HHS Public Access

Author manuscript

Clin Adv Hematol Oncol. Author manuscript; available in PMC 2019 July 15.

Published in final edited form as:

Clin Adv Hematol Oncol. 2018 January ; 16(1): 56–66.

Recent Advances in the Cellular and Molecular Understanding of Myelodysplastic Syndromes: Implications for New Therapeutic Approaches

Andrew M. Brunner, MD and **David P. Steensma, MD**

Dr Brunner is an instructor in medicine at Harvard Medical School and an assistant in medicine at the Center for Leukemiaat Massachusetts General Hospital in Boston, Massachusetts. Dr Steensma is an associate professor of medicine at Harvard Medical School and a senior physician in the Department of Medical Oncology at Dana-Farber Cancer Institute in Boston, Massachusetts.

Abstract

It has been more than 10 years since any new disease-modifying therapies have received regulatory approval for indications related to myelodysplastic syndromes (MDS). Advances in our collective biological understanding of MDS in the last decade, however, have made it possible to hope that effective therapeutics can be designed to improve MDS-associated cytopenias and patients' quality of life, and perhaps even delay clonal progression and extend survival. Classes of MDS-associated mutations and disordered biological pathways targeted by developmental therapeutics include the following: aberrant messenger RNA splicing, neomorphic enzymes in the citric acid cycle with oncogenic activity, overactivated tyrosine and serine-threonine kinases, epigenetic and chromatin remodeling alterations, abnormal telomere dynamics, and failed protection of DNA integrity. At present, treatments for MDS are usually administered as sequential monotherapy, but there is a trend toward clinical trials of combination therapies—in which new agents are added to a DNA hypomethylating agent backbone—for both upfront treatment and the treatment of relapsed/refractory disease. Agents in clinical trials for subsets of MDS include luspatercept, antibodies targeting CD33, isocitrate dehydrogenase inhibitors, deacetylase inhibitors, venetoclax, and immunotherapies designed to overcome immune checkpoint inhibition. These biologically based therapeutics, as well as the encouraging precedent of 7 new approvals by the US Food and Drug Administration in 2017 for the treatment of acute leukemia, offer the prospect that 10 more years will not elapse before another new therapy is approved for MDS.

Keywords

azacitidine; checkpoint inhibitors; deacetylase inhibitors; decitabine; enasidenib; gemtuzumab; guadecitabine; ivosidenib; lenalidomide; luspatercept; MDS; venetoclax

Corresponding author: David P. Steensma, MD, FACP, Division of Hematological Malignancies, Department of Medical Oncology, Dana-Farber Cancer Institute450 Brookline Avenue, Boston, MA 02215, Tel: (617) 632-3712, Fax: (617) 582-7840, David_Steensma@dfci.harvard.edu.

Note: The Disclosures section of this document was updated on May 30, 2019.

Introduction and Epidemiology of Myelodysplastic Syndromes

Myelodysplastic syndromes (MDS) encompass a spectrum of bone marrow malignancies characterized by cytopenias and ineffective clonal hematopoiesis, as well as a risk for evolution to acute myeloid leukemia (AML) in up to 30% of cases. It has long been recognized that the natural history of MDS varies widely according to the pathologic and molecular characteristics of the disease, with some patients having an indolent course that stretches over many years and others rapidly progressive disease with a survival measured in months.[1,2]

Estimates of the incidence of MDS vary, but it is thought that at least 4 to 7 new cases of MDS occur per 100,000 persons per year in the United States and Western Europe, with a median age at diagnosis of approximately 70 years.[3–6] The true incidence and prevalence of MDS have been difficult to estimate owing to the incomplete capture of cases by cancer registries, and estimates also vary based on the methodology employed. For example, incidence figures are lower when stringent pathologic confirmation of an MDS diagnosis is required and higher when criteria are expanded to include factors such as billing codes.[7] Clinical practice patterns may also influence case ascertainment. For instance, older patients with isolated mild cytopenias, who may have low-grade MDS, may be less likely to undergo an evaluation that includes referral to a hematology specialist and marrow biopsy.[8]

MDS are characterized by the World Health Organization (WHO) according to specific morphologic, karyotypic, and cytogenetic abnormalities identified in a diagnostic bone marrow specimen. Bone marrow studies in patients with unexplained cytopenias and suspected MDS should include the following: a full cytogenetic analysis to assess the metaphase karyotype, iron staining of an adequate aspirate sample to evaluate for the presence of ring sideroblasts, a core biopsy, and a peripheral blood smear for morphologic evaluation. Fluorescence in situ hybridization (FISH) analysis may also be of use in identifying recurrent abnormalities, such as del(5q), del(7), and 20q-, among others. FISH is not needed if at least 20 metaphases can be examined, however, and it remains unclear whether the addition of FISH alters cytogenetic risk category assignment.[9] Increasingly, next-generation sequencing with panels of multiple putative leukemic driver genes that are recurrently mutated in MDS is being employed in the clinic, as molecular testing results are of diagnostic and prognostic value.[1,10,11] In 2016, the WHO updated its MDS classification to incorporate a DNA sequencing parameter for the first time: the presence of a mutation in the gene encoding splicing factor component SF3B1.

Risk Stratification and Disease Classification

The risk for death or leukemic transformation among patients with MDS can be characterized by using any of a number of risk stratification algorithms; the 1997 International Prognostic Scoring System (IPSS) and the 2012 Revised International Prognostic Scoring System (IPSS-R) are most commonly employed in clinical practice.[12–15] Although the factors that are assessed in each of these scoring systems vary slightly, all incorporate the depth and number of cytopenias present, the burden of myeloid blast cells found in the bone marrow or blood, and the genetic composition of MDS, primarily through

cytogenetic analysis. Patient risk groups are based on historical cohorts of individuals who were either untreated or received growth factor support alone, which may provide insight into the “natural history” of MDS following diagnosis and can then be used to guide treatment decisions.

Morphology and type of cytopenias have been used to subclassify MDS since the 1982 French-American-British (FAB) classification and are associated with differences in overall survival as well as varying risk for transformation to AML.[12] Subsequent modifications of MDS subgroup classifications[16,17] have reflected the evolving understanding of certain cytogenetic and molecular features and their effect on prognosis and response to therapy.

A challenge in using cytogenetic analysis for defining risk is that approximately one-half of patients will have a normal karyotype. In addition, MDS may be challenging to diagnose in patients with mild cytopenias and minimal dysplasia, particularly when other medical conditions may be contributing to cytopenias or dysplasia. In this setting, rapid-sequencing platforms that can detect recur-rent somatic mutations have emerged as an increasingly important diagnostic tool.[1,18]

MDS that are associated with the chromosomal lesion del(5q), specifically losses that span 5q31-q33 and occur in isolation from other cytogenetic lesions (particularly chromosome 7 abnormalities), often exhibit a specific clinical presentation characterized by macrocytic anemia, thrombocytosis, hypolobated micromegakaryocytes, and a relatively indolent clinical course.[19,20] Patients with MDS who have isolated del(5q) and lower-risk transfusion-dependent disease tend to respond favorably to lenalidomide (Revlimid, Celgene) therapy.[21] As such, these patients represent a distinct subgroup within the WHO classification.

Similarly, more recent studies have identified mutations in *SF3B1* to be common among patients who have MDS with ring sideroblasts. Patients with MDS who have *SF3B1* mutations tend to have a more indolent clinical course.[22–24] The identification of a somatic mutation in *SF3B1* can be useful to confirm a diagnosis of MDS, particularly when other causes of sideroblastic anemia are being considered.[25]

The heterogeneity of MDS across subtypes, as well as variation in outcomes according to clinicopathologic characteristics, introduces several challenges in the management of these patients. As the median age of patients at diagnosis of MDS is older than 70 years, many of them have comorbid conditions that can limit treatment options and present competing risks to their survival. The symptoms of these conditions, such as underlying cardio vascular disease and chronic obstructive pulmonary disease, may be exacerbated by MDS-associated cytopenias, so that patients’ ability to tolerate infectious complications or transfusional iron overload is reduced. Although many deaths in MDS may be attributed to complications of the disease, such as infections or bleeding,[26,27] a high burden of cardiovascular disease has also been noted in this population.[6,28] Comorbidities should be considered when survival is estimated and a treatment strategy is developed for these patients.

