Clinical application and proposal for modification of the International Working Group (IWG) response criteria in myelodysplasia

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The myelodysplastic syndromes (MDSs) are heterogeneous with respect to clinical characteristics, pathologic features, and cytogenetic abnormalities. This heterogeneity is a challenge for evaluating response to treatment. Therapeutic trials in MDS have used various criteria to assess results, making cross-study comparisons problematic. In 2000, an International Working Group (IWG) proposed standardized response criteria for evaluating clinically significant responses in MDS. These criteria included measures of alteration in the natural history of disease, hematologic improvement, cytogenetic response, and improvement in health-related quality of life. The relevance of the response criteria has now been validated prospectively in MDS clinical trials, and they have gained acceptance in research studies and in clinical practice. Because limitations of the IWG criteria have surfaced, based on practical and reported experience, some modifications were warranted. In this report, we present recommendations for revisions of some of the initial criteria. (Blood. 2006;108:419-425)

Introduction

The myelodysplastic syndromes (MDSs) are heterogeneous hematopoietic diseases associated with bone marrow failure, peripheral cytopenias, and a propensity for progression to acute myeloid leukemia (AML).[1,2] Clonal cytogenetic abnormalities can be identified in approximately 50% of cases.[3] To account for the disease heterogeneity, MDS classification systems have been proposed.[4-6] The International Prognostic Scoring System (IPSS) considers the percentage of bone marrow blasts, the number of cytopenias, and bone marrow cytogenetics to predict survival and the potential for progression to AML.[5] Patients with untreated MDS are categorized into 4 IPSS prognostic risk groups—low, intermediate-1, intermediate-2, and high—with median survival times of 5.7, 3.1, 1.2, and 0.4 years, respectively.[5]

Standardized response criteria in trials of MDS are essential to evaluate outcome of therapy, to refine treatment according to patient and disease characteristics, and to permit comparisons among clinical trials. In 2000, an International Working Group (IWG) of investigators proposed standardized response criteria for several purposes: (1) to resolve the difficulties with the variable definitions used to describe the quality and quantity of response, (2) to consider risk-based treatment goals, and (3) to identify clinically meaningful responses across MDS subgroups.[7] The criteria also recognized alleviation of disease-related complications and improvements in quality of life (QOL) as important treatment goals. The IWG criteria have since been adopted in many clinical trials. Limitations of the IWG criteria have surfaced, based on practical experience. This review considers the experience to date with the IWG response criteria and presents recommendations for modifications of the initial criteria.

Risk-based treatment goals in MDS

The selection of therapy for MDS is based on the patient IPSS risk category, age, and performance status.[8,9] Treatment goals range from managing cytopenias and improving quality of life in lower-risk MDS to altering the natural history of disease in higher-risk MDS.

High-intensity therapies (intensive chemotherapy and stem cell transplantation) are generally reserved for patients in IPSS higher-risk groups[8,9] and have been associated with cures in some patients. Younger patients in lower-risk IPSS groups are sometimes also considered for allogeneic stem cell transplantations because of the favorable benefit-to-risk ratio. Although they carry a high risk of treatment-associated morbidity and mortality, their aims are to alter the natural history of the disease (through induction of complete response) and to prolong progression-free survival (PFS) and overall survival. Cytogenetic responses help to establish the degree to which the natural history of MDS may be affected by therapy.[7] Recently, low-intensity therapy with azacitidine has also been shown to alter the natural history of MDS. This observation

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suggests that improving outcome in MDS may be obtained through means other than achievement of complete response (the currently accepted dogma).

Supportive care to manage cytopenias is a standard approach in lower-risk MDS or in patients with higher-risk MDS who cannot tolerate higher-intensity therapy.[8] Many patients in lower-risk MDS succumb to the consequences of cytopenias without disease progression to acute leukemia. Patients with lower-risk MDS often become dependent on frequent red blood cell (RBC) or platelet transfusions[10] and experience repeated infections, bleeding, and morbidity and mortality, all associated with reduction in health-related QOL. Some treatments in lower-risk MDS may improve blood cell counts, achieve transfusion independence, and improve QOL,[7] but they may not necessarily improve survival or PFS.

