Report of an international working group to standardize response criteria for myelodysplastic syndromes

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Standardized criteria for assessing response are essential to ensure comparability among clinical trials for patients with myelodysplastic syndromes (MDS). An international working group of experienced clinicians involved in the management of patients with MDS reviewed currently used response definitions and developed a uniform set of guidelines for future clinical trials in MDS. The MDS differ from many other hematologic malignancies in their chronicity and the morbidity and mortality caused by chronic cytopenias, often without disease progression to acute myeloid leukemia. Whereas response rates may be an important endpoint for phase 2 studies of new agents and may assist regulatory agencies in their evaluation and approval processes, an important goal of clinical trials in MDS should be to prolong patient survival. Therefore, these response criteria reflected 2 sets of goals in MDS: altering the natural history of the disease and alleviating disease-related complications with improved quality of life. It is anticipated that the recommendations presented will require modification as more is learned about the molecular biology and genetics of these disorders. Until then, it is hoped these guidelines will serve to improve communication among investigators and to ensure comparability among clinical trials. (Blood. 2000;96:3671-3674)

Classification

The myelodysplastic syndromes (MDS) are a heterogeneous group of hematopoietic disorders characterized in most patients by peripheral blood cytopenia with hypercellular bone marrow and dysplasia of the cellular elements.[1-3] MDS may develop after exposure to toxins such as benzene, chemotherapy drugs, or high doses of radiation, though its etiology is unknown in more than 80% of patients.

MDS have historically been referred to as oligoblastic leukemia, refractory anemia, smoldering acute leukemia, or preleukemia. In 1982, the French-American-British (FAB) group presented a classification, modified in 1985, that is the most widely used.[1,2] Recently, a World Health Organization (WHO) steering committee proposed modifications to the MDS subtypes. The major changes were a decrease, from 30% blasts to 20% blasts, in the threshold for diagnosing acute myeloid leukemia (AML) and the creation of a category of MDS/myeloproliferative disorders to include patients with chronic myelomonocytic leukemia.[4] However, these recommendations have not yet been uniformly adopted, and the distinction between AML and MDS reflects the pace of the disease, the biologic differences in neoplastic cells, and the number of bone marrow blasts. Thus, because of its known clinical usefulness, we have elected to retain the FAB classification of MDS.

Prognostic factors

MDS are heterogeneous with regard to clinical characteristics, cytologic and pathologic features, and cytogenetics. Even within morphologic subtypes, there are differences in outcome. Therefore, effective and prospective stratification of patients for clinical studies is critical for designing trials and for evaluating and clarifying outcomes of treatments.

Recently an international working group of experienced clinicians developed a prognostic scheme that has been widely adopted.[5] Critical prognostic factors regarding survival and the potential for evolution to AML, which were identified and included in the International Prognostic Scoring System (IPSS), included bone marrow cytogenetics, percentage of bone marrow blasts, and number of cytopenias; age and gender were also important for predicting survival in a multivariate analysis. Within the IPSS, patients were categorized according to these features into relatively low risk (IPSS Low or Intermediate-1) and relatively high risk (IPSS Intermediate-2 or High) subgroups for risk-based treatment options.

Therapeutic goals

The MDS differ from many other hematologic malignancies in their chronicity and in the morbidity and mortality caused by chronic cytopenias, often without disease progression to AML.[6] As such, alleviation of disease-related complications and improved quality of life (QOL) are important goals of therapy. Thus, improvements in cytopenias (ie, clinically meaningful hematologic

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Table 1. Measurement of response/treatment effect in MDS

ALTERING DISEASE NATURAL HISTORY

1. Complete remission (CR)

   Bone marrow evaluation: Repeat bone marrow showing less than 5% myeloblasts with normal maturation of all cell lines, with no evidence for dysplasia.* When erythroid precursors constitute less than 50% of bone marrow nucleated cells, the percentage of blasts is based on all nucleated cells; when there are 50% or more erythroid cells, the percentage blasts should be based on the nonerythroid cells.

   Peripheral blood evaluation (absolute values must last at least 2 months)†:
   Hemoglobin greater than 11 g/dL (untransfused, patient not on erythropoietin)
   Neutrophils 1500/mm^3 or more (not on a myeloid growth factor)
   Platelets 100 000/mm^3 or more (not on a thrombopoetic agent)
   Blasts, 0%
   No dysplasia*

2. Partial remission (PR) (absolute values must last at least 2 months):
   All the CR criteria (if abnormal before treatment), except:

   Bone marrow evaluation: Blasts decreased by 50% or more over pretreatment, or a less advanced MDS FAB classification than pretreatment. Cellularity and morphology are not relevant.

3. Stable disease
   Failure to achieve at least a PR, but with no evidence of progression for at least 2 months.

4. Failure

   Death during treatment or disease progression characterized by worsening of cytopenias, increase in the percentage bone marrow blasts, or progression to an MDS FAB subtype more advanced than pretreatment.

