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Myelodysplastic Syndromes:

Clinical Practice Guidelines in Oncology

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Keywords

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Overview

The myelodysplastic syndromes (MDS) represent myeloid clonal hemopathies with relatively heterogeneous spectrums of presentation. The major clinical problems in these disorders are morbidities caused by cytopenias and the potential for MDS to evolve into acute myeloid leukemia (AML). In the general population, MDS occur in 5 per 100,000 people. However, among individuals older than 70 years, the incidence increases to between 22 and 45 per 100,000 and increases further with age.

Managing MDS is complicated by the generally advanced age of the patients (median ages, 65–70 years), attendant nonhematologic comorbidities, and relative inability to tolerate certain intensive forms of therapy among older patients. In addition, when the illness progresses to AML, these patients experience lower response rates to standard therapy than those with de novo AML.[1]

Diagnostic Classification

Initial evaluation of patients with suspected MDS requires careful assessment of their peripheral blood smear and blood counts, marrow morphology, duration of their abnormal blood counts, other potential causes for their cytopenias, and concomitant illnesses. The French-American-British (FAB) classification initially categorized patients for the diagnostic evaluation of MDS.[2] Dysplastic changes in at least 2 of the 3 hematopoietic cell lines have been used by most histopathologists to diagnose MDS. These changes include megaloblastoid erythropoiesis, nucleocytoplasmic asynchrony in the early myeloid and erythroid precursors, and dysmorphic megakaryocytes.[3] Patients with MDS are classified as having 1 of 5 subtypes of disease: refractory anemia (RA); RA with ringed sideroblasts (RARS); RA with excess of blasts (RAEB); RAEB in transformation (RAEB-T); or chronic myelomonocytic leukemia (CMML). MDS are generally indolent, with patients' blood counts remaining relatively stable over at least several months.

With a moderate degree of variability, patients with RAEB (5%–20% marrow blasts) and those with RAEB-T (20%–30% marrow blasts) generally have a relatively poor prognosis, with a median survival of 5 to 12 months. In contrast, patients with RA (< 5% blasts) or those with RARS (< 5% blasts plus > 15% ringed sideroblasts) have a median survival of 3 to 6 years. The proportion of these individuals whose disease transforms to AML ranges from 5% to 15% in the low-risk RA/RARS group to 40% to 50% in the relatively high-risk RAEB/RAEB-T group. The FAB classification categorizes patients with more than 30% marrow blasts as having AML.

[a]Confirm diagnosis of MDS according to FAB or WHO criteria for classification with application of IPSS (see Classification Systems [pages 33-35]). Percentage of marrow myeloblasts should be reported.

[b]Patients with significant cytopenias and karyotypes t(8;21), t(15;17), and/or inv(16) or variants should be considered AML. (See NCCN Guidelines for Acute Myeloid Leukemia*).

[c]Family HLA - evaluation to include all full siblings; unrelated evaluation to include high-resolution allele level typing for HLA-A, B, C, DR, DQ.

[d]To aid the evaluation for improved response to immunosuppressive therapy.

[e]To assess possible Fanconi anemia or dyskeratosis congenita.

CLASSIFICATION SYSTEMS FOR DE NOVO MDS

FAB[f] Classification of MDS[g]

FAB Subtype	% of Peripheral Blasts	% of Bone Marrow Blasts
Refractory anemia (RA)	< 1	< 5
Refractory anemia with ringed sideroblasts (RARS)	< 1	< 5
Refractory anemia with excess blasts (RAEB)	< 5	5-20
Refractory anemia with excess blasts in transformation (RAEB-T)	≥ 5	21-30
CMML (> 1000 monocytes/mcL blood)	< 5	5-20

2008 WHO[h] Classification of MDS[i]

Subtype	Blood	Bone Marrow
Refractory cytopenia with unilineage dysplasia (RCUD)[j]	Single or bicytopenia	Dysplasia in ≥ 10% of one cell line, < 5% blasts
Refractory anemia with ring sideroblasts (RARS)	Anemia, no blasts	≥ 15% of erythroid precursors with ring sideroblasts, erythroid dysplasia only, < 5% blasts
Refractory cytopenia with multilineage dysplasia (RCMD)	Cytopenia(s), < 1 x 10^9/L monocytes	Dysplasia in ≥ 10% of cells in ≥ 2 hematopoietic lineages, ± 15% ring sideroblasts, < 5% blasts
Refractory anemia with excess blasts-1 (RAEB-1)	Cytopenia(s), ≤ 2%-4% blasts, < 1 x 10^9/L monocytes	Unilineage or multilineage dysplasia, no Auer rods, 5%-9% blasts
Refractory anemia with excess blasts-2 (RAEB-2)	Cytopenia(s), 5%-19% blasts, < 1 x 10^9/L monocytes	Unilineage or multilineage dysplasia, Auer rods, ± 10%-19% blasts
MDS, unclassified (MDS-U)	Cytopenia(s)	Unilineage dysplasia or no dysplasia but characteristic MDS cytogenetics, < 5% blasts
MDS associated with isolated del(5q)	Anemia, platelets normal or increased	Unilineage erythroid dysplasia, isolated del(5q), < 5% blasts

[f]FAB = French-American-British.

[g]Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol 1982;51:189-199.

[h]WHO = World Health Organization.

[i]Brunning R, Orazi A, Germing U, et al. Myelodysplastic syndromes. In: Swerdlow S, Campo E, Harris NL, et al., eds. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissue, 4th ed. Lyon, France: IARC Press; 2008:88-103.

[j]This category encompasses refractory anemia (RA), refractory neutropenia (RN), and refractory thrombocytopenia (RT). Cases of RN and RT were previously classified as MDS Unclassified.

[k]Orazi A, Bennet JM, Germing U, et al. Myelodysplastic/myeloproliferative neoplasms. In: Swerdlow S, Campo E, Harris NL, et al., eds. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th ed. Lyon, France: IARC Press; 2008:76-86.

[l]Ph-negative plus ≥ 2 features: Hb F, PB immature myeloid cells, WBC >10×10^9/L, clonal chromosomal abnormality, GM-CSF hypersensitivity in vitro.

[m]For example, thrombocytosis, leukocytosis, splenomegaly.

[n]Greater than 20% blasts in PB or marrow. Some cases with 20%-29% blasts, especially if arising from MDS, may be slowly progressive and may behave more similar to MDS (RAEB-T by FAB classification) than overt AML.

[o]Arber DA, Brunning RD, Orazi A, et al. Acute myeloid leukemia with myelodysplasia-related changes. In: Swerdlow S, Campo E, Harris NL, et al., eds. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, 4th edition. Lyon, France: IARC Press; 2008:124-126.

[p]IPSS should be used for initial prognostic and planning purposes. The WHO classification-based prognostic scoring system (WPSS) permits dynamic estimation of prognosis at multiple time points during the course of MDS.

[q]Greenberg P, Cox C, LeBeau M, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89:2079-2088; Erratum in: Blood 1998;91:1100. © the American Society of Hematology.

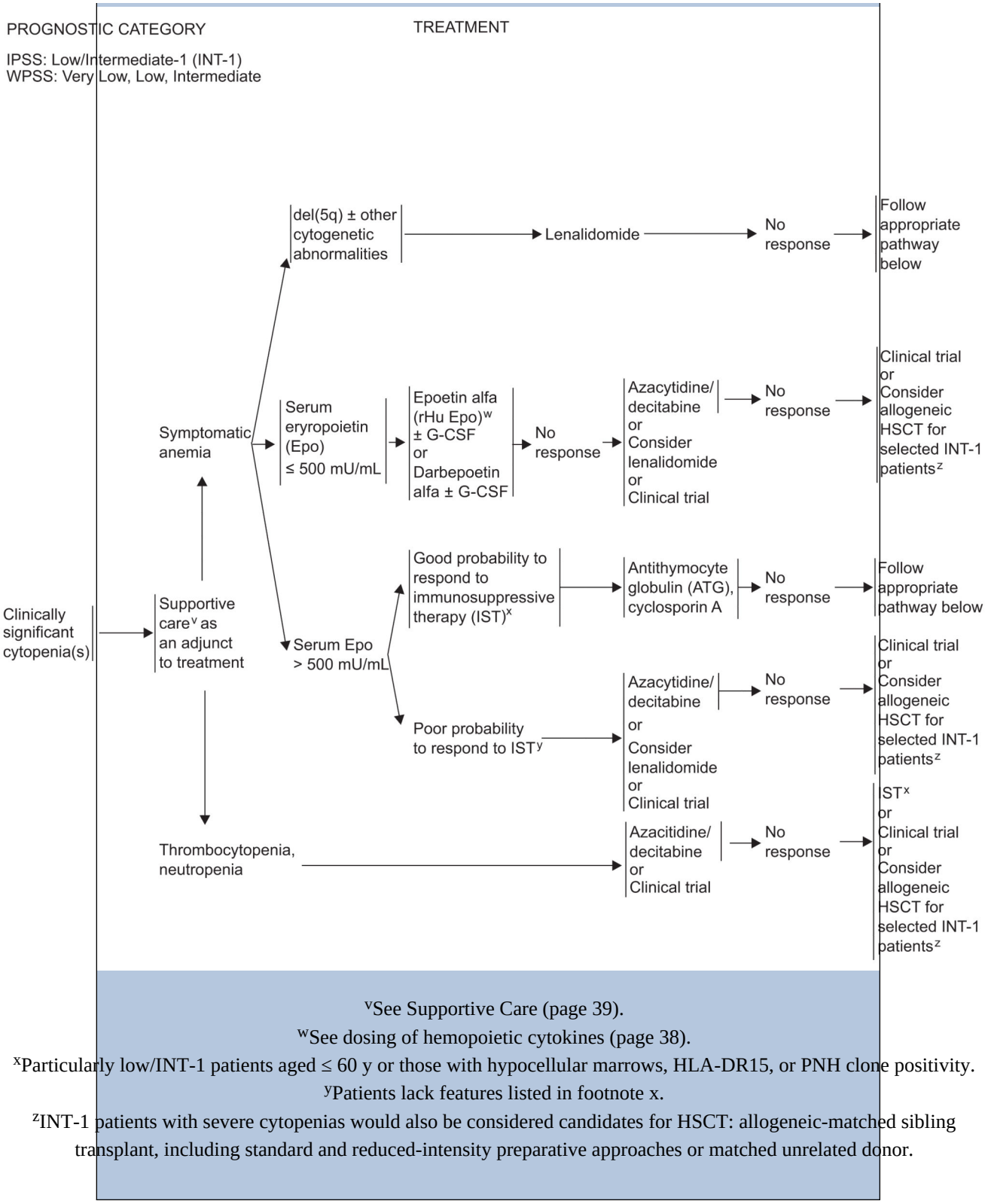
[r]Patients with 20%-30% blasts may be considered as MDS (FAB) or AML (WHO).

[s]Cytogenetics: Good = normal, -Y alone, del(5q) alone, del(20q) alone; Poor = complex 3 abnormalities) or chromosome 7 anomalies; Intermediate = other abnormalities. (This excludes karyotypes t(8;21), inv16, and t(15;17), which are considered to be AML not MDS.)

[t]Cytopenias: neutrophil count < 1800/mcL, platelets < 100,000/mcL, Hb < 10 g/dL.

[u]RBC transfusion requirement = having ≥ 1 RBC transfusion every 8 wk over a 4-mo period.

