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REVIEW ARTICLE

Myelodysplastic syndromes in the United States: an update for clinicians

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Myelodysplastic syndromes (MDS) are heterogeneous malignant bone marrow disorders diagnosed most often in elderly white persons. MDS have significant clinical consequences, including cytopenias leading to infection, bleeding, and death; and approximately one-third of cases progress to acute myeloid leukemia (AML). Only one potentially curative therapy exists—allogeneic hematopoietic stem cell transplant (HSCT)—but this therapy is not widely used due to associated morbidity and mortality in elderly patients. Recent research suggests MDS occurs more frequently than previously thought and may be responsible for a substantial proportion of unexplained anemias in elderly persons. Incidence of MDS is expected to increase with increases in life expectancy. Therefore, we offer this comprehensive narrative update of MDS to inform the medical community treating the population at risk for MDS, with a focus on MDS epidemiology and clinical management in the United States. This review includes a brief historical background of MDS, provides an overview of the population burden of disease, discusses the molecular pathology of MDS, describes the clinical features and management of MDS, and discusses future directions in MDS research. Our objective is to inform general medicine practitioners and call attention to the need for translational research in MDS.

Key words: Bone marrow diseases, hematology, leukemia, malignancy, myelodysplastic syndromes

Key messages

- MDS should be considered in the differential diagnosis of patients with cytopenias, and, regardless of age, if MDS is suspected then referral to a hematologist should be considered to discuss diagnosis and options for therapy.
- Hematopoietic stem cell transplant (HSCT) is the only potentially curative therapy for MDS, but not all patients are candidates.
- There is an urgent need for more translational research in MDS that addresses questions such as the presence of modifiable risk factors for MDS, new therapeutic targets, biomarkers of treatment response or disease progression, and ways to expand access to HSCT to more patients.

Introduction

Myelodysplastic syndromes (MDS) are heterogeneous malignant bone marrow disorders (1). Although clonal marrow cells in MDS can mature, hematopoiesis is ineffective as the cells undergo high rates of apoptosis (1). This results in peripheral blood cytopenias and potentially fatal complications, including infection and bleeding (1,2). MDS is diagnosed primarily in elderly white people and is observed with a slightly higher frequency in men than women (3,4). MDS occur *de novo* and secondary to anti-cancer chemotherapy or ionizing radiation (3,4) and exhibit a broad spectrum of severity and prognosis, although most worsen over time and sometimes exacerbate unpredictably (2,5). Approximately 30% of cases progress to acute myeloid leukemia (AML), although the probability of AML progression increases with increasing disease severity (6,7) (e.g. ~10% for low-risk and 80% for high risk MDS over 2 years) (8). Allogeneic hematopoietic stem cell transplant (HSCT) is potentially curative but is not widely used due to associated morbidity and mortality in older patients (2,9). Nevertheless, MDS remains the third most common indication for allogeneic HSCT in United States (US) adults (10). MDS patients experience significantly worse survival than similar-aged patients without MDS, with an estimated 3-year relative survival of 45% (95% confidence interval (CI) 43%–47%) (11).

MDS is considered by many in the medical community to be a cancer (12) and is now reported to cancer registries (6,11). However, accurate estimates of the population burden of MDS are elusive due in part to diagnostic challenges (13). Therefore, although estimates from population-based cancer registries suggest approximately 10,000 new cases of MDS each year (6), the actual number may be higher. Some investigators estimate as many as 45,000 new cases in the US per year, among persons aged 65 and older alone (14). Finally, it is expected that incidence of MDS will increase with extended life-spans (3). Therefore, it is incumbent

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upon clinicians, especially those treating elderly patients, to become familiar with MDS.

Therefore, we provide a comprehensive review of MDS intended to inform the medical community treating patients who are at risk or are currently under the care of a specialist for MDS. Our review begins with a brief historical narrative of MDS, provides an overview of the population disease burden in the US, reviews MDS molecular pathology, describes the clinical features and management of MDS in the US, and discusses future directions in MDS research.

