Bone Marrow Failure Disease Research Summaries for Patients

FROM THE
2020 AMERICAN HEMATOLOGY SOCIETY ANNUAL MEETING
This publication offers summaries of selected abstracts presented at the December 2020 Meeting of the American Hematology Society. It provides new and updated information about new research into the diagnosis, treatment and prognosis of bone marrow failure diseases with a deep focus on Myelodysplastic Syndromes (MDS) and Acute Myeloid Leukemia (AML) secondary to MDS.

Abstracts were selected by Hetty Carraway, MD with the Taussig Cancer Center at the Cleveland Clinic and Courtney D. DiNardo, MD with The University of Texas MD Anderson Cancer Center and are presented in this print/digital publication as well as summarized in two webinars which are available on the AAMDSIF website at https://www.aamds.org/education/webinars for on-demand viewing.

Although the information in this booklet has undergone a thorough, independent medical review to ensure its accuracy, this information is not intended to be a substitute for the advice of your doctor. You should always seek medical advice from a qualified physician.

Additional resources for patients, families and caregivers living with bone marrow failure diseases are invited to visit our website for the following free resources:

- Patient Guides: www.aamds.org/education/patient-guides-and-fact-sheets
- Patient-Focused Webinars: https://www.aamds.org/education/webinars
- Virtual Patient & Family Conferences: https://www.aamds.org/education/conferences/patients
- MDS Toolkit: www.aamds.org/support/mds-toolkit

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Genetic Analysis for Diagnoses and Treatment Decisions About Clonal Cytopenia of Undetermined Significance and MDS
Constance Baer, PhD; Anna Stengel, PhD; Wolfgang Kern, MD; Claudia Haferlach, MD; Torsten Haferlach, MD

Summary:
Some MDS treatments target certain gene mutations so it is useful to know which genes are mutated in a patient’s bone marrow in order to choose the right treatment option(s).

In clonal cytopenia of undetermined significance (CCUS), counts of certain kinds of blood cells are low but the cause is not known. Some of the blood cells have a mutated gene and patients with CCUS have a 75% chance of developing MDS.

This study compared the mutations in 213 patients with MDS and 363 with CCUS. The investigators wanted to find out whether the genetic testing they use routinely could help diagnose CCUS and offer useful information for treatment decisions.

Key findings:
- Patients with MDS had more mutations (2.8 each) than those with CCUS (2 each).
- More patients (25%) with CCUS had mutations only in the DNMT3A, TET2, and ASXL1 genes than patients with MDS (4%).
- 12% of MDS patients with MDS had an SF3B1 mutation, while 5% of CCUS patients had this mutation. Luspatercept is a treatment option for patients with an SF3B1 mutation.
- 45% of the MDS patients and 28% of the CCUS patients had mutations with a high risk of poor outcomes. For these patients, stem cell transplantation might be a good treatment option.

Conclusions:
- This study identified genetic markers that can be used to help diagnose MDS.
- Mutations in about a third of patients with CCUS and two thirds with MDS could be used to help choose personalized treatments.
Mutations in Seven Genes That Can Help Classify MDS

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Summary:
The National MDS Study (NCT02775383) is monitoring patients being tested for MDS to understand how this disease develops. Study participants are given a diagnosis of MDS, myelodysplastic/myeloproliferative neoplasms, acute myelogenous leukemia (AML), or “other.” The investigators studied whether data on mutations in certain genes could be used to increase the accuracy of diagnoses in patients with shortages of certain blood cells.

In the analysis of bone marrow specimens from 648 patients, 212 were diagnosed with MDS and 436 had an “other” diagnosis from the pathology findings which is when cells are examined under a microscope as well as certain other tests. Pathology findings came from both local laboratories in the hospital and from a central laboratory. The investigators then tested the specimens for mutations in 96 genes to find out whether the mutations matched the diagnoses from pathology findings

Key findings:
- Mutations in seven genes were most useful for telling which patients had MDS or an “other” diagnosis: TP53, SF3B1, U2AF1, ASXL1, TET2, STAG2, and SRSF2.
- For 50 patients who got different diagnoses from local and central laboratories, use of the seven gene mutations identified the same diagnosis as the central laboratory for 37 patients (74% accuracy).
- These reclassified cases included 24 cases of MDS that had been mislabeled as “other” by the local pathology studies.
- Also, 3 of 16 cases misclassified as “other” by the local pathologist were misclassified as MDS.
- In a separate set of samples from 52 patients, the seven genes correctly identified 15 of 21 cases of MDS and misclassified 6 of 31 “other” cases as MDS, for an accuracy of 83%.