See Progressive Disease (page 37)



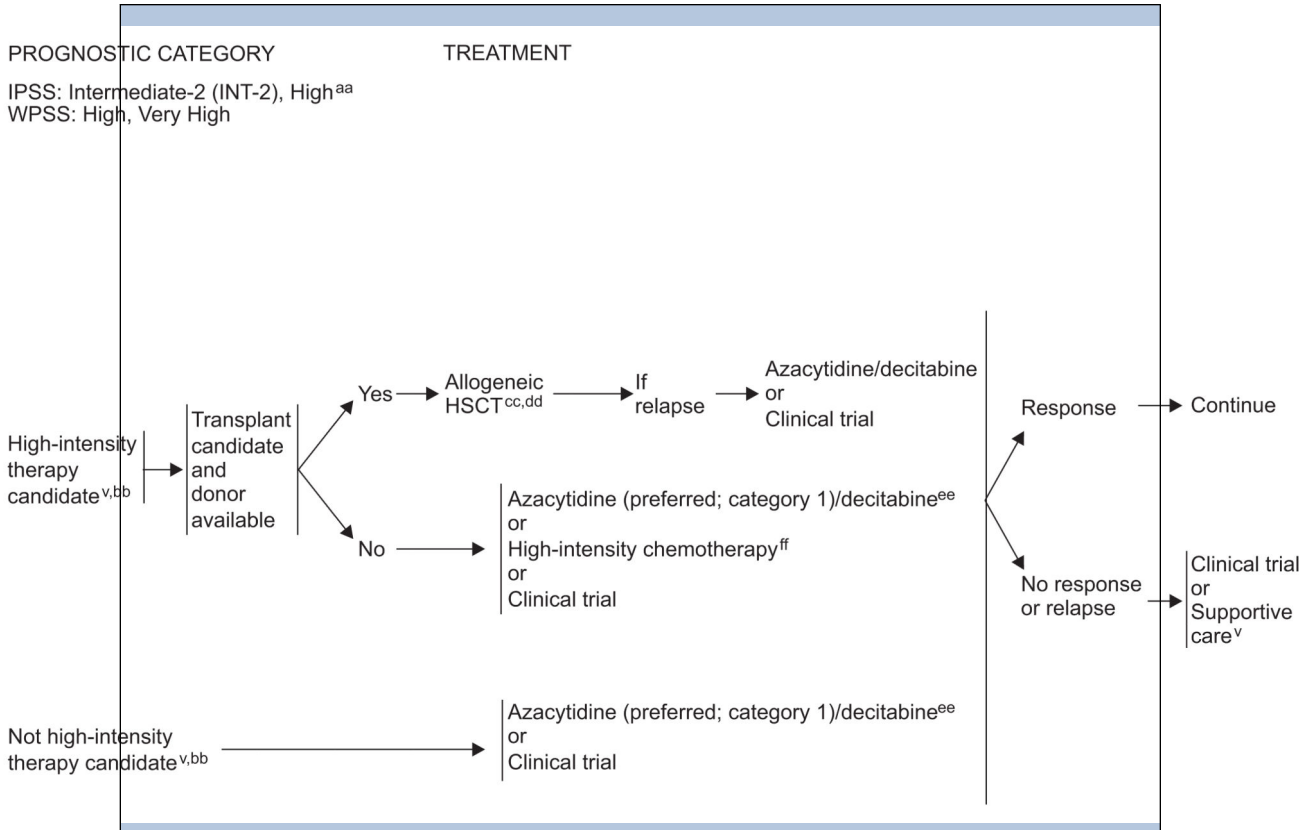
[v]See Supportive Care (page 39).

[w]See dosing of hemopoietic cytokines (page 38).

[x]Particularly low/INT-1 patients aged ≤ 60 y or those with hypocellular marrows, HLA-DR15, or PNH clone positivity.

[y]Patients lack features listed in footnote x.

[z]INT-1 patients with severe cytopenias would also be considered candidates for HSCT: allogeneic-matched sibling transplant, including standard and reduced-intensity preparative approaches or matched unrelated donor.



[v]See Supportive Care (page 39).

[aa]INT-1 patients with severe cytopenias unresponsive to standard therapy would also be considered candidates for allogeneic HSCT.

[bb]Based on age, performance status, major comorbid conditions, psychosocial status, patient preference, and availability of caregiver.

[cc]Azacytidine, decitabine, or other therapy may also be used as a bridge to transplant while awaiting donor availability.

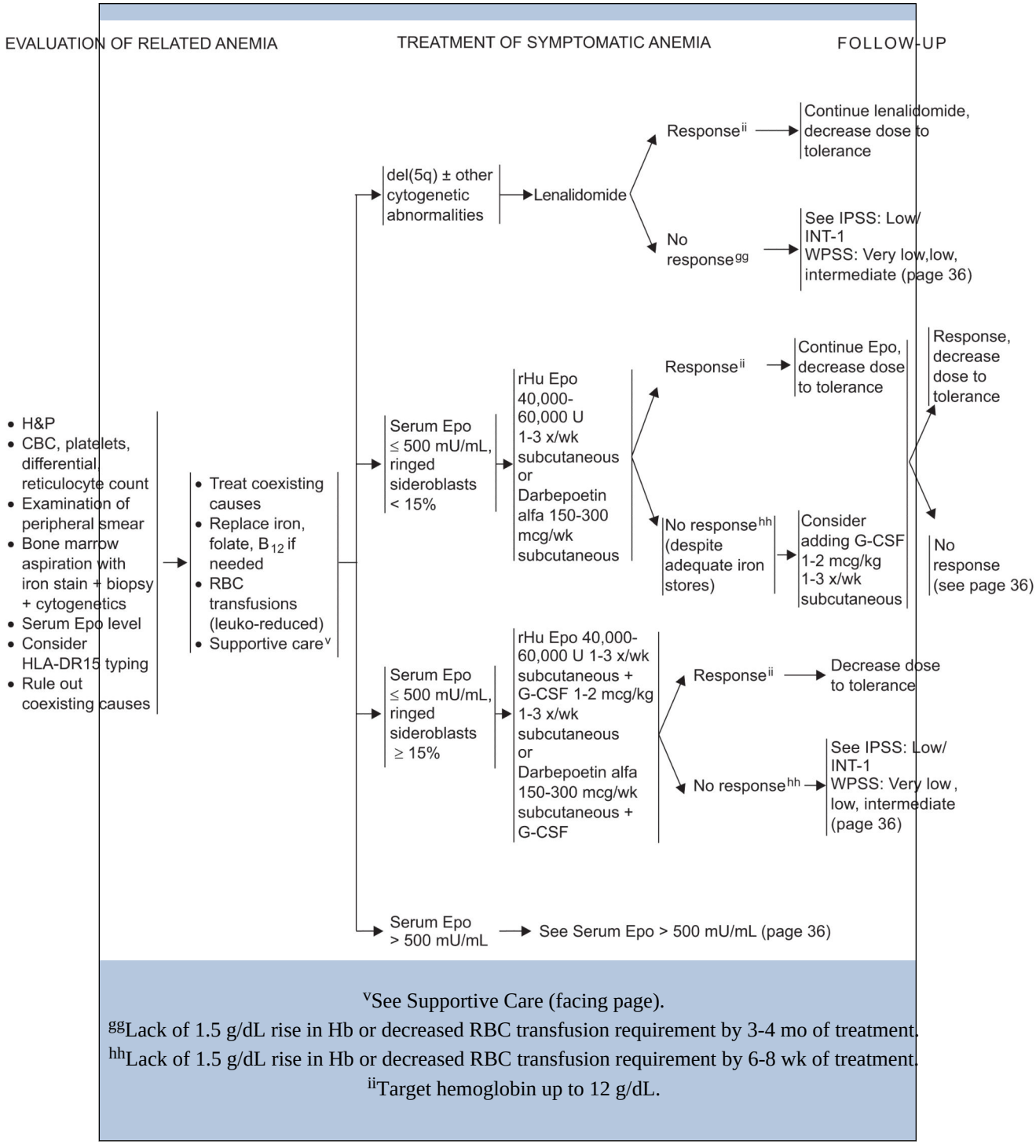
[dd]HSCT: allogeneic-matched sibling, including standard and reduced-intensity preparative approaches or matched unrelated donor.

[ee]While the response rates are similar for both drugs, survival benefit from a phase lll randomized trial is reported for azacytidine and not for decitabine.

[ff]High-intensity chemotherapy:

Clinical trials with investigational therapy (preferred)

Standard induction therapy if investigational protocol unavailable or as a bridge to HSCT.



[v]See Supportive Care (facing page).

[gg]Lack of 1.5 g/dL rise in Hb or decreased RBC transfusion requirement by 3-4 mo of treatment.

[hh]Lack of 1.5 g/dL rise in Hb or decreased RBC transfusion requirement by 6-8 wk of treatment.

[ii]Target hemoglobin up to 12 g/dL.

SUPPORTIVE CARE[1]

- Clinical monitoring
- Psychosocial support
- Quality-of-life assessment
- Transfusions:
  - RBC transfusions (leuko-reduced) for symptomatic anemia, platelet transfusions for thrombocytopenic bleeding, irradiated products suggested for transplant candidates
  - Cytomegalovirus (CMV)-negative blood products are recommended whenever possible for CMV-negative transplant candidates
- Antibiotics for bacterial infections
- Aminocaproic acid or other antifibrinolytic agents may be considered for bleeding refractory to platelet transfusions or profound thrombocytopenia
- Iron chelation:
  If > 20-30 RBC transfusions received, consider daily chelation with deferoxamine subcutaneously or deferasirox orally to decrease iron overload, particularly for Low/INT-1 and for potential transplant patients. For patients with serum ferritin levels > 2500 ng/mL, with the goal of decreasing ferritin levels to < 1000 ng/mL[2]
- Cytokines:
  - Epo; see Anemia pathway (previous page)
  - G-CSF or GM-CSF
    - Not recommended for routine infection prophylaxis
    - Consider use if recurrent or resistant infections in neutropenic patient
    - Combine with Epo for anemia when indicated; see Anemia Pathway (previous page)
    - Platelet count should be monitored

[1]See NCCN Guidelines for Supportive Care; to view the most recent version of all guidelines, visit the NCCN Web site at www.NCCN.org.

[2]Clinical trials in MDS are currently ongoing with oral chelating agents.

In a study evaluating time-to-disease evolution, 25% of patients with RAEB and 55% of those with RAEB-T underwent transformation to AML at 1 year, whereas 35% of those with RAEB and 65% of those with RAEB-T underwent transformation to AML at 2 years.[1] In contrast, the incidence of transformation for RA was 5% at 1 year and 10% at 2 years. None of the patients with RARS developed leukemia within 2 years.

CMML is categorized by the FAB as MDS, although it often has the characteristics of a myeloproliferative disorder. Some groups have separated these patients into proliferative or nonproliferative/dysplastic subtypes, with prognosis mostly depending on the proportion of marrow blasts. Patients with the dysplastic form are classified within the FAB subtypes based on their percent marrow blasts. Within the RAEB and CMML subgroups, an increased proportion of marrow blasts has negative prognostic significance.

In 2001, the WHO proposed a classification for MDS.[4-6] The report suggested modifying the FAB definitions of MDS. Although most prior data require at least 2-line dysplasia for diagnosing MDS, the WHO guidelines accept unilineage dysplasia for diagnosing RA and RARS, provided that other causes of the dysplasia are absent and it persists for at least 6

months. To establish the diagnosis of MDS, careful morphologic review and correlation with the patient's clinical features are important, because several medications and viral infections (including HIV infection) may cause morphologic changes in marrow cells similar to MDS.[1,7]

In 2008, a revision of the WHO classification incorporated new scientific and clinical information, refined diagnostic criteria for previously described neoplasms, and introduced newly recognized disease entities.[8] A new subtype in the MDS classification is refractory cytopenia with unilineage dysplasia, which includes RA (unilineage erythroid dysplasia), refractory neutropenia (unilineage dysgranulopoiesis), and refractory thrombocytopenia (RT; unilineage dysmegakaryocytopoiesis). Refractory neutropenia and RT were previously classified as *MDS unclassifiable*.[9] A review article in the *Blood* discusses the major changes and the rationale behind the changes in the 2008 WHO classification of MDS and AML evolving from MDS.[10]

Other categories within the WHO classification include refractory cytopenia with multilineage dysplasia with or without ring sideroblasts, separating patients with RAEB into those with fewer than 10% marrow blasts (RAEB-1) and those with 10% or more marrow blasts (RAEB-2), 5q minus (del(5q)) syndrome, and MDS unclassified (with MDS cytogenetics, with or without unilineage dysplasia). The del(5q) syndrome, recognized by WHO as a separate MDS category, includes patients with an isolated 5q31-33 deletion and marrow showing less than 5% blasts, often with thrombocytosis.[4-6] This disorder generally has a relatively good prognosis[11] and is highly responsive to lenalidomide therapy.[12]

The MDS/myeloproliferative neoplasms (MPN) category includes CMML (CMML-1 and -2); atypical CML, BCR-ABL1–negative; and juvenile myelomonocytic leukemia as disorders having overlapping dysplastic and proliferative features, and the MDS/MPN unclassifiable group.[13] The distinction between CMML-1 and CMML-2 is based on the percentage of blasts plus monocytes in peripheral blood and bone marrow. CMML had been categorized by FAB as MDS, and by the International MDS Risk Analysis Workshop (IMRAW) as proliferative type (white blood cell [WBC] count ≥ 12,000/mm^3; a myeloproliferative disorder [MPD]) or nonproliferative type (dysplastic MDS).[11]

The WHO classification excludes patients with RAEB-T from MDS (proposing that AML should now include patients with ≥ 20% marrow blasts, rather than the previously used ≥ 30% cutoff). However, MDS not only are related to blast quantitation but also possess a differing pace of disease related to distinctive biologic features that differ from de novo AML.[14,15] Additionally, therapeutic responses generally differ between these patient groups.