Current Treatment of Myelodysplastic Syndromes

When therapeutic strategies for patients with MDS are determined, an evaluation of comorbidities and life expectancy is important. However, decisions regarding the initiation of therapies specific to MDS are largely predicated on the symptomatic burden of disease, the severity of cytopenias, and the risk for progression (Figure). Patients with MDS are typically categorized as having either higher-or lower-risk disease, most commonly by using a binary split of the 4-category IPSS[12] or 5-category IPSS-R.[13]

In addition, the incorporation of somatic mutations into the risk assessment is becoming increasingly important, which may be especially helpful for patients with IPSS-R intermediate-risk disease.[29] Patients with MDS who harbor mutations in certain genes may have higher-risk disease features that “upgrade” their risk from a lower to a higher-risk category.[30] For instance, in one series of 435 patients, those with a mutation in *ASXL1*, *RUNX1*, *ETV6*, *EZH2*, or *TP53* had a disease risk consistent with a higher category than would other-wise have been estimated by using the IPSS.[31] Moreover, an increase in the total number of somatic mutations may be associated with an increased risk for disease progression or death.[32] Although heterogeneity is still found within lower-and higher-risk categories,[14,33,34] therapies for lower-risk disease generally focus on mitigation of cytopenia and symptoms, whereas those employed for higher-risk disease seek to modify the natural history.

Lower-Risk Myelodysplastic Syndromes

In many patients with lower-risk MDS, disease may be diagnosed in the setting of relatively mild cytopenias before they have received any directed treatment—including transfusion support. For patients with indolent disease who do not have transfusional needs and have minimal symptoms, prospective monitoring may be the most appropriate treatment approach. In addition, any non-MDS comorbidities, such as cardiovascular disease, should be addressed. Certain characteristics at diagnosis, such as the presence of an *SF3B1* mutation without other adverse risk features,[24] may help to identify patients who will benefit from this watchful waiting approach.

Once severe cytopenias or transfusion needs develop in patients with lower-risk MDS, therapies are focused on attaining transfusion independence and reducing associated risks, such as transfusional iron overload. The most frequently employed therapy for moderate-to-severe anemia is the off-label use of erythropoiesis-stimulating agents (ESAs), such as epoetin alfa (Epogen, Amgen; Procrit, Janssen Biotech) or darbepoetin alfa (Aranesp, Amgen).[35–38] Several factors may help to predict those patients most likely to benefit from ESA use; on the basis of an analysis of 996 patients, the recently validated Italian and Canadian ITACA score identified a pretreatment serum erythropoietin (EPO) level of less than 100 U/L, IPSS low-risk disease, and a low number of required transfusions (defined here as <1 U of packed red cells over an 8-week period) as predictors of the greatest chance of response.[39] Clinically, the decision to initiate ESA therapy may depend on the convenience of ESA administration, the interval between transfusions, and the symptomatic burden of anemia. Some characteristics, such as a serum EPO level above 500 U/L,[38] portend a very low likelihood of response and merit consideration of an alternative therapy.

The approach to patients who have lower-risk MDS with thrombocytopenia or neutropenia is more challenging, given the limited number of effective therapies. Patients with isolated neutropenia present a particular clinical challenge. Some patients may have uncomplicated neutropenia for long periods without needing intervention; moreover, as regards the use of granulocyte colony–stimulating factor (G-CSF) in MDS, although it may improve neutrophil counts,[40] it is not clear that prophylactic dosing of G-CSF has any effect on MDS progression or infection risk.[41] More recently, the role of thrombopoietin (TPO) agonists has been explored in the treatment of thrombocytopenia associated with MDS. Both romiplostim (Nplate, Amgen) and eltrombopag (Promacta, Novartis) can reduce platelet transfusion needs, improve counts, and modestly reduce clinically significant bleeding events.[42–44] However, given that myeloid blasts occasionally have functional TPO receptors, there has been some concern about potential increases in the percentage of bone marrow blasts during administration, which occurred in fewer than 10% of patients in clinical trials and resolved in most patients after the cessation of TPO-mimetic therapy. The timing of the administration of TPO agents with respect to other therapies is likely also an important consideration in MDS; the concurrent use of eltrombopag and azacitidine delayed platelet recovery and increased transfusion requirements compared with placebo.[45]

There are several settings in which alternatives to ESA therapy should be considered in lower-risk MDS—most notably, patients with endogenous EPO levels above 200 to 500 U/L and patients with MDS who are harboring del(5q) and are transfusion-dependent. In this latter subset of patients, lenalidomide, an immunomodulatory drug (IMiD) that is a derivative of thalidomide, results in transfusion independence in approximately 3 of 4 patients, as well as temporary clearance of the cytogenetically abnormal clone in nearly half of patients.[21,46] It was this impressive response that led to the US Food and Drug Administration (FDA) approval of lenalid-omide for the lower-risk del(5q) subset of patients in 2005. Lenalid-omide also appears to reduce transfusion requirements in approximately one-quarter of patients without del(5q),[47,48] although responses are generally of shorter duration than those achieved with hypomethylating agents. Despite not being approved for this population, lenalidomide is still widely used off label in the clinic.

Another consideration in lower-risk MDS is the use of immunosuppressive therapy. A subset of patients with MDS may have disease that includes T-cell–mediated myelosuppression with features that overlap those of aplastic anemia, and immunosuppressive therapy, which consists of antithymocyte globulin (ATG) plus either cyclosporine or tacrolimus, can be considered for them. Identifying this subset of patients may be challenging, but factors that have correlated with favorable responses include lower-risk disease, with fewer than 5% bone marrow blasts, and patient age younger than 60 years.[49–51]

The presence of hypoplastic disease and of HLA antigen HLA-DR15 also has been reported in some series (but not others) to predict a higher likelihood of responses to this therapy, and in some series, the presence of trisomy 8 or a paroxysmal nocturnal hemoglobinuria clone.[51,52] In lieu of attractive alternative therapies, immunosuppressive therapy can be considered for patients with predictors of response to therapy after their disease fails to respond to ESA treatment.

The treatment design of patients whose MDS is a consequence of a germline disorder may require special consideration. For instance, patients with Fanconi anemia are extremely sensitive to cytotoxic agents and require dose adjustment if treated with such drugs. Inherited telomeropathies can present as MDS, and the treatment of these patients with danazol, a synthetic androgen, may be considered, given data showing telomere elongation and reduced transfusion requirements.[53]

Danazol may also be considered in other patients with lower-risk disease, and several reports suggest efficacy among patients with predominant thrombocytopenia.[54]

For patients whose disease fails to respond to the above approaches, a DNA hypomethylating agent or allogeneic transplant may be considered, as described below for those with higher-risk disease.

Higher-Risk Myelodysplastic Syndromes

Patients with higher-risk disease generally face a more imminent risk for complications, owing to either progressive cytopenias and associated complications or transformation to secondary AML, which is especially challenging to treat. For this subset of patients, the clinical approach is generally focused on disease-modifying therapies—that is, those that will prolong life, preferably without major impairment to quality of life.

