Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet

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Within the myelodysplastic syndrome (MDS) work package of the European LeukemiaNet, an Expert Panel was selected according to the framework elements of the National Institutes of Health Consensus Development Program. A systematic review of the literature was performed that included indexed original papers, indexed reviews and educational papers, and abstracts of conference proceedings. Guidelines were developed on the basis of a list of patient- and therapy-oriented questions, and recommendations were formulated and ranked according to the supporting level of evidence. MDSs should be classified according to the 2008 World Health Organization criteria. An accurate risk assessment requires the evaluation of not only disease-related factors but also of those related to extrahematologic comorbidity. The assessment of individual risk enables the identification of fit patients with a poor prognosis who are candidates for up-front intensive treatments, primarily allogeneic stem cell transplantation. A high proportion of MDS patients are not eligible for potentially curative treatment because of advanced age and/or clinically relevant comorbidities and poor performance status. In these patients, the therapeutic intervention is aimed at preventing cytopenia-related morbidity and preserving quality of life. A number of new agents are being developed for which the available evidence is not sufficient to recommend routine use. The inclusion of patients into prospective clinical trials is strongly recommended. (*Blood*. 2013;122(17):2943-2964)

Introduction

Myelodysplastic syndromes (MDSs) are a group of myeloid neoplasms characterized by peripheral blood cytopenias and increased risk of leukemic evolution.[1] The incidence rate of these conditions is about 5 cases per 100 000 persons per year in the general population, but increases to 20 to 50 cases per 100 000 persons per year after age 60 years.[2-7] This means that approximately 25 000 new cases are expected in Europe each year. Moreover, considering the progressive aging of the population in Europe, the number of MDS patients is destined to increase in the next decades. Altogether, these data suggest that MDS will be one of the most challenging issues for hematologists and health care providers in the near future.

Since MDSs range from indolent conditions with a long natural history to subtypes analogous to acute myeloid leukemia (AML), clinical decision-making concerning treatment modalities and timing of interventions is problematic.[8-10] In addition, data regarding the safety and efficacy of various therapeutic options are often based on uncontrolled phase 2 clinical trials, which can provide insufficient evidence to support the most appropriate management strategy.[11]

The European Leukemia Network (European LeukemiaNet) has therefore promoted a program aimed at developing and continuously updating evidence- and consensus-based guidelines that provide clinical practice recommendations for standardized diagnostic and prognostic procedures and for choosing appropriate therapeutic interventions for adult patients with primary MDS. A similar program has been promoted by the US National Comprehensive Cancer Network (NCCN), and an update of the NCCN guidelines for management of MDS has recently been published.[12]

Design and methods

Within the MDS work package of the European LeukemiaNet, an Expert Panel was selected according to the framework elements of the National Institutes of Health Consensus Development Program; it comprised physicians with specific areas of expertise who are experienced in MDSs and active in both care of patients and clinical research. During the first panel meeting,

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the Expert Panel agreed on the goal of the project: to provide clinical practice recommendations that can support the diagnosis and the appropriate choice of therapeutic interventions in adult patients with primary MDS.

Systematic review of the literature and synthesis of evidence

A systematic review of the literature was performed that included indexed original papers, indexed reviews and educational papers, and abstracts of conference proceedings. The PubMed search for indexed papers and reviews was limited to English-language articles published between 1985 and 2012 that included 10 patients or more. The proceedings of the American Society of Hematology, the European Hematology Association, the International Symposium on Myelodysplastic Syndromes, and the American Society of Clinical Oncology were searched.

The level of evidence was rated according to the Revised Grading System for Recommendations in Evidence-Based Guidelines of the Scottish Intercollegiate Guidelines Network Grading Review Group.[13] Briefly, meta-analyses and systematic reviews of randomized clinical trials (RCTs) or RCTs were graded 1, systematic reviews of case-control or cohort studies were graded 2, nonanalytic studies (eg, case reports, case series) were graded 3, and expert opinion was graded 4.

Consensus phase

The guidelines were developed on the basis of a list of patient- and therapy-oriented questions. A list of key clinical questions was drawn up based on the major issues that emerged from the first panel meeting, pointing to the appropriate diagnostic procedures and the possible and recommendable strategies within each therapeutic category, to the possible and optimal patient subgroups, and to the risks deriving from the therapy. The Expert Panel was invited to formulate evidence-based statements for each clinical question in an independent manner. Three consensus conferences were held to reach a definite consensus.[14,15] Recommendations were formulated and ranked according to the supporting level of evidence. The level of recommendation was graded according to the criteria of the Scottish Intercollegiate Guidelines Network Grading Review Group.[13] A recommendation was rated as A when it was based on at least one meta-analysis, systematic review, or RCT directly applicable to the target population and demonstrating overall consistency of results; B, when it was based on a body of evidence that included systematic reviews of case-control or cohort studies or case-control or cohort studies directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from meta-analysis, systematic review, or RCT; C, when it was based on extrapolated evidence from studies rated as systematic reviews of case-control or cohort studies; and D, when it was based on evidence level 3 or 4.

Diagnostic procedures

The diagnostic criteria aim to distinguish MDSs from reactive causes of cytopenia and dysplasia as well as from other clonal stem cell disorders.[1] The approach to the diagnosis of MDS should begin with the exclusion of nonmalignant causes of cytopenias. Complete information should be collected on prior chemotherapy, irradiation, radioimmunotherapy, radioiodine, and occupational or hobby exposure (especially to benzene).[16-19] Information should also be gathered on concomitant medications, alcohol intake, smoking, tendency to bleeding/bruising, and infection. Especially in young patients, collection of family history should focus on conditions suggestive of inherited bone marrow failure disorders, such as Fanconi anemia and telomere disorders.[20-24] A complete physical examination that includes spleen size should follow. Blood tests of value in the diagnostic workup of suspected MDSs are summarized in Table 1.

Once nonmalignant causes of cytopenia have been excluded, the diagnostic approach to suspected MDSs includes morphologic studies of peripheral blood and bone marrow to evaluate abnormalities of peripheral blood cells and hematopoietic precursors; bone marrow biopsy to assess marrow cellularity, fibrosis, and topography; cytogenetics to identify nonrandom chromosomal abnormalities. It is recommended that all newly diagnosed patients are evaluated at a center with specific hematologic competence, thus providing a comprehensive diagnostic approach.

Repeated bone marrow examinations a few weeks, months, or even years apart are sometimes required to establish the diagnosis and to identify patients with rapid disease progression. The diagnosis of MDS may be difficult in patients with a normal karyotype or noninformative cytogenetics who do not have robust morphologic markers such as ring sideroblasts or excess of myeloblasts. If only unilineage dysplasia is present in the bone marrow, there is no increase in blasts in the peripheral blood or bone marrow, ring sideroblasts represent less than 15% of the erythroid precursors, and none of the recurrent cytogenetic abnormalities is present, then an observation period of 6 months and repeat bone marrow investigation are recommended prior to making the diagnosis of MDS. Such patients usually present with mild cytopenia only, and a rapid disease progression is unlikely.

Table 1. Blood tests of value in the diagnostic workup of suspected MDS

General blood test category	Specific test
Hematology	• WBC count
	• WBC full differential count
	• RBC count
	• Hemoglobin
	• Platelet count
	• RBC indices (mean cell volume)
	• Reticulocyte count
	• RBC, leukocyte and platelet morphology
Biochemistry	• RBC-folate/serum-folic acid
	• Cobalamin
	• Iron
	• Total iron binding capacity
	• Ferritin
	• Lactate dehydrogenase
	• Bilirubin
	• Haptoglobin
	• Direct antiglobulin test (Coombs' test)
	• C-reactive protein
	• Alanine transaminase
	• Aspartate
	• Transaminase
	• Alkaline phosphatase
	• Albumin
	• Uric acid
	• Creatinine
	• Serum protein electrophoresis (serum immunoglobulins)
	• β_2-microglobulin
	• Thyroid function tests
	• Hemoglobin electrophoresis
Virus	• Anti-HIV
	• Anti-parvovirus B19 (hypoplastic MDS)
	• Cytomegalovirus test
	• Hepatitis B antigen and Antihepatitis C virus in transfusion-dependent patients
Other	• Paroxysmal nocturnal hemoglobinuria clone
	• Specific genetic analyses (in patients in whom a suspicion about inherited bone marrow failure has been raised)

WBC, white blood cell.

Table 2. Diagnostic approach to MDS

Diagnostic tool	Diagnostic value	Priority
Peripheral blood smear	• Evaluation of dysplasia in one or more cell lines • Enumeration of blasts	Mandatory
Bone marrow aspirate	• Evaluation of dysplasia in one or more hematopoietic cell lines • Enumeration of blasts • Enumeration of ring sideroblasts	Mandatory
Bone marrow biopsy	• Assessment of cellularity, $CD34^+$ cells, and fibrosis	Mandatory
Cytogenetic analysis	• Detection of acquired clonal chromosomal abnormalities that can allow a conclusive diagnosis and also prognostic assessment	Mandatory
FISH	• Detection of targeted chromosomal abnormalities in interphase nuclei following repeated failure of standard G-banding	Recommended
Flow cytometry immunophenotyping*	• Detection of abnormalities in erythroid, immature myeloid, maturing granulocytes, monocytes, immature and mature lymphoid compartments	Recommended
SNP array	• Detection of chromosomal defects at a high resolution in combination with metaphase cytogenetics	Suggested
Mutation analysis of candidate genes	• Detection of somatic mutations that can allow a conclusive diagnosis and also reliable prognostic evaluation	Suggested

*Standard methods from the International Flow Cytometry Working Group of the European LeukemiaNet are recommended (see supplemental Table 1).

Major efforts have been made to identify novel diagnostic tools that may make the diagnosis of MDS more accurate. These include flow cytometry immunophenotyping[25-29] and screening for recurrent molecular defects by using genome-wide and massive parallel genotyping technology.[30-38] Investigations of value in the diagnostic approach to MDS and their grade of recommendation are reported in Table 2.

Morphology

The assessment of dysplasia on peripheral blood and bone marrow smears is the mainstay for the diagnosis of MDS. For evaluation of morphology and dysplasia in blood and bone marrow, the World Health Organization (WHO) 2008 classification of myeloid neoplasms is recommended.[1]

Blood and marrow smears should be morphologically examined by using May-Grünwald-Giemsa and iron staining. Counting at least 200 cells in blood smears and 500 cells in bone marrow smears, including at least 100 erythroblasts and 30 megakaryocytes, is recommended. To qualify as significant, the recommended requisite percentage of bone marrow dysplastic cells is $\geq$10% of the nucleated cells in the lineage under consideration. The characteristics of peripheral blood and bone marrow dysplasia are summarized in Table 3.[39-41]

The enumeration of blasts is of critical importance for an accurate classification of MDS. According to recently established consensus criteria, myeloblasts are defined on the basis of several nuclear and cytoplasmic characteristics, including high nuclear/cytoplasmic ratio, easily visible nucleoli, fine nuclear chromatin, and variable cytoplasmic basophilia; there may or may not be granules or Auer rods but no Golgi zone is detected. Myeloblasts in MDS should be classified as agranular or granular (irrespective of the number of granules).[40,41]

Evaluation of bone marrow smears must include iron staining (Prussian blue reaction) to evaluate the presence and number of ring sideroblasts. Ring sideroblasts should be defined by using recently established consensus criteria as erythroblasts in which there are a minimum of five siderotic granules covering at least one third of the nuclear circumference.[40]

Bone marrow biopsy

A trephine biopsy should be performed in all cases of suspected MDS in which bone marrow examination is indicated. Bone marrow biopsy may aid the exclusion of other clinical conditions presenting with cytopenia and provide information on marrow cellularity, megakaryocyte component, blast compartment, bone marrow fibrosis, and the presence of nonhematologic cells, such as metastases. Staining should include hematoxylin-eosin or equivalent, Giemsa, immunostaining for myeloperoxidase, glycophorin A or C, CD34, CD117, megakaryocytes (CD61 or CD42b), monocytic cells (KP1/CD68, PGM1/CD68R), CD20 (B lineage), CD3 (T lineage), and Gomori's silver impregnation for bone marrow fibrosis.

