

Myelodysplastic syndromes: moving towards personalized management



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ABSTRACT

The myelodysplastic syndromes (MDS) share their origin in the hematopoietic stem cell but have otherwise very heterogeneous biological and genetic characteristics. Clinical features are dominated by cytopenia and a substantial risk for progression to acute myeloid leukemia. According to the World Health Organization, MDS is defined by cytopenia, bone marrow dysplasia and certain karyotypic abnormalities. The understanding of disease pathogenesis has undergone major development with the implementation of next-generation sequencing and a closer integration of morphology, cytogenetics and molecular genetics is currently paving the way for improved classification and prognostication. True precision medicine is still in the future for MDS and the development of novel therapeutic compounds with a propensity to markedly change patients' outcome lags behind that for many other blood cancers. Treatment of higher-risk MDS is dominated by monotherapy with hypomethylating agents but novel combinations are currently being evaluated in clinical trials. Agents that stimulate erythropoiesis continue to be first-line treatment for the anemia of lower-risk MDS but luspatercept has shown promise as second-line therapy for sideroblastic MDS and lenalidomide is an established second-line treatment for del(5q) lower-risk MDS. The only potentially curative option for MDS is hematopoietic stem cell transplantation, until recently associated with a relatively high risk of transplant-related mortality and relapse. However, recent studies show increased cure rates due to better tools to target the malignant clone with less toxicity. This review provides a comprehensive overview of the current status of the clinical evaluation, biology and therapeutic interventions for this spectrum of disorders.

Definition of myelodysplastic syndromes

The myelodysplastic syndromes (MDS) constitute a spectrum of disorders with variable degrees of cytopenias, morphological dysplasia and risk of progression to acute myeloid leukemia (AML). As such, they provide a clinical model of neoplastic disease capable of progressing from indolent to frankly aggressive. Thus, understanding the nature of MDS permits analysis of clinical and biological factors involved in maintaining clinical stability and those provoking active tumor progression.

Although MDS comprises heterogeneous subcategories these share a common origin in the hematopoietic stem and progenitor cell compartment.¹ The degree of cytopenia partly defines the World Health Organization (WHO) subcategories but certain MDS and subgroups of mixed MDS/myeloproliferative neoplasia (MPN) may present with increased white blood cell, monocyte and platelet counts. Moreover, a diagnosis of MDS can be made in patients with mild or borderline anemia if definite morphological or cytogenetic findings are present.¹

Besides cytopenia, the main defining feature of MDS is the presence of morphological dysplasia of precursor and mature bone marrow blood cells. A number of dysplastic changes have been defined for each lineage of the bone marrow, as listed in Table 1.

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Scope and limitations of this review

While definitions and classifications of MDS until 2001 included chronic myelomonocytic leukemia, in the 2008 WHO classification this former MDS subtype was transferred to a novel entity of mixed MDS/MPN.² MDS and MDS/MPN share several pathogenic features but also display important differences. Clinical trials that constitute the basis for therapeutic recommendations have often enrolled both MDS and MDS/MPN patients. In this review, we will focus on the current WHO diagnosis of MDS but discuss MDS/MPN when relevant for the context.

An area with relevance for MDS are variants of clonal hematopoiesis, defined as the presence of somatic myeloid mutations in the absence of diagnostic criteria for MDS or any other blood cancer.³ Clonal hematopoiesis will be discussed herein as a differential diagnosis of MDS.

The review focuses on adult MDS. However, knowledge about germline conditions potentially predisposing to MDS has vastly increased over these past years, leading baseline investigation of patients with potential MDS to include evaluation of potential germline conditions.⁴

Classification systems

Historical perspective including the French-American-British classification

Morphological depiction of the disease spectrum has been difficult due to the somewhat subjective nature of defining marrow dysplasia and the patients' variable clin-

ical courses. Since its initial description as 'preleukemia' in 1953 a multiplicity of terminologies have been used to describe this entity (Table 2). The French-American-British (FAB) morphological classification in 1982 helped to provide a consensus approach to grouping patients.⁵ MDS emerged as a separate entity in the FAB classification, which recognized one group with an excess of blasts but not fulfilling the criteria for acute leukemia, and, as indicated above, another group with increased monocytosis termed chronic myelomonocytic leukemia, now characterized as an MDS/MPN.

World Health Organization classification

In 2001, the WHO proposed an alternative classification for MDS which was subsequently updated in 2008 and in 2016¹ and currently identifies six MDS entities based on marrow morphology and cytogenetics (Table 3).^{4,6} The denominator used for determining blast percentage was recently redefined to include all nucleated bone marrow cells as opposed to only non-erythroid cells. The division between MDS and AML is a continued area of debate. The clinical outcomes of MDS patients are not only related to the quantity of blasts, but also to a differing pace of disease related to distinctive biological and molecular features compared with those of *de novo* AML.^{1,7,8} The National Comprehensive Cancer Network (NCCN) practice guidelines for MDS (also discussed by the WHO) allow for patients with 20% to 29% blasts AND a stable clinical course for at least 2 months to be considered as having either higher-risk MDS or AML.⁹ Individuals with *FLT3* or *NPM1* mutations are more likely to have AML than MDS.¹⁰ Future challenges will include methods to further stratify patients' clinical courses more effectively, using biological features (e.g., mutations) as adjuncts to morphology.

Table 1. Morphological manifestations of dysplasias (WHO 5.01 and 6.02).*

Dyserythropoiesis	
Nuclear	Nuclear budding Internuclear bridging Karyorrhexis Multinuclearity Megaloblastoid changes
Cytoplasmic	Ring sideroblasts Vacuolization Periodic acid-Schiff positivity
Dysgranulopoiesis	
	Small <i>or</i> unusually large size Nuclear hyposegmentation (pseudo-Pelger-Huet) Nuclear hypersegmentation Decreased granules – agranularity Pseudo-Chédiak-Higashi granules Döhle bodies Auer rods Barr bodies
Dysmegakaryopoiesis	
	Micromegakaryocytes Nuclear hypolobation Multinucleation
Monocytosis	
	No specific morphology but persistent monocytosis $\geq 1 \times 10^9/L$ with monocytes accounting for $\geq 10\%$ of leukocytes
	• Dysplasia may also be visible in peripheral blood films when dysplastic cells are released from the bone marrow

Demographics and clinical presentation

The incidence of MDS was previously based on large regional registries. The Düsseldorf Registry described 216 patients diagnosed between 1996 and 2005, corresponding to an incidence of 4.15 cases per 100,000 popula-

Table 2. Chronology of the terminology for myelodysplastic syndromes.

