How we treat higher-risk myelodysplastic syndromes

Mikkael A. Sekeres[1] and Corey Cutler[2]

[1]Leukemia Program, Cleveland Clinic Taussig Cancer Institute, Cleveland, OH; and [2]Hematologic Malignancies, Dana-Farber Cancer Institute, Boston, MA

Higher-risk myelodysplastic syndromes (MDS) are defined by patients who fall into higher-risk group categories in the original or revised International Prognostic Scoring System. Survival for these patients is dismal, and treatment should be initiated rapidly. Standard therapies include the hypomethylating agents azacitidine and decitabine, which should be administered for a minimum of 6 cycles, and continued for as long as a patient is responding. Once a drug fails in one of these patients, further treatment options are limited, median survival is <6 months, and consideration should be given to clinical trials. Higher-risk eligible patients should be offered consultation to discuss hematopoietic stem cell transplantation close to the time of diagnosis, depending on patient goals of therapy, with consideration given to proceeding to transplantation soon after an optimal donor is located. In the interim period before transplantation, hypomethylating agent therapy, induction chemotherapy, or enrollment in a clinical trial should be considered to prevent disease progression, although the optimal pretransplantation therapy is unknown. (*Blood*. 2014;123(6):829-836)

Introduction

The myelodysplastic syndromes (MDS) are the most commonly diagnosed myeloid neoplasms in the United States, with an incidence rate of 4.6 in 100 000 US citizens, translating to approximately 15 000 new diagnoses yearly.[1] This figure is often considered to be an underestimate, because data derived from the National Cancer Institute's Surveillance, Epidemiology, and End Results program and the North American Association of Central Cancer Registries are likely compromised by under-reporting (thought to be a result of misconceptions about the disease's neoplastic basis and variability in diagnostic prowess) and misclassification (as evidenced by the 50% of patients in such registries identified as "MDS–unclassifiable").[2,3]

MDS represents a constellation of diagnoses increasingly identified by underlying genetic abnormalities, such as the del(5q) syndrome, *SF3B1* mutations in MDS with ring sideroblasts along with other splicing factors, abnormalities along tyrosine kinase pathways (such as *CBL* and *NRAS*), mutated genes involved with epigenetic dysregulation (*TET2*, *DNMT3A, EZH2, IDH1* and 2, and *ASXL1*), and mutations in transcription factors (*RUNX1, ETV6*)[4-33]; and on a disease biology that at some extremes is typified by excessive production of proapoptotic, proinflammatory cytokines and premature death of hematopoietic stem cells, and at others by excessive proliferations, epigenetic regulation, and a block in differentiation.[34-38] Molecular data are becoming disease defining (as with spliceosome mutations in MDS with ring sideroblasts), have been incorporated into prognostic scoring systems and are anticipated to provide additional resolution to these systems, and have been linked to therapeutic responsiveness (discussed later). However, the degree to which they will modify risk estimates in MDS is being explored by an international working group.[5,7,22,39,40]

Treatment decisions in MDS are based on pathology, or a prognostic scoring system appropriated as a default staging system, and are now incorporated into drug labeling.[41] As a result, the classification of MDS patients has become reductionist, with patients divided into those with lower-risk or higher-risk disease, as determined by prognostic systems that are based most commonly on blast percentage, cytogenetic risk groups, and cytopenias, but which may also include age, performance status, transfusion needs, and other clinical (and increasingly molecular) factors.[42-44] Patients with higher-risk disease fall into International Prognostic Scoring System (IPSS) categories of Intermediate-2 and High groups, corresponding largely to IPSS-R groups Very High, High, and, sometimes, Intermediate, and which often correspond to World Health Organization (WHO) histologic subtypes of refractory anemia with excess blasts (RAEB)-1 and RAEB-2, with an expected median overall survival of <2 years.[4,41,45] Whether survival estimates can be adjusted within the modern therapeutic era has not yet been determined. Correlations between IPSS/IPSS-R and WHO classifications are loose, because some patients with excess blasts but normal karyotype and limited cytopenias can live for years, whereas those with few blasts, complex karyotype, and profound cytopenias may have a shortened survival rate.

Treatment options for patients with lower-risk MDS have recently been reviewed.[46] The treatment of an MDS patient with higher-risk disease starts with recognition of the imperative to initiate therapy. Accepting the premise that the IPSS is a default MDS staging system, with Low-High reflecting stages I-IV, and comparing it stage-for-stage with American Joint Committee on Cancer staging for non–small-cell lung cancer, overall survival is worse for patients with MDS.[47,48] Just as it would be poor practice in a patient with stage III or IV lung cancer, acceptable comorbidities, a good performance status, and a desire to receive treatment to recommend watchful waiting simply because that patient does not yet have debilitating symptoms, so too would therapy avoidance be discouraged in a similar MDS patient with Intermediate-2 or High risk of disease. We offer examples of 2 patients and answer the typical questions posed to us by informed patients to illustrate how we approach higher-risk MDS.

Patient 1

A 77-year-old woman presented with complaints of progressive fatigue and dyspnea, needing to rest after climbing one flight of stairs.

Submitted July 31, 2013; accepted December 17, 2013. Prepublished online as *Blood* First Edition paper, December 20, 2013; DOI 10.1182/blood-2013-08-496935.

Her medical history included chronic venous stasis disease and prior coronary artery bypass surgery, and she was taking a β-blocker, an angiotensin-converting enzyme inhibitor, and furosemide. A complete blood cell count included a white blood cell count of 1600/μL, with a neutrophil count of 700/μL, a hemoglobin level of 7.4 g/dL, and a platelet count of 48 000/μL. A bone marrow biopsy revealed trilineage dysplasia with 13% myeloblasts, and she was given a diagnosis of MDS, RAEB-2 subtype. Cytogenetics showed deletion in chromosome 7 and the addition of chromosome 8 (47 XX, del(7q), +8).

What is the prognosis of higher-risk MDS?

Based on the WHO histologic diagnoses of RAEB-2 alone, this patient's median survival was predicted to be approximately 20 months.[44] Applying the IPSS score, she would receive a score of 3.0 (1.5 for blasts 11%-20%, 1.0 for poor-risk cytogenetics that include a chromosome 7 abnormality, and 0.5 for 3 cytopenias), placing her in the High Risk category, with a predicted survival of 0.4 years.[41] The IPSS-R would classify her as having Very High Risk disease, based on a combined score of 9.0 (3.0 for blasts, 3.0 for cytogenetics, 1.5 for severe anemia, 1.0 for severe thrombocytopenia, and 0.5 for neutropenia) and would predict for a similarly poor survival length.[45] For this patient, with the IPSS, 50% of the weight of the total score derived from the blast percentage, whereas with the IPSS-R, greater relative weight was given to poor-risk cytogenetics and degrees of cytopenias. Risk estimates need to be adjusted on an individual patient basis, modulated by factors like performance status and comorbidities. An MDS-specific comorbidity index has been developed and incorporates factors such as cardiac, hepatic, pulmonary, or renal disease, or a solid tumor, into a risk of nonleukemic death.[49]

Although most researchers agree that MDS is a cancer,[7,22,50-52] in an Internet-based survey of 348 MDS patients, 80% reported that their MDS was first described as a "bone marrow disorder," with only 6% to 7% indicating their MDS was first described as either "cancer" or "leukemia."[53] In addition, 42% did not know their blast percentage—results consistent with a separate Internet-based survey of 349 MDS patients in which 33% did not know their MDS subtype.[54] This lack of insight into disease severity has implications for patient expectations and openness to therapy.

