Defining prior therapy in myelodysplastic syndromes and criteria for relapsed and refractory disease: implications for clinical trial design and enrollment

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The recent approval of 3 drugs for the treatment of myelodysplastic syndromes (MDSs) has resulted in a revolution in therapeutic options that was absent a decade ago. At the same time, the changing MDS environment is raising new challenges in clinical trial design and defining new indications for MDS drugs. Many current trials still rely on IPSS-based enrollment criteria, despite the well-recognized limitations of the IPSS. Clinical trialists designing studies struggle with several important trial design challenges, including which patients constitute the “previously treated” and “relapsed/refractory” MDS populations, and how specifically to define disease “progression.” This article considers some of these issues as they relate to study design, including how to identify certain MDS populations and define disease progression.

Introduction

The myelodysplastic syndromes (MDSs) are a collection of clonal bone marrow disorders that, in their most severe forms, approximate acute leukemia, with a predicted survival measured in months. Available treatment options for patients with MDS have increased considerably over the last decade, and our knowledge of the molecular underpinnings of these diseases is beginning to catch up. The recent expansion in therapeutic choices and biologic understanding is clearly demonstrated when one considers that among the 816 patients included in the 1997 International Prognostic Scoring System (IPSS), who were enrolled in 7 registries assembled from the mid-1980s through the mid-1990s, 92% had received no therapy for their MDS other than transfusions, and the IPSS’s cytogenetic risk categorization was based on just 6 common karyotypic results (normal, 5q−, 20q−, −Y, −7/7q−, and complex; the dozens of other less common but recurrent MDS-associated cytogenetic patterns were lumped together unhelpfully as “other”).

Now, in the year 2009, 3 drugs—azacitidine, lenalidomide, and decitabine—are approved by the US Food and Drug Administration (FDA) specifically for MDS-related indications, along with at least 5 hematopoietic growth factors licensed for other indications that can potentially be used for patients with MDS (epoetin, darbepoetin, filgrastim, sargramostim, and pegfilgrastim); whereas the thrombopoietin agonists romiplostim and eltrombopag have activity in MDS, their use is currently restricted to patients with immune thrombocytopenia. “Disease-modulating” therapies used off-label for treating MDS include cytotoxic agents (such as cytarabine and clofarabine) and those with immune-modulating mechanisms of action (such as thalidomide and anti-CD52 monoclonal antibody). The growing number of available therapies makes it more difficult to design clinical trials for the untreated MDS population.

With respect to biologic understanding, although the mechanisms of disease in MDS remain largely obscure, we now understand the prognostic implications of a much broader range of karyotypes than the small number included in the IPSS. The largest MDS cytogenetics database published to date, developed by a German-Austrian consortium and encompassing more than 2200 patients, includes almost 40 recurrent abnormalities clustered into 3 risk groups. Furthermore, when newer tools, such as array-based techniques for globally assessing single nucleotide polymorphisms and loss of heterozygosity, have been applied to MDS, these technologies have uncovered a broad range of previously cryptic chromosomal changes, identifying abnormalities in up to 80% of patients and providing “leads” for future experiments, underscoring the biologic complexity and diversity of these diseases. It is anticipated that newly recognized genetic lesions will be incorporated into future iterations of MDS prognostic scoring systems, though their complexities may necessitate formal, online nomograms, as are used for prostate cancer progression probabilities (http://prostatecancerinfo.org/tips-tools/kattan-nomograms), rather than back-of-the-envelope calculations.

For several reasons, physicians, scientists, and regulatory officials are paying increasing attention to MDS. Aging of the population and the resultant increasing number of MDS diagnoses, recognition that MDS is at least as common as acute myeloid leukemia (AML), and the encouraging precedent of 3 drugs achieving FDA approval for MDS-related indications since 2004 are resulting in a wave of clinical trials of novel treatment approaches and combinations of drugs. At the same time, the changing MDS environment is raising new challenges. Many current trials still rely on IPSS-based enrollment criteria, despite the well-recognized limitations of the IPSS. In addition, clinical trialists designing studies struggle with several important trial design challenges, including which patients constitute the “previously treated” and “relapsed/refractory” MDS populations, and how specifically to define disease “progression.” This article considers some of these issues as they relate to study design, including how to identify certain MDS populations and define disease progression.
Who is the “previously untreated” MDS patient?

