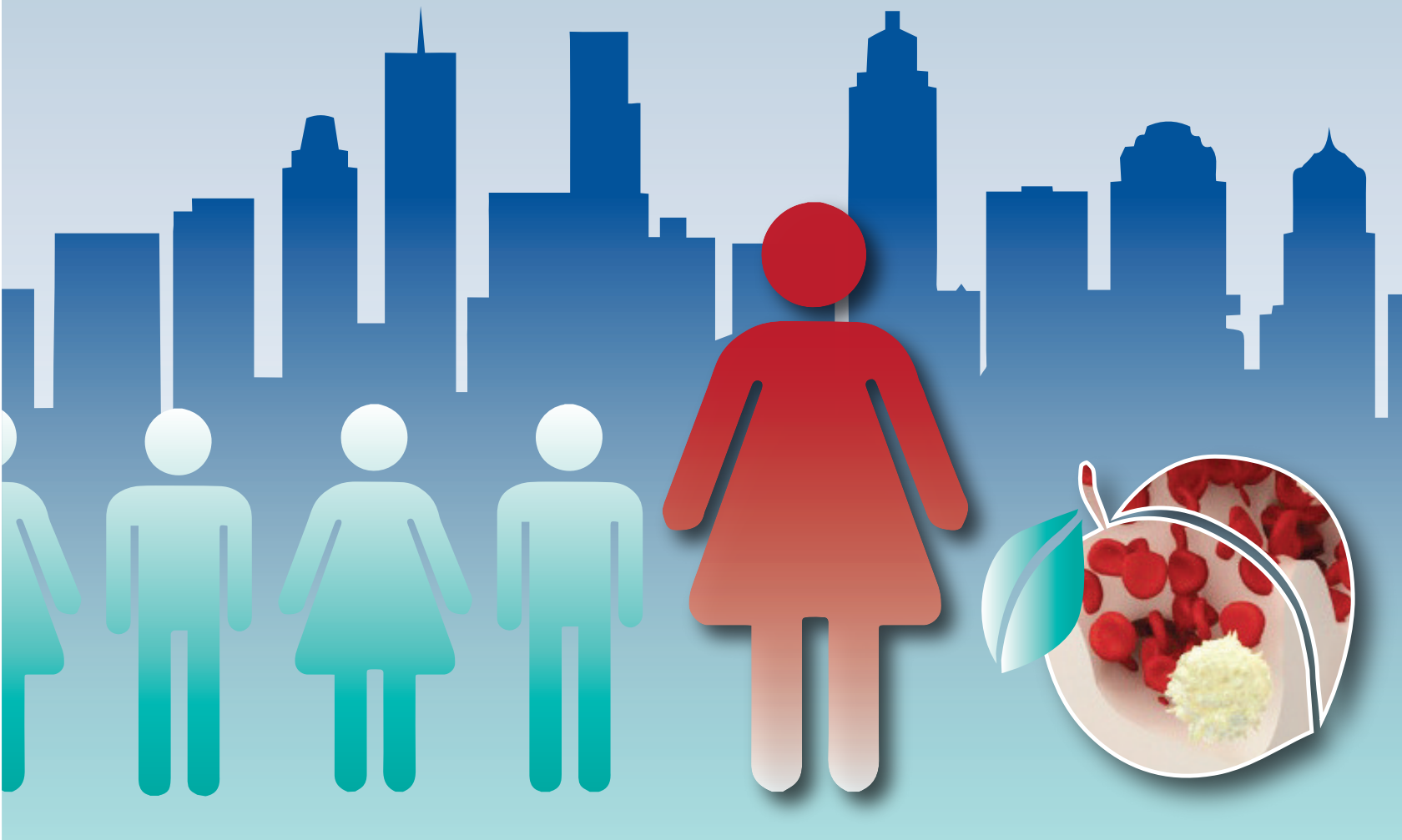
MDS BREAKFAST SYMPOSIUM

Individualizing Therapeutic Strategies for Patients with MDS



PATIENT SUMMARY

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mds foundation
the myelodysplastic syndromes foundation, inc.

Inherited Risk of MDS and AML

Dr. Jude Fitzgibbon (Barts Cancer Institute, London, UK) explained that more than 95% of cases of MDS and acute myelogenous leukemia (AML) do not seem to be inherited. In less than 5% of cases, though, two or more members of a family have AML, MDS, or other bone marrow failure syndromes. The genes associated with inherited MDS/AML have variable penetrance. As a result, some people who carry these genetic variants have symptoms of the diseases, and others do not.