Definition of IWG response criteria in MDS

The IWG criteria define 4 aspects of responses based on treatment goals: (1) altering the natural history of the disease, (2) cytogenetic response, (3) hematologic improvement (HI), and (4) QOL.[7] These have been detailed in a previous publication.[7] We emphasize some of their aspects.

Altering the natural history of the disease

The criteria for complete remission (CR) and partial remission (PR) involve specific improvements in marrow and peripheral blood measurements obtained on 2 or more successive assessments. The response parameters in peripheral blood must be maintained for at least 8 weeks. Responses designated as CR include less than 5% marrow blasts without evidence of dysplasia and normalization of peripheral blood counts, including a hemoglobin level of 110 g/L (11 g/dL) or more (in patients not receiving erythropoietin or transfusions), a neutrophil count of 1.5×10^9/L or more, and a platelet count of 100×10^9/L or more. For PR, patients must demonstrate all CR criteria if abnormal before treatment except that marrow blasts should decrease by 50% or more compared with pretreatment levels, or patients may demonstrate a less-advanced MDS disease classification category than prior to treatment.

Cytogenetic response

The IWG criteria require 20 analyzable metaphases assessed by conventional cytogenetic studies to diagnose or exclude the presence of a cytogenetic abnormality. For a normal karyotype, 20 metaphases are optimal to ensure that enough metaphases have been examined. By the International System for Human Cytogenetic Nomenclature (ISCN) guidelines, a structural cytogenetic abnormality or additional chromosomes (eg, trisomies) consistently identified in 2 or more metaphases is sufficient to report it as such. For chromosome losses (eg, monosomes), 3 or more metaphases are required to establish the abnormal clone. For cytogenetic response, 20 metaphases are optimal (but not necessary) to define the degree of cytogenetic response. Fluorescent in situ hybridization (FISH) to assess changes in a specific cytogenetic abnormality is acceptable. A major cytogenetic response refers to disappearance of a cytogenetic abnormality; a minor cytogenetic response is 50% or more reduction of abnormal metaphases.

Hematologic improvement

The IWG criteria for HI define specific responses of cytopenias in the 3 hematopoietic lineages: erythroid (HI-E), platelet (HI-P), and neutrophil (HI-N).[7] The HIs are measured in patients with pretreatment abnormal values: hemoglobin level less than 110 g/L (11 g/dL) or RBC-transfusion dependence, platelet count less than 100×10^9/L or platelet-transfusion dependence, absolute neutrophil count (ANC) less than 1.0×10^9/L. Pretreatment baseline measures of cytopenias are averages of at least 2 measurements (not influenced by transfusions, ie, no RBC transfusions for at least 1 week and no platelet transfusions for at least 3 days) over at least 1 week prior to therapy. The HI responses are particularly relevant in patients with lower-risk MDS and long-standing cytopenias. Major and minor HI must last for at least 8 weeks.

Health-related QOL and definitions of treatment failure or relapse on prior therapies

Progressive anemia and transfusion dependence are associated with declines in QOL, especially in older patients with MDS.[11,12] A positive correlation has been noted between hemoglobin level and QOL[13]; QOL improvements are significant benefits of MDS treatment.[7,14]

Definitions of treatment failure and relapse enable standardized characterization of response duration[7] and are important for enrollment criteria, stratification, and data interpretation.