Most patients with higher-risk disease will be treated with either azacitidine or decitabine. These are cytosine analogues that inhibit DNA methyltransferase, thereby decreasing global methylation with consequent alteration in gene expression and epitope presentation; they are therefore typically referred to as hypomethylating agents (HMAs) or DNA-methyl transferase inhibitors (DNMTIs). These drugs were approved by the FDA in 2004 (azacitidine) and 2006 (decitabine). The efficacy of HMA therapy in MDS was first shown in a study conducted by the Cancer and Leukemia Group B (CALGB 9221). This study, which began in the mid-1990s, compared HMA treatment vs standard of care and showed a trend toward improved survival in the arm receiving azacitidine.[55] A subsequent phase 3 study of patients with higher-risk MDS, published 5 years after the US marketing approval of azacitidine, confirmed a survival benefit among patients receiving azacitidine at 75 mg/m^2 on days 1 to 7 of a 28-day cycle in comparison with those receiving conventional care regimens (supportive care or cytarabine-based therapy).[56] Decitabine has delayed disease progression when dosed at 20 mg/m^2 on days 1 to 5 of a 28-day cycle,[57] and it is widely considered comparable with azacitidine, although direct comparisons between the 2 agents are lacking. It is not yet known whether the high response rate reported with decitabine in *TP53*-mutant AML also applies to MDS.[58] Patients who have *TP53*-mutant MDS treated with azacitidine also have relatively high response rates.[59]

More recently, orally bioavailable HMA therapies (CC-486 and ASTX727, the latter representing decitabine co-administered with an inhibitor of cytidine deaminase) have been under development, with pharmacokinetic profiles mirroring those of parenteral azacitidine and decitabine.[60,61] Although it is unclear whether these will improve efficacy, they will allow more flexible dosing and possibly improvements in quality of life. Newer parenteral

HMAs, such as guadecitabine (SGI-110), are undergoing phase 3 trials in AML and MDS, as described below.

Another important consideration at the time of diagnosing higher-risk MDS is to determine whether a patient is a candidate for allogeneic hematopoietic stem cell transplant (allo-HCT), the only potentially curative therapy for MDS (in approximately 30%−40% of cases). Indeed, although historically many patients with MDS may not have been considered transplant candidates because of their age at diagnosis, this is a moving target because a number of studies have shown that allo-HCT may be pursued effectively in patients with higher-risk disease, including selected patients older than 70 years.[62–64] A study is currently underway to compare the effect of HCT in the older, Medicare population with intermediate-2 or high-risk MDS on the IPSS with that of other standard treatments (NCT02016781).

Transplant options for both older and younger patients have evolved over the last decade, with donor options expanding and transplant-related toxicity diminishing. The advent of reduced-intensity conditioning in the 1990s expanded the use of this treatment modality to older patients who were not considered candidates for myeloablative therapy.[64–66] Transplant following pre-transplant reduced-intensity conditioning relies more on a graft-versus-leukemia (GvL) effect than does transplant with a myeloablative chemotherapy approach.[67] This approach may be effective in MDS but not in more proliferative diseases, such as AML, because the GvL effect may take time to develop. Nonetheless, a recent study comparing reduced-intensity conditioning with myeloablative chemotherapy conditioning favored myeloablative chemotherapy in otherwise eligible patients, a finding driven largely by those with AML.[68] Other considerations, such as graft donor source, have also changed with expanded alternative donor options, such as haploidentical transplant.[69,70] There has also been conflicting evidence about the use of older matched sibling donors, such as the siblings of most patients with MDS, compared with younger matched unrelated donors.[71,72] Clonal hematopoiesis of indeterminate potential (CHIP), described in further detail below, is common in older donors—more than 10% of patients older than 60 years—and may lead to cytopenias and worse outcomes after transplant, including rare cases of donor-derived leukemia.[73]

The Evolving Molecular Landscape of Myelodysplastic Syndromes

Expanded understanding of the molecular pathophysiology of MDS has provided insight into the biology of this disease while also raising new questions, particularly about the role of somatic mutations in MDS and other hematologic conditions.[18,20,29] As previously noted, the diagnosis of MDS relies on demonstrating a clonal marrow process with resultant ineffective hematopoiesis. Particularly when comorbid conditions may contribute to a cytopenia or the appearance of dysplastic forms, establishing clonality can be useful to support the diagnosis of MDS in lieu of excess blasts. Although cytogenetic abnormalities are identified in only half of patients with MDS, somatic mutations may increase the percentage of patients with MDS who have a characteristic mutation to more than 90%.[32] In a patient with other clear features of MDS, genetic mutations can thus enhance the certainty of a diagnosis; however, the presence of these mutations in patients without dysplasia, or

even without cytopenias, has introduced new challenges to our understanding of their specificity in disease.[74,75]

Increased use of genomic sequencing has also led to the development of a new vernacular to describe disease states associated with somatic mutations when patients do not otherwise meet criteria for MDS. The presence of a mutation at a variant allele frequency of at least 2% without concurrent malignancy or cytopenia represents CHIP and is common in the general population, seen in approximately 10% of those in their eighth decade of life.[74,75] Most patients with CHIP have a single mutation, usually a *DNMT3A* or *TET2* point mutation. Similarly, patients who have a somatic mutation in a leukemia-associated driver gene and a cytopenia but who otherwise do not meet WHO diagnostic criteria for MDS may be characterized as having clonal cytopenias of undetermined significance.[18] Patients who have persistent cytopenias without mutations or evidence of MDS are said to have idiopathic cytopenias of undetermined significance and have a lower risk for progression to WHO-diagnosable MDS or AML.

Although these definitions may help to identify patients at risk for the development of a subsequent hematologic malignancy, the absolute rate of transformation of idiopathic cytopenias of undetermined significance and CHIP to MDS or other cancers is relatively low,[74–76] primarily adding to the challenge of interpreting marrow results and sequencing reports. Indeed, an evolving clinical challenge has emerged in which patients who would not previously have fulfilled criteria for a hematologic malignancy may have an identified clonal process, and it is unclear when and how clinicians should intervene.

Although the evolving molecular landscape of MDS has introduced new challenges, it is also leading to improvements in risk assessment and treatment adaptation. The identification of frequent recurrent mutations in splicing factors in MDS, seen in approximately 50% to 60% of patients with MDS but uncommon in those with CHIP,[77,78] may improve diagnostic and prognostic certainty[22,24] and potentially lead to novel therapeutic targets. Patients who harbor a mutation in the splicing factor gene *SF3B1*, for instance, may have a more indolent course and tend to have better overall survival, particularly when the mutation occurs in isolation. Other mutations may provide insight into particularly aggressive forms of disease, as noted previously.[31] Subclones that harbor or acquire mutations in *RAS* may expand during disease progression,[79,80] presenting a potential target for therapeutic development. Mutations in *TP53*, recognized as predicting poor prognosis across many malignancies,[81] are also associated with adverse outcomes in MDS. Those patients who harbor a mutation in *TP53* and undergo transplant have limited long-term survival (<20%),[11] underscoring the need for novel therapies in this subset of patients.

Emerging Therapeutic Strategies in Myelodysplastic Syndromes

Despite a burst of new therapies for MDS approximately 10 years ago, no new therapies have achieved regulatory approval since decitabine was approved in 2006,[82] and patients whose disease does not respond or progresses on currently available therapies represent an unmet medical need. Current therapy options, excluding transplant, may prolong and improve the quality of life but are not curative. Insight into the molecular pathogenesis of

MDS may provide new therapeutic targets in this group of malignancies. Several ongoing studies are outlined below; this roster is only a selected list of new therapies in development, with the hope for significant improvements in MDS care in the next years (see the eTable at www.hematologyandoncology.net).