Term	Year	Author
Preleukemia	1953	Block <i>et al.</i>
Refractory anemia with ringed sideroblasts	1956	Bjorkman
Refractory normoblastic anemia	1959	Dacie <i>et al.</i>
Smoldering acute leukemia	1963	Rheingold <i>et al.</i>
Chronic erythremic myelosis	1969	Dameshek
Preleukemic syndrome	1973	Saarni and Linman
Subacute myelomonocytic leukemia	1974	Sexauer <i>et al.</i>
Chronic myelomonocytic leukemia	1974	Miescher and Farquet
Hypoplastic acute myelogenous leukemia	1975	Beard <i>et al.</i>
Refractory anemia with excess myeloblasts	1976	Dreyfus
Hematopoietic dysplasia	1978	Linman and Bagby
Subacute myeloid leukemia	1979	Cohen <i>et al.</i>
Dysmyelopoietic syndrome	1980	Streuli <i>et al.</i>
Myelodysplastic syndromes	1982	Bennett <i>et al.</i>

tion/year.¹¹ The median age, 71 years, was similar to that of the Revised International Prognostic Scoring System (IPSS-R) cohort.¹² More recent population-based reports show median ages of 75-76 years. A Swiss study showed an incidence of 3.6 cases per million.¹³ A Swedish study described 1,329 patients with MDS or MDS-MPN, corresponding to a crude annual incidence of 2.9 cases per 100,000 population.¹⁴ The lower incidence reflects that patients were double-reported from hematology and pathology departments, with non-MDS differential diagnoses most likely being excluded. In all registries the incidence sharply increases with age, making MDS one of the most common blood cancers in the elderly population.

The clinical presentation mainly consists of symptoms caused by cytopenia. According to the Swedish Registry 11% and 42% of newly diagnosed patients had hemoglobin levels <8 g/dL and 8-10 g/dL, respectively, and 50% needed erythrocyte transfusions, 40% had platelet counts below $100 \times 10^9/L$, 5% received platelet transfusions, and 20% had neutrophil counts $<0.8 \times 10^9/L$.¹⁴ Hence, symptoms of anemia, such as dyspnea and fatigue, dominate the clinical picture. Bleeding complications and infections become more pronounced during the course of disease. In a recent survey, 309 consecutive patients received a total of 11,350 red cell units and 1,956 platelet units over 777 person-years of follow-up, corresponding to an overall transfusion intensity of 14.6 and 2.5 units/person-year for red blood cells and platelets, respectively.¹⁵

Some MDS patients present with systemic inflammatory and autoimmune diagnoses before, in conjunction with, or after the diagnosis of MDS.¹⁶ A recent French survey of 123 patients with MDS and systemic inflammatory and autoimmune diagnoses reported systemic vasculitis in 32%, connective tissue disease in 25%, inflammatory arthritis in 23%, and neutrophilic disorders in 10% of cases. A significant association was shown between chronic myelomonocytic leukemia and systemic vasculitis. Other symptoms and findings encompassed fever, skin abnormalities including Sweet syndrome, and bleeding due to disturbed coagulation, as recently reviewed.¹⁷ It is important to recognize the MDS diagnosis in these patients, since intervention with corticosteroids and azacitidine may relieve symptoms.

Quality of life

MDS is a disease with a significant impact on every-day life due to cytopenia and the substantial risk of a fatal outcome. Recent studies provide important information about the quality of life in MDS. Troy *et al.* assessed the NCCN distress thermometer and problem list scores in 110 patients.¹⁸ The three most frequently reported symptoms were fatigue, pain and worry. Stauder *et al.* used the prospective European LeukemiaNet Registry to compare health-related quality of life in 1,690 consecutive patients

Table 3. World Health Organization classification of myelodysplastic syndrome.

Name	Dysplastic lineages	Cytopenias*	Ring sideroblasts as % of marrow erythroid elements	BM and PB blasts	Cytogenetics by conventional karyotype analysis
MDS with single lineage dysplasia	1	1 or 2	<15%/ <5% [†]	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia	2 or 3	1-3	<15%/ <5% [†]	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)					
MDS-RS with single lineage dysplasia	1	1 or 2	≥15%/ ≥5% [†]	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with multilineage dysplasia	2 or 3	1-3	≥15%/ ≥5% [†]	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	1-3	1-2	None or any	BM <5%, PB <1%, no Auer rods	del(5q) alone or with 1 additional abnormality except -7 or del(7q)
MDS with excess blasts (MDS-EB)					
MDS-EB-1	0-3	1-3	None or any	BM 5%-9% or PB 2%-4%, no Auer rods	Any
MDS-EB-2	0-3	1-3	None or any	BM 10%-19% or PB 5%-19% or Auer rods	Any
MDS, unclassifiable (MDS-U)					
MDS-U with 1% blood blasts	1-3	1-3	None or any	BM <5%, PB 1%,* no Auer rods	Any
MDS-U with single lineage dysplasia and pancytopenia	1	3	None or any	BM <5%, PB <1%, no Auer rods	Any
MDS-U based on defining cytogenetic abnormality		0	1-3	≥15% [‡]	BM <5%, PB <1%, no Auer rods MDS-defining abnormality
Refractory cytopenia of childhood	1-3	1-3	None	BM <5%, PB <2%	Any

*Cytopenias defined as: hemoglobin <10 g/dL; platelet count <100 $\times 10^9/L$; and absolute neutrophil count <1.8 $\times 10^9/L$. Rarely, myelodysplastic syndrome may present with mild anemia or thrombocytopenia above these levels. The peripheral blood monocyte count must be <1 $\times 10^9/L$. [†]If *SF3B1* mutation is present. [‡]One percent peripheral blood blasts must be recorded on at least two separate occasions. [§]Cases with ≥15% ring sideroblasts by definition have significant erythroid dysplasia, and are classified as myelodysplastic syndrome with ringed sideroblasts with single lineage dysplasia. BM: bone marrow; PB: peripheral blood.

with IPSS low/intermediate-1 risk MDS with an age- and sex-matched reference population.¹⁹ MDS patients reported moderate/severe problems in the dimensions pain/discomfort (50%), mobility (41%), anxiety/depression (38%), and usual activities (36%). Limitations were more frequent in older patients, in females, and in those with a high comorbidity burden or needing red blood cell transfusions. Finally, Efficace and co-workers studied patients with higher-risk MDS and concluded that patient-reported outcomes provide important information regarding the prognosis of patients.²⁰

Disease pathogenesis

A hallmark of MDS is the dysregulated hematopoietic differentiation resulting in impaired differentiation, morphological dysplasia, and cytopenia.⁶⁵ The cell of origin of MDS lies within the hematopoietic stem and progenitor cell compartment and can usually be tracked back to the pluripotent hematopoietic stem cell, implying that MDS is a malignancy for which cure usually cannot be reached with treatments other than allogeneic stem cell transplantation (SCT).²¹ MDS cells accumulate in the bone marrow as a result of a complex interplay between genetic and epigenetic alterations, the bone marrow microenvironment, and the immune system, a process that can develop over several years (Figure 1).

