Current and novel therapeutic approaches in myelodysplastic syndromes

Fayez Estephan, MD,[a] and Ramon V Tiu, MD[a,b]

[a]Department of Translational Hematology and Oncology Research, and [b]Department of Hematologic Oncology and Blood Disorders, Taussig Cancer Institute, Cleveland Clinic, Cleveland, Ohio

Myelodysplastic syndromes (MDS) are a heterogeneous group of hematologic neoplasms with an annual incidence of 4.1 cases per 100,000 Americans. Patients with MDS suffer from chronic cytopenias that may lead to recurrent transfusions, infections, and increased risk for bleeding. They are also at risk for progression to acute myeloid leukemia. Allogeneic hematopoietic cell transplantation is the only potentially curative treatment for MDS, although 3 drugs have been approved by the US Food and Drug Administration for its treatment: lenalidomide, 5-azacitidine, and decitabine. These therapies can be effective in the relief of cytopenias, achievement of cytogenetic remissions, and reduction in bone marrow blasts. 5-azacitidine has also been shown to improve overall survival. However, there remain many unmet needs in the treatment of MDS. Breakthroughs in our understanding of the complex pathogenesis of MDS through epigenetic, genetic, immunologic, and other biological mechanisms have allowed us to develop new therapeutic strategies that can lead to improvements in outcomes in MDS. In this review, we aim to provide an overview of the evolution in classification and risk stratification in MDS and to illustrate how we can use this to guide us in tailoring therapeutic choices in this disease. Responses and outcomes related to commonly used MDS therapies will be discussed together with novel therapies that have evolved with the improved understanding of MDS pathophysiology.

Myelodysplastic syndromes (MDS) are a group of clonal hematopoietic stem cell neoplasms that are characterized by aberrant myeloid lineage differentiation, dysplastic myeloid changes, ineffective hematopoiesis, and increased genomic instability. This is manifested clinically by chronic peripheral blood (PB) cytopenia(s) and an increased risk of progression to acute myeloid leukemia (AML).[1] MDS is not only genetically and morphologically heterogeneous but also can vary significantly in its natural history and prognosis. Some MDS patients have symptomatic disease with survival limited to a few months, whereas others are only minimally symptomatic with survival measured in decades.[2]

MDS is predominantly a disease of the elderly. About 86% of patients with MDS are diagnosed after the age of 60 years, with a median age at diagnosis of 76 years. MDS infrequently occurs in patients aged 50 years or younger, accounting for only 6% of cases.[3] Men have a higher incidence rate of MDS than do women, and whites have higher incidence rates than do other ethnic groups.[3] There was a steady increase in the age-adjusted incidence rate of MDS in the United States during 2001-2008. There were 3.6 cases per 100,000 people in 2001, 3.8 cases in 2002, and 4.1 to 4.6 cases per 100,000 persons from 2003 to 2008.[2] That corresponds to about 15,000-20,000 new cases per year in the United States. As the incidence of MDS is slightly higher than that of AML and survival rates in patients with MDS are considerably higher compared with patients with AML, the prevalence of MDS is far greater than that of AML. Despite this growing prevalence, MDS remains understudied compared with many other hematologic malignancies. Although most MDS cases are de novo, about 10% of MDS patients have secondary or therapy-related MDS.[2] Prognosis in secondary MDS is poorer compared with that in de novo MDS, with more complex cytogenetic abnormalities, and it is expected that rates of secondary MDS will continue to rise with increased use of chemotherapy and radiation for other primary malignancies.

Pathogenesis

Although the pathogenesis of MDS is not fully understood, complex epigenetic, genetic, and immunologic mechanisms contribute to it and account for disease heterogeneity. Aberrant silencing of tumor-suppressor and DNA repair genes mediated by hyper-methylation of their promoters is believed to play an important role in the pathogenesis of MDS. This theory is supported by the unique sensitivity of MDS to drugs such as 5-azacytidine and decitabine that reverse DNA methylation.[4] This DNA repair

Accepted for publication March 27, 2014. Correspondence: Ramon V Tiu, MD; tiur@ccf.org. Disclosures: The authors have no disclosures. Published online 2014. JCSO 2014;12:236-249. ©2014 Frontline Medical Communications. DOI 10.12788/jcso.0057.

TABLE 1 Frequency of the most commonly mutated genes in myelodysplastic syndromes and other myeloid neoplasms

Gene pathway	Gene name	Frequency, %		
		MDS	MDS–MPN	AML
Methylation	*TET2*	12-14	37-46	9-43
	IDH ½	1-5	9	5-10
	DNMT3A	8	12	25
Histone/acetylation	*ASXL1*	21	17-46	17
	EZH2	2	4-12	1
	SETPB1	4.1	9.4	0.9-9.1[a]
Signaling	*CBL*	1-2	5	9
	N-RAS	4	7	9-40
	K-RAS	1	4	5-17
Splicing	*SF3B1*	4[b]	7[c]	5-6
	U2AF1	6-12	8-17	1-10
	SRSF2	6-12	28-47	1-7
Transcriptional factors	*TP53*	8	7	56-78
	RUNX1	9	13	13

AML, acute myeloid leukemia; MDS, myelodysplastic syndromes; MDS–MPN, MDS–myeloproliferative neoplasms

[a]Frequency for de novo and secondary AML respectively. [b]Frequency is 68% in refractory anemia with ring sideroblasts. [c]Frequency is 81% in refractory anemia with ring sideroblasts associated with marked thrombocytosis.

defect may be the cause behind chromosomal instability and repetitive chromosomal defects in MDS.[5,6]

More than 40 recurrently mutated genes have been identified in patients with MDS, with several more being discovered as genome sequencing technologies continue to improve. A recent large study demonstrated that 78% of MDS cases had at least 1 or more of these recurring mutations, which are summarized by the genetic pathways in Table 1.[7] Mutations of splicing factors genes (*SF3B1*, *SRSF2*, *U2AF1*, and *ZRSR2*), for example, are present in 12.4% of MDS patients and have been shown to carry prognostic significance.[8] Mutations in *SF3B1* play a role in the pathogenesis of the MDS subtype refractory anemia with ringed sideroblasts (RARS), with those patients having a more favorable prognosis than those with the wild type gene.[9-11] It is likely that every MDS patient harbors 1 or more somatic driver mutation responsible for the development and progression of the disease. The diverse manner by which these driver mutations coexist can help explain the clinical variability associated with MDS and can therefore aid in disease classification and outcome prediction.[12] These genetic abnormalities are among the strongest prognostic indicators and can also affect therapeutic decision. Clonal karyotypic abnormalities, which are detected using conventional karyotyping, are observed in 50% of patients with MDS. The most common chromosomal aberrations in MDS include deletions of the long arm of chromosome 5 (del5q), monosomy Y, monosomy 7 (7q-); or deletion of its long arm (del7q), trisomy 8, del20q, and complex karyotypes (≥ 3 chromosomal aberrations). These chromosomal changes can be identified through various methods, including metaphase cytogenetics, fluorescence in situ hybridization, or single nucleotide polymorphism array analysis. These cytogenetic abnormalities correlate with the prognosis of patients with MDS (eg, poor prognosis with complex karyotypes and 7q- compared with better prognosis with isolated del5q).[4,13-15] Immunologic aberrations have also been proposed to contribute to the pathogenesis of MDS. For example, in early-stage MDS, an aberrant immune attack on myeloid progenitors resulting in increased apoptosis can contribute to bone marrow (BM) failure. This is supported by the association of some forms of MDS with autoimmune diseases and observed responses in some patients to immunosuppressive therapies.[16]

Tumor necrosis factor-alpha (TNF-α) is a well-recognized cytokine that has been found to promote apoptosis in erythroid cells in the early stages of MDS. Indeed, the ineffective hematopoiesis present in MDS seems to be the result of excessive apoptosis of hematopoietic precursors, which explains the apparent paradox of a hypercellular BM and PB cytopenias.[17] In addition to intrinsic sensitivity to apoptosis induction, the stromal microenvironment has been shown to impair the ability to support differentiation.[18] Other recently elucidated path-

ways that are important in MDS pathogenesis include MAP kinase, aberrations in P38 pathway, and tumor growth factor-beta (TGF-β) pathway.

