How I treat

How I treat patients with myelodysplastic syndromes

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Introduction

Critical issues in determining therapeutic strategies for patients with myelodysplastic syndromes (MDSs), who usually die of bone marrow failure with or without conversion to acute myeloid leukemia (AML), include host factors in these mainly older patients, disease heterogeneity, lack of pathogenetic understanding, and a dearth of effective treatments. Even the issue of whether these clonal disorders should be considered a form of cancer represents an area of controversy.[1] Nonetheless, in the past several years, 4 new drugs (5-azacitidine, decitabine, deferasirox, and lenalidomide) have been approved by the Food and Drug Administration (FDA) for use in MDS. Once the diagnosis and prognosis are established, key decisions in the approach to a patient with MDS include when to initiate treatment, establishment of an optimum supportive strategy, and choosing among available therapies, especially a potentially curative allogeneic stem cell transplantation.

Diagnosis and prognosis

The diagnosis of MDS is an effort that requires clinicians and pathologists to work together. A patient's life, livelihood, and outlook can be profoundly affected by terms used by the treating physician. The typical presentation is unexplained anemia, leukopenia, and/or thrombocytopenia, in an older adult (median age $\geq$ 70 years).[2] However, thrombocytosis may be associated with the 5q− syndrome[3] or in selected patients with refractory anemia with ringed sideroblasts (the RARS-T syndrome).[4] The white count may be elevated in MDS/myeloproliferative disorder overlap syndromes (particularly chronic myelomonocytic leukemia).[5] The prior probability of MDS is increased when a patient with typical features has had a history of exposure to alkylating agents,[6] particularly after a prior "autologous transplant" for non-Hodgkin lymphoma.[7] Indeed, the natural history of secondary MDS is expected to be worse than primary MDS, although whether this inferior outcome is independent of chromosomal status is not clear. Karyotypic analysis of marrow cells often reveals loss of the long arm or all of chromosome 5, loss of the long arm or all of chromosome 7, an extra chromosome 8, or complex abnormalities.[8] Such findings are only supportive of the diagnosis, which depends on noting morphologic features in cells from marrow and blood in the appropriate clinical setting. "Atypical" MDS cases, which are not unusual, include situations where the clinical-pathologic findings are equivocal, such as the combination of cellular dysplasia and marrow fibrosis (overlap between agnogeneic myeloid metaplasia and MDS) or a hypoplastic marrow (overlap between aplastic anemia and MDS). Molecular testing for the JAK2 mutation may be useful in selected patients with the RARS-T syndrome[4] to potentially focus therapies on those used for the myeloproliferative syndromes. Another diagnostic dilemma is that between MDS and AML. This is particularly relevant in an era of change from the French-American-British classification system,[9] requiring more than or equal to 30% marrow or blood blasts, to the newer World Health Organization (WHO) classification system,[10] in which 20% blasts are sufficient for the diagnosis of AML. Retrospective data suggesting that the percentage of marrow blasts (if > 20%) did not have therapeutic or prognostic impact when controlling for age and karyotype[11] prompted this change.

The International Prognostic Scoring System (IPSS)[12] is the most widely used classification system for patients with MDS: 3 factors (the percentage of bone marrow myeloblasts, the diagnostic cytogenetics, and the number of cytopenias) are used to generate a prognostic score. Limitations of the dataset on which the IPSS was based include (1) the lack of inclusion of secondary (after prior cytotoxic therapy) MDS cases, (2) the inclusion of many patients now considered to have AML, (3) the lack of "treated" cases, and (4) the unknown impact of currently available therapies. A recently proposed classification system (Table 1), the WHO classification–based Prognostic Scoring System (WPSS), makes use of the WHO subclassifications and supports the intuitive notion that the need for red cell transfusions predicts for a worse prognosis.[13] The 7 possible scores in the WPSS can be collapsed into very low, low, intermediate, high, or very high-risk groups in which the median survival and risk of progression to AML at 5 years is 140 months/3%, 66 months/14%, 48 months/33%, 26 months/54%, and 9 months/84%, respectively.[13] Ideally, a genetically based classification system, possibly using genomic or proteomic expression patterns in the MDS stem cell, would supplant all the inherent inconsistencies of the available methodology.