The genetic landscape of MDS is quite well delineated. Early studies focused on structural cytogenetic abnormalities, identified by metaphase karyotyping in around 50%

of MDS patients. Most of these abnormalities are unbalanced changes resulting in loss or gain of a large amount of chromosomal material e.g. deletion (del) 5q, monosomy 7, trisomy 8 and del 20q.²² The advent of next-generation sequencing technology resulted in a comprehensive mapping of the MDS genome.²³⁻²⁵ More than 50 genes have been identified as recurrently mutated in MDS. These genes are involved in biological processes such as DNA methylation, chromatin modification, RNA splicing, cohesion formation, regulation of transcription, signaling and DNA repair (Table 4). Some mutations result in specific phenotypes e.g. *SF3B1* and del5q which are described below. Interestingly, some of the recurrently mutated genes e.g., *DNMT3A*, *TET2* and *ASXL1*, are also found in healthy individuals (clonal hematopoiesis of indeterminate prognosis, CHIP), representing pre-leukemic clones with an age-associated incidence and a varying risk of subsequent development of MDS or other myeloid malignancies.^{26,27}

Several of the recurrently mutated genes are epigenetic regulators.^{28,29} The MDS epigenome exhibits distinct pathological patterns, which may be explained in part by such mutations but which can also be a consequence of stochastic epigenetic drift, seen with increasing age.³⁰ In analogy with the epigenetic profile, patients with MDS also demonstrate specific gene expression profiles.³¹⁻³³ Such clusters can be observed for morphological subgroups e.g. MDS with ringed sideroblasts (MDS-RS) and MDS with excess blasts, as well as for specific genetic lesions e.g., del(5q) and *SF3B1*.

Many studies have addressed the composition and function of the immune system in MDS and several immuno-

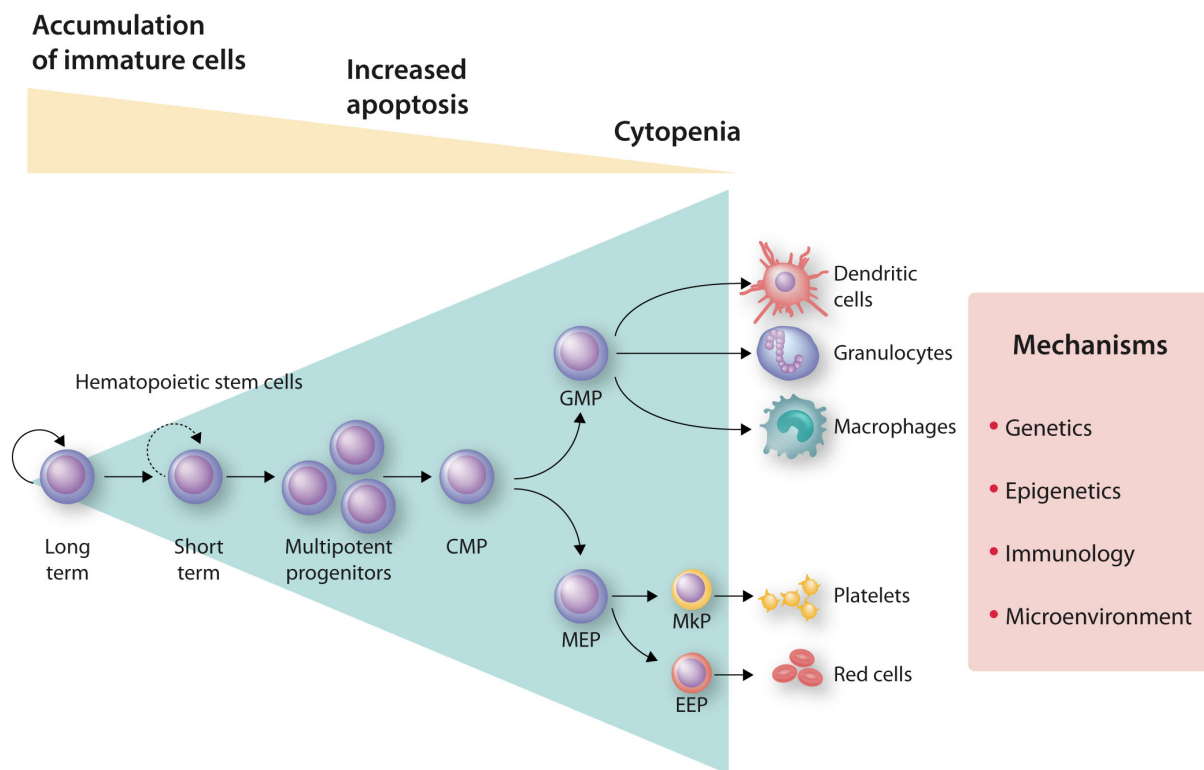


Figure 1. Pathogenesis of myelodysplastic syndromes: underlying mechanisms. CMP: common myeloid progenitors; GMP: granulocyte-monocyte progenitor; MEP: megakaryocyte-erythrocyte progenitor; MkP: megakaryocyte progenitor; EPP: early erythroid progenitor.

logical imbalances have been identified, in particular within the T-cell lineages. In lower-risk MDS, an upregulation of cytotoxic T cells has been observed, whereas higher-risk MDS is characterized by immune escape and upregulation of regulatory T cells.³⁴⁻³⁶ Several studies have identified autonomous large granular lymphocyte T-cell clones in a large proportion of patients with MDS.^{37,38} Similarly, the presence of plasma cell clones has been described.^{39,40} Whether the MDS disease is evoking immune activation or whether an initial immune activation results in selection pressure giving mutated MDS cells a survival advantage is unclear.

The microenvironment in MDS shows abnormal morphological features. Molecular characterization of stromal niche cells has revealed various alterations, including disturbances in differentiation and in stem cell supporting functions.^{41-46 47-49} Again, whether niche-alterations are initiating events or induced by the MDS clone is unknown. Murine models have suggested that manipulation of the niche can induce myeloid malignancies, but solid evidence from MDS patients remains to be presented.⁵⁰⁻⁵²

An important route to develop MDS is by exposure to cytostatic drugs or radiation-therapy, i.e., therapy-related MDS. The mechanisms involved are largely unknown. Case-control studies have demonstrated a higher frequency of underlying CHIP clones in patients developing therapy-related MDS.⁵³⁻⁵⁵ Possibly, the survival pressure that is exerted on hematopoietic stem cells during treatment may give underlying CHIP clones a survival advantage resulting in emergence of the MDS. It has also been proposed that cytostatic/radiation therapy can cause direct DNA damage but evidence for this hypothesis is sparse.

