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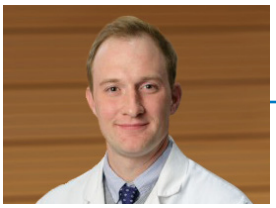
Advances in Transplantation

Your concise update on transplant research: Disease spotlight on myelodysplastic syndromes (MDS)



CASE STUDY

Management of a patient with intermediate-risk MDS

Author: Dr. Brian C. Shaffer, Memorial Sloan Kettering Cancer Center

Presentation: A 53-year-old female presented for consultation with abnormal blood counts. During a pre-surgical evaluation for elective lumbar discectomy, she was found to have mild pancytopenia (see lab results in Table 1).

Complete blood count (CBC) results

TEST	RESULTS
White blood cell count	2,200/µl
Absolute neutrophil count	1,000/µl
Normal differential, no blasts	
Hemoglobin	10.0 g/dl
Mean corpuscular volume	101 fL
Platelets	170,000/µL

Table 1. **Pre-surgical CBC results**

The surgery was cancelled and she was referred for further evaluation.

Past medical history: She had no significant past medical history, except for lumbar disc herniation. She rarely drank alcohol, denied any toxic exposures, and the only supplement she took was a daily multivitamin. She had no constitutional symptoms.

Laboratory evaluation:
Blood studies: Repeat CBC 2 weeks later yielded similar results.

- Vitamin B12, methylmalonate and folate levels were normal
- Serum protein electrophoresis was normal
- Antinuclear antibody and rheumatoid factor were negative

Bone marrow biopsy and aspirate studies performed: Results demonstrated 40-50% cellularity with marked trilineage dysplasia, including hypogranular myeloid forms, erythroid binucleation and nuclear irregularity, and hypolobulated megakaryocytes. There were 18% blasts identified on the aspirate differential. Reticulin fibrosis was 1+/3. Karyotype analysis was normal in 20 metaphases. A repeat bone marrow biopsy performed 2 weeks later demonstrated similar results and blast percentage. Multi-gene sequencing analysis performed on genomic DNA extracted from the bone marrow identified a mutation in the *CBL* gene (T1248G).

Diagnosis: The disease features met the criteria for a diagnosis of myelodysplastic syndrome (MDS) with excess blasts-2. The Revised-International Prognostic

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Most relevant factors in identifying HCT candidates in patients with MDS

An international panel of experts from the European Society for Blood and Marrow Transplantation, European LeukemiaNet, Blood and Marrow Transplant Clinical Trial Group, and the International Myelodysplastic Syndromes Foundation has developed updated HCT treatment decision recommendations for patients with MDS. [7]

Recommendations were classified as patient- or disease-related, and focus on determining which factors can best identify HCT candidates. Table 2 shows the prognostic risk factors most relevant for HCT eligibility and their corresponding measurement tools.

Clinical factors most likely to determine response to treatment modalities include intensive chemotherapy, hypomethylating agents (HMA), immunomodulatory agents, such as lenalidomide, and hematopoietic growth factors.

The panel noted that the most relevant clinical tools to determine HCT eligibility are the IPSS-R and HCT comorbidity index (HCT-CI), and concluded that "fit patients with higher-risk IPSS-R and those with lower-risk IPSS-R with poor-risk genetic features, profound cytopenias, and high transfusion burden are candidates for HCT."

> "Fit patients with higher-risk IPSS-R and those with lower-risk IPSS-R with poor-risk genetic features, profound cytopenias, and high transfusion burden are candidates for HCT."
> — de Witte T, et al.

