REVIEW ARTICLE

Dan L. Longo, M.D., *Editor*

Myelodysplastic Syndromes

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The term "dysplasia," derived from the ancient Greek for abnormal (*dys*) formation (*plasis*), has traditionally been used by pathologists to denote both the aberrant formation of organs or tissues and their resulting abnormal structure. In 1982, "myelodysplasia" was used by the French–American–British (FAB) group to describe the morphologic abnormalities of the myeloid cell lines of hematopoiesis in preleukemic conditions, which were named myelodysplastic syndromes (MDS).[1] In 2001, under the aegis of the World Health Organization (WHO), the FAB classification was revised with the aim of integrating morphologic and genetic information into a working clinical tool.[2] The WHO classification of MDS proved to be a useful basis for clinical decision making[3] and was revised twice, most recently in 2016.[4] In 1997, a collaborative group developed the International Prognostic Scoring System (IPSS) for MDS.[5] The International Working Group for the Prognosis of MDS subsequently issued a revised IPSS (IPSS-R).[6] With the advent of high-throughput approaches to DNA sequencing, somatic gene mutations were detected in most patients with MDS and were found to be associated with clinical outcomes.[7]

MDS occur mainly, but not exclusively, in patients with a median age of about 70 years, and the crude incidence is 4 to 5 cases per 100,000 persons per year.[8] The true incidence is likely to be higher because of incomplete case assessment and underreporting of MDS in cancer registries, and it may be close to 75 per 100,000 among persons over the age of 70 years.[8]

Definitions

MDS are myeloid neoplasms characterized by clonal proliferation of hematopoietic stem cells, recurrent genetic abnormalities, myelodysplasia, ineffective hematopoiesis, peripheral-blood cytopenia, and a high risk of evolution to acute myeloid leukemia (AML).[4] MDS have been traditionally classified as primary MDS, which occur without a known history of cytotoxic therapy or radiotherapy, or therapy-related MDS, which occur as a late complication of treatment. Therapy-related MDS are now included in the WHO category of therapy-related myeloid neoplasms.[9] Myelodysplasia also characterizes overlap myelodysplastic–myeloproliferative neoplasms.[4] The WHO-defined myeloid neoplasms with myelodysplasia, as well as clonal hematopoiesis of indeterminate potential (CHIP)[10,11] and clonal cytopenia of undetermined significance (CCUS),[12-15] which represent precursor conditions, are listed in Table 1.

Guidance for using the WHO classification of MDS is provided in Sections S1 through S4 of the Supplementary Appendix (available with the full text of this article at NEJM.org). The key diagnostic criteria are persistent cytopenia in one or

Table 1. Diagnostic Criteria for Myeloid Neoplasms with Myelodysplasia and Precursor Conditions for Myelodysplastic Syndromes (MDS).*

Disorder	Diagnostic Criteria
Myeloid neoplasms with myelodysplasia	
MDS	Persistent cytopenia in one or more peripheral-blood cell lineages and morphologic dysplasia (≥10% dysplastic cells) in one or more bone marrow cell lineages; on the basis of morphologic and cytogenetic abnormalities, MDS are categorized into the following subtypes: MDS with single-lineage dysplasia MDS with multilineage dysplasia MDS with ring sideroblasts and single-lineage dysplasia or multilineage dysplasia MDS with isolated del(5q) MDS with excess blasts type 1 or type 2 MDS, unclassifiable†
Myelodysplastic–myeloproliferative neoplasms	Myeloid neoplasms with clinical, laboratory, and morphologic features that overlap those of MDS and myeloproliferative neoplasms; myelodysplastic–myeloproliferative neoplasms are divided into the following subtypes: Chronic myelomonocytic leukemia *BCR-ABL1*–negative atypical chronic myeloid leukemia Myelodysplastic–myeloproliferative neoplasm with ring sideroblasts and thrombocytosis Juvenile myelomonocytic leukemia
Therapy-related myeloid neoplasms[9]	MDS, myelodysplastic–myeloproliferative neoplasms, and acute myeloid leukemia that occur as late complications of chemotherapy or radiotherapy
MDS precursor conditions	
CHIP	Normal peripheral-blood cell counts with a somatic mutation, at a variant allele frequency of at least 2%, in a gene that is recurrently mutated in myeloid neoplasms‡
CCUS	Unexplained cytopenia in one or more peripheral-blood cell lineages; a somatic mutation, at a variant allele frequency of at least 20%, in one or more genes that are recurrently mutated in myeloid neoplasms; and insufficient WHO criteria for a diagnosis of MDS, essentially because of lack of overt dysplasia (<10% dysplastic cells in any bone marrow cell lineage), excess blasts, and MDS-defining chromosomal abnormalities[8]§

* Diagnostic criteria for the myeloid neoplasms with myelodysplasia are those defined in the 2016 revision of the World Health Organization (WHO) classification.[4] With respect to clonal hematopoiesis of indeterminate potential (CHIP)[11] and clonal cytopenia of undetermined significance (CCUS),[12,13,15] diagnostic criteria are those defined by expert panels through consensus processes.

† Guidance for the assessment of morphologic manifestations of myelodysplasia is provided in Sections S1 through S4, Figure S1, and Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

‡ Persons with CHIP may have increased values for red-cell distribution width.[11]

§ Although a variant allele frequency of at least 2% was initially suggested for the diagnosis of CCUS, the available evidence indicates that a higher cutoff point (20%) should be used to identify clinically significant clonality.[12-15]

more peripheral-blood cell lineages and morphologic dysplasia in one or more bone marrow cell lineages. The subtypes of MDS are diagnosed on the basis of the number of dysplastic lineages, presence or absence of ring sideroblasts, percentage of bone marrow and peripheral-blood blasts, and type of cytogenetic abnormality (Table 1, and Table S6 in the Supplementary Appendix). Hypoplastic MDS and MDS with fibrosis (Section S4) are not included in the WHO subtypes.[16,17]

PATHOPHYSIOLOGY

The growth and spread of a somatically mutated clone represent the pathophysiological