Single Inherited Mutation

In 2004, Dr. Fitzgibbon and colleagues reported on a father and two daughters who had AML and the same mutation in the *CEBPA* gene. Family members who did not have AML also did not have the mutation. All three patients were treated and went into remission for 10 to 30 years.

Since then, Dr. Fitzgibbon has worked with colleagues all over the world to identify 25 additional patients with AML from 11 families with the *CEBPA* mutation. Remission after the initial treatment is typically quite long in these patients. But because they still have the inherited mutation, they can develop a new leukemia after the first case is cured. Fortunately, these new leukemias can be treated successfully.

Combinations of Inherited Mutations

The situation is more complicated when patients with a genetic predisposition acquire another mutation that is not inherited. For example, two first cousins with an inherited *GATA2* mutation developed high-risk MDS with monosomy 7. Both had acquired *ASXL1* mutations that were not inherited. Although the two cousins underwent hematopoietic stem cell transplantation (HSCT), both died. The inherited *GATA2* mutations predisposed these cousins to develop MDS or AML, and they acquired monosomy 7 and *ASXL1* mutations that triggered their MDS.

Identifying Inherited Mutations Associated with MDS and AML

Dr. Fitzgibbon has collected data on 82 families with inherited MDS and AML. Of these families, 41 have known genetic variants, but the genes involved in the other 41 have not been identified. Genome sequencing of a few individuals from each family could show dozens of genes that are not known to be associated with MDS or AML but might drive the disease in that family. Figuring out which gene is actually the culprit is tricky. But if other families have the same variant, that gene might be worth studying further.

In summary, the challenges for inherited MDS and AML are:

- It can be hard to identify patients with inherited forms of the disease.
- Clinical guidelines do not say much about how to treat inherited MDS and AML.
- Only three or four inherited genetic mutations have been identified in more than a few families with inherited MDS or AML.
- Several other mutations have been found in some families with inherited MDS or AML, but the link between these mutations and the inherited diseases still needs to be established.
- Sibling stem cell donors for patients with inherited MDS or AML need to be carefully screened to make sure that they do not carry the genetic variants that caused the inherited disease.

Abnormal Bone Marrow Cells, Genetics, and MDS Diagnosis

Dr. Luca Malcovati (University of Pavia, Pavia, Italy) explained that MDS occurs when a patient develops one or more somatic mutations in hematopoietic stem cells. These stem cells proliferate more successfully than healthy stem cells, and abnormal clones of bone marrow cells take over the bone marrow. MDS becomes evident when these immature blood-forming cells do not mature properly and do not turn into healthy blood cells.

Clonal Cytopenia of Undetermined Significance

People with clonal cytopenia of undetermined significance (CCUS) have persistently low counts of at least one type of blood cell that are not explained by any other disease. Dr. Malcovati and colleagues have identified a set of genes

that are often mutated in MDS. Patients with CCUS often have at least one of these mutations. Those with two or more of these mutations are likely to develop MDS or another bone marrow failure syndrome within the next 4 years.

Persistent Anemia in Older Adults

When an older patient has anemia or a low count of white blood cells or platelets, doctors rarely investigate further. Up to 20% of adults aged 70 or older have anemia. In about a third of cases, conventional blood tests do not explain the cause of their anemia, and this condition is usually known as unexplained anemia. Older adults with unexplained anemia tend to have higher levels of abnormal clones and mutation patterns that are closely associated with MDS. At least some of these older adults might have very early MDS based on their genetic profiles.

Clonal Hematopoiesis of Indeterminate Potential

Three large studies have now shown that the formation of abnormal bone marrow clones driven by somatic mutations becomes much more common with age. These mutations are very rare in adults in their 30 and 40s, but up to 20% of older adults might have them. Somatic mutations in *DNMT3A* and *TET2*, in particular, might drive the expansion of abnormal clones during aging.

People with age-related abnormal clones have a significantly higher risk of developing a blood cancer in the next year. In addition, older adults with abnormal clones have an increased risk of dying from any cause, and this increased risk is not completely explained by their higher risk of cancer. In fact, some of the mutations are associated with a higher risk of heart-related complications, for example.

Clonal hematopoiesis of indeterminate potential (CHIP) means that the patient has a somatic mutation associated with MDS or another bone marrow failure syndrome but no other signs or symptoms of MDS, or any other bone marrow failure syndrome.