5. Relapse after CR or PR—one or more of the following:
   a) Return to pretreatment bone marrow blast percentage.
   b) Decrement of 50% or greater from maximum remission/response levels in granulocytes or platelets.
   c) Reduction in hemoglobin concentration by at least 2 g/dL or transfusion dependence.§

6. Disease progression
   a) For patients with less than 5% blasts: a 50% or more increase in blasts to more than 5% blasts.
   b) For patients with 5% to 10% blasts: a 50% or more increase to more than 10% blasts.
   c) For patients with 10% to 20% blasts: a 50% or more increase to more than 20% blasts.
   d) For patients with 20% to 30% blasts: a 50% or more increase to more than 30% blasts.
   e) One or more of the following: 50% or greater decrement from maximum remission/response levels in granulocytes or platelets, reduction in hemoglobin concentration by at least 2 g/dL, or transfusion dependence.§

7. Disease transformation
   Transformation to AML (30% or more blasts).

8. Survival and progression-free survival
   (See Table 2.)

CYTOGENETIC RESPONSE

(Requires 20 analyzable metaphases using conventional cytogenetic techniques.)
Major: No detectable cytogenetic abnormality, if preexisting abnormality was present.
Minor: 50% or more reduction in abnormal metaphases.
Fluorescent in situ hybridization may be used as a supplement to follow a specifically defined cytogenetic abnormality.

QUALITY OF LIFE

Measured by an instrument such as the FACT Questionnaire.
Clinically useful improvement in specific domains:
Physical
Functional
Emotional
Social
Spiritual

HEMATOLOGIC IMPROVEMENT (HI)

(Improvements must last at least 2 months in the absence of ongoing cytotoxic therapy.)†
Hematologic improvement should be described by the number of individual, positively affected cell lines (eg, HI-E; HI-E + HI-N; HI-E + HI-P + HI-N).

1. Erythroid response (HI-E)
   Major response: For patients with pretreatment hemoglobin less than 11 g/dL, greater than 2 g/dL increase in hemoglobin; for RBC transfusion-dependent patients, transfusion independence.
   Minor response: For patients with pretreatment hemoglobin less than 11 g/dL, 1 to 2 g/dL increase in hemoglobin; for RBC transfusion-dependent patients, 50% decrease in transfusion requirements.

2. Platelet response (HI-P)
   Major response: For patients with a pretreatment platelet count less than 100 000/mm^3, an absolute increase of 30 000/mm^3 or more; for platelet transfusion-dependent patients, stabilization of platelet counts and platelet transfusion independence.
   Minor response: For patients with a pretreatment platelet count less than 100 000/mm^3, a 50% or more increase in platelet count with a net increase greater than 10 000/mm^3 but less than 30 000/mm^3.

3. Neutrophil response (HI-N)
   Major response: For absolute neutrophil count (ANC) less than 1500/mm^3 before therapy, at least a 100% increase, or an absolute increase of more than 500/mm^3, whichever is greater.
   Minor response: For ANC less than 1500/mm^3 before therapy, ANC increase of at least 100%, but absolute increase less than 500/mm^3.

4. Progression/relapse after HI: One or more of the following: a 50% or greater decrement from maximum response levels in granulocytes or platelets, a reduction in hemoglobin concentration by at least 2 g/dL, or transfusion dependence.§

For a designated response (CR, PR, HI), all relevant response criteria must be noted on at least 2 successive determinations at least 1 week apart after an appropriate period following therapy (eg, 1 month or longer).

*The presence of mild megaloblastoid changes may be permitted if they are thought to be consistent with treatment effect. However, persistence of pretreatment abnormalities (eg, pseudo-Pelger-Hüet cells, ringed sideroblasts, dysplastic megakaryocytes) are not consistent with CR.

†In some circumstances, protocol therapy may require the initiation of further treatment (eg, consolidation, maintenance) before the 2-month period. Such patients can be included in the response category into which they fit at the time the therapy is started.

§In the absence of another explanation such as acute infection, gastrointestinal bleeding, hemolysis, and so on.

Table 2. Definitions of endpoints for clinical trials in MDS

Endpoint	Response category	Definition	Point of measurement
Overall survival	All patients	Death from any cause	Entry into trial
Event-free survival	All patients*	Failure or death from any cause	Entry into trial
Progression-free survival	All patients	Disease progression or death from MDS	Entry into trial
Disease-free survival	CR	Time to relapse	First documentation
Cause-specific death	All patients	Death related to MDS	Death

IPSS should be used as the primary stratification.
Complete blood counts should be evaluated at least monthly, or more often if clinically indicated, to establish the durability of responses.
*Under circumstances in which presentation of event-free survival may be appropriate for responders only, this point should be clearly stated.

improvement) and their associated complications should be objectively measured and evaluated. In addition, some of the newer classes of drugs are more likely to be cytostatic than cytotoxic, or they may induce cellular differentiation; therefore, time to disease progression may be the primary endpoint rather than the response rate. Responses, then, should reflect the goals of the treatments.