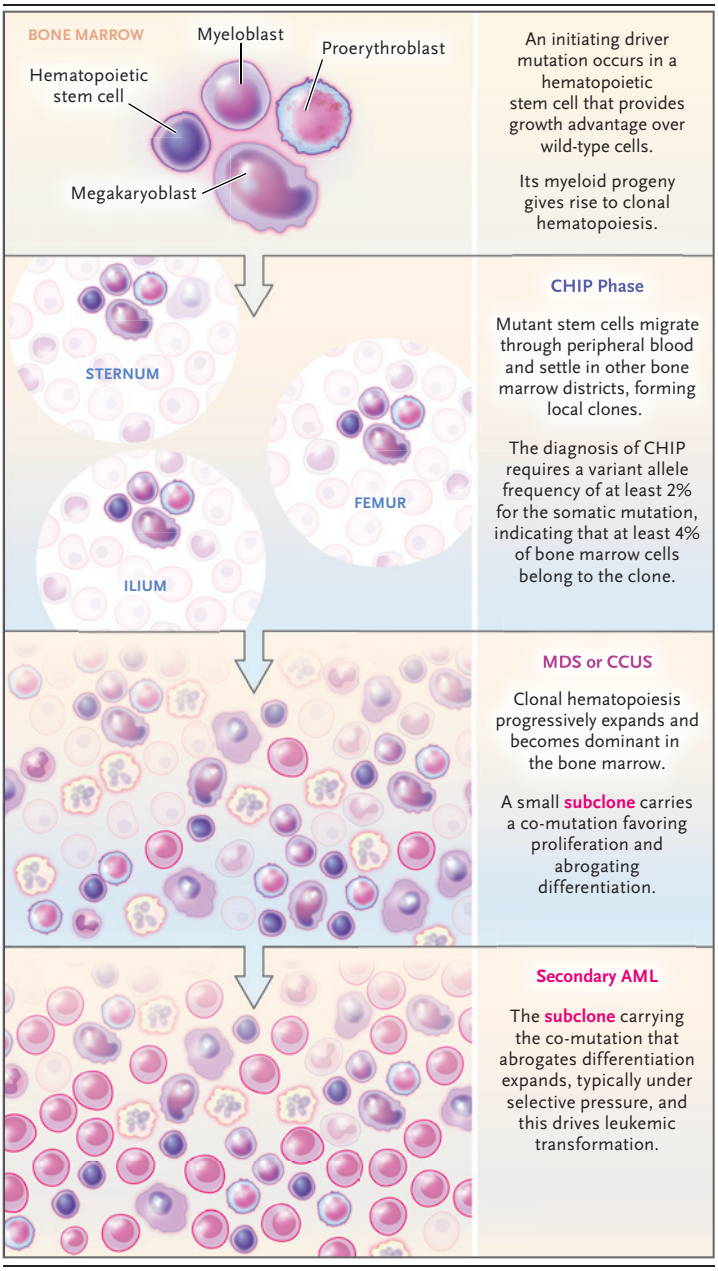

Figure 1. General Model of the Growth and Propagation of Myelodysplastic Hematopoiesis.

Myelodysplastic syndromes (MDS) arise from the growth and spread of a somatically mutated clone of hematopoietic cells and frequently evolve into acute myeloid leukemia (AML). Different phases, corresponding to distinct clinical pictures, can be identified in this process. The first phase is growth of a somatically mutated clone. An initiating driver mutation occurs in a hematopoietic stem cell, generating a local clone composed of mutant stem cells and abnormal hematopoietic progenitor and precursor cells. The second phase (clonal hematopoiesis of indeterminate potential [CHIP]) is characterized by the migration of mutant stem cells and propagation of clonal hematopoiesis. Over time, mutant stem cells migrate through peripheral blood and settle in other bone marrow districts, forming local clones. When hematopoietic cells carrying the somatic mutation account for at least 4% of all bone marrow cells (corresponding to a variant allele frequency of at least 2% for the mutation), the condition is defined as CHIP. Unlike patients with MDS, most patients with CHIP carry a somatic mutation in an epigenetic regulator gene (*DNMT3A*, *TET2*, or *ASXL1*) and only a minority have a mutation in a spliceosome gene (*SF3B1*, *SRSF2*, or *U2AF1*).[10,18] This is consistent with the hypothesis that persons with a spliceosome mutation have more rapid progression to MDS or clonal cytopenia of undetermined significance (CCUS), whereas those with a mutation in an epigenetic regulator can remain stable in the CHIP phase for years.[14] Persons with therapy-related CHIP frequently have mutations in *TP53* or *PPM1D* (Section S10 in the Supplementary Appendix). The third phase (MDS or CCUS) is characterized by clonal dominance. Clonal hematopoiesis progressively expands and eventually becomes dominant in the bone marrow. This process is commonly associated with the occurrence of additional somatic mutations; at the onset of clinical disease, the median number of somatic mutations is 2 to 3. Depending on the extent of clonal dominance, the degree of morphologic dysplasia, and the absence or presence and type of cytogenetic aberrations, this condition can meet the diagnostic criteria for MDS or CCUS. For clonality to be considered clinically significant and indicative of CCUS, the variant allele frequency of the founding mutation should be at least 20%.[15] The fourth phase (secondary AML) is characterized by clonal selection and leukemic transformation. The acquisition of additional driver mutations or the emergence of preexisting ones leads to selection of subclones of hematopoietic cells (encircled in pink) with increasingly impaired differentiation capacity. When the proportion of blast cells increases to 20% or more, a diagnosis of secondary AML can be made.

process that leads to MDS (Fig. 1). The selective advantage of the clone is provided by somatic genetic lesions termed driver mutations.[19] The initiating mutation occurs in a hematopoietic stem cell capable of self-renewal, whereas additional mutations associated with clonal progression may also occur in progenitor cells, conferring a self-renewal capability.[20] Several mutation-driver genes, belonging to different biologic pathways, can lead to MDS, and most patients have combinations of pathway mutations, accounting for the heterogeneity of these disorders.[7,21-25]

MUTATION-DRIVER GENES IN MDS

Recurrently mutated genes include those involving RNA splicing, DNA methylation, histone modification, transcription regulation, DNA-repair control, signaling, and the cohesin complex (Table S8). Only six genes (*SF3B1*, *TET2*, *SRSF2*, *ASXL1*, *DNMT3A*, and *RUNX1*) are mutated in at least 10% of patients who have MDS, with a long tail of additional genes that are mutated less frequently.[24,25] Most mutations are C-to-T transitions at CpG dinucleotides, suggesting that they are due to age-related deamination of methylated cytosines.[26] At the onset of clinical disease, the median number of driver mutations is two or three per patient.[26]

Spliceosome mutations are generally early genetic events that drive clonal dominance and shape the future trajectories of clonal evolution[21,24]; they are heterozygous and mutually exclusive, most likely because of synthetic lethal interactions.[27] Somatic mutations in genes of DNA methylation and histone modification also drive clonal dominance, whereas the remaining mutated genes mainly contribute to clonal progression.[28]

GROWTH AND PROPAGATION OF MYELODYSPLASTIC HEMATOPOIESIS

Through various mechanisms, mutation-driver genes cause clonal outgrowth and propagation of myelodysplastic hematopoiesis (Fig. 1).[29] When most of the bone marrow hematopoietic cells are clonally derived, the disease is clinically manifested as cytopenia and morphologic dysplasia. The paradox of myelodysplastic hematopoiesis is that the founding mutation provides an advantage at the level of stem cells and progenitor cells, combined with a disadvantage at the level of hematopoietic precursors.[30]

The clonal outgrowth of mutant stem cells is favored by an abnormal hematopoietic stem-cell niche.[31] Although microenvironmental alterations might simply be related to aging, mutant hematopoietic cells themselves may alter the stem-cell niche through activation of the innate immune system and related inflammatory signaling.[27,32,33]

SOMATIC MUTATIONS IN EPIGENETIC REGULATORS

The epigenetic regulators *TET2* and *DNMT3A* are among the most commonly mutated genes, not only in MDS[24,25] but also in CHIP and CCUS.[10,14,18] These genes are essential for hematopoietic stem-cell differentiation, and their heterozygous inactivation through mutation enhances self-renewal and impairs differentiation, leading to clonal outgrowth of mutant stem cells.[34] Although mutations in *TET2* and *DNMT3A* may be the sole genetic abnormality in some patients, in most instances, these genes are involved in combinatorial mutation patterns in which co-mutated genes together determine the clinical phenotype.

