Clinical Issues in the Management of Patients with Myelodysplasia

Charles A. Schiffer

The management of patients with myelodysplasia (MDS) can be quite complex and varies according to both the clinical manifestations in individual patients as well as complicating medical conditions. Allogeneic stem cell transplantation is the only curative treatment, but because of the older age of the patient population must be applied selectively, particularly in those with lower risk MDS as well as in patients whose clinical course is more frankly "preleukemic." Issues pertinent to the use of 5-azacytidine, decitabine and lenalidomide in patients with both higher and lower International Prognostic Staging System (IPSS) stage disease are discussed.

As suggested by the phrase myelodysplastic syndromes, there is substantial clinical and biological heterogeneity among patients with myelodysplasia (MDS). Although there have been attempts to define more homogeneous subgroups of patients by morphologic and cytogenetic characteristics, there remains considerable variability among patients within the same “group” as well as a wide range of outcomes in patients allocated to the same risk groups by the International Prognostic Staging System (IPSS), the most widely used prognostic categorization. Furthermore, the disease course is not static and changes over time within the same patient. Because MDS most commonly affects older individuals, comorbid medical problems also significantly influence recommendations about treatment and the management of particular complications. This paper will review some recurring clinical issues commonly encountered in patients with MDS.

Diagnosis

MDS is probably underdiagnosed and is likely to be the cause of many cases of mild to moderate anemia encountered in older patients which are either not evaluated fully or are attributed to “chronic disease” or mild renal insufficiency. Early in the course of the disease, morphologic abnormalities may be either non-existent or quite subtle, and if karyotypic changes are not present, serial marrows may be required, usually prompted by gradual changes in blood counts, to finally arrive at a diagnosis. Conversely, overdiagnosis is sometimes problematic, since it is almost always possible to identify some “dysplastic” or “megakaryoblastoid” cells (particularly in suboptimal preparations) if one looks hard enough and has a bias toward making a diagnosis. Hence, review by experienced hematopathologists or hematologists is advisable. It is uncommon to have to consider MDS-specific therapies in patients in whom the diagnosis is more tenuous, since significant cytopenias, other than anemia, are unusual, although occasionally patients with MDS can present with isolated neutropenia or thrombocytopenia. Future studies will likely evaluate the symptomatic benefit of erythropoietic stimulating agents in selected older patients with mild to moderate reductions in hemoglobin levels.

Treatment

In addition to the use of lineage-specific colony stimulating factors, which can be helpful as supportive care modalities but do not affect the natural history or progression of the MDS clone, three agents are approved by the US Food and Drug Administration (FDA) for the treatment of MDS. All were approved within the last couple of years, although the hypomethylating nucleoside analogues, 5-azacytidine (Vidaza®) and decitabine (DACOGEN®), had been evaluated as antileukemic drugs for decades previously. The most striking results have been seen with lenalidomide (Revlimid®), an orally administered analogue of thalidomide, which has produced dramatic responses in patients with del5q, with normalization of hemoglobin and suppression of the abnormal clone in about two-thirds of patients.

Early Stage (Low IPSS) MDS

Although some patients with MDS have clinical problems associated with neutropenia or thrombocytopenia, symptomatic anemia is usually the initial problem necessitating intervention. Erythropoietin can benefit a fraction of patients, with the highest response rate seen in patients with lower endogenous erythropoietin levels (< 500 IU) and lower transfusion requirements. The addition of low-dose granulocyte colony-stimulating factor (G-CSF) may be of
benefit in selected patients, with a suggestion of higher response rates in patients with refractory anemia with ringed sideroblasts. Eventually, however, erythropoietin therapy is no longer effective in most patients and red blood cell transfusions are needed. Interestingly, I have noted that physicians/patients are often reluctant to stop erythropoietin, even when it is apparent that the hemoglobin is not increasing, the reticulocyte count is very low and transfusions are needed.