Experience with IWG response criteria

Comparing remission rates in higher-risk MDS

Alteration of the natural history of disease is important in higher-risk MDS, which may rapidly progress to AML, and when the median survival is short. Azacitidine, a hypomethylating agent, approved by the US Food and Drug Administration (FDA) for the treatment of MDS, has been associated with a modest alteration of the natural history of MDS and is considered low-intensity therapy. Unlike intensive chemotherapy, azacitidine is relatively safe and is associated with a low incidence of severe drug-related toxicities and with improved outcome and QOL in MDS.[15] The design and conduct of the azacitidine study predated the IWG criteria. The response criteria used (CR allowed persistence of dyshematopoiesis and for response durability for only 4 weeks; PR did not require normalization of peripheral counts) were less stringent than the IWG response criteria. The reported response rates were 7% for CR, 16% for PR, and 37% for improved.[15] In the FDA approval summary, the response rates were 6% for CR, 10% for PR, and 19% for improved.[16] Silverman et al[17] recently reanalyzed the azacitidine response rates by IWG criteria and reported response rates to be CR of 10%, PR of 1%, and HI of 36%; overall response rate was 48%. Response rates for HIs were 22% for HI-E major, 8% for HI-E minor, 21% for HI-P major, 3% for HI-P minor, and 8% for HI-N major.

Recent studies that used the IWG response criteria to evaluate response rates in higher-risk MDS included trials of azacitidine, decitabine, arsenic trioxide, and the oral farnesyltransferase inhibitor tipifarnib (R115777).[17-20] These trials are summarized in Table 1. The guidelines now enable evaluations of the effects of investigational agents in MDS within reasonably comparable study groups or MDS subsets.

Table 1. Remission rates according to the International Working Group response criteria

Treatment	No. patients	IPSS (%)				IWG response				
						% hematologic response			Median survival, mo	% HI-major
		Low	Int1	Int2	High	Overall	CR	PR		
Azacitidine[17]	99	5*	53	23	17	11	10	1	20	36 (+minor)
Decitabine[18]	89		31	43	26	17	9	8	22.3/13.3†	13
Tipifarnib[19]	82		17	39	44	12	7	5	11.9‡	22
Arsenic[20]	101	NA	39§	NA	61‖	1	1	0	NA	20

IWG indicates International Working Group; IPSS, International Prognostic Scoring System; CR, complete remission; PR, partial remission; HI, hematologic improvement; Int1, IPSS intermediate-1; Int2, IPSS intermediate-2; TTL, time to leukemia; NA, not available.

*Evaluated in only 39 of 99 patients.

†Data are for responders and nonresponders, respectively.

‡Time to leukemia or death: 6.4 months.

§Data for combined Low and Int1.

‖Data combined for Int2 and High.

Emerging value of cytogenetic response as an endpoint

Two recent trials of lenalidomide in lower-risk MDS used IWG criteria to assess cytogenetic response.[21,22] In one trial, 12 (60%) of 20 patients with pretreatment cytogenetic abnormalities had cytogenetic responses, including 10 complete cytogenetic responses.[21] Of 12 patients with 5q31.1 deletions, 10 (83%) had a cytogenetic response, including 9 (75%) complete cytogenetic responses. Cytogenetic responses occurred in patients who also had an erythroid response. Evaluation of cytogenetic response in this trial resulted in identification of a cytogenetic subset of MDS with 5q abnormalities that may be highly responsive to lenalidomide. This led to a multi-institutional trial of lenalidomide in 148 patients with lower-risk transfusion-dependent MDS and 5q deletions. In that study, the HI-E rate was 65%, and the complete cytogenetic response rate was 35%.[22] On the basis of the results, lenalidomide was recently approved by the FDA for this indication (December 2005).

In patients with higher-risk MDS, treatment with decitabine was associated with cytogenetic responses.[23] Of the 115 patients with a known karyotype prior to treatment, 65 had abnormal metaphases, and clonal abnormalities were identified in 61. Major (complete) cytogenetic response was observed in 19 (31%) of the 61 patients. Their median survival was 24 months compared with 11 months in patients who had persistent cytogenetic abnormalities despite treatment. These results illustrate the value of using standardized cytogenetic response criteria in both lower- and higher-risk MDS.