What is the recommended treatment for higher-risk MDS, and does treatment need to be started immediately?

Patients with higher-risk MDS should be started on one of the hypomethylating agents—azacitidine or decitabine (Figure 1). DNA methylation occurs at the 5′-position of cytosine in areas of CpG dinucleotide islands, resulting in silencing of gene expression. DNA methyltransferase 1 (DNMT1) maintains existing methylation patterns after DNA replication, whereas members of the TET protein family remove methyl groups from CpGs. Histones undergo posttranslational modifications, leading to activation or repression of gene expression.[55-57] MDS patients generally exhibit genome-wide hypomethylation and CpG island hypermethylation, which results in genetic instability typical of cancer and tumor suppressor genes silencing.

The hypomethylating agents are azanucleosides that act through proteosomic destruction of DNA methyltransferase and resultant chromatin decondensing. This results in depletion of DNA methyltransferase and theoretical reversal of the aberrant methylation that silences tumor suppressor genes, which is more common in higher-risk MDS.[38,58] They also upregulate key regulators of late myeloid (CEBPE) differentiation and induce cell cycle exit associated with upregulation of p27/CDKN1B, the cyclin-dependent kinase inhibitor that mediates cell-cycle exit by differentiation.[59-62] Azacitidine was approved by the US Food and Drug Administration (FDA) for all MDS subtypes based on a phase 3 trial in which it was compared with supportive care,[63] with crossover allowed. Response rates to azacitidine were 14% (complete and partial), and 30% hematologic improvement, when analyzed using the International Working Group criteria.[64] There was a significant delay in transformation to acute myeloid leukemia (AML) or death but a significant prolongation of survival in the treatment arm. Azacitidine was next explored in a phase 3 European trial confined to higher-risk MDS patients randomized to receive the drug or conventional care, which included best supportive care, low-dose cytarabine, or AML-type induction chemotherapy, as selected by investigators before randomization.[65] With a median follow-up of 21.1 months, median overall survival was 24.5 months vs 15 months for patients on the azacitidine vs conventional care arms (hazard ratio [HR] 0.58, $P = .0001$).

Similar to azacitidine, decitabine received FDA approval based on a phase 3 study in all MDS subtypes in which patients were randomized to the drug or to receive supportive care.[66] Based on International Working Group criteria, complete and partial responses occurred in 17% of patients, and hematologic improvement occurred in 13%. There was no significant delay in AML transformation or death for decitabine-treated patients. A phase 3 European study was then conducted, in which higher-risk MDS patients were randomized to decitabine or to best supportive care.[67] Although the complete and partial response rate was 23%—similar to that with azacitidine—there was no survival advantage for decitabine vs supportive care, with a median survival of 10.1 vs 8.5 months, respectively (HR 0.88, $P = .38$).

We recommend that either drug should be administered for a minimum of 6 cycles before concluding whether there is a lack of efficacy. We further suggest that treatment be started as soon as possible because some types of higher-risk MDS, particularly patients with higher blast percentages and complex cytogenetics or chromosome 7 abnormalities, can progress quickly to AML.[41,45] Across azacitidine and decitabine studies, approximately 50% of patients develop Common Toxicity Criteria (CTC) grade 3 or 4 cytopenias,[63-65,67] particularly during the first treatment cycle, necessitating intensive transfusion support and close monitoring, and placing patients at increased risk of febrile neutropenia episodes.

Can dosing of hypomethylating agents be interrupted (nonconsecutive)? Are there molecular markers of response?

Azacitidine received its FDA approval based on 7-day consecutive dosing at 75 mg/m^2 per day, on a 28-day cycle.[63] This was also the dosing schedule used in the European survival study. Yet in a registry study that included 421 patients treated with azacitidine in the US, this schedule was used only 15% of the time[68]—likely because of limited weekend availability of infusion centers, as well as patient preference. In the same study, response rates (assessed as hematologic improvement or better) were similar regardless of the dosing schedule used, although survival could not be assessed. Although 7-day consecutive dosing is preferred, 7-day nonconsecutive dosing (eg, using a 5-2-2 schedule in which the drug is administered Monday-Friday and then Monday and Tuesday of the following week) is acceptable.