Luspatercept (ACE-536)

Patients with lower-risk MDS, whose disease is often characterized by red blood cell transfusion dependence, have limited effective treatment options once their disease stops responding to frontline therapy with an ESA, or if their pre-treatment EPO levels were above 500 U/L. Luspatercept is a modified activin receptor IIB–immunoglobulin G (IgG) Fc fusion protein; it targets transforming growth factor beta (TGF-b) signaling via Smad2/3 and growth and differentiation factor 11 (GDF-11), thereby enhancing erythropoiesis.[83] Certain ESA-resistant anemias may be related to ineffective late erythropoiesis and be responsive to targeting of the TGF-b superfamily.[84,85] Luspatercept has achieved responses, including durable freedom from transfusions, in some patients with MDS, especially those with ring sideroblasts or elevated baseline EPO levels, and a phase 3 study comparing the efficacy of luspatercept with best supportive care in patients who have lower-risk MDS with ring sideroblasts has met accrual and will report in 2018 (MEDALIST; NCT02631070).[86,87]

Spliceosome Modulation

Given the prevalence of splicing factor mutations in MDS, which are thought to be early events in the pathogenesis of this malignancy, the spliceosome complex is an appealing target for new therapies under development. Patients with MDS that harbors a splicing factor mutation, particularly *SF3B1*, have evidence of alternative splicing, especially the use of alternate 3’ exons; targeted agents that bind the spliceosome complex may further perturb splicing by disrupting the remaining wild-type allele.[78,88] On the basis of xenograft models showing selective pressure against splicing factor–mutated cells when exposed to splicing factor modulators, as well as absolute dependence on wild-type splicing even in mutant cells, a phase 1 study to evaluate an orally bioavailable splicing factor modulator, H3B-8800, that targets SF3B1 is currently underway (NCT02841540).[89]

Immune Checkpoint Inhibition

Immunologic dysregulation, including minor alterations of T-cell subsets, immunoglobulin level abnormalities, and paraneoplastic manifestations, is relatively common in patients with MDS, although the link to MDS pathogenesis is still under investigation. HMA therapy may increase the expression of antigens associated with endogenous retroviruses, which are typically suppressed owing to promoter hypermethylation, potentially revealing novel immunologic targets that may be part of the mechanism of clinical efficacy of these agents.[90] Check-point inhibition with agents that block programmed death 1, programmed death ligand 1, and cytotoxic T-lymphocyte–associated antigen 4 are under investigation, both as monotherapy and in combination with azacitidine or decitabine[91,92]; to date, these therapies, including nivolumab (Opdivo, Bristol-Myers Squibb) and ipilimumab (Yervoy, Bristol-Myers Squibb), appear to have quite limited activity as single agents.

DNA Hypomethylation

Given the success of azacitidine and decitabine in MDS, DNA methylation and epigenetic modulation remain targets of interest. Guadecitabine (SGI-110) is a dinucleotide of decitabine and deoxyguanosine that undergoes less degradation by cytidine deaminase; as such, it has been explored as a novel hypomethylating agent for the treatment of MDS.[93] In a phase 1 study of guadecitabine in progressive MDS and AML, a proportion of patients responded to therapy, including approximately one-third of the enrolled patients with MDS.[94] Guadecitabine is currently being explored in patients who have MDS previously treated with azacitidine or decitabine (NCT02907359).

(Histone) Deacetylase Inhibition

Epigenetic alterations are a hallmark of MDS, and much interest has focused on whether histone acetylation may be a viable target in the disease, given the significance of DNA methylation. That said, deacetylase inhibitors that target histones and other proteins (HDAC inhibitors) have achieved limited clinical success in MDS and AML, despite compelling preclinical rationale.[95] A number of studies have failed to show significant efficacy of HDAC inhibitors as monotherapy,[96–98] and in combination with HMA therapy they have consistently increased toxicity (especially fatigue and thrombocytopenia) without improving response.[99–102] Most recently, a randomized study (North American Intergroup Study SWOG S1117) of azacitidine with or without lenalidomide or vorinostat (Zolinza, Merck) showed no significant survival benefit for azacitidine alone compared with azacitidine in combination with vorinostat.[103] A limitation to this study may have been the rate of dose modification owing to toxicity on the combination arms, and the overall challenges of treatment intensification in the general MDS population. Nonetheless, to date, combining HDAC inhibition with HMA therapy has not yielded significant gains in outcomes.

Antibody-Drug Conjugates

MDS with excess blasts that progress to AML are associated with resistance to chemotherapy and a median survival of less than 6 months. Agents that target progenitor cells or excess blasts in MDS, such as those directed at the cell surface marker CD33, remain of interest in higher-risk disease. The antibody-cytotoxin conjugate gemtuzumab ozogamicin (GO; Mylotarg, Pfizer) has been explored in patients with high-risk MDS and AML, both as monotherapy and in combination with HMA therapy; response rates have been encouraging, although coupled with significant myelosuppression.[104,105] GO was reapproved by the FDA for relapsed/refractory CD33-positive AML in 2017 and is now available for use. Vadastuximab talirine, an antibody-drug conjugate that has a linker and a structure different from those of GO, was also being evaluated in patients with higher-risk MDS (NCT02706899) before unexpected adverse events led to trial cessation; bispecific antibodies directed against CD33 are now in development. For these and other agents targeting cell surface markers on progenitors, such as CD123/interleukin 3 receptor subunit alpha (IL3RA), proactive strategies to manage myelosuppression appear to be important because deaths from prolonged cytopenias have occurred.

Inhibition of Activated Cell Signaling Pathways

Several cell signaling pathways are upregulated in MDS cells, particularly as they progress or evolve into AML, and targeted small molecules may have a role in certain subsets of patients with MDS. With recognition of the role of the RAS signaling pathway in MDS, rigosertib has been explored for patients whose disease progresses on HMA therapy. Rigosertib is a small molecule that inhibits polo-like kinase 1 (PLK1) and also acts as a RAS mimetic, competing with RAS for binding to the phosphoinositide-3 kinase (PI3K) family; this results in RAS/MEK/ERK pathway inhibition.[106] In a phase 3 study of patients with MDS progressing on HMA that compared rigosertib vs best supportive care with or without low-dose cytarabine, rigosertib failed to show a survival benefit, and although there were more responses in the rigosertib group, many of these were related to an increase in bone marrow complete remissions without hematologic improvement.[107] A subset of patients with higher-risk disease appeared to respond, and a phase 3 study is ongoing to explore rigosertib in this population (NCT02562443).

Additional small-molecule inhibitors are of interest in MDS, such as inhibitors of mutant *IDH1* and *IDH2*, which encode enzymes in the citric acid cycle that have oncogenic neomorphic activity. Although *IDH1/2* mutations are present in only a small subset of patients with MDS (<15%), early results with the oral chemotherapy agents enasidenib (AG-221; Idhifa, Celgene) and ivosidenib (AG-120) have been encouraging in MDS.[108]

Targeting Anti-apoptotic Proteins

Dysregulated apoptosis is commonly seen in MDS; interestingly, in early, lower-risk MDS, background apoptosis appears to be increased,[109] whereas in advanced MDS, anti-apoptotic proteins are upregulated.[110] A number of members of the Bcl-2 superfamily may present therapeutic targets in MDS at various stages of treatment, and therapies targeting Bcl-2 and Mcl-1 are currently in early therapeutic development. Of these, venetoclax (Venclexta, AbbVie/Genentech), a BH3 mimetic that inhibits Bcl-2 and is approved for 17p-mutated chronic lymphocytic leukemia, is farthest in development and seems to augment responses in combination with azacitidine[111]; several studies are currently underway exploring both combination and monotherapy (NCT02966782 and NCT02942290). Preliminary results from the MD Anderson Cancer Center have indicated a response rate above 75% with a venetoclax/HMA strategy, including in patients with *TP53* mutations whose disease is resistant to other therapies.[112]

Conclusion

MDS, which are hematologic malignancies characterized by ineffective clonal hematopoiesis and a risk for progression to AML, are challenging to treat. Allogeneic transplant is the only curative treatment, and other therapies help only a minority of patients. Progress in the treatment of MDS has been limited during the last decade; however, advances in molecular genomics that have increased our understanding of the pathogenesis of MDS, evolving diagnostic criteria for these malignancies, improved risk stratification tools, and new therapeutic targets have led to the emerging strategies previously described and give hope that outcomes for patients will improve soon.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclosures

Dr Brunner has received institutional research funding from Celgene, Takeda, and Novartis. His effort on this publication was supported by NIH/NCI SPORE in Myeloid Malignancies Grant Number 1P50CA206963. Its contents are solely the responsibility of the authors and do not necessarily represent the official view of NCI or NIH. Dr Steensma is on the data safety monitoring committee for Onconova, Takeda, and Janssen; is on the advisory board for Novartis, Pfizer, Amphivena, and H3B; has equity in Acceleron and Incyte; and has received institutional research funding from Celgene, H3B, Kura, and Syros.

