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Treatment Selection for Myelodysplastic Syndrome Patients in the Community Setting

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Abstract: Myelodysplastic syndromes (MDS) represent a collection of heterogeneous malignant bone marrow stem cell disorders that result in the production of dysplastic and ineffective blood cells. The disease is marked by gradually worsening cytopenias and a variable risk for the eventual transformation to acute myelogenous leukemia (AML). The risk of developing MDS increases with age, and disease onset before 50 years is unusual. Several morphologic subtypes of MDS have been identified. Each of these subtypes has specific prognostic and morphologic and/or cytogenetic features which make it unique. The International Prognostic Scoring System (IPSS) was developed to aid in determining the prognosis of patients with MDS; this system categorizes patients into four risk groups for both overall survival and transformation to AML: low, intermediate-1, intermediate-2, and high. The management of MDS is based on the goal of controlling cytopenia-related symptoms, improving survival, improving quality of life, and decreasing risk of progression to AML. Treatment strategies include supportive care, iron chelation, treatment with hematopoietic growth factors, immunosuppressive therapies including lenalidomide, antithymocyte globulin, chemotherapy (eg, azacitidine, decitabine, low-dose Ara-C, 7+3 chemotherapy), and stem cell transplantation. However, selecting the appropriate therapy for each individual patient is critical to optimize clinical benefit. This monograph discusses treatment selection for the MDS patient, including a discussion of the overall survival and maintenance of MDS patients, how an appropriate therapy should be chosen in the community setting, and how MDS classification and risk stratification impacts treatment decisions.

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Overall Survival and Maintenance of MDS Patients

Lewis R. Silverman, MD

Impact of Current Therapeutic Strategies on Patient Survival

Several studies have investigated patient survival with current myelodysplastic syndrome (MDS) therapies. Two phase III trials have specifically evaluated the survival advantage resulting from therapy with the demethylating agent azacitidine, currently approved for the treatment of MDS.

A Cancer and Leukemia Group B (CALGB) study randomized 191 MDS patients to receive either azacitidine or supportive care.[1] Both low-risk and high-risk MDS according to French-American-British (FAB) classification were represented in this phase III trial. The primary study endpoint (patient response) occurred significantly more frequently in the azacitidine arm compared with the supportive care arm (60% vs 5%, *P*<.001). There was also a significant delay in the median time-to-leukemic transformation or death in patients receiving azacitidine (21 vs 13 months, *P*=.007). Although the overall survival (OS) was improved in patients who received azacitidine, it did not reach statistical significance, most likely due to the trial design, which allowed patients in the supportive care arm to cross over to receive azacitidine if their disease worsened. Therefore, a landmark analysis after 6 months was performed, in which patients were divided into 3 groups: those who had been randomized to receive azacitidine, those who had been randomized to supportive care but crossed over to azacitidine, and those who had been randomized to supportive care and stayed within this treatment arm. This landmark analysis confirmed that patients who had initially been randomized to receive azacitidine achieved a significantly improved survival compared with the other 2 groups (*P*=.03). This was the first major study to suggest that azacitidine conferred a survival advantage in both low-risk and high-risk MDS patients.

A second phase III trial further evaluated the impact of azacitidine on survival in intermediate-2 and high-risk MDS patients.[2] This was an international, multicenter, open-label trial that randomized 358 patients to receive either azacitidine or conventional care (best supportive care, low-dose cytarabine, or intensive chemotherapy, depending on the physician's discretion). The primary endpoint (median OS) was significantly improved in patients receiving azacitidine compared with those receiving conventional care (24.5 vs 15.0 months, hazard ratio [HR] 0.58; 95% confidence interval [CI], 0.43–0.77; *P*=.0001). The 2-year OS was also significantly higher in the azacitidine group compared with the conventional care group (50.8% vs 26.2%; *P*<.0001; Figure 1). Several factors were found to prognostically favor azacitidine therapy, including age, gender, classification, and percentage of bone marrow blasts. There was also a significant benefit for patients either with a complex karyotype or with a chromosome 7 deletion or monosomy. Thus, this study was the first to definitively demonstrate a clear survival advantage for azacitidine therapy in patients with intermediate-2 or high-risk MDS.

Another demethylating agent approved for MDS therapy that has been evaluated for its effect on patient survival is decitabine. In contrast to azacitidine, the survival advantage associated with decitabine is not as clear in intermediate-2 or high-risk MDS patients.

A phase III North American study randomized 170 MDS patients to receive either decitabine or best supportive care.[3] Patients in the decitabine arm achieved a significantly higher rate of response compared with the best supportive care arm (17% vs 0%, *P*<.001). Overall, patients treated with decitabine had an increased time-to-leukemic transformation or death compared with best supportive care (12.1 vs 7.8 months, respectively), although this difference did not achieve statistical significance. However, when patients were classified according to risk, the median time-to-leukemic transformation or death did become significant for patients with intermediate-2 or high-risk disease (12.0 vs 6.8 months, *P*=.03). The same became true for treatment-naive patients as well (12.3 vs 7.3 months, *P*=.08).

The phase III European Organization for Research and Treatment of Cancer (EORTC) 06011 trial, presented at the 2008 American Society of Hematology (ASH) Annual Meeting and Exposition, was a multicenter phase III trial in which 223 MDS patients were randomized to receive either decitabine or best supportive care.[4] In this study, enrollment was restricted to patients with intermediate or high-risk MDS who were 60 years of age or older. The primary endpoint (median OS)

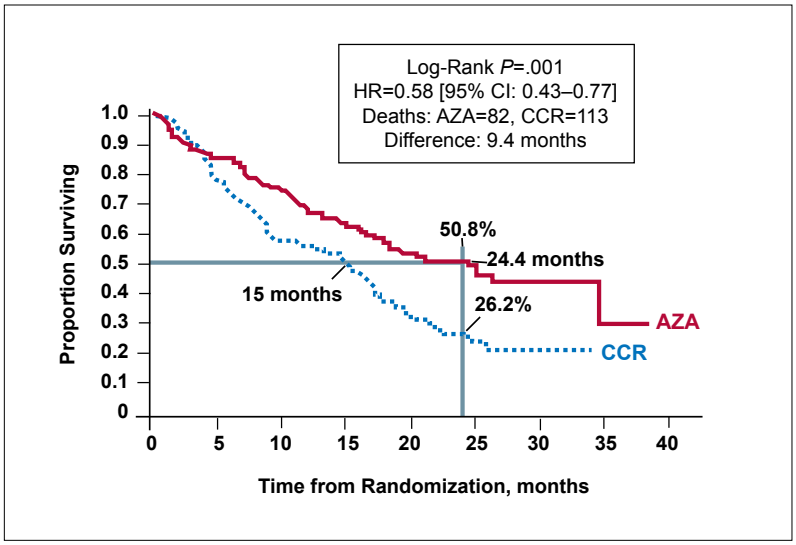

Figure 1. Overall survival: azacitidine vs CCR ITT population.