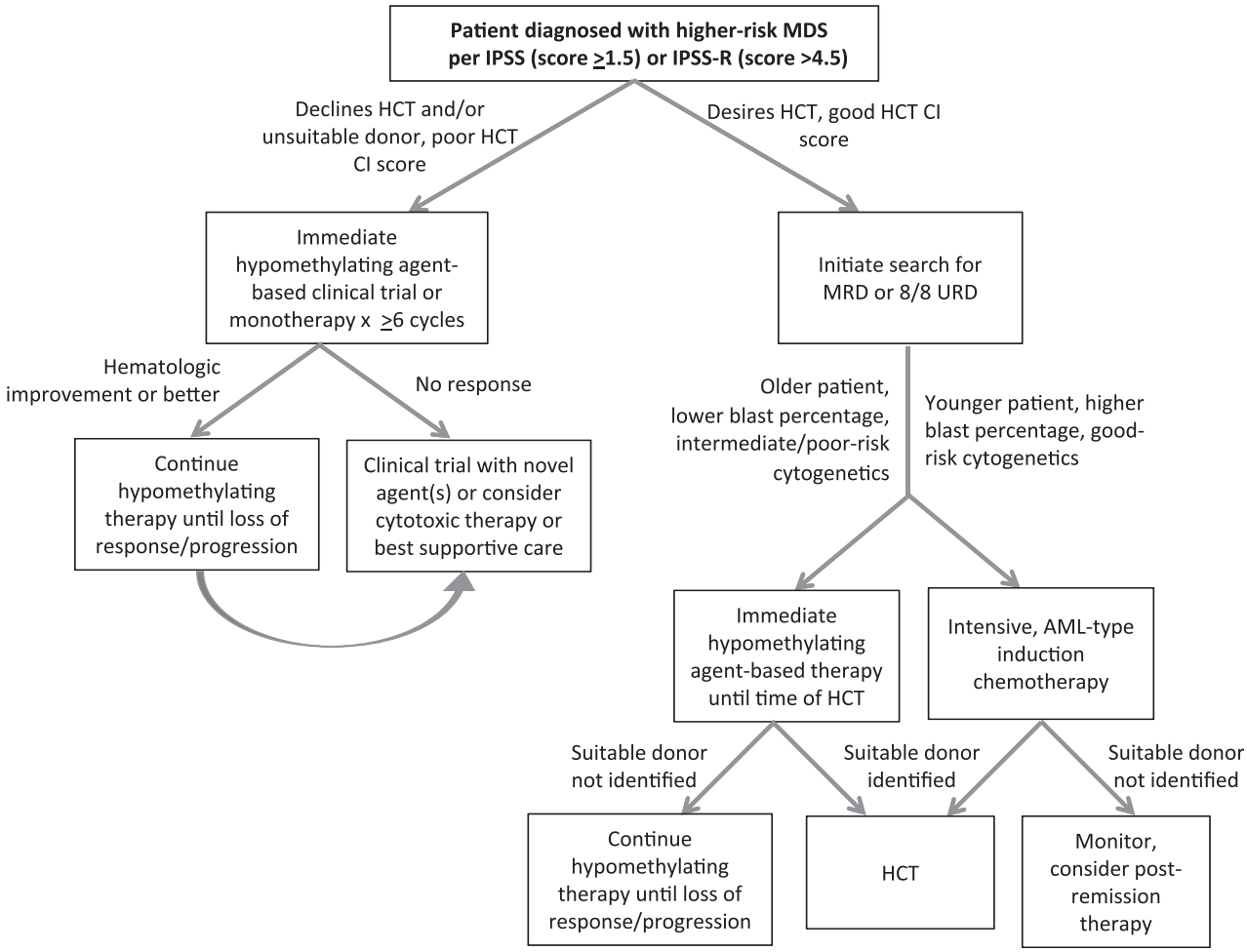

Figure 1. Treatment algorithm for patients with higher-risk MDS.

Decitabine received its initial FDA approval based on a schedule in which the drug was administered at a dose of 15 mg/m^2 every 8 hours over 3 days and repeated every 6 weeks.[66] Subsequently, a schedule more applicable to outpatient treatment, of 20 mg/m^2 per day for 5 days on a 28-day cycle, was shown to have similar, if not better, response rates to the original schedule and has become the de facto standard administration approach.[69,70] Further reductions in decitabine scheduling and dosing, to 3 days of a 28-day cycle and to weekly dosing, at 3.5-20 mg/m^2, are being explored along with subcutaneous administration.[71,72] The standard is to continue a hypomethylating agent for as long as a response persists and to avoid switching drugs (eg, administering decitabine in a patient whose disease is not responding to azacitidine).

Because these drugs work along methylation pathways, efforts have been made to determine whether patients with epigenetic mutations (*DNMT3A, TET2, IDH 1*, or *IDH 2*) are particularly responsive. Itzykson et al identified mutated *TET2* and favorable cytogenetic risk groups as independent markers of higher overall response rate to azacitidine and nearly of improved overall survival ($P = .06$).[73] Similarly, Traina et al examined 92 patients treated with azacitidine or decitabine and found that those harboring TET2 and/or DNMT3A abnormalities were more likely to respond to hypomethylating agents ($P = .03$) and had improved progression-free survival ($P = .04$).[40] Given the limited arsenal of drugs available for higher-risk MDS patients, however, lack of these mutations should not preclude therapy.

Is there any advantage to hypomethylating agent–based combination therapy over monotherapy?

Although a number of drugs have been combined and used to treat higher-risk MDS, 2 combination approaches in particular have been explored in more detail.

Azacitidine has been combined with lenalidomide in higher-risk MDS patients, in the phase 1 and 2 settings, in an attempt to capitalize on the possible in vivo synergism that could be achieved by targeting both the bone marrow microenvironment and cell regulatory mechanisms that likely play a role in disease evolution.[34,35,62,74,75] In the phase 1 study, no maximum tolerated dose was identified. In the phase 2 study, azacitidine was administered at 75 mg/m^2 per day on days 1 to 5, and lenalidomide 10 mg/day was administered on days 1 to 21. The overall response rate in 36 patients (18 from phase 1 and 18 from phase 2) was 72%, including 44% who achieved a complete response and 28% who achieved a hematologic improvement. The median response duration was 17+ months and overall survival among complete response patients was 37+ months.

Studies have also explored combining histone deacetylase inhibitors (HDACi) with hypomethylating agents, based on data demonstrating that optimal transcriptionally silenced (through promoter methylation) gene reexpression in vitro occurred through sequential inhibition of

DNA methyltransferase followed by histone deacetylation.[76,77] The HDACi vorinostat has been studied in combination with azacitidine in the phase 1 setting and showed encouraging overall response rates (64%).[78] This combination was next explored in a phase 2 study targeting higher-risk MDS and AML patients excluded from other clinical studies based on poor performance and comorbidities. Among 30 enrolled patients, the overall response rate was 30%; 80% of patients survived more than 60 days.[79] Whether either of these combinations will produce a superior response rate compared with azacitidine monotherapy is now being explored in North American Intergroup study S1117 (NCT01522976).

The largest prospective, randomized study comparing combination therapy with azacitidine monotherapy was conducted in 136 higher-risk MDS and AML patients.[80] Rates of trilineage response, the primary outcome, and median overall survival were similar for those treated with monotherapy (on a 10-day schedule) and for those treated with azacitidine combined with the HDACi entinostat (24% vs 31% and 17.7 months vs 12.8 months; $P = .15$, respectively). No prospective combination study has ever demonstrated a survival advantage compared with hypomethylating agent monotherapy.

What are the therapeutic options or investigational agents after failure of hypomethylating agents?

For patients who are refractory to or have relapsed after hypomethylating agent therapy, either because of limited numbers of treatment cycles, drug intolerance, or disease evolution caused by the development of abnormalities such as p53, SETBP1, or ASXL1, median survival is only 4.5 to 6 months.[81,82] The purine nucleoside clofarabine produced responses in approximately 30% of patients whose disease failed hypomethylating agents, with overall survival similar to that reported in retrospective data.[81-83] Attempts can also be made to treat these patients with low-dose cytarabine or AML-type induction therapy (in patients with high-blast-percentage MDS), with the expectation that responses will be approximately 50% of those seen in similarly aged de novo AML cohorts.[84,85] No second-line therapy has demonstrated a survival advantage over any other therapy or compared with best supportive care. All such patients should be considered for clinical trials, and drugs in more advanced stages of study for this indication include rigosertib, a polo-like kinase inhibitor; sapacitabine, a purine analog; and the addition of agents to hypomethylating agents in an attempt to "recover" responses.[86-89]

Patient 2

A 60-year-old man presented to his primary care provider with complaints of fatigue, oral mucosal bleeding when brushing his teeth, and easy bruisability. He was found to have a white blood cell count of 3200/μL, with a neutrophil count of 1700/μL, a hemoglobin level of 8.1 g/dL, and a platelet count of 14 000/μL. A bone marrow biopsy revealed trilineage dysplasia with 11% myeloblasts, consistent with a diagnosis of RAEB-2 MDS. Cytogenetics demonstrated a very complex karyotype, with 5 abnormalities. He was active and his only comorbidity was essential hypertension, for which he was taking a calcium-channel blocker. He was referred for evaluation for hematopoietic cell transplantation (HCT), with a calculated HCT-Comorbidity Index score of 0.

Have nontransplant MDS therapies ever been compared with HCT prospectively?