Prognostic classification

Because of the heterogeneity in the morphology as well as outcomes of MDS, attempts at classifying it into subtypes that have common morphology, molecular causes, responses to treatment, and prognosis began only in the 1980s. The French-American-British (FAB) system, introduced in 1976, was the first classification scheme for MDS. This scheme is primarily based on morphology, BM and PB blast percentage, and PB monocyte count.[19,20] The FAB classification designates 5 categories: refractory anemia (RA), RARS, RA with excess blasts (RAEB), chronic myelomonocytic leukemia (CMML), and RAEB in transformation (RAEB-T). Although the FAB system is a diagnostic classification, it also has major prognostic relevance.[21,22]

The International Prognostic Scoring System (IPSS) followed the FAB and it is the result of combined cytogenetic, morphologic, and clinical data from 7 large risk-based MDS studies. Since its inception in 1997, it has formed the foundation for clinical and therapeutic guidelines and has become the standard clinical tool for risk assessment in patients with MDS. [23] The IPSS classifies de novo MDS patients into 4 groups: low risk, intermediate-1 (INT-1), intermediate-2 (INT-2), and high risk, based on BM blast proportion, cytogenetics, and PB cytopenias. The corresponding median overall survival (OS) of these groups is 5.7, 3.5, 1.2, and 0.4 years, respectively.[23] Despite its success as a prognostic scoring system, several limitations of the IPSS became evident over time. This includes its exclusion and thus inapplicability to therapy-related (t)-MDS, proliferative CMML patients with white blood cell count of > 12,000/uL) and MDS/myeloproliferative neoplasms (MPN) overlap phenotypes. The original IPSS also did not account for important prognostic parameters such as red blood cell (RBC) transfusion-dependence, severity of cytopenias, and multilineage dysplasia, and underweighted the prognostic importance of karyotype relative to BM blasts.[24,25] It also included patients with up to 30% of blasts in their BM (considered to have AML by current World Health Organization [WHO] criteria), and it has been demonstrated that the original IPSS underestimated the poor outcome of a significant subgroup of patients classified by the IPSS as low or INT-1 who actually had an aggressive disease course with shorter survival than predicted by the IPSS.[26,27]

To overcome those limitations of the IPSS, a much larger cohort of patients (n = 7,012, compared with the original IPSS cohort of n = 816) was used to update and create what is now called the Revised IPSS (R-IPSS). Compared with the IPSS, the R-IPSS incorporates more chromosomal abnormalities and cytogenetic risk groups, gives more weight to the severity of individual cytopenia(s), decreases the relative weight of BM blasts, and stratifies patients based on these criteria into 5 prognostic groups (very low, low, intermediate, high, and very high) with significantly different outcomes instead of the 4 groups in the IPSS.[28] Although the R-IPSS better defines the risk stratification and the prognosis of MDS patients, it still does not incorporate any of the epigenetic, genetic, and immunologic prognostic markers; and as with the IPSS, it does not address t-MDS and MDS-MPN overlap patients. Furthermore, the multiplicity of factors included and the new cytogenetic categorization makes the assessment cumbersome and difficult to use in its complexity in a typical community setting.

Both the IPSS and R-IPSS were designed for patients at time of a new diagnosis of MDS and may not be as applicable to a patient who has been previously diagnosed or is already undergoing treatment with disease-modifying agents. However, the Groupe Francophone des Myelodysplasies used the R-IPSS in 282 INT-2 to high-risk MDS patients treated with AZA and found that it may provide prognostic value for survival. Using time-dependent covariates, the World Prognostic Scoring System was developed as a dynamic scoring system that can be used at any time during a patient's disease course and takes into account factors such as WHO diagnosis, cytogenetic risk grouping using the original IPSS cytogenetic risk categorization, and RBC transfusion dependence.[29] To overcome the limitations of IPSS, other prognostic scoring systems have been developed. These include the MD Anderson Comprehensive Scoring System (MDACSS), which used data from 1,915 patients. This prognostic model gives weight to age, performance status, and severity of cytopenias. It divides MDS patients into 4 risk groups with distinct differences in survivals. The major advantage of the MDACSS is that it includes patients with CMML, MDS–MPN overlap, and t-MDS; and it is dynamic in nature and therefore can be used for previously diagnosed patients who are seen in the clinic. A disadvantage to this prognostic system is its complexity, which has limited its clinical usage despite its diagnostic precision. Table 2 summarizes the prognostication systems.

Although these prognostic tools were developed to inform clinical decision-making, it is important to remember that none was designed to predict the patient's response to any particular therapeutic modality for MDS.

Management of patients with MDS

Despite the recent advances in MDS drugs, allogeneic hematopoietic cell transplantation (allo-HCT) remains the only potential curative treatment for MDS and other

TABLE 2 Most commonly used prognostic scoring systems in myelodysplastic syndromes

Scoring system	Prognostic parameters		Score	Risk group	Total score	Median OS, y	Leukemia progression
IPSS	BM blasts, %	< 5%	0	Low	0	5.7	9.48[a]
		5-10%	0.5				
		11-20%	1.5	INT-1	0.5-1	3.5	3.3
		21-30%	2.0				
	Cytogenetic risk group[b]	Good	0	INT-2	1.5-2	1.2	1.1
		Intermediate	0.5				
		Poor	1.0	High	≥ 2.5	0.4	0.2
	Number of PB cell lineages affected by cytopenia	0-1	0				
		2-3	0.5				
IPSS-R	BM blasts, %	≤ 2%	0	Very low	< 1.5	8.8	Not reached[a]
		> 2% , < 5%	1				
		5%-10%	2				
		> 10%	3				
	Cytogenetic risk group[c]	Very good	0	Low	> 1.5-3	5.3	10.8
		Good	1				
		Intermediate	2	INT	> 3-4.5	3	3.2
		Poor	3				
		Very poor	4				
	Hemoglobin, g/dL	≥ 10	0	High	> 4.5-6	1.6	1.4
		8-10	1				
		< 8	1.5				
	ANC, x 10^9/L	≥ 0.8	0	Very high	> 6	0.8	0.7
		< 0.8	0.5				
	Platelet count, x 10^9/L	≥ 100	0				
		50-100	0.5				
		< 50	1				
WPSS	WHO classification	RA, RARS, MDS with del(5q) alone	0	Very low	0	>10	0.06[d]
		RCMD	1				
		RAEB-1	2	Low	1	8-9	0.24
		RAEB-2	3				
	Cytogenetic risk group[e]	Good	0	INT	2	4.5-5.5	0.48
		Intermediate	1	High	3	1.8-2.5	0.63
		Poor	2				
	Hb, g/dL (< 9 in men, < 8 in women)	Yes	1	Very high	4	0.5-1	1.0
		No	0				

Continued on next page

TABLE 2 *continued from p. 239*

Scoring system	Prognostic parameters		Score	Risk group	Total score	Median OS, y	Leukemia progression
MDAPSS	BM blasts, %	5-10	1	Low	0-4	4.5	na[f]
		11-29	2				
	WBC count, x 10^9/L	> 20	2	INT-1	5-6	2.1	na
	Hb, g/dL	< 12	2				
	Platelet count, x 10^9/L	50-199	1				
		30-49	2				
		< 30	3	INT-2	7-8	1.2	na
	Age, y	≤ 60	0				
		60-64	1				
		≥ 65	2				
	Performance status	≥ 2	2	High	≥ 9	0.5	na
	Cytogenetic group	Chromosome 7 abnormality or ≥ 3 abnormalities	3				
		All others	0				
LR-MDAPSS	Cytogenetic group	Normal or del (5q) alone	0	Cat-1	0-2	6.6	na
		All others	1				
	Age, y	< 60	0				
		≥ 60	2	Cat-2	3-4	2.25	na
	Hb, g/dL	< 10	1				
	Platelet count, x 10^9/L	50-200	1	Cat-3	> 5	1.2	na
		< 50	2				
	BM blasts, %	≥ 4	1				