HAPLOINSUFFICIENCY PRODUCTION OF MULTIPLE GENE TRANSCRIPTS IN MDS WITH ISOLATED DEL(5Q)

The deletion on the long arm of chromosome 5 is the initiating driver mutation that leads to haploinsufficiency of multiple genes and, in turn, to clinical manifestations[35-41] (Fig. 2A). In particular, haploinsufficiency production of casein kinase 1A1, encoded by *CSNK1A1*, explains both the clonal expansion of mutant stem cells and the efficacy of lenalidomide in suppressing them.[39,40]

ABERRANT RNA SPLICING AND ABNORMAL GENE TRANSCRIPTS IN *SF3B1*-MUTATED MDS

The *SF3B1* mutation identifies a distinct subtype of MDS that is characterized by ring sideroblasts, ineffective erythropoiesis, and macrocytic anemia.[22,49,50] This condition has a relatively good prognosis, although most patients become transfusion-dependent, and specific mutations or co-mutations may be associated with a worse outcome.[50,51] The mutation occurs in a multipotent stem cell,[52] and physiologic expression of *Sf3b1* (K700E) in mice has been shown to expand hematopoietic stem cells and cause progressive macrocytic anemia.[42] The mutant SF3B1 splicing factor preferentially uses cryptic 3′ splice sites, leading to nonsense-mediated decay of multiple transcripts or generation of in-frame isoforms (Fig. 2B).[42-45]

GENETIC COMPLEXITY OF MDS ASSOCIATED WITH MUTATIONS IN *SRSF2* OR *U2AF1*

The spliceosome genes *SRSF2* and *U2AF1* are recurrently mutated in various myeloid neoplasms, which are generally characterized by a poor clinical outcome.[30] Mutated *SRSF2* and *U2AF1*

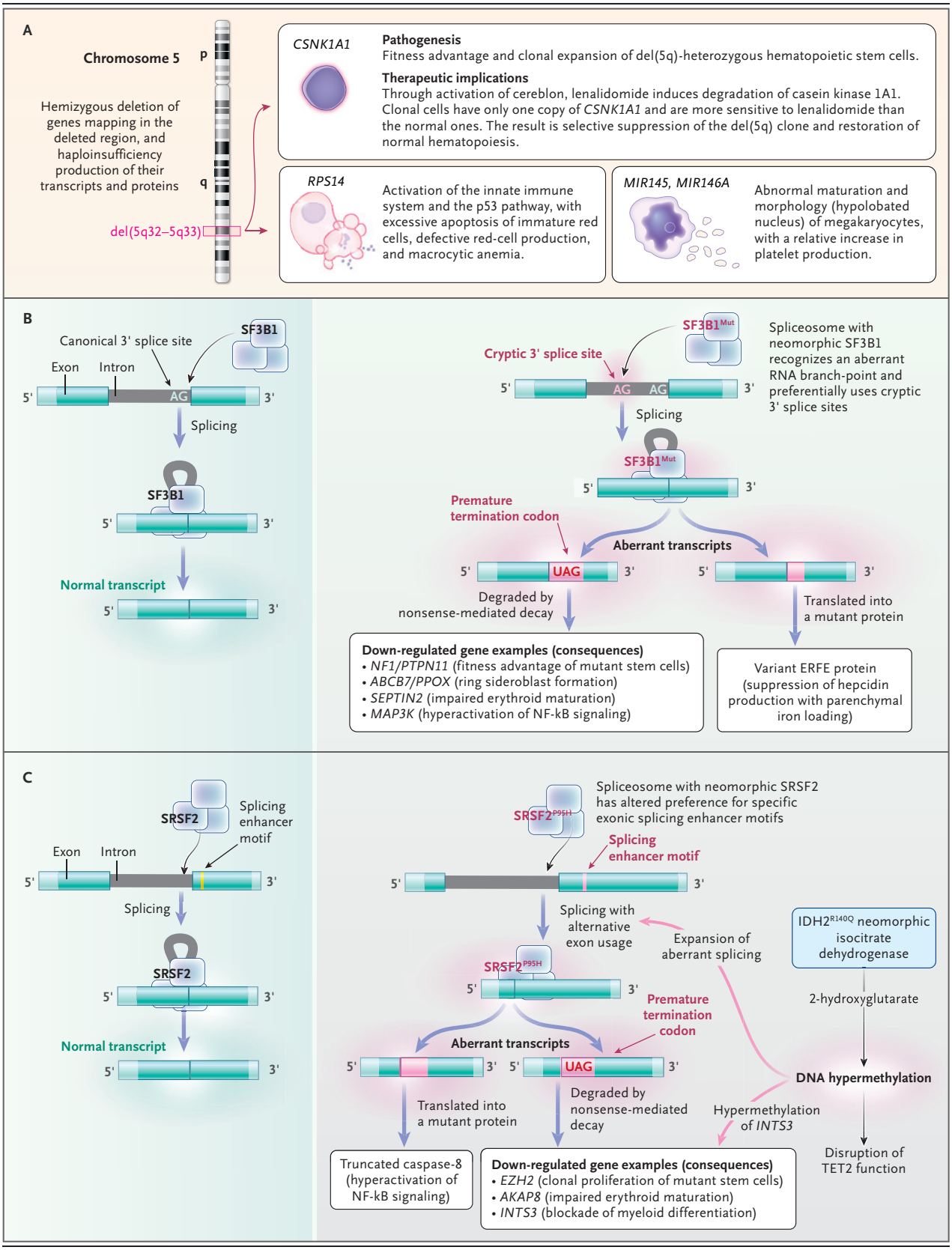

Figure 2 (facing page). Molecular Pathophysiology of Three Subtypes of MDS.

