MDS present with fatigue and lethargy or symptoms related to tissue hypoxia due to anemia.
5. The prognosis of patients with MDS is variable. Overall survival ranges from a few months to several years and can be estimated with the International Prognostic Scoring System (IPSS) or World Health Organization Classification-based Scoring System (WPSS).
6. Palliation of symptoms and improvement in quality of life are the goals of therapy for most patients.
7. Patients with MDS with low or intermediate-1 IPSS risk, serum erythropoietin level less than 500 IU/L, and low requirement for red blood cell (RBC) transfusions are most likely to respond to erythropoietin.
8. Allogeneic hematopoietic stem cell transplantation (HSCT) offers potentially curative therapy to patients with MDS who have a donor and are healthy enough for the procedure.
9. Hypomethylating agents are appropriate for patients with transfusion-dependent or symptomatic MDS who are not candidates for allogeneic HSCT.
10. Antithymocyte globulin is an appropriate treatment option for patients with low or intermediate-1 IPSS risk MDS who express human leukocyte antigen DR15 with symptomatic anemia that is unlikely to respond to erythropoietic agents.
11. Lenalidomide is recommended as a treatment option for patients with symptomatic anemia and low-risk MDS expressing a 5q deletion.

Myelodysplastic syndromes (MDS) encompass a spectrum of clonal myeloid disorders characterized by ineffective hematopoiesis that results in anemia, thrombocytopenia, leukopenia, or a combination of peripheral cytopenias.[1,2] MDS are frequently associated with clonal chromosomal abnormalities, qualitative disorders of blood cells, and a variable propensity for progression to acute myeloid leukemia (AML). The clinical course of patients with MDS varies along a continuum from a rapid progression to AML to years of slowly progressive bone marrow failure.[3,4]

Our understanding of MDS and the available treatment options have advanced in recent years. In 1999, the World Health Organization (WHO) developed a classification system in an attempt to make the categories of MDS more homogenous with respect to natural history of the disease.[2] The International Prognostic Scoring System (IPSS) for MDS was developed to better enable clinicians to categorize patients according to risk for progression to AML and predict median survival from the time of diagnosis.[3] Until 2004, supportive care was the most common therapy for most patients because no medications for treatment of MDS were approved by the Food and Drug Administration (FDA). Three medications (azacitidine, decitabine, and lenalidomide) currently are approved by the FDA for treatment of MDS, and several more are being investigated. The change in classification of MDS, improvement in risk stratification, and development of new treatment options represent steps forward in our understanding and management of MDS.

EPIDEMIOLOGY

1 MDS are primarily a disease of the elderly, with a median age at diagnosis between 60 and 75 years.[5] Males predominate, with an estimated male-to-female ratio of approximately 1.7:1.[6] Overall, an estimated 3 to 12 cases of MDS are diagnosed per 100,000 persons per year. The incidence of MDS increases with age; in patients older than 70 years, an estimated 15 to 50 new cases per 100,000 persons occur per year.[5] Approximately 10,300 new cases are diagnosed in the United States each year, making MDS roughly as common as chronic lymphocytic leukemia.[6] Many experts predict that the prevalence of MDS is likely to 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. MDS have been associated with environmental, occupational, and therapeutic exposures to chemicals or radiation.[7] Environmental exposure to smoking or agricultural chemicals has been associated with an increased risk of developing MDS.[8] MDS also were 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. Occupational exposures to

hair dyes, cereal dusts, exhaust gases, diesel fuel, and industrial solvents, including benzene and toluene, have been associated with development of MDS.[9,10] Individuals with a family history of a hematologic malignancy are at increased risk for developing MDS.[9] MDS are associated with radiation therapy and some types of chemotherapy given for treatment of malignancies and autoimmune disorders.

Approximately 10% to 15% of all cases of MDS are attributed to radiation or chemotherapy and are termed *therapy-related MDS* (t-MDS). Therapy-related MDS have an increased likelihood of progression to AML and a poorer prognosis than de novo MDS.[11,12] The median age at onset of t-MDS depends on the age at exposure to the causative agent, but t-MDS usually is diagnosed in younger patients, with a median age at diagnosis in the fourth to fifth decade of life.[13,14] Chromosomal abnormalities are found in approximately 90% of t-MDS compared to 50% to 60% of de novo MDS.[3,11–13,15]

The risk for developing t-MDS is increased in patients who are older at the time of exposure to the causative agent.[16] Risk for developing t-MDS increases with higher doses of chemotherapy or radiation, longer duration of exposure, and exposure to both chemotherapy and radiation.[11,16,17] Several chemotherapeutic agents have been associated with t-MDS (Table 140–1). The risk for t-MDS from a single agent is difficult to assess because patients usually are 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.[11,12,14,18]

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.[12,16,19,20] The latency period between exposure to alkylating agents and the development of t-MDS is approximately 4 to 7 years. Characteristic chromosomal abnormalities in t-MDS associated with alkylating agents include deletions on chromosome 5 and chromosome 7.[2,13,16]

Topoisomerase II inhibitors, including the epipodophyllotoxins (etoposide and teniposide); anthracyclines (daunorubicin, doxorubicin, epirubicin, idarubicin); and the anthracenedione mitoxantrone, also are associated with t-MDS. t-MDS associated with topoisomerase II inhibitors typically occurs a median of 2 to 3 years after exposure, and patients are more likely to present with AML at diagnosis.[2,18] Chromosomal abnormalities often found in patients with t-MDS associated with topoisomerase II inhibitors include balanced translocations involving the long arm of chromosome 11, band q23, or chromosome 21, band q22.[21,22]

Radioimmunoconjugates, including ibritumomab tiuxetan and iodine-131 tositumomab, are monoclonal antibodies linked to radioactive isotopes. Radiation is delivered to the antibody-bound targeted cell and to neighboring cells through a "cross-fire" effect. t-MDS or AML is reported to occur in 5% to 10% of patients exposed to iodine-131 tositumomab and in 1% to 5% of patients exposed to ibritumomab tiuxetan.[23–27] Both agents are used to treat non-Hodgkin's lymphoma, a patient population likely to receive other therapies associated with t-MDS, including alkylating agents, anthracyclines, and radiation. Therefore, determining the additional risk for t-MDS due solely to exposure to one of these agents is difficult.[23,24,27]

Granulocyte colony-stimulating factor (G-CSF) use during treatment of acute lymphoblastic leukemia (ALL) in pediatric patients has been associated with an increased risk for subsequent development of t-MDS.[28] Although these results must be confirmed, the risk of t-MDS should be considered when G-CSF is administered to pediatric patients.[29] This association has not been observed in adults with ALL, perhaps due to lower overall survival rates.