References

1. Bejar R, Steensma DP. Recent developments in myelodysplastic syndromes. Blood. 2014;124(18): 2793–2803. [PubMed: 25237199]
2. Tefferi A, Vardiman JW. Myelodysplastic syndromes. N Engl J Med. 2009;361(19):1872–1885. [PubMed: 19890130]
3. Ma X, Does M, Raza A, Mayne ST. Myelodysplastic syndromes: incidence and survival in the United States. Cancer. 2007;109(8):1536–1542. [PubMed: 17345612]
4. Ma X Epidemiology of myelodysplastic syndromes. Am J Med. 2012;125(7) (suppl):S2–S5.
5. Cogle CR. Incidence and burden of the myelodysplastic syndromes. Curr Hematol Malig Rep. 2015;10(3):272–281. [PubMed: 26134527]
6. Goldberg SL, Chen E, Corral M, et al. Incidence and clinical complications of myelodysplastic syndromes among United States Medicare beneficiaries. J Clin Oncol. 2010;28(17):2847–2852. [PubMed: 20421543]
7. Cogle CR, Craig BM, Rollison DE, List AF. Incidence of the myelodysplastic syndromes using a novel claims-based algorithm: high number of uncaptured cases by cancer registries. Blood. 2011;117(26):7121–7125. [PubMed: 21531980]
8. Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. Blood. 2004;104(8):2263–2268. [PubMed: 15238427]
9. Yang W, Stotler B, Sevilla DW, et al. FISH analysis in addition to G-band karyotyping: utility in evaluation of myelodysplastic syndromes? Leuk Res. 2010;34(4):420–425. [PubMed: 19800120]
10. Bejar R, Levine R, Ebert BL. Unraveling the molecular pathophysiology of myelodysplastic syndromes. J Clin Oncol. 2011;29(5):504–515. [PubMed: 21220588]
11. Lindsley RC, Saber W, Mar BG, et al. Prognostic mutations in myelodysplastic syndrome after stem-cell transplantation. N Engl J Med. 2017;376(6):536–547. [PubMed: 28177873]
12. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood. 1997;89(6):2079–2088. [PubMed: 9058730]
13. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. Blood. 2012;120(12):2454–2465. [PubMed: 22740453]
14. Garcia-Manero G, Shan J, Faderl S, et al. A prognostic score for patients with lower risk myelodysplastic syndrome. Leukemia. 2008;22(3):538–543. [PubMed: 18079733]
15. Malcovati L, Germing U, Kuendgen A, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. J Clin Oncol. 2007;25(23):3503–3510. [PubMed: 17687155]
16. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood. 2009;114(5):937–951. [PubMed: 19357394]
17. Arber DA, Orazi A, Hasserjian R, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391–2405. [PubMed: 27069254]

18. Steensma DP, Bejar R, Jaiswal S, et al. Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes. Blood. 2015;126(1):9–16. [PubMed: 25931582]
19. Van den Berghe H, Cassiman JJ, David G, Fryns JP, Michaux JL, Sokal G. Distinct haematological disorder with deletion of long arm of no. 5 chromosome. Nature. 1974;251(5474):437–438. [PubMed: 4421285]
20. Lindsley RC, Ebert BL. Molecular pathophysiology of myelodysplastic syndromes. Annu Rev Pathol. 2013;8:21–47. [PubMed: 22934674]
21. List A, Dewald G, Bennett J, et al.; Myelodysplastic Syndrome-003 Study Investigators. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. N Engl J Med. 2006;355(14):1456–1465. [PubMed: 17021321]
22. Papaemmanuil E, Cazzola M, Boultwood J, et al.; Chronic Myeloid Disorders Working Group of the International Cancer Genome Consortium. Somatic SF3B1 mutation in myelodysplasia with ring sideroblasts. N Engl J Med. 2011;365(15):1384–1395. [PubMed: 21995386]
23. Visconte V, Makishima H, Jankowska A, et al. SF3B1, a splicing factor is frequently mutated in refractory anemia with ring sideroblasts. Leukemia. 2012;26(3):542–545. [PubMed: 21886174]
24. Malcovati L, Karimi M, Papaemmanuil E, et al. SF3B1 mutation identifies a distinct subset of myelodysplastic syndrome with ring sideroblasts. Blood. 2015;126(2):233–241 [PubMed: 25957392]
25. Steensma DP. Dysplasia has A differential diagnosis: distinguishing genuine myelodysplastic syndromes (MDS) from mimics, imitators, copycats and impostors. Curr Hematol Malig Rep. 2012;7(4):310–320. [PubMed: 23015360]
26. Dayyani F, Conley AP, Strom SS, et al. Cause of death in patients with lower-risk myelodysplastic syndrome. Cancer. 2010;116(9):2174–2179. [PubMed: 20162709]
27. Fedeli U, Schievano E, Saugo M, Rodeghiero F. Mortality from myelodysplastic syndromes: a multiple causes of death approach. Am J Hematol. 2014;89(4): 450–451.
28. Brunner A, Hobbs G, Amrein P, Ballen K, Grauber T, Fathi A. Population-based cause of death among patients with myelodysplastic syndromes [Society of Hematologic Oncology abstract MDS-170]. Clin Lymphoma Myeloma Leuk. 2016;16(suppl 2):S87–S88.
29. Sperling AS, Gibson CJ, Ebert BL. The genetics of myelodysplastic syndrome: from clonal haematopoiesis to secondary leukaemia. Nat Rev Cancer. 2017;17(1):5–19. [PubMed: 27834397]
30. Bejar R, Papaemmanuil E, Haferlach T, et al. Somatic mutations in MDS patients are associated with clinical features and predict prognosis independent of the IPSS-R: analysis of combined datasets from the International Working Group for Prognosis in MDS-Molecular Committee [ASH abstract 907]. Blood. 2015;126(23)(suppl).
31. Bejar R, Stevenson K, Abdel-Wahab O, et al. Clinical effect of point mutations in myelodysplastic syndromes. N Engl J Med. 2011;364(26):2496–2506. [PubMed: 21714648]
32. Papaemmanuil E, Gerstung M, Malcovati L, et al.; Chronic Myeloid Disorders Working Group of the International Cancer Genome Consortium. Clinical and biological implications of driver mutations in myelodysplastic syndromes. Blood. 2013;122(22):3616–3627. [PubMed: 24030381]
33. Malcovati L, Porta MGD, 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(30):7594–7603. [PubMed: 16186598]
34. Pfeilstöcker M, Tuechler H, Sanz G, et al. Time-dependent changes in mortality and transformation risk in MDS. Blood. 2016;128(7):902–910. [PubMed: 27335276]
35. Davidoff AJ, Weiss SR, Baer MR, et al. Patterns of erythropoiesis-stimulating agent use among Medicare beneficiaries with myelodysplastic syndromes and consistency with clinical guidelines. Leuk Res. 2013;37(6):675–680. [PubMed: 23523473]
36. Santini V Clinical use of erythropoietic stimulating agents in myelodysplastic syndromes. Oncologist. 2011;16(suppl 3):35–42. [PubMed: 21930833]
37. 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(3):379–393. [PubMed: 18540943]