Therefore, the decision to treat patients who have 20% to 30% marrow blasts with intensive AML therapy is complex and should be individualized. Factors such as age, antecedent factors, cytogenetics, comorbidities, pace of disease, and performance status should be considered. To aid this approach, and given the longstanding experience with the FAB categorization, the panel currently endorses reporting using both the FAB and WHO classification systems. Thus, patients with RAEB-T may be considered as having either

MDS or AML. Studies have provided evidence supportive of the use of the WHO proposals.[16,17]

The 2008 WHO classifications have helped clarify the clinical differences between the patients having FAB-classified RAEB-T and those with AML.[18] The current WHO classification lists the entity “AML with myelodysplasia-related changes,” which encompasses patients with AML post-MDS, AML with multilineage dysplasia, and AML with MDS-associated cytogenetic abnormalities.[18] According to this classification, some patients with AML with myelodysplasia-related changes having 20% to 29% marrow blasts, especially those arising from MDS, and considered RAEB-T by the FAB classification, may have disease features that behave more similar to MDS than to AML.

AML evolving from MDS (AML-MDS) is often more resistant to standard cytotoxic chemotherapy than de novo AML, which arises without antecedent hematologic disorder. Patients with high-risk MDS or AML-MDS, and some elderly patients with AML may have a more indolent course in terms of short-term progression compared with patients with standard presentations of de novo AML. Separate treatment protocols for patients with standard presentation of de novo AML and for other patient groups, such as those with MDS-AML, elderly AML, and high-risk MDS, seem appropriate (see NCCN Clinical Practice Guidelines in Oncology [NCCN Guidelines] for Acute Myeloid Leukemia; to view the most recent version of these guidelines, visit the NCCN Web site at www.NCCN.org).

To help provide consistency in diagnostic guidelines of MDS, an International Consensus Working Group recommended that minimal diagnostic criteria for this disease include required diagnostic prerequisites: stable cytopenia (for at least 6 months unless accompanied by a specific karyotype or bilineage dysplasia, in which case only 2 months are needed) and the exclusion of other potential disorders as a primary reason for dysplasia and/or cytopenia. In addition, the diagnosis of MDS requires at least 1 of 3 MDS-related (decisive) criteria: 1) dysplasia (≥ 10% in ≥ 1 of the 3 major bone marrow lineages), 2) a blast cell count of 5% to 19%, and 3) a specific MDS-associated karyotype, such as del(5q), del(20q), +8, or −7/del(7q). Furthermore, several co-criteria help confirm the diagnosis of MDS, including studies with flow cytometry, bone marrow histology and immunohistochemistry, or molecular markers (to detect or exclude abnormal CD34 antigenic expression, fibrosis, dysplastic megakaryocytes, atypical localization of immature progenitors, and myeloid clonality).[19]

Initial Evaluation

Several types of evaluations are needed to determine the clinical status of patients with MDS. Understanding clinical status is necessary for determining diagnostic and prognostic categorization and deciding treatment options. Clinical history should include the timing, severity, and tempo of abnormal cytopenias; prior infections or bleeding episodes; and number of transfusions. Concomitant medications and comorbid conditions require careful assessment. Because MDS are relatively indolent disorders, blood count stability is used to distinguish MDS from evolving AML. Other possible causes for patients’ cytopenias should also be carefully evaluated.

In addition to establishing current blood and reticulocyte counts, clinicians need to evaluate a peripheral blood smear to determine the degree of dysplasia and, thus, potentially dysfunctional cells. Bone marrow aspiration with Prussian blue stain for iron and biopsy are needed to evaluate the degree of hematopoietic cell maturation abnormalities and relative proportions, percentage of marrow blasts, marrow cellularity, presence or absence of ringed sideroblasts (and presence of iron per se), and fibrosis. Marrow cytogenetics should be obtained because they are of major importance for prognosis.

Other useful screening laboratory studies include serum erythropoietin (sEpo), vitamin B_{12}, red blood cell (RBC) folate levels, and serum ferritin. Serum ferritin levels may be nonspecific, particularly in the presence of inflammatory conditions such as rheumatoid arthritis, and therefore obtaining the serum iron levels and total iron binding capacity along with serum ferritin may be helpful.

If patients require platelet transfusions for severe thrombocytopenia, human leukocyte antigen (HLA) typing (A, B) may be helpful. For hematopoietic stem cell transplant (HSCT) candidates, the patient's cytomegalovirus (CMV) status and the full HLA typing (A, B, C, DR, and DQ) of the patient and potential donors are needed. Bone marrow flow cytometry for assessing the percentage of CD34+ cells (blast cells are usually CD34+) and HIV screening, if clinically indicated, may also be valuable in some clinical situations. However, estimates of blast percentage derived from flow cytometry do not provide the same prognostic information as that derived from morphologic evaluation. Accordingly, data from flow cytometry should not be used in lieu of the determination of morphologic blast percentage by an experienced hematopathologist. The screening for paroxysmal nocturnal hemoglobinuria (PNH) and HLA-DR15 is potentially useful for determining which patients may be more responsive to immunosuppressive therapy, particularly in young patients with normal cytogenetics and hypoplastic MDS[20,21] (see Prognostic Stratification, opposite column).

Bone marrow biopsy staining for reticulin is helpful for evaluating the presence and degree of bone marrow fibrosis. Flow cytometry studies should be used to determine the presence of a PNH clone or to assess the possibility of large granular lymphocytic disease. Review of peripheral smear is important to determine the presence of large granular lymphocytic disease.

Additional genetic screening should be considered for patients with familial cytopenias, because it will help evaluate for Fanconi's anemia or dyskeratosis congenita. In addition, this information is of clinical importance because familial MDS is associated with chromosomal fragility, and therefore these patients may have a different response to hypomethylating agents and, more importantly, family members may not be eligible as donors for allogeneic HSCT.

Determining platelet-derived growth factor receptor beta (PDGFRb) gene rearrangements in patients with CMML/MPD with 5q3133 translocations is helpful for evaluation. The activation of this gene encoding a receptor tyrosine kinase for PDGFRb has been shown in

some of these patients.[22,23] Data have indicated that patients with CMML/MPD with these PDGFRb fusion genes may respond well to treatment with imatinib mesylate.[24,25]

The frequency of activating mutations of the tyrosine kinase known as Janus Kinase 2 (JAK2) in MDS and de novo AML is lower compared with myeloproliferative disorders.[26] If thrombocytosis is encountered in patients with MDS, screening for JAK2 mutations may be helpful; a positive result is consistent with the presence of a myeloproliferative component of the disease.[27]

Recent flow cytometric studies suggest the potential efficacy of this methodology for characterizing MDS marrow blast cells and as an aid for assessing prognosis.[28,29] However, because of the nonstandardized nature of these analyses, further investigations are warranted before their routine use can be recommended.

Reports have shown that copper deficiency can mimic many of the peripheral blood and marrow findings seen in MDS.[30-32] Thus, in certain instances assessment of copper and ceruloplasmin levels may be indicated as part of the initial diagnostic workup of suspected MDS. Clinical features associated with copper deficiency include vacuolation of myeloid and/or erythroid precursors,[30-32] prior gastrointestinal surgery,[30,31] and a history of vitamin B_{12} deficiency.[31,33]

Prognostic Stratification

Despite its value for diagnostic categorization of patients with MDS, the prognostic limitations of the FAB classification have become apparent, with variable clinical outcomes within the FAB subgroups. The morphologic features contributing to this variability include the wide range of marrow blast percentages for patients with RAEB (5%–20%) and CMML (1%–20%); lack of inclusion of critical biologic determinants, such as marrow cytogenetics; and the degree and number of morbidity-associated cytopenias. These well-perceived problems for categorizing patients with MDS have led to the development of additional risk-based stratification systems.[34]

The International Prognostic Scoring System (IPSS) for primary MDS emerged from deliberations of the IMRAW.[11] Compared with previously used systems, the risk-based IPSS has markedly improved prognostic stratification of MDS cases. In this analysis, cytogenetic, morphologic, and clinical data were combined and collated from a relatively large group of MDS cases that had been included in previously reported prognostic studies.[11,34] FAB morphologic criteria were used to establish the diagnoses of MDS. In addition, relative stability of peripheral blood counts for 4 to 6 weeks was needed to exclude other possible causes for the cytopenias, such as drugs, other diseases, or incipient evolution to AML. CMML was subdivided into proliferative and nonproliferative subtypes. Patients with proliferative-type CMML (WBC > 12,000/mcL) were excluded from this analysis,[11] whereas those with nonproliferative CMML (WBC ≤ 12,000/mcL and other features of MDS) were included.[35]

Significant independent variables for determining outcome for both survival and AML evolution were found to be marrow blast percentage, number of cytopenias, and cytogenetic

subgroup (good, intermediate, poor). Patients with the chromosome anomalies t(8;21) or inv16 are considered to have AML and not MDS, regardless of the blast count. Age was also a critical variable for survival, although not for AML evolution. The percentage of marrow blasts was divided into 4 categories: 1) less than 5%, 2) 5% to 10%, 3) 11% to 20%, and 4) 21% to 30%. Cytopenias were defined for the IPSS as having hemoglobin level less than 10 g/dL, an absolute neutrophil count less than 1800/mcL, and platelet count less than 100,000/mcL. Patients with normal marrow karyotypes, del(5q) alone, del(20q) alone, and -Y alone had relatively good prognoses (70%), whereas patients with complex abnormalities (≥ 3 chromosome anomalies) or chromosome 7 anomalies had relatively poor prognoses (16%). The remaining patients were intermediate in outcome (14%). Of the patients in the "complex" category, most had chromosome 5 or 7 abnormalities in addition to other anomalies.

To develop the IPSS for MDS, relative risk scores for each significant variable (marrow blast percentage, cytogenetic subgroup, and number of cytopenias) were generated.[11] By combining the risk scores for the 3 major variables, patients were stratified into 4 distinctive risk groups in terms of both survival and AML evolution: low, intermediate-1 (INT-1), intermediate-2 (INT-2), and high.

When either cytopenias or cytogenetic subtypes were omitted from the classification, discrimination among the 4 subgroups was much less precise. Both for survival and AML evolution, the IPSS showed statistically greater prognostic discriminating power than earlier classification methods, including the FAB system.[11]

Recent data indicate that additional clinical variables are additive to the IPSS regarding prognosis for patients with MDS. The WHO prognostic scoring system (WPSS) incorporates the WHO-based morphologic categories, the IPSS cytogenetic categories, and patients' need or lack of dependence on RBC transfusion.[36] This system showed that the requirement for RBC transfusions is a negative prognostic factor for patients in the lower-risk MDS categories. In addition, depth of anemia per se has additive and negative prognostic import for the intermediate IPSS categories.[37] Compared with the 4 groups defined by the IPSS, the WPSS classifies patients into 5 risk groups differing in both survival and risk for AML: very low, low, intermediate, high, and very high. After an initial report by Malcovati et al.[36] regarding the usefulness of WPSS, other studies have confirmed the findings.[38-41] However, whether the WPSS offers an improvement over the IPSS is a matter of ongoing debate. Based on the current available data, the panel included the WPSS in the current version of the treatment algorithm with a category 2B designation.

Therapeutic Options

The patient's IPSS risk category is used in planning therapeutic options because it provides a risk-based patient evaluation (category 2A). In addition, age and performance status are critical determinants because they have a major influence on the patient's ability to tolerate certain intensive treatments. The WPSS provides dynamic estimation of prognosis at any time during the course of MDS.

In patients who were only recently evaluated, determining the relative stability of their blood counts over several months is important to assess disease progression, including incipient transformation to AML. In addition, this assessment permits determination of other possible causes for cytopenias. The patient's preference for a specific approach is also important in deciding treatment options. The therapeutic options for MDS include supportive care, low-intensity therapy, high-intensity therapy, and/or clinical trial. In evaluating results of therapeutic trials, the panel found it important for studies to use the standardized International Working Group (IWG) response criteria.[42,43]

For the MDS therapeutic algorithm, all patients should undergo relevant supportive care. After that, the panel has proposed initially stratifying patients with clinically significant cytopenias into 2 major risk groups: 1) relatively lower-risk patients (who are in the IPSS low and INT-1 categories, or WPSS very low, low, and intermediate categories); and 2) higher-risk patients (who are in the IPSS INT-2 and high categories, or WPSS high and very high categories). Per IWG response criteria, for patients in the lower-risk group, the major therapeutic goal would be hematologic improvement, whereas alteration of the disease natural history is viewed as paramount for those in the higher risk group. Cytogenetic and quality-of-life responses are also important parameters to assess. The algorithms outline management of primary MDS only. Most patients with therapy-related MDS have poorer prognoses than those with primary MDS, including a substantial proportion with poor-risk cytogenetics. These patients are generally man-aged as having higher-risk disease.