Evaluating treatment effects on chronic cytopenias

The IWG response criteria enable definition of single or multilineage responses to specific treatments (Table 2).[20,21,24-30]

Studies with erythropoietin and darbepoetin alfa in low-risk MDS identified transfusion independence as significant for QOL and showed primarily erythroid responses (major HI-E in 29%-47% and minor HI-E in 26%-30% in various studies) without improvements in platelets or granulocytes.[24,31-36]

A recent study of thalidomide in lower-risk MDS defined its role more precisely. At thalidomide doses of 100 to 400 mg daily, responses after more than 3 months of therapy were observed in 14 of 82 patients. All were primarily erythroid responses. Among the 50 patients with RBC transfusion requirements the (erythroid) response rate was 28% (14 of 50 patients).[37] In a study of lenalidomide in patients with lower-risk MDS and transfusion dependence, RBC-transfusion independence was achieved in 20 (63%) of 32 patients who were transfusion dependent at baseline.[21] In a multi-institutional study of 215 similar patients, lenalidomide resulted in a major HI-E response rate of 24% and a minor HI-E response rate of 18%.[38] Lenalidomide and thalidomide induce predominantly erythroid responses; platelet and neutrophil responses are uncommon.[21,28,37]

A study of arsenic trioxide in 101 patients with MDS resulted in major HI-E (11%), major HI-P (6%), and major HI-N (8%) lineages.[20] Valproic acid monotherapy in 18 patients with MDS showed HI in all 3 cell lineages.[33] In this study, HI was achieved in

Table 2. IWG-defined hematologic improvement by cell lineage in patients with MDS

Treatment	No. patients	% IPSS/FAB	% response,* major (minor)		
			HI-E	% HI-P	% HI-N
Lenalidomide[21]	43	Low, 51; Int1, 37; Int2, 9; High, 2	49 (7)	10	17
Darbepoetin alfa[24]	40	Low, 38; Int1, 52; Int2, 10	47 (12)	0	0
Antithymocyte immunoglobulin[25]	20	RA, 65; RARS, 15; RAEB, 20	45 (5)	35 (10)	10 (5)
Antithymocyte immunoglobulin[26]	68	RA, 53; RARS, 4; RAEB, 11	67 (20)	40 (27)	27 (7)
Cyclosporine A[27]	50	Low, 8; Int1, 82; Int2, 10	34 (16)	16 (12)	22 (4)
Thalidomide[28]	83	Low/Int1, 70; High/Int2, 30	13 (5)	0 (1)	0
Thalidomide[29]	29	RA, 14; RARS, 4; RAEB, 3; RAEB-t, 5; CMML, 3	10 (21)	14 (7)	3 (7)
Arsenic trioxide[20]	101	Low/Int1, 39; High/Int2, 61	11 (0)	6 (0)	8 (0)
Valproic acid[30]	18	Low, 17; Int1, 55; Int2, 17; High, 11	11 (0)	11 (0)	6 (0)

IWG indicates International Working Group; MDS, myelodysplastic syndromes; IPSS, International Prognostic Scoring System; FAB, French-American-British; HI-E, hematologic improvement, erythroid response; HI-P, hematologic improvement, platelet response; HI-N, hematologic improvement, neutrophil response; Int1, IPSS intermediate-1; Int2, IPSS intermediate-2; RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts-CB; RAEB, refractory anemia with excess blasts; CMML, chronic myelomonocytic leukemia.

*Some patients achieved responses in more than 1 lineage.

7 patients: 2 major HI-E, 2 major HI-P, and 1 major HI-N, and 2 minor HI-E. One patient also achieved PR. Antithymocyte globulin therapy in lower-risk MDS produced trilineage responses with an overall response rate of 43%, including HI-E in 87%, HI-P in 67%, and HI-N in 33%.[26]

Therefore, the IWG criteria allow identifying approaches that may improve predominately one lineage (eg, anemia or thrombocytopenia) or multiple lineages. This is important for understanding mechanisms of action of various agents, and for selection of medically appropriate applications.