38. Hellström-Lindberg E, Negrin R, Stein R, et al. Erythroid response to treatment with G-CSF plus erythropoietin for the anaemia of patients with myelodysplastic syndromes: proposal for a predictive model. Br J Haematol. 1997;99(2):344–351. [PubMed: 9375752]
39. Buckstein R, Balleari E, Wells R, et al. ITACA: A new validated international erythropoietic stimulating agent-response score that further refines the predictive power of previous scoring systems. Am J Hematol. 2017;92(10):1037–1046. [PubMed: 28675513]
40. Chuncharunee S, Intragumtornchai T, Chaimongkol B, et al. Treatment of myelodysplastic syndrome with low-dose human granulocyte colony-stimulating factor: a multicenter study. Int J Hematol. 2001;74(2):144–146 [PubMed: 11594513]
41. 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(12):2393–2400. [PubMed: 19564636]
42. Kantarjian H, Fenaux P, Sekeres MA, et al. Safety and efficacy of romiplostim in patients with lower-risk myelodysplastic syndrome and thrombocytopenia. J Clin Oncol. 2010;28(3):437–444. [PubMed: 20008626]
43. Giagounidis A, Mufti GJ, Fenaux P, et al. Results of a randomized, double blind study of romiplostim versus placebo in patients with low/intermediate-1-risk myelodysplastic syndrome and thrombocytopenia. Cancer. 2014;120(12): 1838–1846. [PubMed: 24706489]
44. Platzbecker U, Wong RSM, Verma A, et al. Safety and tolerability of eltrombopag versus placebo for treatment of thrombocytopenia in patients with advanced myelodysplastic syndromes or acute myeloid leukaemia: a multicentre, randomised, placebo-controlled, double-blind, phase 1/2 trial. Lancet Haematol. 2015;2(10):e417–e426. [PubMed: 26686043]
45. Dickinson M, Cherif H, Fenaux P, et al. Eltrombopag in combination with azacitidine for first-line treatment of MDS patients with thrombocytopenia: the randomized, placebo-controlled, phase III, Support study [International Symposium on Myelodysplastic Syndromes abstract 37]. Leuk Res. 2017;55(suppl 1): S23–S24.
46. Stone RM. How I treat patients with myelodysplastic syndromes. Blood. 2009;113(25):6296–6303. [PubMed: 19383969]
47. Santini V, Almeida A, Giagounidis A, et al. Randomized phase III study of lenalidomide versus placebo in RBC transfusion-dependent patients with lower-risk non-del(5q) myelodysplastic syndromes and ineligible for or refractory to erythropoiesis-stimulating agents. J Clin Oncol. 2016;34(25):2988–2996. [PubMed: 27354480]
48. 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(1):86–93. [PubMed: 17893227]
49. Sloand EM, Wu CO, Greenberg P, Young N, Barrett J. Factors affecting response and survival in patients with myelodysplasia treated with immunosuppressive therapy. J Clin Oncol. 2008;26(15): 2505–2511. [PubMed: 18413642]
50. Lim ZY, Killick S, Germing U, et al. Low IPSS score and bone marrow hypo-cellularity in MDS patients predict hematological responses to antithymocyte globulin. Leukemia. 2007;21(7):1436–1441. [PubMed: 17507999]
51. Passweg JR, Giagounidis AAN, Simcock M, et al. Immunosuppressive therapy for patients with myelodysplastic syndrome: a prospective randomized multicenter phase III trial comparing antithymocyte globulin plus cyclosporine with best supportive care--SAKK 33/99. J Clin Oncol. 2011;29(3):303–309. [PubMed: 21149672]
52. Sauntharajah Y, Nakamura R, Nam J-M, et al. HLA-DR15 (DR2) is over represented in myelodysplastic syndrome and aplastic anemia and predicts a response to immunosuppression in myelodysplastic syndrome. Blood. 2002; 100(5):1570–1574. [PubMed: 12176872]
53. Townsley DM, Dumitriu B, Liu D, et al. Danazol treatment for telomere diseases. N Engl J Med. 2016;374(20):1922–1931. [PubMed: 27192671]
54. Chan G, DiVenuti G, Miller K. Danazol for the treatment of thrombocytopenia in patients with myelodysplastic syndrome. Am J Hematol. 2002;71(3):166–171. [PubMed: 12410570]

55. 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(10):2429–2440. [PubMed: 12011120]
56. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al.; International Vidaza High-Risk MDS Survival Study Group. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodys-plastic syndromes: a randomised, open-label, phase III study. Lancet Oncol. 2009;10(3):223–232. [PubMed: 19230772]
57. 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(23):3842–3848. [PubMed: 19528372]
58. Welch JS, Petti AA, Miller CA, et al. TP53 and decitabine in acute myeloid leukemia and myelodysplastic syndromes. N Engl J Med. 2016;375(21): 2023–2036. [PubMed: 27959731]
59. Müller-Thomas C, Rudelius M, Rondak I-C, et al. Response to azacitidine is independent of p53 expression in higher-risk myelodysplastic syndromes and secondary acute myeloid leukemia. Haematologica. 2014;99(10):e179–e181. [PubMed: 24972774]
60. Garcia-Manero G, Odenike O, Amrein PC, et al. Successful emulation of IV decitabine pharmacokinetics with an oral fixed-dose combination of the oral cytidine deaminase inhibitor (CDAi) E7727 with oral decitabine, in subjects with myelodysplastic syndromes (MDS): final data of phase 1 study [ASH abstract 114]. Blood. 2016;128(22)(suppl).
61. Savona MR, Gore SD, Kolibaba KS, et al. CC-486 (oral azacitidine) mono-therapy in patients with acute myeloid leukemia (AML) [ASH abstract 452]. Blood. 2015;126(23)(suppl).
62. Muffly L, Pasquini MC, Martens M, et al. Increasing use of allogeneic hematopoietic cell transplantation in patients aged 70 years and older in the United States. Blood. 2017;130(9):1156–1164. [PubMed: 28674027]
63. Brunner AM, Kim HT, Coughlin E, et al. Outcomes in patients age 70 or older undergoing allogeneic hematopoietic stem cell transplantation for hematologic malignancies. Biol Blood Marrow Transplant. 2013;19(9):1374–1380. [PubMed: 23791626]
64. Sorror ML, Sandmaier BM, Storer BE, et al. Long-term outcomes among older patients following nonmyeloablative conditioning and allogeneic hematopoietic cell transplantation for advanced hematologic malignancies. JAMA. 2011;306(17):1874–1883. [PubMed: 22045765]
65. Devine SM, Hoffman R, Verma A, et al. Allogeneic blood cell transplantation following reduced-intensity conditioning is effective therapy for older patients with myelofibrosis with myeloid metaplasia. Blood. 2002;99(6):2255–2258. [PubMed: 11877308]
66. Koreth J, Pidala J, Perez WS, et al. Role of reduced-intensity conditioning allogeneic hematopoietic stem-cell transplantation in older patients with de novo myelodysplastic syndromes: an international collaborative decision analysis. J Clin Oncol. 2013;31(21):2662–2670. [PubMed: 23797000]
67. Weisdorf D, Zhang M-J, Arora M, Horowitz M, Rizzo JD, Eapen M. Graft-versus-host disease induced graft-versus-leukemia effect: greater impact on relapse and disease-free survival following reduced intensity conditioning. Biol Blood Marrow Transplant. 2012;18(11):1727–1733. [PubMed: 22766220]
68. Scott BL, Pasquini MC, Logan BR, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodys-plastic syndromes. J Clin Oncol. 2017;35(11):1154–1161. [PubMed: 28380315]
69. Di Stasi A, Milton DR, Poon LM, et al. Similar transplantation outcomes for acute myeloid leukemia and myelodysplastic syndrome patients with haploidentical versus 10/10 human leukocyte antigen-matched unrelated and related donors. Biol Blood Marrow Transplant. 2014;20(12):1975–1981. [PubMed: 25263628]
70. Ballen KK, Koreth J, Chen Y-B, Dey BR, Spitzer TR. Selection of optimal alternative graft source: mismatched unrelated donor, umbilical cord blood, or haploidentical transplant. Blood. 2012;119(9):1972–1980. [PubMed: 22210876]
71. Alousi AM, Le-Rademacher J, Saliba RM, et al. Who is the better donor for older hematopoietic transplant recipients: an older-aged sibling or a young, matched unrelated volunteer? Blood. 2013;121(13):2567–2573. [PubMed: 23361908]