The bone marrow in MDS is usually hyper- or normocellular, but in a minority of patients (approximately 10%), the bone marrow is hypocellular (hypoplastic MDS).[42-44] This group needs to be distinguished from both aplastic anemia and hypocellular AML. The separation between these entities can be problematic because morphologic differences may be subtle. An increase in the percentage of bone marrow $CD34^+$ cells, the presence of any ring sideroblasts, and dysplasia of either granulocytes or megakaryocytes have been shown to be useful in distinguishing hypoplastic MDS from cases of aplastic anemia.[45] Trephine biopsy may also complement cytologic analysis

Table 3. Characteristics of peripheral blood and bone marrow dysplasia

Cell lineage		
Erythroid	**Myeloid**	**Megakaryocytic**
Peripheral blood		
Anisocytosis	Granulocyte nuclear hypolobation (pseudo Pelger-Huet)	Platelet anisocytosis
Poikilocytosis	Granulocyte cytoplasmic hypogranulation/degranulation	Giant platelets
Basophilic stippling	Blasts	
Bone marrow		
Binuclearity	Bizarre nuclear shapes	Large monolobular forms
Internuclear bridging	Nuclear hypolobation (pseudo Pelger-Huet)	Small binucleated elements
Irregular nuclear edges	Nuclear hypersegmentation	Dispersed nuclei
Megaloblastoid changes	Pseudo Chediak-Higashi granules	Micromegakaryocytes
Ring sideroblasts	Cytoplasmic hypogranulation / degranulation	Degranulation
Cytoplasmic inclusions	Anisocytosis	
Cytoplasmic bridging		
Incomplete hemoglobinization		
Fringed cytoplasm		
Vacuolization		

by providing useful information on megakaryocytic dysplasia, which may be more readily evaluated on bone marrow sections than on smears.

In 10% to 20% of MDS patients, there is a moderate to severe bone marrow fibrosis (ie, grade 2 or 3, according to the European consensus on grading bone marrow fibrosis). MDS with bone marrow fibrosis identifies a distinct subgroup of MDSs with multilineage dysplasia and high transfusion requirement.[46,47] These cases need to be differentiated from other myeloid neoplasms with bone marrow fibrosis, such as chronic myelomonocytic leukemia, primary myelofibrosis, acute megakaryoblastic leukemia, and acute panmyelosis with myelofibrosis. The most recent and most used grading system of bone marrow fibrosis is the European Myelofibrosis Network (EUMNET) consensus.[48]

Immunohistochemistry with anti-CD34 allows the identification and enumeration of $CD34^+$ blast cells. This is particularly useful in the case of an aspirate of suboptimal quality because of bone marrow fibrosis or hypocellularity. However, it should be noted that the WHO classification of MDS is derived only from blast proportion enumerated in bone marrow aspirates and cannot be extrapolated precisely to $CD34^+$ percentage in trephine biopsies.

Flow cytometry immunophenotyping

The diagnosis of MDS is severely hampered by the poor reproducibility of morphologic analysis of dysplasia and the lack of specificity of dysplastic changes, which make the differentiation between MDS and other nonclonal conditions difficult.[49,50]

Flow cytometry immunophenotyping is able to identify specific aberrations in both the immature and mature compartments among different bone marrow hematopoietic cell lineages.[25] Although no single immunophenotypic parameter has been proven to be diagnostic of MDS, combinations of such parameters into scoring systems have been shown to discriminate MDSs from other cytopenias with high sensitivity and acceptable specificity.[26-29,51]

Flow cytometry was proven to be highly sensitive in identifying patients likely to be suffering from a clonal disease process (ie, an MDS lacking specific diagnostic markers such as excess blasts, ring sideroblasts or karyotypic aberrations) rather than cytopenia of undetermined significance, which includes cases of sustained cytopenias in one or more lineages that do not meet the minimal criteria for MDS and cannot be explained by any other hematologic or nonhematologic disease.[52] In addition, flow cytometry is useful for distinguishing refractory anemia from refractory cytopenia with multilineage dysplasia by identifying immunophenotypic abnormalities in myeloid and monocytic compartments.[29]

Although further prospective validation of markers and immunophenotypic patterns against control patients with secondary dysplasia and further standardization in multicenter studies are required, at present, flow cytometry abnormalities involving one or more of the myeloid lineages can be considered as suggestive of MDS.

Standard methods for cell sampling, handling, and processing, and minimal combinations of antibodies for flow cytometry analysis of dysplasia in MDS have recently been established by the International Flow Cytometry Working Group within the European LeukemiaNet (supplemental Table 1 available on the *Blood* Web site).[53,54]

The integration of flow cytometry immunophenotyping following these standards is recommended in the workup of patients with suspected MDS, although the Expert Panel realizes that the implementation of these guidelines may not be immediately feasible in some hematologic centers.

Table 4. Recurrent chromosomal abnormalities that provide presumptive evidence of primary MDS

Abnormality	Frequency (%)*
−5 or del(5q)	10-15
−7 or del(7q)	10
i(17q) or t(17p)	2-3
del(12p) or t(12p)	1-2
del(11q)	1-2
−13 or del(13q)	1-2
del(9q)	1
idic(X)(q13)	1
inv(3)(q21q26.2)	1
t(6;9)(p23;q34)	1
t(3;21)(q26.2;q22.1)	<1
t(1;3)(p36.3;q21.2)	<1
t(11;16)(q23;p13.3)	<1
t(2;11)(p21;q23)	<1

*Frequencies reported in the table were extrapolated from Sole et al,[55] Haase et al,[56] and Schanz et al.[58]

Cytogenetics

Cytogenetic analysis has a major role in determining clonality in patients with suspected MDS. Chromosomal abnormalities are observed in 50% to 60% of patients with MDS; the most frequent single cytogenetic abnormalities include del(5q), monosomy 7 or del(7q), trisomy 8, and del(20q).[55-58]

A cytogenetic analysis of bone marrow aspirate should be performed in all patients with suspected MDS in whom bone marrow examination is indicated, and at least 20 metaphases should be analyzed whenever possible and described according to International System for Human Cytogenetic Nomenclature (ISCN) recommendations.[59]

According to the WHO 2008 criteria, selected recurrent abnormalities are recognized as presumptive evidence of MDS, even in the absence of definitive morphologic features (ie, unequivocal dysplasia in less than 10% of the cells in one or more myeloid lineage) (Table 4).[1] These cases are now included in the "MDS unclassified" category.

In the case of repeated failure of standard G-banding (absent or poor-quality metaphases), fluorescence in situ hybridization (FISH) may complement conventional cytogenetic analysis. In addition, this technique may be useful for clarifying complex aberrations and can detect abnormalities in up to 15% of karyotypically normal MDS patients.[60-62] However, even though FISH is very sensitive, it can be applied only in a targeted way. Hence, a comprehensive screening for chromosomal aberrations cannot be carried out using this technique.

Although the established prognostic scoring systems are based on conventional cytogenetics, some studies showed that chromosomal abnormalities detected by FISH may provide prognostic information[60,61] and may be useful for supporting clinical decision-making in selected cases, such as those with del(5q) or with del(7q) or monosomy 7.

According to the available evidence, the use of FISH to detect targeted chromosomal abnormalities in interphase nuclei is recommended in the case of repeated failure of standard G-banding.

Molecular genetics

Recent developments in microarray technologies have allowed the application of single nucleotide polymorphisms (SNPs) for high-resolution genome-wide genotyping. SNP array-based karyotyping has been applied in a range of studies in patients with various hematologic malignancies and is emerging as an important tool in the

Table 5. Recurrently mutated genes in MDS*

Gene	Frequency (%)	Reference
SF3B1	25-30	36, 38
TET2	20-25	32, 33
RUNX1	10-20	70, 71
ASXL1	10-15	34, 66
SRSF2	10-15	36, 72
TP53	5-10	34, 73
U2AF1	5-10	36, 69
NRAS/KRAS	5-10	71, 74
DNMT3A	5	75, 76
ZRSR2	5	36, 72
EZH2	5	64, 77
IDH1, IDH2	2-3	34, 78
ETV6	2	34
CBL	1-2	34, 63
NPM1	1-2	34, 71
JAK2	1-2	34, 79
SETBP1	1-2	80, 81
SF3A1	1-2	36
SF1	1-2	36
U2AF65	1-2	36
PRPF40B	1-2	36

*Frequencies should be considered only as indicative, since many studies included not only patients with MDS but also patients with other types of myeloid neoplasms.

identification of chromosomal defects that are not detected by standard cytogenetics, suggesting its potential clinical usefulness.[30,31,35]

In a recent study, the combination of metaphase cytogenetics and SNP array karyotyping led to a higher diagnostic yield of chromosomal defects compared with that picked up with metaphase cytogenetics alone, often through detection of novel lesions in patients with normal or noninformative standard cytogenetic results.[35] The concurrent use of SNP array and metaphase cytogenetics in the initial karyotypic analysis of patients with MDS is therefore expected to provide clinically useful diagnostic information that cannot be obtained by the traditional technologies currently in use.

Acquired somatic mutations have been detected in several genes, including *TET2, ASXL1, DNMT3A, CBL, ETV6, EZH2, IDH1, IDH2, KRAS, NPM1, NRAS, RUNX1,* and *TP53*.[32-34,63-68] Recently, mutations in genes encoding for spliceosome components were identified in a high proportion of patients with MDS either with (85%) or without (44%) ring sideroblasts. These genes include *SF3B1, SRSF2, U2AF1,* and *ZRSR2,* and with a lower frequency, *SF3A1, SF1, U2AF65,* and *PRPF40B*.[36-38,69] Table 5 provides a list of recurrently mutated genes in MDS.

Most of these mutated genes can be detected in different myeloid neoplasms and are not specific for MDS, but they may be a valuable means of obtaining evidence of a clonal disorder in patients with suspected MDS. In a comprehensive report, 52% of patients with normal cytogenetics had at least one genomic point mutation.[34] In a more recent study, 74% of patients had at least one oncogenic point mutation or MDS-related copy number change detectable by sequencing.[68] When sequencing and cytogenetics were combined, the fraction of patients with MDS-related oncogenic lesions increased to 78%. Recent studies in chronic myelomonocytic leukemia found diverse mutations in more than 80% of patients.[82]

Although screening for such molecular defects on a routine basis cannot currently be recommended, the spread of massive genotyping technology will soon make it possible for clinicians to detect a broad range of genetic aberrations in peripheral blood at a reasonable cost, making it easier to confirm the diagnosis in patients with suspected MDS.