Clinical significance of QOL in MDS

Measurements of QOL in MDS are increasingly being included as endpoints in treatment trials. Kornblith et al[39] reported improvements in QOL in patients with MDS treated with azacitidine compared with supportive care. In this trial, several instruments were used to measure QOL. These included the European Organization for Research and Treatment of Cancer QOL Questionnaire-CC30, the Mental Health Inventory, and a visual analog scale to indicate perception of improvement following treatment.[39] In contrast, no improvement in QOL as measured by the FACT-An questionnaire was noted in a trial of recombinant human erythropoietin plus recombinant human granulocyte colony-stimulating factor compared with supportive care, even though erythroid responses were achieved in the treatment arm.[32]

Controversies and recommendations for modifying the IWG response criteria

Since publication of the IWG response criteria in 2000, their adoption in clinical trials and experience with their application has increased. Advantages from adopting a standardized set of response criteria have been realized, but several questions and controversies regarding interpretation of the IWG criteria have arisen.

1. Clinical significance of minor responses

The significance of IWG minor HIs in relation to QOL and morbidity is unclear, and reporting them may give a false impression of the benefit of a new treatment. For example, a minor HI-N response could be a small increase of ANC from 0.1 to 0.2×10^9/L. To avoid reporting clinically nonsignificant responses, an HI-N would require an increase of neutrophil counts by at least 100% with an absolute increase of at least 0.5×10^9/L. Similarly, a major HI-P response covers most of the clinically relevant changes in platelet counts, except for significant platelet increases from life-threatening (< 10 to 20×10^9/L) to non–life-threatening levels ($> 20 \times 10^9$/L). Including the latter as HI-P would obviate the need to define a separate minor HI-P. For example, significant platelet responses would be from less than 10×10^9/L to greater than 20×10^9/L, from 12 to 24, 16 to 32, 20 to 40 $\times 10^9$/L, and so forth. After that, an increase by the absolute number of at least 30×10^9/L will apply, eg, 21 to 51, 30 to 60 $\times 10^9$/L, and so forth. Finally, it appears that some minor HI-Es are still relevant for patient QOL and for defining the erythroid activity of a new agent, provided the initial transfusion need is clinically relevant. This is discussed in the following paragraph.

2. Definitions of transfusion dependence and independence

Although these definitions appear simple and intuitive, they did not specify *clinically relevant* transfusion dependence. For example, a patient who receives 2 units of RBCs at diagnosis of MDS because of fatigue and hemoglobin of 90 g/L (9.0 g/dL) would be categorized to have transfusion dependence. If during the course of a therapeutic trial, the same patient is not transfused for a hemoglobin of about 85 to 95 g/L (8.5 to 9.5 g/dL) for any periods of 2 months or longer, this would be categorized as a major HI-E. In the randomized study of decitabine versus supportive care, 27% of patients who had been transfusion dependent prior to study entry could be later categorized as becoming transfusion independent on the *supportive care arm*,[18] highlighting the pitfalls of the definition. If this had been applied to a single-arm trial of a new treatment, it would have been judged to show "positive" results. Most patients require transfusion for hemoglobin values of 90 g/L (9.0 g/dL) or less. RBC transfusions given for such levels would be appropriate for entry onto clinical trials and could reasonably serve as the baseline for response evaluation in terms of defining RBC transfusion independence. At a minimum, a hemoglobin increase of at least 15 g/L (1.5 g/dL) would be a clinically relevant effect on the erythroid series, eg, from 60 to at least 75 g/L (6 to $\geq$ 7.5 g/dL) or from 80 to at least 95 g/L (8 to $\geq$ 9.5 g/dL). Although somewhat arbitrary, a decrease of at least 4 units transfused over an 8-week period of time compared with the 8 weeks' pretreatment would be clinically relevant (eg, from 4 to 0, or 6 to 2, or 8 to 4 units). For example, if a patient has received RBC transfusions for symptomatic anemia with a hemoglobin of 90 g/L (9.0 g/dL), it would be reasonable to expect that a clinically beneficial drug would increase the hemoglobin to at least 105 g/L (10.5 g/dL), or reduce transfusion needs as suggested. It should be noted that the occurrence of bleeding could complicate the evaluation of hemoglobin response and transfusion needs in individual patients.