Although HCT is the only curative treatment of MDS, it has never been compared with non-HCT approaches in a prospective, randomized trial. Thus, whether HCT provides a survival advantage compared with disease-modifying agents for MDS patients has not been determined. However, 2 large prospective studies are being performed to address this question.

A German study is biologically assigning 250 newly diagnosed patients aged 55 to 70 years with higher-risk MDS (IPSS Int-2, High, or Int-1 with poor-risk cytogenetics) (NCT01404741), to HCT, or to no HCT. All subjects initiate therapy with azacitidine. After 4 to 6 cycles, subjects are biologically assigned to HCT or no HCT based on the availability of a suitable donor. Those without a donor continue to receive azacitidine. The trial is powered to detect a meaningful difference in outcome if the 3-year survival in the HCT arm is 50%, compared with 30% in the non-HCT arm.

A Bone Marrow Transplantation Clinical Trials Network study (BMT CTN 1102) began enrolling patients in late 2013. This trial asks the more fundamental question of whether HCT is of value at any time in the disease course. Patients are biologically assigned to HCT or non-HCT therapy based on the availability of a suitable matched, related donor (MRD) or matched, unrelated donor (URD) and are being followed for overall survival, without any mandate for the type of HCT or non-HCT therapy delivered. It is anticipated that >400 subjects are enrolled in the study.

What is the most appropriate timing of HCT?

Single-arm studies that demonstrate improved outcome with early HCT or with transplantation at less advanced disease stages are inherently biased owing to patient selection. Given the lack of prospective, randomized studies, and to more formally determine the optimal timing of transplantation, Koreth and colleagues performed a decision analysis that included >500 patient records from several international databases.[90] The statistical techniques of Markov Modeling and Monte Carlo simulation were used to estimate the outcomes of a prospective clinical trial—one that will likely never be performed—comparing initial MDS treatment with hypomethylating therapy with HCT. The decision analysis examined individuals aged 60 to 70 years (a patient population increasingly being transplanted as commonly as younger adults) and examined only reduced-intensity transplantation approaches, stratifying patients by MDS disease risk. Another decision analysis examining younger patients undergoing myeloablative transplantation has previously been reported.[91] For patients with higher-risk MDS, there was an advantage in life expectancy as well as in quality-adjusted life expectancy for those undergoing early HCT when compared with conventional non-HCT therapies. For both decision models, early after entry there was a survival disadvantage for transplantation because of transplant-related morbidities, with a later plateau on the HCT survival curve providing the overall benefit for HCT in higher-risk MDS patients. Because the intent of such decision analyses is to identify the decision strategy associated with superior outcomes, such as survival or quality-adjusted life years in a patient population, it is not possible to measure lives gained or lost, and decisions for individual patients will necessarily be modulated by a number of donor and recipient factors.

A second decision analysis strategy compared HCT with a cohort of patients who received best supportive care. In this analysis, the decision to proceed to transplantation was at the time of transition from Low to Int-1 IPSS or WHO Prognostic Scoring System risk scores.[92] Thus despite the lack of prospective, randomized data, and given the consistency of findings across all decision analyses, we continue to recommend HCT early after diagnosis of higher-risk MDS when feasible, with recent data supporting no decrement in early survival and a long-term survival rate of 40% to 50%.[93-95] In the 60-year-old male patient, long-term success could be enhanced by his low HCT-CI (irrespective of age) but worsened by poor-risk cytogenetics.[96,97]

Should MDS patients be treated while awaiting HCT?

The role of cytoreductive therapy before HCT is still unknown. Retrospective analyses have examined the impact of pre-HCT hypomethylating agent therapy and AML induction-type chemotherapy on post-HCT outcomes. The largest study included 163 consecutive individuals who underwent HCT after azacitidine, after leukemia-type induction chemotherapy, or after both. Although the entire cohort had higher-risk disease, it is impossible to retrospectively determine which factors were involved in choosing induction chemotherapy or azacitidine therapy first, and whether these factors (eg, better performance status or fewer comorbidities) influenced outcomes. Given these caveats, there were no differences in relapse rates, nonrelapse mortality, event-free survival, or overall survival comparing the azacitidine and induction chemotherapy groups, although the group that received both azacitidine and induction chemotherapy (presumably because of disease progression before HCT) fared significantly worse.[98] A similar but smaller study from Seattle demonstrated a slight advantage to pre-HCT therapy with azacitidine over induction chemotherapy, potentially because of reduced toxicity.[99] Both of these studies, however, lack the size of the original patient population initially considered for transplantation—the denominator—without which it is impossible to determine the role of one pre-HCT approach vs another.

To ask an even more basic question: Is disease-modifying MDS therapy before HCT necessary at all? In retrospective analyses, when pre-HCT azacitidine was compared with no treatment, there was no benefit to azacitidine. As with other retrospective HCT analyses already discussed, these studies were affected by similar selection biases.[100,101] In the absence of prospective data, but given the acceptable toxicity and potential for cytoreduction, we recommend pre-HCT azacitidine or decitabine therapy for patients in whom transplantation is being contemplated. Consistent with recommendations from the European LeukemiaNet and results from the European Intergroup Criant study, in which younger patients (<55 years) achieving CR to induction chemotherapy followed by HCT had a 4-year overall survival rate of 55%, compared with 41% for those not then receiving HCT (HR .81, 95% confidence interval .49-1.35),[102,103] a reasonable pretransplant strategy includes induction chemotherapy for younger MDS patients with very high blast percentages (>15%), favorable or intermediate-risk karyotype disease, and good performance status, or for those who progress on hypomethylating agent therapy. Patients with good-risk cytogenetics may enjoy durable remissions even without HCT. In older patients and those with unfavorable karyotypes, in whom complete response rates are low, pre-HCT induction chemotherapy is discouraged. It is our current practice to offer some form of cytoreductive therapy while awaiting HCT for patients with blast counts >10% to 15%, and those with lower blast percentages are monitored frequently.

What investigational approaches are being used after HCT?

The role of hypomethylating therapy after HCT to lessen relapse risk has also been addressed. De Lima and colleagues performed a phase 1 dose escalation trial of post-HCT azacytidine in 45 subjects and found 32 mg/m^2 per day for 5 days to be the optimal dose, when given on a monthly basis, beginning 40 days from HCT.[104] Although obvious differences in the rate of relapse were not noted in this study, only one-third of patients were treated at the highest tolerated doses. Lenalidomide has been introduced with induction therapy in del (5q) MDS patients before HCT but may trigger acute graft-vs-host disease in the post-HCT maintenance setting.[105,106]

What variables contribute to donor selection in HCT for higher-risk MDS?

The logistics of performing HCT in the typically older, higher-risk MDS patient population are substantial, starting with identification of an appropriate donor. Older patients are more likely to have even older siblings who may be too elderly for stem cell donation or who may have medical comorbidities that preclude safe donation. The question of whether an older MRD is preferable to a younger URD has recently been addressed by the CIBMTR; this analysis confirmed that siblings remain preferable,[107] although a cutoff donor age of 60 years was used by most centers routinely performing HCT. However, in an analysis performed by the EBMT, the use of a younger URD was associated with superior long-term outcomes when compared with MRD and older URD.[108]

For patients who do not have available MRD, a URD search must be done. In a study of 701 adult patients with MDS who underwent transplantation between 2002 and 2006,[94] MRD recipients and 8 of 8 URD recipients had similar disease-free and overall survival, both superior to the disease-free and overall survival rates of patients undergoing 7 of 8 URD transplantation, for whom the likelihood of 3-year disease-free survival was only 29%.