Classification

MDS should be classified according to the WHO criteria, as revised in 2008.[1] This classification is a useful instrument for defining the different subtypes of MDS and also provides clinicians with prognostic information (supplemental Table 2). Numerous studies have documented the clinical utility of the French-American-British (FAB) classification of MDS,[39] but published data provided a convincing base of evidence to refine the definition of disease subtypes.[83-85] These principles were first incorporated into the 2001 WHO classification of myeloid neoplasms.[86] The most important difference between the WHO and FAB classifications was the lowering of the blast threshold for the diagnosis of AML from 30% to 20% blasts in the blood or bone marrow. Although a clear cutoff of bone marrow blasts to discriminate between MDS and AML cannot be easily defined, several studies suggest that patients with 20% to 29% blasts often have clinical features, including response to therapy and survival times, similar to patients with 30% or more blasts.[86] According to WHO proposal, these cases are classified as AML with multilineage dysplasia, a category that includes patients with a prior history of MDS as well as patients who present initially with AML and dysplasia in multiple marrow cell lineages. It must be emphasized, however, that therapeutic decisions for patients with 20% to 29% blasts should be based not only on the percentage of blasts but also on clinical features, rate of disease progression, and genetic data. In fact, some patients with prior MDS and 20% to 29% bone marrow blasts may behave clinically in a manner more similar to MDS than to AML.[87]

Other relevant changes included the introduction of a new category of refractory cytopenia with multilineage dysplasia (RCMD) to identify cases of dysplasia involving 2 or 3 marrow cell lineages. Two subtypes of refractory anemia with excess blasts (RAEB) were also recognized. The WHO classification also recognized MDS associated with isolated del(5q) as a distinct entity. Finally, chronic myelomonocytic leukemia (CMML) was included in a newly created disease category of myelodysplastic/myeloproliferative neoplasms.

This WHO classification was further refined in 2008.[88] This revised classification allowed a more precise subclassification of patients with unilineage dysplasia. In fact, a category of refractory cytopenia with unilineage dysplasia has been introduced, including the entities of refractory anemia, refractory neutropenia, and refractory thrombocytopenia. The two categories of refractory cytopenia with multilineage dysplasia defined in the 2001 WHO classification (ie, RCMD and RCMD-RS) are now recognized as a single unified category; however, the presence of ring sideroblasts is relevant to molecular findings and to response to therapy and should therefore always be reported. The revised classification also refined the criteria for RAEB 1 (RAEB-1) to include patients with 2% to 4% blasts in the peripheral blood, even if the percentage in the bone marrow is less than 5%. Patients with 5% to 19% peripheral blood blasts or 10% to 19% blasts in the bone marrow are classified as having RAEB-2.

Risk assessment

MDSs are an extremely heterogeneous group of disorders, ranging from indolent conditions with a near-normal life expectancy to forms approaching AML. A risk-adapted treatment strategy is mandatory for conditions showing such a highly variable clinical course. Prognostic factors may be subdivided into those related to the patient's

characteristics and general health condition and those related to the characteristics of the MDS clone.

Disease-related factors

The definition of risk related to the characteristics of MDS is based on the use of prognostic scoring systems combining multiple clinical and hematologic variables.[89-91] In 1997, on behalf of the International Myelodysplasia Risk Analysis Workshop (IMRAW), Greenberg et al[85] developed the International Prognostic Scoring System (IPSS) based on bone marrow blasts, cytogenetic abnormalities, and number of cytopenias (supplemental Table 3). The IPSS proved to be useful for predicting survival and risk of leukemic evolution in patients with MDS and has been the reference for clinical decision-making as well as for the design and analysis of clinical trials in these disorders.

Additional factors were recently found to be of additive prognostic value to the IPSS, including multilineage dysplasia, severe anemia/transfusion dependency, and bone marrow fibrosis.[46,47,92-97] These variables were integrated into a WHO classification-based prognostic scoring system (WPSS), which is able to classify patients into 5 risk groups with different survivals and probabilities of leukemic evolution (supplemental Table 4).[98,99] This scoring system has been validated in different populations of MDS patients and was recently incorporated in evidence- and consensus-based therapeutic guidelines.[12] Accounting for multilineage dysplasia, severe anemia or transfusion dependency, and bone marrow fibrosis within the WPSS categorization enables more accurate definition of the prognosis of individual patients with MDS, in particular those in low or intermediate-1 IPSS risk groups.[100]

A risk model for patients with primary or secondary MDS and CMML that refines the prognostic precision of the IPSS was defined to include both disease- and patient-related variables (performance status, age, platelet count, hemoglobin, bone marrow blasts, white blood cell count, and karyotype). The prognostic model divided patients into 4 prognostic groups with significantly different outcomes irrespective of previous treatments.[97]

More recently, the International Working Group for Prognosis in MDS revised the IPSS on the basis of a large multicenter cohort of untreated patients with MDS.[101] On the basis of a large data set that allowed the prognostic value of even less frequent karyotypic abnormalities to be estimated, 5 cytogenetic risk groups were determined representing the basis for the revised prognostic scoring system (IPSS-R), together with refined categories for bone marrow blasts and peripheral blood cytopenias (supplemental Table 5).[101]

Although additional prognostic factors have been identified and new prognostic scoring systems have been shown to further improve the stratification of MDS patients, the scientific evidence on the efficacy and safety of the currently available therapeutic agents is derived from clinical studies adopting the IPSS score as the reference score for including patients and analyzing results. As a consequence, evidence-based therapeutic recommendations refer to patients stratified according to IPSS. Therefore, it is recommended that all patients with MDS should be risk stratified according to the IPSS. In addition, prospective registries and clinical studies should also include stratification according to the WPSS and the IPSS-R.

Prognostic relevance of flow cytometry. Flow cytometry immunophenotyping may provide prognostic information. The combination of multiple flow cytometric abnormalities into numerical scores was shown to be of additive value to reference prognostic scoring systems. Although this approach cannot be recommended on a routine basis, flow cytometry immunophenotyping can be useful for identifying subsets of patients with a distinct clinical course and response to treatment.[26,29,102,103]

Prognostic relevance of somatic mutations. Mutations in several genes have been reported to influence overall survival and risk of disease progression.[34,38] The available evidence suggests that the integration of somatic mutations into prognostic scoring systems may provide more accurate risk stratification of individual patients and further refine clinical decision-making in MDS.[34,67] The spread of massive genotyping methods will soon make it possible for clinicians to detect a broad range of point mutations. As underscored above, although the screening of such molecular defects cannot be recommended on a routine basis at present, it is likely to become accessible in the near future and to result in a major improvement in prognostic stratification and monitoring of response to treatment.

Patient-related factors

Different factors related to individual general health status may affect clinical outcome and decision-making in patients with cancer. These include age, functional ability (performance status), comorbidity, physical reserves (frailty), nutritional status, and cognition.

Increasing age is an independent adverse prognostic factor in MDS,[90,104] and age-adjusted estimates of survival probability have been provided in various prognostic scoring systems.[85,101] However, chronological age may be distinct from biological or functional age, and additional factors should be considered when evaluating the eligibility of patients to disease-modifying treatments.

Many scales for the measurement of individual functional ability (performance status) were tested in patients with hematologic malignancy, including MDS, and used as a selection criterion to enter clinical trials.[105,106] However, these functional assessment scores provide only small amounts of information pertinent to the management of elderly patients. A high prevalence of comorbid diseases has been reported in patients with MDS.[107-109] One or more comorbidities were found in more than half the patients at the time of diagnosis, and they had a significant impact on survival.[110] Heart disease was the most frequent comorbidity, and a significantly higher prevalence of cardiac complications was reported in patients with severe anemia and red cell transfusion dependency.[108,111]

Problems related to the presence of comorbid conditions appear to be different in low- and high-risk patients with MDS. In low-risk patients, comorbidity affects the prognosis by directly increasing the risk of non-leukemic death. Conversely, in high-risk patients, the clinical relevance of mild or moderate comorbidity is overcome by the severity of the MDS. In these patients, however, comorbidity influences the outcome by reducing eligibility for and tolerance of treatments.[110]

Sorror et al[112] found that comorbidity predicts posttransplantation outcome, and they developed the Hematopoietic Cell Transplantation Comorbidity Index as an instrument that captures pretransplantation comorbidities and can be used in predicting posttransplantation outcomes and stratifying patients with MDS and AML. Several comorbidity scores have been tested in the general MDS patient population. These include general measures, such as the Charlson comorbidity index or the Adult Comorbidity Evaluation-27,[107,109,113] and disease-specific measures, such as the MDS-Specific Comorbidity Index.[111]

The prognostic relevance of comorbidity may have important implications in the management of patients with MDS, and accounting for both disease- and patient-related factors considerably improves risk stratification according to disease-related criteria, particularly in the lower-risk groups.

Monitoring patients and criteria for response to treatment

Patients should undergo regular follow-up including blood tests. If a patient is considered to be a candidate for therapeutic intervention at disease progression or in case of a planned therapeutic intervention or clinical study, regular clinical visits including repeated bone marrow evaluations with cytogenetic analysis are mandatory. The frequency of these visits depends on the disease risk and the therapeutic choice and should be relatively frequent if allogeneic stem cell transplantation (SCT) is an option.

The heterogeneity of MDS complicates the evaluation of response to treatment. Standardized response criteria are essential to evaluate outcome of therapy, to refine treatment according to patient- and disease-related characteristics, and to enable comparisons among clinical trials. Standardized response criteria in MDS were defined by the International Working Group (IWG) in 2000[114] and revised in 2006.[115] The IWG criteria define different aspects of responses on the basis of treatment goals: complete or partial remission and cytogenetic response for treatments altering the natural history of the disease, hematologic improvement, and quality of life (QOL) (supplemental Table 6). The adoption of these criteria is recommended for both clinical management and the design of clinical trials.

Measurements of QOL in MDSs are increasingly used in the clinical management of patients and included as end points in treatment trials. Several instruments have been used to measure QOL,[116] including the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30)[117-120] and the Functional Assessment of Cancer Therapy (FACT) questionnaire.[121-124] Although no specific instrument can be recommended at this stage, the implementation in clinical practice of a rigorous assessment of patient-reported outcomes is strongly encouraged.