3. Significance of minimal residual disease in CR

In patients who meet the criteria for CR, persistence of dysplasia may be subjective and may have no clinical relevance. Dysplastic changes that preclude reporting a CR may produce false-negative results. Dysplastic changes have been reported in 10% to 40% of blinded normal marrows, as well as following chemotherapy (hydroxyurea, cytarabine, azacitidine, decitabine).[9,40,41] As an example, the incidence of complete cytogenetic response was 35% in the lenalidomide study (a true reflection of a morphologic CR), whereas the incidence of "morphologic CR" was only 22%.[22] CRs should be reported with and without persistence of dysplastic changes, and outcomes of the 2 groups evaluated.

4. Clinical benefit associated with a response duration of 8 weeks versus 4 weeks

It may prove helpful to define response duration based on higher-risk versus lower-risk disease. In higher-risk MDS, a CR or PR lasting for 4 weeks or more may be associated with improved survival based on experience with AML and MDS.[42] The need for an additional marrow confirmatory specimen a month later is often impractical and has not been required in recent guidelines. In lower-risk MDS, durability of a response (mostly HI) should be sustained for 8 weeks or more to prove clinically beneficial.

Table 3. Proposed modified International Working Group response criteria for altering natural history of MDS[7]

Category	Response criteria (responses must last at least 4 wk)
Complete remission	Bone marrow: ≤ 5% myeloblasts with normal maturation of all cell lines*
	Persistent dysplasia will be noted*†
	Peripheral blood‡
	Hgb ≥ 11 g/dL
	Platelets ≥ 100×10^9/L
	Neutrophils ≥ 1.0×10^9/L†
	Blasts 0%
Partial remission	All CR criteria if abnormal before treatment except:
	Bone marrow blasts decreased by ≥ 50% over pretreatment but still > 5%
	Cellularity and morphology not relevant
Marrow CR†	Bone marrow: ≤ 5% myeloblasts and decrease by ≥ 50% over pretreatment†
	Peripheral blood: if HI responses, they will be noted in addition to marrow CR†
Stable disease	Failure to achieve at least PR, but no evidence of progression for > 8 wks
Failure	Death during treatment or disease progression characterized by worsening of cytopenias, increase in percentage of bone marrow blasts, or progression to a more advanced MDS FAB subtype than pretreatment
Relapse after CR or PR	At least 1 of the following:
	Return to pretreatment bone marrow blast percentage
	Decrement of ≥ 50% from maximum remission/response levels in granulocytes or platelets
	Reduction in Hgb concentration by ≥ 1.5 g/dL or transfusion dependence
Cytogenetic response	Complete
	Disappearance of the chromosomal abnormality without appearance of new ones
	Partial
	At least 50% reduction of the chromosomal abnormality
Disease progression	For patients with:
	Less than 5% blasts: ≥ 50% increase in blasts to > 5% blasts
	5%-10% blasts: ≥ 50% increase to > 10% blasts
	10%-20% blasts: ≥ 50% increase to > 20% blasts
	20%-30% blasts: ≥ 50% increase to > 30% blasts
	Any of the following:
	At least 50% decrement from maximum remission/response in granulocytes or platelets
	Reduction in Hgb by ≥ 2 g/dL
	Transfusion dependence
Survival	Endpoints:
	Overall: death from any cause
	Event free: failure or death from any cause
	PFS: disease progression or death from MDS
	DFS: time to relapse
	Cause-specific death: death related to MDS

Deletions to IWG response criteria are not shown.