Discovery of myelodysplastic syndromes

The relatively recent discovery of MDS followed from the study of anemia, which was enabled by a series of improvements in microscope technologies, tissue stains, and *in vivo* bone marrow biopsy techniques in the late nineteenth and early twentieth centuries (5). Detailed study by Giovanni Guglielmo and others during the 1920s to 1940s revealed the existence of several blood abnormalities in anemic patients, some of which would eventually become labeled as MDS (5,15). In 1949 Hamilton-Paterson (16) observed that some patients with anemia that was refractory to vitamin B12 developed acute leukemia, and this observation of a 'pre-leukemic' syndrome was described again in 1953 (5,17). In 1973 Saarni and Linman (18) reviewed the medical literature and identified common clinical and pathological features of pre-leukemias (5). However, some investigators proposed the term 'pre-leukemia' was misleading as a substantial proportion of patients never progressed to leukemia and survived long periods before dying of other causes (5). Instead, it was suggested that these illnesses be called 'myelodysplastic diseases' or 'myelodysplasia' (5). In 1976 and 1982 the French–American–British (FAB) Working Group proposed the first standard classification of MDS based primarily on morphological features (19,20). Subsequent revisions of this classification were incorporated in the World Health Organization (WHO) classification published in 2001 and updated in 2008 (21). MDS is currently diagnosed based on the WHO classification using a combination of morphologic and genetic abnormalities, and clinical features (22,23).

Epidemiology of myelodysplastic syndromes in the United States

Data from the Surveillance Epidemiology and End Results (SEER) program and the North American Association of Central Cancer Registries (NAACCR) show there were an estimated 9700 new cases of MDS in the US during 2004 based on an age-adjusted incidence rate of 3.27 per 100,000 during 2001–2003 (6). Rates were significantly higher in men (4.43 per 100,000) than women (2.53 per 100,000) (6). Incidence was highest in whites, but not significantly different from other races (6). However, incidence was significantly higher in non-Hispanics (3.23 per 100,000) compared with Hispanics (2.83 per 100,000) (6). Rates were lowest in persons under age 40 (0.14 per 100,000) and increased with each 10-year increase in age, with incidence of 20.05 per 100,000 in persons aged 70–79 and 35.49 per 100,000 in persons aged 80 and older (6). Moderate increases in incidence over time were attributable to changes in compliance with reporting requirements (6).

Population-based cancer registries likely under-report MDS incidence as many patients are treated in community health care settings where reporting may be incomplete (13,14). Furthermore, patients with unexplained anemia may have MDS but not receive an MDS diagnosis (13). Therefore, alternative approaches to estimating incidence have been applied using medical claims data. Goldberg et al. (14) used International Classification of Diseases for Oncology Clinical Modification (ICD-9-CM) codes to estimate there were 45,000 new cases of MDS among the Medicare beneficiary population in 2003 (14). This estimate, which is restricted to persons aged 65 and older, is greatly out of proportion with the number of new cases occurring among persons of all ages during 2004 as reported to SEER (6). However, this study likely overestimated the true number of incident cases as it used a non-specific indicator of MDS, and it did not exclude prevalent cases (11). In a later study by Cogle et al. (11) four algorithms for identifying MDS, each using a combination of data reported to SEER and requests for diagnostic services associated with MDS in Medicare claims, and that excluded prevalent cases, were implemented and compared. This study identified one algorithm with high sensitivity and specificity for detecting MDS (compared to SEER case registration) and estimated an incidence rate of 75 per 100,000 among persons aged 65 and older during 2005 (11). For the same demographic during 2005, the incidence of MDS reported in SEER was 20 per 100,000 (11). Interestingly, many of the cases detected algorithmically in this study were reported in SEER as having another cancer but were not reported to SEER after developing MDS as their second malignancy, as required by SEER reporting guidelines (11). Although these examples illustrate several difficulties affecting the precision of population-based estimates of MDS disease burden, it is clear from these investigations that MDS is far more common than originally thought. For example, the aforementioned review by Saarni and Linman (18) uncovered fewer than 200 reported cases of pre-leukemia (5).