Patients undergoing hematopoietic stem cell transplantation (HSCT) are at increased risk for development of t-MDS. Conditioning regimens given prior to HSCT usually include high doses of alkylating agents, or etoposide, often in combination with total-body irradiation. As many as 8% to 20% of patients with non-Hodgkin's lymphoma treated with autologous HSCT will be diagnosed with t-MDS within 10 years of transplantation.[30–32] Risk factors for development of t-MDS following HSCT include the antecedent conventional chemotherapy, prior radiation therapy, a low stem cell dose, older age at time of transplant, and use of total-body irradiation in the conditioning regimen.[30,31,33,34]

TABLE 140-1 Therapies Associated with Therapy-Related Myelodysplastic Syndrome

Alkylating Agents	Topoisomerase II Inhibitors	Miscellaneous
Busulfan	Daunorubicin	Azathioprine
Carmustine	Doxorubicin	Carboplatin
Chlorambucil	Epirubicin	Cladribine
Cyclophosphamide	Etoposide	Cisplatin
Dacarbazine	Idarubicin	Fludarabine
Ifosfamide	Mitoxantrone	Iodine-131 tositumomab
Lomustine	Teniposide	Yttrium-90 ibritumomab tiuxetan
Mechlorethamine		Radiation therapy
Melphalan		Total-body irradiation
Procarbazine		
Temozolomide		

Data from Blaszkowsky and Erlichman[109] and Pederson-Bjergaard et al.[110]

PATHOPHYSIOLOGY

3 Knowledge of normal hematopoiesis is needed to understand the pathophysiology of MDS (see Chap. 103 for a more detailed description of hematopoiesis). The pathophysiology underlying MDS is complex and not fully elucidated. A multistep model for the pathogenesis of MDS has been proposed, although the precise transformation necessary for myelodysplasia to occur is unknown.[9,35–40] The manifestations of MDS likely are due to a combination of immune dysregulation and genomic instability, which creates a dysplastic, clonal population of cells in a milieu unable to support normal hematopoiesis.[35,36,40]

Hematopoietic stem cells are immature cells capable of self-renewal and subsequent differentiation into mature blood cells.[39] As hematopoietic stem cells differentiate, they become committed to pluripotent lymphoid or myeloid cells. The pluripotent stem cells undergo highly regulated steps of proliferation, differentiation, and maturation to form functionally mature cells in the peripheral blood. The pluripotent cells differentiate into clonal cell lines; lymphoid precursors give rise to B-cell, T-cell, and natural killer cell lymphocytes, whereas pluripotent myeloid precursors differentiate into erythrocytes, monocytes, granulocytes, and platelets.[1,41,42]

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 decreased myeloperoxidase activity, leading to an increased susceptibility to infection, despite a normal quantity of neutrophils.[43] Platelets may be normal in quantity but have impaired aggregation.[39]

BONE MARROW MICROENVIRONMENT

The myelodysplastic clone is associated with cellular dysfunction, including excess secretion of cytokines, defective differentiation, genomic instability, and reduced response to regulatory cytokines.[1,36,41] In contrast to the peripheral blood cytopenias characteristic of MDS, bone marrow cells often have a paradoxically high rate of cellular division. Apoptosis, or programmed cell death, also is increased, leading to futile cycling of precursor cells and impaired production of mature peripheral blood cells.[1,44–46] Overproduction of proapoptotic and inflammatory cytokines, such as tumor necrosis

factor-α and interleukin-6, may contribute to this process.[35,36,38,40] The extent of apoptosis appears to decrease as MDS evolves into AML.[40]

Patients with MDS frequently have evidence of immune dysregulation, such as impaired immune surveillance and autoimmune reactions.[9,39] Cytopenias can be related to an autoimmune T-cell–mediated response. The ability of immunosuppressive agents to reverse this effect in vitro led to human studies of cyclosporine and antithymocyte globulin to treat MDS. Clinical responses to immunosuppression confirm the role of immune dysregulation in the pathophysiology of MDS. Whether B cells and T cells are a part of the MDS clonal population or a secondary reaction is unclear.[40,47]

GENOMIC INSTABILITY

In the multistep model for development of MDS, one or more transformations occur that confer a growth advantage to the dysplastic cell, which leads to a clonal population.[35,39] The requisite transformations in genetic material have not been identified. Chromosomal abnormalities are detected by cytogenetic analysis in 50% to 60% of patients with MDS.[3,15] Multiple cytogenetic abnormalities, including 5q or 20q deletions and trisomy 7, correlate with the clinical course of MDS and have been incorporated into prognosis assessment.[3] Deletions on chromosome 5q occur in more than 12% of patients and are of particular interest because multiple genes involved in hematopoiesis are located there.[15,36] In addition, MDS with 5q deletions as the sole genetic aberration are recognized as a distinct subtype of MDS with a favorable prognosis.[3] Changes in the expression of p53, p15, Fas ligand, and Bcl-2 also have been noted in MDS.[40] These transformations may influence the expression of tumor suppressor genes, transcription factors, and cell cycle regulators, providing the dysplastic stem cell with a growth advantage.[37]

EPIGENETICS

In addition to changes detected on chromosomal analysis, several transformations have been identified that may contribute to myelodysplasia that do not result from alteration of the nucleic acid sequence in deoxyribonucleic acid (DNA). The term *epigenetic* refers to mechanisms that regulate the expression of DNA and are stable and heritable but also may be reversible. Epigenetic changes have been identified in numerous malignancies and are of particular importance in the context of MDS.[48–50]

In the mammalian genome, only cytosine located 5' to a guanosine (CpG) can be methylated. Near the promoter regions for many genes are areas rich in CpG, known as *CpG islands*. In normal cells, these regions are unmethylated, and normal expression of DNA occurs. Increased methylation (hypermethylation) of CpG islands occurs via DNA methyltransferase and is associated with aberrant gene silencing, which may lead to further genetic instability and dysfunction of the cell cycle. Decreased methylation (hypomethylation) may lead to reexpression of previously silenced genes. Hypermethylation and gene silencing have been noted in patients with MDS, and reversal of this process is the pharmacologic target of azacitidine and decitabine.[48–50]

CLINICAL PRESENTATION AND DIAGNOSIS

CLINICAL PRESENTATION OF MYELODYSPLASTIC SYNDROMES[9,37,39]

General

- 4 Patients with MDS may develop anemia, neutropenia, or thrombocytopenia or multiple peripheral cytopenias.
- Patients may be asymptomatic, with cytopenia(s) discovered on complete blood count with differential.