CCR=conventional care regimen; ITT=intent to treat

was not significantly different between the 2 treatment groups (HR, 0.88; 95% CI, 0.66–1.17; *P*=NS). The median OS was 10.1 versus 8.5 months for decitabine versus supportive care, respectively. A similar nonsignificant trend was also observed for time to leukemic progression or death (HR, 0.85; *P*=NS). However, the median progression-free survival (PFS) was significantly lengthened among patients receiving decitabine (6.6 vs 3.0 months; HR, 0.68; 95% CI, 0.52–0.88; *P*=.004). A superior overall response rate was also achieved among patients receiving decitabine compared with those receiving best supportive care; 34% versus 2% achieved at least a hematologic improvement (HI).

Maintenance Therapy using Current Therapeutic Strategies

To date, there has not been a clinical trial which has clearly established the most effective length of time an MDS patient should be treated with azacitidine as maintenance therapy.

In the aforementioned CALGB azacitidine phase III trial, patients who responded to therapy remained on that therapy until they either progressed or relapsed following HI or a partial response (PR).[1] Patients who had achieved a complete response (CR) received 3 cycles of therapy, after which treatment was stopped. All but 1 patient relapsed. Although these patients subsequently received other treatment, their second response was not as robust as their primary response and was less durable. In the international phase III trial comparing azacitidine versus conventional care, patients with stable disease (SD), HI, or a PR or CR continued their therapy until either progressing or relapsing.[2] However, it is important to note that a survival advantage may be apparent in patients even in the absence of a CR. This was reported in an abstract presented at the 2008 American Society of Clinical Oncology (ASCO) Annual Meeting, which demonstrated that MDS patients receiving azacitidine still achieved a 2-year OS that was statistically significant compared with conventional care, regardless of whether they achieved a CR (78.4%; *P*<.0001), PR (67.5%; *P*=.006), SD (41.3%; *P*=.041), or a HI (71.7%, *P*<.0001).[5]

These data, together with preclinical in vitro and animal model evidence, suggest that continued maintenance exposure to azacitidine may be beneficial for MDS patients. Therefore, the current recommendations are for MDS patients to continue maintenance therapy for as long as they continue to benefit from the therapy.

In the AZA-001 study presented at ASH 2008, azacitidine maintenance therapy was found to possibly optimize the benefit of therapy in intermediate-2 or high-risk MDS patients.[6] Approximately half (51%) of patients achieved a HI or better after a median of 14 cycles of azacitidine therapy. The median was 2 cycles, with 87% achieving first response by 6 cycles. Interestingly, 48% of patients who received azacitidine maintenance therapy went on to achieve a higher response category. It was also shown that for patients who went on to achieve a CR after having an initial HI or a PR as their first response, the median time to that CR was 3.2 months. Similarly, the median time to second response for patients who went on to achieve a PR following initial HI was 2.3 months. These data suggest that there is a incremental benefit in continuing maintenance azacitidine therapy in patients who had exhibited any clinical benefit.

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Choosing an Appropriate Therapy for Lower-risk MDS in the Community Setting

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Although surveys in the United States have suggested that MDS occurs with an annual incidence of 15,000, this is likely an underestimate, due to the large numbers of patients who present with mild cytopenias in the community setting. At this very early disease stage, an MDS diagnosis cannot be made unless typical chromosomal abnormalities are identified in the bone marrow. Many of these patients will not have final confirmation of an MDS diagnosis until disease progression, since a bone marrow examination is often not performed until it is apparent that the patient will need treatment.

The majority of community hematologists and oncologists are now comfortable with the International Prognostic Scoring System (IPSS) prognostic scheme, as well as the FAB morphologic classification for MDS. However, these same physicians are often less comfortable with the clinical utility of the newer classification schemes. The World Health Organization (WHO) morphologic classification adds some clinical utility by splitting off isolated 5q- syndrome, clarifying the description of refractory anemia with ringed sideroblasts (RARS) to require greater than 15% ringed sideroblasts, and separating refractory anemia with excess blasts (RAEB)-I and RAEB-II. Changing the diagnosis to AML when 20–30% blasts are present in the bone marrow is only of minimal benefit, since the major differences in the treatment decisions for patients with marrow blasts counts above 10% (RAEB-II or AML) are usually based on the pace of disease progression, transfusion dependence, severity of cytopenias other than anemia, performance status, and patient preference. While the extent of lineage dysplasia may be important, concordance between pathologists is not assured. The clinically useful portions of this classification are gaining community acceptance. The WHO classification-based Prognostic Scoring System (WPSS) is designed to replace the IPSS. It combines the WHO morphologic classification with the karyotype and transfusion requirement. It has the major advantage of being prognostic at any time after diagnosis rather than only at initial diagnosis, as is the case for the IPSS. However, both scoring systems ignore the more detailed description of highly prognostic karyotype abnormalities[1] and the severity of thrombocytopenia and leukopenia as independent prognostic indicators.[2,3] Further, the WPSS is more complicated, and unless clinicians become more confidant of the reproducibility of the WHO morphologic classification, the WPSS will not gain wide acceptance.[4]

The majority (60–70%) of all patients who present in the community setting have lower risk disease (either IPSS low- or intermediate-1 risk disease). In contrast, only 20–30% of patients in most published clinical trials are lower risk. Therefore, even though these patients represent the majority of those seen in the community setting, there are limited data which allow for data-driven decisions in this lower-risk group.