Molecular pathology of myelodysplastic syndromes

The state of knowledge concerning the molecular pathology of MDS has been reviewed recently (1,24). The emerging picture suggests a complex pathobiology that poses many puzzling questions about underlying disease mechanisms. The genesis of MDS is within an abnormal hematopoietic stem cell that develops a growth advantage relative to other cells in the bone marrow (1,24). Although the initiating event that establishes this growth advantage is unclear, the result is apparent: daughter cells derived from the abnormal stem cell rapidly proliferate and overtake the bone marrow (1,24). Despite maturation arrest observed at various stages, and in contrast with other malignancies, the clonal cells in MDS partially maintain their ability to differentiate (1,24). The clonal cells also undergo high rates of apoptosis, which results in peripheral blood cytopenias (1,24). The resulting cytopenias are variable and depend on the cell lineage undergoing the highest level of apoptosis (1,24). Dysplastic cells that do enter the circulating blood represent those cells most resistant to apoptosis among all of the malignant clones (1,24). Patients with low-risk disease exhibit the highest rates of bone marrow apoptosis (1,24). Thus, a lack of apoptosis in patients with high-risk disease is especially relevant in a therapeutic approach that relies on intact apoptosis pathways (1,24). The source of apoptosis sensitivity, including the specific apoptosis pathways, and the distribution of this sensitivity across different clonal generations and disease subgroups, and its therapeutic implications, remain high-priority areas of study in MDS (1,24).

Approximately half of MDS exhibit abnormal karyotypes with characteristic chromosomal abnormalities associated with clinical presentation and natural history of disease, and this information is incorporated into MDS classification systems (1,2). However, while it remains true that nearly half of all MDS patients exhibit *normal* karyotypes, this does not imply an absence of genetic prognostic information in these patients (25). For example, a

study of 439 patients with MDS identified somatic mutations in at least 1 of 111 cancer-associated genes among 51% of patients overall, and 52% of patients with normal cytogenetics (26). Interestingly, mutations in *ASXL1*, *RUNX1*, *TP53*, *EZH2*, *CBL*, and *ETV6* were associated with overall survival after adjustment for International Prognostic Scoring System (IPSS) risk group, and mutations in these genes were observed in 29% of patients with normal cytogenetics (26).

The presence of mutations associated with survival even in normal karyotype MDS offers an exciting opportunity to improve our understanding of MDS pathobiology and improve clinical management of the disease. However, novel genomic approaches such as whole-genome sequencing (WGS) may be required to reveal the extent of genetic alterations and their clinical relevance in MDS. For example, Walter et al. (27) demonstrated that a candidate gene approach is inferior to WGS for defining the clonal architecture in MDS, and that there appears to be no single gene or set of genes that are commonly mutated in founding MDS clones. In another study Walter (28) and colleagues used WGS to demonstrate that the persistence of a founding clone was universally observed in MDS cases that progressed to AML. These observations may have substantial translational impact as they suggest the genetic heterogeneity of MDS is extensive, and that candidate gene approaches may not be sufficient for understanding MDS pathobiology and identifying novel therapeutic targets. Whole-genome and exome sequencing studies have already identified previously unknown mutations in RNA splicing machinery that are associated with ineffective hematopoiesis and that occur frequently in particular subtypes of MDS (29–31). However, it is important to note that despite the potential clinical utility of these approaches, none are currently combined into routine clinical practice.

It is also now recognized that MDS cells harbor an abnormal epigenome that shows global hypermethylation of promoter regions of important genes, including tumor suppressors (32). These methylation abnormalities are passed on through clonal generations and are believed to be important in determining the aberrant differentiation of hematopoietic cells observed in MDS. However, it remains uncertain whether these methylation patterns are a result of, or develop along with, genetic changes that are observed in MDS (32). In addition, although hypomethylation is believed to be a primary mechanism of action for hypomethylating agent (HMA) therapy (32), global methylation and methylation of tumor suppressor genes is not consistently associated with response to therapy (33), indicating the possible importance of other host or disease-related factors in determining response to HMA and/or implying other possible mechanisms of action for HMA.

