Response:

Myelodysplastic syndromes standardized response criteria: further definition

We read with interest Dr Raza’s letter1 in response to the International Working Group’s (IWG’s) proposal to provide standardized response criteria in myelodysplastic syndromes (MDSs).2 Developing consistent guidelines for MDSs presents a challenge since the clinical course of the disease may fluctuate prior to and during therapeutic intervention. These criteria were designed to create a standardized format so that results from different studies could be compared and to minimize the likelihood that arbitrarily designed response definitions would be used. In addition, the criteria developed were to be clinically relevant and response durability defined.

There are often a number of subtle issues that do not become apparent until such guidelines are applied, as has been noted with the newer guidelines in chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphomas (NHLs),3,4 and presumably will also be the case with the new acute myeloid leukemia (AML) guidelines in development. When clinicians attempt to apply such guidelines either to clinical practice or to a clinical research study, some degree of judgment must be used. Regarding Dr Raza’s comment about definitions of baseline values, the values used should accurately represent the laboratory values at the time the patient is entered into the trial. As we indicated in Table 1, “all relevant response criteria must be noted on at least 2 successive determinations at least 1 week apart after an appropriate period,,” and such criteria would also be consistently applied at baseline (eg, at least 2 successive determinations at least 1 week apart within a 1 month period).

Regarding Dr Raza’s request for a definition of the term “transfusion dependence,” we consider this term to indicate the average number of transfusions within a defined period (eg, within several months prior to therapy). Thus, as stated in Table 1, responses to treatment would reflect decreases in these values over a similar baseline period. Transfusion independence, by definition, would necessitate no requirement for such blood products over the specified period of time.

Dr Raza was concerned that too many forms of responses were included. Rather, we believe the inclusion of the various types of responses is important because it reflects the clinically relevant intent of the treatment. For example, an anemic patient with a normal platelet count receiving low-intensity therapy may experience an increase in hemoglobin and platelet values following treatment. But the only clinically relevant response in this case would be erythroid (HI-E). In contrast, patients receiving high-intensity therapy (attempting to alter the natural history of the disease) would have their responses based on levels of remission of the disease. Cytogenetic and quality-of-life responses would be valuable to determine for both types of treatment.

We concur with Dr Raza’s statement about the value of having applied these criteria previously. In fact, in addition to the extensive clinical trials experience of the IWG investigators, a number of prior studies have used these criteria to varying degrees and, thus, provided a practical model for some of the proposed criteria guidelines.5-7 Despite these experiences, we do believe that some modification of these parameters will be needed as we accumulate new knowledge. As stated in our report, “We anticipate that these recommendations may require modifications as more is learned about the molecular biology and genetics of these disorders.”2(p3674) Dr Raza suggests having each of the French-American-British (FAB) subtypes of MDSs (refractory anemia [RA], RA with ringed sideroblasts [RARS], RA with excess of blasts [RAEB], chronic myelomonocytic leukemia [CMML]) treated as separate entities. Such stratification of MDS patients can certainly be used and is consistent with our guidelines. We anticipate that, in the coming years, “treatment choice” and “treatment development” will be guided increasingly according to molecularly defined subtypes of MDS. An important recent addition to the FAB morphologic categories has been the International Prognostic Scoring System (IPSS) for MDSs.8 As we stated, this approach provides an improved stratification system for “clarifying outcomes of treatments and for designing clinical trials . . . using risk-based criteria for patient entry and evaluation.”2(p3673) Our group strongly advocates that responses to therapy be evaluated in the context of prognostically relevant stratification.

Our hope is that these response guidelines will help expedite the development of new and more effective therapies for patients with MDSs.


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References

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