The first approach to these lower risk patients is generally a "watch-and-wait" strategy, during which time the diagnosis can be verified and other existing comorbidities can be determined. For isolated anemia, the most common presentation of MDS, the standard National Comprehensive Cancer Network (NCCN) guidelines are generally followed.[5] These suggest treatment with erythropoietin for patients with a serum erythropoietin level of 500 mU/mL or lower and adequate iron stores.

Generally, a longer-acting formulation of erythropoietin, darbepoietin alfa, is preferred, to decrease the need for frequent patient visits. Patients with serum ferritin levels less than 500 mU/mL will often receive parenteral iron. This strategy is not included in the NCCN guidelines, but is commonly used in the community setting. Once disease progression has become evident, G-CSF may be added, especially in patients with RARS.

Lenalidomide remains the standard of care for 5q- disease with dramatic and durable responses in the majority of patients. Since severe cytopenias are frequent with this treatment, very close monitoring is mandatory. Less commonly, lenalidomide may be initiated for non 5q- disease.

Treatment of thrombocytopenia with "idiopathic thrombocytopenic purpura (ITP)-like treatment" can yield responses of over 50%. Danazol has been reported to be particularly effective in small studies and may have an additional benefit of stimulating erythropoiesis.[6] Romiplostim (Nplate) has been released by the Food and Drug Administration (FDA) only for ITP with a warning against using it in MDS. Studies indicate an excellent platelet response to romiplostim in MDS, but with some patients having a transient increase in blast count.[7] There is concern that it might cause disease progression. No such increase in blasts was seen when this thrombopoietic agent was combined with azacitidine in lower risk patients. Azacitidine-induced thrombocytopenia was prevented in those patients, and there was no suggestion that it caused progression of MDS.[8]

Correction of both thrombocytopenia and leukopenia with growth factors is possible. However, the effect on long-term patient outcome of these treatments is unknown.

There is good evidence that immune modulation is appropriate for some patients in a variety of situations, including the presence of bone marrow hypocellularity, HLA-DR15, PNH clone, or a T-cell abnormality, as these patients can exhibit a good response to therapy with steroids, cyclosporine, and/or antithymocyte globulin (ATG).

Bone marrow transplantation is not ignored as a therapeutic option among these lower risk younger patients, but it is delayed unless there is a poor response to initial therapy.

Azacitidine and Decitabine Regimens

Once options such as growth factors, immunomodulation, and lenalidomide have been exhausted, it is then necessary to choose the appropriate demethylating agent. There are not a sufficient amount of data in the literature to assist in the selection of these agents in lower risk MDS patients, as there are no studies establishing a survival advantage in this population.[9] In the higher risk group, it is clear that the available data strongly favor azacitidine over decitabine largely based on the survival advantage seen in the Fenaux study.[10] The FDA-approved schedule for azacitidine and decitabine are either inconvenient or impractical in the community setting. The approved decitabine regimen is 15 mg/m^2 given intravenously every 8 hours for 9 doses, every 4–6 weeks, requiring hospitalization. Azacitidine is approved for 75 mg/m^2, given subcutaneously or intravenously daily for 7 consecutive days, every 28 days. Weekend administration is difficult, in part because azacitidine has to be mixed on the day of administration and weekend staffing is either expensive or unavailable.

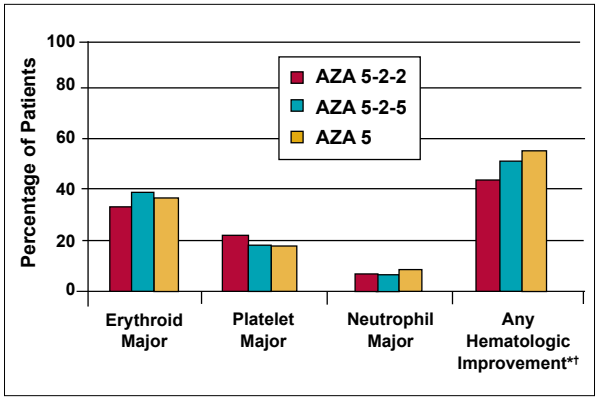

Figure 1. Hematologic improvement.

*Patients counted only once for best response in an improvement category.
†Minor improvement at top of hematologic improvement columns.

One study compared 3 schedules of decitabine.[11] Although the authors of this study concluded that a 5-day regimen of 20 mg/m^2 intravenous decitabine was optimal, there was no direct comparison to the FDA-approved 3-day dosage, thereby limiting the conclusions which can be drawn. Although this modified 5-day regimen has been widely adopted for use, it has never effectively been studied for its survival advantage.

Similarly, we recently reported the results of a study that compared subcutaneous azacitidine regimens in MDS patients.[12] Importantly, only approximately 30% of patients in this study had higher-risk MDS, a reflection of the usual distribution observed in the community setting. This study used 3 regimens which avoided the necessity of treatment on weekends: AZA 5-2-2 (75 mg/m^2 azacitidine for 5 days, followed by 2 days of no treatment, then 75 mg/m^2 azacitidine for another 2 days), AZA 5-2-5 (50 mg/m^2 azacitidine for 5 days, followed by 2 days of no treatment, then 50 mg/m^2 azacitidine for another 5 days);and AZA 5 (75 mg/m^2 azacitidine for 5 days). The results of this study showed that all 3 regimens produced substantial rates of hematologic improvement and transfusion independence, which were similar to those previously published for the approved 7-day regimen (Figure 1). A total of 67%, 55%, and 60% of patients who were transfusion-dependent in the 5-, 7-, and 10-day treatment arms, respectively, achieved transfusion independence after