AML, acute myeloid leukemia; ANC, absolute neutrophil count; BM, bone marrow; Cat, category; del(5q), deletion in long arm of chromosome number 5; dL, deciliter; g, gram; Hb, hemoglobin; INT, intermediate; IPSS, International Prognostic Scoring System; L, liter; LR-MDAPSS, Lower-risk MD Anderson Comprehensive Scoring System; MDAPSS, MD Anderson Comprehensive Scoring System; na, not applicable; OS, overall survival; PB, peripheral blood; PS, performance status; RA, refractory anemia, RAEB, refractory anemia with excess blasts; RARS, refractory anemia with ring sideroblasts; RBC, red blood cells; RCMD, refractory cytopenia with multilineage dysplasia; R-IPSS, Revised International Prognostic Scoring System; WBC, white blood count; WHO, World Health Organization; WPSS, WHO classification-based Prognostic Scoring System

[a]Time to 25% AML evolution measured in years.
[b]R-IPSS, Good = Normal, -Y, del(5q), del (20q); Poor = chromosome 7 abnormality, complex (> 3 abnormalities); Intermediate = +8 and any other single or double abnormality.
[c]R-IPSS, Very good = del(11q), -Y; Good = normal, del(20q), del(5q)alone or with one other abnormality, del(12p); Intermediate = +8, del(7q), i(17q), +19, +21, any single or double abnormality not listed, 2 or more independent clones; Poor = del(3q), -7, double with del(7q), complex with 3 abnormalities; Very poor = complex with more than 3 abnormalities.
[d]Cumulative probability of AML progression in 5 years.
[e]WPSS, Good = Normal, -Y, del(5q), del (20q); Poor = chromosome 7 abnormality, complex (> 3 abnormalities); Intermediate = +8 and any other single or double abnormalities not included in the good or poor risk category.
[f]Only 10% of patients eventually transformed to AML. Factors associated with significant AML progression were IPSS INT-1 vs LR BM blast, infection at presentation, and chromosome 7 anomalies by univariate analysis and only BM blasts, chromosome 7 anomalies and infection by multivariate analysis.

myeloid neoplasms. As such, it should always be considered as a potential therapeutic option, especially in higher-risk MDS. However, fewer than 5% of MDS patients can benefit from allo-HCT because of their advanced age, associated comorbidities, and/or lack of suitable donors.[30] After it has been determined that the patient is not a candidate for transplant, the next step in management is to decide whether to use disease modifying agents that can alter the disease course or supportive therapies that include expectant management, RBC and platelets transfusion, hematopoietic growth factors, antibiotics, and iron chelation agents when needed. Three disease-modifying agents have

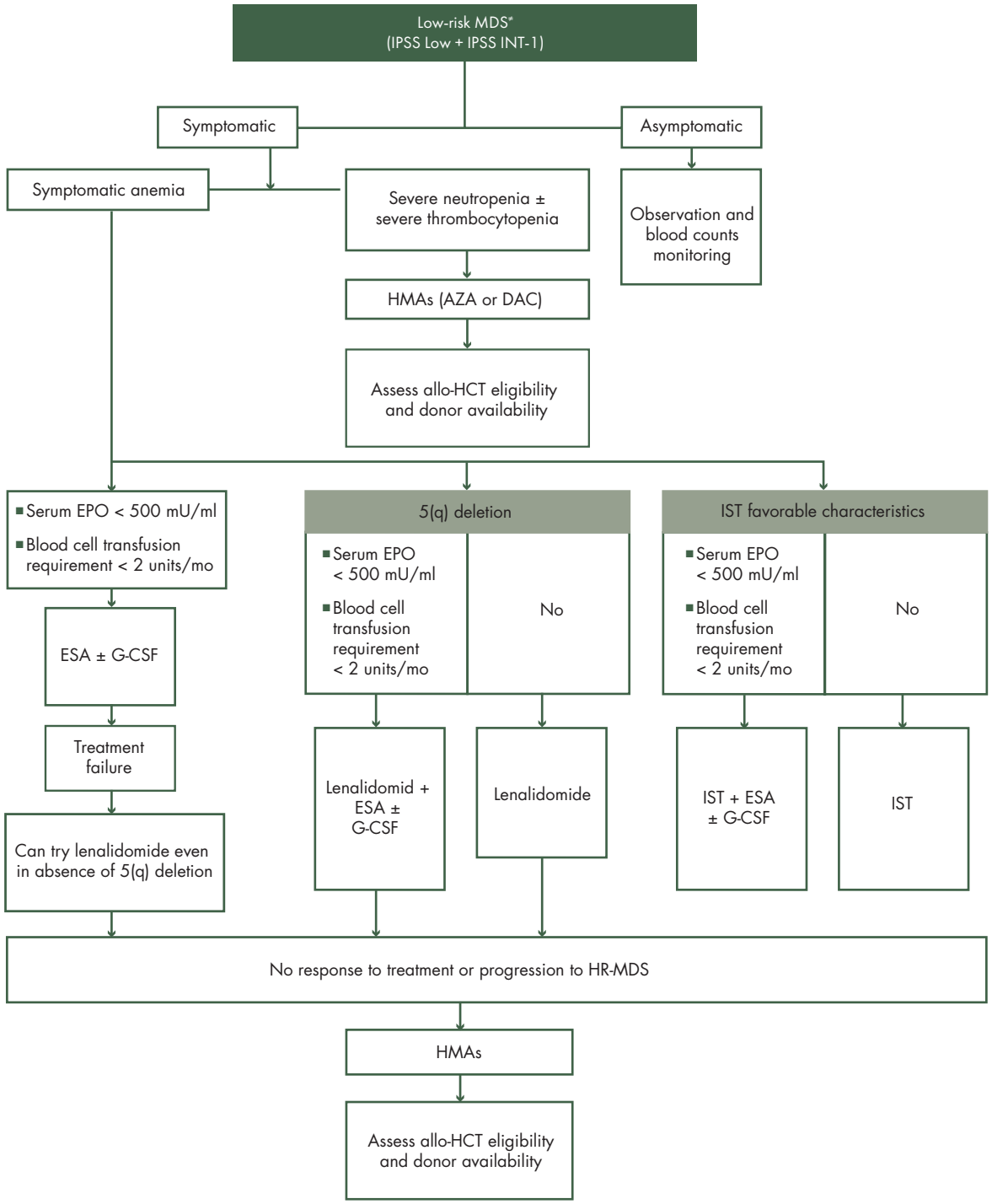

FIGURE 1 A summary of the treatment decision for patients with lower-risk myelodysplastic syndromes. Clinical trials should always be considered in patients with MDS.

Allo–HCT, allogeneic hematopoietic cell transplant; AZA, azacitidine; DAC, decitabine; EPO, erythropoietin; ESA, erythropoiesis-stimulating agent; G-CSF, granulocyte colony stimulating factor; HR-MDS, high-risk MDS; HMA, hypomethylating agents; IPSS, International Prognostic Scoring System; IPSS-INT-1, International Prognostic Scoring System–Intermediate 1; IST, immunosuppressive therapy; MDS, myelodysplastic syndromes

been approved by the US Food and Drug Administration (FDA) for the treatment of MDS: lenalidomide, an immunomodulatory agent that is approved for lower-risk and transfusion-dependent patients with del (5q) chromosomal abnormality; and azacitidine and decitabine, 2 DNA methyltransferase inhibitors (DNMTi) that have bee approved for all MDS patients but are most effective for higher-risk patients. Treatment goals are generated depending on the patient's risk stratification, age, and comorbidities. Despite the aforementioned limitations of the IPSS, it is still the most commonly used prognostic system for therapeutic decision making. IPSS patients are divided into 2 major risk groups: lower-risk (LR) MDS (low- and INT-1-risk groups) and higher-risk (HR) MDS (INT-2- and high-risk groups).