Panel A shows the role of haploinsufficiency production of multiple gene transcripts in the pathophysiology of MDS with isolated del(5q). As a sole genetic lesion, the 5q32–5q33 deletion accounts for the clonal nature of the disease, the macrocytic anemia, the mild thrombocytosis, and the efficacy of lenalidomide treatment. In del(5q)-heterozygous stem cells, haploinsufficiency production of casein kinase 1A1, encoded by *CSNK1A1*, confers a growth advantage that leads to clonal expansion.[39] In mutant erythroblasts, haploinsufficiency of *RPS14* results in activation of the innate immune system and the p53 pathway, causing the excessive apoptosis that is responsible for the macrocytic anemia.[35,37,41] In megakaryocytes, haploinsufficiency of *MIR145* and *MIR146A*, which are physiological repressors of megakaryocytopoiesis, results in abnormal maturation with dysplastic features (e.g., hypolobated nucleus) of these precursors and a relative increase in platelet production.[36,38] Haploinsufficiency of *CSNK1A1* also explains the efficacy of lenalidomide in this subtype of MDS.[39,40]

Panel B shows the role of production of abnormal gene transcripts in the pathophysiology of *SF3B1*-mutated MDS. Hematopoietic cells are heterozygous for the mutation, and therefore, in each cell, about half the splicing events are run by normal spliceosomes, whereas the remaining half are operated by spliceosomes that include a mutant SF3B1 splicing factor. The mutation alters RNA branchpoint recognition, causing preferential use of cryptic 3′ splice sites that cluster within 10 to 30 bp upstream of canonical sites and resulting in insertion of nucleotides at the authentic exon–exon junction.[42-44] Only trace amounts of aberrant transcripts of several genes can be detected in *SF3B1*-mutated myelodysplastic cells.[43] Most aberrant transcripts are rapidly degraded by nonsense-mediated decay, mainly because the inserted nucleotide sequence harbors a premature termination codon; the final result is reduced production of canonical transcript, and, in turn, of protein.[43] This reduced transcript production affects several genes with various consequences, as shown in the examples. Aberrant 3′ splice-site selection may also lead to generation of in-frame isoforms. This is the case with *ERFE*, encoding erythroferrone, an erythroid regulator of hepcidin: the variant ERFE protein contributes to parenchymal iron loading.[45]

Panel C shows the synergic interaction between abnormal splicing and epigenetic dysregulation in MDS with the *SRSF2* (P95H)–*IDH2* (R140Q) co-mutation.[24,46] The *SRSF2* mutation gives rise to a neomorphic splicing factor with an altered preference for specific exonic splicing enhancer motifs that results in alternative exon usage.[47] This generates aberrant transcripts harboring a premature termination codon that may be rapidly degraded by nonsense-mediated decay or translated into a variant protein, with various pathological consequences, as shown in the examples.[43,44,47] The *IDH2* (R140Q) mutation results in neomorphic enzyme activity, 2-hydroxyglutarate generation, and DNA hypermethylation that disrupts the function of epigenetic regulators, in particular *TET2*.[48]

cause different splicing aberrations, primarily altered exon usage, from those caused by *SF3B1*.[43,44,47,53] A common missplicing event (i.e., use of a cryptic exon harboring a premature termination codon) leads to down-regulation of *EZH2*, a gene that is recurrently inactivated by loss-of-function mutations in myeloid neoplasms.[54]

Somatic mutations in *SRSF2* and *U2AF1* involve increased R-loop formation, which can cause genomic instability, and are almost invariably involved in combinatorial mutation patterns.[44,55] For instance, the *SRSF2* (P95H)–*IDH2* (R140Q) co-mutation is found in both MDS and AML.[24,46,56] The interplay between the two mutated genes leads to a myeloid malignant process through coordinated alterations in RNA splicing and epigenetic regulation (Fig. 2C).[46,48]

LEUKEMIC TRANSFORMATION

The evolution to AML is a process of clonal selection in which both linear and branching evolutionary patterns may occur.[57,58] Mutations driving leukemic transformation may already be present at the onset of clinical disease but expand only later, typically under selection pressure.[59] Transformation into AML may occur with different patterns. Thus, *SF3B1*-mutated MDS has a long-lasting chronic phase, and only a minority of cases eventually evolve to AML, typically through acquisition or expansion of somatic mutations in *RUNX1* or *EZH2*, which substantially modify the disease pattern.[50,51] On the other hand, cases of MDS with combinations of mutated genes such as *SRSF2*, *U2AF1*, *RUNX1*, *STAG2*, or *IDH2* are typically characterized by excess blasts at the onset of clinical disease and gradually progress to AML, with a clear continuum between the myelodysplastic and leukemic phases, which are distinguishable only on the basis of the 20% blast threshold.[58]

GERMLINE PREDISPOSITION TO MYELOID NEOPLASMS

Although MDS are mainly sporadic diseases affecting older people, there is growing evidence that a portion of patients, frequently but not exclusively those under the age of 50 years, have a genetic predisposition to myeloid neoplasms.[60] In these cases, the driving somatic mutation occurs on the background of a germline lesion that is responsible for a faster mutational rate

Table 2. Conditions with a Germline Genetic Predisposition for the Development of Myeloid Neoplasms.*

Condition	Main Features
Conditions without clinical manifestations before the development of a myeloid neoplasm	
DDX41-associated susceptibility to myeloid neoplasms	Heterozygous germline mutation in *DDX41*; acquisition of a somatic mutation in the normal *DDX41* allele typically leading to MDS or AML, most commonly in the sixth or seventh decade of life; a *DDX41* mutation in about 4% of patients with MDS, about half of whom have both germline and somatic mutations
CEBPA-associated predisposition to AML	Heterozygous germline mutation in *CEBPA*; acquisition of a somatic mutation in the normal *CEBPA* allele, leading to biallelic AML; evolution to AML may also be associated with somatic mutations in *GATA2*, *WT1*, or *KIT*
Familial platelet disorders, characterized by thrombocytopenia, platelet dysfunction, or both	
RUNX1-related familial platelet disorder	Heterozygous germline mutation in *RUNX1*; clinical manifestations including tendency toward bleeding and mild or moderate thrombocytopenia; dysmegakaryopoiesis, possibly observed before malignant transformation; progression to a hematologic neoplasm, typically associated with acquisition of a somatic mutation in the second *RUNX1* allele but possibly with acquisition in other genes (e.g., *PHF6* and *BCOR*)
ANKRD26-related thrombocytopenia	Heterozygous germline mutation in *ANKRD26*; typically mild or moderate thrombocytopenia and mild bleeding in patients; bone marrow examination showing dysmegakaryopoiesis with small binucleated megakaryocytes; associated with increased risk of myeloid neoplasms in adulthood
ETV6-related thrombocytopenia	Heterozygous germline mutation in *ETV6*; mild thrombocytopenia with hypolobated small megakaryocytes in the bone marrow, and mild-to-moderate bleeding in patients; associated with increased risk of both myeloid and lymphoid neoplasms
Inherited bone marrow failure syndromes	
Fanconi's anemia	Bone marrow failure and congenital anomalies associated with germline mutations in genes involved in DNA repair (e.g., the *FANC* genes), causing genomic instability; selective pressure within hematopoiesis, giving rise to mutant clones that may typically lead to MDS or AML in the second decade of life or young adulthood
Diamond–Blackfan anemia	Red-cell aplasia associated with germline mutations in ribosomal protein genes(e.g., *RPS19*), causing aberrant ribosome biogenesis; coexisting congenital malformations in approximately 50% of patients; associated with increased risk of MDS and AML