Table 1. Grade 3/4 Hematologic Adverse Events

Event	AZA 5-2-2 (N=50) n (%)	AZA 5-2-5 (N=48) n (%)	AZA 5 (N=50) n (%)
Neutropenia	21 (42)	15 (31)	11 (22)
Thrombo-cytopenia	13 (26)	7 (15)	6 (12)
Anemia	12 (24)	7 (15)	5 (10)
Leukopenia	7 (14)	4 (18)	4 (8)
Febrile neutropenia	4 (8)	4 (8)	1 (2)

Table 2. Associated Annual Drug Cost By Regimen*

Regimen	Associated Drug Cost (Annual)
Decitibine (3-day regimen)	$84,600
Decitibine (5-day regimen)	$62,500
Azacitidine (7-day regimen)	$56,000
Azacitidine (5-day regimen)	$40,000

*Prices based on *Red Book 2009: Pharmacy's Fundamental Reference* (Red Book Drug Topics) at 1.75 m^2/surface area without cost of administration or ancillary drugs.

each respective azacitidine treatment. The AZA 5 group had a substantially reduced rate of adverse events (Table 1). This study did not include direct comparison to the FDA-recommended standard dosage of azacitidine, and survival data have not yet been reported.

A retrospective study presented at ASH 2008 also looked at the efficacy of several different azacitidine dosages in lower risk MDS patients. The investigators showed a similar rate of hematologic response for each dosing regimen; there was a survival advantage for responding patients.[13]

Community physicians are left in a position in which they have no good data to decide which demethylating agent or dosing regimen to use in the lower risk group of patients. Most physicians will choose those regimens and agents with which they are most familiar, which have the lowest toxicity, and which are the simplest to administer. There are cost issues involved which complicate this decision. For instance, the standard 3-day regimen of decitabine is associated with an annual drug cost of approximately $84,600, whereas that of the 5-day regimen is approximately $62,500. In contrast, the annual drug cost for the standard 7-day azacitidine regimen is approximately $56,000, and that of the 5-day azacitidine regimen costs approximately $40,000. This cost differential can translate to significant savings for both the patient and health care system (Table 2).

The clinical trial currently being designed to directly compare azacitidine and decitabine will be limited to intermediate-2 and high-risk MDS patients, ignoring our most commonly seen patients.

An important issue in the community setting is the treatment of patients who have failed demethylating therapy. In a study of 14 MDS patients who had either experienced treatment failure, lack of response, or intolerance to azacitidine, an overall response rate of 28% was observed after switching to decitabine.[14]

A decade ago, there were very few active MDS studies. Major advances in the understanding and treatment of patients with MDS have emerged over the last 10 years. However, care for this rapidly enlarging group of older patients with multiple comorbidities remains extremely challenging for the hematologist/oncologist who must also use all his/her skills as a general internist.

I anticipate additional progress for MDS patients with clinical research now in progress, which utilizes combinations of molecules with established efficacy and several new molecules, some of which have relatively low toxicity.

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MDS Classification and Risk Stratification

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MDS represents a group of clonal stem cell disorders characterized by ineffective hematopoiesis, as well as a variable propensity to leukemic evolution.[1] The hallmark clinical feature of MDS—ineffective hematopoiesis—results from the accelerated apoptotic death of the hematopoietic progenitor cells and their maturing progeny.[2] This leads to bone marrow failure and progressive peripheral cytopenias, causing patients to present with anemia, neutropenia, and thrombocytopenia. Several biologic processes have been implicated in defining MDS phenotype, including chromosomal and epigenetic DNA abnormalities, accelerated apoptosis, an impaired response to cytokines, and alteration in the bone marrow microenvironment such as increased medullary angiogenesis.[3] Because MDS is generally a disease of older individuals (median age at diagnosis between 60–75 years), treatment of this disease is particularly challenging due to existing comorbidities in this elderly patient population.

MDS Classification Systems

MDS is a heterogeneous disease composed of subtypes with diverse clinical and laboratory characteristics. Several classification systems have been proposed over the years to provide a reproducible method of risk stratification of such patients and to estimate survival and risk for leukemic evolution. The first classification system was the FAB scheme, reported in 1982, which subdivided MDS into 5 subgroups based on morphologic criteria including the number of ringed sideroblasts and monocytes and the percentage of myeloblasts (Table 1).[4,5] In the FAB system, lower-risk MDS includes refractory anemia (RA) and RARS, whereas higher-risk MDS includes CMML, RAEB, and refractory anemia with excess blasts in transformation (RAEB-t).

It was soon recognized that the FAB system had several significant limitations. For example, it did not incorporate important distinctive cytogenetic subsets.[2] Additionally, the vast survival range of patients classified into the RAEB subtype made it difficult to estimate prognosis for this group. Finally, it did not classify an MDS subtype in which dysplasia is confined to a single nonerythroid myeloid lineage.

Initially proposed in 1997 and reported in 2002, the WHO classification scheme represented an attempt to improve the prognostic power of FAB. It reclassified CMML as a disorder of mixed myelodysplastic and myeloproliferative features, subdivided RAEB into 2 groups: RAEB-I with 5–9% blasts and RAEB-II with 10–19% blasts (Table 2).[6] Additionally, RAEB-t category was eliminated in favor of a lower blast threshold (at least 20%) for AML. The WHO classification scheme was validated in a retrospective analysis of 1,600 MDS patients, finding a significant difference in prognosis according to the new RAEB categories.[7] In 2008, the WHO classification was updated to recognize the category of refractory cytopenia with unilineage dysplasia and to allow for the diagnosis of MDS when dysplasia is present in less than 10% of cells when accompanied by a cytogenetic abnormality considered as presumptive evidence for a diagnosis of MDS.

The IPSS was developed in 1997.[9] The IPSS generated a scoring system to estimate patient survival and risk of progression to AML for each FAB MDS subtype

Table 1. French-American-British Classification and Survival

French-American British Classification	Median Survival, months (range)	Leukemic Transformation, % (range)
RA (refractory anemia)	37 (19–64)	11 (0–20)
RARS (RA with ringed sideroblasts)	49 (21–76)	5 (0–15)
CMML (chronic myelomonocytic leukemia)	22 (8–60)	20 (3–55)
RAEB (RA with excess blasts)	9 (7–15)	23 (11–50)
RAEB-t (RA with excess blasts in transformation)	6 (5–12)	48 (11–75)

Data adapted from Bennett JM et al. *Br J Haematol.* 1982;51:189. Gallagher A et al. *Haematologica.* 1997;82:191.