Treatment options: general thoughts

Myelodysplasia is an incurable disease with non-transplantation therapy, but highly variable in its natural history. Treatment considerations must take into account many factors, including the pathologic diagnosis, the prognosis based on the IPSS or WPSS, the unique disease features in that particular patient (eg, is thrombocytopenia predominant?), feasibility of performing a clinical trial, the appropriateness of a bone marrow transplantation, and indeed the philosophy of the patient and the family concerning his or her care. In addition, if the patient has secondary MDS, tolerability of therapy is probably worse because of previous exposure to DNA-damaging agents. Predicting how patients with secondary MDS will respond is difficult because of a lack of data and exclusion of such patients from most clinical trials. Any

Table 1. WHO classification–based prognostic scoring system for MDS

Variable	Score			
	0	1	2	3
WHO category	RA, RARS, 5q−	RCMD, RCMD-RS	RAEB-1	RAEB-2
Karyotype*	Good	Intermediate	Poor	—
Transfusion requirement†	No	Regular	—	—

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Risk groups: 0 indicates very low; 1, low; 2, intermediate; 3 to 4, high; and 5 to 6, very high. Score is obtained by adding the scores for each variable.

RA indicates refractory anemia; RARS, refractory anemia with ringed sideroblasts; 5q−, myelodysplastic syndrome with isolated del(5q) and marrow blasts less than 5%; RCMD, refractory cytopenia with multilineage dysplasia; RCMD-RS, refractory cytopenia with multilineage dysplasia and ringed sideroblasts; RAEB-1, refractory anemia with excess of blasts-1; RAEB-2, refractory anemia with excess of blasts-2; and —, not applicable.

*Karyotype was as follows: good, −Y, 5q−, NL; poor, −7, complex; and intermediate, all others.

†RBC transfusion dependency was defined as having at least one RBC transfusion every 8 weeks over a period of 4 months.

recommendations for therapies in this article should be interpreted with caution when considering patients with secondary MDS. Although many biologic features, including increased marrow angiogenesis, increased apoptosis in low-risk subsets, and abnormal cytokine release, have been said to be characteristic of MDS, there is no unifying pathophysiology or subset-specific pathogenesis. Exceptions include chromosome translocation-based activation of the PDGFRβ tyrosine kinase on the long arm of chromosome 5 in those rare chronic myelomonocytic leukemia patients with the appropriate karyotype[14] and the recently described ribosomal protein haploinsufficiency in the 5q− syndrome.[15] Imatinib and lenalidomide are highly effective in the aforementioned situations, respectively. However, significant clinical response rates in other, much more common MDS settings with any available agents are less than 20% to 30%. The National Cancer Center Network guidelines are very useful in considering the appropriate therapy for given patients with MDS, subdividing treatment based on whether the patient has lower (low or intermediate-1) risk IPSS or higher (intermediate-2 or high) risk disease.[16] I will describe a somewhat different exercise, which could be helpful in fashioning an initial treatment strategy for the patient with MDS, based on answering a series of simple questions.

To treat or not?

There are patients who have MDS based on sound pathologic and clinical criteria who might best be served by observation. Treatment should be reserved, and potentially the diagnosis transmitted to the patient and family, only if there are symptoms resulting from anemia or other cytopenias or perhaps presymptomatic anemia or severe thrombocytopenia. Many patients, especially those who are older and frail or who have equivocal diagnostic features, benefit from a period of observation before any discussion about the need for therapy is made. For example, supportive therapy might be the best choice for older patients who have refractory anemia with ringed sideroblasts.[17] The choice between therapies is hampered by a relative lack of prospective randomized trials. When reviewing the mainly phase 2 clinical trials evaluating therapies in MDS, one must consider publication bias, patient selection, and the use of standardized response criteria.[18]

Neutropenia without a history of infection is a poor justification for initiation of therapy. Although studies performed in the 1980s documented that the neutrophil count increased in most patients treated with granulocyte colony-stimulating factor[19] or granulocyte-macrophage colony-stimulating factor,[20] randomized studies did not demonstrate any real clinical benefit, although the feared promotion of leukemia did not clearly occur despite an increase in marrow blasts in some patients.[20] If treatment is to be initiated because of a need to ameliorate symptoms, improve blood counts,

or to attempt to lengthen survival, the options include hematopoietic growth factors, DNA-hypomethylating agents, immunosuppressive therapy, lenalidomide, clinical trials, or stem cell transplantation. Transfusional support is a given, with the caveat that routine use of platelet transfusions to support nonbleeding (even severely) thrombocytopenic patients is not advisable.