Conclusions:
- The results suggest that pathology findings should be combined with studies of these seven genes to improve MDS diagnosis.
Personalized Tool to Increase Accuracy of MDS Diagnosis
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Summary:
In histology and cytology examinations, a doctor looks at a patient’s cells under a microscope. These examinations are an important part of diagnosing MDS. Different doctors and labs can come up with a different diagnosis after looking at the same cells, especially when patients have shortages of all types of blood cells and no abnormally shaped blood cells.

The investigators developed a system that uses information on gene mutations and blood cell counts to tell whether a patient has MDS or another bone marrow disease. Study data came from 2,697 patients (average age 70 years) seen at hospitals in the United States, Germany, and Italy. All patients were given a diagnosis of MDS, chronic myelomonocytic leukemia, myelodysplastic/myeloproliferative neoplasm, myeloproliferative neoplasm, clonal cytopenia of undetermined significance, or idiopathic cytopenia of undetermined significance.

Key findings:
• The most commonly mutated genes in all patients with MDS were SF3B1 (27%), TET2 (25%), ASXL1 (19%), SRSF2 (16%), and DNMT3A (11%).
• The five most commonly mutated genes in the other bone marrow failure diseases were different from those in MDS.
• The most important factors for accurate diagnoses included number of mutations found in each specimen; proportion of abnormal immature blood cells; patient age and gender; blood counts; and whether the patient had mutations in JAK2, EZH2, KRAS, or SF3B1.
• The final model was 95% accurate at diagnosing MDS versus another bone marrow failure disease.

Conclusions:
• The investigators developed a system that can help tell whether a patient has MDS or another bone marrow failure disease.
• The model can help doctors make accurate diagnoses for patients with low blood cell counts and might have MDS.
**SF3B1 Mutations in MDS with Ringed Sideroblasts**

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**Summary:**
Treatments are needed for patients who have MDS with ring sideroblasts and an SF3B1 mutation when their disease does not respond to standard treatment with azacitidine (Vidaza) or decitabine (Dacogen). These treatments are part of a group of medications called hypomethylating agents (HMAs). Understanding the role of SF3B1 mutations in this disease could help scientists develop new treatment options.

This study was designed to understand the role of SF3B1 mutations on immature red blood cells. Another goal was to find out how HMA treatment could overcome defective red blood cell formation resulting from mutated SF3B1. The study used cells from two healthy donors and five patients whose MDS with ring sideroblasts had not been treated and who had SF3B1 mutations.

**Key Findings:**
- Most stem cells of MDS patients were immature red blood cells.
- The large numbers of immature red blood cells in the bone marrows of MDS patients crowded out myeloid and lymphoid cells, which are involved in the immune system.
- The SF3B1 mutation stopped the red blood cell maturation process at the last step.
- HMA therapy did not affect abnormal red blood cell maturation in patients with the mutation.

**Conclusions:**
- The results show the effect of SF3B1 mutations on different stages of red blood cell formation.
- The results have implications for the development of treatments that lead to lasting remission in patients with MDS with ring sideroblasts.
Ring Sideroblast Development in MDS with SF3B1 Mutations
Courtnee Clough, Joseph Pangallo, PhD; Martina Sarchi, MD; Stephanie Busch, B.S., Janis L. Abkowitz, MD; Robert K. Bradley, PhD and Sergei Doulatov, PhD

Summary:
The fact that 80% of patients who have MDS with ring sideroblasts also have SF3B1 mutations suggests that these mutations cause ring sideroblasts.

The investigators collected stem cells from patients who had MDS with ring sideroblasts and monitored the formation of ring sideroblasts.