Table 2. World Health Organization Classification

Category	Description	BM Blasts, %
RA	Refractory anemia (unilineage erythroid dysplasia)	<5
RARS	Refractory anemia with ringed sideroblsts (>15%) [unilineage erythroid dysplasia]	<5
RCMD	Refractory cytopenia with multilineage dysplasia	<5
RCMD-RS	Refractory cytopenia with multilineage dysplasia and ringed sideroblasts (>15%)	<5
RAEB-I	Refractory anemia with excess blasts (5–9% blasts)	5–9
RAEB-II	Refractory anemia with excess blasts (10–20% blasts)	10–19
MDS 5q-	MDS with isolated del(5q)	<5
MDS unclassifiable	Cannot be classified in above categories	<5

CMML is included in the group of mixed meloproliferative/ myelodysplastic disorders.

Data adapted from Harris NL, et al. *J Clin Oncol.* 1999;17:3835. MDS=myelodysplastic syndrome

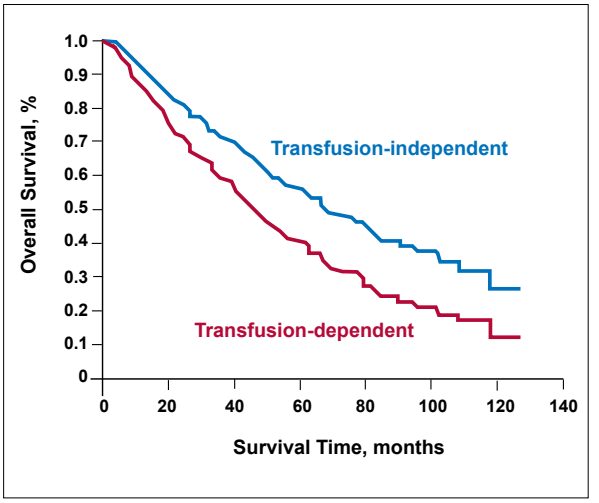

Figure 1. Impact of RBC transfusion dependence on survival.

Data adapted from Cazzola M, Malcovati L. *N Engl J Med.* 2005;352:536.

(except CMML). This scoring system used the percentage of bone marrow blasts (<5%, 5–10%, 11–20%, or 21–30%), karyotype (poor, intermediate, or good), and cytopenias (0/1 or 2/3). As such, the IPSS identified 4 risk subgroups (low, intermediate-1, intermediate-2, and high), which provided estimates for median survival and time to AML. For example, low risk was associated with a time interval to 25% AML transformation of 9.4 years and a median survival of 5.7 years, while high risk was associated with a time interval to 25% AML transformation of 0.2 years and a median survival of 0.4 years. Using the IPSS, the individual patient prognosis can be established to aid in the selection of appropriate treatment interventions. Because of its simplicity and applicability to each MDS patient, the IPSS system has become widely used in the community clinic.

However, a major drawback of the IPSS criteria is its lack of consideration of transfusion requirement. This is especially important when taking into consideration the data showing that transfusion dependency significantly decreases MDS patient survival.[10,11] In a study of 374 MDS patients, in which patients were grouped according to whether or not they developed transfusion dependence over the course of their illness, it was shown that those with a transfusion requirement had a significantly lower probability of survival (HR, 1.58; *P*=.005; Figure 1).[12] It is still a matter of debate if this worsened survival is due to the underlying disease that results in transfusion dependency or if it is related to the development of iron overload. Recently, the WPSS was developed; it allows for the prediction of survival and risk of AML transformation at any point during the course of the disease.[8] The elements of this scoring system are WHO subgroups, karyotype (according to IPSS grouping), and the need for transfusion. Using the WPSS scoring system, 5 distinct risk groups were generated: very low, low, intermediate, high, and very high. Each of these risk groups exhibit significantly different OS and probability to leukemic transformation.[8] It may very well be that the perfect classification system has yet to emerge; investigators are studying various prognostic tools such as immunophenotyping, molecular markers, and gene expression profiles to prognosticate and further refine MDS subgroups.

One important question to be determined is the value of adding fluorescence in situ hybridization (FISH) to cytogenetic analysis in the evaluation of MDS. It has been reported that FISH can indeed detect occult clonal abnormalities, but its use remains controversial. For example, in a study of 57 MDS patients who were shown to have a normal karyotype using conventional cytogenetic analysis, occult cytogenetic defects were detected in approximately 15% using FISH.[13] Other studies have also argued for the utility of adding FISH analysis.[14-16] We conducted a single-institution study and presented it at ASH 2008, in which both cytogenetic and

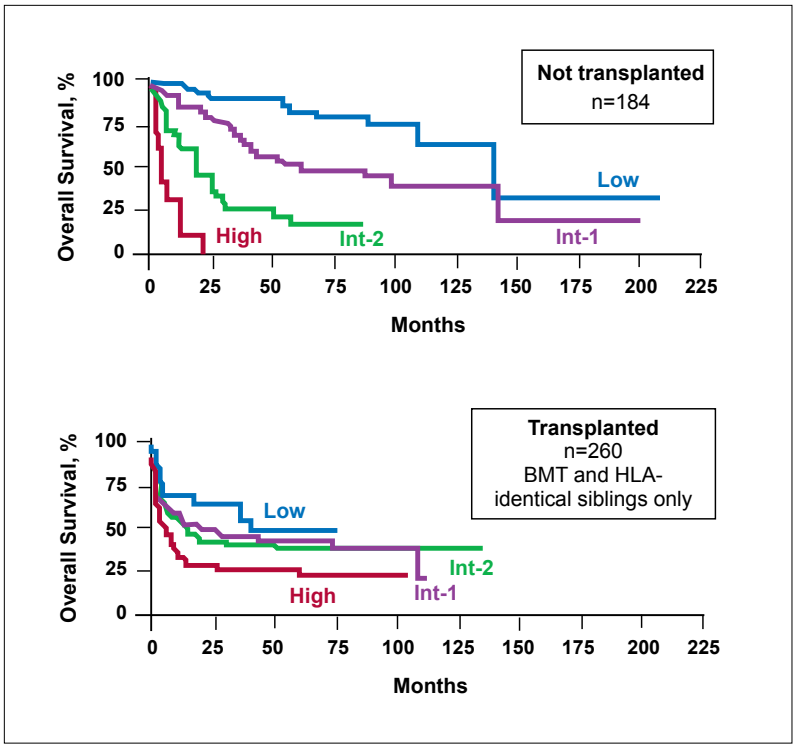

Figure 2. Full-intensity allogeneic SCT and MDS timing of SCT.