To transplant or not?

The oft-stated mantra that the only curative modality in the treatment of patients with MDS is allogeneic stem cell transplantation does not mean that every patient diagnosed with MDS should be referred for such a procedure. Patients can reasonably safely be transplanted in the standard (myeloablative) fashion up to age 55 to 60 years. In young patients with MDS who are candidates for "full transplantation," the intrinsic biologic aggressiveness of the disease (eg, the IPSS score) must be strongly factored into the decision. The outcome after transplantation for those with indolent disease is superior to that in patients with more aggressive MDS.[21,22] However, because of the possibility of diminishing overall life expectancy resulting from treatment-related mortality in those with good prognosis, it is recommended that allogeneic transplantation be used in low and intermediate-1 IPSS patients only after disease progression, whereas patients with more aggressive histology/prognosis should be transplanted immediately on recognition that a donor exists.[23] Recent data suggest that lower risk patients (according to the WHO or WPSS) do very well with allogeneic transplantation, whereas those with 5% to 20% marrow blasts have only a 25% to 28% 5-year overall survival.[24]

Second, because of the very small difference in treatment-related mortality between sibling-matched transplantations and molecularly typed matched unrelated donor transplantation, I make no distinction about whether there is a family donor or a registry donor when deciding about a transplantation. In summary, it is appropriate to refer young patients with MDS with a relatively poor prognosis for an allogeneic transplantation.

The role of nonmyeloblative or reduced-intensity conditioning (RIC) in MDS is currently being explored. It is clear that treatment-related mortality associated with this modality is no higher than that seen with full transplantations in younger patients, thereby making it a reasonable consideration for MDS patients between 55 and 70 to 75 years of age (Table 2).[25] The major problem is the lack of long-term data with regard to disease relapse. At this time, it is reasonable to consider nonmyeloblative transplantation in patients with high-risk disease between 55 and 72 years of age, particularly if a sibling donor exists. There is very little information about unrelated RIC transplantations in this age group.

Another related issue, particularly relevant for RIC transplantations, is excess marrow myeloblasts or the relevance of disease

Table 2. Ablative versus RIC allotherapy in MDS/AML patients more than 50 years of age

	Relapse, %	TRM, %
Ablative	38	37
RIC	56	24

Adapted from Alyea et al[25] with permission.
TRM indicates transplantation-related mortality.

control. In AML patients, it is clear that fewer marrow blasts at the time of transplantation portend for a better outcome than if the transplantation is done in the presence of more fulminant disease. Whether this result shows that chemoresponsivity indicates a biologically more indolent disease or there is intrinsic value in pretransplantation cytoreduction is unclear. Nonetheless, the presence of more than 5% to 10% blasts in the marrow of an MDS patient probably makes transplantation, particularly with RIC, less likely to succeed. Overall, approximately 25% of RIC allotransplantations for MDS result in long-term disease-free survival. It is therefore reasonable to administer one or 2 cycles of "MDS-induction therapy" with a DNA-hypomethylating agent in an attempt to "perform an in vivo purge" of the marrow blasts before the allogeneic procedure.[26] Although one can expect a reduction in marrow blasts in less than half the cases so treated, toxicity with 5-azacitidine or decitabine is relatively small, and the chance of making the patient ineligible for a transplantation because of treatment-related toxicity with one of these agents is even smaller. Whether or not this approach, based largely on anecdotal experience, is beneficial would really require a randomized trial of pretreatment therapy before allogeneic transplantation, and no such trial is planned.

In summary, any MDS patient with higher risk disease as well as lower risk patients (young transfusion-requiring persons) less than 70 to 75 years of age should be at least theoretically considered for an allogeneic transplantation. Data reporting outcomes for RIC transplantations for those between the ages of 65 to 75 years are sparse; medical therapy is probably most appropriate in all but highly selected older patients.

Hematopoietic growth factors?