Therapeutic options

Watchful-waiting strategy

Evidence supporting the appropriateness of a watchful-waiting strategy is drawn from retrospective studies, including observational studies and decision analyses. In a retrospective study of a large, single-center cohort of MDS patients, standardized mortality rates were used in an analysis of mortality rates of MDS patients classified into WHO subgroups, demonstrating that life expectancy of patients age 70 years or older with refractory anemias or MDS with isolated del(5q) was not significantly shorter than that of the general population.[93] More recently, a survival analysis using a Cox regression model with time-dependent covariates showed that as long as their disease remains stable, patients with a very low WPSS risk have a mortality not significantly different from that of the general population.[98]

A clinical decision analysis from the International Bone Marrow Transplant Registry (IBMTR) examining 3 strategies for patients with newly diagnosed MDS and deemed suitable for myeloablative allogeneic SCT from HLA-identical sibling donors (transplantation at diagnosis, transplantation at leukemic progression, and transplantation at an interval from diagnosis but prior to leukemic progression) showed that delayed allogeneic SCT is associated with maximal life expectancy for MDS patients with low- or intermediate-1 IPSS risk.[125]

Adult patients with primary MDS, low IPSS risk, and asymptomatic cytopenia do not need any treatment and should be followed regularly (recommendation level D). In addition, patients with intermediate-1 IPSS risk, asymptomatic cytopenia, no blast excess, and no poor-risk cytogenetic abnormality may be followed without specific treatment (recommendation level D). This watchful-waiting strategy might change in the future if safe treatments capable of modifying the natural history of the disease are developed. It must be emphasized that patients should understand that the safety of the watchful-waiting approach is dependent upon regular monitoring. The goals of such follow-up include the early recognition of worsening cytopenia, increasing number of circulating or bone marrow blasts, and karyotypic evolution.

HLA typing

HLA typing a patient and his or her siblings provides information for the option of an allogeneic SCT from a matched family donor. Knowing that there is a fully compatible donor informs the option for a potentially curative procedure to be performed whenever indicated. Patients with MDS and IPSS intermediate-1, intermediate-2, or high risk who are eligible for allogeneic SCT should be HLA typed (recommendation level D).

Allogeneic SCT

Recommendations on allogeneic SCT in patients with MDS derive from prospective randomized and nonrandomized trials, as well as cohort studies.[126-133] In a series of 387 adult patients with MDS and IPSS low, intermediate-1, intermediate-2, or high risk who underwent an allogeneic SCT from an HLA-identical sibling, cumulative incidences of transplant-related mortality were 32% at 1 year and 37% at 3 years, with cumulative incidences of relapse of 17% at 1 year and 23% at 3 years, resulting in disease-free survival rates in the entire cohort of 53% at 1 year and 40% at 3 years. Disease stage was a significant factor affecting the outcome after transplantation. Bone marrow blasts and IPSS risk showed an inverse correlation with relapse-free survival after transplantation, with a disease-free survival rate at 5 years of 60% in patients with low or intermediate-1 risk, 36% to 44% in those with intermediate-2 risk, and 28% to 30% in high-risk patients.[130]

Prospective comparisons of different transplantation timing strategies are not available in the literature. The optimal timing of HLA-matched allogeneic SCT for MDS was investigated in a previously mentioned clinical decision analysis from the IBMTR.[125] A Markov model was constructed to examine 3 alternative transplantation strategies for newly diagnosed MDS. The study concluded that life expectancy of patients with low or intermediate-1 IPSS risk at diagnosis was higher when transplantation was delayed but performed before the progression to AML, whereas for intermediate-2- and high-risk disease, immediate transplantation was associated with maximal life expectancy. However, several potential sources of bias were acknowledged in this analysis, including potential patient selection and unavailability of longitudinal clinical data.

Age at transplantation was identified as one of the most important prognostic factors: the older the age, the shorter the overall and disease-free survival.[130,134] In a retrospective analysis for the European Group for Blood and Marrow Transplantation (EBMT) group that included all MDS subtypes, transplant-related mortality rates were 30%, 43%, and 50% in patients younger than age 20, between 20 and 40, and older than 40 years, respectively.[134] Comparable results were reported by the above-mentioned study from the IBMTR.[130] Not at odds with this evidence, recent data

suggest that allogeneic SCT is feasible in carefully selected patients older than 60 years of age, with acceptable morbidity and mortality.[133,135,136] SCT for patients between 60 and 70 years of age is becoming more common, and a definite age cutoff cannot be identified.

Allogeneic SCT from matched unrelated donor has been associated with a high transplant-related mortality compared with transplantation from an HLA-identical sibling.[126,134,137] However, in recent years, high-resolution donor-recipient HLA matching has significantly improved the outcome of this procedure.[138] In a prospective study from the French Society of Bone Marrow Transplantation and Cell Therapy comparing the outcome of allogeneic marrow SCT from HLA-identical siblings vs HLA-allelic matched unrelated donors (10/10) in patients with standard-risk hematologic malignancy including MDS, the effect of donor type was not significant.[139] In accordance with these data, retrospective studies from the EBMT evaluating long-term outcome after allogeneic SCT from matched sibling and unrelated donors did not find significant difference between the two groups.[133,140]

Disease risk scored according to the IPSS, age, and presence of comorbidity graded according to the Hematopoietic Cell Transplantation Comorbidity Index were recognized as the most relevant clinical variables to be considered in order to judge a patient eligible for allogeneic SCT. The decision to perform an allogeneic SCT should be shared as much as possible with the patient, whose attitude to risk should be taken into account. Fit patients up to age 65 to 70 years with IPSS intermediate-2 or high risk and those with IPSS intermediate-1 risk with excess blasts or poor-risk cytogenetics are candidates for allogeneic SCT (recommendation level B).

Remission induction therapy before allogeneic SCT. Evidence on remission induction chemotherapy before allogeneic SCT has been derived from prospective, nonrandomized, or retrospective clinical trials. Large retrospective multicenter studies demonstrated that the percentage of bone marrow blasts at the time of transplantation significantly affects the outcome.[129,130] However, the retrospective design of these studies introduces the potential for bias due to patient selection during induction therapy. In fact, a treatment-related mortality up to 16% has been reported in patients mainly with intermediate-2 or high IPSS risk MDS who are eligible for allogeneic SCT and are receiving remission induction chemotherapy.[127]

On the basis of the available evidence, intensive chemotherapy should be administered to those patients with 10% or more bone marrow blasts who are candidates for allogeneic SCT within a clinical trial or a prospective registry (recommendation level D).

The use of hypomethylating agents to prepare MDS patients with an excess of marrow blasts for allogeneic SCT has been reported in retrospective studies[141,142] and is being tested in clinical trials. The evidence available so far does not allow recommendation on the use of hypomethylating agents for this purpose outside clinical trials or prospective registries (recommendation level D).

Source of hematopoietic stem cells. The source of stem cells was investigated in randomized and nonrandomized studies.[128,129,143,144] A randomized study that included 228 recipients of matched sibling allogeneic SCT for myeloid malignancies, 36 of whom were affected by either early or advanced MDS, did not show a statistically significant difference in the probability of relapse of the underlying disease between the groups transplanted with cells from the peripheral blood or bone marrow.[128] Conversely, significantly different probabilities of survival at 30 months after transplantation were noted in the groups receiving cells from the peripheral blood or bone marrow (68% and 60%, respectively; $P = .04$). Although the study was not powered for subgroup analysis, there was a trend in favor of peripheral blood recipients among the patients with MDS. In a post hoc analysis in which patients were grouped retrospectively into those with early disease (including refractory anemia with ringed sideroblasts) and those with advanced disease, the overall survival of patients with early disease was not different between the groups, whereas there was an overall survival benefit in patients with advanced disease favoring the peripheral blood group. In a large, retrospective comparison of bone marrow and granulocyte colony-stimulating factor (G-CSF)–mobilized peripheral blood progenitor cells for allogeneic SCT using HLA-identical sibling donors in 234 patients with either low- or high-risk MDS, the survival was significantly better among recipients of peripheral blood progenitor cells, except for patients with either refractory anemia or high-risk cytogenetics.[129] A prospective, randomized phase 3 trial of unrelated donor peripheral blood vs bone marrow stem cells in patients with hematologic neoplasms, including 93 patients with early or advanced MDS, showed that peripheral blood stem cells from unrelated donors were associated with significantly shorter time to neutrophil and platelet engraftment and lower incidence of graft failure, but higher rates of chronic graft-versus-host disease compared with bone marrow. Rates of acute graft-versus-host disease, relapse, nonrelapse mortality, and overall survival were similar in the two groups. No interaction was reported between disease risk and stem cell source, but results were not reported according to diagnosis.[145]

On the basis of the available evidence, peripheral blood stem cells are the preferred source of stem cells for allogeneic transplantation from an HLA-matched donor in patients with MDS (recommendation level D).

Preparative regimen for allogeneic SCT. Recommendations regarding preparative regimens for allogeneic SCT are based on prospective and retrospective studies. A study by Anderson et al[137] compared the outcomes of patients with refractory anemia undergoing allogeneic SCT according to two different preparative regimens consisting of busulfan and cyclophosphamide or cyclophosphamide and total-body irradiation and found no significant difference. Sierra et al[130] studied 452 patients undergoing HLA-identical sibling bone marrow transplantation for primary MDS (IPSS low, intermediate-1, intermediate-2, or high risk) that used diverse conditioning regimens, and found that the most commonly used preparative regimens were associated with similar outcomes.

On the basis of this evidence, no specific recommendation can be given on the best myeloablative conditioning regimen.

Several studies have investigated the use of reduced intensity conditioning (RIC) regimens in patients with MDS.[132,133,135,146-152] Martino et al[132] reported the results of a multicenter retrospective, EBMT Registry–based study on 836 patients with IPSS intermediate-1, intermediate-2, or high risk MDS undergoing transplantation from an HLA-identical sibling donor according to type of regimen—either RIC or standard myeloablative conditioning regimen. The 3-year relapse rate was significantly increased after RIC, but the nonrelapse mortality rate was decreased in the RIC group, resulting in a comparable overall survival between the two groups. Similar results were obtained in a retrospective multicenter analysis of patients with either early or advanced MDS who were age 50 years or older and who received a transplant within the context of the EBMT group.[133]

For MDS patients with a contraindication to a standard myeloablative preparative regimen due to comorbidity, RIC allogeneic SCT should be considered, preferably within a clinical trial (recommendation level D).

Remission induction chemotherapy

The evidence regarding remission induction chemotherapy in patients with MDS has been acquired from prospective randomized and nonrandomized trials, as well as retrospective studies. Randomized controlled trials included comparisons of high-dose vs low-dose chemotherapy; different types of induction, consolidation, and maintenance schemes; administration of G-CSF, interleukin-11, or interleukin-2; and multidrug resistance modulators.[153-162]

For induction regimens, standard doses of cytosine arabinoside (ara-C), defined as 100 to 200 mg/m^2 every 12 to 24 hours for 5 to 10 days, were combined with anthracyclines (idarubicin, daunorubicin, mitoxantrone),[127,131,154,163] nucleoside analogs (fludarabine),[160,164-166] or topoisomerase inhibitors (topotecan, etoposide).[127,131,154,167,168] The rates of complete remissions ranged from 24% to 79%, and the relapse rate ranged from 33% to 91%. The treatment-related mortality rate ranged from 2% to 42%. Various treatment schedules based on intermediate or high doses of ara-C were also reported, either alone or in association with fludarabine, anthracyclines, or topotecan.[157,159,169-172] The complete remission rate ranged from 34% to 80%, with a treatment-related mortality ranging from 0% to 36%. Cumulative probability of survival estimated at 4 or 5 years in patients treated with intensive chemotherapy ranged between 8% and 33%.[168,173] Younger age, good performance status, and favorable cytogenetics according to IPSS stratification were found to be independent prognostic factors associated with survival.