Transfusion requirements can vary widely, influenced by the presence of the following:
• other medical problems, which can demand higher hemoglobin levels to alleviate symptoms of weakness or angina,
• alloantibodies to RBC,
• clinically apparent or more subtle splenomegaly.
• occult gastrointestinal hemorrhage with thrombocytopenia, platelet dysfunction and occasionally angiodysplasia as contributing factors.

The morbidity of chronic anemia is probably underestimated. Although most patients report symptomatic improvement following transfusion, they generally remain fatigued, with some limitations of their activities. Particularly as the frequency of transfusions increases, it is common to see patients whose hemoglobin levels vary between 7 and 9 gm%, such that they are virtually never without symptoms of fatigue. A common error is to delay transfusions until the patient becomes symptomatic, allowing the hemoglobin to drop to undesirably low levels, rather than anticipating the interval between transfusions, which in most patients is relatively predictable, thereby avoiding very low hemoglobin levels. Patients are also often undertransfused, with 2 units seeming to be the most common "dose." There is variation in the size and duration of storage among RBC units, and many patients require 3 or more units to reach higher levels, which can then be easier to maintain with avoidance of the dips to lower levels.

The major long-term concern with chronic transfusion therapy is iron overload with resultant cardiac or hepatic sequelae. Because of the necessity for parenteral administration, deferoxamine was underutilized in the past, particularly in elderly patients in whom other concurrent medical problems might have been expected to limit survival. The recent approval of the oral iron chelator deferasirox (Exjade®) will likely help address the issue of patient tolerance and acceptability, although it is not yet known whether the rate of iron removal will be sufficient to keep ahead of the iron accumulation associated with the ongoing chronic transfusion need. Deferasirox therapy is costly, particularly in older patients caught in the Medicare co-pay bind, and has some side effects, particularly diarrhea, that can sometimes limit its use. In addition, it is not expected to have an effect on the underlying disease, although rare patients have been described in whom MDS seemed to improve with effective long-term chelation therapy. At this time, oral chelation therapy should be considered in patients who have a demonstrated need for chronic transfusion and who have not exhibited changes suggestive of evolution toward AML or other significant medical problems that would be expected to limit their survival before the effects of iron overload become clinically important. An observation period of ~ 1 year, during which time such patients might have received 20+ units of RBC, is a reasonable interval to evaluate these issues.

Thus, therapy directed toward the MDS becomes an important consideration even in patients with “low risk” disease. Indeed, these patients are not necessarily low risk, with a recent publication confirming the intuitive observation that survival decreases once patients begin to require regular RBC transfusions. In the subgroup of patients with the 5q− abnormality, therapy with lenalidomide is an obvious consideration, given the extremely high response rate. The duration of responses are not well defined and it is unclear, given the significant myelosuppression associated with this therapy, whether 5q− patients who are moderately anemic but not transfusion dependent would benefit from earlier treatment with lenalidomide. Therapy of the 5q− syndrome is discussed in detail in another chapter of this symposium.

The data using the FDA-approved agents in the majority of patients who do not have the 5q− change are less complete and less compelling. Although 5-azacytidine and decitabine were approved for use in all risk groups of MDS, there is in fact very little information about their effectiveness in the lower-risk IPSS group of patients. In the original randomized trial with 5-azacytidine, there were only 23 patients in the IPSS low or INT-1 group, half of whom were randomized to supportive care, while only 28 INT-1 patients were treated with decitabine in that randomized “pivotal” trial. Twenty-seven percent of patients with refractory anemia (RA) or refractory anemia with ringed sideroblasts achieved either a CR (9%) or PR (18%) with 5-azacytidine, while 14% of decitabine patients with INT-1 MDS had either a CR or PR. Other patients had “hematologic improvement,” with some becoming at least transiently transfusion independent. Multiple courses of treatment are required with both agents, often with accompanying myelosuppression, with a median time to response of 2-4 months and response duration of generally < 1 year. Therefore, patients should understand that treatment with these agents necessitates a long-term commitment. Similarly, because it can sometimes be difficult to determine whether patients are likely to respond even after the first couple of courses, treating physicians should not stop therapy prematurely. It is important that additional clinical trials be conducted with these agents in lower risk IPSS patients to define the response rate with more confidence.