Symptoms

- If symptomatic, the patient may report fatigue, lethargy, malaise, palpitations, and dyspnea on exertion 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 due to infection and immune dysfunction
- Petechiae, bruising, epistaxis, gingival bleeding, excessive vaginal bleeding, bruising or hematuria due to thrombocytopenia

Laboratory Tests

- Complete blood count with differential
- Anemia often is macrocytic or normocytic with a low reticulocyte index
- More than 80% of patients present with a hemoglobin less than 10 g/dL
- Serum vitamin B_{12} and folic acid levels
- Testing for the human immunodeficiency virus (HIV)
- Serum erythropoietin level

Other Diagnostic Tests

- Bone marrow biopsy and aspirate: send for morphologic examination, cytochemical staining, immunophenotyping, and cytogenetics (chromosome analysis)
- Repeat bone marrow biopsy of patients with MDS often is required because dysplastic features may progress over time or the bone marrow may be unevenly distributed

CLASSIFICATION AND PROGNOSIS

Several classification systems and models for predicting risk for MDS have been developed. The most widely used systems include the French-American-British (FAB) classification system, the WHO classification scheme, and the IPSS (Tables 140–2 and 140–3).

The FAB classification was published in 1977 as a system for categorizing myelodysplasia and acute leukemia based on morphology of bone marrow aspirates.[51] Patients are classified into five subgroups based on the percentage of bone marrow or peripheral blood blasts, with the exception of refractory anemia with ringed sideroblasts and chronic myelomonocytic leukemia. Several limitations to the FAB classification system have been identified.[1,52] For example, it is not possible to predict based on morphology whether an anemia will be "refractory" to therapy; this determination is made after a trial of a medication. Another limitation is that the distinctions based on blast percentage are arbitrary and may not correlate with disease outcome. The inclusion of patients with megakaryocytic and granulocytic abnormalities in refractory anemia and in refractory anemia with ringed sideroblasts creates the possibility for a heterogeneous population within the same subclass. In addition, most clinicians now consider chronic myelomonocytic leukemia to be classified as myeloproliferative disorder. Finally, the FAB classification system does not incorporate cytogenetic abnormalities that are predictive of disease outcome. These limitations led to the proposal of the WHO classifications for MDS. The WHO classification scheme was developed to improve the homogeneity of the patient groups and, therefore, the ability to predict prognosis.

The WHO classification scheme reorganized MDS into eight categories on the basis of morphology, genetic features, and number of cell lines affected (Table 140–2).[2] According to the WHO classification, patients are categorized based on bone marrow or peripheral blood blast

TABLE 140-2 World Health Organization Classification of Myelodysplastic Syndromes

Classification	Blood	Bone Marrow
Refractory anemia (RA)	Anemia No or rare blasts	Erythroid dysplasia only <5% blasts <15% ringed sideroblasts
Refractory anemia with ringed sideroblasts (RARS)	Anemia No blasts	Erythroid dysplasia only <5% blasts ≥15% ringed sideroblasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Multilineage cytopenias No or rare blasts No Auer rods Monocytes <1,000 cells/mm^3	Dysplasia in ≥10% of cells in ≥2 myeloid cell lines <5% blasts <15% ringed sideroblasts No Auer rods
Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS)	Multilineage cytopenias No or rare blasts No Auer rods Monocytes <1,000 cells/mm^3	Dysplasia in ≥10% of cells in >2 myeloid cell lines <5% blasts ≥15% ringed sideroblasts No Auer rods
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenias <5% blasts No Auer rods Monocytes <1,000 cells/mm^3	Unilineage or multilineage dysplasia 5%–9% blasts No Auer rods
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenias 5%–19% blasts ±Auer rods Monocytes <1,000 cells/mm^3	Unilineage or multilineage dysplasia 10% to 19% blasts ± Auer rods
Myelodysplastic syndrome, unclassified (MDS-U)	Cytopenias No or rare blasts No Auer rods	Unilineage dysplasia in granulocytes or megakaryocytes <5% blasts No Auer rods
Myelodysplastic syndrome associated with isolated deletion of 5q	Anemia <5% blasts Platelets normal or increased	Normal to increased megakaryocytes with hypolobated nuclei <5% blasts No Auer rods Isolated del(5q)
Acute myeloid leukemia	–	≥20% blasts

Data from Vardiman et al.[2] and Malcovati et al.[53]

percentage and whether dysplasia or cytopenias result in anemia alone or affect other myeloid cell lines. The most significant changes in the WHO classification compared with the FAB classification include the following: patients with anemia alone were separated from those with multiple myeloid lines affected; patients with greater than 20% blasts in the marrow now are considered to have acute leukemia; patients with deletion on chromosome 5 now are in a distinct category; and chronic myelomonocytic leukemia is classified as a myelodysplastic/myeloproliferative disorder. Two studies have demonstrated the ability of the WHO classification to identify patient subgroups with differences in survival and responses to erythropoietin and filgrastim. Patients with refractory anemia or refractory anemia with ringed sideroblasts had prolonged overall and leukemia-free survival and improved response to therapy compared with those with refractory cytopenia with multilineage dysplasia or refractory anemia with excessive blasts.[52,53] Although this classification scheme may help predict the prognosis of MDS, it has not been shown to predict response to a given therapy.[9]

5 Based on an observational study over several years of mostly untreated MDS patients, the IPSS was developed to identify factors that would predict the progression of MDS.[3] Multivariate analysis 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 140–3). The National Comprehensive Cancer Network (NCCN) guidelines divide patients into two categories for therapeutic options: those with low and intermediate-1 IPSS risk, and those with intermediate-2 and high IPSS risk MDS.[54]

TABLE 140-3 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
Hemoglobin <10 g/dL
Platelet count <100,000 cells/mm^3
Karyotype: Good: Normal, isolated 5q deletion, isolated 20q deletion, -Y
Intermediate: Any other abnormalities
Poor: Trisomy 7, complex or >3

Score	Risk Group	Median Survival (y)	NCCN Guideline Treatment Category
0	Low	5.7	Low
0.5–1	Intermediate-1	3.5	
1.5–2.0	Intermediate-2	1.2	High
≥2.5	High	0.4	

NCCN, National Comprehensive Cancer Network.
Data from Greenberg et al.[3] and Malcovati et al.[55]

The WHO Classification-based Scoring System (WPSS) was developed to blend the assets of the IPSS and WHO models.[55] The WPSS incorporates cytogenetic information and transfusion dependency into the WHO classification scheme to create a dynamic model facilitating prediction of survival and leukemic evolution in MDS patients at any time during their course of disease. It will be incorporated into future clinical trials to assess risk and implement risk-adapted treatment strategies. Recently published clinical trials classify patients according to the WHO classification scheme and stratify patients by IPSS risk.

TREATMENT

Treatment of MDS has rapidly evolved during the last few years because of discoveries about the biology of MDS, availability of new methods for predicting the natural history of the disease and response to a given therapy, and development of new therapeutic strategies (Fig. 140–1).