Key Findings:
• By day 18, 25% to 40% of red blood cells formed in cells from patients with MDS with ring sideroblasts were ring sideroblasts. None of the samples from people who did not have MDS were ring sideroblasts.
• Overexpression of two genes, TMEM14C and ABCB7, increased the formation of healthy red blood cells instead of ring sideroblasts in cells with SF3B1 mutations.

Conclusions:
• Faulty splicing of certain genes involved in certain chemical reactions with iron cause the formation of ring sideroblasts.
• This faulty splicing seems to result from mutations in several genes.
Effects of Mutations in Cell-Signaling Genes on Progression from MDS to Acute Myelogenous Leukemia

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Summary:
Cells send signals to make changes in other cells, and certain genes control cell signaling. Mutations in genes that control cell signaling are more common after MDS progresses to acute myelogenous leukemia (AML) than in MDS. This study examined whether mutations in signaling genes play a role in progression of MDS to AML. The research team analyzed specimens from 44 patients at the time they had an MDS diagnosis and again later when they developed AML (an average of 306 days later). The researchers looked for 285 gene mutations that are common in MDS and secondary AML (AML that has progressed from MDS).

Key Findings:
• The investigators found 32 different mutations in signaling genes in 15 of the 44 secondary AML samples.
• They detected only 11 of these mutations in the samples collected before these patients’ MDS progressed to AML.
• Of 33 mutations in signaling genes in samples from 19 patients with MDS, only 11 were still there when the MDS progressed to AML.
• Six MDS specimens and 10 secondary AML specimens had several different mutations in signaling genes.

Conclusions:
• Almost half of patients with MDS that progresses to AML have mutations in signaling genes.
• Signaling gene mutations seem to be major drivers of progression from MDS to secondary AML.
• Cells with these mutations could be targets for new treatments.
Combination of Venetoclax with Azacitidine for Higher-Risk MDS
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Summary:
The standard treatment for higher-risk MDS in patients who are not eligible for stem cell transplantation is a hypomethylating agent (decitabine or azacitidine), but not all patients respond to this treatment, and those who do survive an average of just 15 months.

Previous studies in cells from patients with higher-risk MDS have shown promising results from a combination of venetoclax with a hypomethylating agent.

This ongoing Phase 1b clinical trial (NCT02942290) is evaluating the combination of venetoclax and azacitidine as the first treatment for higher-risk MDS. As of December 31, 2019, the researchers had given the combination treatment to 57 patients (75% male, average age 71 years), and the research team had monitored their outcomes for up to 13 months.

Key findings:
- All patients had at least one side effect. The most common side effect was constipation which was reported in 54% of patients. Other common side effects, both in 51% of patients, were low white blood cell count with fever and nausea.
- Almost all patients, 97%, had a serious side effect. The most common ones were low white blood cell count (51% of patients), low white blood cell count with fever (46%), and shortage of platelets (30%).
- Most patients, 77%, responded to the treatment, and they continued responding for an average of 15 months.
- On average, patients had no disease progression for about 18 months.
- Patients had less fatigue and fewer breathing problems.

Conclusions:
- The combination of venetoclax and azacitidine has promising response rates, and its side effects are acceptable.
Combination of Sabatolimab with Azacitidine or Decitabine for Acute Myelogenous Leukemia or High-Risk MDS

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Summary:
Sabatolimab is an experimental treatment that targets TIM-3, a receptor on immune cells and immature leukemia cells. Healthy bone marrow cells do not have TIM-3. By blocking TIM-3, sabatolimab might help the immune cells kill immature leukemia cells in the bone marrow.

This Phase 1b trial (NCT03066648) is testing the combination of sabatolimab with decitabine (Dacogen) or azacitidine (Vidaza) in adults with acute myelogenous leukemia (AML) or higher-risk MDS. Participating patients have not been treated with azacitidine or decitabine previously and they are not eligible for intensive chemotherapy. The study team is treating patients with increasing doses of sabatolimab and standard doses of decitabine or azacitidine in 28-day cycles.