Finally, recent work has also identified disruptions in the post-translational effects of miRNA on hematopoiesis as potentially influential in both MDS and leukemia; and interactions between stromal cells in the microenvironment and hematopoietic cells may be of importance in the initiation and progression of MDS (1). More information is expected to emerge in the future from these relatively new areas of investigation in MDS (1).

Diagnosis and prognosis of myelodysplastic syndromes

Differential diagnosis of myelodysplastic syndromes

Most patients with MDS present with cytopenias affecting one or more cell lines (2). In patients who present with anemia, a diagnosis of MDS begins with ruling out alternative processes that can cause anemia (2). This begins with determining whether anemia is the sole finding on a complete blood count, or whether platelet and white blood cell counts are also abnormal (34). If anemia is the sole finding, then the reticulocyte count and index can be used to determine whether the anemia is present without a compensatory increase in bone marrow erythrocyte production, which leaves the possibility that further investigation may reveal a bone marrow disorder such as MDS (34). Similarly, among patients presenting with thrombocytopenia, it is critical to follow a systematic process to rule out alternative diagnoses (35). The first step is careful examination of a peripheral blood smear for characteristic morphologic findings that suggest alternative pathologies, e.g. platelet clumping that would suggest artificial thrombocytopenia, or giant platelets suggestive of a hereditary thrombocytopenia, or increased red cell fragmentation suggestive of microangiopathic processes (35). If the examination of the peripheral blood smear is only significant for isolated thrombocytopenia then the differential diagnosis would include immune thrombocytopenic purpura, drug-induced thrombocytopenia, and viral infections (e.g. HIV), among others (35). On the other hand, the presence of circulating myeloblasts or Pelger–Huet dysplastic white blood cells may suggest a primary bone marrow disorder such as MDS (35). Bone marrow aspirate is ordered if no explanation is evident for the presenting cytopenias, and diagnosis of MDS can be made based on the presence of dysplastic cells from one or more lineages (2). Referral to a hematologist should be considered for any patient suspected of having MDS, regardless of the patient's age.

Prognosis

Classification of MDS subtype, prognosis, and selection of therapy has historically been made based on several different systems, with some systems having applicability to different patient subgroups (e.g. *de novo* versus secondary MDS) and others being variously useful in predicting survival and selecting therapy (2,7,8,36–38). The most widely used prognostic classification system for MDS is the IPSS and the revised IPSS (IPSS-R), which take into account the number of circulating blasts, presence and depth of cytopenias, and cytogenetic abnormalities (36). The IPSS-R improves upon the IPSS by allowing for more precise prognostication for intermediate-risk patients as compared to the IPSS (36). The IPSS-R is expected to supersede the IPSS for MDS prognostication in the future (25,39), and US-based treatment guidelines already incorporate the IPSS-R for therapy selection (40). Therefore, we review the IPSS-R here and explain how it is used in the clinic.

The IPSS-R was developed by the International Working Group for Prognosis in MDS using a sample of 7012 patients diagnosed with primary MDS from 11 countries who had not received therapy known to alter the course of MDS (36). The derivation of the IPSS-R and improvements over the original IPSS (7) have been described in detail (36). Briefly, the system categorizes patients into five risk groups (very low, low, intermediate, high, and very high), each with a different risk of death from any cause and AML progression (36). To determine the IPSS-R risk category for a particular patient, the physician must first calculate the patient's IPSS-R score based on five important factors associated with prognosis in MDS: the patient's cytogenetic profile (very poor, poor, intermediate, good, and very good), bone marrow blast percentage, and depth of cytopenias (hemoglobin (g/dL), platelet count ($\times 10^9$/L), and absolute neutrophil count ($\times 10^9$/L)) (36). The score in each of these five areas is summed to arrive at an overall IPSS-R score. The IPSS-R score is then used to infer the risk category as shown in Table I: very low (score $\leq$ 1.5), low (score $>$ 1.5 to 3.0), intermediate (score $>$ 3.0 to 4.5), high (score $>$ 4.5 to 6), and very high (score $>$ 6) (36). The resulting

Table I. Identifying the IPSS-R risk category based on the IPSS-R score.