Supportive Care

Currently, the standard of care in the community for MDS includes supportive care (see page 39 and the NCCN Guidelines for Supportive Care; to view the most recent version of all guidelines, visit the NCCN Web site at www.NCCN.org). This entails observation, clinical monitoring, psychosocial support, and quality-of-life assessment. Major efforts should be directed toward addressing the relevant quality-of-life domains (e.g., physical, functional, emotional, spiritual, social) that adversely affect patients. Supportive care should include RBC transfusions for symptomatic anemia as needed (generally leukocyte-reduced) or platelet transfusions for severe thrombocytopenia or thrombocytopenic bleeding. The panel reached nonuniform consensus based on differing institutional policies regarding the necessity for routine irradiation of blood products used in patients with MDS; however, the panel agreed that all directed-donor and transfused products for potential stem cell transplant patients should be irradiated. Additionally, CMV-negative blood products are recommended whenever possible for CMV-negative recipients. Aminocaproic acid or other antifibrinolytic agents may be considered for bleeding refractory to platelet transfusions or profound thrombocytopenia.

Hematopoietic cytokine support should be considered for refractory symptomatic cytopenias.[44] For example, recombinant human granulocyte colony stimulating factor (G-CSF) or granulocyte-monocyte CSF (GM-CSF) treatment could be considered for neutropenic patients with MDS with recurrent or resistant bacterial infections. The use of recombinant human erythropoietin to treat symptomatic anemia is discussed in Evaluation and Treatment of Related Anemia (see page 49).

Management of Iron Overload

RBC transfusions are a key component of the supportive care for patients with MDS. Although specific therapies may alleviate the need for an RBC transfusion, a substantial proportion of patients may not experience response to these treatments and may develop iron overload and its consequences.[45] Thus, effective treatment of transfusional siderosis in patients with MDS is germane.

Studies in patients requiring relatively large numbers of RBC transfusions (e.g., those with thalassemia and MDS) have shown the pathophysiology and adverse effects of chronic iron overload on hepatic, cardiac, and endocrine function. Increased non-transferrin-bound iron levels, generated when plasma iron exceeds transferrin's binding capacity, combines with oxygen to form hydroxyl and oxygen radicals. These toxic elements cause lipid peroxidation and cell membrane, protein, DNA, and organ damage.[46,47]

Although limited, retrospective evidence suggests that organ dysfunction can result from iron overload in patients with MDS.[48,49] Retrospective data suggest that transfusional iron overload might be a contributor of increased mortality and morbidity in early-stage MDS.[50] The WPSS has shown that RBC transfusion requirement is a negative prognostic factor for patients with MDS.[36]

For patients with chronic RBC transfusion need, serum ferritin levels and associated organ dysfunction (heart, liver, and pancreas) should be monitored. The panel recommends monitoring serum ferritin levels and number of RBC transfusions received to assess iron overload as a practical a means to determine iron stores. Monitoring serum ferritin may be useful, with the goal of decreasing ferritin levels to less than 1000 mcg/L. Experts recognize that these measurements, although useful, are less precise than SQUID (Superconducting Quantum Interference Device) or the more recent development of specific measurement of hepatic iron content using MRI.[51,52]

Reversal of some of the consequences of iron overload in MDS and other iron overload states (e.g., thalassemia) using iron chelation therapy has been shown in patients in whom the most effective chelation occurred.[43,47] This included transfusion independence in a portion of a small group of carefully studied patients with MDS who had undergone effective deferoxamine chelation for 1 to 4 years.[53] In addition, improvement in cardiac iron content was shown in these patients after chelation.[36,54] These findings have major implications for altering the morbidity of patients with MDS, particularly those with preexisting cardiac or hepatic dysfunction.

The current clinical availability of 2 oral iron chelators in the United States,[55] deferoxamine and deferasirox,[56,57] now provides potentially useful drugs to more readily treat this iron overload state. Although not available in the United States, a third chelating agent, deferiprone, is licensed in Europe for the treatment of iron overload in patients with β-thalassemia when deferoxamine is inadequate or contraindicated.[58]

Clinical trials in MDS are ongoing with oral iron chelating agents to determine whether iron chelation alters the natural history of patients with MDS who are transfusion-dependent. A

recent NCCN task force report titled Transfusion and Iron Overload in Patients with Myelodysplastic Syndromes presents the available evidence regarding iron chelation in patients with MDS.[59]

The panel recommends considering chelation with deferoxamine SC or deferasirox/ICL670 orally once daily to decrease iron overload in patients with low or INT-1 risk disease who have received or are anticipated to receive greater than 20 RBC transfusions, for whom ongoing RBC transfusions are anticipated, and for those with serum ferritin levels greater than 2500 ng/mL, with the goal of decreasing ferritin levels to less than 1000 ng/mL.

Recently a black box warning by the FDA and Novartis was added to deferasirox. After postmarketing use of deferasirox, cases of acute renal failure or hepatic failure were reported, some with a fatal outcome. Most of the reported fatalities occurred in patients with multiple comorbidities and in advanced stages of their hematologic disorders. Additionally, there were postmarketing reports of cytopenias, including agranulocytosis, neutropenia, and thrombocytopenia, and of gastrointestinal bleeding in patients treated with deferasirox, with some patients dying. The relationship of these episodes to treatment with deferasirox has not yet been established. However, the panel recommends closely monitoring patients on deferasirox therapy, including measuring their serum creatinine and/or creatinine clearance and performing liver function tests before initiation of therapy and regularly thereafter.

Low-Intensity Therapy

Low-intensity therapy includes the use of low-intensity chemotherapy or biologic response modifiers. Although this type of treatment is mainly provided in the outpatient setting, certain treatments may require supportive care or occasional hospitalization afterwards (e.g., to treat infections).

Hypomethylating Agents

As a form of relatively low-intensity chemotherapy, the DNA methyltransferase inhibitor (DMTI) hypomethylating agents 5-azacytidine (AzaC) and decitabine (5-aza-2′-deoxycytidine) have been shown in randomized phase III trials to decrease the risk of leukemic transformation and, in a portion of the patients, improve survival.[60,61] For AzaC, hematologic responses occurred in 60% of patients in the azacitidine arm (7% complete response, 16% partial response, 37% improved) compared with an overall 5% response rate in those receiving supportive care. Additionally, the time to progression to AML or death was improved in those who received AzaC earlier in the course of disease, suggesting that the drug prolonged the duration of stable disease. Subsequently Silverman et al.[62] provided a summary of 3 studies of AzaC in a total of 306 patients with high-risk MDS. In this analysis, which included patients receiving either subcutaneous or intravenous delivery of the drug (75 mg/m^2/d for 7 days every 28 days), complete remissions were seen in 10% to 17% of patients treated with AzaC, partial remissions were rare, and 23% to 36% of patients had hematologic improvement. Of the responses, 90% were seen by cycle 6 and the median number of cycles to first response was 3. The authors concluded that AzaC provided important clinical benefits for patients with high-risk MDS. Data from a randomized trial for higher-risk MDS show that AzaC is superior to conventional care (standard chemotherapy

or supportive care) regarding overall survival.[63] Patients randomized to AzaC enjoyed a superior median survival (24 vs. 15 months) compared with those in the control arm, thus providing support for the use of this agent in higher-risk disease.

AzaC therapy should be considered for treating patients with progressing or relatively high-risk MDS. The drug is generally administered at a dose of 75 mg/m^2/d subcutaneously for 7 days monthly for at least 4 to 6 courses. Treatment courses may need to be extended further or may be used as a bridging therapy to more definitive therapy (e.g., HSCT for patients whose marrow blast counts require lowering before that procedure). This drug is FDA-approved for treating patients with MDS.

Similarly, the other DMTI hypomethylating agent, decitabine, given intravenously and administered with a regimen that required hospitalization, has also shown encouraging results in patients with higher-risk MDS. Because the treatment regimen was generally associated with low-intensity-type toxicities, it is also considered to be low intensity therapy. The drug has shown cytogenetic conversion in approximately 30% of patients,[64,65] with an overall response rate of 49% and a 64% response rate in patients with a high-risk IPSS score. The results of these studies were substantially similar to those for AzaC.[66,67]

The results of a phase III randomized trial of decitabine (15 mg/m^2 intravenous infusion over 3 hours every 8 hours [i.e., 45 mg/m^2/d] on 3 consecutive days every 6 weeks for up to 10 cycles) versus supportive care in adult patients with primary and secondary MDS with IPSS INT-1– (31%), INT-2– (44%) and high- (26%) risk disease indicated higher response rates, remission duration, time to AML progression, and survival benefit in patients with INT-2– and high-risk subtypes.[60,66] Overall response rates (complete plus partial responses) were 17%, with an additional 13% having hematologic improvement. The probability of progression to AML or death was 1.68-fold greater for patients receiving supportive care than for those receiving decitabine. Based on this study and 3 supportive phase II trials,[68] the FDA also approved this drug for treating patients with MDS.

Alternate dosing regimens using lower doses of decitabine administered in an outpatient setting are currently being evaluated.[69] In 2007, Kantarjian et al.[70] provided an update of their results in 115 patients with higher-risk MDS using alternative and lower-dose decitabine treatment regimens. Patients received 1 of 3 different schedules of decitabine, including both subcutaneous and intravenous administration, and received a mean of 7 courses of therapy. Responses were improved with this longer duration of therapy. Overall, 80 patients (70%) experienced response, with 40 (35%) experiencing a complete response and 40 (35%) a partial response. The median remission duration was 20 months and the median survival 22 months.

Kantarjian et al.[71] also compared the 3 different schedules of decitabine in a randomized study, with 95 patients with MDS or CMML receiving either 20 mg/m^2 intravenously daily for 5 days; 20 mg/m^2 subcutaneously daily for 5 days; or 10 mg/m^2 intravenously daily for 10 days. The 5-day intravenous schedule was considered the optimal schedule, with a complete response rate of 39% compared with 21% in the 5-day subcutaneous arm and 24% in the 10-day intravenous arm ($P < .05$).

Currently, azacytidine and decitabine are considered therapeutically relatively similar, although the improved survival of higher-risk patients treated with AzaC compared with control patients in a phase III trial supports the preferred use of AzaC in this setting. “Failure to respond to hypomethylating agents” is considered if a lack of complete response, partial response, or hematologic improvement is seen; frank progression to AML occurs, in particular with loss of control (proliferation) of peripheral counts; or excess toxicity precludes continuation of therapy. The minimum number of courses before considering the treatment a failure should be 4 to 6 courses.

Because data have predominantly indicated altered natural history and decreased evolution to AML in patients who experience response to treatment, the major candidates for these drugs are patients with IPSS INT-2– or high-risk MDS, such as:

- Those who are not candidates for high-intensity therapy.
- Those who are potential candidates for allogeneic HSCT but for whom delay in receipt of that procedure is anticipated (e.g., because of time needed to further reduce the blast count, improve the patient’s performance status, or identify a donor). In these circumstances, the drugs may be used as bridging therapy for that procedure.
- Those who experience relapse after allogeneic HSCT.

Biologic Response Modifiers and Immunosuppressive Therapy

Available non–chemotherapy, low-intensity agents (biologic response modifiers) include antithymocyte globulin (ATG), cyclosporine, thalidomide, lenalidomide, anti-tumor necrosis factor receptor fusion protein, and vitamin D analogues, all of which have shown some efficacy in phase I and II trials.[1,72-77]

Use of anti-immune–type therapy with ATG with or without cyclosporine[74,75] has been shown in several studies to be most efficacious in patients with MDS with HLA-DR15 histocompatability type, marrow hypoplasia, normal cytogenetics, low-risk disease, and evidence of a PNH clone.[20,21] The NIH group updated their analysis of 129 patients treated with immunosuppressive therapy involving ATG and cyclosporine alone or in combination.[78] This study showed markedly improved response rates in younger (age ≤ 60 years) and INT-1–risk patients and those with high response probability characteristics as indicated by their prior criteria (HLA-DR15+, age, and number of transfusions).[78]

Encouraging data have been presented for treating patients with lower-risk MDS with lenalidomide.[12,79] Beneficial results have been particularly evident for patients with del(5q) chromosomal abnormalities.[12,79,80] In a multicenter phase II trial of lenalidomide, given at a dose of 10 mg/d for 21 days every 4 weeks or 10 mg daily to 148 patients with MDS with del(5q) and RBC transfusion-dependent anemia, with or without additional cytogenetic abnormalities, the response to lenalidomide was rapid (median time to response, 4.6 weeks; range, 1–49 weeks) and sustained. RBC transfusion independence (assessed at 24 weeks) occurred in 66% of patients with IPSS low/INT-1 compared with 52% of patients with higher-risk disease.[12] Cytogenetic responses occurred in 76% of patients; 55% had a

complete cytogenetic response. However, common adverse events occurred (in ~50% of patients) that required treatment interruption or dose reduction because of potentially serious but generally transient neutropenia and/or thrombocytopenia. Thus, careful monitoring of patients' blood counts during treatment is mandatory when using this agent, particularly in those with renal dysfunction (from the drug's renal route of excretion). The FDA recently approved lenalidomide for treating patients with MDS with del(5q).