Preliminary analysis of a large phase trial of > 200 patients with non-5q−, low IPSS MDS treated with lenalidomide reported transfusion independence in ~ 25% of patients with some others enjoying “hematologic im-
A problem in interpreting these and other reports which describe “hematologic improvement” is that the original IPSS response criteria had some looseness in this definition and, particularly in patients with modest transfusion requirements before treatment, physician decisions about when to transfuse, which often vary over time even within the same patient, can artificially influence (usually inflate) the apparent response rate. This issue was addressed in a recent update of the response criteria, which attempted to make the definition of erythroid response more clinically relevant by requiring an absolute increase in hemoglobin level of > 1.5 gm% compared to a pretransfusion baseline and an absolute reduction of at least 4 units of transfused RBC over an 8-week period compared to the number of transfusions given the previous 8 weeks. Despite this “tightening” of the response criteria, clinicians should be critical when evaluating the importance of responses that do not result in transfusion independence. Thus, the decision about whether to use these agents in lower IPSS patients must be highly individualized, balancing the toxicity to be expected from a particular treatment against the predicted benefit. Certainly, more information with the nucleoside analogues would be of interest. In the interim, therapy with lenalidomide may be attractive in some circumstances given the oral route of administration as well as the relatively rapid time to response, should responses occur.

Lastly, immunosuppressive therapy with antithymocyte globulin +/- cyclosporine should be considered in selected patients, particularly since the responses can be sustained for many years in some responders. Responses are seen most frequently, but not exclusively, in patients with refractory anemia and perhaps in the subgroup of patients with hypocellular bone marrows. There is no information about the response rate following other types of therapy in patients with hypocellular MDS and it should be noted that it sometimes can be difficult to distinguish hypoplastic MDS from aplastic anemia. Retrospective analyses suggest that responses may be highest in individuals with HLA-DR15 and further studies to help predict the likelihood of benefit in individual patients are needed, since the published response rates vary considerably among different trials. Elimination of clonal T lymphoid populations, which may suppress normal hematopoiesis, is one possible explanation for the responses seen.

Transplantation
Allogeneic transplantation is the only curative treatment for MDS. Because of the older age of patients with MDS and the mortality and morbidity associated with graft-versus-host disease (GVHD), transplantation has generally been reserved for patients with higher risk MDS or MDS transforming to AML. There is an appreciable relapse rate in these more “AML-like” patients. There is less experience with transplantation in patients with lower risk disease, although the available data would indicate that the relapse rate is lower, with the major cause of death due to transplant-related complications. Experience with reduced-intensity transplantation for patients with MDS is beginning to accumulate and it is clear that such transplants are more easily tolerated, at least in the short term, with evidence of substantial graft-versus-leukemia (or -MDS) effect. Although longer term follow-up and studies evaluating the effects of different induction or immunosuppressive regimens on relapse rate and GVHD are desirable, it may be that transplant should be considered more often in some patients with low or INT-1 IPSS scores.