5q- syndrome

Although the mechanisms underlying anemia in patients with del(5q) remain elusive, haploinsufficiency and dependence of erythroid cells on casein kinase (CK1 α), encoded for by a gene within the common deleted region of del(5q), appear to be of central importance. The drug lenalidomide induces ubiquitination of CK1 α through the E3 ubiquitin ligase cereblon, resulting in CK1 α degradation.⁵⁶ Such degradation in the haploinsufficient del(5q) cells sensitizes these cells to lenalidomide, providing a basis for the therapeutic effects of the drug in these patients. Additionally, the E3 ubiquitin ligase RNF41 is a principal target responsible for erythropoietin receptor (EpoR) stabilization. Data suggest that lenalidomide also

has E3 ubiquitin ligase inhibitory effects thus inhibiting RNF41 auto-ubiquitination and promoting membrane accumulation of signaling competent JAK2/EpoR complexes that augment responsiveness to erythropoietin.⁵⁷

Myelodysplastic syndrome with ringed sideroblasts and SF3B1 mutations

The characteristic mitochondrial ferritin accumulation in MDS-RS is associated with reduced expression of the iron transporter protein gene *ABCB7*.^{58,59} In two pivotal papers, Papaemmanuil *et al.* and Yoshida *et al.* described recurrent mutations in splicing factor 3b subunit 1 (*SF3B1*) in more than 80% of patients with MDS-RS.^{60,61} Subsequent studies identified aberrant splicing of genes involved in erythropoiesis and mitochondrial function, but the molecular and cellular links between the *SF3B1* mutation and ineffective erythropoiesis remain elusive.⁶²⁻⁶⁴ Recent studies have tracked back the *SF3B1* mutations to multipotent hematopoietic stem cells and described how MDS-RS erythropoiesis can be confidently modeled *in vitro*, leading to new possibilities to assess the effects of novel compounds.^{65,66} From a clinical perspective MDS-RS with *SF3B1* mutations appears as a clinically and morphologically distinct entity with affected patients having a favorable survival, a low risk of leukemic transformation but a high risk of developing refractory transfusion dependence.^{66,67}

Genetic predisposition to myeloid neoplasms

Myeloid neoplasms with germline predisposition were recognized as a separate entity in the WHO 2016 classification.¹ Individuals with germline predisposition exhibit an increased risk of developing myeloid neoplasms, mainly AML and MDS. Estimates suggest that at least 5% to 15% of patients with MDS or AML carry germline pathogenic variants.^{68,69}

Germline mutations are divided into those predisposing to myeloid neoplasms without a pre-existing disorder, mutations with pre-existing platelet dysfunction, and mutations associated with organ dysfunction. *GATA2* and *RUNX1* mutations are relatively common and mandate continuous surveillance of asymptomatic carriers, because of the high risk of such subjects developing a myeloid neoplasm.^{21,68,70} Mutations in the telomerase complex usually lead to a complicated clinical presentation with multi-organ involvement, and mutations in the *SAMD9* and *SAMD9L* genes are associated with a high risk of progression to monosomy 7 MDS.^{71,72} More recently identified

Table 4. Mutations in myelodysplastic syndromes.

Functional group	Included genes
DNA methylation	<i>DNMT3A, TET2, IDH1, IDH2</i>
Chromatin modification	<i>EZH2, SUZ12, EED, JARID2, ASXL1, KMT2, KDM6A, ARID2, PHF6, ATRX</i>
Cohesin complex formation	<i>STAG2, RAD21, SMC3, SMC1A</i>
RNA splicing	<i>SF3B1, SRSF2, U2AF1, U2AF2, ZRSR2, SF1, PRPF8, LUC7L2</i>
Transcription	<i>RUNX1, ETV6, GATA2, IRF1, CEBPA, BCOR, BCORL1, NCOR2, CUX1</i>
Cytokine receptor/tyrosine kinase	<i>FLT3, KIT, JAK2, MPL, CALR, CSF3R</i>
Other signaling	<i>GNAS, GNB1, FBWX7, PTEN</i>
Checkpoint/cell cycle	<i>TP53, CDKN2A</i>
DNA repair	<i>ATM, BRCC3, FANCL</i>
Other	<i>NPM1, SETBP1, DDX41</i>

homozygous mutations in *ERCC6L2* have been shown to predispose to the development of somatic *TP53* mutations and severe AML.⁷³ Mutations in *DDX41* predispose to myeloid neoplasms at higher ages than most other predisposing mutations, making this an important gene to analyze in potential adult sibling donors.⁷⁴

Determining the diagnosis of myeloid neoplasms with germline predisposition is of crucial clinical significance since it may tailor therapy, dictate the selection of donors and conditioning regimens for allogeneic hematopoietic SCT, and enable relevant prophylactic measures and early intervention. The Nordic MDS group recently published a practical guideline program for diagnosis and management of such conditions.⁴

Risk assessment and prognostication

Clinical variables for risk-based classification

A number of disparate methods have been developed to clinically characterize MDS patients and evaluate their prognosis. These classification approaches incorporated a mixture of clinical features, including marrow blasts and cytogenetics, differing cytopenias, age, lactate dehydrogenase levels, and cytogenetic abnormalities. The International MDS Risk Analysis Workshop clarified these features and generated the consensus International Prognostic Scoring System for MDS (IPSS), dividing patients with MDS into four risk categories based on their cytopenias, marrow blast percentage and cytogenetic subgroup, with median survivals ranging from 0.4 to 5.7 years.⁷⁵ This classification method proved useful for prognostic evaluation and clinical trial design.

Over the ensuing 15 years, additional features were suggested to provide prognostic information in MDS, including ferritin and β_2 -microglobulin levels, marrow fibrosis, the patient's comorbidities and performance status, and novel cytogenetic subgroups as well as refined morphological assessment of MDS.^{2,76-81} To examine the prognostic impact of these variables, the coalescence of data from a new set of untreated primary MDS patients from multiple international institutions provided another global database of 7,012 patients via the International Working Group for Prognosis in MDS (IWG-PM) project. This database generated the Revised-IPSS (IPSS-R) allowing for a more comprehensive cytogenetic analysis, providing five cytogenetic subgroups based on an increased number of specific prognostic chromosomal categories ($n=15$)¹² compared to the six in the IPSS.⁷⁵ In addition and importantly, the revised system incorporated depth of cytopenias and differing marrow blast percentages. The revised model demonstrated five major prognostic categories (Figure 2). Some patients in the IWG-PM project were also assessed by the WHO classification-based Prognostic Scoring System (WPSS) parameters, including red cell transfusion dependence and WHO-defined clinical subgroups, with similar prognostic efficacy.⁸²

Since 2012, the IPSS-R has been a standard for evaluation of risk-based clinical outcomes, and design of therapeutic strategies and clinical trials based on prognostic risk-based features. The European LeukemiaNet and the American NCCN MDS practice guidelines recommend treatment based on the IPSS-R, age and performance status.^{9,83} The IPSS-R has been confirmed to be a valuable method for risk-classifying MDS patients, albeit with some degree of variability.⁸⁴⁻⁸⁸