Shwachman–Diamond syndrome	Bone marrow failure with neutropenia, exocrine pancreatic dysfunction, and other variable abnormalities associated with biallelic germline mutations in *SBDS*; associated with increased risk of MDS and AML; possibly the first clinical manifestations in young adults with reduced phenotypic expression of the genetic disease are features of MDS (i.e., Shwachman–Diamond syndrome can remain unrecognized until the development of MDS)
Dyskeratosis congenita (X-linked telomere disease)	Bone marrow failure, dystrophic nails, patchy skin hyperpigmentation, and oral leukoplakia associated with germline mutations in *DKC1*, mapping on the X chromosome and encoding dyskerin; associated with pulmonary fibrosis and increased risk of MDS and AML
Other telomerase complex disorders	Telomere diseases associated with germline mutations in *TERC*, *TERT*, or more rarely, other genes of the telomerase complex; haploinsufficiency of the mutated genes as the mechanism of disease; considerable variability in penetrance, even within families; clinical manifestations of the disease at any age, from early infancy to late adulthood, including bone marrow failure, pulmonary fibrosis, liver disease, and less commonly, mucocutaneous abnormalities; all these disorders conferring a predisposition to MDS and AML
Miscellaneous syndromes featuring abnormalities of hematopoiesis and other organs	
GATA2-spectrum disorders (GATA2 deficiency syndrome)	Heterozygous germline mutation in *GATA2*; haploinsufficiency resulting in a protean disorder that may include abnormalities of hematopoiesis, lymphatics, and immunity; four clinical syndromes associated with GATA2 deficiency (MonoMAC syndrome [monocytopenia and mycobacterial infections]; dendritic-cell, monocyte, and lymphocyte deficiency; Emberger's syndrome [lymphedema, congenital deafness, and monosomy 7]; and familial MDS and AML); MDS development in childhood or adulthood
MIRAGE syndrome	Myelodysplasia, infection, restriction of growth, adrenal hypoplasia, genital phenotypes, and enteropathy (MIRAGE) associated with germline gain-of-function mutations in *SAMD9*, located on chromosome 7q21.2; patient presenting with cytopenia in the first decade of life, with possible progression to MDS or AML with monosomy 7 or other abnormalities of chromosome 7; development of clones that have lost or inactivated the mutant *SAMD9* allele (genetic reversion), possibly resulting in spontaneous improvement of hematopoiesis
SAMD9L-related ataxia–pancytopenia	Cerebellar ataxia and cytopenia associated with germline gain-of-function mutations in *SAMD9L*, located on chromosome 7q21.2; mild neurologic and hematologic manifestations remaining unrecognized; patients recovering spontaneously from cytopenia or progressing to MDS or AML with monosomy 7 through various mechanisms of genetic reversion
ERCC6L2-associated bone marrow failure syndrome	Bone marrow failure associated with biallelic germline mutations in *ERCC6L2*; patients presenting with pancytopenia in the first 2 to 3 decades of life; reports of cerebral and craniofacial abnormalities; reports of progression to MDS or AML

* The information is from Arber et al.,[4] Schwartz et al.,[62] Bluteau et al.,[63] Kennedy and Shimamura,[60] Rio-Machin et al.,[64] and Brown et al.[65] This is not an exhaustive list of conditions with a germline genetic predisposition to myeloid neoplasms. AML denotes acute myeloid leukemia.

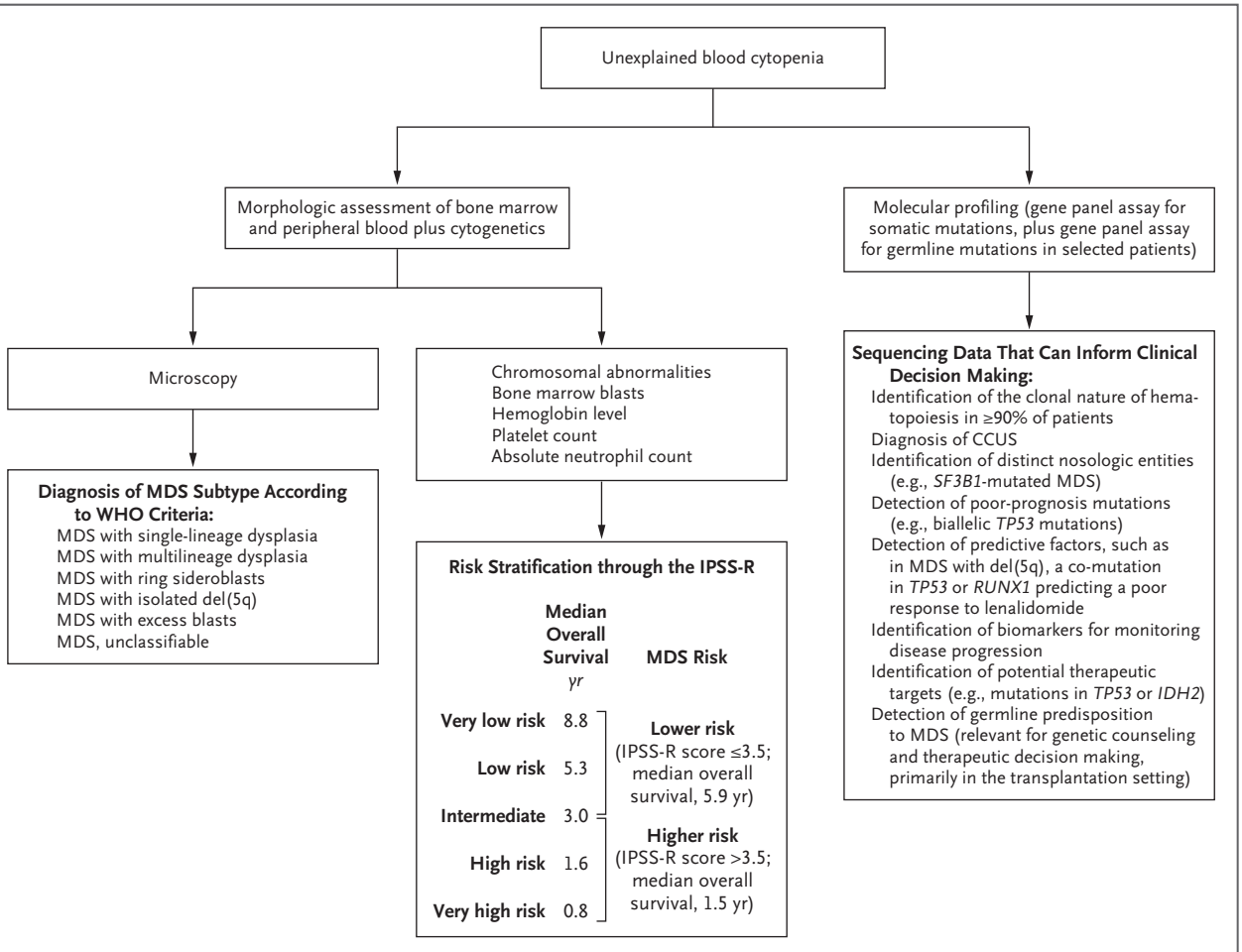

Figure 3. Diagnosis of MDS and Risk Stratification.