Lower-risk MDS

Patients in this group are either asymptomatic or have symptoms related to peripheral cytopenias and mostly related to anemia, such as persistent fatigue and dyspnea on exertion. Asymptomatic patients may only need periodic PB count monitoring. In symptomatic LR-MDS patients, the goal of therapy is to minimize the need for blood transfusions, alleviate symptoms, and improve their quality of life. The 3 most commonly used drugs for the treatment of these groups of patients are erythropoiesis-stimulating agents (ESAs), immune suppressive therapy (IST), and lenalidomide (Figure 1). Supportive management through careful blood count monitoring and judicious use of transfusion of blood components, antibiotics, and iron chelation may also be appropriate for some LR-MDS.

ESAs – epoetin, darbepoetin. Anemia is the most commonly encountered cytopenia in MDS patients. About 80%-90% of MDS patients develop anemia during the course of the disease and of those, 40% become transfusion dependent.[29,31] Anemia in MDS is the result not only of ineffective erythropoiesis but also the lack of response to erythropoietin. ESAs are the most commonly used therapy for MDS even though they have not been approved by the FDA for the treatment of MDS-related anemia.[32,33] Before starting treatment with an ESA, it is important to correct any contributing factor to anemia, such as nutritional deficiencies (iron and folate) and gastrointestinal (GI) bleeding.[30]

The doses of ESAs used for MDS-related anemia, a condition associated with relative intrinsic resistance to erythropoietin, are higher than those used for renal disease-related anemia, which is usually associated with normal BM responsiveness. According to the National Comprehensive Cancer Network management guidelines for myelodysplastic syndromes, the recommended starting doses are 40,000-60,000 units given 1-3 times a week for the recombinant human erythropoietin alpha (rEPO) and 150-300 mcg/week for the longer-acting form of darbepoetin, with both agents administered subcutaneously. Darbepoetin, administered every 3 weeks at a dose of 500 mcg also seems effective in correcting anemia associated with LR-MDS.[34,35] A minimum of 6-8 weeks of ESA treatment is recommended to evaluate ESA response before deciding to discontinue therapy.

ESAs in MDS have been associated with increased risk of thromboembolic events compared with ESAs in certain solid tumors.[36] About 40% of LR-MDS patients treated with ESAs achieve significant erythroid response with median response duration of 2 years, without an increased risk of leukemia progression.[37,38] Based on a meta-analysis of 162 MDS trials conducted during 1985-2005, ESAs have been shown to provide an OS benefit and to decrease the rate of disease progression compared with non-ESA therapies. However, this has not been proven in any prospective, randomized clinical trial. Granulocyte colony stimulating factors can be synergistic with ESAs to augment erythroid response rate especially in patients with RARS.[33] In LR-MDS transfusion depended patients who failed ESA treatment, lenalidomide should be taken into consideration even without (5q-) syndrome.

Lenalidomide. The (5q-) syndrome is a subgroup of MDS characterized by deletion of the long arm of chromosome 5. Patients with this syndrome usually have refractory macrocytic anemia, normal or increased platelet count, low BM blast percentage, and small hypolobated dysplastic megakaryocytes. They also have an indolent course and lower rates of leukemic progression.[39,40] Lenalidomide, an orally bioavailable derivative of thalidomide, is an immunomodulatory agent that can lead to high response rates in LR-MDS patients with 5q deletion. In a phase 2 trial, transfusion independence (TI) was achieved in 67% of patients, with a median response rate of more than 2 years. In addition, complete cytogenetic response was observed in 45% of patients and partial cytogenetic response was observed in 73% of patients, indicating a direct cytotoxic effect of lenalidomide on the neoplastic clone. There was also significant improvement in quality of life and reduction in leukemic progression noted in patients who responded to lenalidomide therapy.[40,41] On the basis of those findings, lenalidomide was approved by the FDA for the treatment of LR-MDS (IPSS low or INT-1) patients with (5q) deletion. Despite the encouraging results of lenalidomide in this group of patients, no prospective study has shown a survival benefit with long-term usage.[41]

Lenalidomide also has efficacy in non-del5q patients. TI was achieved in 26% of non-del5q patients after a median of 4.8 weeks of treatment and responses were generally robust with a median duration of response of 41 weeks.[42]

In higher-risk MDS (HR-MDS) patients with (5q) deletion, TI was achieved in 25% of the patients with a median duration of TI of 6.5 months.[43]

Side effects observed with lenalidomide therapy include: skin rash, dryness and pruritus, fatigue and muscle cramps, nausea and GI disturbance, appearance of new cytopenia(s) especially neutropenia and thrombocytopenia, or worsening of existing cytopenia(s) and associated complications (bleeding, fatigue, and infection).

Immunosuppressive therapy. Multiple prospective studies have been conducted to assess response to IST as a therapeutic intervention for MDS. In a large analysis of 139 MDS patients who received IST cyclosporine A (CSA), antithymocyte globulin (ATG), or both, the median follow-up was 3 years. The overall response rate (ORR) was 30% (8% for CSA, 24% for ATG, 48% for combination).[44] Hematologic response to IST is usually slow and may require up to 6 months to fully manifest. Several factors have been associated with higher hematologic response to IST in patients with MDS, including patients with younger age (< 60 years), female gender, LR-MDS, BM hypocellularity, normal karyotype, HLA-DR 15 histocompatibility type, trisomy 8, and presence of a paroxysmal nocturnal hemoglobinuria clone. Based on these favorable characteristics, a scoring system to identify patients who will best respond to IST therapy has been developed.[34,44] Patients with IPSS-LR who fail therapy and those with severe thrombocytopenia or severe neutropenia can be considered for hypomethylating agent (HMA) therapy and allo-HCT if eligible.[45]

Higher-risk MDS

Patients with HR-MDS have very poor prognosis, with a survival of less than 1 year if they are not treated.[23] In appropriate candidates, allo-HCT can cure up to 40% of MDS patients; therefore eligibility for transplant should be evaluated in all HR-MDS patients.[46] The goal of treatment in patients who are not eligible for transplant is to modify the natural course of the disease and to prolong survival using HMAs and in some cases, high-intensity chemotherapy (Figure 2).

Hypomethylating agents. HR-MDS are associated with a higher number of methylated gene loci in the promoter-associated CpG islands. The increased number of methylated loci is associated with disease progression from LR-MDS to HR-MDS.[47] HMAs (azacitidine [AZA] and decitabine [DAC]) are inhibitors of DNA methyltransferases, which are the enzymes responsible for cytosine methylation.[48] HMA therapy has been approved by the FDA for all subtypes of MDS patients. In clinical practice, it is usually used in patients with an initial diagnosis of HR-MDS and in LR-MDS patients who have failed previous and other treatments.