The notion of using hematopoietic growth factors to treat the cytopenias of patients with MDS is attractive but certainly limited by the problem of an intrinsically deranged and therefore potentially unresponsive marrow stem cell. Nonetheless, virtually every patient with MDS and anemia at some point receives an erythropoietic growth factor. There is incomplete information and confusion about the likelihood of response, the optimal dose, and whether to use a short- or long-acting agent. When recombinant erythropoietin was first introduced, not surprisingly, the recommended dose was identical to that used in the initial indication for erythropoietin, namely, chronic renal failure (150 U/kg subcutaneously 3 times a week).[27] Such an approach is impractical because of the Medicare requirement that allows reimbursement only if patients receive such medicine in a clinic setting. The optimal dose of erythropoietin in MDS is unclear, but recent studies have called for at least 40 000 to 60 000 units weekly.[28] With the availability of long-acting recombinant erythropoietin, darbopoietin, it has become common practice to administer the latter agent at a dose of 200 to 300 μg every week or every other week.[28-30] One can expect that 25% of patients will respond (reduce their transfusion requirement by at least 50% or increase hemoglobin by 1 g/dL). Response can take 8 weeks or more; it is common practice to increase the dose

once or even twice before concluding that the patient is unresponsive to single-agent erythropoietin. Patients who are not transfusion dependent at baseline or who have relatively low intrinsic levels of serum erythropoietin (< 500 mIU/mL) are more likely to respond[31] with response duration in 1 to 2 years. Lack of response could be the result of insufficient iron stores, but the presumptive usual problem is an intrinsically unresponsive marrow. Many patients are kept on erythropoietin long after benefit seems doubtful in the hope that "if we stop the erythropoietin, the situation will get even worse," but this idea leads to an overuse of an expensive medicine. Finally, recent concern about the tumorigenic effect of erythropoietin in solid tumors[32] has made it much more difficult to obtain and use the drug, even though there are no data about long-term deleterious effects in MDS patients; MDS advocacy groups have issued statements supporting continued availability and third-party payments for this indication.

The effect of erythropoietin may be enhanced by the addition of low-dose granulocyte colony-stimulating factor, which, as previously mentioned, has little role in MDS as an anti-infective or disease-modifying agent. The hemoglobin response to erythropoietin may be improved from 25% to 40% with this combined approach,[33,34] and recent comparative studies[28,35] (looking at treated vs untreated patients) support such combined growth factor treatment. This approach may be worth trying in selected patients whose primary problem is anemia, especially in the presence of ringed sideroblasts.

There are no useful currently available cytokines for thrombocytopenic MDS patients. A recent report of a phase 1 trial demonstrated that the thrombopoietin agonist AMG531 (romiplostim) improved platelet counts in MDS patients, both as a single agent[36] and in support of 5-azacitidine-treated patients.[37] But it is unclear at this time what further MDS-specific developmental steps will be taken with this agent, now approved for the treatment of immune thrombocytopenic purpura.[38]

In summary, a several-month trial of erythropoietin is a reasonable option in anemic patients, mainly in those with low-risk disease and baseline serum erythropoietin levels less than 500 IU/mL. If no benefit is seen or if a response has waned, the drug should be stopped. Myeloid growth factors should only be used alone in those rare neutropenic MDS patients with recurrent pyogenic infections.

To chelate or not?

Although iron overload in heavily transfused MDS patients could account for unexplained heart failure, diabetes, or other endocrine dysfunction, as is the case in many patients with thalassemia,[39] there are absolutely no definitive data concerning the frequency of such complications, let alone whether patient outcomes might be improved by the use of chronic iron chelation therapy. On the other hand, there are reports demonstrating the adverse independent prognostic effect of a large red cell transfusion burden[40] as well as a high serum ferritin level.[41] Until recently, the only available iron chelation agent in the United States was deferoxamine, which had to be given over 8 to 12 hours per day subcutaneously. Side effects, including local inflammation and cataracts, plus the cumbersome delivery schedule, made it universally detested by patients. With the approval of deferasirox,[42] an oral chelator capable of mobilizing significant amounts of iron,[43] it is now logistically easier to prophylax potential problems stemming from iron overload. Deferasirox has been approved for all situations in which iron overload could be a problem, but there are no specific studies showing that it definitely reduces complications in MDS patients. The drug is