HCT eligibility recommendations

PROGNOSTIC RISK FACTOR	MEASUREMENT TOOLS
Patient-related	
Age (chronological)	Calendar, IPSS-R
Performance status (functional ability)	Karnofsky status ≥ 80%
Frailty (reduced physical fitness)	Specific tools have to be tested in HCT
Comorbidities	HCT-CI
Disease-related	
Percentage of marrow blasts	IPSS-R, WPSS, WHO
Cytogenetic risk groups	IPSS-R, WPSS, CPSS
Severity of cytopenias	IPSS-R, WPSS
Marrow fibrosis	WHO criteria
Transfusions burden	WPSS
Flow cytometry	ELN flow cytometry score
Molecular mutations	No specific tools yet
Disease status (after non-HCT treatment interventions)	
Erythropoietin-stimulating agent failure	High Epo levels, high transfusion intensity
Lenalidomide failure	Absence of 5q-
Hypomethylating agents failure	HMA-therapy-specific risk score
Intensive chemotherapy	MDS-specific risk score

Table 2. **HCT eligibility recommendations from the European Society for Blood and Marrow Transplantation, European LeukemiaNet, Blood and Marrow Transplant Clinical Trial Group and the International Myelodysplastic Syndromes Foundation.**
CI=comorbidity index, ELN=European LeukemiaNet, Epo= erythropoietin, WHO=World Health Organization, WPSS=WHO classification-based Prognostic Scoring System, CPSS=CMML-specific prognostic scoring system, IPSS-R=International Prognostic Scoring System-Revised

New scoring system predicts HCT outcomes of patients with MDS

Researchers studying 2,133 patients with MDS undergoing allogeneic HCT developed an improved prognostic scoring system predictive of HCT outcomes that integrates patient- and disease-specific factors beyond the IPSS-R scoring system. [3]

Patient outcomes from 2000 to 2012 were reported to the CIBMTR® (Center for International Blood and Marrow Transplant Research®). A multivariate model identified 5 independent predictors of survival: age, Karnofsky performance status less than 90%, cytogenetics, and at the time of transplant, blood blasts greater than 3% and platelet count of 50 × 10^9/L or less.

Researchers created a 4-category system (shown in Table 3) with an overall score range from 0 to 7, and increasing scores indicating greater risk. Patients were assigned a score of 2 if older than age 50 and a monosomal karyotype, and scores of 0 or 1 for the 4 other patient factors. Table 3 shows the probability of 3-year overall survival (OS) after HCT in the HLA-matched training cohort.

Three-year OS by prognostic score in HLA-matched training cohort

RISK GROUP (SCORE)	N	3-YEAR OS (%)	HR (95% CI)	P-VALUE
Low (0-1)	98	71	1.00	N/A
Intermediate (2-3)	459	49	1.76 (1.24 to 2.49)	p=0.0017
High (4-5)	237	41	2.87 (1.99 to 4.14)	p<0.001
Very high (≥ 6)	45	25	6.75 (4.28 to 10.67)	p<0.001

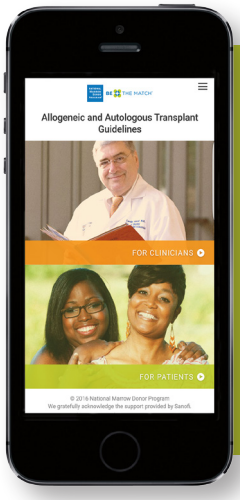
Table 3. **Prognostic scoring by risk group for 3-year overall survival**
HR=hazard ratio, CI=confidence interval

A higher risk score was predictive of both increased relapse and treatment-related mortality (TRM) (p<0.001) in HLA-matched patients (n=1,728).

> **"The scoring system uses readily available clinical data and can be calculated quickly, facilitating patient consultation with respect to allogeneic HCT."**
> **— Shaffer BC, et al.**

When researchers applied their prognostic score to a second cohort of 405 patients undergoing 1- to 2-HLA loci-mismatched transplant, the prognostic score was predictive of relapse in this cohort (p=0.04), but not TRM, disease-free survival or OS.

The authors concluded that their proposed system offers improved prognostic capability by quick calculation from clinical data, particularly for patients in the low-, intermediate- and high-risk subgroups.



Somatic mutations improve transplant prognostics in MDS

A study of 401 patients with MDS, or AML evolving from MDS (MDS/AML), showed that *ASXL1*, *RUNX1*, and *TP53* mutations were independent predictors of higher rates of relapse and lower OS (p<0.001 and p=0.017, respectively) after transplantation. [3]

Overall, 87% of patients carried 1 or more oncogenic mutation and lesion. Researchers used massively parallel sequencing to examine tumor samples collected pre-transplant for somatic mutations in 34 recurrently mutated genes.