Conclusion

Every patient with higher-risk MDS should be well informed about the seriousness of the disease. Only then can a conversation occur about the role of hypomethylating agent–based therapy, clinical trials, and HCT, which remains the only curative option for MDS. Ongoing randomized studies will help clarify the superiority of monotherapy or combinations of active drugs, and of hypomethylating agent–based therapy or HCT.

Authorship

Contribution: M.A.S. and C.C. developed the manuscript concept and wrote the manuscript.

Conflict-of-interest disclosure: M.A.S. has served on advisory boards for Amgen and Celgene. C.C. has served on an advisory board for Celgene.

Correspondence: Mikkael A. Sekeres, M.D., M.S., Leukemia Program, Cleveland Clinic Taussig Cancer Institute, Desk R35, 9500 Euclid Ave, Cleveland, OH 44195; e-mail: sekerem@ccf.org.

References

1. Cancer Statistics Review SEER. 1975-2008: Myelodysplastic Syndromes (MDS), Chronic Myeloproliferative Disorders (CMD), and Chronic Myelomonocytic Leukemia (CMML). *http://seer.cancer.gov/csr/1975_2008/results_merged/sect_30_mds.pdf*:Section30.
2. Rollison DE, Howlader N, Smith MT, et al. Epidemiology of myelodysplastic syndromes and chronic myeloproliferative disorders in the United States, 2001-2004, using data from the NAACCR and SEER programs. *Blood.* 2008; 112(1):45-52.
3. Cogle CR, Craig BM, Rollison DE, List AF. Incidence of the myelodysplastic syndromes using a novel claims-based algorithm: high number of uncaptured cases by cancer registries. *Blood.* 2011;117(26):7121-7125.
4. Vardiman J, Thiele J, Arber D, et al. The 2008 Revisions of the WHO classification of myeloid neoplasms and acute leukemia: rationale and important changes. *Blood.* 2009;114(5):937-951.
5. Visconte V, Rogers HJ, Singh J, et al. SF3B1 haploinsufficiency leads to formation of ring sideroblasts in myelodysplastic syndromes. *Blood.* 2012;120(16):3173-3186.
6. Gondek LP, Tiu R, O'Keefe CL, Sekeres MA, Theil KS, Maciejewski JP. Chromosomal lesions and uniparental disomy detected by SNP arrays in MDS, MDS/MPD, and MDS-derived AML. *Blood.* 2008;111(3):1534-1542.
7. Tiu RV, Gondek LP, O'Keefe CL, et al. Prognostic impact of SNP array karyotyping in myelodysplastic syndromes and related myeloid malignancies. *Blood.* 2011;117(17):4552-4560.
8. Mohamedali A, Gäken J, Twine NA, et al. Prevalence and prognostic significance of allelic imbalance by single-nucleotide polymorphism analysis in low-risk myelodysplastic syndromes. *Blood.* 2007;110(9):3365-3373.
9. O'Keefe CL, Tiu R, Gondek LP, et al. High-resolution genomic arrays facilitate detection of novel cryptic chromosomal lesions in myelodysplastic syndromes. *Exp Hematol.* 2007; 35(2):240-251.
10. Thiel A, Beier M, Ingenhag D, et al. Comprehensive array CGH of normal karyotype myelodysplastic syndromes reveals hidden recurrent and individual genomic copy number alterations with prognostic relevance. *Leukemia.* 2011;25(3):387-399.
11. Kolquist KA, Schultz RA, Furrow A, et al. Microarray-based comparative genomic hybridization of cancer targets reveals novel, recurrent genetic aberrations in the myelodysplastic syndromes. *Cancer Genet.* 2011;204(11):603-628.
12. Maciejewski JP, Tiu RV, O'Keefe C. Application of array-based whole genome scanning technologies as a cytogenetic tool in haematological malignancies. *Br J Haematol.* 2009;146(5):479-488.
13. Jacoby MA, Walter MJ. Detection of copy number alterations in acute myeloid leukemia and myelodysplastic syndromes. *Expert Rev Mol Diagn.* 2012;12(3):253-264.
14. Gondek LP, Haddad AS, O'Keefe CL, et al. Detection of cryptic chromosomal lesions including acquired segmental uniparental disomy in advanced and low-risk myelodysplastic syndromes. *Exp Hematol.* 2007;35(11): 1728-1738.
15. Kosmider O, Gelsi-Boyer V, Cheok M, et al; Groupe Francophone des Myélodysplasies. TET2 mutation is an independent favorable prognostic factor in myelodysplastic syndromes (MDSs). *Blood.* 2009;114(15):3285-3291.
16. Langemeijer SM, Kuiper RP, Berends M, et al. Acquired mutations in TET2 are common in myelodysplastic syndromes. *Nat Genet.* 2009; 41(7):838-842.
17. Harada Y, Harada H. Molecular pathways mediating MDS/AML with focus on AML1/RUNX1 point mutations. *J Cell Physiol.* 2009; 220(1):16-20.
18. Harada Y, Harada H. Molecular mechanisms that produce secondary MDS/AML by RUNX1/AML1 point mutations. *J Cell Biochem.* 2011; 112(2):425-432.
19. Harada H, Harada Y, Niimi H, Kyo T, Kimura A, Inaba T. High incidence of somatic mutations in the AML1/RUNX1 gene in myelodysplastic syndrome and low blast percentage myeloid leukemia with myelodysplasia. *Blood.* 2004; 103(6):2316-2324.