A phase II study evaluated lenalidomide treatment in 214 transfusion-dependent patients with low- or INT-1–risk MDS without del(5q).[81] Results showed 26% of the non-del(5q) patients (56 of 214) experienced transfusion independence after a median of 4.8 weeks of treatment. Transfusion independence continued for a median duration of 41 weeks, and the median rise in hemoglobin was 3.2 g/dL (range, 1.0–9.8 g/dL) for these patients. A 50% or greater reduction in transfusion requirement was noted in an additional 37 patients (17%), yielding an overall rate of hematologic improvement of 43%. The most common grade 3/4 adverse events were neutropenia (30%) and thrombocytopenia (25%). Further evaluation in more extended clinical trials is needed to determine the efficacy of this drug and other agents in patients with MDS without del(5q). The panel recommends that lenalidomide be considered for treatment of symptomatically anemic non-del(5q) patients whose anemia did not respond to initial therapy.

High-Intensity Therapy

High-intensity therapy includes intensive induction chemotherapy or HSCT.[1,82] Although these approaches have the potential to change the natural history of the disease, they also have an attendant greater risk of regimen-related morbidity and mortality. The panel recommends giving these treatments in the context of clinical trials. Recent comparative studies have not shown benefit between several different intensive chemotherapy regimens (including idarubicin-, cytarabine-, fludarabine-, and topotecan-based regimens) in MDS.[83]

A high degree of multidrug resistance occurs in marrow hematopoietic precursors from patients with advanced MDS,[84] with decreased responses and shorter response durations associated with many standard regimens of induction chemotherapy. Thus, chemotherapeutic agents used to treat "resistant-type" AML, and agents that modulate this resistance, are now being evaluated for treating patients with advanced MDS. Although several studies using multidrug resistance modulators were positive in this setting,[85,86] others were not.[87] Further clinical trials evaluating other multidrug resistance modulators are ongoing.

Allogeneic HSCT from an HLA-matched sibling donor is a preferred approach for treating a portion of patients with MDS, particularly those with high-risk disease.[88-96] Matched nonmyeloablative transplant regimens[97,98] and matched unrelated donor stem cell transplants[99-101] are becoming options at some centers to treat these patients. In certain investigative settings, autologous bone marrow or peripheral blood stem cell transplantation is being considered.[102] Whether transplants should be performed before or after patients experience remission following induction chemotherapy has not been established.[103] Comparative clinical trials are needed to determine these points.

Recommended Treatment Approaches

Therapy for Lower-Risk Patients (IPSS Low, INT-1 or WPSS Very Low, Low, and Intermediate)

Regarding the algorithm for therapeutic options for lower-risk patients with clinically significant cytopenias, the panel recommends stratifying these patients into several groups. Those with del(5q) chromosomal abnormalities and symptomatic anemia should receive lenalidomide. Other patients with symptomatic anemia are categorized based on levels of sEpo. Those with levels of 500 mU/mL or less should be treated with recombinant human erythropoietin or darbepoetin with or without G-CSF (see Evaluation and Treatment of Related Anemia, opposite page). Non-responders should be considered for treatment with azacytidine or decitabine or for lenalidomide therapy. In addition, these patients or nonresponders to this therapy could be considered for participation in a clinical trial with other relevant agents, or for allogeneic HSCT (see Allogeneic HSCT, opposite column).

Anemic patients with sEpo levels greater than 500 should be evaluated to determine whether they have a good probability of responding to immunosuppressive therapy. The most appropriate candidates include those who either are aged 60 years or younger (with IPSS low, INT-1 MDS or WPSS very low, low, or intermediate), are HLA-DR15–positive, have a PNH-positive clone, or have hypoplastic MDS. Immunosuppressive therapy consists of ATG or cyclosporine. Nonresponders to immunosuppressive therapy would be considered for treatment with azacytidine, decitabine, or a clinical trial. Patients with sEpo levels greater than 500 mU/mL who have a low probability of responding to immunosuppressive therapy should be considered for treatment with azacytidine, decitabine, or lenalidomide. Others or nonresponders to that therapy could be considered for a clinical trial or for allogeneic HSCT. Patients with other serious cytopenias (particularly clinically severe thrombocytopenia) should be considered for treatment with azacytidine or decitabine or a clinical trial. Patients who experience no response this treatment should be considered for treatment with immunosuppressive therapy, a clinical trial, or allogeneic HSCT.

Careful monitoring for disease progression and consideration of the patient’s desires play major roles in the timing and decision to embark on treatment for lower- or higher-risk disease.

Therapy for Higher-Risk Patients (IPSS INT-2, High or WPSS High, Very High)

Treatment for higher-risk patients depends on whether they are believed to be candidates for intensive therapy (e.g., allogeneic HSCT, intensive chemotherapy). Clinical features relevant for this determination include patient age, performance status, absence of major comorbid conditions, psychosocial status, patient preference, and availability of a suitable donor and caregiver. In addition, the patient’s personal preference for type of therapy needs particular consideration. Supportive care should be provided for all patients.

Intensive Therapy

Allogeneic HSCT—The potential for patients to undergo allogeneic HSCT depends on several factors, including patient age, performance status, major comorbid conditions,

psychosocial status, availability of a caregiver, IPSS or WPSS score, and availability of a suitable donor. For those who are transplant candidates, the first choice of donor has remained an HLA-matched sibling, although results with HLA-matched unrelated donors have improved to levels comparable to those obtained with HLA-matched siblings. With the increasing use of cord blood or HLA haploidentical related donors, HSCT has become a viable option for many patients. High-dose conditioning is typically used for younger patients, whereas the approach using reduced/low-intensity conditioning (RIC) for HSCT is generally the strategy in older individuals.[104]

To aid therapeutic decision-making regarding the timing and selection of patients for HSCT, a study compared outcomes in patients with MDS aged 60 years or younger who underwent HSCT from HLA-matched siblings with those in nontreated patients with MDS from the IMRAW/IPSS database. Using a Markov decision analysis, this investigation indicated that IPSS INT-2 and high-risk patients aged 60 years or younger had the highest life expectancy if transplantation occurred (from HLA-identical siblings) soon after diagnosis, whereas patients with IPSS low-risk MDS had the best outlook if HSCT was delayed until disease progression. Patients in the INT-1 risk group only had a slight gain in life expectancy if HSCT was delayed, and therefore decisions should probably be made on an individual basis in these patients (e.g., dependent on platelet or neutrophil counts).[105] A study published in 2008 retrospectively evaluated the impact of the WHO classification and WPSS on the outcome of patients who underwent allogeneic HSCT.[38] The data suggest that lower-risk patients (based on WPSS risk score) do very well with allogeneic HSCT, with a 5-year overall survival of 80%. With increasing WPSS scores, the probability of 5-year survival after HSCT declined progressively to 65% (intermediate risk), 40% (high risk), and 15% (very high risk).[38]

Based on recent data regarding RIC for transplantation from 2 reported series[106,107] and 2 comprehensive reviews of this field,[108,109] patient age and disease status generally dictate the type of conditioning to be used. Patients older than 55 or 60 years, particularly if they have fewer than 10% marrow myeloblasts, would generally undergo HSCT after RIC; if the blast count is high, pre-HSCT debulking therapy is generally given. Younger patients, regardless of marrow blast burden, will generally receive high-dose conditioning. Variations on these approaches would be considered by the individual transplant physician based on these features and the specific regimen used at that center. Some general recommendations were presented recently in a review in *Blood*.[110]

Intensive Chemotherapy

For patients eligible for intensive therapy lacking a stem cell donor, or those requiring reduction of marrow blast count, intensive induction chemotherapy should be considered.[111] Although the response rate and durability of this treatment is lower than for standard AML, this treatment (particularly in clinical trials with novel agents) could be beneficial in a portion of patients. For patients with a potential stem cell donor who require reduction of tumor burden (i.e., to decrease the marrow blast count), even a partial remission may be adequate to permit the HSCT. For this purpose, AzaC, decitabine, and participation in clinical trials are also available treatment options.

Nonintensive Therapy

For higher-risk patients who are not candidates for intensive therapy, the use of AzaC, decitabine, or participation in a relevant clinical trial should be considered. Based on the recently published results of the phase III trial showing superior median survival in patients receiving AzaC compared with best supportive care, the panel made this a preferred category 1 recommendation compared with decitabine. Preliminary results of another recent trial comparing decitabine with supportive care in higher-risk patients failed to show a survival advantage, although response rates are similar to those reported previously for AzaC.[112] However, no trials have compared AzaC and decitabine directly.

For some patients eligible for HSCT therapy requiring a reduction in tumor burden, the use of AzaC or decitabine may be a bridge to usefully decrease the marrow blast count enough to permit the transplant.

Supportive Care Only

For patients with adverse clinical features or disease progression despite therapy and absence of reasonable specific antitumor therapy, good supportive care should be maintained.

Evaluation and Treatment of Related Anemia

Major morbidities of MDS include symptomatic anemia and its associated fatigue. Much progress has been made in improving the management of this anemia. However, along with giving specific treatment for anemia related to MDS, health care providers must identify and treat any coexisting causes of anemia.

Standard assessments should be performed to look for other causes of anemia, such as gastrointestinal bleeding, hemolysis, renal disease, and nutritional deficiency. If needed, iron, folate, or vitamin B_{12} studies should be obtained and the cause of depletion corrected if possible. After excluding these causes and providing proper treatment for them, treatment for the MDS-related anemia should be considered further. Currently, the standard of care for symptomatic anemic patients is RBC transfusion support (using leuko-poor products). If the patient is a potential HSCT candidate, the panel recommends that CMV-negative (if the patient is CMV-negative serologically) and irradiated transfused products be considered.

Anemia related to MDS generally presents as a hypoproductive macrocytic anemia, often associated with suboptimal elevation of sEpo levels.[1,113] To determine FAB subtype, iron status, and the level of ring sideroblasts, bone marrow aspiration with iron stain, biopsy, and cytogenetics should be examined. Patients also should be considered for HLA-DR15 typing.

Individuals with symptomatic anemia and del(5q) with or without other cytogenetic abnormalities should receive a trial of lenalidomide. Those with normal cytogenetics, less than 15% marrow ringed sideroblasts, and sEpo levels of 500 mU/mL or less may respond to erythropoietin if relatively high doses of recombinant human erythropoietin are administered.[44,114,115] The required erythropoietin dose is 40,000 to 60,000 units given 1 to 3 times a week subcutaneously. Erythroid responses generally occur within 6 to 8 weeks of

treatment.[116-119] A more prompt response may be obtained by starting at the higher dose; this dose is much higher than that needed to treat renal causes of anemia wherein marrow responsiveness would be relatively normal. If a response occurs, the recommendation is to continue this dose but attempt to decrease it to tolerance. The literature supports daily or 2- to 3-times-per-week dosing.

Iron repletion must be verified before instituting erythropoietin or darbepoetin therapy. If no response occurs with these agents alone, the addition of G-CSF should be considered. Evidence suggests that G-CSF (and to a lesser extent GM-CSF) has synergistic erythropoietic activity when used in combination and markedly enhances the erythroid response rates.[115-118] This is particularly evident for patients with 15% or more ringed sideroblasts in the marrow (and sEpo level ≤ 500 mU/mL), because the very low response rates in this subgroup to erythropoietin or darbepoetin alone are markedly enhanced when combined with G-CSF.[117,118]

For the erythroid synergistic effect, relatively low doses of G-CSF are needed to help normalize the neutrophil count in initially neutropenic patients or to double the neutrophil count in those who are initially normal. For this purpose, an average of 1 to 2 mcg/kg is administered subcutaneously daily or 1 to 3 times a week.[115-118] Refrigerated multidose vials (withdrawing all contents at one time into separate syringes and leaving them in the refrigerator until used) permit more efficient use of G-CSF, decreasing its cost. Patients may be taught to self-administer the drug. Again, detection of erythroid responses generally occurs within 6 to 8 weeks of treatment. If no response occurs in this timeframe, this treatment should be considered a failure and discontinued. If treatment failure occurs, deficient iron stores should be ruled out and treated. Clinical trials or supportive care are also treatment options in these patients. A predictive and validated model has been developed for predicting erythroid responses to erythropoietin plus G-CSF, based on the patient's basal sEpo level and number of previous RBC transfusions.[118,120] Improved quality of life has been shown in patients experiencing response.[120] This cytokine treatment is not suggested for patients with endogenous sEpo levels greater than 500 mU/mL because of the very low erythroid response rate to these drugs.