IPSS-R score	IPSS-R risk category	Median survival (95% CI) (y)
≤1.5	Very low	8.8 (7.8–9.9)
>1.5 to 3	Low	5.3 (5.1–5.7)
>3 to 4.5	Intermediate	3.0 (2.7–3.3)
>4.5 to 6	High	1.6 (1.5–1.7)
>6	Very high	0.8 (0.7–0.8)

Data shown in this table were extracted from Greenberg, et al. (36).
IPSS-R = International Prognostic Scoring System–Revised.

prognosis is relevant for a person aged 70 years (36). Age-adjusted estimates of the risk category are easily obtained by the clinician using a formula derived by IPSS-R investigators (36). Clinicians can easily calculate the age-adjusted IPSS-R risk score using an online tool provided by the MDS Foundation (41).

Improving prognostication for patients with myelodysplastic syndromes

The IPSS-R was derived and validated using data obtained at diagnosis only (36). Two other models are described as time-dependent, accounting for disease progression (8,37). All of these systems were derived prior to widespread HMA use. A recent study suggested HMA can overcome the adverse prognosis for patients in the worst IPSS-R category (42), although these results require replication in a larger sample. As novel therapeutics that have the potential to modify the natural history of MDS are introduced in the clinic, it will be important to re-evaluate existing prognostic systems and determine if additional information is necessary to improve prognostic ability for MDS patients. For example, a recent study identified gene expression profiles in CD34 + cells, sampled from the bone marrow of MDS patients, that outperformed clinical factors alone (IPSS, age, and gender) or in combination with the expression profiles for prediction of survival (43). Another potential source of prognostic information lies in WGS (26–31,44,45). As mentioned previously, WGS allows investigators to detect somatic mutations with potential clinical relevance in a more efficient manner than candidate gene sequencing (27,28). However, it remains to be seen whether such information can predict outcomes independent of prognosis defined by systems like IPSS-R, or whether such information may be combined with existing prognostic systems to monitor response to therapy and adjust the prognosis as therapy is administered.

Therapeutic approaches in MDS

The choice of therapy for MDS is guided by the patient's risk stratification at diagnosis, and treatment guidelines have been developed by independent groups (40,46). We discuss MDS therapy here primarily in the context of guidelines from the US-based National Comprehensive Cancer Network (NCCN) (40) supplemented with expert recommendations (39). These recommendations discuss therapeutic approaches for low- and high-risk patients (39,40), and the latest NCCN guidelines incorporate the IPSS-R (40). In addition to discussing therapy for low- and high-risk MDS, we give special attention to HSCT as this is the only potentially curative therapy at this time and several questions remain concerning its use in both low- and high-risk MDS (47,48). Finally, we close the section on MDS therapy by discussing adjunct therapies and rare subgroups of MDS.