20. Steensma DP, Gibbons RJ, Mesa RA, Tefferi A, Higgs DR. Somatic point mutations in RUNX1/CBFA2/AML1 are common in high-risk myelodysplastic syndrome, but not in myelofibrosis with myeloid metaplasia. *Eur J Haematol.* 2005;74(1):47-53.
21. Boultwood J, Perry J, Pellagatti A, et al. Frequent mutation of the polycomb-associated gene ASXL1 in the myelodysplastic syndromes and in acute myeloid leukemia. *Leukemia.* 2010;24(5): 1062-1065.
22. Bejar R, Stevenson K, Abdel-Wahab O, et al. Clinical effect of point mutations in myelodysplastic syndromes. *N Engl J Med.* 2011;364(26):2496-2506.
23. Makishima H, Jankowska AM, Tiu RV, et al. Novel homo- and hemizygous mutations in EZH2 in myeloid malignancies. *Leukemia.* 2010; 24(10):1799-1804.
24. Xu F, Li X, Wu L, et al. Overexpression of the EZH2, RING1 and BMI1 genes is common in myelodysplastic syndromes: relation to adverse epigenetic alteration and poor prognostic scoring. *Ann Hematol.* 2011;90(6):643-653.
25. Walter MJ, Ding L, Shen D, et al. Recurrent DNMT3A mutations in patients with myelodysplastic syndromes. *Leukemia.* 2011; 25(7):1153-1158.
26. Thol F, Winschel C, Lüdeking A, et al. Rare occurrence of DNMT3A mutations in myelodysplastic syndromes. *Haematologica.* 2011;96(12):1870-1873.
27. Makishima H, Cazzolli H, Szpurka H, et al. Mutations of e3 ubiquitin ligase cbl family members constitute a novel common pathogenic lesion in myeloid malignancies. *J Clin Oncol.* 2009;27(36):6109-6116.
28. Kosmider O, Gelsi-Boyer V, Slama L, et al. Mutations of IDH1 and IDH2 genes in early and accelerated phases of myelodysplastic syndromes and MDS/myeloproliferative neoplasms. *Leukemia.* 2010;24(5):1094-1096.
29. Rocquain J, Carbuccia N, Trouplin V, et al. Combined mutations of ASXL1, CBL, FLT3, IDH1, IDH2, JAK2, KRAS, NPM1, NRAS, RUNX1, TET2 and WT1 genes in myelodysplastic syndromes and acute myeloid leukemias. *BMC Cancer.* 2010;10:401.
30. Patnaik MM, Hanson CA, Hodnefield JM, et al. Differential prognostic effect of IDH1 versus IDH2 mutations in myelodysplastic syndromes: a Mayo Clinic study of 277 patients. *Leukemia.* 2012;26(1):101-105.
31. Yoshida K, Sanada M, Shiraishi Y, et al. Frequent pathway mutations of splicing machinery in myelodysplasia. *Nature.* 2011; 478(7367):64-69.
32. Visconte V, Makishima H, Maciejewski JP, Tiu RV. Emerging roles of the spliceosomal machinery in myelodysplastic syndromes and other hematological disorders. *Leukemia.* 2012;26(12):2447-2454.
33. Makishima H, Visconte V, Sakaguchi H, et al. Mutations in the spliceosome machinery, a novel and ubiquitous pathway in leukemogenesis. *Blood.* 2012;119(14):3203-3210.
34. Allampallam K, Shetty V, Mundle S, et al. Biological significance of proliferation, apoptosis, cytokines, and monocyte/macrophage cells in bone marrow biopsies of 145 patients with myelodysplastic syndrome. *Int J Hematol.* 2002; 75(3):289-297.
35. Bellamy WT, Richter L, Sirjani D, et al. Vascular endothelial cell growth factor is an autocrine promoter of abnormal localized immature myeloid precursors and leukemia progenitor formation in myelodysplastic syndromes. *Blood.* 2001;97(5):1427-1434.
36. Schipperus M, Sonneveld P, Lindemans J, et al. The effects of interleukin-3, GM-CSF, and G-CSF on the growth kinetics of colony-forming cells in myelodysplastic syndromes. *Leukemia.* 1990;4(4):267-272.
37. Sugimoto K, Hirano N, Toyoshima H, et al. Mutations of the p53 gene in myelodysplastic syndrome (MDS) and MDS-derived leukemia. *Blood.* 1993;81(11):3022-3026.
38. Jiang Y, Dunbar A, Gondek LP, et al. Aberrant DNA methylation is a dominant mechanism in MDS progression to AML. *Blood.* 2009;113(6): 1315-1325.
39. Bejar R, Stevenson KE, Caughey BA, et al. Validation of a prognostic model and the impact of mutations in patients with lower-risk myelodysplastic dyndromes. *J Clin Oncol.* 2012; 30(27):3376-3382.
40. Traina F, Visconte V, Elson P, et al. Impact of molecular mutations on treatment response to DNMT inhibitors in myelodysplasia and related neoplasms. *Leukemia.* 2013.
41. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood.* 1997;89(6):2079-2088.
42. Germing U, Hildebrandt B, Pfeilstöcker M, et al. Refinement of the international prognostic scoring system (IPSS) by including LDH as an additional prognostic variable to improve risk assessment in patients with primary myelodysplastic syndromes (MDS). *Leukemia.* 2005;19(12):2223-2231.
43. Kantarjian H, O'Brien S, Ravandi F, et al. Proposal for a new risk model in myelodysplastic syndrome that accounts for events not considered in the original International Prognostic Scoring System. *Cancer.* 2008; 113(6):1351-1361.
44. Malcovati L, Porta MG, Pascutto C, et al. Prognostic factors and life expectancy in myelodysplastic syndromes classified according