Darbepoetin alfa is a longer-acting form of erythropoietin. Studies predominantly involving patients with lower-risk MDS have shown a substantial proportion of erythroid responses, with the initial trials showing response rates of 40% and 60% (combined major and minor responses using IWG response criteria).[121,122] Results of clinical trials in patients with MDS have suggested that the overall response rates to darbepoetin are similar to or possibly higher than those to epoetin.[121-124] These response rates may be partly from the dosage used (150–300 mcg/week, subcutaneously) or because better-risk patients were enrolled in studies of darbepoetin compared with epoetin. Features predictive of response have included relatively low basal sEpo levels, low percentage of marrow blasts, and relatively few prior RBC transfusions.

In March 2007 and 2008, the FDA announced alerts and strengthened safety warnings for the use of erythropoiesis stimulating agents (ESAs). They noted that increased mortality, possible tumor promotion, and thromboembolic events were observed in patients without

MDS receiving ESAs when dosing has targeted hemoglobin levels greater than 12 g/dL (study patients had chronic kidney failure; were undergoing radiation therapy for various malignancies, including head and neck, advanced breast, lymphoid, and non–small cell lung cancers; had cancer and were not undergoing chemotherapy; or were orthopedic surgery patients).

However, ESAs have been used safely in large numbers of adult patients with MDS and have become important for symptomatic improvement of those affected by anemia caused by this disease, often with a decrease in RBC transfusion requirements. The panel recommendations for use of ESAs in MDS have evolved from these and more recent data. In addition, studies assessing the long-term use of erythropoietin with or without G-CSF in patients with MDS compared with either randomized[125] or historical controls[126,127] have shown this treatment has no negative impact on survival or AML evolution. In addition, results of the studies by Jadersten et al.[126] indicated improved survival in patients with low-risk MDS with low transfusion need treated with these agents. The study by Park et al.[127] further indicated improved survival and decreased AML progression in IPSS low/INT-1 patients treated with erythropoietin/G-CSF compared with the historical controls from the IMRAW database. Thus, these data do not indicate a negative impact of these drugs in the treatment of MDS. Given these data, the panel endorses and reiterates its prior recommendations for ESA use in the management of symptomatic anemia in patients with MDS, but with a change in the target hemoglobin level (i.e., with the goal of achieving a target hemoglobin of ≤ 12 g/dL).

In July 2007, the Centers for Medicare & Medicaid Services modified the scope of their decision regarding the use of ESAs in cancer and related neoplastic conditions to make no national coverage determination (NCD) on the use of ESAs in MDS (i.e., not restricting ESA use in MDS through the NCD). Thus, local Medicare contractors may continue to make reasonable and necessary determinations on uses of ESAs that are not determined by the NCD.

Clinical trials with other experimental agents that are reportedly capable of increasing hemoglobin levels should be explored in patients not experiencing response to standard therapy. These drugs should be used in the context of therapeutic approaches for the patient’s underlying prognostic risk group.

Summary

These suggested practice guidelines are based on extensive evaluation of the reviewed risk-based data and indicate useful current approaches for managing patients with MDS. Four drugs have recently been approved by the FDA for treating specific subtypes of MDS: lenalidomide for MDS patients with del(5q) cytogenetic abnormalities; azacytidine and decitabine for treating patients with higher-risk or nonresponsive MDS; and deferasirox for iron chelation of iron overloaded patients with MDS. However, because a substantial proportion of patient subsets with MDS lack effective treatment for their cytopenias or for altering disease natural history, clinical trials with these and other novel therapeutic agents along with supportive care remain the hallmark of management for this disease. The role of

thrombopoietic cytokines for management of thrombocytopenia in MDS needs further evaluation. In addition, further determination of the effects of these therapeutic interventions on the patient's quality of life is important.[116,119,120,128,129] Progress toward improving management of MDS has occurred over the past few years, and more advances are anticipated using these guidelines as a framework for coordination of comparative clinical trials.

Appendix 1

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g., randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines™ is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way.

Disclosures for the NCCN Guidelines Panel for Myelodysplastic Syndromes

At the beginning of each NCCN Guidelines panel meeting, panel members disclosed any financial support they have received from industry. Through 2008, this information was published in an aggregate statement in *JNCCN* and online. Furthering NCCN's commitment to public transparency, this disclosure process has now been expanded by listing all potential conflicts of interest respective to each individual expert panel member.

Individual disclosures for the NCCN Guidelines for Myelodysplastic Syndromes panel members can be found on page 56. (The most recent version of these guidelines and accompanying disclosures, including levels of compensation, are available on the NCCN Web site at www.NCCN.org.)

These guidelines are also available on the Internet. For the latest update, please visit www.NCCN.org.

Appendix 2

Individual Disclosures of the NCCN Myelodysplastic Syndromes Panel

Panel Member	Clinical Research Support	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
Eyal Attar, MD	None	Celgene Corporation	None	None	12/4/09
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Clara D. Bloomfield, MD	None	None	None	None	9/28/09
Carlos M. De Castro, MD	Celgene Corporation; Cephalon, Inc.; and Pharmion Corporation	Alexion Pharmaceuticals, Inc.; Celgene Corporation; Jannsen Pharmaceutica Products, LP; and Pharmion Corporation	None	None	7/7/09
H. Joachim Deeg, MD	None	None	None	None	12/8/09
James M. Foran, MD	Eisai Inc.; Genzyme Corporation; and Medarex, Inc.	Celgene Corporation; and Sunesis Pharmaceuticals, Inc.	None	None	2/9/10
Karin Gaensler, MD	None	None	None	None	9/21/10
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Peter L. Greenberg, MD	Amgen Inc.; Celgene Corporation; Eisai Inc.; GlaxoSmithKline; Novartis Pharmaceuticals Corporation; and Onconova	Amgen Inc.; and Novartis Pharmaceuticals Corporation	None	None	4/23/10
David Head, MD	None	None	None	None	9/21/10
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Michael M. Millenson, MD	None	Amgen Inc.; Celgene Corporation; and GlaxoSmithKline	None	sanofi-aventis U.S.	12/8/09
Stephen D. Nimer, MD	None	None	None	None	12/28/09

Panel Member	Clinical Research Support	Advisory Boards, Speakers Bureau, Expert Witness, or Consultant	Patent, Equity, or Royalty	Other	Date Completed
Margaret R. O'Donnell, MD	National Cancer Institute	Anti-soma	None	None	5/24/10
Mark A. Schroeder, MD	None	None	None	None	6/4/10
Paul J. Shami, MD	Genzyme Corporation	Genzyme Corporation; Novartis Pharmaceuticals Corporation; and Novartis Pharmaceuticals Corporation	None	None	10/7/10
Richard M. Stone, MD	Novartis Pharmaceuticals Corporation	Celgene Corporation; Cephalon, Inc.; Genzyme Corporation; and Merck & Co., Inc.	None	None	2/9/10
James E. Thompson, MD	None	None	None	None	4/28/10
Peter Westervelt, MD, PhD	None	Celgene Corporation; and Novartis Pharmaceuticals Corporation	None	None	10/6/09

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References

1. Greenberg, P. The myelodysplastic syndromes. In: Hoffman, R.; Benz, E.; Shattil, S., et al., editors. Hematology: Basic Principles and Practice. 3rd ed.. Churchill Livingstone; New York, NY: 2000. p. 1106-1129.
2. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. Br J Haematol. 1982; 51:189–199. [PubMed: 6952920]
3. Kouides PA, Bennett JM. Morphology and classification of the myelodysplastic syndromes and their pathologic variants. Semin Hematol. 1996; 33:95–110. [PubMed: 8722681]
4. Brunning, R.; Bennett, J.; Flandrin, G., et al. Myelodysplastic syndromes. In: Jaffe, E.; Harris, N.; Stein, H., et al., editors. WHO Classification of Tumours. Pathology and Genetics of Haematopoietic and Lymphoid Tissues. IARC Press; Lyon, France: 2001. p. 61-73.
5. Harris NL, Jaffe ES, Diebold J, et al. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid tissues: report of the Clinical Advisory Committee meeting-Airlie House, Virginia, November 1997. J Clin Oncol. 1999; 17:3835–3849. [PubMed: 10577857]
6. Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. Blood. 2002; 100:2292–2302. [PubMed: 12239137]
7. Kaloutsi V, Kohlmeyer U, Maschek H, et al. Comparison of bone marrow and hematologic findings in patients with human immunodeficiency virus infection and those with myelodysplastic syndromes and infectious diseases. Am J Clin Pathol. 1994; 101:123–129. [PubMed: 8116565]
8. Swerdlow, S.; Campo, E.; Harris, NL., et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. IARC Press; Lyon, France: 2008. p. 88-103.
9. Brunning, R.; Orazi, A.; Germing, U., et al. Myelodysplastic syndromes/neoplasms. In: Swerdlow, SH.; Campo, E.; Harris, NL., et al., editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed.. IARC Press; Lyon, France: 2008. p. 88-103.

10. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the WHO classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood. 2009; 114:937–951. [PubMed: 19357394]
11. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. Blood 1997;89:2079-2088. Erratum in: Blood. 1998; 2091:1100.
12. List A, Dewald G, Bennett J, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. N Engl J Med. 2006; 355:1456–1465. [PubMed: 17021321]
13. Orazi, ABJ.; Germing, U.; et al.Swerdlow, SH.; Campo, E.; Harris, NL., et al., editors. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed.. IARC Press; Lyon, France: 2008. Myelodysplastic/myeloproliferative neoplasms; p. 76-86.
14. Albitar M, Manshouri T, Shen Y, et al. Myelodysplastic syndrome is not merely “preleukemia”. Blood. 2002; 100:791–798. [PubMed: 12130488]
15. Greenberg P, Anderson J, de Witte T, et al. Members of the International MDS Study Group. Problematic WHO reclassification of myelodysplastic syndromes. J Clin Oncol. 2000; 18:3447–3452. [PubMed: 11013289]
16. Germing U, Gattermann N, Strupp C, et al. Validation of the WHO proposals for a new classification of primary myelodysplastic syndromes: a retrospective analysis of 1600 patients. Leuk Res. 2000; 24:983–992. [PubMed: 11077111]
17. Nosslinger T, Reisner R, Koller E, et al. Myelodysplastic syndromes, from French-American-British to World Health Organization: comparison of classifications on 431 unselected patients from a single institution. Blood. 2001; 98:2935–2941. [PubMed: 11698274]
18. Arber, D.; Porwit, A.; Brunning, RD., et al. Acute myeloid leukaemia with myelodysplasia-related changes. In: Jaffe, ES.; Harris, NL.; Stein, H.; Vardiman, JW., editors. Acute Myeloid Leukemia and Related Precursor Neoplasms. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. 4th ed.. IARC Press; Lyon, France: 2008. p. 124-126.
19. Valent P, Horny HP, Bennett JM, et al. Definitions and standards in the diagnosis and treatment of the myelodysplastic syndromes: consensus statements and report from a working conference. Leuk Res. 2007; 31:727–736. [PubMed: 17257673]
20. Dunn DE, Tanawattanacharoen P, Boccuni P, et al. Paroxysmal nocturnal hemoglobinuria cells in patients with bone marrow failure syndromes. Ann Intern Med. 1999; 131:401–408. [PubMed: 10498555]
21. Sauntharajah Y, Nakamura R, Nam JM, et al. HLA-DR15 (DR2) is overrepresented in myelodysplastic syndrome and aplastic anemia and predicts a response to immunosuppression in myelodysplastic syndrome. Blood. 2002; 100:1570–1574. [PubMed: 12176872]
22. Baxter EJ, Kulkarni S, Vizmanos JL, et al. Novel translocations that disrupt the platelet-derived growth factor receptor beta (PDGFRB) gene in BCR-ABL-negative chronic myeloproliferative disorders. Br J Haematol. 2003; 120:251–256. [PubMed: 12542482]
23. Steer EJ, Cross NC. Myeloproliferative disorders with translocations of chromosome 5q31-35: role of the platelet-derived growth factor receptor Beta. Acta Haematol. 2002; 107:113–122. [PubMed: 11919393]
24. Apperley JF, Gardembas M, Melo JV, et al. Response to imatinib mesylate in patients with chronic myeloproliferative diseases with rearrangements of the platelet-derived growth factor receptor beta. N Engl J Med. 2002; 347:481–487. [PubMed: 12181402]
25. Magnusson MK, Meade KE, Nakamura R, et al. Activity of STI571 in chronic myelomonocytic leukemia with a platelet-derived growth factor beta receptor fusion oncogene. Blood. 2002; 100:1088–1091. [PubMed: 12130532]
26. Steensma DP, Dewald GW, Lasho TL, et al. The JAK2 V617F activating tyrosine kinase mutation is an infrequent event in both “atypical” myeloproliferative disorders and myelodysplastic syndromes. Blood. 2005; 106:1207–1209. [PubMed: 15860661]
27. Szpurka H, Tiu R, Murugesan G, et al. Refractory anemia with ringed sideroblasts associated with marked thrombocytosis (RARS-T), another myeloproliferative condition characterized by JAK2 V617F mutation. Blood. 2006; 108:2173–2181. [PubMed: 16741247]