To convert hemoglobin from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

MDS indicates myelodysplastic syndromes; Hgb, hemoglobin; CR, complete remission; HI, hematologic improvement; PR, partial remission; FAB, French-American-British; AML, acute myeloid leukemia; PFS, progression-free survival; DFS, disease-free survival.

*Dysplastic changes should consider the normal range of dysplastic changes (modification).[41]

†Modification to IWG response criteria.

‡In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 4-week period. Such patients can be included in the response category into which they fit at the time the therapy is started. Transient cytopenias during repeated chemotherapy courses should not be considered as interrupting durability of response, as long as they recover to the improved counts of the previous course.

Stability of the improved counts would be sufficient to define CR or PR without a need to repeat a second bone marrow study.

5. Significance and definition of cytogenetic response in MDS

Although it is logical that a complete cytogenetic response, as in AML, would also prolong survival in MDS, there are presently little data to support this assumption.[23] The previous definitions of major (disappearance of cytogenetic abnormality) or minor (≥ 50% reduction) cytogenetic response, borrowed from the experience in chronic myeloid leukemia, may be confusing. As in AML, a complete cytogenetic response would require disappearance of the chromosomal abnormality (without appearance of new ones). A partial cytogenetic response would refer to at least a 50% reduction of the chromosomal abnormality. The latter needs to be also prospectively evaluated for its prognostic significance.

6. Downgrading of French-American-British (FAB) category in PR

A PR, defined as downgrading of a FAB (or IPSS) category, may be problematic: a minor decrease of the marrow blasts percentage by 2%, eg, from 21% to 19%, may be referred to as a PR. A PR should require at least a 50% reduction of marrow blasts and normalization of peripheral counts.

7. Achievement of marrow CR without recovery of counts

This appears to be worthwhile but not covered by the existing criteria (eg, CR or PR), particularly with higher pretreatment marrow blasts (≥ 10%). For example, patients may experience a reduction of marrow blasts from between 20% and 25% to 5% or less with or without improved cytopenias. Such patients may benefit in terms of longer-term outcome. Their response (marrow CR) should be noted as a response with or without HI.

8. Issue of need to continue chemotherapy or myelosuppressive therapy and associated intermittent cytopenias in MDS

As more experience is gained (eg, with azacitidine, decitabine, tipifarnib), it appears that timely and prolonged therapy is needed to achieve optimal and durable response in MDS. When chemotherapy or myelosuppressive therapies are used, they are often associated with transient cytopenias in between courses of therapy. Withholding therapy for 1 to 2 months to define durability of response for at least 4 to 8 weeks may be detrimental. Defining the response at the end of chemotherapy may not capture CR or other responses when relapse occurs after 2 to 10 months. Accepting transient cytopenias and transfusion needs expected as part of the chemotherapy or myelosuppressive programs, as long as the counts recover to the response levels prior to a course of therapy, would allow a definition of a durable response on chemotherapy or myelosuppressive regimens. In general, this would apply to patients with higher-risk MDS. However, as in the instance of lenalidomide, considerable benefit may also be seen in patients with lower-risk IPSS scores.

9. Neutrophil response

A neutrophil count of 1×10^9/L is the acceptable threshold of increased risk of infection and is part of the CR criteria in AML.[42] Because higher-risk MDS is often treated with AML-type therapies, it may be reasonable to use the same cut-off value for MDS to reduce the confusion in response criteria because many agents and strategies may target the 2 entities of AML and MDS.