Adapted from Cutler et al. *Blood.* 2004;104:579.

BMT=bone marrow transplantation
MDS=myelodysplastic syndrome;
SCT=stem cell transplant

FISH analyses were performed on 62 MDS patients.[17] This FISH panel was designed to detect abnormalities on chromosomes 5, 7, 8, 11, and 20. A concordance of 69% was identified between the 2 methods. Importantly, FISH was able to detect additional chromosomal abnormalities in 10 patients, 7 of whom had a normal karyotype and 3 with an abnormal karyotype by conventional cytogenetic analysis. This resulted in an upgrade in IPSS score in 7 patients (low to intermediate-1 risk in 4 patients, intermediate-1 to intermediate-2 risk in 2 patients, and intermediate-2 to high risk in 1 patient). Two patients had chromosome 7 abnormalities by FISH only; given the poor prognosis associated with this cytogenetic abnormality, one can argue that such a finding may have an important therapeutic implication. However, this point has to be addressed in prospective trials evaluating the outcome of such patients with such occult clonal abnormalities relative to method of detection and the timing of treatment initiation.

Using Patient Risk to Determine Therapy

Patients who have low to intermediate-1 risk disease should have their erythropoietin level checked. If it is less than 500 mIU/mL, a trial of recombinant human erythropoietin should ensue. If the erythropoietin level is higher than 500 mIU/mL, it is unlikely that the patient will respond, and other therapeutic options should be considered.

For transfusion dependent patients with low or intermediate-1 risk disease and chromosome 5q deletion, lenalidomide is the standard of care. This recommendation is based on the results of a phase II study in which 148 patients with del 5q abnormalities with or without additional chromosomal abnormalities were enrolled and received single-agent lenalidomide.[18] This trial showed that three-quarters of the patients (76%) experienced a reduced transfusion dependency, with the majority (67%) becoming transfusion independent. Further, this transfusion independence proved to be durable, with a median duration of 2.2 years. In contrast, the treatment for patients with low or intermediate-1 risk disease without a chromosome 5q deletion is not as straightforward. A separate study of lenalidomide in this population reported that only one-quarter of patients (26%) achieved transfusion independence.[19] Further, the duration of transfusion independence was also found to be much shorter (median duration of 41 weeks). Therefore, these patients and those with higher-risk disease and del 5q deletion should be considered for enrollment in clinical trials because there is a need to better understand the biology underlying this particular subtype of MDS.

Other treatment strategies have been investigated in this setting. For example, patients with low-risk MDS may benefit from immunosuppressive therapy.[20] ATG has been evaluated for the treatment of a MDS patient subset in whom an immune etiology as a contributing factor to their cytopenias is suspected. Candidates for ATG therapy include those with a paroxysmal nocturnal hemoglobinuria (PNH) clone, who are under 70 years of age, have only a brief transfusion history, and have a hypocellular marrow. Several clinical trials have been conducted, demonstrating the efficacy of this approach and the durability of remissions achieved.[21-23]

The hypomethylating agents azacitidine and decitabine have both shown efficacy in patients with low or intermediate-1 risk MDS, resulting in reduction or elimination of transfusion dependency.[24] For example, the CALGB 9221 study, a phase III controlled trial of azacitidine as a therapy in MDS, randomized 191 patients to either subcutaneous azacitidine or supportive care; 25% of patients enrolled had RA and RARS.[25] Superior response (60% vs 5%, P<.001) and median time to leukemic transformation or death were observed for the azacitidine compared with the supportive care-only arm (21 vs 13 months, respectively; P=.007). Of the 65 azacitidine-treated patients who were transfusion-dependent at baseline, 45% achieved transfusion independence.[26] In patients in the AZA-001 trial with intermediate-2 and high risk IPSS, azacitidine treatment led to a doubling of the median 2-year OS, which was 50.8% and 26.2% in patients receiving azacitidine and supportive care, respectively (P<.0001). It should be pointed out that a survival advantage has not yet been demonstrated for patients with lower-risk disease who were treated with azacitidine; prospective clinical trials evaluating this outcome are important to conduct. Similarly, in a phase III randomized trial evaluating decitabine versus best supportive care in 170 MDS patients, decitabine resulted in a superior response rate (17% vs 0%, P<.001).[27] In addition, decitabine treatment led to an increased median time to AML progression or death compared with supportive care, although this difference was not statistically significant (12.1 vs 7.8 months); this trial did not include patients with IPSS of 0.

Regarding the role of allogeneic transplantation in patients with low to intermediate-1 risk disease, an important study published in 2004 showed that the timing of allogeneic stem cell transplantation (SCT) is critical for determining optimal survival in different MDS subtypes.[28] Using a Markov model, the authors evaluated 3 distinct SCT timings—at diagnosis, at the point of leukemic progression, and during the interval after diagnosis but prior to leukemic progression (Figure 2). Interestingly, this study reported that for patients with low and intermediate-1 disease, the maximal OS benefit was observed when SCT was delayed after diagnosis but conducted prior to AML progression. This was especially true in younger patients (<40 years). In contrast, for patients with intermediate-2 or high risk disease, OS was maximized when SCT occurred at diagnosis. This study shows the importance of patient selection to improve the outcome of MDS patients relative to the timing of SCT therapy.