IPSS-R prognostic risk-based categories for MDS

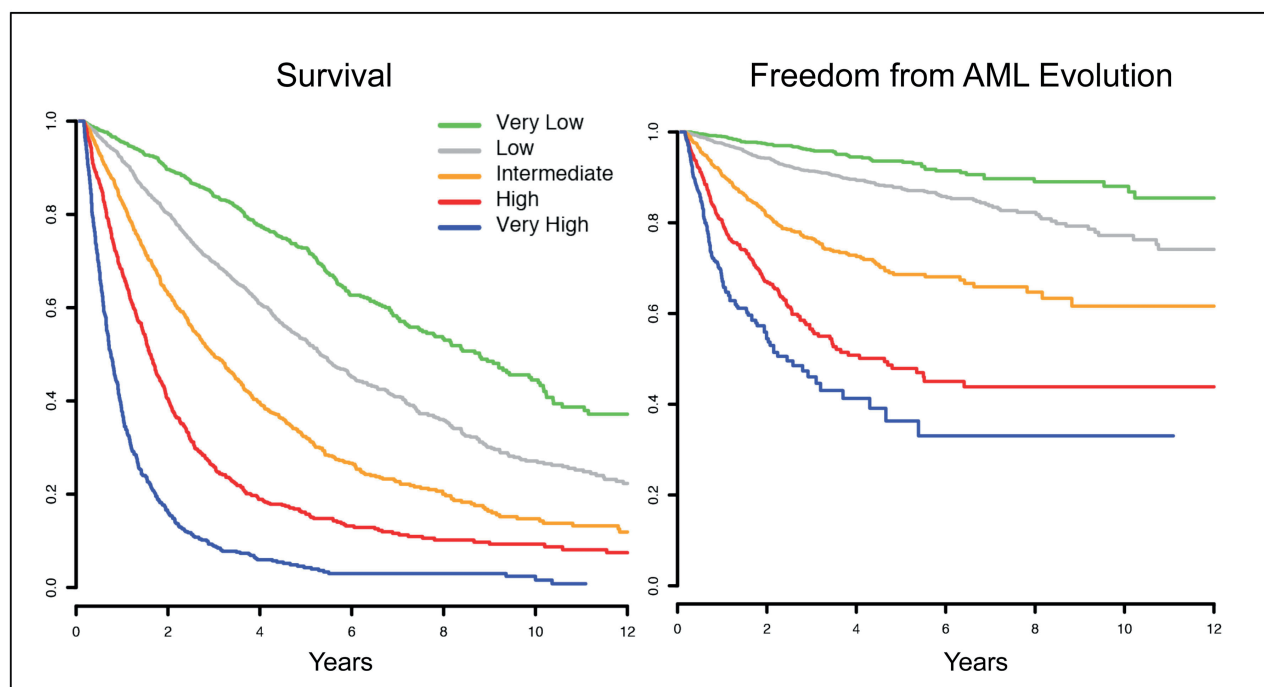


Figure 2. Clinical outcomes of patients with myelodysplastic syndrome in relation to Revised International Prognostic Scoring System prognostic risk-based categories. Survival, $n = 7012$, $P < 0.001$. Evolution to acute myeloid leukemia, $n = 6485$, $P < 0.001$.¹² IPSS-R: Revised International Prognostic Scoring System; AML: acute myeloid leukemia.

Genomics in the International Prognostic Scoring System risk assessment

Recent molecular studies have demonstrated the major impact on survival and disease progression of specific somatic mutations, including those that are additive to the IPSS-R clinical characterization.^{23-25,89-91} At least five genes - *TP53*, *ASXL1*, *EZH2*, *ETV6*, and *RUNX1* - have an adverse prognostic impact whereas *SF3B1* has a positive impact. Additionally, a group of approximately 60 genes have been recurrently demonstrated to be involved in the various subtypes of MDS, with varying incidence levels (Table 4). Bone marrow samples from a representative cohort of over 3,000 MDS patients were sequenced using a next-generation sequencing panel optimized for myeloid disease. Analysis of *TP53* mutations in 380 patients enabled segregation of patients according to two *TP53* states: a mono-allelic state in which one wildtype allele remained and a multi-hit/bi-allelic state in which *TP53* was altered multiple times by either mutations, deletions or copy neutral loss of heterozygosity (67% of *TP53*-mutated patients).⁹² *TP53* state rather than mutation alone was found to be an independent diagnostic and prognostic biomarker in MDS. Mono-allelic *TP53* patients had more favorable disease than multi-hit *TP53* patients and were enriched in low-risk WHO subtypes. Critically, multi-hit *TP53* was associated with a worse overall survival as compared to mono-allelic *TP53*, and with more pronounced AML transformation.⁹²

Patients' management

MDS is a complex disease displaying marked inter-individual differences with regard to disease mechanisms and potential therapeutic options. Compared to many other blood cancers, the diagnostic process is more challenging and effective targeted treatments less abundant. In

Europe, the MDS-Europe platform offers comprehensive consensus-based MDS guidelines for diagnosis, prognosis and treatment derived from two consecutive European Union research projects (www.mds-europe.eu).⁸³ Moreover, many Western countries have local web-based guidelines with links from mds-europe.org. In the USA the NCCN guidelines (www.nccn.org/professionals/physician_gls/PDF/mds.pdf)⁹ offer the same service.

Diagnostic work-up

The diagnostic work-up follows the recommendations in the WHO 2016 classification.¹ Cornerstones are bone marrow morphology and histopathology, and cytogenetic analysis. Flow cytometry immune-phenotyping is recommended but not mandatory.⁹³ It is a necessary tool to exclude certain differential diagnoses, such as paroxysmal nocturnal hemoglobinuria and large granular lymphocytic leukemia. Molecular genetics, mainly targeted DNA sequencing, is strongly recommended, in particular in patients who are candidates for active treatment.^{25,60} Differential diagnoses of MDS encompass a long list of both benign and malignant diagnoses, as summarized in Table 5. Since management depends on a correct diagnosis, many national cancer programs mandate that diagnosis and prognosis are established in multi-professional conferences.

Clonal cytopenia of unknown significance

Clonal hematopoiesis becomes more prevalent with increasing age and may be present in the absence of cytopenias [CHIP/aging-related clonal hematopoiesis (ARCH)]. Interestingly, a recent study based on the Danish twin registry failed to show a clear relation between CHIP

Table 5. Causes of cytopenia and/or dysplasia other than myelodysplastic syndromes.