The approved regimens of HMAs in the treatment of MDS result in an ORR of 40%-60 % and a complete remission (CR) of 10%-20%, with a median CR duration of 12-14 months and a partial remission (PR) of 10-20 months.[49-51] The regimens also improve the quality of life in MDS patients and delay progression to leukemia. Both of the drugs can lead to improvements in blood counts and a reduction of transfusion needs.[49-51] However, only AZA has also been shown to prolong median OS in HR-MDS patients in a phase 3 study.[50] Therapy with an HMA is not curative and patients are maintained on treatment as long as they are responding and not experiencing major side effects. Eventually, however, all patients will lose response to HMAs. In the first randomized phase 3 trial on AZA, it was compared with best supportive care in patients with MDS of all subtypes. Although AZA showed benefit in terms of survival and delay in AML transformation, it didn't significantly prolong survival as an endpoint because the study allowed crossover between AZA and supportive care arms.[51] Subsequently, a large phase 3 study was conducted on 358 patients with HR-MDS; patients were randomized to receive either AZA or best conventional care regimen (best supportive care, low-dose cytarabine, or induction chemotherapy) without crossover. Patients in the AZA group received 75 mg/m^2 daily doses for 7 consecutive days of a 28-day cycle with a median of 9 treatment cycles. Results from the study showed a 9% ORR with AZA, compared with 21% in the conventional care arm. More important, however, the median OS was significantly prolonged in the AZA arm (25 months) compared with the conventional-care arm (15 months), which resulted in a survival advantage of 9.5 months.[50] The median number of cycles to achieve a response is 3, and at least 4-6 cycles of AZA may be needed to achieve the best clinical response.[52] Further improvement may occur with continued treatment and is recommended as long as the patient maintains response and has no major side effects.[53] In clinical practice, outpatient administration of AZA daily for 7 consecutive days is often not feasible because of the limitations of available office hours. To address this issue, other AZA dosing schedules have been evaluated and found to result in similar responses. However, it remains unclear if these alternative dosing schedules have the same survival benefit.[54] Decitabine (DAC) is another HMA with FDA approval at a dose of 15 mg/m^2 every 8 hours over 3 days, repeated every 6 weeks, and 20 mg/m^2 over 1 hour intravenously (IV) daily for 5 days of a 28-day cycle.[55,49] DAC was compared with best supportive care in 2 randomized, phase 3 studies. One was conducted in patients with mixed MDS risk groups[49] and the other was conducted in Europe on HR-MDS only.[56] None of these studies has shown a sig-

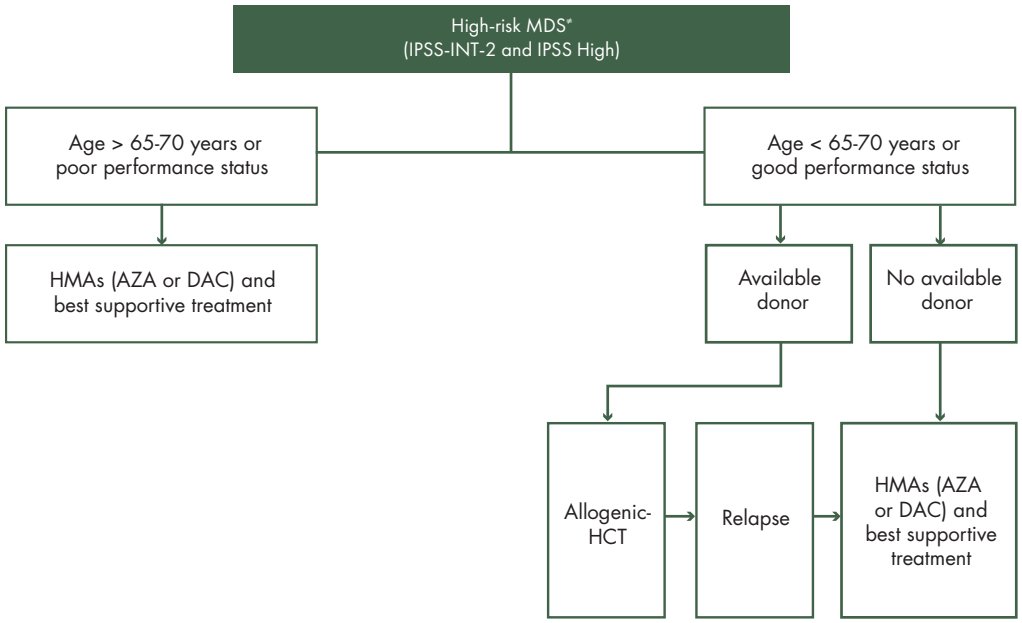

FIGURE 2 A summary of the treatment decision for patients with higher-risk myelodysplastic syndromes. Clinical trials should always be considered in patients with MDS.

Allo–HCT, allogeneic hematopoietic cell transplant; AZA, azacitidine; DAC, decitabine; HMA, hypomethylating agents; IPSS, International Prognostic Scoring System; IPSS-INT-2, International Prognostic Scoring System–Intermediate-2

nificant survival advantage. Patients who do not respond to HMA therapy and progress to AML have very poor outcomes, with a median OS of less than 6 months.[57]

The most common side effect of HMA therapy is myelosuppression. There is controversy over whether dose reduction, delaying a cycle, or maintaining the same dosing is indicated in this case.[58,59] Ways to obviate this include dose adjustment and judicious use of growth factors. Other less common side effects are fatigue, gastrointestinal disturbance, and local reactions to subcutaneous injection (SQ). IV administration of AZA (same dose/schedule) is a reasonable alternative in cases of significant local reactions to the SQ formulation or limited SQ tissue owing to cachexia.[58,60]

High-intensity chemotherapy. The use of intensive induction chemotherapy regimens similar to those used in AML results in modest clinical responses and significant toxicity, especially in elderly patients, who comprise the majority of MDS patients. The CR rate associated with intensive chemotherapy of MDS is lower compared with patients with de novo AML (40%-60%) and usually lasts for less than a year. There are some studies that show that the outcome of patients who receive intensive chemotherapy for treatment of AML arising from MDS is worse compared with de novo AML patients.[49,61] Therefore, given the high toxicity associated with chemotherapy and the absence of superior outcomes compared with HMA therapy, the use of intensive chemotherapy in MDS is usually restricted to younger patients with good performance status requiring cytoreduction before allo-HCT.[62]

Novel therapies

Treatment for MDS remains an unmet medical need, and allo-HCT is the only curative option for MDS. The increasing knowledge about the complex pathogenesis of MDS, the key genetic alterations that drive progression, and the mechanisms of action and resistance to current therapies will be vital for the development of novel and targeted treatments.

Histone deacetylase inhibitors – vorinostat, panobinostat, entinostat, and belinostat. Drugs that inhibit a group of enzymes called histone deacetylases (HDACs) that are important in posttranslational histone modification and exert epigenetic control over gene expression have been tested in MDS. Inhibition of HDACs pharmacologically may result in cell cycle arrest and subsequent apoptosis.[48] Although histone deacetylase inhibitors (HDACIs) have demonstrated very modest single-agent activity in MDS and AML clinical trials, synergistic antileukemic activity can be achieved in vitro by combining HMA therapy and HDACIs.[63] HDACIs can also be used with AZA in combination strategies (see *Combination strategies*).

P38-MAPK inhibitor. The accelerated apoptosis seen in LR-MDS is a result of intrinsic clone susceptibility and pro-inflammatory cytokines that suppress the normal and MDS clone. The P38 mitogen-activated protein kinase (MAPK) pathway is a divergent pathway for several inflammatory signals. It is overactivated in LR-MDS.[64] SCIO-469 (a P38-MAPK inhibitor) was tested in 62 patients with LR-MDS in a phase 1/2 clinical study. Hematological improvement (HI) was reported in 29% of patients (18% erythroid response, 12% platelet response, and 25% neutrophil response).[65] Arry-614 is a potent dual inhibitor of P38-MAPK and of Tie 2 (angiopoietin receptor). In a phase 1 multicenter study, single daily dose was escalated to 1,200 mg orally daily with no maximum tolerated dose (MTD) reached. The twice-a-day dose cohort was discontinued given dose-limiting toxicities at 300 mg twice daily level. The most common side effects were rash and diarrhea. Overall, HI was 30% (erythroid 20%, platelets 32%, and neutrophils 31%). The response rate was higher at the 1,200 mg dose (38%) and 67% had a bilineage response.[66]

Transforming growth factor beta – LY2157299, sotatercept. Myelosuppressive cytokines such as TGF-β are important regulators of hematopoiesis. The levels of TGF-β were found to be increased in the plasma and BM progenitors of patients with MDS, and its constitutive activation leads to ineffective hematopoiesis in LR-MDS.[67] Sotatercept is a chimeric protein composed of the Fc portion of the IgG receptor fused to the Activin receptor 2 protein. Inhibition of TGF receptor I leads to increased hematopoietic colony formation from primary MDS hematopoietic progenitors in vitro.