Effects of somatic mutations on the probability of relapse and OS is shown in Table 4.

The impact of *ASXL1*, *RUNX1*, and *TP53* mutations on post-transplant survival was independent from IPSS-R. Combining both somatic mutations and IPSS-R risk improved the ability to risk stratify the disease, because more prognostic information was captured at an individual level. Based on this prognostic combination, post-HCT outcomes predictions changed significantly for 34% of the cohort.

Based on the improvement in predictions, patients with high-risk disease may benefit from undergoing HCT at an early disease stage and discussing the possible use of post-HCT prophylaxis to prevent relapse.

Researchers concluded that integrating somatic mutation information significantly increases the ability to capture prognostic information in patients with MDS and MDS/AML, and may therefore lead to improved clinical decision-making with these patients undergoing allogeneic HCT.

Prognostic value of gene mutations for post-transplantation outcomes in univariate analysis

VARIABLE	MUTATION FREQUENCY %	PROBABILITY OF RELAPSE			OVERALL SURVIVAL		
		HR	95% CI	P	HR	95% CI	P
ASXL1	17	1.89	1.34 to 2.56	<0.001	1.73	1.23 to 2.18	0.003
RUNX1	23	1.78	1.26 to 2.27	0.001	1.69	1.1 to 2.23	0.008
IDH1/2	3-7	1.74	1.17 to 2.38	0.002	1.42	0.95 to 2.16	0.04
TP53	13	1.95	1.54 to 2.57	<0.001	1.92	1.48 to 2.37	0.001

Table 4. **Post-transplant outcomes predicted by genetic mutations.**
HR=hazard ratio, CI=confidence interval

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Scoring System (IPSS-R) risk score was 4, based on 1 point for "good" (normal) cytogenetics plus 3 points for blast percentage >10. This led to the classification of intermediate-risk disease.

Therapy: Given her high blast count, the patient began initial cytoreduction with 5-azacitidine 75 mg/m^2/d subcutaneously for 7 consecutive days, every 4 weeks. She had no complications and no significant change in her blood counts at the end of each cycle. After 4 cycles, a repeat bone marrow biopsy demonstrated resolution of dysplastic features in the myeloid and erythroid series, persistent dysplastic megakaryocytes and 3-5% blasts. The *CBL* gene mutation was again detected.

HCT consultation: She was referred for consultation to consider hematopoietic cell transplantation (HCT). Her only sibling was unsuitable for stem cell donation, but a preliminary search of the Be The Match Registry® demonstrated numerous matched adult unrelated donors.

CASE DISCUSSION:

This case highlights several factors facing both leukemia and transplant specialists in the management of patients with intermediate-risk myeloid malignancies. Approximately 75-85% of patients with MDS or acute myeloid leukemia (AML) have at least one identifiable somatic mutation in a relevant oncogene. [1, 2]

The rapid expansion in availability of genomic sequencing data has outpaced clinical decision algorithms concerning treatment choices about whether to perform or forgo HCT. Fortunately, several recent publications have shed light on the subject and have begun to provide guidance to the physician and patient. [1-4]

In the context of this case, a *CBL* mutation stratifies this patient as having a higher risk for relapse. *CBL*, which codes for an E3-ubiquitin ligase, is responsible for negatively regulating several oncogenic pathways including RAS/*MAPK*. [5,6] A recent publication by Lindsley et al. analyzed the role of somatic mutations in blood specimens obtained from 1,514 patients with MDS prior to HCT (summarized on page 6). [1] Patients with detectable RAS pathway mutations, defined as those affecting the function of *NRAS, KRAS, PTPN11, CBL, NF1, RIT1, FLT3* and *KIT*, had a higher incidence of relapse after HCT than patients without RAS pathway mutations.

This difference was seen predominantly in patients who received reduced intensity conditioning, where the 2-year incidence of relapse was 48.8% versus 22.7% ($p<0.001$) in patients with and without RAS-mutated MDS, respectively. This compares to 27% versus 18.6% ($p=0.31$) in patients receiving myeloablative conditioning.