In summary, our understanding of MDS as a disease entity continues to evolve. We now have several therapeutic options that, when used judiciously, can result in a meaningful improvement in the patients' quality of life. For patients who do not respond to available therapies, enrollment in clinical trials is highly recommended.

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Combination Therapies for MDS

Bart L. Scott, MD

Romiplostim plus Azacitidine

Thrombocytopenia is a frequent complication of MDS, and the c-mpl receptor and its associated ligand thrombopoietin have been investigated as a therapeutic target to improve platelet production.[1] Romiplostim is a recombinant version of the thrombopoietin ligand that similarly stimulates platelet production and contains a peptide fragment that is structurally divergent from the endogenous thrombopoietin ligand.[2] This unique feature of romiplostim prevents the production of neutralizing antibodies.

In an ongoing multicenter double-blind phase II trial presented at ASH 2008, romiplostim was evaluated as combination therapy with azacitidine in patients with low- or intermediate-risk MDS.[3] All 40 patients received 4 cycles of azacitidine. Patients were divided into 3 groups, randomized to receive either placebo (n=13), or 1 of 2 romiplostim dosages (500 µg, n=13; or 750 µg, n=14) weekly. A planned interim analysis was presented at ASH 2008, which occurred after all patients had either completed or withdrawn from treatment. The primary study endpoint, the incidence of clinically significant thrombocytopenic events, was defined as low platelet counts (<50 x 10^9/L) after week 3 of treatment, or receipt of a platelet transfusion at any point during treatment. The incidence of clinically significant thrombocytopenic events was 85% for placebo versus 62% and 71% for patients receiving 500 µg or 750 µg romiplostim, respectively (Table 1). Similarly, the incidence of platelet transfusions in each group was 69% for placebo versus 46% and 36% for 500 µg or 750 µg romiplostim. Compared with placebo, romiplostim also improved platelet counts during each azacitidine cycle. In the safety analysis, it was determined that 100% of patients experienced 1 or more adverse events, and 77%, 46%, and 71% of the placebo, 500 µg romiplostim, and 750 µg romiplostim groups, respectively, experienced a serious adverse event. A treatment-related serious adverse event was observed in 2 patients treated with romiplostim (1 arthralgia in a patient receiving 500 µg romiplostim and 1 rash and hypersensitivity in a patient receiving 750 µg romiplostim). A bleeding event of grade 3 or higher occurred in 2 patients receiving placebo, 1 patient receiving 500 µg romiplostim, and no patients receiving 750 µg romiplostim. Although 2 patients died in the placebo group, none of the patients who received romiplostim died.

When this study was presented at ASH 2008, it was reported that 1 patient, who had received 500 µg romiplostim, had progressed to AML, raising concern that romiplostim may accentuate leukemic progression. The authors of this study concluded that romiplostim, in combination with azacitidine, was well tolerated and that it reduced the incidence of clinically significant thrombocytopenic events as well as the need for platelet transfusion. However, this study needs to further mature before it can be determined exactly how romiplostim will affect the ultimate outcomes.

Table 1. Romiplostim for Patients With Lower-Risk MDS Receiving Azacitidine: Results

Adapted from Kantarjian et al. ASH 2008, Abstract 224.

AE=adverse event; AML=acute myelogenous leukemia; IWG=International Working Group; ORR=overall response rate.

Efficacy	Placebo (n=13)	Romiplostim 500 mg (n=13)	Romiplostim 750 mg (n=14)
Thrombocytopenic Events	85%	62%	71%
Platelet Transfusions	69%	46%	36%
ORR (Modified IWG)	2 (15%)	1 (8%)	1 (7%)
Safety			
Serious AEs	10 (77%)	6 (46%)	10 (71%)
Bleeding Events	7 (54%)	8 (62%)	7 (50%)
Grade ≥3	2	1	0
Progression to AML	0	1	0

Response	Decitabine (n=41)	Decitabine/Valproic Acid (n=31)
Patients With MDS/CMML	**N=23**	**N=21**
CR	7 (30%)	10 (48%)
CRi/HI	6 (26%)	6 (26%)
Patients With AML	**N=18**	**N=10**
CR	6 (33%)	1 (10%)
CRi/HI	2 (11%)	4 (40%)
Grade 3/4 Adverse Events		
Neurologic	0	4
Nausea	0	2
Hyperbilirubinemia/Mucositis/Diarrhea	1/1/1	0

Table 2. Decitabine With or Without Valproic Acid in Patients With MDS and AML

Adapted from Issa et al. ASH 2008, Abstract 228.

CMML=chronic myelomonocytic leukemia; CRi= complete response with incomplete blood count recovery; HI=hematologic improvement

Lenalidomide plus Azacitidine

A phase I multicenter study evaluated the combination of azacitidine plus lenalidomide in patients with higher-risk MDS.[4] The rationale for this combination was based on the efficacy each of these drugs have as a single-agent therapy in both lower- and higher-risk MDS. The primary objective of this study was to establish the safety of this combination, as well as to define the maximum tolerated dose and any dose-limiting toxicities. A total of 19 patients (median age, 68 years) were enrolled in this 3+3 trial design. A total of 6 dosing cohorts were established, testing combinations of 50 mg/m^2 or 75 mg/m^2 subcutaneous azacitidine administered on days 1–5 only or 1–5 and 8–12, and 5 or 10 mg oral lenalidomide administered on days 1–14 or 1–21 of a 28-day cycle. The median interval from MDS diagnosis was 5 weeks (range, 2–106 weeks), and the median follow-up was 5 months (range, 1–13 months). Patients had either intermediate-1 (n=3), intermediate-2 (n=9), or high-risk (n=6) disease. No dose-limiting toxicity was reported at any dosage, and the maximum tolerated dosage was not reached. Grade 3/4 nonhematologic adverse events included febrile neutropenia (n=2), atrial fibrillation (n=1), monocular blindness (n=1), basal cell skin carcinoma (n=1), central nervous system (CNS) hemorrhage (n=1), shortness of breath (n=1), and perforated appendix (n=1). When evaluating hematologic toxicity, a median decrease in absolute neutrophil count (ANC) of 21% was reported, as was a 1% decrease in platelets. Neutropenia caused a delay in cycle 2 of therapy for 2 patients, but no dose reductions were required. A preliminary analysis of the efficacy of the combination showed that the overall response rate was 71% (41% CR, 6% PR, 18% HI, and 3% marrow CR). Considering both the safety and efficacy data, the authors of this study determined that the optimal dosage of this combination was 75 mg/m^2 subcutaneous azacitidine (days 1–5) and 10 mg oral lenalidomide (days 1–21). Future analysis of this and other trials will help to determine the true efficacy of this combination, as well as whether any benefit in efficacy mitigates an increase in toxicity.