Table 3. Responses to lenalidomide in 5q− and non-5q− MDS patients

	Non-5q−	5q−
Transfusion independence	26%	67%
Median hemoglobin rise	3.2 g/dL	5.4 g/dL
Median time to response	4.8 weeks	4.6 weeks
Complete cytogenetic response	10%	44%

Modified from List et al[45] and Raza et al[46] with permission.

expensive and not without side effects. With all these caveats, it is probably reasonable to use deferasirox at a starting dose of 20 mg/kg per day in chronically transfused patients who, by virtue of low IPSS scores, are expected to live for many years.[44] Given the lack of prospective data demonstrating a benefit for the use of deferasirox, it should be stopped for financial or side effect concerns.

Is 5q− present?

Approximately 5% of patients with MDS present with a "5q−" syndrome typified by middle-aged to older females with profound anemia, well-preserved platelet counts, and 5q− as a sole karyotypic abnormality in a diagnostic bone marrow specimen.[3] For these patients and for patients with 5q− cytogenetic abnormality alone without the syndrome, or 5q− with other cytogenetic abnormalities, an effective therapy has emerged. Lenalidomide, a relatively nonsedating immunomodulatory thalidomide congener, produces a 67% rate of transfusion independence and major increases in the hemoglobin with manageable side effects (Table 3).[45] Myelosuppression is the main side effect and may represent a therapeutic effect analogous to the aplastic period seen after imatinib treatment of patients with advanced CML. Although the FDA-approved label for lenalidomide calls for dose modification if myelosuppression is noted, recent data suggest that a more aggressive dosing scheme might be considered if optimal support can be provided.[47] The median time to response is 4.4 weeks; the median duration of the response has not yet been reached. It is important to recognize that the clinical trial detailing this impressive response rate was restricted to those with low-risk and IPSS-1 disease, platelet counts greater than 50 000, and neutrophil counts greater than 500.[45]

From a biologic standpoint, even more impressive than the high rate of red cell response rate was the significant likelihood of elimination of the karyotypically abnormal clone, implying that major disease-modifying activity is possible, although natural history studies have not yet been performed. Although there are problems with myelosuppression and cost, lenalidomide does appear to be a major advance for patients with 5q− chromosome abnormalities and should be used as initial therapy in such patients who require treatment. Whereas the National Cancer Center Network guidelines in the United States have endorsed the standard practice of administering lenalidomide to patients with 5q− MDS who would have been candidates for this pivotal trial, the European Medical Evaluation Authority noted that it was difficult to determine whether lenalidomide increased the risk of AML[48] and refused approval on that basis. The basis for concern was the lack of a comparative group.

Immunosuppressive therapy?

Because of the prolonged natural history of patients with low and intermediate-1 risk IPSS MDS and the fact that the pathophysiol-ogy more closely resembles a bone marrow failure state than leukemia, it makes sense that one would consider a different spectrum of therapeutic approaches. One should consider whether the patient is in the (difficult to define) subgroup who might benefit from immunosuppressive therapy. Immune-mediated suppression of normal stem cell function, analogous to the situation in aplastic anemia, has been postulated to account for cytopenias in some MDS patients. Selected patients treated with either cyclosporine A[49] or an antithymocyte-globulin–based regimen[50] can experience improvements in cytopenia in about one-third to one-half of the cases. Patients who are HLA D15 positive, who tend to be younger, or who have lower platelet count irrespective of marrow cellularity are more likely to respond to such immunosuppressive manipulations.[51] Conversely, another study suggests that hypocellularity and low IPSS score are predictors of response to immunosuppressive therapy.[52] Clearly, this therapy carries risk of infection and, in the case of antithymocyte globulin (ATG), has infusion-related side effects that can be difficult to manage. Studies to define the optimal patients in whom such therapy is appropriate remain to be developed. Nonetheless, for a relatively young patient without excess blasts, ATG may be worth a trial given the occasional dramatic response.

How should non 5q−, nonimmunosuppressive therapy, nontransplantation candidate patients be treated?