10. Distinction of MDS from AML by blast percentage of 20% (World Health Organization [WHO]) versus 30% (IPSS and FAB definitions); implications in relation to definitions of CR and progression

The new WHO recommendations define AML by the presence of 20% or more blasts (instead of the previous criteria by FAB and IPSS requiring the presence of 30% or more blasts). This creates issues related to patient entry, response definition, and definition of progression. Patients with 20% to 29% blasts (old category of refractory anemia with excess blasts in transformation [RAEBT], and generally high-risk IPSS) may still benefit from, and could be treated with, low-intensity or MDS-specific programs, if the inclusion criteria allow study entry. Response criteria would be identical to other patients on trial. Progression would be defined as a return to the previous marrow state prior to the intervention.

On the basis of the previous discussion we propose modifications in the original IWG criteria as shown in Tables 3 and 4. These modifications consolidate major and minor HIs into clinically relevant HI (minor HI deleted) and implement additional changes detailed briefly here: (1) minimum duration of CR or PR at least 4 rather than 8 weeks; CR definition requiring no more than 5% rather than less than 5% blasts; persistent dysplasia allowed in CR; (2) major and minor HIs replaced by one set of clinically relevant HI for erythroid, platelet, and neutrophil responses; (3) "complete" cytogenetic response instead of "major" for disappearance of chromosomal abnormality; partial cytogenetic response instead of "minor" for reduction by at least 50% of chromosomal abnormality; (4) inclusion of marrow CR (blasts $\leq 5\%$) without recovery of counts as a new response category; (5) downgrading of MDS FAB category not considered a PR; (6) intermittent myelosuppression attributed to chemotherapy not to interrupt defining durability of a response, as long as the counts recover to the pretherapy levels; (7) neutrophil response for CR or PR requiring an increase of neutrophil counts to at least 1.0×10^9/L (not 1.5×10^9/L); and (8) definition of AML according to WHO classification (presence of 20% or more blasts).

Conclusions

Since their introduction in 2000, the IWG response criteria have been adopted in many clinical trials and are now widely used in research studies. They provide a standardized set of clinically meaningful response measures in different MDS risk categories, enable comparison of results across different strategies, and facilitate interpretation of data. Use of the IWG criteria in MDS with modifications based on experience appears justified. The proposed modifications are highlighted in Tables 3 and 4.

Table 4. Proposed modified International Working Group response criteria for hematologic improvement[7]

Hematologic improvement*	Response criteria (responses must last at least 8 wk)†
Erythroid response (pretreatment, < 11 g/dL)	Hgb increase by ≥ 1.5 g/dL
	Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 wk compared with the pretreatment transfusion number in the previous 8 wk. Only RBC transfusions given for a Hgb of ≤ 9.0 g/dL pretreatment will count in the RBC transfusion response evaluation†
Platelet response (pretreatment, $< 100 \times 10^9$/L)	Absolute increase of $\geq 30 \times 10^9$/L for patients starting with $> 20 \times 10^9$/L platelets
	Increase from $< 20 \times 10^9$/L to $> 20 \times 10^9$/L and by at least 100%†
Neutrophil response (pretreatment, $< 1.0 \times 10^9$/L)	At least 100% increase and an absolute increase $> 0.5 \times 10^9$/L†
Progression or relapse after HI‡	At least 1 of the following:
	At least 50% decrement from maximum response levels in granulocytes or platelets
	Reduction in Hgb by ≥ 1.5 g/dL
	Transfusion dependence

Deletions to the IWG response criteria are not shown.

To convert hemoglobin levels from grams per deciliter to grams per liter, multiply grams per deciliter by 10.

Hgb indicates hemoglobin; RBC: red blood cell; HI: hematologic improvement.

*Pretreatment counts averages of at least 2 measurements (not influenced by transfusions) $\geq$ 1 week apart (modification).

†Modification to IWG response criteria.

‡In the absence of another explanation, such as acute infection, repeated courses of chemotherapy (modification), gastrointestinal bleeding, hemolysis, and so forth. It is recommended that the 2 kinds of erythroid and platelet responses be reported overall as well as by the individual response pattern.

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