Therapy for low-risk myelodysplastic syndromes

Low-risk (very low and low by IPSS-R) patients are typically not treated until they become transfusion-dependent (39,40). For low-risk MDS patients, treatment is typically sequential, starting with erythroid growth factors, followed by lenalidomide, and then HMA where subsequent therapies are applied when the previous therapy no longer produces adequate response (39,40). The combination of erythropoietin (Epo) with or without granulocyte-colony stimulating factor (G-CSF) can ameliorate anemia and have a positive impact on quality of life, especially among those with low transfusion need and a low serum Epo. In one study, low-risk MDS with low transfusion need (defined as less than 2 units of red blood cells (RBC) per month) were observed to have a longer survival when Epo + G-CSF were administered, but no impact was observed on leukemic transformation (49). The Food and Drug Administration (FDA) has approved lenalidomide (Revlimid, Celgene, Summit, New Jersey, USA) for low-risk MDS patients with abnormalities in chromosome 5q. With lenalidomide, 67% of transfusion-dependent patients with low-risk MDS and 5q abnormalities achieve transfusion independence (40). In addition, lenalidomide has activity in patients with low-risk MDS without 5q abnormalities albeit with lower response rates. Finally, the FDA recently approved two HMA for use in MDS: azacitidine (for all MDS) and decitabine (for IPSS intermediate and high risk MDS) (2). These drugs target the abnormal epigenetics observed in MDS cells: global hypermethylation and, in particular, hypermethylation and silencing of tumor suppressor gene expression believed to be important in establishing and/or maintaining the MDS phenotype (32). While azacitidine and decitabine have demonstrated superior response rates or a longer time to AML transformation when compared with supportive care alone (50–53), these results are based primarily on studies in high-risk MDS patients, and no randomized trial has directly compared these two HMAs with each other or with lenalidomide (2). HMA are typically used in transfusion-dependent low-risk MDS cases only when they are refractory to erythroid growth factors and/or lenalidomide (39). HSCT is not recommended for low-risk MDS patients that respond to non-transplant therapies as it does not extend the already prolonged life expectancy for these patients (39,54,55). Finally, the existence of a subgroup of low-risk MDS with poor prognosis is apparent, although these cases are as yet difficult to identify a priori (39). Future incorporation of molecular information into prognostic systems may assist with identifying such patients in whom early intervention with more aggressive therapy may be appropriate (39).

Therapy for high-risk myelodysplastic syndromes

Patients with high-risk MDS (intermediate, high, and very high by IPSS-R) who are candidates for HSCT (see the discussion of HSCT below) should receive this therapy whenever possible and agreeable by both physician and patient (39,40). Patients aged 65–70, without a donor, and who have circulating blast percentage ≥ 10% without adverse cytogenetics may be considered for remission induction chemotherapy (46).

High-risk MDS patients who are not HSCT candidates or are otherwise not amenable to HSCT are currently offered HMA, with azacitidine being the primary choice (39). Azacitidine has been tested in two phase III trials. In one study, 191 intermediate- and high-risk MDS patients were randomized to receive azacitidine (75 mg/m^2 daily for 7 days every 28 days) or best supportive care (BSC) (51). The median time to AML transformation or death was 21 months (95% CI 16–27 months) in the azacitidine arm, and 12 months (95% CI 8–15 months) in the BSC arm, and patients on azacitidine reported significantly better physical functioning, less psychosocial stress, positive affect, less dyspnea, and shorter time in fatigue compared with BSC (51). In another phase III study, 358 intermediate- and high-risk patients were randomized

to azacitidine (also 75 mg/m^2 daily for 7 days every 28 days) or a conventional care regimen (CC) (50). Median overall survival was 24 months on azacitidine versus 15 months on CC ($P < 0.001$); and median time to AML transformation was 18 months on azacitidine versus 11 months on CC ($P < 0.001$) (50). Decitabine has also been compared to BSC in two phase III trials that enrolled intermediate- and high-risk MDS patients. One study demonstrated an improvement in quality of life for patients on decitabine (52), and another showed overall improvement (complete or partial response, or hematological improvement) in 30% of patients on decitabine versus 7% on BSC ($P < 0.001$) (53). However, neither study showed significant differences in time to AML transformation or survival associated with decitabine (52,53).