Differential diagnosis	Diagnostic tests
Aplastic anemia, pure red cell aplasia	Histology, cytology, parvovirus B19
Metastatic carcinoma	Histology, immunohistochemistry
Toxic bone marrow injury (alcohol, lead, zinc, copper deficiency, nonsteroidal anti-rheumatic drugs, etc.)	History, laboratory tests
Reactive bone marrow changes (infections e.g. sepsis, HIV, hepatitis, tuberculosis and other chronic infections, autoimmune diseases, thyroid disease, etc.), copper deficiency	Cytology, history, laboratory tests
Paroxysmal nocturnal hemoglobinuria	Immunophenotyping
Immune thrombocytopenia	History, course
Megaloblastic anemia	Vitamin B12/folic acid concentration
Hypersplenic syndromes	History/clinical features (splenomegaly)
Acute leukemia (especially erythroleukemia, FAB-M6)	Cytology, histology, immunophenotyping, genetic and molecular genetic testing
Myeloproliferative diseases (especially CMML, aCML, PMF)	Histology, cytogenetic and molecular genetic testing
Hairy cell leukemia, large granular lymphocytic leukemia	Cytology, immunophenotyping, molecular genetic testing (<i>BRAF</i> , <i>STAT3</i>), T-cell receptor
Congenital dyserythropoietic anemia (rare)	Molecular genetic testing
Idiopathic cytopenia of undetermined significance	ICUS minimal diagnostic criteria
Clonal cytopenia of undetermined significance	CCUS diagnostic criteria

HIV: human immunodeficiency virus; FAB: French-American-British; CMML: chronic myelomonocytic leukemia; aCML: atypical chronic myeloid leukemia; PMF: primary myelofibrosis; ICUS: idiopathic cytopenia of undetermined significance; CCUS: clonal cytopenia of undetermined significance.

and survival and did not point towards a common genetic basis.⁹⁴ The term clonal cytopenia of unknown significance defines individuals with myeloid mutations and some degree of cytopenia, but without fulfilling criteria for MDS or other hematologic diagnoses. The type and number of mutations, and variant allele frequencies are potential predictors of risk of progression and are currently being evaluated and reviewed in large cohorts.^{95,96} Single mutations in *TET2* or *DNMT3A* with limited variant allele frequencies are observed in a relatively large fraction of individuals above 60 years and could thus be considered normal, while the presence of more than one mutation and any splice factor mutation may predict a high risk of developing MDS. Patients with clonal cytopenia of unknown significance, in particular if they are potential candidates for curative treatment, should be followed up, but results are presently too divergent to allow for precise recommendations.

Risk-based therapeutic decision-making

In addition to disease-specific variables, patient-related factors are also essential for risk estimation. Age and comorbidities, naturally, influence the spectrum of available therapies. A number of comorbidity and so-called frailty scores have been developed both for MDS and blood cancers in general and, accounting for both disease- and patient-related factors, considerably improve risk stratification. Several comorbidity scores have been tested in the general MDS patient population, including the MDS-Specific Comorbidity Index and the Charlson comorbidity index.^{97,98}

Therapeutic options

Therapeutic options for patients with MDS vary from supportive care to allogeneic SCT, depending on disease- and patient-related risk factors. Table 6 provides an overview of therapeutic options and is divided into treatments which either are formally approved by the FDA and/or EMA or are part of long-standing routine treatment used for MDS, albeit having been approved for other diagnosis, or are in the process of being approved. As the MDS-Europe and NCCN guidelines are relatively specific about indications and dosing, these will not be detailed in the present review.

Supportive care

Supportive care is a cornerstone of the management of all MDS and MDS/MPN patients.⁹¹ Recent studies show reduced progression-free survival and quality of life in patients with a higher density of transfusions.^{15,19,99} A Nordic study showed that quality of life improved in patients responding to growth factors, but also in non-responders transfused to a target hemoglobin of >12 g/dL.¹⁰⁰ A British study showed that higher transfusion targets were associated with improved quality of life.¹⁰¹ Indeed, increasing evidence suggests that transfusion therapy should be tailored according to the patient's subjective symptoms and not to specific hemoglobin trigger levels.⁸³

Severe thrombocytopenia with the need for transfusions becomes increasingly frequent with time.¹⁴ Consensus-based guidelines agree that platelet transfu-

sions should be governed by trigger platelet count levels during active treatment with chemotherapy and hypomethylating agents (HMA), but mainly based on bleeding symptoms during untreated chronic thrombocytopenia. Eltrombopag and romiplostim are licensed (the latter only in the USA) for the treatment of severe chronic immune thrombocytopenia. The results from the pivotal studies in lower-risk and higher-risk MDS did not generate licensing in any region, even though some positive responses were observed.^{102,103} Eltrombopag did not improve the outcome of patients treated with azacytidine in a randomized phase III study.¹⁰³ These compounds may relieve bleeding symptoms in patients with lower-risk hypoplastic MDS with severe thrombocytopenia, and are sometimes used for such individuals. Granulocyte colony-stimulating factor (G-CSF) is not indicated for low neutrophil counts, but can be used as supportive care in the case of neutropenia caused by HMA treatment, in particular after recurrent infectious events.^{9,83}

Iron chelation

Close to 50% of MDS patients need red blood cell transfusions as supportive care.^{21,30,50} Transfusion dependence leading to iron overload has a negative impact on organ function as well as infectious complications in some analyses.¹⁰⁴⁻¹⁰⁶ In cases of iron overload, the transferrin binding of iron is overwhelmed and free non-transferrin bound iron, a redox active component in the plasma, appears to be an important mediator of tissue damage.¹⁰⁷⁻¹¹⁰

Prior observational studies have indicated that iron overload may contribute to poorer clinical outcomes in patients with low/intermediate-1-risk MDS.^{111,112} Although studies have shown that iron chelation therapy may improve patients' outcomes, most studies had limitations, such as

Table 6. Therapeutic options for myelodysplastic syndrome.

Approved by EMA or FDA or part of standard care

- Transfusion therapy
- Iron chelation¹
- Erythropoiesis-stimulating factors
- Immunosuppressive treatment
- Lenalidomide for lower-risk del(5q) MDS
- Azacytidine²
- Decitabine³
- Induction chemotherapy
- Stem cell transplantation

Available therapeutic options, but not approved for MDS by EMA or FDA

- Venetoclax (+ HMA hypomethylating agents or low-dose cytarabine)⁴
- Luspatercept⁵
- Eltrombopag, romiplostim⁶
- Ivosidenib (*IDH1*) and enasidenib (*IDH2*)⁷

¹Desferrioxamine, deferasirox and deferiprone available in Europe. ¹Desferrioxamine and deferasirox available in the USA. ²Approved for International Prognostic Scoring System (IPSS) intermediate-2 and high-risk myelodysplastic syndrome (MDS), and acute myeloid leukemia (AML) with 20-29% myeloblasts by the European Medicines Agency (EMA). Approved for all MDS and AML with 20-29% myeloblasts by the Food and Drug Administration (FDA). ³Approved for IPSS intermediate-2 and high-risk MDS by the FDA. Approved for AML by the FDA and EMA. ⁴Approved for AML (in combination with hypomethylating agents, low-dose ara-C) by the FDA. Approved for chronic lymphocytic leukemia by the EMA. ⁵Expected FDA approval in April 2020. ⁶Eltrombopag and romiplostim approved for immune thrombocytopenic purpura, thrombocytopenia associated with hepatitis C, and aplastic anemia by the FDA. Only eltrombopag approved by the EMA. ⁷Approved for AML by the FDA. Not approved by the EMA.

being retrospective analyses or registry studies.¹¹³⁻¹¹⁷ Currently, the drugs used for iron chelation are deferasirox (oral), deferioxamine (intravenous via an infusion pump) and deferiprone (oral). A prospective randomized, double-blind study was performed, which assessed event-free survival and safety of deferasirox compared with placebo.¹¹⁸ Although not demonstrating an improvement in overall survival, the median event-free survival was prolonged by approximately 1 year with deferasirox treatment. Clinical guidelines include recommendations for the use of iron chelation therapy in some populations of MDS patients. However, debate regarding the clinical utility of iron chelation therapy remains.^{9,82,119-122}