28. Ogata K, Nakamura K, Yokose N, et al. Clinical significance of phenotypic features of blasts in patients with myelodysplastic syndrome. Blood. 2002; 100:3887–3896. [PubMed: 12393641]
29. Wells DA, Benesch M, Loken MR, et al. Myeloid and monocytic dyspoiesis as determined by flow cytometric scoring in myelodysplastic syndrome correlates with the IPSS and with outcome after hematopoietic stem cell transplantation. Blood. 2003; 102:394–403. [PubMed: 12649150]
30. Gregg XT, Reddy V, Prchal JT. Copper deficiency masquerading as myelodysplastic syndrome. Blood. 2002; 100:1493–1495. [PubMed: 12149237]
31. Haddad AS, Subbiah V, Lichtin AE, et al. Hypocupremia and bone marrow failure. Haematologica. 2008; 93:e1–5. [PubMed: 18166767]
32. Koca E, Buyukasik Y, Cetiner D, et al. Copper deficiency with increased hematogones mimicking refractory anemia with excess blasts. Leuk Res. 2008; 32:495–499. [PubMed: 17706281]
33. Prodan CI, Bottomley SS, Vincent AS, et al. Hypocupremia associated with prior vitamin B12 deficiency. Am J Hematol. 2007; 82:288–290. [PubMed: 16986134]
34. Sanz GF, Sanz MA, Greenberg PL. Prognostic factors and scoring systems in myelodysplastic syndromes. Haematologica. 1998; 83:358–368. [PubMed: 9592987]
35. Bennett JM, Catovsky D, Daniel MT, et al. The chronic myeloid leukaemias: guidelines for distinguishing chronic granulocytic, atypical chronic myeloid, and chronic myelomonocytic leukaemia. Proposals by the French-American-British Cooperative Leukaemia Group. Br J Haematol. 1994; 87:746–754. [PubMed: 7986717]
36. Malcovati L, Porta MG, Pascutto C, et al. Prognostic factors and life expectancy in myelodysplastic syndromes classified according to WHO criteria: a basis for clinical decision making. J Clin Oncol. 2005; 23:7594–7603. [PubMed: 16186598]
37. Kao JM, McMillan A, Greenberg PL. International MDS risk analysis workshop (IMRAW)/IPSS reanalyzed: impact of cytopenias on clinical outcomes in myelodysplastic syndromes. Am J Hematol. 2008; 83:765–770. [PubMed: 18645988]
38. Alessandrino EP, Della Porta MG, Bacigalupo A, et al. WHO classification and WPSS predict posttransplantation outcome in patients with myelodysplastic syndrome: a study from the Gruppo Italiano Trapianto di Midollo Osseo (GITMO). Blood. 2008; 112:895–902. [PubMed: 18497321]
39. Cermak J, Kacirkova P, Mikulenkova D, Michalova K. Impact of transfusion dependency on survival in patients with early myelodysplastic syndrome without excess of blasts. Leuk Res. 2009; 33:1469–1474. [PubMed: 19646756]
40. Malcovati L, Germing U, Kuendgen A, et al. Time-dependent prognostic scoring system for predicting survival and leukemic evolution in myelodysplastic syndromes. J Clin Oncol. 2007; 25:3503–3510. [PubMed: 17687155]
41. Park MJ, Kim HJ, Kim SH, et al. Is International Prognostic Scoring System (IPSS) still standard in predicting prognosis in patients with myelodysplastic syndrome? External validation of the WHO Classification-Based Prognostic Scoring System (WPSS) and comparison with IPSS. Eur J Haematol. 2008; 81:364–373. [PubMed: 18637029]
42. Cheson BD, Bennett JM, Kantarjian H, et al. Report of an international working group to standardize response criteria for myelodysplastic syndromes. Blood. 2000; 96:3671–3674. [PubMed: 11090046]
43. Greenberg, P.; Baer, M.; Bennett, J., et al. NCCN Clinical Practice Guidelines in Oncology. National Comprehensive Cancer Network; Rockledge, PA: 2001. NCCN Myelodysplastic Syndromes Guidelines. Version 1, 2001, CD-ROMTo view the most recent version of the guideline, go to www.NCCN.org
44. Greenberg P. The role of hemopoietic growth factors in the treatment of myelodysplastic syndromes. Int J Pediatr Hematol Oncol. 1997; 4:231–238.
45. Greenberg PL. Myelodysplastic syndromes: iron overload consequences and current chelating therapies. J Natl Compr Canc Netw. 2006; 4:91–96. [PubMed: 16403408]
46. Farquhar MJ, Bowen DT. Oxidative stress and the myelodysplastic syndromes. Int J Hematol. 2003; 77:342–350. [PubMed: 12774921]
47. Hershko C, Link G, Cabantchik I. Pathophysiology of iron overload. Ann N Y Acad Sci. 1998; 850:191–201. [PubMed: 9668540]

48. Jaeger M, Aul C, Sohngen D, et al. Secondary hemochromatosis in polytransfused patients with myelodysplastic syndromes. Beitr Infusionsther. 1992; 30:464–468. in German. [PubMed: 1284762]
49. Schafer AI, Cheron RG, Dluhy R, et al. Clinical consequences of acquired transfusional iron overload in adults. N Engl J Med. 1981; 304:319–324. [PubMed: 6777701]
50. Malcovati L. Impact of transfusion dependency and secondary iron overload on the survival of patients with myelodysplastic syndromes. Leuk Res. 2007; 31(Suppl 3):S2–6. [PubMed: 18037415]
51. Brittenham GM, Badman DG. Noninvasive measurement of iron: report of an NIDDK workshop. Blood. 2003; 101:15–19. [PubMed: 12393526]
52. St Pierre TG, Clark PR, Chua-anusorn W, et al. Noninvasive measurement and imaging of liver iron concentrations using proton magnetic resonance. Blood. 2005; 105:855–861. [PubMed: 15256427]
53. Jensen PD, Heickendorff L, Pedersen B, et al. The effect of iron chelation on haemopoiesis in MDS patients with transfusional iron overload. Br J Haematol. 1996; 94:288–299. [PubMed: 8759889]
54. Jensen PD, Jensen FT, Christensen T, et al. Evaluation of myocardial iron by magnetic resonance imaging during iron chelation therapy with deferrioxamine: indication of close relation between myocardial iron content and chelatable iron pool. Blood. 2003; 101:4632–4639. [PubMed: 12576333]
55. Cohen AR, Galanello R, Piga A, et al. Safety and effectiveness of long-term therapy with the oral iron chelator deferiprone. Blood. 2003; 102:1583–1587. [PubMed: 12763939]
56. Nisbet-Brown E, Olivieri NF, Giardina PJ, et al. Effectiveness and safety of ICL670 in iron-loaded patients with thalassaemia: a randomised, double-blind, placebo-controlled, dose-escalation trial. Lancet. 2003; 361:1597–1602. [PubMed: 12747879]
57. Piga A, Galanello R, Cappellini MD, et al. Phase II study of ICL670, an oral chelator, in adult thalassaemia patients with transfusional iron overload: efficacy, safety, pharmaco kinetics (PK) and pharmacodynamics (PD) after 18 months of therapy. Blood. 2003; 102 abstract. Abstract 412.
58. Olivieri NF, Koren G, Hermann C, et al. Comparison of oral iron chelator L1 and desferrioxamine in iron-loaded patients. Lancet. 1990; 336:1275–1279. [PubMed: 1978115]
59. Greenberg, P.; Rigsby, CK.; Stone, RM., et al. NCCN Task Force Report: transfusion and iron overload in patients with myelodysplastic syndromes. Available at: http://www.nccn.org/JNCCN/PDF/2009_Transfussion_MDS_TF.pdf [Accessed November 22, 2010]
60. Kantarjian H, Issa JP, Rosenfeld CS, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. Cancer. 2006; 106:1794–1803. [PubMed: 16532500]
61. Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. J Clin Oncol. 2002; 20:2429–2440. [PubMed: 12011120]
62. Silverman LR, McKenzie DR, Peterson BL, et al. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. J Clin Oncol. 2006; 24:3895–3903. [PubMed: 16921040]
63. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. Lancet Oncol. 2009; 10:223–232. [PubMed: 19230772]
64. Lubbert M, Wijermans P, Kunzmann R, et al. Cytogenetic responses in high-risk myelodysplastic syndrome following low-dose treatment with the DNA methylation inhibitor 5-aza-2′-deoxycytidine. Br J Haematol. 2001; 114:349–357. [PubMed: 11529854]
65. Wijermans P, Lubbert M, Verhoef G, et al. Low-dose 5-aza-2′-deoxycytidine, a DNA hypomethylating agent, for the treatment of high-risk myelodysplastic syndrome: a multicenter phase II study in elderly patients. J Clin Oncol. 2000; 18:956–962. [PubMed: 10694544]
66. Saba H, Rosenfeld C, Issa JP, et al. First report of the phase III north American trial of decitabine in advanced myelodysplastic syndrome (MDS). Blood. 2004; 104 abstract. Abstract 67.

67. van den Bosch J, Lubbert M, Verhoef G, Wijermans PW. The effects of 5-aza-2′-deoxycytidine (Decitabine) on the platelet count in patients with intermediate and high-risk myelodysplastic syndromes. Leuk Res. 2004; 28:785–790. [PubMed: 15203276]
68. Saba HI, Lubbert M, Wijermans PW. Response rates of phase 2 and phase 3 trials of decitabine (DAC) in patients with myelodysplastic syndromes (MDS). Blood. 2005; 106 abstract. Abstract 2515.
69. Kantarjian H, O'Brien S, Giles F, et al. Decitabine low-dose schedule (100 mg/m2/Course) in myelodysplastic syndrome (MDS). Comparison of 3 different dose schedules. Blood. 2005; 106 abstract. Asbtract 2522.
70. Kantarjian HM, O'Brien S, Shan J, et al. Update of the decitabine experience in higher risk myelodysplastic syndrome and analysis of prognostic factors associated with outcome. Cancer. 2007; 109:265–273. [PubMed: 17133405]
71. Kantarjian H, Oki Y, Garcia-Manero G, et al. Results of a randomized study of 3 schedules of low-dose decitabine in higher-risk myelodysplastic syndrome and chronic myelomonocytic leukemia. Blood. 2007; 109:52–57. [PubMed: 16882708]
72. Deeg HJ, Gotlib J, Beckham C, et al. Soluble TNF receptor fusion protein (etanercept) for the treatment of myelodysplastic syndrome: a pilot study. Leukemia. 2002; 16:162–164. [PubMed: 11840280]
73. Deeg HJ, Jiang PY, Holmberg LA, et al. Hematologic responses of patients with MDS to antithymocyte globulin plus etanercept correlate with improved flow scores of marrow cells. Leuk Res. 2004; 28:1177–1180. [PubMed: 15380342]
74. Jonásová A, Neuwirtová R, Cermák J, et al. 164 Promising cyclosporin a therapy for myelodysplastic syndrome. Leuk Res. 1997; 21:S53–53.
75. Molldrem JJ, Caples M, Mavroudis D, et al. Antithymocyte globulin for patients with myelodysplastic syndrome. Br J Haematol. 1997; 99:699–705. [PubMed: 9401087]
76. Raza A, Meyer P, Dutt D, et al. Thalidomide produces transfusion independence in long-standing refractory anemias of patients with myelodysplastic syndromes. Blood. 2001; 98:958–965. [PubMed: 11493439]
77. Strupp C, Germing U, Aivado M, et al. Thalidomide for the treatment of patients with myelodysplastic syndromes. Leukemia. 2002; 16:1–6. [PubMed: 11840256]
78. Sloand EM, Wu CO, Greenberg P, et al. Factors affecting response and survival in patients with myelodysplasia treated with immunosuppressive therapy. J Clin Oncol. 2008; 26:2505–2511. [PubMed: 18413642]
79. List A, Kurtin S, Roe DJ, et al. Efficacy of lenalidomide in myelodysplastic syndromes. N Engl J Med. 2005; 352:549–557. [PubMed: 15703420]
80. Nimer SD. Clinical management of myelodysplastic syndromes with interstitial deletion of chromosome 5q. J Clin Oncol. 2006; 24:2576–2582. [PubMed: 16735711]
81. Raza A, Reeves JA, Feldman EJ, et al. Phase 2 study of lenalidomide in transfusion-dependent, low-risk, and intermediate-1 risk myelodysplastic syndromes with karyotypes other than deletion 5q. Blood. 2008; 111:86–93. [PubMed: 17893227]
82. Tricot G, Boogaerts MA. The role of aggressive chemotherapy in the treatment of the myelodysplastic syndromes. Br J Haematol. 1986; 63:477–483. [PubMed: 3730285]
83. Estey EH, Thall PF, Cortes JE, et al. Comparison of idarubicin + ara-C-, fludarabine + ara-C-, and topotecan + ara-C-based regimens in treatment of newly diagnosed acute myeloid leukemia, refractory anemia with excess blasts in transformation, or refractory anemia with excess blasts. Blood. 2001; 98:3575–3583. [PubMed: 11739159]
84. Sonneveld P, van Dongen JJ, Hagemeijer A, et al. High expression of the multidrug resistance P-glycoprotein in high-risk myelodysplasia is associated with immature phenotype. Leukemia. 1993; 7:963–969. [PubMed: 8100604]
85. Advani R, Saba HI, Tallman MS, et al. Treatment of refractory and relapsed acute myelogenous leukemia with combination chemotherapy plus the multidrug resistance modulator PSC 833 (Valspodar). Blood. 1999; 93:787–795. [PubMed: 9920827]
86. Wattel E, Solary E, Hecquet B, et al. Quinine improves results of intensive chemotherapy (IC) in myelodysplastic syndromes (MDS) expressing P-glycoprotein (PGP). Updated results of a

randomized study. Groupe Francais des Myelodysplasies (GFM) and Groupe GOELAMS. Adv Exp Med Biol. 1999; 457:35–46. [PubMed: 10500778]

