# Review of the Response Criteria for Myelodysplastic Syndrome

*a report by*

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Myelodysplastic syndromes (MDS) are a heterogeneous group of bone marrow disorders that cause chronic blood cytopenias and may progress to acute myeloid leukaemia (AML). In recent years there has been a steady increase in the number of therapies available to treat MDS, which has necessitated the development of standardised response criteria to allow comparison between different treatment modalities. Therapeutic goals vary in MDS, with some treatments aimed at symptom control while others aim to alter disease biology and improve survival. Both treatment approaches are relevant in different contexts, and the International Working Group (IWG) criteria have been developed to encompass a range of clinically pertinent measurements to monitor disease response. The evaluation of new therapies in MDS is difficult because of disease heterogeneity, and most clinical trials analyse patient cohorts based on diagnostic classification and risk assessment. Classification of MDS is primarily based on the morphology of blood and bone marrow. The French–American–British (FAB) system[1,2] classified patients into separate diagnostic groups with an increased proportion of myeloblasts defining disease with a more aggressive clinical course. The FAB classification was modified by the World Health Organization (WHO) to account for dysplastic changes (refractory anaemia with multilineage dysplasia with or without ringed sideroblasts), lowering the threshold of the number of blasts to be considered AML, recognising a new subtype of MDS based on cytogenetic abnormality (5q- syndrome) and separating chronic myelomonocytic leukaemia into a separate diagnostic group.[3] These classification changes are clinically relevant and provide prognostic information.[4] Risk assessment of MDS patients in clinical trials typically utilises the International Prognostic Scoring System (IPSS).[5] The IPSS is based on the bone marrow myeloblast percentage, the number of blood cytopenias and cytogenetic changes present in untreated MDS patients at diagnosis. This system then provides stratification of patients into low-, intermediate-1-, intermediate-2- and high-risk groups for determining overall survival and risk of disease transformation to AML. IPSS low- and intermediate-1-risk patients are considered low-risk MDS and intermediate-2- and high-risk patients are considered high-risk MDS.

## Treatment Goals in Myelodysplastic Syndromes

Initial formulation of a management strategy for an individual patient with MDS should consider age, co-morbidities and disease risk. Patients with low-risk MDS (IPSS low and intermediate-1) typically have prolonged survival and experience symptoms related to chronic anaemia. Treatment goals in this group usually aim to alleviate symptomatic cytopenias and improve quality of life. Treatment options vary and can include transfusion of blood products, growth-factor therapies (erythropoietin with or without colony-stimulating factors), non-growth-factor therapies with immunomodulators (lenolidamide and antithymocyte globulin) and epigenetic drug treatment (azacytidine and decitabine). Assessment of clinical response to therapy in low-risk disease should reflect the specific treatment goals with measurement of changes in anaemia and quality of life. High-risk MDS (IPSS intermediate-2 and high) are characterised by progressive pancytopenia and a significant risk of transformation to AML. Patient survival is significantly shorter than in the low-risk group. Treatment for these patients is focused on altering the natural course of the disease and prolonging survival. Therapies are typically more intensive, with consideration of allogeneic bone marrow transplantation in younger patients. Measurement of response to therapy in high-risk MDS has used similar criteria to AML, with measures of bone marrow blast percentage and resolution of bone marrow abnormalities.

## Response Criteria for Myelodysplastic Syndromes

The IWG criteria were developed by a panel of clinicians to provide standardised measurements relevant to the different treatment goals of both low- and high-risk disease. Initial recommendations were released in 2000[6] and a subsequent revision published in 2006.[7] The IWG was not the first group to define response criteria for MDS. The Cancer and Leukemia Group B (CALGB) have used their own criteria, which in one study were compared with IWG criteria.[8] The differences between the two groups included duration of response (≥4 weeks for CALGB; ≥8 weeks for IWG), target haemoglobin values (different values per gender for CALGB; similar between sexes in IWG) and the fact that the IWG uses haematological improvement by major and minor responses. The IWG criteria have become the standard for defining response to therapy in MDS. The IWG criteria evaluate four broad areas of disease response: alteration of the natural history of the disease, cytogenetic responses, haematological improvement (HI) and quality of life assessment.

### *Alteration of Disease Course*

Disease response is measured on the basis of improvement in bone marrow characteristics (myeloblast percentage and morphological features) and peripheral blood cytopenias. At least two separate measurements are required to show maintenance of response lasting more than four weeks. A complete remission (CR) is achieved when peripheral blood counts normalise, bone marrow dysplasia resolves and the myeloblast percentage returns to normal at less than 5% of nucleated cells. A partial remission (PR) is obtained when a decrease of at least 50% in the above-noted variables occurs, or if patients fall into a lesser disease classification compared with their pre-treatment state. Taking this into account, alteration of the natural history of MDS is particularly important in younger patient populations with more aggressive disease, where prolonging survival is the primary goal of treatment. Most disease-modifying therapies were initially studied prior to the IWG criteria. Chief among these were studies involving the hypomethylating agents 5-azacytidine (azacytidine) and 5-aza-2'-deoxycytidine (decitabine). Based on two phase II trials[9,10] and a randomised phase III trial,[11] azacytidine was the first hypomethylating agent to be approved by the US Food and Drug Adminstration (FDA) for MDS. Following the modification of the FAB classification by the WHO and the introduction