The available scientific data suggest that CHIP develops when a mutation occurs in a hematopoietic stem cell, most commonly in an epigenetic regulator or a splicing factor gene. Early on, the variant allele frequency (VAF) of the mutation is low, and the abnormal bone marrow clones expand without any signs of MDS. When a second mutation happens, the clones grow, the VAF rises, and the patient develops mild, unexplained blood cell shortages and CCUS. The larger the abnormal clone, the more severe the blood cell shortage. Finally, the VAF rises enough and the clones get large enough to result in MDS. The specific VAF associated with each stage in MDS development probably varies by gene mutation.

In conclusion, analysis of genetic mutations might be useful for:

- Diagnosing patients suspected of having MDS or at higher risk of developing MDS.
- Providing useful information for classification, prognosis, and decisions about treatment.
- Identifying patients with CHIP.
- Diagnosing older patients with unexplained anemia that needs further investigation.

Role of the Immune System and Inflammation in MDS

Dr. Shahram Kordasti (King's College Hospital, London, UK) discussed the role of the immune system in MDS. Normally, the immune system fights off antigens associated with infections or malignant cells. An impaired immune system is believed to play an important role in the development of MDS. The MDS interferes with the proper functioning of the immune system, and, in turn, the impaired immune system helps the disease progress.

T Regulatory Cells

Patients with MDS have a higher proportion of immune suppressor cells known as T regulatory (Treg) cells. These proportions are highest in those with high-risk MDS. Patients who have low-risk MDS but a high percentage of Tregs also have a higher risk of progression to AML and a poorer prognosis.

Dr. Kordasti has used a new technology, mass cytometry, to identify two different types of Tregs in patients with aplastic anemia, another bone marrow failure syndrome, and MDS. His study showed that the frequency of these

types of Tregs can be used to predict responses to immunosuppressive therapies in patients with aplastic anemia. These Tregs might also be useful for predicting disease progression in MDS.

Inflammation and Immune Cell Death

The body uses inflammation to protect itself and its cells from injuries and irritants by rapidly neutralizing the proportion of myeloid-derived suppressor cells (MDSCs), which play a key role in inflammatory responses, rises in the bone marrow of some people with MDS. This seems to interfere with the formation of healthy blood cells and a functioning immune system. Furthermore, patients with high-risk MDS have more MDSCs than those with low-risk MDS.

The death of bone marrow cells, that can produce an immune response, occurs in the development of all types of cancer. When these cells die, proteins that are not usually exposed become available. These proteins present antigens to the immune system, leading to the expansion of T cells. In addition, somatic mutations in certain genes lead to abnormal immune responses.

The combination of the death of bone marrow cells with mutations in some genes leads to low levels of persistent inflammation (also known as "smoldering" inflammation). This inflammation can lead to more alterations in genes and turn cells into cancer cells. As a result, the MDS progresses toward AML.

It is important to develop innovative tests to detect smoldering inflammation at an early stage and potentially prevent disease progression by controlling the harmful inflammation while sparing the healthy immune response. This is the current focus of many cancer immunology research teams around the word.

Treatments for Higher-Risk MDS

Dr. Rami Komrokji (H. Lee Moffit Cancer Center & Research Institute, Tampa, Florida) defined higher-risk MDS as intermediate-2 or high-risk MDS according to the International Prognostic Scoring System. Based on this definition, one third of patients with MDS have higher-risk disease. Dr. Komrokji also reviewed the new definition of higher-risk MDS based on new clinical risk models and somatic gene mutations.

Current Hypomethylating Agents

Treatment for higher-risk MDS typically starts with a hypomethylating agent (HMA). If the patient seems to be eligible for HSCT, the next steps are to find a well-matched donor and assess whether the patient is well enough for the procedure. If so, the transplant takes place. But if not, that patient will probably continue HMA treatment. Patients on HMAs usually take them until they stop working. At that point, only experimental therapies are available.

Azacitidine (Vidaza), an HMA, has been the standard treatment for higher-risk MDS for the last decade based on a clinical trial, published in 2009, showing that this drug increases survival. Patients whose counts of at least one type of blood cell increases with HMAs tend to survive longer. Patients whose disease is stable for several months with azacitidine treatment have a lower risk of death than patients with progressive disease.

The original clinical trials of decitabine (Dacogen), another HMA, did not show that the drug increased survival in higher-risk MDS. But those studies used a different dose than the one doctors use now. More recent data show that median survival with decitabine treatment is close to that with azacitidine in real-world experience. No studies have compared the effects of azacitidine to those of decitabine on survival in patients with higher-risk MDS. Recent research suggests that decitabine can clear P53 mutated clones and might be used as a treatment for patients who have these clones and are waiting for transplant.

