How We Treat Higher-Risk Myelodysplastic Syndromes

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Abstract

Higher-risk myelodysplastic syndromes (MDS) are defined as patients who fall into higher risk group categories in the original or revised International Prognostic Scoring System (IPSS). 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 patient fails one of these drugs, options are limited, median survival is less than 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 prior to transplantation, hypomethylating agent therapy, induction chemotherapy or a clinical trial should be considered to prevent disease progression, although the optimal pre-transplantation therapy is unknown.
Introduction

The myelodysplastic syndromes (MDS) are the most commonly diagnosed myeloid neoplasms in the United States, with an incidence rate of 4.6/100,000 U.S. citizens, translating to approximately 15,000 new diagnoses, yearly. This figure is often considered to be an underestimate, as 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 due to 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”).

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); and on a disease biology that at some extremes is typified by excessive production of pro-apoptotic, pro-inflammatory cytokines and premature death of hematopoietic stem cells, and at others by excessive proliferations, epigenetic regulation, and a block in differentiation. 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 below). The degree to which they will modify risk estimates in MDS, though, is being explored by an International Working Group.

Treatment decisions in MDS are based on pathology or a prognostic scoring system appropriated as a default staging system, and now incorporated into drug labeling. 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.\textsuperscript{43-45} 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 often corresponding to World Health Organization (WHO) histologic subtypes of refractory anemia with excess blasts (RAEB)-1 and -2, with an expected median overall survival of less than 2 years.\textsuperscript{4,42,46} Whether survival estimates can be adjusted within the modern therapeutic era has not been determined. Correlations between IPSS/IPSS-R and WHO classifications are loose, as some patients with excess blasts but normal karyotype and limited cytopenias can live for years, while those with few blasts, complex karyotype, and profound cytopenias may have a truncated survival.

Treatment options for lower-risk MDS have recently been reviewed.\textsuperscript{47} Treatment of an MDS patient with higher-risk disease starts with recognition of the imperative of initiating therapy. Accepting the premise that the IPSS is a default MDS staging system, with Low-High reflecting Stages 1-4, and comparing it stage-for-stage with American Joint Committee on Cancer staging for non-small cell lung cancer, overall survival is worse for MDS.\textsuperscript{48,49} Just as it would be poor practice in a patient with stage 3 or 4 lung cancer, acceptable comorbidities, a good performance status, and a desire to receive treatment to recommend watchful waiting just because that patient doesn’t yet have debilitating symptoms, so too would therapy avoidance be discouraged in a similar MDS patient with Intermediate-2 or High risk 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 presents with complaints of progressive fatigue and dyspnea, having now to rest after climbing one flight of stairs. Her medical history includes chronic venous stasis disease and prior coronary artery bypass surgery, for which she takes a beta-blocker, and angiotensin converting enzyme inhibitor, and furosemide. A complete blood cell count includes a white blood cell count (WBC) of 1600/µL with a neutrophil count of 700/µL, a hemoglobin of 7.4 g/dL, and a platelet count of 48000/µL. A bone marrow biopsy reveals trilineage dysplasia with 13% myeloblasts, and she is given a diagnosis of MDS, RAEB-2 subtype. Cytogenetics show deletion in chromosome 7 and 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 is predicted to be approximately 20 months. Applying the IPSS, 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. 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. For this patient, with the IPSS, 50% of the weight of the total score derives from the blast percentage, whereas with the IPSS-R, greater relative weight is 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 non-leukemic death.
While most agree that MDS is a cancer, in an Internet-based survey of 348 MDS patients, 80% reported that their MDS was first described as a “bone marrow disorder,” with only 6-7% indicating their MDS was first described as either “cancer” or “leukemia.” 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. 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 5mC-position of cytosine in areas of CpG dinucleotide islands, resulting in silencing of gene expression. DNA methyltransferase 1 (DNMT1) maintains existing methylation patterns following DNA replication, whereas members of the TET protein family remove methyl groups from CpGs. Histones undergo post-translational modifications, leading to activation or repression of gene expression. 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. 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. Azacitidine was approved by the U.S. Food and Drug Administration (FDA) for all MDS subtypes based on a Phase 3 trial
in which it was compared to supportive care, with cross over allowed. Response rates to azacitidine were 14% (complete and partial), and 30% hematologic improvement, when analyzed using International Working Group (IWG) criteria. There was a significant delay in transformation to AML or death, but not 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 to conventional care, which included best supportive care; low-dose cytarabine; or AML-type induction chemotherapy, as selected by investigators prior to randomization. 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 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. Using IWG criteria, complete and partial responses occurred in 17% of patients, and hematologic improvement 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. While the complete and partial response rate was 23% - similar to azacitidine - there was no survival advantage for decitabine vs. supportive care, with a median survival of 10.1 vs. 8.5 months, respectively (hazard ratio 0.88, p=0.38).