Prior therapies

Most MDS specialists would likely agree that patients being followed by “watchful waiting” (ie, monitoring of blood counts and symptoms without any drug intervention to alter the natural history of disease), and patients who are receiving red cell or platelet transfusions without additional therapy, would constitute an “untreated” patient population.2,12 In a recent study characterizing MDS patients in the United States that was based on more than 4500 surveys completed by 101 physicians, only 20% to 25% of established lower-risk patients (defined in the survey as an IPSS score of 1.0 or lower) and 12% to 20% of established higher-risk patients (defined as an IPSS score higher than 1.0) would fall into this untreated category.22 Thus, the vast majority of the present MDS population potentially eligible for clinical trials could be considered currently or previously treated.

Similarly, most MDS experts would also agree that patients treated with 1 of the 3 FDA-approved MDS drugs should be considered previously treated. All 3 drugs have demonstrated intermediate markers of clinical activity, including complete and partial remissions and durable hematologic improvement in treated patients, and all have shown at least a modicum of clonal activity, as measured by cytogenetic responses.3,4,12,23-25

Less than 5% of MDS patients will undergo stem cell transplantation—the only potentially curative treatment modality—even with the availability of reduced-intensity conditioning approaches.22 Further modifications of conditioning regimens may modestly increase this proportion. Although some patients with MDS will die with the disease rather than from it, the lack of curative therapy for most patients implies that up to 95% of treated patients eventually could be classified as having relapsed MDS (ie, disease that improves and then worsens to at least the pretreatment severity), refractory disease (ie, disease that is unchanged despite therapy), or progressive disease (ie, disease that worsens rather than improves during therapy).

Erythropoiesis-stimulating agents and colony-stimulating factors

A more difficult question is whether to consider the use of erythropoiesis-stimulating agents (ESAs) and colony-stimulating factors (CSFs) as being part of the spectrum of watchful waiting or supportive care, or as prior therapies. In the same physician survey mentioned above,22 more than half of both low- and higher-risk patients with MDS had used or were using ESAs, either alone or in combination with other agents. Other survey data support the idea that ESAs are by far the most commonly used MDS therapy,26 and this is reflected in published treatment guidelines (eg, those of the National Comprehensive Cancer Network)27 that recommend ESAs as a first-line treatment. Should patients who either fail to respond to ESAs (refractory), or who experience improvement in hemoglobin or a decrease in transfusion requirements for a time but then worsen again (relapsed), be considered as a relapsed/refractory population, or as an untreated population for clinical trial enrollment purposes?

The answer depends on whether ESAs are considered to be disease-modifying therapy. What does it mean to modify the natural history of a disease such as MDS? There are certainly biologic criteria that could be used. For example, does a drug result in cytogenetic responses, implying a change in the composition of hematopoietic clones in the marrow? Is the degree of dysplasia or marrow fibrosis substantially reduced, accompanied by hematopoietic improvement? Does a specific treatment alter bone marrow vascularity, or reduce levels of inflammatory cytokines?

But the ultimate measure of a disease-modifying therapy is whether a given treatment improves a patient’s overall survival. Although it has not been demonstrated prospectively whether ESAs are capable of altering survival in MDS, 3 large retrospective studies suggest a survival advantage for ESAs, administered either alone or in combination with CSFs. One potential explanation for this phenomenon is in minimizing transfusion needs in these patients, and thus the deleterious effects on survival of transfusion dependence (as demonstrated by Malcovati et al, though this may reflect differing disease biology, rather than an impact of transfusions on the disease),28 along with the salutary effect of minimizing iron overload. Accepting the caveat that retrospective studies of drug exposure are inherently susceptible to patient selection bias, there is at least the possibility that ESAs represent disease-modifying treatment.