Allogeneic hematopoietic stem cell transplant (HSCT) for treatment of myelodysplastic syndromes

Transplantation of hematopoietic stem cells from a related or unrelated donor (i.e. allogeneic) to a patient with MDS has the potential to cure the disease (47). HSCT begins with a conditioning regimen that suppresses the immune system to reduce risk of rejection and eliminate malignant cells (56). This is followed by replacement of the marrow with donor-supplied stem cells (from peripheral blood, bone marrow, or umbilical cord blood) and subsequent activity of the donor-supplied cells against any remaining malignant cells not eliminated during the conditioning regimen (called the 'graft-versus-tumor' effect) (56). This procedure is known to be successful in patients who are referred to a transplant center (48). For example, a study from the International Bone Marrow Transplant Registry (IBMTR) included 452 MDS patients who received HSCT from a matched sibling donor and showed 3-year disease-free survival of 40% (95% CI 36%–45%) (47). Although this compares favorably with lower disease-free survival rates seen with other non-transplant therapies, the cumulative incidence of transplant-related mortality at 3 years in this study was 37% (95% CI 32%–42%) (47).

This highlights the reality that despite the potential success of HSCT, there are substantial complications associated with the procedure, including graft-versus-host disease (GVHD) in which the engrafted cells recognize histocompatibility antigens expressed by host cells and mount an immune response against the host (56). In addition, patients require post-transplant immunosuppressive therapy resulting in increased susceptibility to infection (56). Because HSCT is used primarily in high-risk MDS patients, and these patients are typically elderly and present with co-morbid conditions, many are not good candidates for transplant (48). In addition, until recently, HSCT was not covered by Medicare, and this may have excluded otherwise eligible patients from receiving this therapy (57). In fact, a survey of physicians treating MDS in the US showed that only 4% of recently diagnosed patients received or were considered for HSCT (9). However, given the expanded coverage by Medicare for HSCT (provided patients are treated on a clinical trial) and improvements in HSCT that have been made over the past few decades (58), many more MDS patients are expected to receive HSCT in the future (48,57). The Center for International Blood and Marrow Transplant Research recorded over 7500 allogeneic HSCT in 2011, of which nearly 550 (7.3%) were for MDS (59).

Despite improvements in HSCT and expanded insurance coverage, many important questions remain to be addressed concerning HSCT use in MDS (48). Some factors like donor source (human leukocyte antigen (HLA)-matched related versus matched unrelated donors) have been shown to be important predictors of outcome in MDS patients (60). In addition, the timing of HSCT may be critical depending on the patient's risk stratification at diagnosis. Recent studies demonstrated that IPSS intermediate-2 or high-risk patients benefit from transplantation soon after diagnosis, whereas IPSS low and intermediate-1 risk patients have better-quality adjusted life expectancy when transplant is delayed until their disease progresses (54,55). Interestingly, age does not appear to be an important determinant of post-HSCT outcomes among transplant-eligible MDS patients (61–63). However, to evaluate properly the contemporary role of HSCT for older MDS patients, a prospective comparative trial of HSCT to non-HSCT therapies is needed. Two trials have been proposed to address this critical question. The first is a European phase II biologic assignment trial of 230 patients who are 55–70 years of age (ClinicalTrials.gov NCT01404741). The second is a US biologic assignment trial of 400 patients who are 50–75 years of age with intermediate-2 or high-risk IPSS (Blood and Marrow Transplant Clinical Trials Network #1102; in design phase) (63). Biologic assignment implies that patients with either HLA-identical sibling or well-matched (HLA-A, B, C, and DRB1 matched) unrelated donor will be assigned to the HSCT arm and those who do not have these donor sources will be assigned to the non-HSCT arm (64). A true randomization to compare these two therapeutic approaches would require that all patients enrolled must have a suitable donor, then patients would be randomized to HSCT or non-HSCT arms. True randomization in trials evaluating HSCT historically has failed as many patients with suitable donors randomly assigned to the non-HSCT arm will undergo HSCT leading to significant contamination of the study (64). The primary outcome of the US trial is 3-year overall survival. The primary hypothesis states that patients 50–75 years of age with high-risk MDS will have a survival advantage with HSCT at 3 years compared to non-HSCT therapies (15% absolute difference in overall survival). Future Medicare reimbursements for HSCT for Medicare patients with MDS will be informed by the results of this trial. In addition to these issues, other questions regarding optimal conditioning regimens (e.g. ClinicalTrials.gov NCTN01339910) and the utility of pre-HSCT therapy, including whether HMA should be used pre-transplant, remain to be answered and thus present significant challenges for determining the optimal use of HSCT in MDS (39,48).