Should lenalidomide be tried? Although lenalidomide is clearly indicated for patients with 5q− MDS who otherwise would fit the criteria outlined in the phase 2 trial noted in "Is 5q– present?", it is reasonable to consider using this drug in selected patients with non 5q− MDS. Results of a trial in which 214 patients with non 5q− MDS were treated with lenalidomide at a starting dose of 10 mg daily (either continuously or on a cycle of 21 days on, 7 days off) were recently published.[46] Eligibility for this trial required low or intermediate-1 IPSS risk MDS and excluded patients with secondary MDS or those who platelet counts were less than 50 000/μL or whose neutrophil counts were less than 1000/μL. A total of 26% experienced a reduction in their transfusional needs (Table 3), which is roughly comparable with what is often obtained with erythropoietin or DNA-hypomethylating agents. The median time to response was 4 weeks and the duration of response was 7 months.[46] Lenalidomide is not FDA-approved for use in non 5q− MDS patients, so third-party payment issues can be challenging. Although orally administered, lenalidomide may be less likely to induce a transfusion-independent response in lower-risk MDS than 5-azacitidine where rates of 40% have been reported.[53,54] When initiating a therapeutic trial, one must pay heed to the potential for thrombocytopenia and neutropenia. Given the lack of reasonable alternatives, an anemic, low-risk MDS patient could merit a therapeutic trial of lenalidomide.

Should a DNA-hypomethylating agent be used? Clinically, those with MDS subtypes with excessive numbers of marrow myeloblasts resemble the situation in high-risk (older patient or adverse chromosome prognosis) AML. Rare patients who present with less than or equal to 20% marrow myeloblasts but have karyotypic abnormalities typical of good risk AML (translocation that involve the CBF gene inv16 and t(8;21)) should be treated with aggressive induction and postremission therapy as per AML. The class of drugs most useful in MDS and applicable to all subtypes are the DNA-hypomethylating agents 5-azacitidine and decitabine. Each drug underwent phase 3 comparison to a control arm consisting of supportive care. The azacitidine trial, conducted by the Cancer and Leukemia Group B,

Table 4. Protocols

| | Protocol 8421: IV azacitidine (n = 48) | Protocol 8921: SC azacitidine (n = 70) | Protocol 9221 | | | Protocols 8921 and 9221: SC azacitidine (n = 169) |
			SC azacitidine* (n = 99)	Observation only† (n = 41)	SC azacitidine after observation (n = 51)	
IWG response, no. of patients (%)						
CR	7 (15)	12 (17)	10 (10)	0 (0)	3 (6)	22 (13)
PR	1 (2)	0 (0)	1 (1)	0 (0)	2 (4)	1 (1)
HI‡	13 (27)	16 (23)	36 (36)	7 (17)	13 (25)	52 (31)
Erythroid response, major	10 (21)	11 (16)	22 (22)	1 (2)	8 (16)	33 (20)
Erythroid response, minor	2 (4)	3 (4)	8 (8)	4 (10)	4 (8)	11 (7)
Platelet response, major	9 (19)	6 (9)	21 (21)	2 (5)	3 (6)	27 (16)
Platelet response, minor	0 (0)	2 (3)	3 (3)	0 (0)	1 (2)	5 (3)
Neutrophil response, major	2 (4)	0 (0)	8 (8)	1 (2)	2 (4)	8 (5)
Neutrophil response, minor	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Overall: CR + PR + HI	21 (44)	28 (40)	47 (47)	7 (17)	18 (35)	75 (44)

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IWG indicates International Working Group; MDS, myelodysplastic syndrome; IV, intravenous; SC, subcutaneous; CR, complete remission; PR, partial remission; and HI, hematologic improvement.

*Patients randomly assigned to azacitidine.

†Patients randomly assigned to observation who did not cross over to azacitidine.

‡Patients with HI (major or minor) were counted only once in the overall response.