The first retrospective ESA survival study compared 121 Nordic MDS patients treated with ESAs and CSFs to a disease- and time-matched cohort of 237 patients in Pavia, Italy, who received no growth factor therapy.29 Those receiving ESA-based therapy lived longer than the Pavia cohort (HR = 0.61, 95% CI: 0.44-0.83, P = .002). The second study, from the GFM group, compared 403 ESA-treated patients with the ESA-untreated subset of patients from the cohorts used to define the IPSS (HR = 0.43, 95% CI: 0.25-0.72).30 Although the rate of AML transformation was similar in the 2 groups, overall survival was better in the ESA-exposed cohort. Finally, a third analysis—a systematic review—examined 162 trials published over a 20-year period that enrolled lower-risk MDS patients (refractory anemia or refractory anemia with ring sideroblasts), and compared 1587 patients treated with ESA-based therapy to 1005 patients treated with non–growth factor approaches.31 Patients who received ESA-based therapy had significantly better survival at 6, 12, 18, and 24 months of follow up, compared with the non–growth factor group. All 3 studies attempted to control for selection bias by adjusting for differences between patient groups in baseline characteristics.

One recently published prospective study from the Eastern Cooperative Oncology Group randomized MDS patients to receive ESAs with or without granulocyte CSF (n = 53) to supportive care alone (n = 57), allowing crossover to active therapy for nonresponders, and reported results with a median of 5.8 years of follow up.32 Survival did not differ between those randomized to ESAs versus those receiving supportive care, analyzed by intention to treat and by therapy actually received, though admittedly the study had only 80% power to detect a 46% reduction in the hazard rate in the ESA arm. ESA responders lived a median of 5.5 years, compared with 2.3 years for nonresponders (P = .004).

Another consideration with respect to evaluating treatment with ESAs is whether failure to respond to ESAs marks a patient as less likely to respond to other therapies, compared with those “treatment-naive” patients who have never received ESAs at all. Unfortunately, no published clinical trials of which we are aware have distinguished patients who had previously been exposed to ESAs from those who had not, when reporting objective responses. Patients for whom ESAs have failed are inevitably
further out from their diagnoses than ESA-naive patients, on average, because of the time required to undergo an ESA trial; perhaps this makes them somewhat more likely to have evolved diseased hematopoietic subclones that are intrinsically resistant to treatment.

In summary, indirect evidence suggests that ESA-based therapy may modestly alter the natural history of MDS (ie, not just improving cytopenias, but also altering survival, even though karyotypic responses are not seen with ESAs). We feel that ESA therapy should be considered a “prior therapy” in those who have received it. Patients who respond to ESAs, and then lose their response, could be considered to have relapsed disease, similar to those who worsen after an initial response to non–ESA-based therapies. As ESAs have not been shown to have a direct, cytotoxic effect on the MDS clone, as opposed to some other MDS therapies, and the survival of patients failing ESAs is unknown, patients relapsing from treatment with these agents alone should be considered in a disease category of “previously growth factor treated,” and stratified as such for future clinical trials of disease-modifying drugs.

**Who is the relapsed or refractory MDS patient?**

One aspect of defining relapsed or refractory disease depends on the categorization of prior therapy. Another is in determining when a patient has relapsed.

**Relapse: lower-risk MDS**

For lower-risk MDS, relapse should be determined based on clinical grounds alone, predicated on the pattern of blood counts or transfusion needs. A typical scenario would involve a patient with refractory cytopenia with unilineage dysplasia along erythroid cell lines (ie, refractory anemia) who is treated continuously with a drug and experiences an erythroid hematologic improvement, with an increase in hemoglobin levels of 20 g/L (2 g/dL). After maintaining this response for 6 months, the patient’s hemoglobin drops again to baseline levels. Clinically, the patient has not improved from baseline after experiencing a transient improvement, and thus has relapsed. As lower-risk MDS patients have a low bone marrow blast percentage to start with, and determinations of degrees of dysplasia are not widely accepted to be accurate assessment methodologies, performing a repeat bone marrow biopsy may not be helpful, unless the goal is to determine progressive disease (discussed in the next section). For patients with multiple cytopenias who undergo therapy, experience improvement in more than one cell line, but then lose the response in one of those cell lines while maintaining it in others, relapse should be defined more narrowly, and should depend wherever possible on specific cell line response goals identified a priori—much like calling a shot in billiards. When the billiard ball falls in the “called” hole, it counts; if it falls in the wrong hole, it should not count, either for response or for relapse.