87. Greenberg PL, Lee SJ, Advani R, et al. Mitoxantrone, etoposide, and cytarabine with or without valspodar in patients with relapsed or refractory acute myeloid leukemia and high-risk myelodysplastic syndrome: a phase III trial (E2995). J Clin Oncol. 2004; 22:1078–1086. [PubMed: 15020609]
88. Anderson JE, Appelbaum FR, Fisher LD, et al. Allogeneic bone marrow transplantation for 93 patients with myelodysplastic syndrome. Blood. 1993; 82:677–681. [PubMed: 8329721]
89. De Witte T, Zwaan F, Hermans J, et al. Allogeneic bone marrow transplantation for secondary leukaemia and myelodysplastic syndrome: a survey by the Leukaemia Working Party of the European Bone Marrow Transplantation Group (EBMTG). Br J Haematol. 1990; 74:151–155. [PubMed: 2180469]
90. Demuynck H, Verhoef GE, Zachee P, et al. Treatment of patients with myelodysplastic syndromes with allogeneic bone marrow transplantation from genotypically HLA-identical sibling and alternative donors. Bone Marrow Transplant. 1996; 17:745–751. [PubMed: 8733692]
91. Jurado M, Deeg HJ, Storer B, et al. Hematopoietic stem cell transplantation for advanced myelodysplastic syndrome after conditioning with busulfan and fractionated total body irradiation is associated with low relapse rate but considerable nonrelapse mortality. Biol Blood Marrow Transplant. 2002; 8:161–169. [PubMed: 11939606]
92. Kerbauy DM, Chyou F, Gooley T, et al. Allogeneic hematopoietic cell transplantation for chronic myelomonocytic leukemia. Biol Blood Marrow Transplant. 2005; 11:713–720. [PubMed: 16125642]
93. Nevill TJ, Fung HC, Shepherd JD, et al. Cytogenetic abnormalities in primary myelodysplastic syndrome are highly predictive of outcome after allogeneic bone marrow transplantation. Blood. 1998; 92:1910–1917. [PubMed: 9731047]
94. Scott BL, Sandmaier BM, Storer B, et al. Myeloablative vs nonmyeloablative allogeneic transplantation for patients with myelodysplastic syndrome or acute myelogenous leukemia with multilineage dysplasia: a retrospective analysis. Leukemia. 2006; 20:128–135. [PubMed: 16270037]
95. Wallen H, Gooley TA, Deeg HJ, et al. Ablative allogeneic hematopoietic cell transplantation in adults 60 years of age and older. J Clin Oncol. 2005; 23:3439–3446. [PubMed: 15824415]
96. Anderson J, Thomas ED. The Seattle experience with bone marrow transplantation for MDS. Leuk Res. 1997; 21(Suppl 1):S51.
97. de Lima M, Anagnostopoulos A, Munsell M, et al. Nonablative versus reduced-intensity conditioning regimens in the treatment of acute myeloid leukemia and high-risk myelodysplastic syndrome: dose is relevant for long-term disease control after allogeneic hematopoietic stem cell transplantation. Blood. 2004; 104:865–872. [PubMed: 15090449]
98. Giralt S, Estey E, Albitar M, et al. Engraftment of allogeneic hematopoietic progenitor cells with purine analog-containing chemotherapy: harnessing graft-versus-leukemia without myeloablative therapy. Blood. 1997; 89:4531–4536. [PubMed: 9192777]
99. Anderson JE, Anasetti C, Appelbaum FR, et al. Unrelated donor marrow transplantation for myelodysplasia (MDS) and MDS-related acute myeloid leukaemia. Br J Haematol. 1996; 93:59–67. [PubMed: 8611476]
100. Castro-Malaspina H, Harris RE, Gajewski J, et al. Unrelated donor marrow transplantation for myelodysplastic syndromes: outcome analysis in 510 transplants facilitated by the National Marrow Donor Program. Blood. 2002; 99:1943–1951. [PubMed: 11877264]
101. Deeg, H. Hematology 2005: American Society of Hematology Education Program Book. American Society of Hematology; Washington, DC: 2005. Optimization of transplant regimens for patients with myelodysplastic syndromes (MDS); p. 167-173.
102. De Witte T, Suciu S, Verhoef G, et al. Intensive chemotherapy followed by allogeneic or autologous stem cell transplantation for patients with myelodysplastic syndromes (MDSs) and acute myeloid leukemia following MDS. Blood. 2001; 98:2326–2331. [PubMed: 11588026]
103. Fukumoto JS, Greenberg PL. Management of patients with higher risk myelodysplastic syndromes. Crit Rev Oncol Hematol. 2005; 56:179–192. [PubMed: 15979321]

104. Alyea EP, Kim HT, Ho V, et al. Comparative outcome of nonmyeloablative and myeloablative allogeneic hematopoietic cell transplantation for patients older than 50 years of age. Blood. 2005; 105:1810–1814. [PubMed: 15459007]

105. Cutler CS, Lee SJ, Greenberg P, et al. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for low-risk myelodysplasia is associated with improved outcome. Blood. 2004; 104:579–585. [PubMed: 15039286]

106. Laport GG, Sandmaier BM, Storer BE, et al. Reduced-intensity conditioning followed by allogeneic hematopoietic cell transplantation for adult patients with myelodysplastic syndrome and myeloproliferative disorders. Biol Blood Marrow Transplant. 2008; 14:246–255. [PubMed: 18215785]

107. McClune B, Weisdorf DJ, DiPersio JF, et al. Non-myeloablative hematopoietic stem cell transplantation in older patients with AML and MDS: Results from the center for International Blood and Marrow Transplant Research (CIBMTR). Blood. 2008; 112 abstract. Abstract 346.

108. Kindwall-Keller T, Isola LM. The evolution of hematopoietic SCT in myelodysplastic syndrome. Bone Marrow Transplant. 2009; 43:597–609. [PubMed: 19252532]

109. Oliansky DM, Antin JH, Bennett JM, et al. The role of cytotoxic therapy with hematopoietic stem cell transplantation in the therapy of myelodysplastic syndromes: an evidence-based review. Biol Blood Marrow Transplant. 2009; 15:137–172. [PubMed: 19167676]

110. Deeg H, Sandmaier BM. Who is fit for allogeneic transplantation? Blood. 2010; 116:4762–4770. [PubMed: 20702782]

111. Beran M, Shen Y, Kantarjian H, et al. High-dose chemotherapy in high-risk myelodysplastic syndrome: covariate-adjusted comparison of five regimens. Cancer. 2001; 92:1999–2015. [PubMed: 11596013]

112. WijerMans P, Suciu S, Baila L, et al. Low dose decitabine versus best supportive care in elderly patients with intermediate or high risk MDS not eligible for intensive chemotherapy: final results of the randomized phase III study (06011) of the EORTC leukemia and German MDS study groups. Blood. 2008; 112 abstract. Abstract 226.

113. Jacobs A, Janowska-Wieczorek A, Caro J, et al. Circulating erythropoietin in patients with myelodysplastic syndromes. Br J Haematol. 1989; 73:36–39. [PubMed: 2803975]

114. Hellstrom-Lindberg E. Efficacy of erythropoietin in the myelodysplastic syndromes: a meta-analysis of 205 patients from 17 studies. Br J Haematol. 1995; 89:67–71. [PubMed: 7833279]

115. Negrin RS, Stein R, Doherty K, et al. Maintenance treatment of the anemia of myelodysplastic syndromes with recombinant human granulocyte colony-stimulating factor and erythropoietin: evidence for in vivo synergy. Blood. 1996; 87:4076–4081. [PubMed: 8639764]

116. Casadevall N, Durieux P, Dubois S, et al. Health, economic, and quality-of-life effects of erythropoietin and granulocyte colony-stimulating factor for the treatment of myelodysplastic syndromes: a randomized, controlled trial. Blood. 2004; 104:321–327. [PubMed: 15054036]

117. Hellstrom-Lindberg E, Ahlgren T, Beguin Y, et al. Treatment of anemia in myelodysplastic syndromes with granulocyte colony-stimulating factor plus erythropoietin: results from a randomized phase II study and long-term follow-up of 71 patients. Blood. 1998; 92:68–75. [PubMed: 9639501]

118. Hellstrom-Lindberg E, Negrin R, Stein R, et al. Erythroid response to treatment with G-CSF plus erythropoietin for the anaemia of patients with myelodysplastic syndromes: proposal for a predictive model. Br J Haematol. 1997; 99:344–351. [PubMed: 9375752]

119. Spiriti MA, Latagliata R, Niscola P, et al. Impact of a new dosing regimen of epoetin alfa on quality of life and anemia in patients with low-risk myelodysplastic syndrome. Ann Hematol. 2005; 84:167–176. [PubMed: 15592833]

120. Hellstrom-Lindberg E, Gulbrandsen N, Lindberg G, et al. A validated decision model for treating the anaemia of myelodysplastic syndromes with erythropoietin + granulocyte colony-stimulating factor: significant effects on quality of life. Br J Haematol. 2003; 120:1037–1046. [PubMed: 12648074]

121. Mannone L, Gardin C, Quarre MC, et al. High-dose darbepoetin alpha in the treatment of anaemia of lower risk myelodysplastic syndrome results of a phase II study. Br J Haematol. 2006; 133:513–519. [PubMed: 16681638]

122. Musto P, Lanza F, Balleari E, et al. Darbepoetin alpha for the treatment of anaemia in low-intermediate risk myelodysplastic syndromes. Br J Haematol. 2005; 128:204–209. [PubMed: 15638854]

123. Giraldo P, Nomdedeu B, Loscertales J, et al. Darbepoetin alpha for the treatment of anemia in patients with myelodysplastic syndromes. Cancer. 2006; 107:2807–2816. [PubMed: 17115424]

124. Stasi R, Abruzzese E, Lanzetta G, et al. Darbepoetin alfa for the treatment of anemic patients with low- and intermediate-1-risk myelodysplastic syndromes. Ann Oncol. 2005; 16:1921–1927. [PubMed: 16166176]

125. Greenberg PL, Sun Z, Miller KB, et al. Treatment of myelodysplastic syndromes patients with erythropoietin with or without granulocyte colony-stimulating factor: results of a prospective randomized phase III trial by the Eastern Cooperative Oncology Group (E1996). Blood. 2009; 114:2393–2400. [PubMed: 19564636]

126. Jadersten M, Malcovati L, Dybedal I, et al. Erythropoietin and granulocyte-colony stimulating factor treatment associated with improved survival in myelodysplastic syndrome. J Clin Oncol. 2008; 26:3607–3613. [PubMed: 18559873]

127. Park S, Grabar S, Kelaidi C, et al. Predictive factors of response and survival in myelodysplastic syndrome treated with erythropoietin and G-CSF: the GFM experience. Blood. 2008; 111:574–582. [PubMed: 17940203]

128. Kornblith AB, Herndon JE II, Silverman LR, et al. Impact of azacytidine on the quality of life of patients with myelodysplastic syndrome treated in a randomized phase III trial: a Cancer and Leukemia Group B study. J Clin Oncol. 2002; 20:2441–2452. [PubMed: 12011121]

129. Thomas, M. Health-related quality of life for those with myelodysplastic syndrome: conceptualization, measurement and implications. In: Greenberg, PL., editor. Myelodysplastic Syndromes: Clinical and Biological Advances. Cambridge University Press; Cambridge, England: 2006. p. 263-295.

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