to WHO criteria: a basis for clinical decision making. *J Clin Oncol.* 2005;23(30):7594-7603.

45. Greenberg PL, Tuechler H, Schanz J, et al. Revised international prognostic scoring system for myelodysplastic syndromes. *Blood.* 2012; 120(12):2454-2465.
46. Fenaux P, Adès L. How we treat lower-risk myelodysplastic syndromes. *Blood.* 2013; 121(21):4280-4286.
47. Howlader NNA, Krapcho M, Garshell J, et al. Cronin KA (eds). SEER Cancer Statistics Review, 1975-2010. Bethesda, MD: National Cancer Institute; 2013.
48. Putila J, Remick SC, Guo NL. Combining clinical, pathological, and demographic factors refines prognosis of lung cancer: a population-based study. *PLoS ONE.* 2011;6(2):e17493.
49. Della Porta MG, Malcovati L, Strupp C, et al. Risk stratification based on both disease status and extra-hematologic comorbidities in patients with myelodysplastic syndrome. *Haematologica.* 2011;96(3):441-449.
50. Schanz J, Tüchler H, Solé F, et al. A new, comprehensive cytogenetic scoring system for primary myelodysplastic syndromes and oligoblastic AML following MDS derived from an international database merge. *J Clin Oncol.* 2012;30(8):820-829.
51. Walter MJ, Shen D, Shao J, et al. Clonal diversity of recurrently mutated genes in myelodysplastic syndromes. *Leukemia.* 2013;27(6):1275-1282.
52. Walter MJ, Shen D, Ding L, et al. Clonal architecture of secondary acute myeloid leukemia. *N Engl J Med.* 2012;366(12): 1090-1098.
53. Sekeres MA, Maciejewski JP, List AF, et al. Perceptions of disease state, treatment outcomes, and prognosis among patients with myelodysplastic syndromes: results from an internet-based survey. *Oncologist.* 2011;16(6): 904-911.
54. Steensma DP, Heptinstall KV, Johnson VM, et al. Common troublesome symptoms and their impact on quality of life in patients with myelodysplastic syndromes (MDS): results of a large internet-based survey. *Leuk Res.* 2008; 32(5):691-698.
55. Rodríguez-Paredes M, Esteller M. Cancer epigenetics reaches mainstream oncology. *Nat Med.* 2011;17(3):330-339.
56. Abdel-Wahab O, Figueroa ME. Interpreting new molecular genetics in myelodysplastic syndromes. *Hematology Am Soc Hematol Educ Program.* 2012;2012:56-64.
57. Estey EH. Epigenetics in clinical practice: the examples of azacitidine and decitabine in myelodysplasia and acute myeloid leukemia. *Leukemia.* 2013;27(9):1803-1812.
58. Shen L, Kantarjian H, Guo Y, et al. DNA methylation predicts survival and response to therapy in patients with myelodysplastic syndromes. *J Clin Oncol.* 2010;28(4):605-613.
59. Fero ML, Rivkin M, Tasch M, et al. A syndrome of multiorgan hyperplasia with features of gigantism, tumorigenesis, and female sterility in p27(Kip1)-deficient mice. *Cell.* 1996;85(5): 733-744.
60. Saunthararajah Y, Triozzi P, Rini B, et al. p53-Independent, normal stem cell sparing epigenetic differentiation therapy for myeloid and other malignancies. *Semin Oncol.* 2012;39(1): 97-108.
61. Schermelleh L, Haemmer A, Spada F, et al. Dynamics of Dnmt1 interaction with the replication machinery and its role in postreplicative maintenance of DNA methylation. *Nucleic Acids Res.* 2007;35(13):4301-4312.
62. Hu Z, Negrotto S, Gu X, et al. Decitabine maintains hematopoietic precursor self-renewal by preventing repression of stem cell genes by a differentiation-inducing stimulus. *Mol Cancer Ther.* 2010;9(6):1536-1543.
63. Silverman LR, Demakos EP, Peterson BL, et al. Randomized controlled trial of azacitidine in patients with the myelodysplastic syndrome: a study of the cancer and leukemia group B. *J Clin Oncol.* 2002;20(10):2429-2440.
64. Silverman LR, McKenzie DR, Peterson BL, et al; Cancer and Leukemia Group B. Further analysis of trials with azacitidine in patients with myelodysplastic syndrome: studies 8421, 8921, and 9221 by the Cancer and Leukemia Group B. *J Clin Oncol.* 2006;24(24):3895-3903.
65. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al; International Vidaza High-Risk MDS Survival Study Group. Efficacy of azacitidine compared with that of conventional care regimens in the treatment of higher-risk myelodysplastic syndromes: a randomised, open-label, phase III study. *Lancet Oncol.* 2009;10(3):223-232.
66. Kantarjian H, Issa JP, Rosenfeld CS, et al. Decitabine improves patient outcomes in myelodysplastic syndromes: results of a phase III randomized study. *Cancer.* 2006;106(8): 1794-1803.
67. Lübbert M, Suciu S, Baila L, et al. Low-dose decitabine versus best supportive care in elderly patients with intermediate- or high-risk myelodysplastic syndrome (MDS) ineligible for intensive chemotherapy: final results of the randomized phase III study of the European Organisation for Research and Treatment of Cancer Leukemia Group and the German MDS Study Group. *J Clin Oncol.* 2011;29(15): 1987-1996.
68. Sekeres MA, Maciejewski JP, Donley DW, et al. A study comparing dosing regimens and efficacy of subcutaneous to intravenous azacitidine (AZA) for the treatment of myelodysplastic syndromes (MDS). *ASH Annual Meeting Abstracts.* 2009;114(22):3797.
69. Kantarjian H, Oki Y, Garcia-Manero G, et al. Results of a randomized study of 3 schedules of low-dose decitabine in higher-risk myelodysplastic syndrome and chronic myelomonocytic leukemia. *Blood.* 2007;109(1): 52-57.
70. Steensma DP, Baer MR, Slack JL, et al. Multicenter study of decitabine administered daily for 5 days every 4 weeks to adults with myelodysplastic syndromes: the alternative dosing for outpatient treatment (ADOPT) trial. *J Clin Oncol.* 2009;27(23):3842-3848.
71. Garcia-Manero G, Jabbour E, Borthakur G, et al. Randomized open-label phase II study of decitabine in patients with low- or intermediate-risk myelodysplastic syndromes. *J Clin Oncol.* 2013;31(20):2548-2553.
72. Mahfouz RZ, Rickki E, Juersivich JA, et al. Non-cytotoxic differentiation therapy based on mechanism of disease produces complete remission in myelodysplastic syndromes (MDS) with high risk cytogenetics. *ASH Annual Meeting Abstracts.* 2012;120(21):1696.
73. Itzykson R, Kosmider O, Cluzeau T, et al; Groupe Francophone des Myelodysplasies (GFM). Impact of TET2 mutations on response rate to azacitidine in myelodysplastic syndromes and low blast count acute myeloid leukemias. *Leukemia.* 2011;25(7):1147-1152.
74. Sekeres MA, List AF, Cuthbertson D, et al. Phase I combination trial of lenalidomide and azacitidine in patients with higher-risk myelodysplastic syndromes. *J Clin Oncol.* 2010; 28(13):2253-2258.
75. Sekeres MA, Tiu RV, Komrokji R, et al. Phase 2 study of the lenalidomide and azacitidine combination in patients with higher-risk myelodysplastic syndromes. *Blood.* 2012; 120(25):4945-4951.
76. Cameron EE, Bachman KE, Myöhänen S, Herman JG, Baylin SB. Synergy of demethylation and histone deacetylase inhibition in the re-expression of genes silenced in cancer. *Nat Genet.* 1999;21(1):103-107.
77. Gore SD, Baylin S, Sugar E, et al. Combined DNA methyltransferase and histone deacetylase inhibition in the treatment of myeloid neoplasms. *Cancer Res.* 2006;66(12):6361-6369.
78. Silverman LR, Verma A, Odchimar-Reissig R, et al. A phase I trial of the epigenetic modulators vorinostat, in combination with azacitidine (azaC) in patients with the myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML): a study of the New York Cancer Consortium. *ASH Annual Meeting Abstracts.* 2008;112(11): 3656.
79. Garcia-Manero G, Estey EH, Jabbour E, et al. Phase II study of 5-azacitidine and vorinostat in patients (pts) with newly diagnosed myelodysplastic syndrome (MDS) or acute myelogenous leukemia (AML) not eligible for clinical trials because poor performance or presence of other comorbidities. *ASH Annual Meeting Abstracts.* 2011;116(21):604.
80. Prebet T, Gore SD, Sun Z, et al. Prolonged administration of azacitidine with or without entinostat increases rate of hematologic normalization for myelodysplastic syndrome and acute myeloid leukemia with myelodysplasia-related changes: results of the US Leukemia Intergroup Trial E1905. *ASH Annual Meeting Abstracts.* 2010;116(21):601.
81. Prébet T, Gore SD, Esterni B, et al. Outcome of high-risk myelodysplastic syndrome after azacitidine treatment failure. *J Clin Oncol.* 2011; 29(24):3322-3327.
82. Jabbour E, Garcia-Manero G, Batty N, et al. Outcome of patients with myelodysplastic syndrome after failure of decitabine therapy. *Cancer.* 2010;116(16):3830-3834.
83. Sekeres MA, Roboz GJ, Odenike O, et al. Preliminary results of fixed-dose oral clofarabine (CLO) in patients who have failed hypomethylating agents for the treatment of myelodysplastic syndromes (MDS). *ASH Annual Meeting Abstracts.* 2010;116(21):1869.
84. Bello C, Yu D, Komrokji RS, et al. Outcomes after induction chemotherapy in patients with acute myeloid leukemia arising from myelodysplastic syndrome. *Cancer.* 2011; 117(7):1463-1469.
85. Mohan SR, Fu A, Tiu RV, et al. Prior therapy with DNA methyltransferase inhibitors (DNMTI) predicts for lower remission rates and worse survival in secondary acute myeloid leukemia patients (sAML) receiving remission induction therapy. *ASH Annual Meeting Abstracts.* 2010; 116(21):4033.
86. Kantarjian H, Garcia-Manero G, O'Brien S, et al. Phase I clinical and pharmacokinetic study of oral sapacitabine in patients with acute leukemia and myelodysplastic syndrome. *J Clin Oncol.* 2010;28(2):285-291.
87. Seetharam M, Fan AC, Tran M, et al. Treatment of higher risk myelodysplastic syndrome patients unresponsive to hypomethylating agents with ON 01910.Na. *Leuk Res.* 2012;36(1):98-103.
88. Komrokji RS, Raza A, Lancet JE, et al. Phase I clinical trial of oral rigosertib in patients with myelodysplastic syndromes. *Br J Haematol.* 2013;162(4):517-524.
89. Sekeres MA, O'Keefe C, List AF, et al. Demonstration of additional benefit in adding lenalidomide to azacitidine in patients with