GOALS OF THERAPY

6 The goals of treatment vary with disease-specific factors, including the type of MDS, risk for progression to AML and death, rate of disease progression, and patient factors, including age, organ function, performance status, and presence of symptoms related to myelodysplasia.[56] The only curative therapy is allogeneic HSCT, but most patients lack a suitable donor or are not healthy enough to undergo this intensive therapy.[7] The goals of therapy for most patients include palliation of symptoms and improvement in quality of life. Lower-intensity treatment with a DNA hypomethylating agent or immunotherapy may improve overall survival and provide symptom palliation and enhanced quality of life without significant toxicity.[54,57,58]

GENERAL APPROACH TO TREATMENT

Therapy for MDS is generally determined by current symptoms, IPSS risk for progression to AML or death, patient age and comorbidities, likelihood of response to a given therapy, and patients'

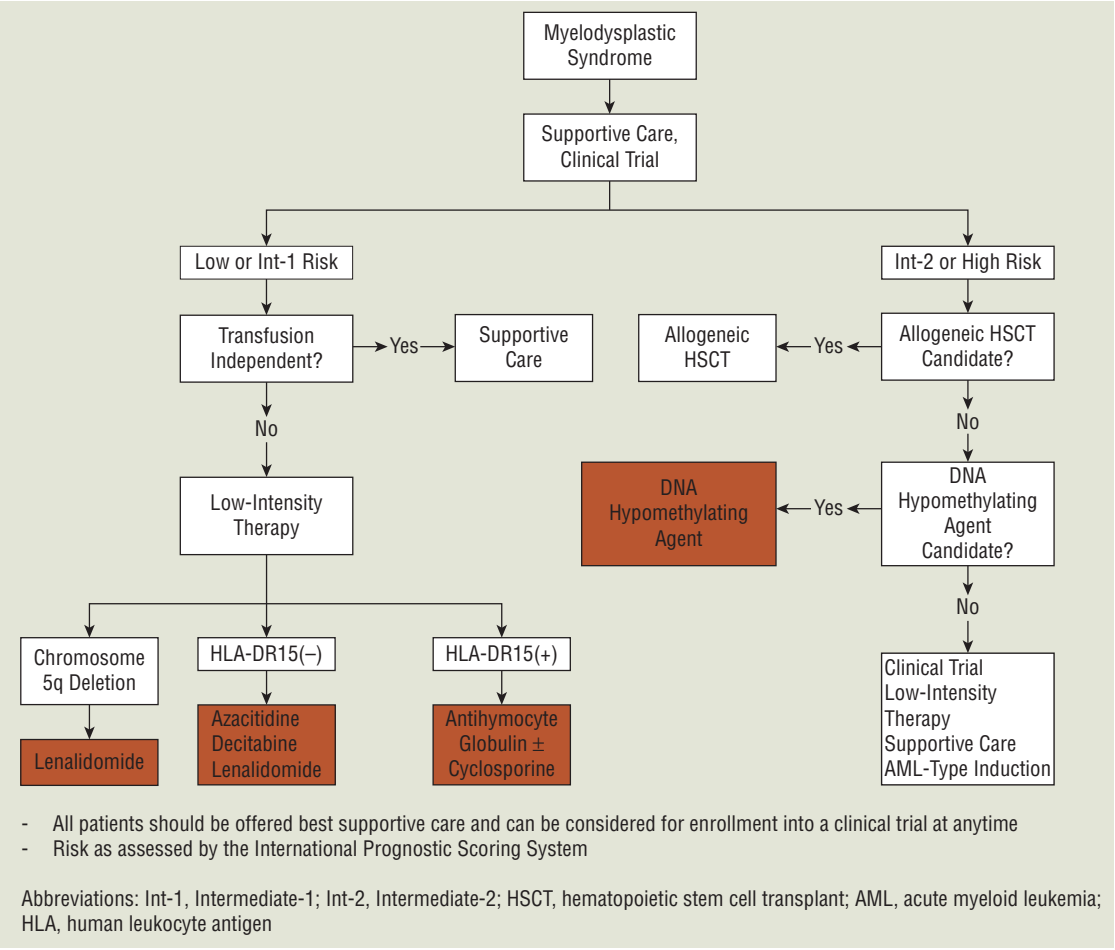

FIGURE 140-1. Myelodysplastic syndromes treatment algorithm.

treatment preferences. Approximately 40% to 60% of patients with MDS receive supportive care alone.[15] In general, patients with low and intermediate-1 IPSS risk scores have a better prognosis, and lower-intensity therapies are used if therapy is indicated. Patients with intermediate-2 and high-risk MDS have a poorer prognosis and are generally candidates for allogeneic HSCT; patients who are not transplant candidates may benefit from a DNA hypomethylating agent.[58] Some patients will not be fit for intensive therapy and may benefit from low-intensity therapy. Clinicians should recognize that the clinical course of MDS is not static. MDS may progress, and patients may have changes in comorbidities or symptoms over time, necessitating a change in treatment strategy or a change to supportive care alone. As therapy for MDS is generally palliative and each therapy works for a minority of patients, enrollment in a suitable clinical trial is a viable treatment approach.[59]

When making decisions regarding therapy, clinicians should carefully interpret and compare the results of clinical trials in MDS because of differences in patient characteristics and definitions of response between trials. As described previously, differences in patient characteristics can result in varying clinical courses and prognoses. Some studies use changes in hemoglobin as the primary end point, while others use changes in red blood cell (RBC) transfusion requirements or quality of life as the primary end point.[56] Use of RBC transfusion requirement as a primary end point is problematic because decisions concerning RBC transfusions are highly individualized and may not be consistent between different clinicians, and the same clinician may treat similar patients differently or the same patient differently over time. The relationship between changes in hemoglobin or decreases in RBC transfusion requirements and improved quality of life is not clear. Frequent assessment of quality of life with validated instruments is recommended because patients with significant adverse effects necessitating hospitalization or increased clinic visits due to therapy may not experience overall improvement in quality of life.[59]

SUPPORTIVE CARE

The mainstay of therapy for patients with MDS is supportive care. The NCCN guidelines recommend that patients with symptomatic anemia should receive leukoreduced RBC transfusions, and those with bleeding due to thrombocytopenia should receive platelet transfusions.[54] Hematopoietic cytokine support should be considered in patients with refractory, symptomatic cytopenias. Patients with evidence of infection should have appropriate diagnostic evaluation based on history and physical examination and then appropriate antimicrobial therapy. Iron chelation should be considered in low-risk patients who have received more than 20 to 30 RBC transfusions and are anticipated to continue to require transfusions.[54]

Infection

Patients with MDS may be neutropenic or have functional defects in neutrophils, predisposing them to infection.[43] Neutropenic patients with evidence of infection or fever of unknown origin should receive empiric broad-spectrum, intravenous antibiotics.[60] In MDS, the most frequently isolated organisms are bacteria, and the most common sites of infection are the lungs, urinary tract, and bloodstream.[39,61] Patients with evidence of infection should have appropriate diagnostic evaluation based on history and physical examination and then appropriate antimicrobial therapy.