Erythropoiesis-stimulating agents

Erythropoiesis-stimulating agents (ESA) constitute standard treatment for the anemia of lower-risk MDS.^{9,83} Both the EMA and FDA have evaluated numerous studies on the effects of ESA in the treatment of anemia in MDS, although both agencies formally approved erythropoietin and darbepoetin only recently, based on placebo-controlled trials.^{123,124} Erythropoietin α and β and later darbepoetin have been extensively evaluated for MDS and were shown to improve hemoglobin levels and reduce transfusion needs in 40% to over 60% of patients with an overall duration of 18-24 months.¹²⁵ Higher doses (60,000 to 80,000 U per week) may give a slightly better response rate in transfusion-dependent patients.¹²⁶ Lower serum erythropoietin levels are associated with higher response rates. There is no evidence from any trial or registry that treatment with ESA is associated with an increased risk of disease progression or leukemic transformation.¹²⁵

A study of a large cohort of patients included in the European Union MDS Registry recently added significant novel information. Patients with symptomatic anemia who did not require transfusions and were treated with ESA had a significantly better response rate and longer time to a permanent transfusion need than those treated after the onset of regular transfusions.¹²⁷ This led to an important change in the European guidelines, which now recommend treatment at the onset of symptomatic anemia. Relapse of anemia is usually not associated with disease progression and the biological reasons for treatment failure are yet to be explored. Several randomized phase II studies and epidemiological investigations also showed that the addition of low-dose G-CSF to erythropoietin may improve the response rate to ESA, and improve overall survival.¹²⁸⁻¹³⁰ The synergistic effect is seen particularly in MDS-RS and is related to the anti-apoptotic effects of G-CSF on mitochondria-mediated apoptosis.

Lenalidomide for del(5q)

An initial clinical trial showed that MDS patients with the del(5q31) chromosomal abnormality were particularly responsive to lenalidomide, demonstrating a major reduction in transfusion requirements and reversal of cytogenetic abnormalities.¹³¹ These effects were confirmed and extended in a larger phase II trial and a subsequent phase III, randomized, placebo-controlled trial which demonstrated erythroid response rates of ~50-60%, including a transfusion independence rate of ~28% together with concomitant cytogenetic responses.¹³² A phase III randomized trial in lower-risk, ESA-refractory, non-del(5q) patients comparing lenalidomide alone with lenalidomide in conjunction with recombinant human

erythropoietin suggested that lenalidomide may restore sensitivity of MDS erythroid precursors to erythropoietin.¹³³ These data led to the recommendation in the NCCN and MDS-Europe guidelines on the symptomatic treatment of anemic del(5q) MDS patients with lenalidomide.^{9,83} The negative impact of *TP53* mutations (present in ~30% of these patients) on responsiveness and outcome after lenalidomide is notable.¹³⁴

Immunosuppressive treatment

Treatment with immunosuppressive agents such as antithymocyte globulin and cyclosporine A may improve cytopenias in certain patients with MDS.¹³⁵⁻¹³⁸ As recently described in a well-performed meta-analysis there are few large prospective studies, follow-up times in many studies are short, and each study has used different immunosuppressive regimens.¹³⁹ In an analysis of 570 patients with a median age of 62 years, 80% of patients had low or intermediate-1 IPSS scores, the complete response and red cell transfusion independence rates were 12.5% and 33%, respectively, and the rate of progression to AML was 8.6% per patient-year. Immunosuppressive therapy has not been confidently evaluated in relation to mutational profiles. Both European and USA guidelines identify a group of younger, lower-risk MDS patients with hypo- or normoplastic bone marrow and normal karyotype, with the exception of trisomy 8, who may respond to immunosuppressive therapy. Some responders may experience durable and possibly permanent responses, indicating that immunosuppressive therapy may be considered prior to SCT in patients with these features.

Hypomethylating agents

Azacitidine

Based on early phase I/II studies, two large randomized phase III studies were designed to evaluate the effects of azacitidine in MDS.¹⁴⁰⁻¹⁴² The CALGB9221 trial included patients with all subtypes of MDS, and showed improved overall response rate and progression-free survival in the azacitidine arm. The second randomized study, AZA-001, was designed to demonstrate a possible difference in overall survival.¹⁴³ The median overall survival for the azacitidine-treated patients was 24.5 months vs. 15 months for patients assigned to the control arm. Both studies showed that responses are often delayed until the patient has received ≥ 3 treatment cycles.^{142,143} Azacitidine is approved in Europe for the treatment of higher-risk MDS and in the USA for the treatment of all MDS subgroups.

Some phase II studies have also shown effects in lower-risk MDS although the clinical benefits and risks in this population are still unclear and no studies have provided evidence for prolonged survival in this group of patients.^{141,144-146} A large randomized study (NCT01566695) is assessing the effect of oral azacitidine in lower-risk MDS and will perhaps bring more clarity on its role in the treatment of these patients.

Much effort has been given to identifying factors that could predict response. Predictive models based on basic clinical data have not generated clinically meaningful tools.¹⁴⁷⁻¹⁴⁹ Neither have studies on mutational profiles resulted in robust response prediction. Better responses have been reported for patients with *TET2*, *ASXL1* and *EZH2* mutations but the data are conflicting.¹⁴⁹⁻¹⁵²

Decitabine

Decitabine has been evaluated in two phase II studies assessing higher-risk MDS patients.^{153,154} Both studies showed similar efficacy, with overall response rates of 32-39% and median survivals of ~20 months. The safety and efficacy data were similar to those for azacytidine, although phase III data, available for azacytidine, are lacking for decitabine. Both HMA are recommended by the NCCN for treating higher-risk patients, with a special focus also as a bridge to allogeneic SCT for eligible patients. High response rates have been reported for *TP53*-mutated AML patients treated with a 10-day decitabine regimen, although the durations of the responses were short.¹⁵⁵

Intensive chemotherapy

Since the advent of HMA and other disease-modifying drugs, the use of intensive chemotherapy has decreased substantially but it may be considered after failure to benefit from HMA in younger fit patients, particularly as bridging-therapy to SCT. The rate of complete responses achieved with intensive chemotherapy is around 50%, which is lower than that for *de novo* AML patients, and time to relapse is often short.¹⁵⁶⁻¹⁵⁸ The clinical benefit of this approach for non-SCT candidates in whom azacytidine therapy has failed has not been established.

Allogeneic stem cell transplantation

SCT is the only potentially curative treatment for patients with MDS. Due to potential severe complications, SCT is generally offered only to fit patients up to around 70-75 years of age. Historical data document long-term survival rates of between 25% and 45% with non-relapse mortality and relapse occurring in approximately a third of the patients.¹⁵⁹⁻¹⁶¹ A more recent prospective study found a higher 2-year relapse-free survival of 60%.¹⁶² Since the median age (50 years) in that study was relatively low, the outcome does not represent a real-world population.