A recent randomized phase 3 study (Criant study) compared the value of allogeneic vs autologous SCT and chemotherapy in patients with IPSS intermediate-1, intermediate-2, or high-risk MDS or MDS-AML.[168] Patients achieving a complete remission after induction chemotherapy were assigned on an intention-to-treat basis to receive allogeneic SCT after 1 course of consolidation chemotherapy according to the availability of an HLA-identical sibling donor. Patients without a donor and in complete remission after the consolidation course were randomly assigned between a second consolidation course and autologous peripheral blood SCT. The results showed that the existence of a stem cell donor resulted in a better disease-free survival in patients with intermediate or poor cytogenetic characteristics, whereas no significant difference was noticed between patients with or without a donor in a low cytogenetic risk category. Four-year overall and disease-free survival from randomization in patients without a donor who were receiving consolidation chemotherapy with high-dose ara-C were 27% and 22%, respectively. Autologous SCT did not provide longer survival than intensive chemotherapy. Cytogenetic characteristics were the most significant disease-associated prognostic factor.

An international, multicenter, controlled, parallel-group, open-label phase 3 trial compared the outcome of 358 MDS patients classified according to FAB criteria with intermediate-2 or high risk IPSS who were randomly assigned (1:1) to receive azacitidine or conventional care, including best supportive care, low-dose ara-C, or intensive chemotherapy as selected by investigators before random assignment.[174] The analysis of results from the investigator preselection subgroup showed that the differences in overall survival and time to AML transformation between azacitidine and intensive chemotherapy were not statistically significant.

Induction chemotherapy should be considered for fit patients without a suitable donor who are younger than age 65 to 70 years and have 10% or more bone marrow blasts without adverse cytogenetic characteristics (recommendation level B). All patients who achieve complete remission after induction chemotherapy without suffering severe complications should receive postremission chemotherapy (recommendation level B).

Autologous SCT

The available evidence on autologous SCT in patients with MDS or MDS-AML has been drawn from prospective randomized and nonrandomized trials, as well as cohort studies.[127,131,134,163,167,168,171,172,175-177] Overall, the feasibility of autologous transplantation in patients without a suitable donor ranged from 49% to 61%, the main reasons for failure being poor harvest and early relapse after induction chemotherapy. The most common conditioning regimens contained busulfan and cyclophosphamide, whereas in a few studies, cyclophosphamide was combined with other drugs (busulfan and etoposide) or rarely, with total-body irradiation. The transplant-related mortality rates ranged from 0% to 27%, and 4-year overall survival rates ranged from 39% to 18%. Transplantation in first complete remission, age younger than 40 years, and favorable cytogenetics were predictive of survival after autologous SCT in most studies.

A randomized trial included a total of 1770 patients with high-risk MDS or de novo or secondary AML who were randomly assigned up-front for induction therapy with standard dose or high-dose ara-C and postremission maintenance or autologous SCT. There were no significant differences in the results between the two randomized induction arms or between the two postremission therapy arms or in the outcome of patients with secondary AML or MDS compared with those with de novo AML.[177] The Criant study reported above, which compared the value of allogeneic vs autologous SCT and chemotherapy in patients with IPSS intermediate-1, intermediate-2, or high risk MDS or MDS-AML, indicated that autologous SCT did not provide longer survival than intensive chemotherapy.[168]

Based on the available evidence, no recommendations can be given at present on the use of autologous SCT for patients without a suitable donor who are receiving intensive chemotherapy.

Low-dose chemotherapy

The use of low-dose ara-C (LDAC) and low-dose oral melphalan has been reported in patients with MDS. The evidence on the use of LDAC has been drawn from systematic reviews of the literature and randomized controlled trials.[178-187] One hundred forty-one patients with one of the FAB-defined subtypes of MDS were included in a combined Eastern Cooperative Oncology Group and Southwest Oncology Group randomized phase 3 study comparing LDAC (10 mg/m^2 subcutaneously twice daily for 21 consecutive days) vs supportive treatment.[183] The overall response rate to a single cycle of LDAC was 32%, with a median duration of response of 5.9 months (range, 1.4 to 33.5 months). A decreased transfusion requirement after 3 months was observed in patients in the LDAC arm, although infections were more common in this arm. There was no difference in overall survival and time to progression for patients treated with LDAC or supportive care. The study design did not, however, allow firm conclusions to be drawn on the efficacy of this treatment modality in MDS. In a randomized phase 3 study by the EORTC Leukemia Cooperative Group, 201 patients with MDS and excess blasts were treated with LDAC either alone or in combination with granulocyte-macrophage CSF (GM-CSF) or interleukin-3. The overall response rate according to study response criteria was 38.6% with no statistically significant difference among the 3 arms; the overall median progression-free survival was 9.1 months.[187] A multicenter study in 102 consecutive patients with early or advanced MDS or MDS-AML treated with LDAC identified a low platelet count and the

presence of two or more chromosomal aberrations as relevant predictive factors for poor response to treatment.[185]

The use of low-dose melphalan was investigated in two prospective cohort studies that included (overall) 42 high-risk MDS patients and resulted in a 38% to 40% overall response rate with minimal toxicity. Response rate was highest in patients with hypocellular marrow, excess of blasts, and normal karyotype.[188,189]

The available evidence is insufficient to recommend routine use of low-dose ara-C, whereas it is adequate to recommend that this schedule should not be used in patients with poor-risk cytogenetics (recommendation level B). There is not sufficient evidence to make recommendations on the use of low-dose melphalan, which should be restricted to clinical trials.

Hypomethylating agents

Two pyrimidine nucleoside analogs—5-azacytidine and decitabine (5-aza-2′-deoxycytidine)—have been extensively investigated in clinical studies of patients with MDS. The literature on the use of these agents includes prospective randomized trials and prospective or retrospective nonrandomized studies.[117,120,174,190-195] A crossover trial from the Cancer and Leukemia Group B (CALBG) included 191 patients with MDS classified according to FAB criteria who were randomly assigned to standard supportive care or subcutaneous azacitidine 75 mg/m^2 per day for 7 days every 28 days for 4 cycles.[192] Significantly higher complete and partial remission rates were observed in the azacitidine-treated group compared with the rates in those receiving supportive care (60% vs 5%, according to study response criteria) with low treatment-related mortality (<1%). The median duration of response was 15 months. Transformation to AML was 2.8-fold more frequent in the supportive-care group than in the azacitidine group, suggesting that azacitidine may delay transformation to AML. A further analysis of the combined results of three CALGB clinical trials with azacitidine that used the WHO classification system for MDS and AML and the IWG response criteria suggested a clinical benefit from receiving azacitidine among the patients with high-risk MDS.[196]

In an international, multicenter, controlled, parallel-group, open-label phase 3 trial, 358 MDS patients classified according to FAB criteria with IPSS intermediate-2 or high risk were randomly assigned (1:1) to receive azacitidine (75 mg/m^2 per day for 7 days every 28 days) or conventional care, including best supportive care, LDAC, or intensive chemotherapy, as selected by investigators before random assignment.[174] Azacitidine was given for a median of 9 cycles (interquartile range, 4 to 15 cycles). On the basis of Kaplan-Meier estimates, 50.8% of patients in the azacitidine group were alive at 2 years compared with 26.2% in the conventional care group ($P <$ .0001). Results from the investigator preselection subgroup analysis of overall survival showed significant differences favoring the study drug between azacitidine and best supportive care, and azacitidine and LDAC, whereas in the comparison between azacitidine and intensive chemotherapy, the difference was not statistically significant. The median time to AML transformation was 17.8 months in the azacitidine group compared with 11.5 months in the conventional care group. A significant difference in time to AML transformation was noticed for azacitidine vs best supportive care, whereas time to progression to AML did not differ significantly in the comparisons of azacitidine with either LDAC or intensive chemotherapy. Peripheral cytopenias were the most common grade 3 to 4 adverse events for all treatments.

A recent study of 282 consecutive MDS patients with high or intermediate-2 risk who were receiving azacitidine in a compassionate, patient-named program identified previous LDAC treatment, bone marrow blasts >15%, and abnormal karyotype as independent predictive factors for lower response rates. Complex karyotype predicted shorter responses. Performance status >2, intermediate- and poor-risk cytogenetics, presence of circulating blasts, and red blood cell (RBC) transfusion requirement (>4 units over 8 weeks) independently predicted poorer overall survival.[197]

In a phase 2 study in 66 MDS patients with IPSS intermediate-1, intermediate-2, or high risk, treatment with decitabine produced an overall response rate of 49%.[190] Response rates according to study response criteria of 48%, 42%, and 75% were observed in the good, intermediate, and poor risk cytogenetic groups, respectively. In a randomized study of 170 MDS patients with IPSS intermediate-1, intermediate-2, or high risk assigned to receive decitabine or supportive care alone, the overall response rate was 17% in the decitabine arm, including 9% complete responses vs 0% in the supportive care arm.[194] Patients treated with decitabine tended to have a longer median time to development of AML or death compared with patients treated with supportive care alone, but the median survival was not significantly different between the two groups.

A randomized study compared three different decitabine schedules (20 mg/m^2 intravenously daily for 5 days, 20 mg/m^2 subcutaneously daily for 5 days, and 10 mg/m^2 intravenously daily for 10 days) in patients with advanced MDS. The 5-day intravenous schedule with the highest dose-intensity was selected as optimal.[195]

In a recent randomized trial, patients with primary or treatment-related MDS or CMML with IPSS intermediate-1, intermediate-2, or high risk, age 60 years or older, and ineligibility for intensive chemotherapy were assigned to receive either low-dose decitabine or best supportive care.[120] In the decitabine arm, 13% of patients achieved a complete response, 6% achieved a partial response, and 15% had hematologic improvement. The median number of decitabine courses administered was 4, equaling approximately 6 months of treatment. Progression-free survival, but not AML-free survival, was significantly longer with decitabine than with best supportive care. The prolongation of overall survival with decitabine vs best supportive care was not statistically significant (median overall survival, 10.1 vs 8.5 months, respectively).

Although the Expert Panel agreed that it is not possible to draw a definitive conclusion on the use of one drug with respect to the other from the available evidence, the advantage in overall survival reported for azacitidine makes this agent preferable at present. On the basis of this evidence, patients with IPSS intermediate-2 or high-risk disease who are not eligible for AML-like chemotherapy and/or allogeneic STC should be treated with azacitidine (recommendation level A). In addition, fit patients with IPSS intermediate-2 or high risk MDS and poor-risk cytogenetics who lack a stem cell donor should receive treatment with azacitidine (recommendation level B). This agent may also be offered to fit patients without poor-risk cytogenetics who lack a stem cell donor as an alternative to remission induction chemotherapy (recommendation level B).