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 risk of infection.[1,35,62] Therapy with G-CSF or GM-CSF may be considered in patients with recurrent neutropenic fevers but has not been shown to be beneficial as chronic monotherapy because it does not reliably prevent infection and has no impact on survival.[35,39,62]

Erythropoietin is a protein produced by the kidney in response to hypoxia that stimulates proliferation and differentiation of erythroid cells. Anemic patients with MDS may have a lower than expected endogenous serum erythropoietin level relative to the degree of anemia present or an elevated erythropoietin level. The mechanism of action of erythropoietin in MDS is not clear, but erythropoietin may stimulate a normal clone of cells that was unresponsive to a low endogenous level of erythropoietin, stimulate a dysplastic clone to differentiate that is less responsive to endogenous erythropoietin, or induce apoptosis.[63] An immunomodulatory effect of erythropoietin, G-CSF, or GM-CSF also has been proposed.

7 Treatment with erythropoietin alone may result in hematologic improvement and transfusion independence in low and intermediate-1 IPSS risk patients. A meta-analysis of 17 studies with 205 patients with MDS found an overall response rate of 16%.[64] The doses required to produce a response in MDS are higher than those used to treat renal causes of anemia, with doses in the range from 40,000 to 60,000 units subcutaneously two to three times per week.[54] Doses should be titrated up or down, as clinically indicated, to achieve a hemoglobin level of 10 to 12 g/dL. Because response to erythropoietin in MDS may be delayed, patients should receive at least 8 weeks of therapy before treatment is discontinued.[39] Patients with low and intermediate-1 IPSS risk MDS who have a serum erythropoietin level less than 500 IU/L and a history of fewer than 2 units of RBC transfusions per month are most likely to respond to erythropoietin.[54]

Darbepoetin 150 mcg or 300 mcg subcutaneously weekly has been studied in phase II trials, with 35% to 55% of patients achieving increases in hemoglobin of 2 g/dL or transfusion independence (i.e., major erythroid response by International Working Group [IWG] criteria).[65,66] Further studies with darbepoetin are ongoing to define the efficacy, optimal dosing, and schedule of this agent.

The addition of G-CSF to erythropoietin or darbepoetin may provide a synergistic effect on hematologic improvement.[67–69] Long-term followup of 123 patients from three uncontrolled phase II studies showed a 37% major erythroid response rate by IWG criteria in patients given erythropoietin and G-CSF.[68] Most of the patients enrolled and those who responded had low or intermediate-1 IPSS risk scores. The median doses required to maintain a stable response were erythropoietin 30,000 units/week and G-CSF 225 mcg/week. Those patients with a complete or partial response had improvements in quality of life.[67,69] A recently published study reported a 50% response rate by IWG 2006 criteria in a group of 433 patients with MDS treated with erythropoietin or darbepoetin, with or without filgrastim.[69] Predictors of response included low and intermediate-1 IPSS risk, RBC transfusion independence, serum erythropoietin level <200 IU/L, and shorter interval between diagnosis and treatment. The addition of G-CSF was not significantly associated with response. Although these results are promising, the data require confirmation in a prospective, randomized controlled trial before combination therapy is recommended for all patients.

Some but not all studies have shown that patients who respond to colony-stimulating factors have improvements in quality of life.[67] The value of this costly intervention has not been evinced. Nonetheless, the therapy is well tolerated, and the NCCN recommends a trial in low and intermediate-1 IPSS risk patients who have a serum erythropoietin level less than 500 IU/L and a limited transfusion history.[54]

Transfusion

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 g/dL.[37,39,70] Some clinicians use a threshold of 10 g/dL in patients with a significant cardiac history to avoid myocardial infarction due to tissue hypoxia.[37,70] Platelet transfusion is generally reserved for patients with evidence of bleeding to avoid alloimmunization from repeated platelet transfusions, which leads to refractoriness to donor platelets.[37,39,70]

Iron Overload

Chronic iron overload can result in cardiac, hepatic, and endocrine dysfunction after several years of RBC transfusions. The median overall survival from MDS is several years, and the impact of iron overload and iron chelation in MDS remains to be defined.[71] Transfusion-dependent patients with evidence of iron overload have decreased overall survival compared to similar patients not requiring transfusions.[7,53] Whether this difference reflects a different underlying biology of the MDS in those who require RBC transfusion or morbidity from iron overload is unclear. In a series of 11 patients given deferoxamine for several years, Jensen et al.[72] demonstrated a reduction in RBC transfusion in 64% of patients, with 46% becoming transfusion independent. However, the impact of iron chelation on organ function or survival is not clear. Although supporting data in MDS are lacking, many clinicians recommend that iron chelation be started after 20 to 30 RBC transfusions or when serum ferritin levels exceed 1,500 to 2,500 ng/mL for patients with low-risk MDS who have an anticipated survival of at least 1 year.[54,70,73] Deferoxamine requires continuous subcutaneous infusion for 8 to 12 hours/day and is cumbersome to administer. FDA approval of deferasirox, an oral iron chelator, may facilitate patient compliance and lead to more widespread implementation of iron chelation for MDS.

CLINICAL CONTROVERSY

Initiation of iron chelation in patients with MDS is controversial because iron chelation has not been shown to change the natural history of MDS despite the anticipated prevention or reversal of end-organ damage associated with iron overload.[71] Clinical trials to evince the role of iron chelation in MDS have been initiated.[54]

■ PHARMACOLOGIC THERAPY

Pharmacotherapy of MDS is intended to change the natural history of MDS. Pharmacotherapy often is divided into *high-intensity therapy*, including HSCT and AML-type induction chemotherapy, and *low-intensity therapy*, including DNA hypomethylating agents and immunotherapy. Table 140–4 lists the responses reported in selected clinical trials of lower-intensity therapies. Although no therapy other than allogeneic HSCT has shown an improvement in disease-free survival, less toxic therapeutic modalities are being evaluated in an attempt to improve quality of life and disease-free survival for patients with MDS.