As of June 25, 2020, the study had enrolled 48 patients with AML, 39 with higher-risk MDS, and 12 with chronic myelomonocytic leukemia. On average, patients had been treated with sabatolimab for about 4 months.

Key Findings:
- Common side effects with the combination of sabatolimab and decitabine or azacitidine were low platelet counts, low white blood cell counts (with or without fever), anemia, and pneumonia.
- Only 6% of patients with AML and none with MDS stopped the treatment because of side effects.
- Among 35 patients MDS whose responses could be evaluated, 63% responded, and 90% of these responses lasted for at least 6 months.
- Eight patients with higher-risk MDS had a stem cell transplant after being in this trial.

Conclusions:
- Patients with higher-risk MDS or AML tolerated the combination of sabatolimab with decitabine or azacitidine well.
- This combination treatment had promising effects on leukemia cells.
Venetoclax with Reduced-Intensity Conditioning Chemotherapy Before Stem Cell Transplantation for High-Risk Acute Myelogenous Leukemia or MDS

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Summary:
Patients with MDS or acute myelogenous leukemia (AML) who have certain genetic mutations or abnormal chromosomes often have a relapse after stem cell transplantation. Outcomes after a relapse are poor.

MDS and AML patients typically undergo conditioning treatment before stem cell transplantation which can consist of chemotherapy, radiation therapy, or both. Conditioning treatment suppresses the immune system to prevent rejection of the donor stem cells. It also makes room in the patient’s bone marrow for the donor stem cells to grow and destroys any cancer cells in the bone marrow. In reduced-intensity conditioning, smaller doses than standard regimens are used of chemotherapy, radiation therapy, or both.

This study assessed the safety and efficacy of adding venetoclax to reduced-intensity conditioning chemotherapy with fludarabine and busulfan. The study included 22 patients (average age 64 years) with AML, MDS, or myelodysplastic/myeloproliferative neoplasms. Of these patients, 12 (55%) had a TP53 mutation and 65% had abnormal chromosomes—both markers of poor outcomes. Patients were treated with increasing doses of venetoclax starting 8 days and lasting until 1 day before their transplant.

Key Findings:
• Serious side effects included diarrhea (3 patients) and rash (4 patients).
• Donor stem cells engrafted in all 22 patients, meaning that the transplanted cells grew in the bone marrow and began to make healthy white blood cells.
• By 100 days after transplantation, 16 of 21 patients whose outcomes could be assessed were in complete remission.
• At 6 months, 84% of patients were still alive.

Conclusions:
• The addition of venetoclax to fludarabine and busulfan reduced-intensity conditioning for stem cell transplantation does not increase the risk of serious side effects.
• This combination treatment is promising for patients with high-risk MDS or AML.
Gene Mutations for Prognosis in Shwachman-Diamond Syndrome

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Summary:
People with Shwachman-Diamond Syndrome (SDS) have a high risk of developing MDS or acute myelogenous leukemia (AML). When they do develop MDS or AML, outcomes are often poor.

This study identified somatic gene mutations in people with SDS. Somatic mutations are changes in a gene that happen after conception in a patient’s cells, are not inherited, and are not passed on to the patient’s children.

The investigators tested genes in specimens from 110 people with SDS. They then compared mutations with outcomes to understand the effects of these mutations.

Key Findings:
• Of 98 patients who had mutations in both alleles of the SBDS gene, 74 (76%) had somatic mutations.
• Of 83 patients with SDS who did not develop MDS or AML, 60 (72%) had abnormal blood cells in the bone marrow and 40 of those 60 (67%) had more than one mutation.
• Among 33 patients with a TP53 mutation, 30 (91%) also had an EIF6 mutation.
• Patients with TP53 mutations were more likely to develop a bone marrow cancer.

Conclusions:
• EIF6 mutations do not contribute to development of bone marrow cancer in patients with SDS.
• Changes in TP53 in patients with SDS can be detected years before these patients develop MDS or AML.
• Early detection of TP53 mutations in patients with SDS might show whether these patients are likely to develop MDS or AML later.
• Early detection may help patients and their treating hematologist/oncologist make better choices about treatment options.