Valproic Acid Plus Decitabine/Azacitidine

A phase II study investigated the benefit of combining 2 epigenetic therapies—decitabine and the histone deacetylase (HDAC) inhibitor valproic acid.[5] In this study, 76 patients with either MDS (n=43), AML (n=23), or CMML (n=8) were enrolled and randomized to receive either decitabine alone or decitabine plus valproic acid. Approximately half of the patients (54%) had abnormal cytogenetics, most with either complex or poor karyotypes. The results observed at a median follow-up of 14 months showed that 35% of patients remained on therapy. Response data (only available for 67 patients) showed an overall response was achieved in 46% of patients (Table 2). Specifically among patients with MDS, the overall response rate was 46%. When patients were analyzed according to treatment group, there was a nonsignificant increase in the overall response rate among patients receiving the combination versus single-agent treatment (52% vs 43%). There was also a nonsignificant improvement in the median time to first response with the combination versus single-agent therapy (57 days vs 64 days). Among MDS patients, the median OS was 14.9 months, but there was no difference in survival between the 2 treatment groups after the first year of therapy. Clinically significant neurotoxicity, including somnolence or confusion, was experienced by several patients receiving the decitabine plus valproic acid combination. These results prompted the authors to conclude that valproic acid only modestly improved response to decitabine, and had no impact on OS. Nevertheless, it should be noted that the dosage of valproic acid (50 mg/kg by mouth, days 1–7) may not have been sufficient. It is also important to remember that there are several different HDAC inhibitors, which may not be all equally active. Therefore, despite the modest

results observed in this study, it does not necessarily negate the future investigation of novel combinations of hypomethylating agents with HDAC inhibitors.

Presented at the 2008 ASH annual meeting were results of a phase II study of the combination of 5-azacitidine, valproic acid, and ATRA in patients with intermediate-2/high-risk MDS.[6] Valporic acid was given at 600–1,500 mg daily, then 5-AZA was added at a standard dose of 75 mg/m^2 daily, subcutaneously, 7 days for 8 cycles. In case of minor response, SD, or failure after 4 cycles, ATRA was added at 30 mg/m^2 orally daily, on days 8–27 for 4 cycles. Of the 62 enrolled patients, diagnosis was RAEB for 37 patients (60.7%), RAEB-t for 21 (32.8%), and CMML for 4 (6.5%). Out of 27 patients who completed 8 treatment cycles, 8 patients (29.6%) obtained CR and PR, 3 patients (11.1%) showed HI, and 10 patients (37.4%) showed a SD. Transformation into AML or progression occurred in 20 patients. Red blood cell transfusion needs signficantly decreased; data showed that the combination is safe and feasible in poor prognosis MDS patients.

Vorinostat plus Azacitidine

A phase I/II study of vorinostat in combination with azacitidine was presented at the 2008 ASCO annual meeting.[7] Among the 20 patients entered in the trial, 14 had MDS, 6 had AML, and the median age was 68 years. Of the 11 evaluable patients, 9 responded; 4 out of 5 patients with poor risk cytogenetics responded. No grade 3 or 4 nonhematologic toxicities were reported; grade 2 anorexia and fatigue was observed. Investigators concluded that the combination is safe and tolerated in repetitive cycles.

Etanercept plus Azacitidine

We have recently completed a phase II study at our institution, in which we investigated the combination of azacitidine with the anti-TNFα-directed therapy etanercept.[8] This combination was based on preclinical evidence showing an increase in TNFα receptor subtype 2 expression with more advanced MDS.[9] Notably, the subtype 2 receptor only transmits proliferative signals. Thus, etanercept-mediated inhibition of this signaling pathway may reduce MDS disease progression, while protecting normal stem cells which express the TNFα receptor subtype 1. In a pilot study of 14 MDS patients, etanercept monotherapy induced modest favorable responses, including improvements in hemoglobin level, decreased transfusion requirement, and improved platelet and neutrophil counts.[10] These and other data prompted the initiation of a phase II trial which enrolled 32 MDS patients, the majority of whom had intermediate- or high-risk disease. Treatment with the combination therapy resulted in CR (n=9), PR (n=2), marrow CR (n=10), and SD (n=7) after 3 months (Figure 1). Further, several hematologic improvements were noted, including erythroid response, platelet response, and neutrophil response.

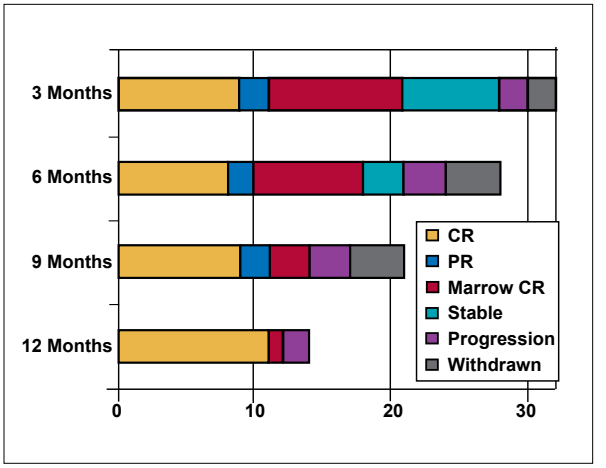

Figure 1. Azacitidine plus etanercept.

Responses by International Working Group criteria at 3 month intervals. Patients with disease progression and patients who were withdrawn from the study were not included in subsequent months.

CR=complete response; PR=partial response.

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