High-Intensity Therapies

Hematopoietic Stem Cell Transplantation 8 Allogeneic HSCT offers potentially curative therapy to patients with MDS who have a suitable donor and are healthy enough for the procedure. Unfortunately, only approximately 8% of patients meet those requirements.[7] Approximately 30% to 50% of patients treated with allogeneic HSCT have prolonged disease-free survival.[74–79] However, 20% to 50% of patients succumb to treatment-related mortality, and many of the remaining patients relapse. Outcomes vary based on patient age and

TABLE 140-4 Results from Selected Trials of Low-Intensity Treatment for Myelodysplastic Syndromes

Medication	Number of Patients	Median Age	Percent of Patients by IPSS Risk Category				Response Criteria	Complete Response (%)	RBC Transfusion Independence (%)	Overall Hematologic Improvement (%)
			Low	*Int-1*	*Int-2*	*High*				
Azacitidine[86]	191	69	5[a]	53	23	17	Other	7	45	37
Decitabine[88]	170	70	–	31	43	26	IWG	9	NR	30
Antithymocyte globulin[93]	61	60	18	67	5	10	Other	NR	34	NR
Cyclosporine[94]	50	55	8	82	10	–	IWG	0	NR	60
Lenalidomide[102] (5q deletions)	148	71	37	44	5	–	IWG	NR	67	76
Lenalidomide[105]	214	72	43	36	4[b]	–	IWG	NR	26	43
Thalidomide[97]	83	67	25	45	14	6	IWG	0	NR	20

IPSS, International Prognostic Scoring System; Int-1, Intermediate-1; Int-2, Intermediate-2; RBC, red blood cell; IWG, International Working Group; NR, not reported.
[a]Evaluated in 39 of 99 patients.
[b]Includes IPSS, Int-2, and High.

comorbidities, time from diagnosis to transplant, FAB subtype of MDS, percentage of bone marrow blasts at the time of HSCT, IPSS risk category, type of conditioning regimen prior to HSCT, and dose and source of stem cells. Complications of allogeneic HSCT are described in greater detail in Chapter 142.

Because of the high rate of treatment-related mortality in patients with MDS, allogeneic HSCT usually is not recommended for low-risk patients because these patients may have indolent disease for several years, and early transplant may shorten overall survival. The International MDS Risk Assessment Workshop (IMRAW) 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.[80] 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.

Nonmyeloablative transplants are being evaluated for treatment of MDS. Patients who undergo nonmyeloablative conditioning tend to have lower treatment-related mortality but a higher rate of relapse.[74] Direct comparison of the results of nonmyeloablative transplants versus conventional myeloablative transplants is difficult because patients treated with nonmyeloablative transplants tend to be older or have significant comorbid illnesses. A prospective randomized study has been initiated to evaluate the role of nonmyeloablative conditioning for MDS prior to allogeneic HSCT.[74]

CLINICAL CONTROVERSY

As knowledge about how best to improve overall survival and quality of life in MDS increases, the role of allogeneic HSCT continues to be reevaluated. Questions that will require investigation include the following: Which patients should undergo transplantation? What is the optimal time to undergo HSCT? What type of conditioning regimen should be used?

Intensive chemotherapy followed by autologous HSCT has been evaluated in patients who achieve complete remission with induction chemotherapy, are able to collect an adequate number of stem cells, and are healthy enough for the procedure.[36] Of the patients who undergo autologous HSCT, 15% to 30% will have prolonged disease-free survival, a similar percentage will die of nonrelapse mortality, and 50% to 70% will relapse.[81,82] The role of autologous HSCT should be reevaluated in light of newer, less intensive therapies.

AML-Type Induction Chemotherapy Patients with intermediate-2 or high-risk MDS may be candidates for intensive chemotherapy with AML-type induction combination chemotherapy regimens, including anthracyclines, cytarabine, fludarabine, and topotecan.[55] AML-type induction therapy is described in detail in Chapter 137. Intensive chemotherapy offers complete remission rates of 40% to 60% but is associated with a duration of response of only 10 to 12 months.[35–37,83] With current supportive care measures, including antibiotic and cytokine support, treatment-related mortality is less than 10%.[36] Patients younger than 55 years who have a normal karyotype and good performance status are most likely to benefit, but this approach cures fewer than 15% of patients.[35,83] 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.

Low-Intensity Therapies

DNA Hypomethylating Agents Both azacitidine and decitabine exert their pharmacologic effects by interfering with DNA methylation. They are nucleoside analogs structurally similar to cytosine and capable of being incorporated into DNA in place of cytosine.[84] When incorporated 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 silenced by aberrant hypermethylation are activated. In vitro studies have confirmed that these agents can lead to the reexpression of previously silenced genes.[84,85] The activity of both agents is concentration and time dependent, and trials continue to evaluate the optimal route, dose, schedule, and duration of therapy.

Azacitidine was evaluated in a phase III, multicenter, randomized trial of patients diagnosed with any classification of MDS based on FAB criteria.[86] Patients in lower-risk categories of MDS, including refractory anemia and refractory anemia with ringed sideroblasts, were required to meet additional criteria for significant bone marrow dysfunction. A total of 191 patients (median age 68 years) were randomized to treatment with either supportive care alone or supportive care plus azacitidine 75 mg/m^2 subcutaneously once daily for 7 continuous days, repeated every 28 days. Use of any hematopoietic growth factor was not permitted. Responses based on Cancer and Leukemia Group B (CALGB) criteria occurred in 60% of patients in the azacitidine arm compared to 5% in the supportive care alone arm. Of the patients requiring transfusions at study entry, 45% treated with azacitidine became transfusion independent. The rate of progression to AML was significantly lower in the azacitidine arm (15%) compared to supportive care alone (38%). Overall survival with azacitidine was increased, although the difference did not reach statistical significance. A quality-of-life analysis identified a significant advantage to treatment with azacitidine compared to supportive care alone with regard to measures of physical functioning, fatigue, dyspnea, psychosocial distress, and positive affect.[87]

Decitabine was recently evaluated in a multicenter randomized phase III trial of patients diagnosed with MDS based on FAB criteria.[88] Patients were required to have an IPSS risk category of intermediate-1 or greater. A total of 170 patients were randomized to either supportive care alone or supportive care plus treatment with decitabine 15 mg/m^2 intravenous infusion every 8 hours for 3 days, repeated every 6 weeks. Use of hematopoietic growth factors was allowed. The overall response rate by IWG criteria was 17% in the decitabine group compared to 0% in the supportive care arm. Thirteen percent of patients in the decitabine arm experienced hematologic improvement compared to 7% with supportive care alone. The decitabine group showed a trend toward a longer time to AML or death, but the difference between the treatment arms was not statistically significant. Of the patients who had clonal abnormalities at baseline and underwent followup cytogenetic evaluation, 35% in the decitabine arm had a complete cytogenetic response compared with 10% in the supportive care arm. Improvements in quality-of-life measures, including global health status, fatigue, and dyspnea, were observed in the treatment arm. In a recently published randomized phase II study, decitabine 20 mg/m^2 given intravenously once daily for 5 days demonstrated a 41% complete response rate.[89] This regimen can be given in the outpatient setting and appears to be at least as effective as the FDA-approved dosing regimen.[89]

The primary toxicity of both azacitidine and decitabine is myelosuppression, including leukopenia, granulocytopenia, and thrombocytopenia. Infectious complications, including febrile neutropenia, have been reported with azacitidine and decitabine.[86,88] Because nausea and vomiting may occur, use of an antiemetic is recommended prior to each dose. Erythema at the site of subcutaneous administration can occur in patients treated with azacitidine. Both agents are associated with a low risk of hepatotoxicity.