Hematopoietic growth factors

The evidence for the use of hematopoietic growth factors in patients with MDS has been derived from meta-analyses and systematic reviews of the literature, randomized controlled trials, and prospective and retrospective nonrandomized clinical studies, investigating the use of erythropoiesis-stimulating agents as monotherapy or in combination with G-CSF or GM-CSF.[122,124,198-202]

Several studies have investigated epoetin alfa or beta (rHuEpo) as monotherapy at doses ranging from 30 000 to 60 000 U per week, administered in single or multiple subcutaneous injections. Two

randomized controlled phase 3 trials evaluated the use of rHuEpo vs placebo. The first trial included 20 patients with refractory anemia treated with a dose between 1600 and 3200 U/kg per week administered intravenously. A response was observed in 12.5% of the evaluable patients.[198] The second trial enrolled 87 patients with less than 10% bone marrow blasts and a hemoglobin concentration below 9 g/dL. Patients were treated with 150 U/kg per day subcutaneously for 8 weeks, and the overall response rate was 36.8%.[199] Patients without excess blasts, without transfusion requirement prior to erythropoietin treatment, and with low pretreatment serum erythropoietin levels (<150 to 200 U/L) had a higher probability of response.

The effects of rHuEpo and G-CSF have been assessed in several phase 2 trials and randomized phase 3 trials.[122,202] One randomized study comparing treatment with rHuEpo and G-CSF vs supportive care in low-grade anemic MDS showed that the active treatment significantly improved RBC count.[122] A more recent randomized trial comparing the effect of rHuEpo vs rHuEpo and G-CSF given for 8 weeks in low-risk MDS showed a significantly higher response rate in patients receiving the combination of growth factors.[202] The addition of G-CSF produced responses in about 50% of patients who had not responded to erythropoietin alone.

Another prospective randomized phase 3 trial evaluated the efficacy and long-term safety of rHuEpo with or without G-CSF plus supportive care vs supportive care alone in 118 anemic patients with lower-risk MDS, including refractory anemia, refractory anemia with ring sideroblasts (RARS), and RAEB with less than 10% bone marrow blasts, or nonproliferative CMML according to the FAB group criteria.[124] Patients crossed over from the supportive care arm to the treatment arm after a 4-month period of observation if they did not have an erythroid response. The response rates according to study response criteria in the rHuEpo vs supportive care alone arms were 36% vs 9.6%, respectively, rising to 47% in the rHuEpo arm including subsequent study steps. No differences were found in the overall survival of patients in the rHuEpo vs supportive care arms or in the incidence of transformation to AML.

A predictive model for response to rHuEpo and G-CSF in MDS patients was developed and validated in prospective studies.[203,204] Three groups of patients were identified on the basis of serum erythropoietin levels (<500 mU/mL or ≥500 mU/mL) and transfusion needs (<2 RBC units per month or ≥2 RBC units per month) with response to treatment rates according to study response criteria of 74%, 23%, and 7%.

Two large retrospective studies compared the outcome of patients treated with rHuEpo or darbepoetin with or without GCS-F with that of patients receiving best supportive care and found that treatment was associated with improved overall survival but did not influence the risk of leukemic transformation.[205,206]

The efficacy and safety of darbepoetin alfa with or without G-CSF in patients with predominantly IPSS low- or intermediate-1–risk MDS were reported in prospective phase 2 trials and retrospective studies.[118,119,206-213] After accounting for patient selection and response criteria, erythroid response rates obtained with darbepoetin alfa were as high as those observed with rHuEpo.

Other erythropoiesis-stimulating agents have been tested in clinical conditions other than MDS, including anemia of chronic kidney disease and chemotherapy-induced anemia in cancer.[214-219] Taking the information gained from these experiences as translated evidence, it would be reasonable to believe that equipotent doses of these agents could give the same clinical effects as those of rHuEpo. However, there is no direct evidence on the safety and efficacy of these agents in MDS.

Patients with IPSS low or intermediate-1 risk, with moderate to severe anemia (hemoglobin below 10 g/dL), serum erythropoietin level below 500 mU/mL, and/or red cell transfusion requirement lower than 2 RBC units per month should be considered for therapy with epoetin alfa or beta at an initial dose ranging from 30 000 to 60 000 IU per week (recommendation level A). Those patients who do not respond to epoetin alone after 8 weeks of treatment should be given G-CSF (300 μg/week in 2 to 3 divided doses) in combination (recommendation level A).

Although the scientific evidence on darbepoetin alfa is not comparable to that available for epoetin alfa or beta in terms of number and size of studies, the results suggest that the use of equipotent doses of this agent may result in clinical effects similar to those obtained with epoetin alfa or beta (recommendation level D).

Recently, thrombopoiesis-stimulating agents (ie, romiplostim, eltrombopag) have been tested in clinical trials that included patients with MDS.[220,221] Concomitant administration of romiplostim with disease-modifying agents such as azacitidine was also reported.[222] A multicenter, open-label, sequential-cohort, dose-escalation phase 1/2 study evaluated the efficacy and safety of romiplostim in thrombocytopenic patients with low- or intermediate-1–risk MDS. A durable platelet response by IWG 2000 criteria was achieved by 46% of patients. Treatment-related serious adverse events occurred in 11% of patients. Bone marrow evaluations revealed transiently increased blast counts in 9% of patients, and 5% had AML progression during the study.[220] A randomized, double-blind, placebo-controlled study evaluated safety and efficacy of romiplostim in thrombocytopenic MDS patients with IPSS low- or intermediate-1–risk disease. Because of data monitoring committee concerns regarding the transient increases in blast cell counts and the potential risk of progression to or treatment of AML, the trial was terminated prematurely, and the study drug was discontinued. Safety regarding risk of disease progression to AML is still under investigation.[223,224] Ongoing clinical trials are currently testing eltrombopag as a single agent or in combination in thrombocytopenic patients with MDS or secondary AML.[225,226] The available evidence does not allow any recommendations to be made on the use of thrombopoiesis-stimulating agents, which should be restricted to clinical trials.

Immunomodulatory drugs

Thalidomide has been used for treatment of MDS patients in prospective and retrospective nonrandomized clinical trials.[227-229] The rationale for these studies was to use the anticytokine and anti-angiogenic effects of this drug for improving the efficiency of hematopoiesis. Treatment with thalidomide as a single agent was able to reduce or abolish transfusion dependence in a fraction of patients, but long-term treatment was significantly affected by neurologic toxicity.

Lenalidomide, a 4-amino-glutarimide analog of thalidomide lacking this adverse effect was investigated in phase 2 studies and in a randomized phase 3 trial.[230-233] List et al[230] treated 43 patients with transfusion-dependent or symptomatic anemia (88% with IPSS low or intermediate-1 risk) with lenalidomide at 25 or 10 mg per day or 10 mg per day for 21 days of every 28-day cycle. Twenty-four patients had a response, and 20 achieved sustained independence from transfusion. The response rate was highest among patients with a clonal interstitial deletion involving chromosome 5q31 and in patients in lower IPSS risk categories.

A phase 2 multicenter trial then evaluated lenalidomide therapy for transfusion-dependent patients with low- or intermediate-1–risk MDS with 5q deletion.[231] One hundred forty-eight patients were

included, and they received 10 mg of lenalidomide for 21 days every 4 weeks or daily. Seventy-six percent had a reduced need for transfusions, and 99 patients (67%) no longer required transfusions, regardless of karyotype complexity. The response to lenalidomide was rapid (median time to response, 4.6 weeks), and the median duration of transfusion independence had not been reached after a median of 2 years of follow-up. Among 85 evaluable patients, 62 had cytogenetic improvement and 38 of these 62 had a complete cytogenetic remission. Moderate-to-severe neutropenia, often requiring the use of G-CSF, and thrombocytopenia were the most common adverse events during lenalidomide treatment. The study design did not allow any conclusion to be drawn on the risk of progression to AML during treatment with lenalidomide.

More recently, a randomized, multicenter, double-blind phase 3 study compared the efficacy and safety of lenalidomide (10 mg and 5 mg) against placebo in RBC transfusion-dependent patients with low- or intermediate-1–risk MDS with 5q deletion.[233] Crossover to lenalidomide or to a higher dose of lenalidomide was allowed after 16 weeks. RBC transfusion independence for more than 26 weeks was achieved in 56.1% of the patients in the lenalidomide 10-mg group and by 42.6% in the 5-mg group. Cytogenetic response rates were 50% (10 mg) and 25% (5 mg). The most common grade 3 or 4 adverse events in patients treated with lenalidomide during the double-blind phase were neutropenia (75.4% and 73.9% in patients receiving 10 mg and 5 mg of lenalidomide, respectively), thrombocytopenia (40.6% and 33.3%), and deep venous thrombosis (5.8% and 1.4%). G-CSF or GM-CSF was used to prevent or reduce neutropenia in 39 patients (56.5%) in the lenalidomide 10-mg group and 38 patients (55.1%) in the 5-mg group. The cumulative risk of AML in the lenalidomide groups combined was 16.8% at 2 years and 25.1% at 3 years. The authors emphasized that the population of patients with 5q deletion recruited in their study included cases with RBC transfusion dependency, additional chromosomal abnormalities, and medullary blasts of up to 10%, making it difficult to estimate the rate of AML progression associated with the use of lenalidomide. Although no obvious increase in AML progression with lenalidomide treatment has been noticed, continued follow-up is needed.

By using next-generation sequencing in a proportion of patients with low-risk MDS and an isolated del(5q) mutation of TP53 was found that renders them at higher risk for disease progression. The proportion of *TP53* mutated cells was shown to increase with disease progression. Moreover, the mutated subclone may be insensitive to lenalidomide and may gradually progress despite a strong inhibitory effect on the total proportion of cells carrying del(5q) leading to a transient partial cytogenetic remission.[67]

A multicenter phase 2 trial evaluated lenalidomide therapy in transfusion-dependent patients with low- or intermediate-1–risk MDS without 5q deletion.[232] Two hundred fourteen patients were enrolled to receive 10 mg oral lenalidomide daily or 10 mg on days 1 to 21 of a 28-day cycle. Forty-three percent of patients responded to treatment according to the modified IWG 2000 criteria. A total of 26% patients achieved RBC transfusion independence, and 19% had a cytogenetic response. The most common grade 3 to 4 adverse events were neutropenia (30%) and thrombocytopenia (25%). By using gene expression profiling, a molecular signature was identified that predicts lenalidomide response in MDS patients lacking 5q deletion.[234]

On the basis of the available evidence, it is recommended that patients with 5q deletion without additional chromosomal abnormalities or excess blasts, with a low or intermediate-1 IPSS score and transfusion-dependent anemia, who are not candidates for treatment with or have failed a therapeutic trial with hematopoietic growth factors, should be offered lenalidomide. The inclusion of these patients in a prospective registry is strongly recommended in order to maximize the information regarding the safety of this treatment modality (recommendation level C). Patients with 5q deletion and an intermediate-1 IPSS score due to additional chromosomal abnormalities or an excess of blasts, who are not candidates for treatment with or have failed a therapeutic trial with hematopoietic growth factors, may be offered lenalidomide within a clinical trial or a prospective registry (recommendation level C). Patients with 5q deletion, a low or intermediate-1 IPSS score, and evidence of *TP53* mutation have a significantly higher risk of transformation to AML, which should be considered in the choice between lenalidomide and alternative therapeutic options (recommendation level D).