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

Can dosing of hypomethylating agents be interrupted (non-consecutive)? Are there molecular markers of response?

Azacitidine received its FDA approval based on 7 day consecutive dosing, at 75 mg/m²/day, on a 28-day cycle. 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 — likely because of limited weekend availability of infusion centers, and patient preference. In the same study, response rates (assessed as hematologic improvement or better) were similar regardless of the dosing schedule used, though survival could not be assessed. While 7 day consecutive dosing is preferred, 7-day non-consecutive dosing (e.g., 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.

Decitabine received its initial FDA approval based on a schedule in which the drug was administered at a dose of 15 mg/m² every 8 hours over 3 days and repeated every 6 weeks. Subsequently, a schedule more applicable to outpatient treatment, of 20 mg/m²/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. Further reductions in decitabine schedule and dose, to 3 days of a 28-day cycle and to weekly dosing, at 3.5-20mg/m², are being explored along with subcutaneous administration. The standard is to continue a hypomethylating agent for as long as a response persists, and to avoid switching drugs (e.g., administering decitabine in a patient failing azacitidine).

As these drugs work along methylation pathways, efforts have been made to determine whether patients with epigenetic mutations (DNMT3A, TET2, IDH 1 or 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 \( (p=.06) \). 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 \( (p=.04) \). Given the limited arsenal of drugs available for higher-risk MDS patients, though, lack of these mutations should not preclude therapy.

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

While a number of drugs have been combined and used to treat higher-risk MDS, two 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 setting, 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.\(^{34,35,63,75,76} \) In the phase 1 study, No maximum tolerated dose was identified. In the phase 2 study, azacitidine was administered at 75mg/m\(^2\)/day on days 1-5, and lenalidomide 10 mg/day on days 1-21. The overall response rate in 36 patients (18 from phase 1 and 18 from phase 2) was 72%, including 44% achieving a complete response and 28% achieving a hematologic improvement. The median response duration was 17+ months and overall survival among CR 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.\(^{77,78} \) The HDACi vorinostat has been studied in combination with azacitidine in the phase 1 setting and showed encouraging overall response rates
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. Whether either of these combinations will produce a superior response rate compared to azacitidine monotherapy is now being explored in North American Intergroup study S1117 (NCT01522976).

The largest prospective, randomized study comparing combination therapy to azacitidine monotherapy was conducted in 136 higher-risk MDS and AML patients. 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 to 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 following hypomethylating agent therapy, either because of limited numbers of treatment cycles, drug intolerance, or disease evolution, due to acquisition of abnormalities such as p53, SETBP1, or ASXL1, median survival is only 4.5-6 months. The purine nucleoside clofarabine produced responses in approximately 30% of patients failing hypomethylating agents, with overall survival similar to that reported in retrospective data. 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. No second-line therapy has demonstrated a survival advantage over any other therapy, or compared to 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 analogue; and addition of agents to hypomethylating agents in an attempt to “recover” responses.87-90

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 bruising. He was found to have a WBC of 3200/µL with a neutrophil count of 1700/µL, a hemoglobin of 8.1 g/dL, and a platelet count of 14000/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 is active, and his only comorbidity is essential hypertension, which he takes a calcium channel blocker. He is referred for evaluation for hematopoietic cell transplantation (HCT), with a calculated HCT-Comorbidity Index score of 0.

Have non-transplant MDS therapies ever been compared to HCT prospectively?