Adjunct therapies and rare subgroups of MDS

In addition to the therapies discussed above, prophylactic antibiotics and iron chelation are often prescribed for MDS patients, although there is no evidence from randomized studies that suggest these interventions are indicated (39). However, given that iron accumulation is common in MDS, chelation therapy is recommended by the NCCN for IPSS low- or intermediate-1-risk patients who have or are expected to receive 20 red blood cell transfusions, and whose serum ferritin levels are over 2500 ng/mL (40). The goal of iron chelation under these guidelines is to reduce serum ferritin to < 1000 ng/mL (40).

Although the majority of MDS exhibit a hyperplastic bone marrow, a minority (10%–15%) of cases appear hypoplastic (1,24). These variants of MDS occur in younger patients, are associated with more severe cytopenias, and may be associated with dysregulated immune function (1,24). Therefore, it has been hypothesized that these patients may benefit from immunomodulatory therapies such as antithymocyte globulin (ATG), steroids, or cyclosporine (39,40). Investigations of immunomodulatory therapies for MDS are in the early stages, and the utility of these therapies for hypoplastic MDS is not yet clear (39). In the mean time, some investigators recommend HSCT for younger patients with hypoplastic MDS (39).

Finally, the therapeutic options for patients with relapsed or refractory MDS are limited. Low-risk MDS patients who are

refractory to erythroid growth factors, lenalidomide, and HMA may be recommended for HSCT or a clinical trial (39). Unfortunately, there are currently no therapies available for high-risk MDS patients who fail treatment with HMA. HSCT may be successful for these patients, but unfortunately not all are candidates for the therapy (39). Resistance to HMA is not yet fully understood (32).

Future directions in MDS research

As life-spans increase, it is expected that the incidence of MDS will also increase (3). Therefore, it is important to focus on questions that have immediate translational relevance for therapy, prevention, and control of MDS. Such questions might include: What impact do patient medical history, family history of hematopoietic or other cancer, and patient lifestyle have on survival after MDS diagnosis or progression to AML, and how do these factors interact with host genotype? Are there any modifiable risk factors associated with MDS or with progression to AML? What are the promising new therapeutic targets in MDS? Can we identify candidate biomarkers for treatment response, disease progression, or other clinically relevant end-points? What are the molecular characteristics that distinguish asymptomatic or suspected MDS cases from those who have frank disease? Because of the relative rarity of MDS, to answer these questions it will be most efficient for investigators to form collaborations to facilitate close follow-up of multi-institutional MDS patient cohorts with adequate numbers of high-quality biological specimens accompanied by detailed demographic and outcome data collected in a standardized manner (65).

Conclusion

MDS are a complex group of diseases that are likely more common than originally thought (6,11,18). Clinicians treating elderly patients with unexplained anemia should be concerned about MDS (13). Clinicians should also become familiar with registry reporting requirements for MDS, thus enabling population-based assessment of disease burden (6,11). In addition, clinicians should be aware of contemporary MDS therapies and encourage patients to enroll in clinical trials.

Due to the relative rarity of MDS, it will be necessary for investigators to form multi-institutional collaborations to address questions of translational importance in MDS. The National Heart Lung and Blood Institute recently announced its intent to support the formation of a multi-institutional longitudinal MDS patient cohort intended to facilitate translational research into MDS (notice #NOT-HL-13-172). This study will collect biospecimens at regular intervals and document outcomes over a 7-year period in a cohort of 2000 recently diagnosed MDS patients and 500 age-matched suspected cases of MDS. Such a rich biospecimen repository and close follow-up of MDS patients will enable application of technologies like WGS to provide insight into MDS pathogenesis, thereby improving prognosis, identifying new therapeutic targets, and possibly leading to individualized therapy for MDS.

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