Indolemine 2, 3 dioxygenase 1 inhibitor. IDO1 is a rate-limiting enzyme in the catabolic pathways of tryptophan. It is overactivated in different cancers and blocks tumor specific cytotoxic T-cell activity, which is a key element for the induction of tumor immune tolerance. IDO1 inhibition increases T-cell proliferation and decreases regulatory T cells.[68] INCB024360 is a novel, potent, and selective inhibitor of the enzyme IDO1 that will be tested in a phase 2 study in patients with MDS.

Aminopeptidase inhibitor – tosedostat. Inhibition of the aminopeptidase enzyme depletes intracellular amino acid pools that are crucial for tumor cell survival. Tosedostat, an oral inhibitor of aminopeptidase, was tested in phase 1 and phase 2 studies in MDS-AML and was well tolerated. Thrombocytopenia was the most common toxicity observed.[69]

Hedgehog inhibitors. The Hedgehog pathway is active in many hematologic malignancies and seems to be responsible for drug resistance.[70] Inhibition of this pathway may hold promise for overcoming drug resistance and to possibly achieve cure or long-term control of MDS. An example of this approach is the use of the smoothened inhibitor PF-04449913, which interferes with the sonic hedgehog self-renewal pathway in stem cells. A first in-human phase 1 study of PF-04449913 in patients with AML, primary myelofibrosis, chronic myelogenous leukemia, and MDS demonstrated efficacy in all 4 diseases. One of the 3 patients with LR-MDS achieved a reduction in spleen size and an HI in platelets and neutrophils. Of the 18 patients with AML, 1 had a decrease in BM blasts, from 92% to 1%, without HI. Another 5 patients had at least a 50% reduction in the BM blasts.[71]

Thrombopoeitin-stimulating agents. Thrombocytopenia is found in 20%-30% of patients with MDS and is associated with poor outcome. Two TPOs, romiplostim and eltrombopag, have been approved for immune thrombocytopenia and are being investigated in MDS. They have been shown to improve thrombocytopenia in MDS,[72,73] but concerns have been raised about the risk of leukemic progression.[74]

JAK-STAT inhbitors – momelotinib, ruxolitinib. The clinical use of JAK inhibitors has been primary limited to patients with myelofibrosis (MF). Patients with MF suffer from splenomegaly-related constitutional symptoms. Constitutional symptoms and splenomegaly are generally not an issue in primary MDS compared with MF, although they can be seen in MDS–MPN overlap syndrome, such as CMML.[75] An ongoing clinical trial is evaluating the efficacy of ruxolitinib in CMML. Momelotinib is a selective JAK inhibitor, which in early studies has shown to have additional efficacy in potentially improving anemia. Although the mechanism for anemia response remains unclear, if confirmed, momelotinib may be a useful therapeutic option for patients with MDS.

Glutathione S-transferase 1-1 inhibitor. Ezatiostat is a glutathione S-transferase 1-1 inhibitor that shares structural homology with native glutathione and can thus displace it from its binding site, which is needed to inhibit the Jun kinase pathways. This leads to the activation of pro-apoptotic Jun kinase proteins in cancer cells that express glutathione S-transferase pi-1 (GSTP1-1). Ezatiostat promotes growth and maturation of normal hematopoietic progenitors and induces apoptosis in cancer cell lines.[76] A recent phase 2 trial of ezatiostat using 2 dosing schedules for low-/INT-1-risk MDS (n = 89) led to RBC transfusion reduction in 29% of patients and independence in 11%.[77]

Multikinase inhibitor. ON 01910.na is a multikinase inhibitor that blocks various kinases, including polo-like

kinase-1 (PLK1), phosphoinositide 3-kinase (PI3), and Akt kinase that displays selectivity for neoplastic cells containing these activated pathways.[78] A recent trial on MDS patients who have failed HMA therapy demonstrated that ON 01910.na reduced BM blasts and demonstrated a positive correlation between BM response and OS, with a median survival of more than 1 year. Only 30% of HR-MDS patients who fail HMA therapy survive for more than a year.[79]

Based on those results, ON 01910.na has entered phase 3 clinical trial on HR-MDS patients who have failed treatment with HMAs.

Mammalian target of rapamycin inhibitors. The mTOR inhibitors have shown antitumor activity in multiple solid malignancies owing to their antiproliferative effects. Recently, a nuclear transcription factor has been discovered in many myeloid malignancies called ecotropic viral integration site 1. EVI-1 genetic translocation leads to activation of this factor and results in increased activity of the mTOR pathway, leading to decreased differentiation and increased proliferation of blood cells.[80] mTOR inhibitors are currently being studied as an alternative therapeutic approach in the treatment of myeloid malignancies, including MDS.[81]

Combination strategies

Except for allo-HCT, AZA is the only drug that has been shown prospectively to prolong survival in patients with MDS. However, AZA monotherapy is effective in only half of the patients, with a modest CR rate of 10%-20%. Furthermore, treatment with AZA is noncurative, and patients eventually lose their response to therapy usually after 2 years of treatment.[82] Patients with MDS who develop primary or secondary resistance to HMAs have dismal prognosis with a reported median OS of less than 6 months.[57] Therefore, novel therapeutic approaches are desperately needed. Given the proven survival advantage of AZA, HMA-based platforms represent an appealing combination approach. The goal of these combination strategies is to increase and prolong the response rate to AZA and ultimately prolong survival compared with AZA monotherapy.

In a phase 2 study in patients with HR-MDS, encouraging results were observed when AZA (75 mg/m^2 day 1 through 5 every 28 days) was combined with lenalidomide (10 mg daily day 1 through 21). Of 36 patients with HR-MDS in a phase 2 study, the ORR was 72% (modified international working group criteria) and 44% achieved CR. Twenty-two percent of the patients suffered febrile neutropenia.[83]

Early-phase trials that evaluated the combination of valproic acid or sodium phenylbutyrate, both older HDACIs, with AZA or DAC showed that the combinations were safe and associated with modest clinical activity.[84]Several newer HDACIs (eg, entinostat, belinostat, vorinostat, panobinostat) have been evaluated in early-phase trials in combination with HMAs. Pracinostat was combined with AZA in a phase 2 study, and the combination resulted in a CR-CRi rate of 78% (7 of 9 patients).[85] A randomized phase 2 study of 150 patients that compared AZA monotherapy with AZA plus vorinostat did not find a significant difference in median OS between the 2 groups after a median follow-up of 17 months (18 months in the monotherapy arm vs 13 months in the combination arm; $P = .15$)[86]

Combination therapies have also been evaluated to improve erythroid responses in patients with LR-MDS. A trial evaluating the use of a combination regimen of lenalidomide and rEPO in transfusion-dependent LR-MDS patients who didn't respond to either of the agents alone showed some activity. In the first stage of the trial, patients were treated with lenalidomide monotherapy (10 or 15 mg daily) for 16 weeks. Erythroid nonresponders received the combination regimen using rEPO at 40,000 U per week. In the first stage with lenalidomide monotherapy, 6 of 7 patients (86%) with 5q LR-MDS and 8 of 32 patients (25%) with non-5q LR-MDS (17.7% for the 10-mg dose; 33.3% for the 15-mg dose) achieved HI-E. Twenty-three patients received the combination therapy, and 6 of them (26%) achieved HI-E, including 4 of 19 patients (21.1%) with non-5q. These encouraging results led to a randomized phase 3 trial to evaluate the benefits of lenalidomide plus rEPO therapy.

Conclusion

MDS is a heterogeneous hematologic disease both clinically and pathophysiologically. Advances in our current understanding of disease biology through the identification of various genetic mutations, epigenetic mechanisms, and immune regulatory pathways have allowed us to gain better understanding of disease complexity and clinical variability. The identification of a myriad of genetic mutations has led to changes in the way we understand this disease. In terms of diagnosis, new genetic mutations have served as clonal markers for disease, which in certain circumstances have led to successful disease diagnosis in otherwise unclear diagnostic cases of MDS. For example, *SF3B1* mutations can distinguish nonclonal cases of sideroblastic anemias from cases of RARS and RARS-T. In terms of prognosis, new molecular mutations can lead to better disease risk stratification and are finding their way in new disease risk stratification schemes. New data has also shown that these genetic mutations may be predictive of therapeutic response.[87] Lastly, these new genetic markers offer the possibility for new therapeutic targets in MDS, which can improve patient outcomes.