Optimal timing of SCT is essential, considering that patients with high-risk MDS have a high risk of both relapse and mortality after SCT.¹⁶³ A general recommendation is to transplant higher-risk patients as part of an upfront process, while lower-risk MDS patients should be monitored and transplanted upon disease progression. Defining which patients should be considered low- and high-risk is therefore crucial for a correct transplantation plan. All three prognostic scoring systems (IPSS, IPSS-R and WPSS) are predictive of survival after allogeneic SCT.^{160,161,164,165} Genetic aberrations have a large impact on relapse risk. Relapse-free survival at 5 years in the five IPSS-R cytogenetic risk groups ranges between 10% and 42%.^{160,166} In addition, mutations in *TP53* and the *RAS*-pathway genes have been reported to be risk factors for relapse.¹⁶⁷⁻¹⁶⁹

Disease status is also important for SCT outcome.^{161,168,170} Disease-modifying treatment is usually given to patients with a more proliferative disease, aiming for the best possible remission before SCT. The usefulness of such treatment has, however, not been tested in prospective clinical trials. Retrospective studies have demonstrated similar outcomes for treated and untreated patients although selection bias is an obvious potential pitfall in these studies.¹⁷¹⁻¹⁷³ Similarly, retrospective studies have not shown any advantage for either HMA or intensive chemotherapy as disease-modifying treatment before SCT.¹⁷⁴

Retrospective studies have shown higher relapse rates but lower non-relapse mortality for reduced intensity conditioning, generating similar overall survival rates.^{159,161,162} Good results have been reported for the fludarabine plus treosulfan regimen which is often used in younger patients.¹⁷⁵⁻¹⁷⁷

The prognosis after a post-SCT relapse is dismal although donor lymphocyte infusions and HMA may reverse the relapse in some cases.¹⁷⁸ No validated minimal residual disease markers are yet available for MDS. The Nordic MDS group is presently conducting a clinical trial (NCT02872662) in which patient-specific mutations are tracked in serial post-SCT samples using digital droplet PCR. Preliminary data indicate that these markers may predict relapse and can be used for initiation of pre-emptive treatment.

Investigational therapies for myelodysplastic syndromes

There are limited therapeutic options available to exploit our increasing understanding of the molecular pathophysiology of MDS. As indicated above, only one therapy, lenalidomide, targets a specific clinical subset [patients with del(5q) cytogenetics], and two epigenetic modulators (azacytidine and decitabine) have been approved for the treatment of patients with presumed hypermethylation. Recurrently mutated intracellular functional pathways are frequently implicated in MDS and a number of novel therapies targeting these molecular defects have recently shown potential utility for treating MDS patients. In addition, drugs capable of modifying the toxic marrow microenvironmental influences for erythropoiesis have been developed.

IDH1 and *IDH2* mutation inhibitors

Understanding of the pathophysiology of *IDH1/2* mutations in MDS and AML has led to development of clinical *IDH1* and *IDH2* mutation inhibitors. *IDH1* and *IDH2* mutations occur in approximately 5-12% of MDS patients (P51). Recent data have shown encouraging results from the use of ivosidenib or enasidenib for patients with *IDH1* or *IDH2* mutations, respectively.^{179,180}

BCL2 inhibitor

The anti-apoptotic protein B-cell leukemia/lymphoma-2 (*BCL2*) is overexpressed in hematologic malignancies including some cases of MDS, in which it has been implicated in the maintenance and survival of myeloid cells, resistance to therapy, and poor clinical outcomes.¹⁸¹ In recent studies in higher-risk MDS patients either previously untreated or resistant to HMA, initial data suggest potential clinical efficacy of the *BCL2* inhibitor, venetoclax, when combined with azacytidine.^{182,183}

Drugs acting on p53

In hematologic malignancies, including MDS, *TP53* mutations confer a poor prognosis. These mutations are particularly common in therapy-related MDS and a portion of patients with del(5q) cytogenetics.¹⁸⁴ The drug APR-246 restores wildtype conformation to the mutant p53 and has recently shown beneficial clinical activity in MDS.^{185,186} Another approach to reactivate p53-mediated tumor suppression is to inhibit the frequently overex-

pressed p53 suppressor proteins MDMX and MDM2 in tumors. ALRN-6924, a cell-penetrating stapled α -helical peptide disrupts the interaction between p53 and endogenous inhibitors thereby reactivating p53-mediated tumor suppression in AML cells.¹⁸⁷ Phase I/II clinical testing with these drugs is ongoing.

Telomerase inhibition

Defective maintenance of telomere integrity is a hallmark of cancer and is implicated in the pathogenesis of MDS. In MDS, telomere erosion and dysfunction potentiate persistent DNA damage and accumulation of molecular alterations.^{188,189} Evidence suggests that telomere erosion can suppress hematopoietic stem cell self-renewal, repopulating capacity, and differentiation. Imetelstat is a telomerase inhibitor that targets cells with short telomeres and highly active telomerase, and has been shown in early clinical studies to have activity in myeloid malignancies.¹⁹⁰ Initial data on the use of imetelstat in lower-risk MDS patients resistant to ESA has shown encouraging erythroid responses.¹⁹¹

Luspatercept

Increased levels of the transforming growth factor β (TGF β) superfamily inhibitors of erythropoiesis (predominantly growth and differentiation factor-11) occur within MDS erythroid cells.¹⁹² Luspatercept, a recombinant fusion protein, is considered to bind TGF β superfamily ligands and reduce SMAD2 and SMAD3 signaling, reduce ery-

throid hyperplasia, and enhance erythroid maturation and hemoglobin levels in MDS.^{193,194} In a recent phase III trial, luspatercept was shown to reduce the severity of anemia in transfusion-dependent patients with MDS-RS who had disease refractory to or were unlikely to respond to ESA (38% of patients achieved transfusion independence).¹⁹⁵ This drug is currently undergoing USA FDA review for therapeutic use in MDS-RS.

Future considerations

Given the stem cell origin and the multiplicity of molecular abnormalities in MDS, it is difficult to identify potentially effective drugs that can be used to treat a high proportion of patients. Recent studies have demonstrated the feasibility of *ex vivo* drug cytotoxicity platforms to screen effectively for multiple, potentially useful and novel drugs in myeloid neoplasms, including MDS, to provide functional data to guide personalized therapy for treatment-refractory patients with myeloid malignancies and to accurately predict clinical responses *in vivo*.¹⁹⁶⁻¹⁹⁸ Such studies will likely synergize with molecular data and emerging genomics- and cellular-based precision medicine approaches such as *in silico* computational biology modeling.^{199,200} Ultimately, combining both genomics-based and *ex vivo* functional data may further refine precision therapy in myeloid neoplasms such as MDS and translate into improved patients' outcomes.

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