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of the IWG criteria, data from these three studies were re-analysed to account for these changes.[8] In the azacytidine arms, the CR attained ranged from 10 to 17%, the partial response (PR) from 0 to 2% and the HI from 23 to 36%. When the WHO classification was utilised, more patients were reclassified with AML. IWG criteria applied to the experimental arms showed a CR range of 7–12%, a PR of 0–4% and an HI of 23–32%. Furthermore, the overall response rates ranged from 35 to 48% and the median survival was increased from 12.9 months in the control arms to 19.3 months in the azacytidine group. These findings show that patients with AML obtain benefit from azacytidine. The overall response rates for MDS patients were consistent with previous response criteria, but the IWG criteria are still important because they provide a uniform standard that allows better comparison between trials.

### *Cytogenetic Response*

Cytogenetic abnormalities are present in approximately 50% of patients with MDS.[12] Resolution of a measurable cytogenetic abnormality with drug therapy reflects activity of the agent against the MDS clone with recovery of normal haematopoiesis. For the proper evaluation of cytogenetic response, the IWG suggests analysis of 20 metaphases as optimal. Chromosomal abnormalities should be reported if at least two metaphases are involved. An abnormal clone is established by three or more metaphases. A complete cytogenetic response is defined as a resolution of all chromosomal abnormalities. A partial cytogenetic response is defined as 50% or more reduction in chromosomal abnormalities. A landmark study that illustrates the importance of cytogenetic response also led to the FDA approval of lenalidomide for transfusion-dependent patients with lower-risk disease associated with a 5q- deletion[13]. All patients in the study received either daily doses or 21 days of a 28-day cycle of lenalidomide. Eighty-five of the 148 total patients were available for cytogenetic evaluation at baseline and week 24. Complete cytogenetic response was accomplished in 38 patients (45%) and a partial cytogenetic response was attained in 24 patients (28%). Of these 62 patients, 61 became transfusion-independent. Another recent trial involving three dosing schedules for decitabine in higher-risk MDS patients contained 51 participants available for assessment of cytogenetic response.[14] A complete cytogenetic response was reported in 17 patients (33%), and a partial cytogenetic response was noted in 12 patients (24%). Thirty-eight patients with a cytogenetic response to therapy also attained a survival benefit. Of these patients, 87% had a complete cytogenetic response, establishing a correlation between survival and cytogenetic response.

### *Haematological Improvement*

Improvements in haemoglobin concentration were an important end-point in clinical trials that established the role of hematopoietic cytokine therapy in MDS. Improved haemoglobin concentration with consequent reduction in red cell transfusion is a clinically relevant response for low-risk disease, and measurements of HI have been developed to assess erythroid responses for other treatment modalities. The IWG criteria separate HI into erythroid (HI-E), neutrophil (HI-N) and platelet (HI-P) responses.

A recent systematic review[15] of studies published from 1990 and 2005 involving MDS patients treated with erythropoietin (EPO) revealed that erythroid response rates were higher in the IWG-applied studies compared with the non-IWG studies, although less transfusion dependence was noted in the IWG studies. In a separate trial, List and associates used transfusion dependency or symptomatic anaemia as part of their inclusion criteria for MDS patients to receive lenalidomide.[13,16] In their pilot study for lenalidomide use in MDS patients with anaemia, 56% had an erythroid response with either transfusion independence or elevation of haemoglobin concentration. In the subsequent multicentre phase II trial, 76% of patients had a reduced need for red cell transfusions as a result of lenalidomide treatment. The response was rapid and 62% of patients had a durable response to treatment for at least one year. These studies demonstrated that suppression of the 5q clone resulted in both haematological and cytogenetic improvements. Finally, the IWG criteria define response for individuals in whom one or more cytopenias may be the primary source of morbidity.

### *Quality of Life Assessment*

Quality of life assessment is important, particularly in a low-risk, elderly population that may not want to be exposed to the side effects of intensive chemotherapy. Several assessment tools have been incorporated into recent clinical trials, including the Mental Health Inventory (MHI) and the European Organisation for Research and Treatment of Cancer (EORTC).[11,17] In a phase III CALGB trial (9221), the azacytidine arm was associated with higher response rates as well as a delayed risk of leukaemic transformation. Patients in the experimental arm also achieved a significant improvement in fatigue, physical functioning, dyspnoea, positive affect and psychological distress. Given the relatively low side effect profile of azacytidine compared with more intensive regimens, the association between improved quality of life with better therapeutic responses and reduced leukaemic transformation confirms the benefit of a hypomethylating agent in the elderly population.

### Conclusion

Standardised response criteria provide clinicians with better measurement tools to evaluate the increasing number of treatments available for MDS. The IWG criteria facilitate the comparison of drug response rates between clinical trials, allow coupling of treatment to specific therapeutic goals and improve overall assessment of the outcome of treatment programmes. ■


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