Because this patient is relatively young and had a high blast burden in the bone marrow at diagnosis, a favorable HCT comorbidity index score (HCT-CI) of zero, and a matched unrelated donor, I would recommend HCT with myeloablative conditioning. Given her response to hypomethylating agents, I would offer this patient maintenance 5-azacytidine after HCT as part of a clinical trial.

My current practice with respect to HCT for patients with MDS is consistent with the recent recommendations offered by an expert panel on the subject. [7] In this context, the HCT-CI and the IPSS-R prognostic tools, as well as patient preference, determine transplant eligibility. [8-10]

Anticipated outcomes after HCT (available at BeTheMatchClinical.org/MDS) are useful to counsel patients about their prognosis. Patients with intermediate- to very high-risk IPSS-R scores, who are suitably fit, should proceed to HCT either up front or after an initial trial of cytoreduction if their blast percentages are greater than 10%. Those with lower-risk disease without high-risk features, or who are unfit, should consider whether to defer HCT.

Genomic aberrations may become most useful in counseling patients with intermediate IPSS-R risk MDS, where the presence of such mutations may imply an increased risk of adverse outcomes. Della Porta and colleagues found that the presence of driver somatic mutations increased risk of relapse after HCT and may be instructive to further stratify patients with otherwise intermediate IPSS-R risk MDS (summarized on page 4). [3]

Future of the field: Ultimately**,** it will require further investigation to determine whether genomic sequencing is predominantly a prognostic tool *versus* one that can be used therapeutically to select patients for specific treatments, including HCT. I believe we are now beginning to see evidence of the latter. While some caution must be exercised in the use of these data to guide therapeutic decisions, it is clear that genome sequencing studies provide prognostic information and should be used to counsel patients when available. Prospective studies in the future will clarify the role of somatic mutations in clinical decision algorithms for patients with MDS and AML.

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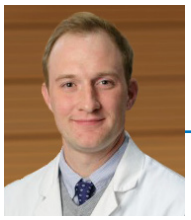

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Dr. Brian Shaffer is a board-certified hematologist and Assistant Professor at Memorial Sloan Kettering Cancer Center. He specializes in bone marrow transplantation for acute leukemia and myelodysplastic syndromes. His research focuses on HLA and KIR immunogenetics in the selection of matched unrelated and haploidentical donors. His other clinical interests include development of novel graft-versus-host disease prophylaxis platforms for HLA mismatched donors and methodology to prevent leukemia relapse after transplantation.

Genetic mutations guide therapy recommendations in patients with MDS

TP53, RAS pathway and *JAK2* V617F mutations predict allogeneic transplant outcomes in patients with MDS, according to a multi-center study of 1,514 transplant recipients. [1]

> "Analysis of mutations in patients with MDS at the time of HCT can predict outcomes and identify subgroups of patients who will derive the most benefit from particular conditioning regimens."
> —Lindsley RC, et al.

Researchers performed targeted sequencing of 129 genes on pre-transplant blood samples from patients registered with the CIBMTR and found *TP53* mutations in 19% of the cohort. A multivariate analysis showed that *TP53* mutations were significantly associated with poor OS (HR 1.71, 95% CI 1.45-2.02, p<0.001) and a shorter time before relapse (HR 2.03, 95% CI 1.60-2.58, p<0.001), independent of recipient age, performance status, hematologic status at time of HCT, bone marrow blast count and karyotype.

Mutations in any of the genes involved in the RAS signaling pathway were independently associated with a shorter time to relapse (HR 1.56, 1.18-2.05, p<0.002), but myeloablative conditioning negated the risk. *JAK2* V617F mutations were associated with higher non-relapse mortality (HR 2.10, 1.36-3.24, p<0.001).

By combining key clinical factors with *TP53, PPM1D,* and *JAK2* mutations, researchers identified 6 prognostic MDS subgroups that can guide pre- and post-HCT therapy recommendations.

The researchers concluded that assessing genetic mutations "will help physicians identify patients for whom a transplant is appropriate, and the intensity of treatment most likely to be effective."