References

1. Tefferi A, Vardiman JW. Myelodysplastic syndromes. N Engl J Med. 2009;361:1872-1885.
2. Sekeres MA. Epidemiology, natural history, and practice patterns of patients with myelodysplastic syndromes in 2010. J Natl Compr Canc Netw. 2011;9:57-63.
3. Ma X, Does M, Raza A, Mayne ST. Myelodysplastic syndromes: incidence and survival in the United States. Cancer. 2007;109:1536-1542.
4. Abdel-Wahab O. Molecular genetics of acute myeloid leukemia: clinical implications and opportunities for integrating genomics into clinical practice. Hematology. 2012;17(suppl 1):39S-42S.
5. Mohamedali A, Gaken J, Twine NA, et al. Prevalence and prognostic significance of allelic imbalance by single-nucleotide polymorphism analysis in low-risk myelodysplastic syndromes. Blood. 2007;110:3365-3373.
6. Cheson BD, Greenberg PL, Bennett JM, et al. Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia. Blood. 2006;108:419-425.
7. Papaemmanuil E, Gerstung M, Malcovati L, et al. Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood. 2013;122:3616-3627.
8. Thol F, Kade S, Schlarmann C, et al. Frequency and prognostic impact of mutations in SRSF2, U2AF1, and ZRSR2 in patients with myelodysplastic syndromes. Blood. 2012;119:3578-3584.
9. Visconte V, Rogers HJ, Singh J, et al. SF3B1 haploinsufficiency leads to formation of ring sideroblasts in myelodysplastic syndromes. Blood. 2012;120:3173-3186.
10. Visconte V, Makishima H, Jankowska A, et al. SF3B1, a splicing factor is frequently mutated in refractory anemia with ring sideroblasts. Leukemia. 2012;26:542-545.
11. Visconte V, Makishima H, Maciejewski JP, Tiu RV. Emerging roles of the spliceosomal machinery in myelodysplastic syndromes and other hematological disorders. Leukemia. 2012;26:2447-2454.
12. Raza A, Galili N. The genetic basis of phenotypic heterogeneity in myelodysplastic syndromes. Nat Rev Cancer. 2012;12:849-859.
13. Tiu RV, Visconte V, Traina F, Schwandt A, Maciejewski JP. Updates in cytogenetics and molecular markers in MDS. Curr Hematol Malig Rep. 2011;6:126-135.
14. Gondek LP, Tiu R, O'Keefe CL, Sekeres MA, Theil KS, Maciejewski JP. Chromosomal lesions and uniparental disomy detected by SNP arrays in MDS, MDS/MPD, and MDS-derived AML. Blood. 2008;111:1534-1542.
15. Tiu RV, Gondek LP, O'Keefe CL, et al. Prognostic impact of SNP array karyotyping in myelodysplastic syndromes and related myeloid malignancies. Blood. 2011;117:4552-4560.
16. Epling-Burnette PK, Bai F, Painter JS, et al. Reduced natural killer (NK) function associated with high-risk myelodysplastic syndrome (MDS) and reduced expression of activating NK receptors. Blood. 2007;109:4816-4824.
17. Goyal R, Qawi H, Ali I, et al. Biologic characteristics of patients with hypocellular myelodysplastic syndromes. Leuk Res. 1999;23:357-364.
18. Aizawa S, Nakano M, Iwase O, et al. Bone marrow stroma from refractory anemia of myelodysplastic syndrome is defective in its ability to support normal CD34-positive cell proliferation and differentiation in vitro. Leuk Res. 1999;23:239-246.
19. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol. 1982;51:189-199.
20. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the acute leukaemias. French-American-British (FAB) cooperative group. Br J Haematol. 1976;33:451-458.
21. Germing U, Kundgen A. Prognostic scoring systems in MDS. Leuk Res. 2012;36:1463-1469.
22. Varela BL, Chuang C, Woll JE, Bennett JM. Modifications in the classification of primary myelodysplastic syndromes: the addition of a scoring system. Hematol Oncol. 1985;3:55-63.
23. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997;89:2079-2088.
24. Morel P, Hebbar M, Lai JL, et al. Cytogenetic analysis has strong independent prognostic value in de novo myelodysplastic syndromes and can be incorporated in a new scoring system: a report on 408 cases. Leukemia. 1993;7:1315-1323.
25. Toyama K, Ohyashiki K, Yoshida Y, et al. Clinical implications of chromosomal abnormalities in 401 patients with myelodysplastic syndromes: a multicentric study in Japan. Leukemia. 1993;7:499-508.
26. Zeidan AM, Smith BD, Komrokji RS, Gore SD. Prognostication in myelodysplastic syndromes: beyond the International Prognostic Scoring System (IPSS). Am J Med. 2013;126:e25.
27. 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.
28. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012;120:2454-2465.
29. Malcovati L, Porta MG, Pascutto C, et al. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. J Clin Oncol. 2005;23:7594-7603.
30. Greenberg PL. Current therapeutic approaches for patients with myelodysplastic syndromes. Br J Haematol. 2010;150:131-143.
31. Santini V. Clinical use of erythropoietic stimulating agents in myelodysplastic syndromes. Oncologist. 2011;16(suppl 3):35S-42S.
32. Casadevall N, Durieux P, Dubois S, et al. Health, economic, and quality-of-life effects of erythropoietin and granulocyte colony-stimulating factor for the treatment of myelodysplastic syndromes: a randomized, controlled trial. Blood. 2004;104:321-327.
33. 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.
34. Greenberg PL, Attar E, Bennett JM, et al. NCCN Clinical Practice Guidelines in Oncology: myelodysplastic syndromes. J Natl Compr Canc Netw. 2011;9:30-56.
35. Gabrilove J, Paquette R, Lyons RM, et al. Phase 2, single-arm trial to evaluate the effectiveness of darbepoetin alfa for correcting anaemia in patients with myelodysplastic syndromes. Br J Haematol. 2008;142:379-393.
36. Smith SW, Sato M, Gore SD, et al. Erythropoiesis-stimulating agents are not associated with increased risk of thrombosis in patients with myelodysplastic syndromes. Haematologica. 2012;97:15-20.
37. Park S, Grabar S, Kelaidi C, et al. Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-CSF: the GFM experience. Blood. 2008;111:574-582.
38. Davidoff AJ, Weiss Smith S, Baer MR, et al. Patient and physician characteristics associated with erythropoiesis-stimulating agent use in patients with myelodysplastic syndromes. Haematologica. 2012;97:128-132.
39. Bejar R, Levine R, Ebert BL. Unraveling the molecular pathophysiology of myelodysplastic syndromes. J Clin Oncol. 2011;29:504-515.
40. 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.
41. 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.
42. 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.
43. 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.
44. Sloand EM, Wu CO, Greenberg P, Young N, Barrett J. Factors affecting response and survival in patients with myelodyspla-