higher-risk myelodysplastic syndromes. *Am J Hematol.* 2011;86(1):102-103.

90. Koreth J, Pidala J, Perez WS, et al. Role of reduced-intensity conditioning allogeneic hematopoietic stem-cell transplantation in older patients with de novo myelodysplastic syndromes: an international collaborative decision analysis. *J Clin Oncol.* 2013;31(21): 2662-2670.
91. Cutler CS, Lee SJ, Greenberg P, et al. A decision analysis of allogeneic bone marrow transplantation for the myelodysplastic syndromes: delayed transplantation for low-risk myelodysplasia is associated with improved outcome. *Blood.* 2004;104(2):579-585.
92. Alessandrino EP, Porta MG, Malcovati L, et al; on behalf of Gruppo Italiano Trapianto di Midollo Osseo (GITMO). Optimal timing of allogeneic hematopoietic stem cell transplantation in patients with myelodysplastic syndrome. *Am J Hematol.* 2013.
93. Platzbecker U, Schetelig J, Finke J, et al; German MDS Study; Cooperative Transplant Study Group; Fred Hutchinson Cancer Research Center; Groupe Francophone des Myelodysplasies. Allogeneic hematopoietic cell transplantation in patients age 60-70 years with de novo high-risk myelodysplastic syndrome or secondary acute myelogenous leukemia: comparison with patients lacking donors who received azacitidine. *Biol Blood Marrow Transplant.* 2012;18(9):1415-1421.
94. Saber W, Cutler CS, Nakamura R, et al. Impact of donor source on hematopoietic cell transplantation outcomes for patients with myelodysplastic syndromes (MDS). *Blood.* 2013; 122(11):1974-1982.
95. Platzbecker U, Schetelig J, Finke J, et al. Allogeneic hematopoietic cell transplantation in patients age 60-70 years with de novo high-risk myelodysplastic syndrome or secondary acute myelogenous leukemia: comparison with patients lacking donors who received azacitidine. *Biol Blood Marrow Transplant.* 2012;18(9): 1415-1421.
96. Deeg HJ, Scott BL, Fang M, et al. Five-group cytogenetic risk classification, monosomal karyotype, and outcome after hematopoietic cell transplantation for MDS or acute leukemia evolving from MDS. *Blood.* 2012;120(7): 1398-1408.
97. McClune BL, Weisdorf DJ, Pedersen TL, et al. Effect of age on outcome of reduced-intensity hematopoietic cell transplantation for older patients with acute myeloid leukemia in first complete remission or with myelodysplastic syndrome. *J Clin Oncol.* 2010;28(11):1878-1887.
98. Damaj G, Duhamel A, Robin M, et al. Impact of azacitidine before allogeneic stem-cell transplantation for myelodysplastic syndromes: a study by the Société Française de Greffe de Moelle et de Thérapie-Cellulaire and the Groupe-Francophone des Myélodysplasies. *J Clin Oncol.* 2012;30(36):4533-4540.
99. Gerds AT, Gooley TA, Estey EH, Appelbaum FR, Deeg HJ, Scott BL. Pretransplantation therapy with azacitidine vs induction chemotherapy and posttransplantation outcome in patients with MDS. *Biol Blood Marrow Transplant.* 2012;18(8):1211-1218.
100. Lübbert M, Bertz H, Rüter B, et al. Non-intensive treatment with low-dose 5-aza-2′-deoxycytidine (DAC) prior to allogeneic blood SCT of older MDS/AML patients. *Bone Marrow Transplant.* 2009;44(9):585-588.
101. Field T, Perkins J, Huang Y, et al. 5-Azacitidine for myelodysplasia before allogeneic hematopoietic cell transplantation. *Bone Marrow Transplant.* 2010;45(2):255-260.
102. de Witte T, Hagemeijer A, Suciu S, et al. Value of allogeneic versus autologous stem cell transplantation and chemotherapy in patients with myelodysplastic syndromes and secondary acute myeloid leukemia. Final results of a prospective randomized European Intergroup Trial. *Haematologica.* 2010;95(10):1754-1761.
103. Malcovati L, Hellström-Lindberg E, Bowen D, et al; European Leukemia Net. Diagnosis and treatment of primary myelodysplastic syndromes in adults: recommendations from the European LeukemiaNet. *Blood.* 2013;122(17):2943-2964.
104. de Lima M, Giralt S, Thall PF, et al. Maintenance therapy with low-dose azacitidine after allogeneic hematopoietic stem cell transplantation for recurrent acute myelogenous leukemia or myelodysplastic syndrome: a dose and schedule finding study. *Cancer.* 2010; 116(23):5420-5431.
105. Sockel K, Bornhaeuser M, Mischak-Weissinger E, et al; German MDS and Cooperative Transplant Study Group (GCTSG). Lenalidomide maintenance after allogeneic HSCT seems to trigger acute graft-versus-host disease in patients with high-risk myelodysplastic syndromes or acute myeloid leukemia and del(5q): results of the LENAMAINT trial. *Haematologica.* 2012;97(9):e34-e35.
106. Möllgård L, Saft L, Treppendahl MB, et al. Clinical effect of increasing doses of lenalidomide in high-risk myelodysplastic syndrome and acute myeloid leukemia with chromosome 5 abnormalities. *Haematologica.* 2011;96(7):963-971.
107. Alousi AM, Le-Rademacher J, Saliba RM, et al. Who is the better donor for older hematopoietic transplant recipients: an older-aged sibling or a young, matched unrelated volunteer? *Blood.* 2013;121(13):2567-2573.
108. Kröger N, Zabelina T, de Wreede L, et al; MDS subcommittee of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). Allogeneic stem cell transplantation for older advanced MDS patients: improved survival with young unrelated donor in comparison with HLA-identical siblings. *Leukemia.* 2013;27(3): 604-609.