Most adult patients with hematopoietic failure due to myelodysplastic syndrome (MDS) are treated with supportive care measures, including hematopoietic growth factors (epoetin alfa, darbepoetin alfa, filgrastim, pegfilgrastim, sargramostim), red blood cell or platelet transfusions, and antimicrobial agents. Allogeneic stem cell transplantation can be curative, but only a small subset of patients are eligible for transplantation, and until recently there were few options other than supportive care for transplant-ineligible patients. Since 2004, the US Food and Drug Administration (FDA) has approved three new therapies specifically for the indication of MDS: two DNA methyltransferase inhibitors (azacitidine and decitabine) and an immunomodulatory agent (lenalidomide). Several other drugs are used by clinicians for treatment of patients with MDS, but are not specifically FDA-approved for this indication. With several therapeutic options available, yet none of them effective in the majority of cases, it can be challenging for clinicians to choose the most appropriate treatment for an individual patient. Here we discuss a risk-based management approach to MDS that incorporates recent data regarding these new therapies. While many questions remain about the optimal use of newer agents, the long-standing perception of MDS as a syndrome where therapeutic nihilism is the only realistic approach is slowly beginning to change.

With their review, Drs. Steensma and Tefferi set out to define risk-based management of myelodysplastic syndrome (MDS). They thoroughly summarized the available data and, in the process, helped to emphasize how little we truly know about the disease. For those who are asked to manage this increasingly recognized patient population, decisions must be made based on this small amount of data. Yet if we hope to make a difference, some standardization of treatment and collaboration is critical. For those of us who are relatively new to the field of MDS, it is helpful to step back and look at the changes made over time. We can then compare this disease to other malignancies for which significant advances have been made in the past, so that we can contribute to future progress.

Changing Classifications
First of all, is MDS technically still considered a premalignancy (aka preleukemia) as it once was? If that is the case, it may not be useful to compare it to other true malignancies. However, since the US Food and Drug Administration (FDA)-approved treatments for MDS are quite toxic, perhaps there is no real difference, making this an irrelevant point. Knowing who is best served with these toxic treatments is a must, again leading to the need for standardization and collaboration. Finding nontoxic treatments to prevent progression in low-risk patients would be ideal, but unfortunately, there is not much to review in this regard. Clearly, there is a lot of work to be done. So what has changed? Classification systems have, for one. When classification systems are created, oftentimes they represent distinct pathologic entities in their earliest forms, but they don't always correlate with what one begins to see clinically in individual patients. As more patients are recognized and followed, it seems that their course then influences changes in classification. Ideally, scientists, pathologists, and clinicians make discoveries that collectively help to fit the pieces of the puzzle so that, ultimately, the patients could benefit. Therefore, creating a useful classification system is an enormous challenge that is subject to change as long as advances in one field or another are achieved. The very reality that classification systems have changed for MDS, as they have for other malignancies such as lymphoma, is a testament to the fact that people are investigating this entity and making new discoveries. Fortunately, this is the case.

Clinical Relevance
The World Health Organization (WHO) classification system is the clinicians' current guide to diagnosis, but is it useful? The basic principle of the WHO system was to "utilize not only morphologic findings but also all available information, including genetic, immunophenotypic, biologic, and clinical features to define specific disease entities..." It attempts to incorporate those
disease characteristics that have proved to have clinical and biologic relevance into a useful, working nomenclature."[1] This was not an easy task, with over 100 people contributing. Unanimity over every decision was impossible, and certainly complaints surfaced about the proposal after it was initially discussed. Regardless, many groups have sought to test its clinical relevance, have found it to be useful in a prognostic sense, and are now applying its use to specific treatments.[2-4] As more treatments are discovered, its relevance will likely change again. While classifications remain static, disease does not. Therefore, appropriately following a patient’s disease course and then using that information to make further decisions about treatment is essential.

Response Criteria
This leads to the next change regarding how to monitor disease. Fortunately, this issue has been addressed and recently readdressed on a large scale. The International Working Group proposed response criteria for MDS trials in order to evaluate therapy outcomes, refine treatments, and permit comparisons of data.[5] This proposal recognizes four different aspects of response, including: (1) altering the natural history of disease (which relates to improvements in survival and progression), (2) cytogenetic response (which may or may not relate to number 1), (3) hematologic improvement, and (4) quality of life. Hopefully, if such collaborations and standardization occur, the goal will become one—to prolong life and to make it more livable at the same time. On a positive note, 10 years ago there weren’t many data to review. Hopefully the fact that this article was solicited is a sign that MDS will be a popular area for recruitment of scientists and clinicians in the future, so that the trend can continue. For newcomers, it looks like important groundwork has been laid. Thanks are in order to those who have done so much to achieve the most difficult part, and who continue to contribute to our understanding of MDS and its management.

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