Who might such patients be? First, the IPSS is a bit dated and mixes patients with heterogeneous disease presentations and biology. As with all prognostic formulas, it is not designed to be predictive of the outcome in individual patients. In general, it “rates” findings suggestive of progression toward AML (marrow blasts, karyotype) more highly, according only 0.5 of a possible 3 points to bi- or trilineage cytopenias. The IPSS was created from the score at a given point in time, and the course of patients with MDS obviously varies over time. In addition, more patients succumb to problems from cytopenias or advanced age than from leukemia. Consider, for example, a 36-year-old asymptomatic man who was found to have abnormal blood counts at the time of a routine examination. His hemoglobin was 11 gm%, platelets 111,000/µL, neutrophils 500/µL. Bone marrow showed trilineage dysplasia with 2% blasts; cytogenetics revealed a t(1;16) in 50% of metaphases. This patient’s IPSS score would be 0.5 or INT-1, the same score as a patient with more preserved blood counts and 5% marrow blasts. However, the neutropenia is probably a more profound risk factor for both complications and death in the short run, particularly since neutrophil counts often worsen during intercurrent illnesses or viral infections.

More refined scoring systems that incorporate other clinical and biological factors are in development. As noted above, the expected survival decreases significantly when patients become RBC transfusion dependent. The dire prognostic implications of deletions of chromosomes 5 and/ or 7 and complex cytogenetic abnormalities are well known. A recent large analysis of more than 2,000 patients with MDS provides some insight into the clinical behavior of patients with less common cytogenetic abnormalities and translocations, such as the t(1;16) mentioned above. In the future, it is hoped that gene array analyses will increase our rudimentary understanding of the biology of MDS, providing clinically relevant prognostic information as well. In the interim however, patients need management decisions and, unfortunately, the data using the currently available treatments are sobering. The choice of therapy must
be individualized with the recognition that any of these scoring systems provide only rough predictions of the clinical course in an individual.

Lastly, the management of MDS, and particularly earlier stage MDS, is more of a marathon than a sprint, with ongoing changes in other medical conditions and the MDS itself that have to be considered at different times during the patient’s course. It should be kept in mind that “low risk” MDS can still be an awful disease and that consideration of transplant is appropriate in selected patients unresponsive to available therapies, whose disease has declared itself to be progressive and inexorable, even in the absence of signs of leukemic transformation.

**Higher Stage MDS**

The initial decision in patients with more advanced IPSS is whether allogeneic transplantation is feasible, and in younger patients, it is important to assess donor availability soon after diagnosis, particularly in those with increased blasts or more worrisome cytogenetic changes. Relapse remains a major problem however, and although graft versus MDS is likely to be the major determinant of elimination of the clone, innovative conditioning regimens, such as the addition of targeted delivery of ionizing radiation with labeled monoclonal antibodies, are of interest.

Most patients are older and not suitable candidates for transplantation. Therapy with 5-azacytidine and decitabine should be considered in many such patients, although the side effects of the treatment and the multiple courses of therapy that are required can make treatment less advisable in older patients with problems with transportation, absence of care providers, etc. There is no information about the response rate with the alternative drug in patients who have failed to respond to the other agent, and no data with lenalidomide in patients with more advanced MDS. Preliminary findings suggest that alternative, lower-dose outpatient schedules of decitabine may be more effective (and convenient) than the inpatient regimen approved for licensing, perhaps because the lower doses are actually more effective at producing hypomethylation of DNA and renewed gene expression.

A small randomized trial noted complete responses in 41% of patients treated with 20 mg/m²/day of decitabine given as a 1-hour infusion for 5 days. Further studies to optimize dose and schedule of both 5-azacytidine and decitabine, as well as combinations with other drugs, are beginning. Combinations with other agents that might also affect gene expression, such as histone deacetylase inhibitors, are of particular interest.

The management of patients whose disease is progressing with cytopenias and an increasing number of blasts poses a major clinical dilemma. The WHO classification somewhat arbitrarily shifted the definition of AML to include patients with greater than 20% blasts, thereby eliminating the FAB group of refractory anemia with excess blasts in transformation (RAEB-T). There is probably no difference in outcome with chemotherapy in this spectrum of patients with 20+% blasts and the issue with regard to treatment is not the “name,” but rather the pace of disease and the manner in which it is affecting the patient. Of importance is that many patients at the MDS/AML “border” can remain clinically stable for long periods of time, with low but “safe” platelet and neutrophil counts and minimal changes in blast number. Because unsuccessful therapy can result in shortened survival, many patients benefit from close follow-up and deferral of treatment. Eventually, however, a decision about treatment is required. Options include the following:

- **Supportive care alone**: Red blood cell transfusions with hydroxyurea when blast counts increase in the peripheral blood may be suitable for patients with poor performance status (PS) and/or other severe medical problems. To provide some perspective, a recent analysis of older patients with AML treated by SWOG on clinical trials noted that 30-day mortality was 64% in patients > 75 years of age with PS > 2 but only ~ 15% in patients with a PS of 0-1; results in patients 66-75 years of age were ~ 35% and 14%, respectively.

- **Investigational agents**: This approach is mentioned most often in older patients or those with secondary leukemia or prior myelodysplasia because of the very poor long-term outcome in such individuals (i.e., “it’s hard to do worse”). However, conventional induction therapy is not totally futile since ~ 30% of such patients reach CR with relief from the risks of the cytopenias that accompany untreated AML. Although the benefit for responders is usually measured in months rather than years, ineffective therapy is of no value and usually equates with death from infection or other complications. The potential loss of the benefits of CR must be considered before deciding to evaluate therapy with as yet unproved response rates, including the use of “non-cytotoxics” with a putative advantage of avoidance of the acute side effects of chemotherapy. Unlike other cancers, there is generally only one initial “crack” at achieving response because of the increasing mortality associated with prolonged periods of cytopenias.

- **5-Azacytidine/decitabine**: Although the original randomized trials included patients who would have been classified as RAEB-T, CR rates overall were < 20% and often required multiple courses of therapy. Experience in patients with higher blast levels is more limited, particularly with 5-azacytidine, but is likely to be similar, although the alternative schedules of decitabine, as noted above, may be somewhat better.

- **Conventional induction chemotherapy**: “Standard” chemotherapy with anthracycline and cytarabine (“3 and 7”) is reasonably well tolerated by older patients with adequate organ function and PS and achieves CR rates of 40-55% in patients > 60 years of age with “de novo” AML, which is biologically very similar to MDS/AML. There are multiple well-accepted explanations.
for the inferior outcome seen in AML in older patients, including evolution from myelodysplastic syndromes even in some patients with apparently “de novo” AML; a high incidence of chromosomal abnormalities associated with drug resistance; overexpression by the leukemia cells of drug resistance proteins such as p-glycoprotein with an indication that the AML frequently arises in more primitive hematopoietic stem cells; poorer tolerance of the side effects of therapy; alterations in drug metabolism related to subtle or more clinically obvious abnormalities in renal or hepatic function; impaired marrow reserve with delays in count recovery following induction and consolidation chemotherapy. Nonetheless, induction therapy generally provides the best chance to achieve CR. Newer agents such as clofarabine29-31 have shown promise in small studies in older patients when used as single agents, and studies in patients with MDS would be of interest. In general, however, given the profound benefits of newer antiemetic agents and the development of less toxic antifungal agents, it is not the administration of the particular chemotherapeutic drugs themselves that is problematic, but rather the consequences of cytopenias and the inherent drug resistance of the leukemia in older patients. It is not known whether such newer agents would have higher response rates than standard induction treatment.

Conclusions

Although there have been substantial improvements in supportive care and the introduction of new agents with some potential to produce objective benefit for a minority of patients with different stages of MDS, therapy is still largely palliative and remains unsatisfactory overall. Innovative clinical trials are needed and should be supported by referral of suitable patients. Our understanding of the fundamental biology of this complex stem cell disorder remains inadequate, and it is hoped that ongoing gene expression array, epigenetic and proteome studies will be helpful in identifying less empiric approaches for treatment in the future. In the interim, the management of MDS requires a thoughtful approach by experienced physicians to provide amelioration of symptoms and maximal extension of life.

References

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