72. Kröger N, Zabelina T, de Wreede L, et al.; MDS subcommittee of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Trans-plantation (EBMT). Allogeneic stem cell transplantation for older advanced MDS patients: improved survival with young unrelated donor in comparison with HLA-identical siblings. Leukemia. 2013;27(3):604–609. [PubMed: 22821073]
73. Gibson CJ, Kennedy JA, Nikiforow S, et al. Donor-engrafted CHIP is common among stem cell transplant recipients with unexplained cytopenias. Blood. 2017;130(1):91–94. [PubMed: 28446434]
74. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. N Engl J Med. 2014;371(26):2488–2498. [PubMed: 25426837]
75. Genovese G, Kähler AK, Handsaker RE, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. N Engl J Med. 2014;371(26):2477–2487. [PubMed: 25426838]
76. Malcovati L, Gallì A, Travaglino E, et al. Clinical significance of somatic mutation in unexplained blood cytopenia. Blood. 2017;129(25):3371–3378. [PubMed: 28424163]
77. Graubert TA, Shen D, Ding L, et al. Recurrent mutations in the U2AF1 splicing factor in myelodysplastic syndromes. Nat Genet. 2011;44(1):53–57. [PubMed: 22158538]
78. Saez B, Walter MJ, Graubert TA. Splicing factor gene mutations in hematologic malignancies. Blood. 2017;129(10):1260–1269. [PubMed: 27940478]
79. Shih L-Y, Huang C-F, Wang P-N, et al. Acquisition of FLT3 or N-ras mutations is frequently associated with progression of myelodysplastic syndrome to acute myeloid leukemia. Leukemia. 2004;18(3):466–475. [PubMed: 14737077]
80. Meggendorfer M, de Albuquerque A, Nadarajah N, et al. Karyotype evolution and acquisition of FLT3 or RAS pathway alterations drive progression of myelodysplastic syndrome to acute myeloid leukemia. Haematologica. 2015;100(12):e487–e490. [PubMed: 26294738]
81. Muller PAJ, Vousden KH. p53 mutations in cancer. Nat Cell Biol. 2013;15(1):2–8. [PubMed: 23263379]
82. Sekeres MA, Steensma DP. Boulevard of broken dreams: drug approval for older adults with acute myeloid leukemia. J Clin Oncol. 2012;30(33):4061–4063. [PubMed: 23008302]
83. Suragani RNVS, Cadena SM, Cawley SM, et al. Transforming growth factor-b superfamily ligand trap ACE-536 corrects anemia by promoting late-stage erythropoiesis. Nat Med. 2014;20(4):408–414. [PubMed: 24658078]
84. Eshghi S, Vogelezang MG, Hynes RO, Griffith LG, Lodish HF. a4b1 integrin and erythropoietin mediate temporally distinct steps in erythropoiesis: integrins in red cell development. J Cell Biol. 2007;177(5):871–880. [PubMed: 17548514]
85. Attie KM, Allison MJ, McClure T, et al. A phase 1 study of ACE-536, a regulator of erythroid differentiation, in healthy volunteers. Am J Hematol. 2014;89(7):766–770. [PubMed: 24715706]
86. Giagounidis A, Platzbecker U, Germing U, et al. Luspatercept treatment leads to long term increases in hemoglobin and reductions in transfusion burden in patients with low or intermediate-1 risk myelodysplastic syndromes (MDS): preliminary results from the phase 2 PACE-MDS Extension Study [ASH abstract 92]. Blood. 2015;126(23)(suppl).
87. Platzbecker U, Germing U, Götze K, et al. Luspatercept response in ESA-naïve/RS+ patients and RS-patients with low-intermediate risk myelodysplastic syndromes (MDS) [ASH abstract 5551]. Blood. 2016;128(22)(suppl).
88. Lee SC-W, Dvinge H, Kim E, et al. Modulation of splicing catalysis for therapeutic targeting of leukemia with mutations in genes encoding spliceosomal mutations. Nat Med. 2016;22(6):672–678. [PubMed: 27135740]
89. Steensma DP, Maris MB, Yang J, et al. H3B-8800-G0001–101: a first in human phase I study of a splicing modulator in patients with advanced myeloid malignancies [ASCO abstract TPS7075]. J Clin Oncol. 2017;35(15)(suppl).
90. Chiappinelli KB, Strissel PL, Desrichard A, et al. Inhibiting DNA methylation causes an interferon response in cancer via dsRNA including endogenous retroviruses. Cell. 2015;162(5):974–986. [PubMed: 26317466]

91. Garcia-Manero G, Daver NG, Montalban-Bravo G, et al. A phase II study evaluating the combination of nivolumab (nivo) or ipilimumab (ipi) with azacitidine in pts with previously treated or untreated myelodysplastic syndromes (MDS) [ASH abstract 344]. Blood. 2016;128(22)(suppl).
92. Garcia-Manero G, Tallman MS, Martinelli G, et al. Pembrolizumab, a PD-1 inhibitor, in patients with myelodysplastic syndrome (MDS) after failure of hypomethylating agent treatment [ASH abstract 345]. Blood. 2016;128(22) (suppl).
93. Srivastava P, Paluch BE, Matsuzaki J, et al. Immunomodulatory action of SGI-110, a hypomethylating agent, in acute myeloid leukemia cells and xenografts. Leuk Res. 2014;38(11): 1332–1341. [PubMed: 25260825]
94. Issa JJ, Roboz G, Rizzieri D, et al. Safety and tolerability of guadecitabine (SGI-110) in patients with myelodysplastic syndrome and acute myeloid leukaemia: a multicentre, randomised, dose-escalation phase 1 study. Lancet Oncol. 2015;16(9):1099–1110. [PubMed: 26296954]
95. Quintás-Cardama A, Santos FPS, Garcia-Manero G. Histone deacetylase inhibitors for the treatment of myelodysplastic syndrome and acute myeloid leukemia. Leukemia. 2011;25(2):226–235. [PubMed: 21116282]
96. Cashen A, Juckett M, Jumonville A, et al. Phase II study of the histone deacetylase inhibitor belinostat (PXD101) for the treatment of myelodysplastic syndrome (MDS). Ann Hematol. 2012;91(1):33–38. [PubMed: 21538061]
97. Garcia-Manero G, Yang H, Bueso-Ramos C, et al. Phase 1 study of the histone deacetylase inhibitor vorinostat (suberoylanilide hydroxamic acid [SAHA]) in patients with advanced leukemias and myelodysplastic syndromes. Blood. 2008;111(3):1060–1066. [PubMed: 17962510]
98. DeAngelo DJ, Spencer A, Bhalla KN, et al. Phase Ia/II, two-arm, open-label, dose-escalation study of oral panobinostat administered via two dosing schedules in patients with advanced hematologic malignancies. Leukemia. 2013;27(8): 1628–1636. [PubMed: 23385375]
99. Issa J-P, Garcia-Manero G, Huang X, et al. Results of phase 2 randomized study of low-dose decitabine with or without valproic acid in patients with myelodys plastic syndrome and acute myelogenous leukemia. Cancer. 2015;121(4):556–561. [PubMed: 25336333]
100. Uy GL, Abboud CN, Cashen AF, et al. Phase I study of panobinostat plus decitabine in elderly patients with advanced MDS or AML [ASH abstract 1060]. Blood. 2010;116(21)(suppl).
101. Garcia-Manero G, Montalban-Bravo G, Berdeja JG, et al. Phase 2, randomized, double-blind study of pracinostat in combination with azacitidine in patients with untreated, higher-risk myelodysplastic syndromes. Cancer. 2017;123(6): 994–1002. [PubMed: 28094841]
102. Kirschbaum M, Gojo I, Goldberg SL, et al. A phase 1 clinical trial of vorinostat in combination with decitabine in patients with acute myeloid leukaemia or myelodysplastic syndrome. Br J Haematol. 2014;167(2):185–193. [PubMed: 25040094]
103. Sekeres MA, Othus M, List AF, et al. Randomized phase II study of azacitidine alone or in combination with lenalidomide or with vorinostat in higher-risk myelodysplastic syndromes and chronic myelomonocytic leukemia: North American Intergroup Study SWOG S1117. J Clin Oncol. 2017;35(24):2745–2753. [PubMed: 28486043]
104. Nand S, Godwin J, Smith S, et al. Hydroxyurea, azacitidine and gemtuzumab ozogamicin therapy in patients with previously untreated non-M3 acute myeloid leukemia and high-risk myelodysplastic syndromes in the elderly: results from a pilot trial. Leuk Lymphoma. 2008;49(11):2141–2147. [PubMed: 19021057]
105. Daver N, Kantarjian H, Ravandi F, et al. A phase II study of decitabine and gemtuzumab ozogamicin in newly diagnosed and relapsed acute myeloid leukemia and high-risk myelodysplastic syndrome. Leukemia. 2016;30(2):268–273. [PubMed: 26365212]
106. Athuluri-Divakar SK, Vasquez-Del Carpio R, Dutta K, et al. A small molecule RAS-mimetic disrupts RAS association with effector proteins to block signaling. Cell. 2016;165(3):643–655. [PubMed: 27104980]
107. Garcia-Manero G, Fenaux P, Al-Kali A, et al.; ONTIME study investigators. Rigosertib versus best supportive care for patients with high-risk myelodysplastic syndromes after failure of hypomethylating drugs (ONTIME): a randomised, controlled, phase 3 trial. Lancet Oncol. 2016;17(4):496–508. [PubMed: 26968357]