Given the large proportions of patients who do not respond or stop responding to HMAs, the field needs to

do a better job of identifying patients who will benefit from HMAs. Other important priorities are expanding rates and durations of responses, as well as finding new drugs, including new HMAs.

Predicting Response

No existing clinical tools predict which patients will respond to HMA treatment or the outcomes when HMAs do not work. Patients with a mutation in the *TP53* gene are more likely to respond to HMAs than patients without this mutation, and outcomes are similar or better than with intensive chemotherapy. Unfortunately, outcomes are still poor in patients with a *TP53* mutation. Some studies have found that response rates to HMAs are somewhat higher in patients with a *TET2* mutation and wild-type *ASXL-1*.

Once disease progresses during HMA treatment for higher-risk MDS, the outcomes are typically poor. Patients who never respond to HMAs tend to survive only 5 or 6 months. Those who respond at first but then stop responding survive about 7 months. Their outcomes might be better if they have HSCT or enroll in a clinical trial.

New HMAs, Combination Treatments, and Novel Treatments

Studies are testing new forms of HMAs (including oral azacitidine, oral decitabine, and SGI-110). Several studies have added different therapies to HMAs but have not found these combinations to be beneficial. More studies of promising combinations with azacitidine are ongoing, including combinations with checkpoint inhibitors and antiapoptotic agents (such as venetoclax [VENCLEXTA]). Studies are also using new types of treatments, such as splicing inhibitors, p53 modulators, and IDH-1/2 inhibitors, in certain groups of patients who have the genetic mutations that these treatments target. Finally, the U.S. Food and Drug Administration has recently approved CPX-351 (Vyxeos), a new formulation of two traditional chemotherapy drugs, daunorubicin and cytarabine, for secondary and treatment-related AML.

How to Improve the Timing of Stem Cell Transplantation for MDS

Dr. John Koreth (Dana-Farber Cancer Institute, Boston, Massachusetts) explained that HSCT is the only curative treatment for MDS. Even in patients with high-risk MDS, this procedure can lengthen survival. About 1,000 to 1,500 patients with MDS undergo HSCT in the United States every year.

HSCT Timing

The timing of HSCT is a complicated issue. For patients who are younger than 60 or 65, studies that used mathematical modeling found that the best timing depends on the International Prognostic Scoring System (IPSS) category. For patients with intermediate-2 risk or high-risk MDS, HSCT soon after diagnosis maximizes life expectancy. But for those with low-risk or intermediate-1 risk, delaying HSCT for a few years lengthens survival, as long as the HSCT is done before the MDS progresses to AML.

For patients aged 60–70 years, some mathematical modeling evidence shows that HSCT with reduced-intensity conditioning does not extend life expectancy in patients with low-risk or intermediate-1 risk MDS. But for patients with intermediate-2 or high-risk MDS, survival is longer with HSCT than with HMA treatment.

Data from a recent study that evaluated outcomes in patients aged 50–70 years with MDS found that about twice as many patients who underwent HSCT survived for at least 4 years as those who had other treatments. Ongoing clinical trials are comparing the outcomes of HSCT with reduced-intensity conditioning to other treatments in patients with MDS.

Conditioning Treatments

Studies are also assessing different types of conditioning treatment for HSCT. A 2017 phase III clinical trial in 129 patients with MDS or AML found that relapse risk and survival were similar in patients treated with standard conditioning and those with reduced-intensity conditioning. But another phase III trial in 272 patients

with MDS or AML found that patients with MDS who were treated with reduced-intensity conditioning had a higher risk of relapse, although overall survival was similar for both conditioning regimens. The authors concluded that standard-intensity conditioning might be the best option for younger, healthier patients.

Predicting Outcomes

Researchers have studied the ability of different MDS classification systems to predict outcomes after HSCT. Both the IPSS and revised IPSS (IPSS-R) predicted survival and relapse after HSCT in a study of 374 patients with MDS and 145 with AML. Whether patients had certain abnormalities in their chromosomes also, and independently, predicted their likelihood of surviving and having a relapse.

Mutations in certain genes can also be used to predict outcomes. For example, patients with mutations in *TP53*, *RAS* pathway mutations, or a combination of these mutations do not seem to survive as long after HSCT as patients without these mutations.