Immunotherapy Immunosuppressive strategies targeting T cells, including corticosteroids, antithymocyte globulin, and cyclosporine, have been evaluated in patients diagnosed with MDS. Clinically significant adverse events and low response rates have limited the widespread use of corticosteroids as a therapeutic option for MDS. Antithymocyte globulin and cyclosporine continue to be evaluated alone and in combination as treatment for patients with MDS.[47]

Antithymocyte globulin has been investigated primarily in patients with intermediate-1 and low-risk MDS. Because of the potential for infectious complications, serum sickness, and variation in response rates, treatment with antithymocyte globulin may not be beneficial for all patients.[90] Patients with an human leukocyte antigen (HLA) type of DR15, younger age, and a short duration of transfusion dependence are most likely to respond.[47,91,92] Antithymocyte globulin usually is given at a dose of 40 mg/kg/day intravenously for 4 consecutive days, along with a course of corticosteroids for prevention of serum sickness. [91,92] Responses generally occur within 8 months, and approximately one third of patients who are transfusion dependent achieve durable transfusion independence.[91–93]

Cyclosporine has been evaluated in patients with MDS. It appears that patients who respond to antithymocyte globulin also are likely to respond to cyclosporine. Most patients treated with cyclosporine were classified as having refractory anemia, and patients expressing HLA DR15 were more likely to respond. Adverse events reported include renal failure and septicemia.[94] Addition of cyclosporine to antithymocyte globulin does not improve disease response to treatment.[95] The role of immunosuppression in treating patients with MDS is being evaluated in a prospective randomized controlled trial.

Immunomodulating Drugs Thalidomide and lenalidomide are immunomodulating drugs, frequently referred to in the literature as *IMiDs*. Thalidomide originally was marketed in Europe as a sedative and antiemetic. Following widespread use, birth defects in children of women taking thalidomide were noted, leading to withdrawal of thalidomide from the market in the 1960s. Thalidomide later was discovered to possess antiinflammatory, antiangiogenic, and antiapoptotic properties, which led to investigation of the drug as a potential treatment of MDS, with responses reported in 11% to 56% of patients treated and with few complete responses.[96–98] Poor patient tolerance limits the use of thalidomide; 15% to 64% of patients in clinical trials discontinue therapy because of intolerable adverse effects. Common adverse effects include fluid retention, peripheral neuropathy, thrombosis, sedation, and constipation.

Lenalidomide is structurally similar to thalidomide but offers a distinct side-effect profile and potentially enhanced therapeutic effects.[99,100] Lenalidomide is more potent in vitro than thalidomide with respect to T-cell modulation and inhibition of tumor necrosis factor-α, a proapoptotic and proinflammatory cytokine. Compared with thalidomide, lenalidomide is less commonly associated with fluid retention, 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 discontinuation of treatment.[100] Lenalidomide undergoes substantial renal elimination. Dose reductions in patients with renal insufficiency are recommended to decrease the likelihood of significant marrow suppression.[101]

An uncontrolled trial of lenalidomide in 43 patients with MDS reported an overall response in 56%, with 62% of patients who were transfusion dependent becoming transfusion independent.[102] A subgroup of patients expressing a clonal deletion on chromosome 5q were noted to have an 83% complete response rate. These encouraging results led to a subsequent phase II trial of patients with a 5q deletion and transfusion-dependent anemia. Complete resolution of cytogenetic changes was noted in 45% of patients, with 67% of patients achieving transfusion independence.[103] The median time to response was 4 weeks. These results led to FDA approval of lenalidomide 10 mg orally once daily for treatment of low-risk MDS with a 5q deletion.

Based on the activity of lenalidomide in low-risk MDS patients, the drug is being evaluated in patients with higher-risk MDS. Preliminary results of A phase I/II trial of lenalidomide were recently reported in patients with higher-risk MDS with a 5q deletion and other cytogenetic abnormalities.[104] Responses by IWG criteria occurred in 6 of 29 evaluable patients (21%), but significant myelosuppression was reported and most patients required hospitalization. Patients with thrombocytopenia or additional cytogenetic complexity progressed rapidly despite the intervention. In another phase II study of 214 patients with low and intermediate-1 risk MDS without 5q deletions, lenalidomide therapy resulted in transfusion independence in 26% of patients, with 43% achieving hematologic improvement by IWG criteria.[105]

Lenalidomide produces high rates of sustained transfusion independence in patients with low and intermediate-1 risk MDS with 5q deletions. The response rate to lenalidomide is lower in patients with higher-risk MDS, and those without a 5q deletion. Careful consideration of the risks and benefits are needed prior to initiating lenalidomide in patients with higher-risk MDS or those without a 5q deletion.

TREATMENT OF MDS BASED ON IPSS RISK STRATIFICATION

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.[54,59]

Low or Intermediate-1 IPSS Risk

Patients with low or intermediate-1 risk may be managed with supportive care alone; those who are likely to respond to erythropoietic agents should be managed with this strategy because it is well

tolerated.[54] Patients with endogenous erythropoietin less than 500 IU/L and a low transfusion requirement are most likely to respond to erythropoietin. Addition of low-dose G-CSF may benefit some patients who do not respond to erythropoietin alone. Most patients eventually will stop responding to erythropoietic agents and develop an increased need for transfusions; these patients may benefit from more intensive therapy.[59]

9 The NCCN recommends DNA hypomethylating agents (azacitidine and decitabine) for low and intermediate-1 risk patients with clinically significant neutropenia or thrombocytopenia and patients with anemia that is unlikely to respond to or has not responded to a trial of erythropoietin.[54] Small numbers of low and intermediate-1 risk MDS patients have enrolled in those clinical trials, and further research is needed to delineate the place of these agents in therapy for these patients. Responses often require 2 to 4 months of therapy, and the duration of response is generally less than 1 year. Azacitidine and decitabine have not been compared in a head-to-head trial, and the clinical trials of each agent enrolled different patient populations and used different response criteria, making it difficult to determine if one agent is superior. DNA hypomethylating agents are appropriate for low and intermediate-1 risk MDS patients who are transfusion dependent or who are symptomatic despite management with best supportive care.[59]

10 The current NCCN treatment guideline for MDS recommends immunosuppressive therapy (antithymocyte globulin or cyclosporine) as a treatment option for patients with low-risk MDS expressing HLA DR15 and symptomatic anemia who are unlikely to respond to erythropoietic agents.[54] The potential benefit of transfusion independence must be considered carefully in the context of complications that can arise from immunosuppressive treatments.