Various strategies have been used to treat patients with MDS, often with varying objectives. Low-intensity therapies, defined as treatments capable of permitting predominantly outpatient management (eg, cytokines, certain biologic response modifiers, immunosuppressive therapy), are often directed at patients with low risk MDS (IPSS Low and Intermediate-1). The goals of many of these low-intensity therapies are improvement in blood counts, disease palliation, and enhanced quality of life.[7] Such treatments are not necessarily associated with improved survival or progression-free survival. Thus, hematologic improvement is appropriate for measuring responses to this type of treatment.

The aim of other low-intensity therapies (low-dose chemotherapy, 5-azacytidine; low-dose cytarabine) and high-intensity therapies (aggressive anti-leukemic chemotherapy, stem cell transplantation) is to induce hematologic responses (complete remission [CR] or partial remission [PR]) and to alter the natural history of the disease (prolonging survival, progression-free survival). Cytogenetic responses may be helpful to determine the degree to which the natural history of the disease may be altered.

There are no curative therapies for patients with MDS other than bone marrow transplantation, which is successful in only a subset of treated patients.[8-11] As a result, numerous therapies have been and are being evaluated to improve the outlook for these patients. However, the published results of clinical trials are difficult to interpret for a number of reasons, including patient selection bias, sample size, and inconsistent response criteria. For example, hematologic improvement has been used to indicate variable levels of increase in one hematologic lineage in some studies or multilineage improvement in others.[12-14]

Several new agents are used in clinical trials for MDS, including 5-azacitidine, decitabine, amifostine, topotecan, and others.[12,13,15-18] In addition to defining comparable patient groups among studies and collecting complete prognostic factor information, the availability of uniform response criteria would improve analysis of clinical trials in MDS.

An approach to standardizing response criteria

To resolve the problems resulting from variability in definitions of the quality and quantity of response in MDS, a group of international investigators with expertise in MDS convened to establish standardized response criteria for clinical trials involving patients with MDS. Some of the response categories (hematologic improvements) are more relevant to therapies designed with palliative intent, whereas others (complete remission, partial remission) are relevant to the goals of treatments directed at altering the natural history of the disease. The proposal for evaluating response is shown in Table 1 and indicates 4 levels of response criteria based on the intent of specific therapies: hematologic response, altering the natural history of the disease, cytogenetic response, and quality of life. Although data are lacking regarding the correlation between cytogenetic response and clinical outcome in MDS, based on the valuable role of this parameter in the management and prognosis of patients with chronic myelogenous leukemia,[19,20] we have included this category to facilitate prospective evaluation.

Similarly, whereas only limited data exist regarding the value of quality of life instruments in assessing treatment outcomes in MDS, such methods of evaluation have been valuable for patient assessment in other neoplasms.[21,22] QOL studies are most valuable in randomized trials, not only with placebo controls but also when comparing 2 approaches. QOL studies may also be useful in single-arm trials to assess interactions among disease-related symptoms, treatment-related toxicity, and disease response. These aims should be defined prospectively. We anticipate that the use of this criterion in appropriate clinical trials, using instruments such as the WHO Performance Score or the FACT Questionnaire,[22] will provide valuable insights into patients' physical, functional, emotional, and social status.

Also critical for evaluating and clarifying outcomes of treatments and for designing clinical trials is to stratify patients effectively and prospectively using risk-based criteria for patient entry and evaluation (FAB subtype or, perhaps more important, IPSS risk group[5]). For example, comparison of survival or progression-free survival for patients at IPSS low risk would differ from those at IPSS high risk and should be indicated as such. Such stratification could include age, performance status, and prognostic risk category, as suggested by the National Comprehensive Cancer Network Panel on MDS.[5,7]

Conclusion

The goals of clinical research in MDS are to prolong the survival of patients and to improve their quality of life. In phase 2 trials, in which the activity of a new agent may be the most important objective, response rates are valuable and may provide support for approval by regulatory agencies. However, in some clinical settings, incremental increases in response rates have not translated into prolongation of time to treatment failure or survival. In MDS, added objectives for patients with this often indolent, chronic illness are to reduce morbidity associated with cytopenias (diminish transfusion requirements, infections, or bleeding) and to improve quality of life. In this regard, we believe that the use of risk-based prognostic stratification and clinically relevant response

criteria would be valuable for evaluating clinical outcomes and for trial design in MDS.

It will be important to apply these guidelines prospectively in large trials and to critically assess their validity and usefulness. Uniform criteria will help to determine the impact of a specific clinical outcome on patient survival or improved quality of life. The IPSS should be used as the primary stratification factor. In addition, studies should prospectively assess whether there is a difference in outcome for patients from 0 to 6 months, 6 to 12 months, and longer than 12 months from diagnosis of MDS. We have also set an arbitrary threshold for minor cytogenetic response at 50% normal metaphases; future studies must better correlate cytogenetic response with survival. We anticipate that these recommendations may require modification as more is learned about the molecular biology and genetics of these disorders. We hope that these guidelines will serve to improve communication among investigators and to ensure comparability among clinical trials.

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