Immunosuppressive therapy

On the basis of early observations that individual patients with hypoplastic MDS responded to immunosuppression, antithymocyte globulin (ATG) was tested in nonrandomized phase 2 studies and in randomized phase 2 and 3 trials.[235-247] Overall, the response rates in the phase 2 studies were approximately 30% in patients without excess blasts, whereas only a minority of patients with RARS or RAEB responded to treatment. Young age (<60 years), combination ATG plus cyclosporine A (CSA) treatment, low IPSS risk, hypocellularity, short duration of transfusion requirement, and HLA-DR15 phenotype were reported as factors predictive of a better response to ATG.[237,239,245,246] A retrospective study comparing outcomes of patients treated with ATG or CSA in combination or singly with those of MDS patients reported to the IMRAW who received only supportive care found that immunosuppressive therapy was associated with improved overall and progression-free survival.[246]

Recently, a prospective randomized, multicenter phase 3 trial compared ATG plus CSA with best supportive care in patients with MDS stratified by IPSS risk score (low, 18%; intermediate-1, 56%; intermediate-2, 14%; high, 1%; not evaluable, 11%).[247] Forty-five patients received horse ATG for 5 days and oral CSA for 180 days, and 43 patients received best supportive care (median patients' ages, 62 and 65 years, respectively). Patients were included because of transfusion dependency on RBC or platelets or severe neutropenia. Patients were allowed to cross over from the best supportive care arm to the ATG plus CSA arm at the time of disease progression or after 6 months in case of nonresponse. The rate of hematologic responses defined according to study response criteria was significantly higher with ATG plus CSA than with best supportive care. In a multivariable model, response at 6 months was significantly associated with hypoplastic marrow. No significant differences were found in transformation-free survival and overall survival estimates. When treatment was modeled as a time-dependent covariate, allowing for crossover of patients, no significant difference was observed in death rate. There was a significantly higher rate of serious adverse events in the ATG plus CSA arm than in the best supportive care arm; these serious adverse events included major hemorrhage, cardiac events, serum sickness/fever, thrombosis, and severe infection.

A prospective, randomized, phase 2 study compared horse ATG and rabbit ATG in patients with low-risk MDS.[242] No significant difference was observed between the two treatment arms with regard to clinically relevant responses, overall survival, or adverse effects, but the sample size was small (n = 35).

On the basis of available evidence, immunosuppressive therapy with ATG plus 6 months of oral CSA should be considered in patients younger than age 60 years, with less than 5% marrow blasts, normal cytogenetics, and transfusion dependency who are not

candidates for treatment with or for whom a therapeutic trial with hematopoietic growth factors has failed (recommendation level A). The use of ATG is highly recommended in the presence of a hypoplastic bone marrow (recommendation level C). The available evidence does not allow any recommendations to be made on maintenance therapy in patients responding to immunosuppressive therapy.

Red cell transfusion and iron chelation therapy

Available evidence on the criteria for the use of red cell transfusion and iron chelation therapy in MDS is limited; thus, general criteria issued for chronic disorders with transfusion-dependent anemia, in particular thalassemia, may be adopted as translated evidence.

The onset of regular RBC transfusion requirement in MDS patients is associated with a worse prognosis. Although transfusion policies may vary in part among centers and countries, this observation has been confirmed by different reports, including registry studies. Several components may contribute to the detrimental effect of transfusion dependency, including more aggressive disease, severe anemia, and toxicity related to transfusions themselves. A recent retrospective study adopting a Cox proportional hazards regression model with time-dependent covariates found that hemoglobin levels lower than 9 g/dL in males and 8 g/dL in females were independently related to reduced overall survival and higher risks of non-leukemic death and cardiac death.[99] A recent prospective phase 2 trial showed that targeted RBC transfusion therapy to reach a hemoglobin level of 12 g/dL had the same positive effect on QOL as treatment with erythropoiesis-stimulating agents.[119]

The Expert Panel pronounced that the objective of RBC transfusion therapy is to improve QOL and to avoid anemia-related symptoms and ischemic organ damage. No single hemoglobin concentration can be recommended as being the optimal level below which red cell support should be given. The decision should be based on the patient's symptoms and comorbidity. As a general recommendation, all patients with severe anemia (hemoglobin lower than 8 g/dL) and those with symptomatic milder anemia should receive RBC transfusion (recommendation level D).

Patients receiving regular transfusion invariably develop secondary iron overload. Whole blood contains about 0.47 mg/mL of iron, while pure RBC concentrates contain about 1.16 mg/mL of iron; thus, one unit of blood contains 200 to 250 mg of iron, and an iron overload can occur after 20 to 25 transfusions.

To date, there is limited evidence on the role of iron in organ damage in patients with MDS. In an autopsy study of 135 patients with chronic acquired anemia, approximately 60% of patients who had received more than 75 units of RBCs had cardiac iron deposits.[248] In 1981, Schafer et al[249] reported the pathologic consequences of acquired transfusional iron overload in adult patients with refractory anemia or aplastic anemia who had received a mean of 120 units of RBCs. In that study, 10 of 15 liver biopsy specimens contained between 7 and 26 times the normal levels of iron and typically showed portal fibrosis. Impaired cardiac left ventricular function, glucose intolerance with a reduced insulin output, and limited pituitary adrenocorticotropin and gonadotropin reserves were reported. The authors concluded that widespread subclinical organ dysfunction can result from transfusional iron overload developing in adulthood. Recently, studies in adult MDS patients with chronic transfusion dependency that used T2* magnetic resonance imaging reported a high prevalence of iron loading in the liver, whereas cardiac iron deposition was seen in a small fraction of patients after a heavy transfusion burden.[250-253]

Retrospective studies found that an elevated serum ferritin significantly worsens the survival of transfusion-dependent MDS patients.[93] This survival decrement was restricted to patients diagnosed with refractory anemias according to the WHO criteria. In addition, elevated pretransplantation serum ferritin levels were found to be associated with lower survival rates in patients with MDS who underwent allogeneic SCT, suggesting that iron overload may affect transplantation outcome for patients with MDS, as it does in thalassemia.[254-259]

Several studies have investigated the use of iron-chelating agents in MDS patients with transfusion-dependent anemia. A report on MDS patients receiving desferrioxamine as a continuous, subcutaneous 12-hour infusion by pump found that this chelating agent induced effective iron depletion in a significant proportion of patients.[260] A small randomized trial compared within-patient urinary iron excretion and long-term efficacy of subcutaneous 12-hour continuous infusion vs twice-daily bolus injections in 27 adult patients with secondary iron overload, including patients with MDS.[261] A significant decrease of serum ferritin was noted during treatment, with the urinary iron excretion being similar with the two methods of administration.

Two studies evaluated the efficacy and toxicity of treatment with deferiprone in adult patients with transfusion iron overload including patients with MDS. Negative iron balance was obtained in a significant proportion of patients, but cases of agranulocytosis occurred.[262,263]

Deferasirox was tested in prospective studies on patients with iron overload who had various transfusion-dependent anemias, including patients with MDS.[264-267] A prospective 1-year study enrolled 1744 patients, including 341 patients with MDS, and reported a significant decrease in serum ferritin and labile plasma iron from baseline.[265,266] Sixty-six percent of MDS patients experienced adverse events that were considered by the investigator to be drug-related, the most common of which were diarrhea, other gastrointestinal symptoms, and skin rash; 85 of the 341 patients with MDS had increases in serum creatinine that required dose reduction in 34 of them. A recent retrospective analysis that used IWG 2006 criteria to evaluate hematologic response to deferasirox in a cohort of MDS patients with iron overload showed that iron chelation therapy may be associated with an improvement in hematologic parameters in a fraction of patients (erythroid, platelet, and neutrophil responses were observed in 21%, 13%, and 22% of patients, respectively).[268]

More recently, an open-label, single-arm, 3-year prospective, multicenter phase 2 trial assessed the safety and efficacy of deferasirox in low- or intermediate-1–risk MDS patients. Eligible patients had serum ferritin equal to or higher than 1000 μg/L, had received 20 or more units of RBCs, and had ongoing transfusion requirements. Median serum ferritin decreased 23% from baseline over the first year of treatment, 36.7% in patients who completed 2 years, and 36.5% in patients who completed 3 years of treatment. Labile plasma iron levels normalized in all patients with abnormal baseline levels. Reduction in serum ferritin significantly correlated with ALT improvement ($P < .001$). Over the 3-year study, 138 (79.8%) of 173 patients discontinued therapy, mainly because of adverse events (24.8%), abnormal laboratory values (13.2%), or death (16.1%). The most common drug-related adverse events were gastrointestinal disturbances and increased serum creatinine.[269]

Prospective randomized studies evaluating the impact of iron chelation therapy on survival of patients with MDS are not available in the literature. An effective iron chelation therapy was demonstrated to prevent the impact of iron overload on nonrelapse

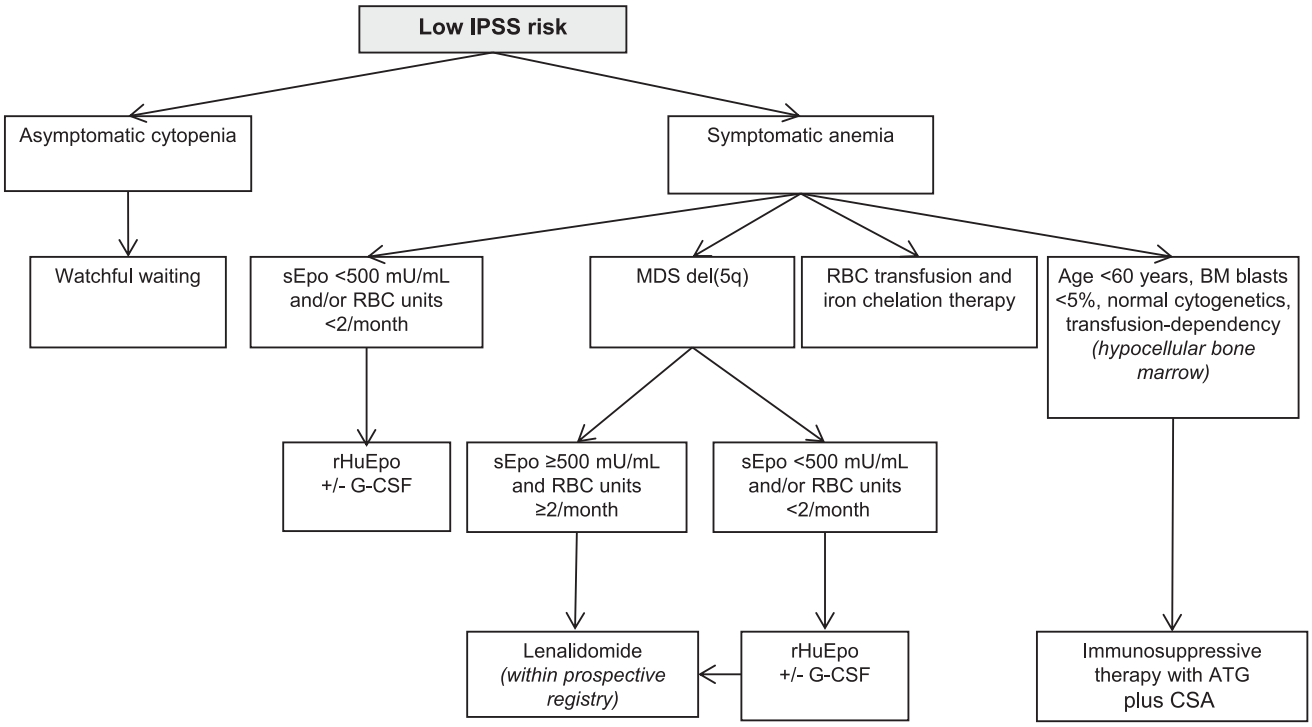

Figure 1. Therapeutic algorithm for adult patients with primary MDS and low IPSS score. BM, bone marrow; sEpo, serum erythropoietin.

mortality in transfusion-dependent thalassemia patients undergoing allo-SCT[270,271]; however, there is no direct evidence on the efficacy of iron chelation therapy on posttransplantation outcome in MDS patients undergoing allogeneic SCT.