In a large clinical trial, 26% of low and intermediate-1 risk MDS patients without a chromosome 5 deletion achieved transfusion independence with lenalidomide therapy.[105] These results suggest that lenalidomide may be an appropriate therapy in patients with low and intermediate-1 risk MDS without chromosome 5 deletion.[105]

Patients with an isolated deletion of chromosome 5q and no excess marrow blasts are a distinct WHO category of MDS termed 5q–syndrome. This subtype of MDS is characterized by severe refractory anemia often requiring frequent RBC transfusions.[106] 5q–Syndrome is associated with a low risk for progression to AML and a prolonged survival. Therapy with lenalidomide leads to transfusion independence in two thirds of patients and cytogenetic remissions in 45% patients. 11 Lenalidomide currently is recommended for patients with symptomatic anemia and low-risk MDS expressing a 5q deletion.[54,106,107] Patients with multiple cytogenetic abnormalities, including chromosome 5 deletions, may respond to lenalidomide, although the response rate is lower.

Intermediate-2 or High IPSS Risk

Patients with intermediate-2 or high-risk disease who are candidates for intensive therapy should receive an allogeneic HSCT, if possible, because it is the only curative option for MDS.[54,59] Patients may receive intensive chemotherapy to achieve disease control during the process of finding a donor and referral to a transplant center. They also may proceed directly to allogeneic HSCT without cytoreduction. The NCCN guidelines suggest that high-intensity chemotherapy without subsequent allogeneic HSCT be conducted as part of a clinical trial for intermediate-2 and high-risk MDS patients.[54] However, 40% to 60% of patients may achieve a complete response with conventional induction therapy for AML, and, although transient, this may ameliorate cytopenias and offer some short-term benefits.[59]

DNA hypomethylating agents should be considered for intermediate-2 and high-risk MDS patients who are not eligible for allogeneic HSCT based on the observation that azacitidine prolongs survival in these patients.[58]

Although clinical trials are beginning to determine which therapies are effective in patients with different risk categories, none of the therapeutic options have been directly compared in a clinical trial. In addition, how to manage patients who progress or do not respond to initial therapy is not clear.

PHARMACOECONOMIC CONSIDERATIONS

Data on the cost effectiveness of the various therapeutic options for MDS are limited. The two reports available used different methodologies, and one study was performed in the United States and the other in France. Therefore, comparing the two strategies is difficult, and there may be differences in what is perceived as beneficial to society.

A prospective, randomized trial compared patients treated with best supportive care to patients treated with erythropoietin plus G-CSF for 1 year.[67] Information on resource use was collected prospectively. The Functional Assessment of Cancer Therapy (FACT) questionnaire was used to assess quality of life. Mean costs per subject were £8,746 for supportive care verus £26,723 for rHG-CSF plus erythropoietin. The difference was attributed to drug costs because there was no difference in transfusion requirements. The findings from this study show that combination therapy is expensive and does not improve quality of life. However, another study reported improved quality of life in patients who responded to therapy with erythropoietin and G-CSF. Therefore, the value of this intervention remains controversial.[67]

A retrospective cost analysis based on the results of the phase II study of patients with MDS with deletion 5q with or without additional cytogenetic abnormalities showed that the cost of treatment with lenalidomide was offset largely by the decrease in cost of transfusions and erythropoietin.[108] The investigators reported an annual cost of $63,385 for lenalidomide compared to $54,940 for best supportive care. The authors reported a cost-effectiveness ratio of $35,050 per quality-adjusted life-year, a ratio that is within the generally acceptable range for a new therapy. However, this analysis was based on assumptions regarding the quality of life in transfusion dependence and transfusion independence rather than direct measurements of quality of life.

Further clinical trials should include measurement of quality of life because this is the primary goal of therapy for most patients with MDS. Many of the therapies for MDS do not improve overall survival and are implemented with the goal of improving quality of life. Formal quality-of-life assessment and cost effectiveness analyses will aid in determining the most appropriate therapy for patients.

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.[56] The IWG for MDS recently updated guidelines for response criteria in MDS clinical trials to categorize patient responses into more clinically relevant categories that correlate with quality of life or morbidity.[56,57] Based on these criteria, the four treatment goals are altering the natural history of the disease, cytogenetic response, hematologic improvement, and quality of life. Patients with MDS should have regular followup with a history, physical examination, and complete blood counts. The frequency of followup varies with the natural history of each patient from weekly to every 6 months.

CONCLUSIONS

MDS is a common hematologic malignancy in elderly patients. The disease varies along a spectrum, from an indolent disease from which patients may die of other causes to rapid progression to AML.

Research has led to a better understanding of the biology of the disease and better classification systems to stratify patients and predict natural history or response to therapeutic interventions. Several new therapeutic modalities have been developed, and therapies that have been used for several years continue to be refined. Although knowledge about MDS has greatly advanced in the last decade, many questions remain unanswered. The goal for future therapies should be to prolong disease-free survival and improve quality of life in patients with MDS. Clinical trials will need to evaluate these end points to evince the value of a therapeutic intervention.

ABBREVIATIONS

ALL: acute lymphoblastic leukemia

AML: acute myeloid leukemia

CALGB: Cancer and Leukemia Group B

DNA: deoxyribonucleic acid

FAB: French-American-British

FACT: Functional Assessment of Cancer Therapy

FDA: Food and Drug Administration

G-CSF: granulocyte colony-stimulating factor

GM-CSF: granulocyte-macrophage colony-stimulating factor

HLA: human leukocyte antigen

HSCT: hematopoietic stem cell transplantation

IMiD: immunomodulating drug

IMRAW: International MDS Risk Analysis Workshop

IPSS: International Prognostic Scoring System

IWG: International Working Group

MDS: myelodysplastic syndromes

MDS-U: myelodysplastic syndrome, unclassified

NCCN: National Comprehensive Cancer Network

RAEB-1: Refractory Anemia with Excess Blasts-1

RAEB-2: Refractory Anemia with Excess Blasts-1

RAEB-T: Refractory Anemia with Excess Blasts in Transformation

RBC: Red blood cell

RCMD-RS: Refractory Cytopenia with Multilineage Dysplasia and Ringed Sideroblasts

t-MDS: therapy-related MDS

WHO: World Health Organization

WPSS: World Health Organization Classification-based Scoring System

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