sia treated with immunosuppressive therapy. J Clin Oncol. 2008;26:2505-2511.
45. Sauntharajah Y. Key clinical observations after 5-azacytidine and decitabine treatment of myelodysplastic syndromes suggest practical solutions for better outcomes. Hematology Am Soc Hematol Educ Program. 2013;2013:511-521.
46. Scott BL, Sandmaier BM, Storer B, et al. Myeloablative vs nonmyeloablative allogeneic transplantation for patients with myelodysplastic syndrome or acute myelogenous leukemia with multilineage dysplasia: a retrospective analysis. Leukemia. 2006;20:128-135.
47. Jiang Y, Dunbar A, Gondek LP, et al. Aberrant DNA methylation is a dominant mechanism in MDS progression to AML. Blood. 2009;113:1315-1325.
48. Griffiths EA, Gore SD. DNA methyltransferase and histone deacetylase inhibitors in the treatment of myelodysplastic syndromes. Semin Hematol. 2008;45:23-30.
49. 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.
50. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol. 2009;10:223-232.
51. 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.
52. Silverman LR. Hypomethylating agents in myelodysplastic syndromes changing the inevitable: the value of azacitidine as maintenance therapy, effects on transfusion and combination with other agents. Leuk Res. 2009;33(suppl 2):18S-21S.
53. Kantarjian HM, O'Brien S, Huang X, et al. Survival advantage with decitabine versus intensive chemotherapy in patients with higher risk myelodysplastic syndrome: comparison with historical experience. Cancer. 2007;109:1133-1137.
54. 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.
55. 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.
56. 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.
57. Prebet T, Gore SD, Esterni B, et al. Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. J Clin Oncol. 2011;29:3322-3327.
58. Fenaux P, Bowen D, Gattermann N, et al. Practical use of azacitidine in higher-risk myelodysplastic syndromes: an expert panel opinion. Leuk Res. 2010;34:1410-1416.
59. Steensma DP, Stone RM. Practical recommendations for hypomethylating agent therapy of patients with myelodysplastic syndromes. Hematol Oncol Clin North Am. 2010;24:389-406.
60. Steensma DP. Art of oncology: new voices wanted. J Clin Oncol. 2011;29:3343-3344.
61. Garcia-Manero G. Myelodysplastic syndromes: 2011 update on diagnosis, risk-stratification, and management. Am J Hematol. 2011;86:490-498.
62. Knipp S, Hildebrand B, Kundgen A, et al. Intensive chemotherapy is not recommended for patients aged >60 years who have myelodysplastic syndromes or acute myeloid leukemia with high-risk karyotypes. Cancer. 2007;110:345-352.
63. Yang H, Hoshino K, Sanchez-Gonzalez B, Kantarjian H, Garcia-Manero G. Antileukemia activity of the combination of 5-aza-2'-deoxycytidine with valproic acid. Leuk Res. 2005;29:739-748.
64. Navas T, Zhou L, Estes M, et al. Inhibition of p38alpha MAPK disrupts the pathological loop of proinflammatory factor production in the myelodysplastic syndrome bone marrow microenvironment. Leuk Lymphoma. 2008;49:1963-1975.
65. Sokol L, Cripe L, Kantarjian H, et al. Randomized, dose-escalation study of the p38alpha MAPK inhibitor SCIO-469 in patients with myelodysplastic syndrome. Leukemia. 2013;27:977-980. 66. Garcia-Manero G, Sekeres MA, List AF, et al. Phase 1 Dose-escalation/expansion study of the p38/Tie2 inhibitor ARRY-614 in patients with IPSS low/Int-1 risk myelodysplastic syndromes [ASH abstract 387]. Blood. 2013:122.
67. Verma A, List AF. Cytokine targets in the treatment of myelodysplastic syndromes. Curr Hematol Rep. 2005;4:429-435.
68. Muller AJ, DuHadaway JB, Donover PS, Sutanto-Ward E, Prendergast GC. Inhibition of indoleamine 2,3-dioxygenase, an immunoregulatory target of the cancer suppression gene Bin1, potentiates cancer chemotherapy. Nat Med. 2005;11:312-319.
69. Lowenberg B, Morgan G, Ossenkoppele GJ, et al. Phase I/II clinical study of Tosedostat, an inhibitor of aminopeptidases, in patients with acute myeloid leukemia and myelodysplasia. J Clin Oncol. 2010;28:4333-4338.
70. Kobune M, Takimoto R, Murase K, et al. Drug resistance is dramatically restored by hedgehog inhibitors in CD34+ leukemic cells. Cancer Sci. 2009;100:948-955.
71. Jamieson C, Cortes JE, Oehler V, et al. Phase 1 dose-eEscalation study of PF-04449913, an oral Hedgehog (Hh) inhibitor, in patients with select hematologic malignancies [ASH abstract 424]. Blood. 2011;118:424.
72. Kantarjian HM, Mufti GJ, Fenaux P, et al. Treatment with the thrombopoietin (TPO)-receptor agonist romiplostim in thrombocytopenic patients (Pts) with low or intermediate-1 (int-1) risk myelodysplastic syndrome (MDS): Follow-up AML and survival results of a randomized, double-blind, placebo (PBO)-controlled study [ASH abstract 421]. Blood. 2012;120:421.
73. Oliva EN, Santini V, Zini G, et al. Efficacy and safety of eltrombopag for the treatment of thrombocytopenia of low and intermediate-1 IPSS risk myelodysplastic syndromes: interim analysis of a prospective, randomized, single-blind, placebo-controlled trial (EQoL-MDS) [ASH abstract 923]. Blood. 2012;120:923.
74. Sekeres MA, Kantarjian H, Fenaux P, et al. Subcutaneous or intravenous administration of romiplostim in thrombocytopenic patients with lower risk myelodysplastic syndromes. Cancer. 2011;117:992-1000.
75. Sonbol MB, Firwana B, Zarzour A, Morad M, Rana V, Tiu RV. Comprehensive review of JAK inhibitors in myeloproliferative neoplasms. Ther Adv Hematol. 2013;4:15-35.
76. Galili N, Tamayo P, Botvinnik OB, et al. Prediction of response to therapy with ezatiostat in lower risk myelodysplastic syndrome. J Hematol Oncol. 2012;5:20.
77. 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.
78. Chapman CM, Sun X, Roschewski M, et al. ON 01910.Na is selectively cytotoxic for chronic lymphocytic leukemia cells through a dual mechanism of action involving PI3K/AKT inhibition and induction of oxidative stress. Clin Cancer Res. 2012;18:1979-1991.
79. Raza A, Greenberg PL, Olnes MJ, Silverman LR, Wilhelm F. Final phase I/II results of rigosertib (ON 01910.Na) hematological effects in patients with myelodysplastic syndrome and correlation with overall survival [ASH abstract 3822]. Blood. 2011;118;3822.
80. Yoshimi A, Goyama S, Watanabe-Okochi N, et al. Evi1 represses PTEN expression and activates PI3K/AKT/mTOR via interactions with polycomb proteins. Blood. 2011;117:3617-3628.
81. Janakiram M, Thirukonda VK, Sullivan M, Petrich AM. Emerging therapeutic targets in diffuse large B-cell lymphoma. Curr Treat Options Oncol. 2012;13:82-101.
82. Zeidan AM, Gore SD, Komrokji RS. Higher-risk myelodysplastic syndromes with del(5q): is sequential azacitidine-lenalidomide combination the way to go? Expert Rev Hematol. 2013;6:251-254.
83. Sekeres MA, Tiu RV, Komrokji R, et al. Phase 2 study of the lenalidomide and azacitidine combination in patients with higher-risk

myelodysplastic syndromes. Blood. 2012;120:4945-4951.
84. Soriano AO, Yang H, Faderl S, et al. Safety and clinical activity of the combination of 5-azacytidine, valproic acid, and all-trans retinoic acid in acute myeloid leukemia and myelodysplastic syndrome. Blood. 2007;110:2302-2308.
85. Quintas-Cardama A, Kanatarjian HM, Ravandi F et al. Very high rates of clinical and cytogenetic response with the combination of the histone deacetylase inhibitor pracinostat (SB939) and 5-Azacitidine in high-risk myelodysplastic syndrome [ASH abstract 3821]. Blood. 2012;119;3821.
86. Prebet TG, Gore S, Sun Z. Prolonged administration of azacitidine with or without entinostat increases rate of hematologic normalization for myelodysplastic syndrome and acute myeloid leukemia with myelodysplasia-related changes: results of the US Leukemia Intergroup Trial E1905 [ASH abstract 601]. Blood. 2010;116:601.
87. Traina F, Visconte V, Elson P, Tabarroki A, Jankowska AM, Hasrouni E, et al. Impact of molecular mutations on treatment response to DNMT inhibitors in myelodysplasia and related neoplasms. Leukemia. 2014;28:78-87.