was performed in the early 1990s; response assessments were based on a protocol-specific set of criteria[53] but have been recalculated[54] (Table 4) using the more recently developed International Working Group[18] criteria. An early crossover design dampened any potential survival benefit attributable to azacitidine. However, the results demonstrated a delay in time to transformation to AML in those initially randomized to the study drug. There was a much higher response rate in the experimental arm (7% complete response [CR], 16% partial response [PR]),[53] and an ancillary quality of life study proved that patients randomized to azacitidine fared better.[55] Approved by the FDA in 2004, the drug is relatively easy to use and well tolerated, except for myelosuppression, easily controlled nausea, and minor to moderate irritations at the skin injection site. The approved dose is 75 mg/m^2 by subcutaneous or intravenous injections given daily for 7 days. There are preliminary reports of equal efficacy on a 5-day or 5-0-2 schedule[56] (weekends skipped), which would be less cumbersome. However, no long-term efficacy data are available, and only the approved daily dosing (7 times per week) schedule is associated with a survival benefit compared with conventional care.[57] The drug should be given for 4 cycles (assuming no interim progression) before determining whether benefit has occurred. Second, it can often be difficult to distinguish between drug-induced versus disease-related low blood counts. A suggested dose modification scheme based on low blood counts and mid-cycle marrow examinations in the package insert may be of limited utility. I administer 4 cycles at 75 mg/m^2 subcutaneously for 7 days every 28 days, rarely make dose adjustments, and do a bone marrow after cycle 4 to determine whether additional cycles are indicated. Occasionally, patients will have dramatic responses with marked improvement in their blood counts, but for many, the decision to continue or not is relatively difficult. Preliminary results from a trial that randomized patients with higher-risk MDS to azacitidine or physician choice (either best supportive care, low-dose Ara-C, or induction chemotherapy) have been recently published.[57] Patients randomized to azacitidine enjoyed a superior median survival compared with those on the control arm (24 vs 15 months), which provides more support for the use of this agent in high-risk MDS. Other results from this trial suggest that survival benefit may accrue even

without the patient having a CR or PR,[58] and that prolonged therapy is advisable,[59] suggesting the need for a new paradigm when thinking about this "chronically suppressive agent."

In the late 1990s, a phase 3 of a randomized trial of decitabine versus observation was conducted.[60] Based on prior experience in Europe,[61] the dose was 15 mg/m^2 every 8 hours intravenously for 9 doses (which requires hospitalization). Decitabine at this dose is probably a bit more myelosuppressive than 5-azacitidine; most patients did not receive more than 2 cycles. In the higher-risk group of patients, there was a prolongation in time to transformation in AML or death. The response rates to decitabine calculated using IWG criteria (CR 9%, PR 8%, hematologic improvement [HI] = 13%)[60] were similar to those observed with 5-azacitidine (CR 10%, PR 1%, HI = 36%).[54] The drug was approved by the FDA in the spring of 2006. The requirement to admit patients every month makes it less attractive than the subcutaneously administered 5-azacytadine at the MDS-approved dose. Preliminary results of a recent trial of decitabine versus best supportive care in higher-risk MDS patients failed to demonstrate a survival advantage[62] (in contrast to the findings with 5-azacitidine). Although this difference might have been to trial design issues, at this time 5-azacitidine should be considered the treatment of choice for high-risk MDS patients. However, a more recently developed novel dosing schedule of daily infusions of 20 mg/m^2 decitabine per day for 5 days has shown promising results based on a Bayesian-design randomized phase 2 trial done at the M. D. Anderson Cancer Center (Houston, TX).[63] This schedule has been widely adopted because of ease of administration. Confirmatory studies[64] are underway that seem to justify the routine use of this dose and schedule in MDS. Either 5-azacitidine or decitabine is appropriate in any MDS patient not likely to respond to lenalidomide or ATG.

New agents in MDS

A full discussion of novel therapies is beyond the scope of this review. Nonetheless, the importance of testing new agents in this disease should be obvious based on the lack of cures with current