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

A German study that will biologically assign 250 newly diagnosed patients aged 55-70 years with higher risk MDS (IPSS Int-2, High or Int-1 with poor-risk cytogenetics) (NCT01404741) to HCT or no HCT. All subjects will initiate therapy with azacitidine. After 4-6 cycles, subjects will then be biologically assigned to HCT or no HCT based on the availability of a suitable donor. Those without a donor will 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 to 30% in the non-HCT arm.
A Bone Marrow Transplantation Clinical Trials Network study (BMT CTN 1102) will begin 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 will be 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 will be followed for overall survival, without any mandate for the type of HCT or non-HCT therapy delivered. It is anticipated that over 400 subjects will be enrolled to 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 due 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 over 500 patient records from several international databases. 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 to HCT. The decision analysis examined individuals aged 60-70 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. 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, due to transplant-related morbidities, with a later plateau on the HCT survival curve providing the overall benefit for HCT in higher-risk MDS patients. As 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 to 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 World Health Organization Prognostic Scoring System risk scores. Thus, despite the lack of prospective, randomized data, 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 40-50%. In this patient, long-term success could be enhanced by his low HCT-CI (irrespective of age), but worsened by poor-risk cytogenetics.

Should MDS patients be treated while awaiting HCT?

The role of cytoreductive therapy prior to 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 following both. While 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 (e.g., better performance status or fewer comorbidities) influenced outcomes. Given these caveats, there were no differences in relapse rates, non-relapse 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 due to disease progression prior to HCT) fared significantly worse. A similar, but smaller, study from Seattle demonstrated a slight advantage to pre-HCT therapy
with azacitidine over induction chemotherapy, potentially due to reduced toxicity. Both of these studies, though, 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 versus another.

To ask an even more basic question, is disease-modifying MDS therapy prior to HCT necessary at all? In retrospective analyses, when pre-HCT azacitidine was compared to no treatment, there was no benefit to azacitidine. As with other retrospective HCT analyses already discussed, these studies were affected by similar selection biases. In the absence of prospective data, but given the acceptable toxicity and potential for cyto reduction, 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 OS rate of 55%, compared to 41% for those not then receiving HCT (Hazard ratio .81, 95% confidence interval .49-1.35), A reasonable pre-transplant 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/or those with unfavorable karyotypes, in whom CR rates are low, pre-HCT induction chemotherapy is discouraged. It is our current practice to offer some form of cyto reductive therapy while awaiting HCT for patients with blast counts exceeding 10-15%, and those with lower blast percentages are monitored frequently.

**What investigational approaches are being used following HCT?**

The role of hypomethylating therapy following HCT has also been addressed, to lessen relapse risk. De Lima and colleagues performed a Phase I, dose escalation trial of post-HCT azacytidine in 45 subjects.
and found 32 mg/m²/d for 5 days to be the optimal dose, when given on a monthly basis, beginning 40
days from HCT. While 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 prior to HCT, but may trigger acute graft-versus-host disease
in the post-HCT maintenance setting.  

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 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 donor is preferable to a younger URD donor has
recently been addressed by the CIBMTR; this analysis confirmed that siblings remain preferable, although a cut-off 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 unrelated donor was associated with
superior long-term outcomes, when compared with matched sibling donors, and older unrelated
donors.  

For individuals who do not have available MRD donors, an URD search must occur. In a study of 701
adult patients with MDS who underwent transplantation between 2002 and 2006, MRD recipients
and 8/8 URD recipients had similar disease-free and overall survival, both superior to the disease-free
and overall survival rates of patients undergoing 7/8 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/or 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-based therapy or HCT.

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Conflicts of Interest: MAS has served on advisory boards for Amgen and Celgene. CC has served on an advisory board for Celgene.
References


Figure 1: Treatment Algorithm for Patients with Higher-risk Myelodysplastic Syndromes
Figure 1. Patient diagnosed with higher-risk MDS per IPSS (score ≥1.5) or IPSS-R (score

Declines HCT and/or unsuitable donor, poor HCT CI score

Immediate hypomethylating agent-based clinical trial or monotherapy x ≥6 cycles

Desires HCT, good HCT CI score

Initiate search for MRD or 8/8 URD

Hematologic improvement or better

No response

Continue hypomethylating therapy until loss of response/progression

Clinical trial with novel agent(s) or consider cytotoxic therapy or best supportive care

Older patient, lower blast percentage, intermediate/poor-risk cytogenetics

Immediate hypomethylating agent-based therapy until time of HCT

Younger patient, higher blast percentage, good-risk cytogenetics

Intensive, AML-type induction chemotherapy

Suitable donor not identified

Suitable donor identified

Suitable donor not identified

Continue hypomethylating therapy until loss of response/progression

HCT

Monitor, consider post-remission therapy
How we treat higher-risk myelodysplastic syndromes

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