In the conventional approach to diagnosis, key measures are blood counts, the number of dysplastic lineages, the proportion of ring sideroblasts, the blast percentage, and the type of chromosomal abnormalities. With the use of these measures, diagnoses of MDS are made according to the World Health Organization (WHO) criteria (Table S6), and the Revised International Prognostic Scoring System (IPSS-R) is used to estimate the risk of evolution to AML and expected survival (Table S10). Molecular profiling can substantially inform clinical decision making. Potential sequencing platforms include gene-panel, whole-exome, whole-genome, and error-corrected sequencing.[58] The simplest approach involves a gene-panel assay for detection of somatic mutations and, in selected patients (e.g., those who are <50 years of age or have evidence of familial disease), a gene-panel assay for detection of germline mutations. These assays can include genomewide, single-nucleotide polymorphisms for detection of copy-number variants and loss of heterozygosity. CCUS denotes clonal cytopenia of undetermined significance.

in hematopoietic cells or for selective pressure driving clonal outgrowth.[61] The new category of myeloid neoplasms with a germline predisposition has been included in the WHO classification,[4] and an updated list is shown in Table 2.[60,62-65]

Individual predisposition disorders are rare but collectively may account for up to 15% of all cases of MDS.[60] Detecting the germline mutation is important not only for genetic counseling but also for clinical decision making, particularly in the context of transplantation.[66]

DIAGNOSIS AND RISK STRATIFICATION

CONVENTIONAL APPROACH TO THE DIAGNOSIS OF MDS

Cytopenia in at least one hematologic cell line is an essential diagnostic criterion for MDS.[8,67]

Once common causes of cytopenia have been ruled out, the conventional diagnostic workup includes bone marrow aspiration to detect morphologic dysplasia and blasts, bone marrow biopsy to assess marrow cellularity and fibrosis, and conventional cytogenetics to detect nonrandom chromosomal abnormalities (Fig. 3).[4] These abnormalities include del(5q), +8, –7/del(7q), del(20q), and complex karyotype (Table S2).

MOLECULAR PROFILING

Gene sequencing improves the diagnostic process (Fig. 3). Identifying the clonal nature of hematopoiesis is not a requirement in the WHO classification[4] but simplifies the differential diagnosis. Recurrent chromosomal abnormalities are detected in only about 50% of cases[30]; however, when cytogenetics is combined with gene sequencing, 90% or more of patients with MDS are found to carry a clonal genetic lesion.[25] A portion of patients with unexplained cytopenia do not meet the current diagnostic criteria for MDS but carry somatic mutations in genes that are recurrently mutated in myeloid neoplasms (Table S8).[12,13] These patients have CCUS, a condition that can be diagnosed only by means of molecular profiling.[13]

In patients with unexplained cytopenia who are under the age of 50 years and in those with evidence of familial disease, the possibility of a germline predisposition to myeloid neoplasms should always be considered (Table 2).[60] This condition can also be present in older adults, typically in patients with *DDX41*-mutated MDS, who frequently carry a germline mutation in one parental allele and a somatic mutation in the other allele.[68] The question of germline predisposition becomes clinically relevant whenever transplantation with a graft from a family donor is planned, since the donor may carry a predisposing mutation. A gene panel specifically designed for germline mutation analysis may inform decision making in these cases.[60]

RISK STRATIFICATION BASED ON THE IPSS-R

MDS encompass a wide spectrum of conditions that vary with respect to the risk of death from complications of cytopenia or evolution to AML.[30] The IPSS-R is universally used for risk stratification in MDS.[6] On the basis of cytogenetic abnormalities, the percentage of marrow blasts, the hemoglobin level, the platelet count, and the absolute neutrophil count, this prognostic model defines five major prognostic categories (Table S10). In clinical practice, a cutoff IPSS-R score of 3.5 allows clinicians to distinguish between patients with lower-risk MDS (score ≤3.5; median survival, 5.9 years) and those with higher-risk MDS (score >3.5; median survival, 1.5 years) (Fig. 3).[69] Lower-risk MDS and higher-risk MDS account for about two thirds and one third of all cases, respectively, at the clinical onset of disease.[69]

PROGNOSTIC RELEVANCE OF SOMATIC MUTATIONS

Cytogenetic abnormalities have prognostic relevance in MDS but are already incorporated in the IPSS-R. Also, whereas IPSS-R scores indicate the behavior of aggregate MDS, individual cases may deviate substantially from median values. Molecular profiling can improve risk stratification and inform clinical decision making (Fig. 3). For instance, a biallelic defect in *TP53* predicts a risk of leukemic transformation and death independent of the IPSS-R score.[70] Somatic mutations can also be used as biomarkers for monitoring disease progression and minimal residual disease.[58,71]

ACCOUNTING FOR PATIENT-CENTERED FACTORS

Coexisting conditions and frailty are common in older patients and are independently associated with a shorter overall survival.[72,73] Geriatric assessment testing allows clinicians to personalize care for patients with MDS, primarily by detecting areas of vulnerability and predicting toxic effects of treatment.[74]

TREATMENTS

With multiple areas of uncertainty regarding the therapeutic options that are currently available, a patient-centered care model represents the best approach to the treatment of MDS. The initial step is assessing a patient's eligibility for allogeneic stem-cell transplantation, which is the only potentially curative treatment but is associated with substantial morbidity and mortality.[75,76] Counseling should be aimed at personalizing the decision regarding transplantation in a shared process that gives full consideration to the patient's values and wishes. Once eligibility for