Dr. Koreth concluded that HSCT is an underused curative therapy for MDS. He suggested basing decisions about HSCT on patient characteristics, disease severity, and gene mutations. Finally, he recommended considering patient fitness and disease characteristics in decisions about conditioning intensity.

List of Acronyms

AML: acute myelogenous leukemia

HMA: hypomethylating agent

HSCT: hematopoietic stem cell transplant

IPSS: International Prognostic Scoring System

IPSS-R: revised International Prognostic Scoring System

MDS: myelodysplastic syndromes

WHO: World Health Organization

Glossary of Terms

Acute myelogenous leukemia *(AML, also known as acute myeloid leukemia)***:** A rapidly growing disease in which the bone marrow and blood have too many myeloblasts (immature white blood cells)

Anemia: Low levels of red blood cells or hemoglobin, a protein in red blood cells that transports oxygen

Antibody: Protein made by the immune system that defends the body from a specific type of antigen

Antigen: Substance (e.g., chemical, bacteria, pollen, or virus) that the body's immune system does not recognize

Aplastic anemia: Failure of bone marrow to make enough blood cells

Bone marrow failure: Failure of bone marrow to produce blood cells

Clones: Abnormal copies of immature blood cells

Conditioning treatment: Used to kill all remaining cancer cells before stem cell transplantation

Epigenetic: Change in the chemical structure of DNA that does not change the DNA coding sequence

Hematopoietic stem cells: Stem cells in the bone marrow that form blood cells

Hematopoietic stem cell transplant (HSCT): Infusion of healthy hematopoietic stem cells from a healthy donor with the same HLA (immune system) markers as the patient. The donor's stem cells (known as a graft) enter the bone marrow, where they form healthy blood cells.

Hypomethylating agents (HMAs): Category of drugs—including azacytidine (Vidaza) and decitabine (Dacogen)—that block the methyl groups attached to genes needed for normal blood cell development, preventing the silencing of certain genes involved in controlling cancer, and allowing normal functioning of tumor-suppressor genes

Immune system: Enables the body to defend itself from foreign substances (such as viruses and bacteria).

Immunosuppressive therapy: Drugs to weaken the patient's immune system, stop it from attacking the bone marrow, and help the bone marrow make more healthy blood cells.

International Prognostic Scoring System (IPSS): Often used by doctors to classify MDS severity

Monosomy 7: Only one copy, not the usual two copies, of chromosome 7

Penetrance: Proportion of people with a particular genetic change (such as a mutation in a specific gene) who exhibit signs and symptoms of a genetic disorder

Reduced-intensity conditioning: Use of lower doses than typical conditioning treatments to potentially make HSCT safer

Revised IPSS (IPSS-R): Takes more information into account than the IPSS and categorizes patients into five risk groups instead of four

Somatic mutation: Change in a gene that happens after conception in a patient's cells, is not inherited, and is not passed on to the patient's children

Splicing factor: Gene that controls the splicing together of certain sequences in RNA to form messenger RNA molecules. Messenger RNA contains the genetic coding information needed to make proteins.

T regulatory (Treg) cells: Control the activity of other T cells, which are a type of white blood cell that helps protect the body from infection

Variant allele frequency: Frequency of selected mutated genes

Wild-type gene: natural, nonmutated (unchanged) form of a gene

More than 20 years ago, the MDS Foundation, Inc. was established by a group of global physicians and researchers to provide an ongoing exchange of information relating to MDS. Until the Foundation was created, no formal organization had been devoted solely to MDS. Due to a persistent rise in awareness and diagnosis of MDS, as well as continued growth in the research efforts surrounding MDS, the need for our Foundation has only increased over time.

Each year we continue to expand our reach worldwide to meet the many growing needs of the patients and families affected by myelodysplastic syndromes, as well as the healthcare professionals who dedicate their lives to caring for these patients, and researching treatment options and a cure for this disease.

WE UNDERSTAND WHAT IS IMPORTANT…

For the newly diagnosed patient, offering a balance of education and gentle support, coupled with empowering each patient and caregiver with the tools to self-manage their disease and seek the best options for treatment.

For our healthcare professional partners, offering educational programs that include the latest updates in MDS research, direct access to international working groups dedicated to the study of MDS and MPNs, and, when possible, the funds needed for this research.

For our industry partners, the sharing of information related to treatments and clinical studies, while also working to incorporate the much needed patient voice into these clinical studies. Overall, creating an environment where patients, families, and professionals effectively work together towards the common goals of better treatment options, improved quality of life, and eventually a cure for MDS.

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