108. Stein EM, Fathi AT, DiNardo CD, et al. Enasidenib (AG-221), a potent oral inhibitor of mutant isocitrate dehydrogenase 2 (IDH2) enzyme, induces hematologic responses in patients with myelodysplastic syndromes (MDS) [ASH abstract 343]. Blood. 2016;128(22)(suppl).

109. Parker JE, Fishlock KL, Mijovic A, Czepulkowski B, Pagliuca A, Mufti GJ. 'Low-risk' myelodysplastic syndrome is associated with excessive apoptosis and an increased ratio of proversus anti-apoptotic bcl-2-related proteins. Br J Haematol. 1998;103(4):1075–1082. [PubMed: 9886323]

110. Kerbauy DB, Deeg HJ. Apoptosis and antiapoptotic mechanisms in the progression of MDS. Exp Hematol. 2007;35(11):1739–1746. [PubMed: 17976524]

111. Jilg S, Kauschinger J, Reidel V, et al. Combination of 5-azacytidine and ABT-199 has a synergistic apoptotic effect in high-risk MDS/sAML after HMA failure [ASH abstract 4297]. Blood. 2016;128(22)(suppl).

112. Pollyea DA, Dinardo CD, Thirman MJ, et al. Results of a phase 1b study of venetoclax plus decitabine or azacitidine in untreated acute myeloid leukemia patients ≥ 65 years ineligible for standard induction therapy [ASCO abstract 7009]. J Clin Oncol. 2016;34(15)(suppl).

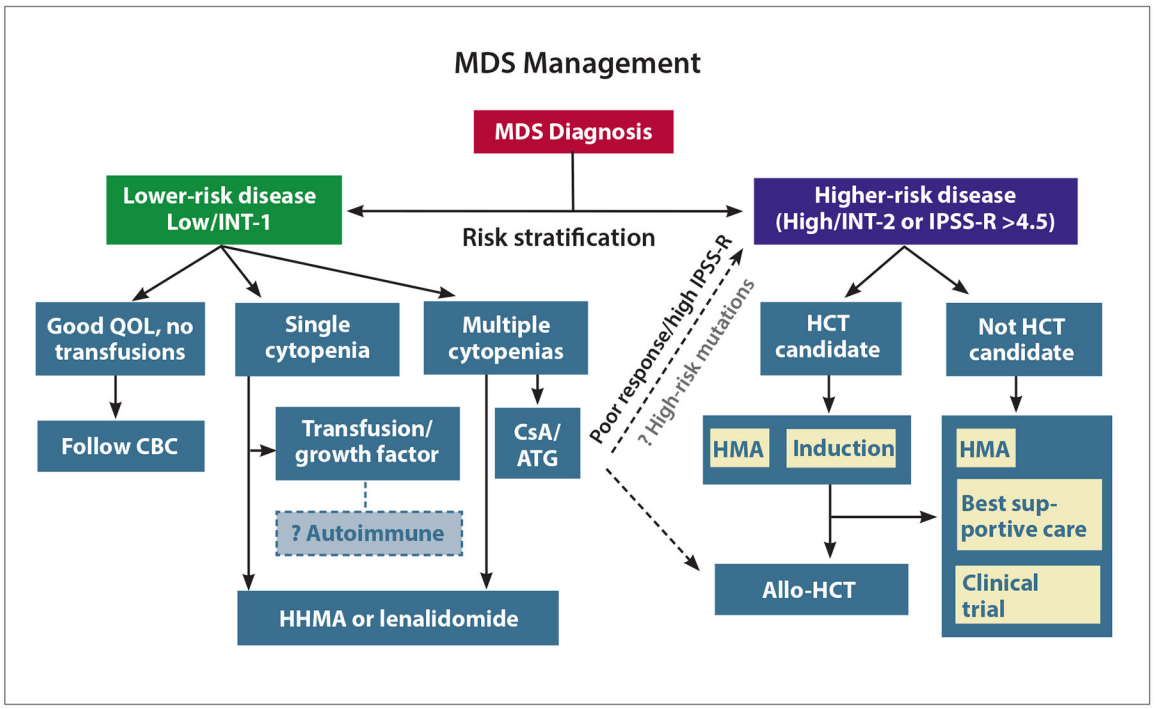

Figure.

Approach to therapeutics in myelodysplastic syndromes. Clinical trial enrollment should be considered at all stages. Patients should be risk stratified with a tool such as the IPSS-R. Some patients with lower-risk disease who have mild cytopenias and are minimally symptomatic may just be observed with serial CBCs. Patients who have anemia alone can be administered an erythropoiesis-stimulating agent if their serum erythropoietin level is less than 500 U/L, or can receive lenalidomide if they have del(5q). The approach for other patients is challenging and may involve immunosuppressive therapy with CsA and ATG, a combination growth factor approach, lenalidomide despite the absence of del(5q), or a hypomethylating agent. For patients with higher-risk disease, the key decision is whether the patient is an allogeneic stem cell transplant candidate. If the patient is a transplant candidate, the transplant should be performed as soon as possible, potentially with a hypomethylating agent as a bridge. If not, the patient should receive therapy with a hypomethylating agent; in this setting, azacitidine has improved survival compared with conventional care. “Induction” might include CPX-351 instead of the conventional cytarabine-anthracycline “3&7” combination.

Allo-HCT, allogeneic hematopoietic stem cell transplant; ATG, antithymocyte globulin; CBC, complete blood cell count; CsA, cyclosporine-A; HCT, hematopoietic stem cell transplant; HMA, hypomethylating agent; INT, intermediate risk; IPSS, International Prognostic Scoring System; IPSS-R, Revised International Prognostic Scoring System; MDS, myelodysplastic syndromes; QOL, quality of life.