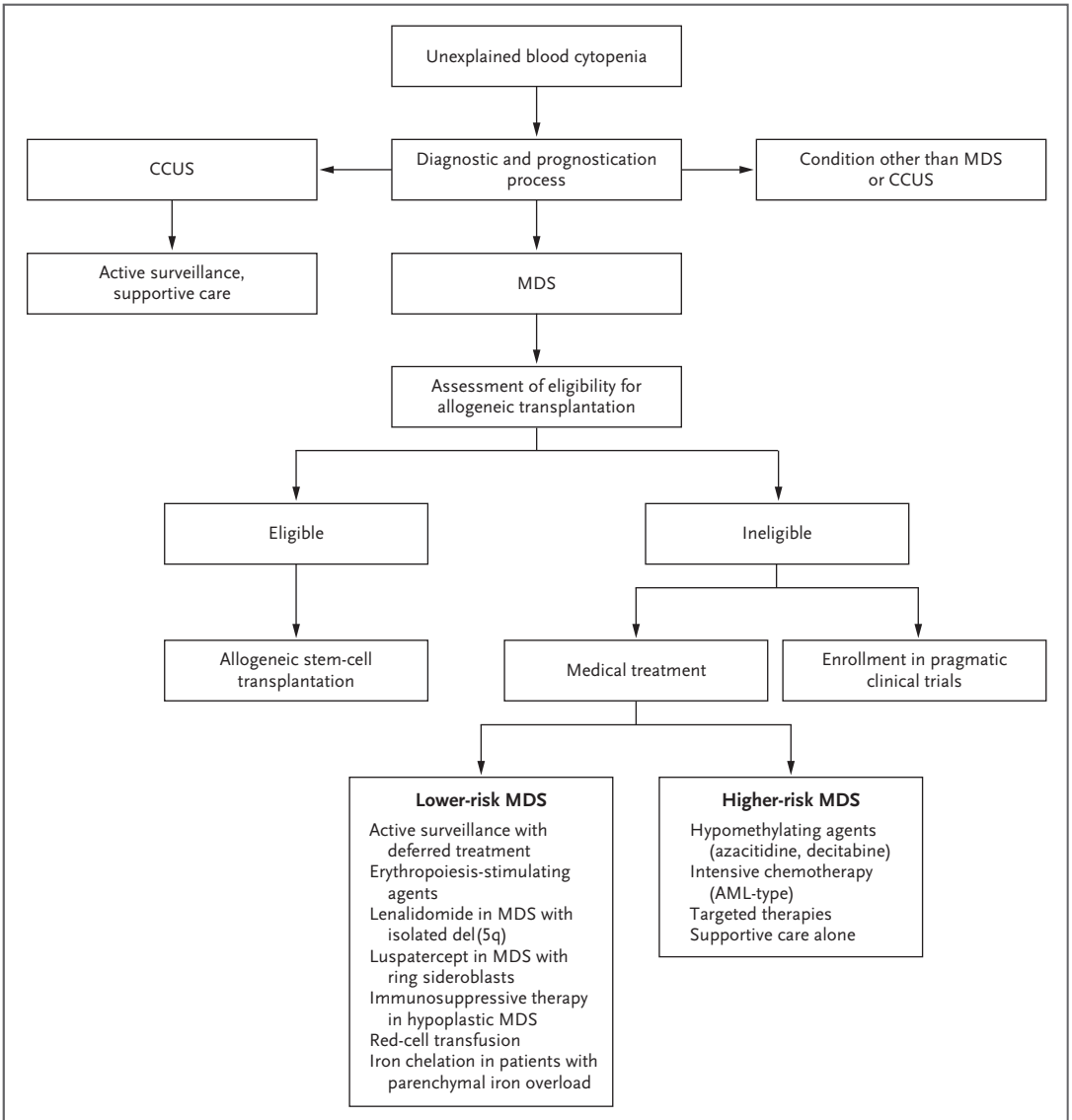

Figure 4. Patient-Centered Approach to the Treatment of MDS.

At each step, the patient's values and wishes are a key component in a shared decision-making process. On the basis of the relative proportions of patients with lower-risk MDS and those with higher-risk MDS (approximately two thirds and one third, respectively) and the median age of these patients (approximately 70 years), only a minority of patients are eligible for allogeneic transplantation. In patients with lower-risk MDS, the choice of a medical treatment is largely based on the specific disease subtype, particularly in MDS with del(5q) and MDS with ring sideroblasts, conditions that are likely to respond to lenalidomide and luspatercept, respectively, with amelioration of anemia. Most patients with higher-risk MDS are treated with a hypomethylating agent, but only a minority of them have a benefit; this supports the enrollment of such patients in first-line, pragmatic clinical trials testing novel combinations of drugs in real-life settings.[77] Management of clonal cytopenia of undetermined significance (CCUS) comprises active surveillance with monitoring two to four times per year and supportive care.[15]

transplantation has been established, appropriate planning of the therapeutic program can be initiated (Fig. 4).

MDS with a germline predisposition pose particular problems.[65,66] Notably, the risk of treatment-related death may substantially influ-

ence the clinical outcome, as recently observed in patients with the Shwachman–Diamond syndrome and MDS.[78] Patients with germline mutations in predisposition genes should be preferentially treated within research protocols in partnership with experts in the field.[65,66]

ALLOGENEIC STEM-CELL TRANSPLANTATION

Whereas only a portion of patients with lower-risk MDS are potential candidates for transplantation at the clinical onset of disease, all patients with higher-risk MDS should be assessed for eligibility at the time of diagnosis (Table S11). Patients with good performance status and no or few coexisting conditions are the best candidates for transplantation, whereas those with poor performance status or multiple coexisting conditions should be preferentially considered for medical treatments (Table S12).[76] The conventional upper age limit for transplantation is around 70 years, but greater attention is currently being given to biologic age, with several centers performing transplantations in fit patients in their late 70s. About 40 to 50% of patients with MDS survive for 5 years after transplantation.[75,76,79,80] Somatic mutations in *TP53*, particularly biallelic defects, are the most powerful predictor of relapse and shorter survival.[70,80,81]

MEDICAL TREATMENTS FOR LOWER-RISK PATIENTS

Not all patients need to be treated immediately. When treatment is required, the main objective is to ameliorate cytopenia, primarily anemia, and improve the quality of life.[67,82]

Active Surveillance with Deferred Treatment

Mild cytopenia may be compatible with a good quality of life, and patients with mild cytopenia need only to be followed regularly. A complete blood count should be performed every 3 to 6 months, with a marrow examination once a year or whenever there is a clinically significant drop in blood counts.

Erythropoiesis-Stimulating Agents

Administration of erythropoiesis-stimulating agents can increase red-cell production and ameliorate anemia in patients with lower-risk MDS; this is the first therapeutic option for most such patients with anemia.[67] A serum erythropoietin level below 200 mU per milliliter is the most reliable predictor of a response, whereas a high transfusion requirement predicts treatment failure.[83] The median duration of a response is on the order of 1 to 2 years.