The Expert Panel agreed that iron chelation should be considered in transfusion-dependent patients with RA, RARS, or MDS with isolated 5q deletion and a serum ferritin level higher than 1000 ng/mL after approximately 25 units of red cells (recommendation level D). MDS patients who are potentially candidates for allo-SCT can be considered for appropriate iron chelation therapy prior to the conditioning regimen for transplantation (recommendation level D).

Platelet transfusion

The platelet levels that predispose thrombocytopenic MDS patients to hemorrhage are not well defined and differ considerably between patients. Available evidence on the criteria for the use of platelet transfusions in MDS is scanty; thus, general criteria issued

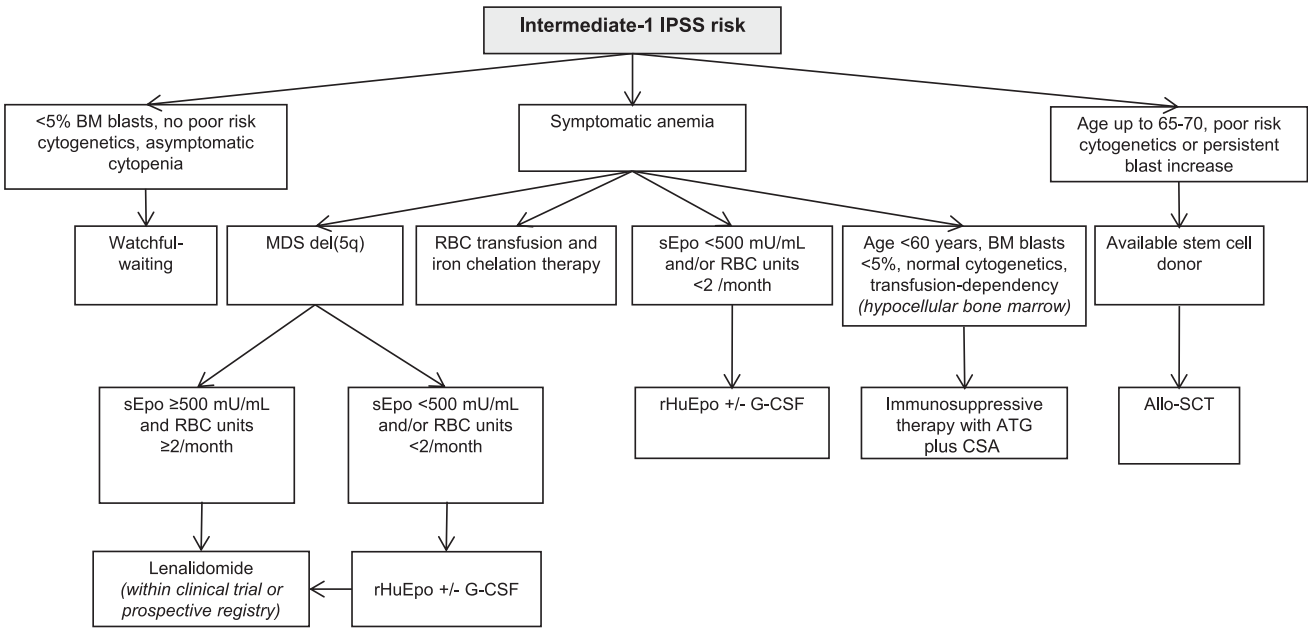

Figure 2. Therapeutic algorithm for adult patients with primary MDS and intermediate-1 IPSS score.

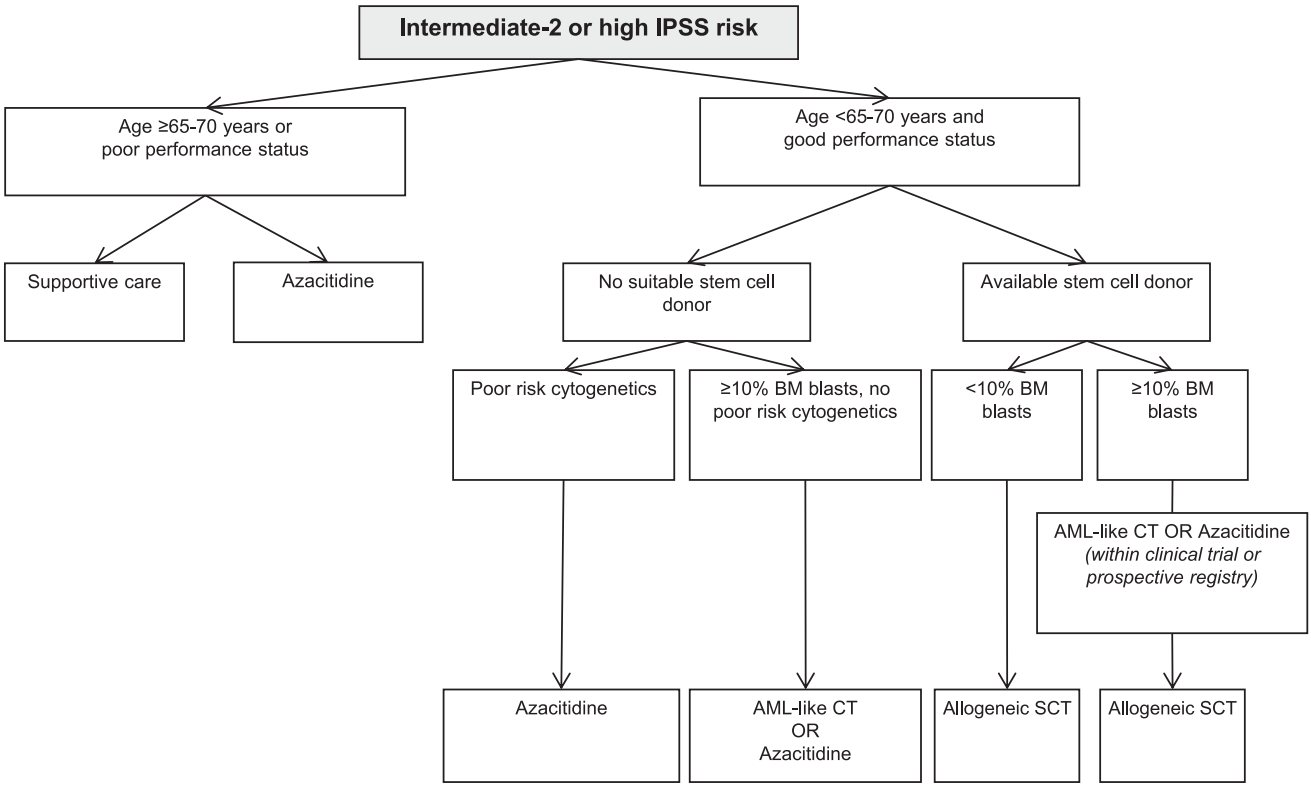

Figure 3. Therapeutic algorithm for adult patients with primary MDS and intermediate-2 or high IPSS score. CT, chemotherapy.

for acute leukemia and lymphomas may be adopted as translated evidence.[272-274]

Prophylactic administration of platelet transfusions is recommended in patients with a platelet count lower than 10×10^9/L, or in those with a platelet count lower than 20×10^9/L and any risk factor for bleeding (fever, infections, rapid platelet decrease, invasive procedure), provided that thrombocytopenia is transient. Long-standing thrombocytopenia does not routinely require prophylactic administration of platelet transfusions (recommendation level D).

Discussion

These guidelines provide practice recommendations for the diagnosis and therapy of adult patients with primary MDS. The recommendations are based on a systematic review of the scientific literature published in the last 25 years and are ranked according to the level of evidence. Even so, in the field of MDS, as in other settings of hematology and oncology, most evidence was derived from uncontrolled nonrandomized trials and did not have a level of detail sufficient to sustain everyday clinical decisions. Formal consensus methodology was, therefore, adopted to combine the best available scientific evidence with collective judgment by experts to yield a statement regarding the appropriateness of each treatment.

The evaluation of the appropriateness of a procedure or treatment did not include economic aspects. Although cost considerations are an important factor in deciding whether a procedure or treatment should ultimately be made available to patients, this discussion must include a broader group of individuals (physicians, consumers, funding bodies) and must take place after physicians have judged a treatment or procedure as effective. A cost-effectiveness analysis is outside the scope of this project and should be devolved to national working groups.

The Expert Panel was unanimous in considering that the heterogeneity of the disease strongly sustains a risk-adapted treatment strategy (therapeutic algorithms based on IPSS risk are reported in Figures 1-3). An accurate risk assessment requires the evaluation of not only disease-related factors but also of those related to extrahematologic comorbidity. The assessment of individual risk enables the identification of fit patients with a poor prognosis who are candidates for up-front intensive treatments. In fit patients with low-risk disease who are potential candidates for intensive therapy, the immediate risk of treatment-related morbidity and mortality may be excessively high, and delayed treatment strategies may result in prolonged survival. However, these strategies are to be planned at the time of diagnosis, and a close follow-up and an optimal management of cytopenias are mandatory to prevent disease complications or progression that might preclude these patients from intensive treatments.

A high proportion of MDS patients are not eligible for potentially curative treatment because of advanced age and/or clinically relevant comorbidities and poor performance status. In these patients, the therapeutic intervention is aimed at preventing cytopenia-related (usually anemia) morbidity and preserving QOL. In this light, the implementation into clinical practice of a rigorous assessment of patient-reported outcomes is strongly encouraged.

A number of new agents are being developed for which the available evidence is not sufficient to recommend routine use. The inclusion of patients in clinical trials is strongly recommended to obtain the maximal information on safety and efficacy of new treatments. The inclusion of patients in national and international registries is also encouraged in order to obtain data on the disease and on the implementation of treatment strategies in everyday

clinical practice and to establish an optimal frame for biological and translational studies in the field of MDS.

The European LeukemiaNet[275] aims to provide a continuous update of the present guidelines and monitor their implementation in clinical practice as a base for improving the clinical management of patients with MDS and for identifying patients who might be candidates for investigational treatments.

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Authorship

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