nontransplantation therapy and the lack of available agents with significant clinical activity (except for lenalidomide in 5q− MDS). I rarely use AML-type induction chemotherapy in MDS, given the change in classification of refractory anemia with excess blasts in transformation to AML and the lack of curability with a chemotherapy-only approach. The novel chemotherapeutic agents clofarabine,[65] a nucleoside analog, and cloretazine,[66] an alkylating agent, are being tested in patients with high-risk AML, including those older than age 70 and those older than age 60 with adverse cytogenetic features, representing a population similar in age and biology to high-risk MDS. If the drugs are proven useful in the high-risk AML situation, there might be some justification for using them in high-risk MDS as well. One important class of new agents are the histone deacetylase inhibitors,[67] which, along with the DNA-hypomethylating agents, are designed to promote transcription of genes whose expression is silenced. This "epigenetic approach" is a subject of much ongoing clinical research including a US intergroup trial involving a combination of 5-azacitidine plus MS275,[68] one such drug in development. The other major US intergroup trial designed for low-risk MDS patients involves lenalidomide with or without darbopoietin to determine whether the presumptive mechanistic utility of lenalidomide signaling via the erythropoietin receptor can be enhanced by the growth factor.[69] Some of the more promising recent trials have included (1) farnesyl transferase inhibitors,[70] erroneously thought to target mutant ras activity, (2) c-jun modification,[71] and (3) MAP kinase inhibition.[72] All patients with MDS should be considered for a clinical trial with the possible exception of those with 5q−. However, because of the recently demonstrated efficacy of the DNA-hypomethylating agents, some think it is unethical to withhold such a therapy from higher-risk patients. At the very least, one should consider a clinical trial in which a DNA-hypomethylating agent is used as part of a novel combination regimen.
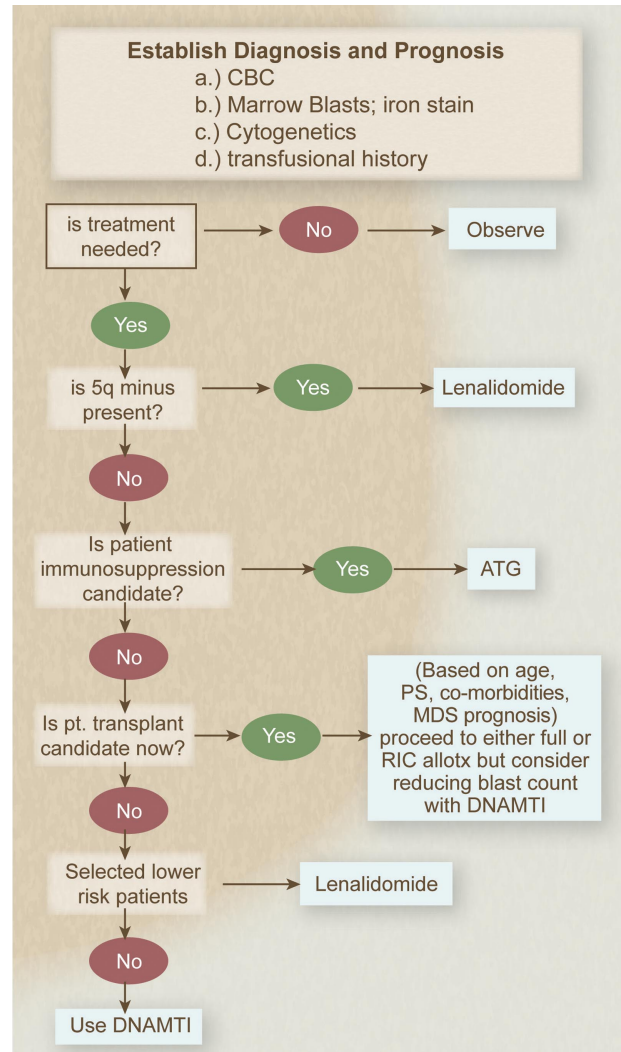
In conclusion, MDS remains a challenge for clinicians because of the older patient milieu, the disease heterogeneity, and the lack of effective medical therapy. Beyond enrolling as many MDS patients as possible in clinical trials, my therapeutic algorithm (Figure 1) is straightforward: (1) consider allogeneic transplantation in all patients with high-risk MDS if feasible; (2) use lenalidomide in patients with 5q− chromosomal abnormalities; and (3) in all other patients, use a DNA-hypomethylating agent. The details herein can obviously be quite complex, and because virtually every patient will fail the initial therapeutic maneuver, there remain no easy answers but much research to be done in this field.

Figure 1. Approach to therapy of MDS patients. Consider erythroid-stimulating agents in any patients with baseline (erythropoietin) less than 500 mIU/mL; add low-dose granulocyte colony-stimulating factor if no response after 8 weeks of therapy (especially if RARS [refractory anemia with ringed sideroblasts]). Consider iron chelation in selected lower-risk chronically transfused patients. DNAMTI indicates DNA methyl transferase inhibitors; and RIC, reduced intensity conditioning. Professional illustration by Debra T. Dartez.

Authorship

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