Lenalidomide in MDS with Isolated del(5q)

Lenalidomide induces transfusion independence in about two thirds of patients with lower-risk MDS and isolated del(5q), and many patients with a response to lenalidomide have a cytogenetic remission, clearly indicating that this is a true targeted therapy (Fig. 2A).[84] After 2 to 3 years, however, most patients have a reemergence of the del(5q) clone and a recurrence of anemia. Relapse is caused by selection of hematopoietic cells that are resistant to lenalidomide and frequently carry a somatic mutation in *TP53* or *RUNX1*, which typically drives leukemic transformation.[85-87]

Lenalidomide yields transfusion independence in about a quarter of patients who have MDS without isolated del(5q), but responses are short-lived and treatment is associated with clinically significant adverse events.[88] The off-label use of lenalidomide in patients who do not have del(5q) or do not depend on transfusions is common in the United States but does not provide any survival benefit.[89]

Luspatercept in MDS with Ring Sideroblasts

Luspatercept is a recombinant fusion protein that binds transforming growth factor β superfamily ligands to enhance late-stage erythropoiesis. In a study involving transfusion-dependent patients who had MDS with ring sideroblasts, luspatercept treatment resulted in transfusion independence in 38% of cases.[90] Luspatercept is approved for the treatment of transfusion-dependent patients with MDS and ring sideroblasts who have not had a response to erythropoiesis-stimulating agents (Table S14).

Immunosuppressive Therapy in Hypoplastic MDS

In a subgroup of transfusion-dependent patients with hypoplastic MDS, transfusion independence can be achieved with immunosuppressive therapy, primarily antithymocyte globulin combined with cyclosporine (Table S14).[91] This treatment may be considered in younger persons with a normal blast count who are ineligible for allogeneic transplantation.

Red-Cell Transfusion and Iron Chelation

The vast majority of patients with MDS become dependent on regular red-cell transfusions during their clinical course.[92] Although a hemoglobin level of 8 g per deciliter is generally used as a transfusion threshold, a more liberal regimen may promote a better quality of life.[93] Transfusion dependence can lead to parenchymal iron overload and its clinical consequences (Section S9).[92] In patients with lower-risk MDS, deferasirox treatment has been shown to prolong event-free survival.[94] Iron chelation may be considered in patients with lower-risk MDS who have parenchymal iron overload, as documented by increased transferrin saturation and serum ferritin levels.

MEDICAL TREATMENTS FOR HIGHER-RISK MDS

Patients with higher-risk MDS have a median life expectancy of less than 2 years. For such patients, treatment is aimed not only at ameliorating cytopenias but also at preventing evolution to AML and thus prolonging survival.[67] Several drugs can modulate myelodysplastic hematopoiesis, but available treatments fail to eradicate it, mainly because their selective pressure leads to the emergence of resistant subclones.

Hypomethylating Agents

The use of a hypomethylating agent, azacitidine or decitabine, currently represents the most common initial treatment in patients with higher-risk MDS who are ineligible for transplantation. About half the patients treated with azacitidine have a hematologic response, including some with a complete response.[95] Treatment is associated with prolonged survival, although the survival benefit observed in real-life studies is on the order of a few months, which is shorter than the survival in the registration study.[77,95] Responses can also be observed in patients with adverse cytogenetic features or high-risk mutations, but patients with biallelic defects in *TP53* invariably have a poor outcome.[70] Unfortunately, azacitidine treatment does not eliminate founder clones, which continue to drive hematopoiesis,[96] and is therefore not curative.

A few studies have investigated azacitidine- or decitabine-based combinations of drugs. In a phase 2–3 trial, patients with higher-risk MDS were assigned to receive azacitidine, azacitidine plus lenalidomide, or azacitidine plus vorinostat; no significant difference in overall response rate was observed among the different groups.[97] In contrast, venetoclax combined with azacitidine or decitabine was shown to be effective and had an acceptable side-effect profile in elderly patients with AML, with a hematologic remission achieved in two thirds of them.[98] Studies evaluating venetoclax combinations in patients with higher-risk MDS are ongoing (Table S15).

Intensive Chemotherapy

With the advent of hypomethylating agents, AML-type chemotherapy is used less frequently in patients with MDS. Nonetheless, it may be considered in patients below the age of 60 years who have 10% or more bone marrow blasts without adverse cytogenetic characteristics and are ineligible for transplantation.[67] In older patients with secondary AML, treatment with CPX-351, a liposomal encapsulation of cytarabine and daunorubicin, was shown to be associated with prolonged survival, as compared with conventional intensive chemotherapy.[99] Ongoing clinical trials are evaluating the use of CPX-351 in patients with higher-risk MDS (Table S15).

Novel Targeted Therapies

Mutations in *TP53*, *IDH2*, and *IDH1* are collectively found in 10 to 20% of patients with MDS (Table S8), and drugs targeting these mutated genes are being evaluated in clinical trials (Table S15). Enasidenib, an oral inhibitor of mutant IDH2 proteins, can induce molecular remissions and hematologic responses in patients with *IDH2*-mutated AML or MDS.[56,100] APR-246 is a low-molecular-weight compound that reactivates mutant p53. Clinical trials of APR-246 in combination with azacitidine are ongoing (Table S15).

First-Line, Pragmatic Clinical Trials

As monotherapy, hypomethylating agents have not substantially changed the natural history of higher-risk MDS. About half of patients with higher-risk MDS have no documented benefit from treatment with hypomethylating agents,

and the outcome is dismal after treatment failure.[77] Novel drugs are now available, and some combinations with hypomethylating agents are promising (Table S15). However, because of restrictive enrollment criteria, less than 5% of patients with MDS are currently enrolled in conventional clinical trials, which are primarily designed to determine drug efficacy.[77] To define the real-world effectiveness of novel treatments and inform clinical practice, we need pragmatic trials conducted in real-life settings with broad patient groups.[101] Patients with higher-risk MDS who are ineligible for transplantation should be offered participation in these trials as part of collaborative research projects involving both referral centers and community practices.[77]

Supportive Care

In older patients with MDS, geriatric assessment frequently shows clinically significant coexisting conditions, frailty, or both, which are independently associated with poor survival.[74] The choice of a treatment that might provide a small survival benefit but with the risk of serious complications should be evaluated in a shared decision-making process. Relying on supportive care with red-cell transfusions and antimicrobial drugs may be a wise decision in these cases.

CONCLUSIONS

Although our understanding of the pathophysiology of MDS has improved remarkably in recent years, therapeutic advances overall have been limited so far. Improving the efficacy and safety of allogeneic transplantation would allow many more patients to be cured. However, the major effort should be directed at developing more effective treatments for the many patients who are ineligible for transplantation. Integration of a large international collaboration of clinical and research data into an ontology-based, mechanistic classification of MDS would be a starting point.[102] The hope is that combining this dynamic representation of the disease with pragmatic clinical trials in real-life settings will lead to substantial improvements in the management of MDS.

Disclosure forms provided by the author are available with the full text of this article at NEJM.org.

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