One special challenge is to avoid erroneously concluding that a patient has relapsed based on cytopenias, when those cytopenias may be therapy induced. This can be avoided in 2 ways. First, determination of relapse should be based only on the cell line(s) that were affected at baseline. Second, relapse should be declared only after a drug “washout” period of at least 4 to 6 weeks, which would allow for drug-induced cytopenias to resolve (although with some agents, these cytopenias may be more durable) and any delayed beneficial affects of drug therapy to become manifest.

**Relapse: higher-risk MDS**

For higher-risk MDS patients, relapse should be determined based on both clinical and biologic grounds, and thus a repeat bone marrow biopsy is a requirement, even in the presence of detectable blasts in the peripheral blood. Patients in the higher-risk categories almost always have an increased blast percentage in their bone marrows at baseline, and this percentage is easily quantifiable. In this scenario, such a patient might have 8% bone marrow blasts at the start of therapy, 3% blasts in the setting of improved peripheral blood counts for 6 months on therapy, but then 9% blasts in the setting of compromised peripheral blood counts subsequently, and be declared to have relapsed disease. The dual assessment of improved bone marrow blast percentage and improved peripheral blood counts is requisite to declare unequivocally a beneficial treatment effect. Although improvement in either the biologic or clinical picture with stability or worsening of the other would seem a pyrrhic victory at best, clinical data from the AZA-001 study indicates that patients without a clear biologic and clinical response may yet experience improved survival, highlighting a potential limitation of the International Working Group (IWG) response criteria and the need for repeated clinical assessments before terminating therapy. Thus, this should not be considered a relapse. As with lower-risk disease, a washout period of 4 to 6 weeks to allow for resolution of drug-induced cytopenias should be considered for patients with improvement in bone marrow blast percentage before declaring disease relapse or drug failure.

**Refractory disease**

Patients with either lower- or higher-risk disease should be considered refractory to treatment when peripheral blood counts do not improve, and in the setting of higher-risk disease, when bone marrow blast percentage does not diminish, after an adequate trial of therapy. Most experts would agree that an “adequate” trial of drugs constitutes 4 to 6 months of therapy, as almost 90% of first responses occur within this time period for both of the DNA methyltransferase inhibitors, lenalidomide, and ESAs. For more cytotoxic agents, and for antithymocyte globulin, 1 to 2 cycles of therapy may be adequate to assess for refractory disease, though in the latter case longer follow-up may be necessary to assess for delayed responses. “Stable disease” should be included in this category, as it has not, to our knowledge, been demonstrated that these patients have a survival superior to those with refractory disease.

**Defining progressive disease in MDS**

Developing a clear definition of progressive MDS (ie, evolution to a form of the disease associated with poorer survival, worse quality of life, or both, compared with an earlier state) is becoming more important, as drugs both new and old are increasingly scrutinized to ensure that they have efficacy in terms of measurable and meaningful clinical end points, and are safe. For example, ESAs appear to improve hemoglobin and
reduce transfusion needs in patients with MDS, but if this benefit were someday shown to come at the cost of increased progression or poorer overall survival (as has become evident in the use of ESAs for the treatment of chemotherapy-induced anemia), enthusiasm for ESA use would quickly diminish. In fact, prospective treatment trials with ESAs are currently in development to address just this question, and it has proven challenging to devise a suitable definition of progressive disease within such studies.

The International Working Group (IWG) criteria for treatment response in MDS, first published in 2000 and revised in 2006, are a useful benchmark for comparing results across therapeutic trials, and were landmark for reigning in the heterogeneity of response definitions across MDS trials. With respect to criteria for refractory, relapsed, and progressive MDS (Table 1), the IWG used somewhat different terminology from that used in this paper, as well as criteria somewhat different terminology from that used in this paper, as well as criteria for progressive disease (both increased blasts and worsened cytopenias) distinct from AML transformation.

The IWG criteria, although helpful for standardizing response and disease definitions, have not been validated. Although it makes intuitive sense that worse cytopenias or increasing blast proportion is a poor prognostic sign, it has not been formally established that, for example, “for patients with less than 5% blasts: a 50% or more increase in blasts to more than 5% blasts.” (one of the IWG progression criteria) is associated with measurably worse outcomes than if a patient’s blast proportion remains stable, or if the blast numbers change a little but do not cross the 5% threshold. Another limitation of the IWG criteria is the reliance on the 1982 French-American-British classification for definition of treatment failure, rather than the now widely used 2001 World Health Organization (WHO) classifications that postdated the first IWG version, or the 2008 WHO classifications that postdate the modified IWG criteria. These updated classification systems raise new questions, such as whether refractory cytopenia with multilineage dysplasia (a WHO term not in the IPSS) should be considered progression from refractory anemia (more restrictively defined in the WHO than the French-American-British classification), if other progression criteria are not met, given that refractory cytopenia with multilineage dysplasia has been shown to have a worse outcome than isolated refractory anemia. There are also mathematic quirks with IWG progression criteria resulting from the use of arbitrary thresholds; for instance, using the IWG criteria, a patient whose blast count increased from 4% to 6% could be considered to have progressive disease, whereas the patient whose blast count increased from 11% to 19% would not, even though the latter patient’s blast increase is greater in both relative and absolute terms, and clinically more significant.

The IWG criteria for refractory/relapsed disease and disease progression are based primarily on cytopenias and their clinical consequence, and morphologic assessment of blast proportion. Other nonmorphologic criteria for disease progression might be used, such as acquisition of a higher-risk molecular abnormality (eg, a TP53 mutation or loss of heterozygosity)—but such findings, too, are poorly validated as prognostic markers in the context of disease evolution over time, and have been instead examined in the context of cohort studies of patients with mutations versus those without. An additional limitation is that testing for such mutations is not universally available. Nevertheless, as the field moves beyond a purely morphologic classification, such markers will become more important, and have the potential to be used collectively within “good,” “intermediate,” or “poor” categories within subsections of prognostic or diagnostic criteria. It is still too premature to advocate designing clinical trials around such markers, however.

In our intention here is not to propose a universally useful definition for disease progression—we have no better data to work from than the investigators who designed the IWG criteria. Instead, we wish to highlight the need for more consistent definitions and formal validation studies, and to point out the limitations of the existing criteria. One aspect of more clearly defining progressive disease, for example, is in rigorously collecting and evaluating prior blood count and transfusion data, which may not be possible in some cases given the lack of unified medical records. Criteria for establishing disease states and responses to therapy are not written in stone, and must change with evolving classification systems, technologies for determining disease-defining abnormalities, and evolving therapies that make definitions for response effete. We propose that the next iteration of the IWG criteria incorporates studies that shed new light on how patients may or may not respond to therapies; and be sensitive to minimum requirements for duration of therapy before declaring no effect, and to the consequence of a given therapy on inducing treatment-related cytopenias. In defining disease progression, criteria should incorporate the latest pathologic classification systems and incorporate worsening morphology into the definition; rely not
on an isolated blast percentage increase, but on a relative increase or trend; and be sensitive to evolving molecular work in identifying lesions that portend a quicker disease evolution.

Conclusions

Evolution in our collective understanding of the pathobiology of MDS and its treatment options will continue to prompt reassessment of trial enrollment criteria, and definitions of refractory or relapsed MDS and disease progression. Studies of the natural history of MDS, including the prognostic importance of specific changes during the disease course rather than just the pattern of response of markers at baseline, remain important, and inform our definitions of response and refractoriness. The next wave of MDS clinical trials should incorporate these changes in biologic and clinical understanding in developing treatment labels that mirror our transformed clinical practice.

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