



Aplastic Anemia & MDS
International Foundation

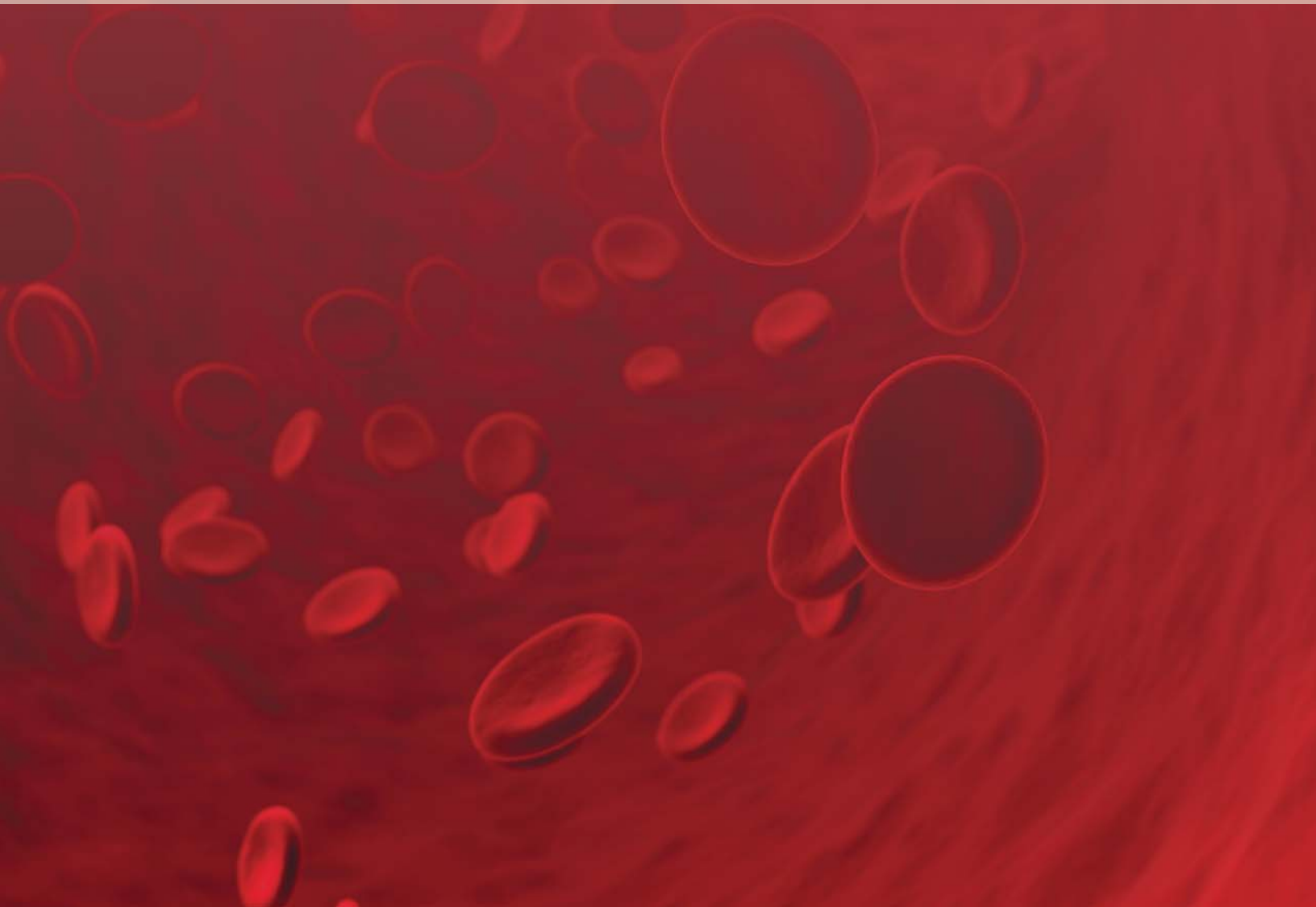


BONE MARROW FAILURE DISEASE
SCIENTIFIC SYMPOSIUM 2010

Building a Collaborative Research Community That Saves Lives



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Aplastic Anemia & MDS International Foundation

Dear Friends,

It is with great pleasure that we present this patient summary of the presentations at the Aplastic Anemia & MDS International Foundation (AA&MDSIF) *Bone Marrow Failure Disease Scientific Symposium* held March 11 & 12, 2010 in Bethesda, Maryland. This symposium brought together virtually all of the world's experts on the biology and treatment of aplastic anemia, myelodysplastic syndromes, paroxysmal nocturnal hemoglobinuria and related disorders. It was a very special opportunity for us to focus on these diseases, consider what is known, and explore new and emerging ideas and directions.

The Aplastic Anemia and MDS International Foundation is committed to providing patients and their families with answers, support and hope. While each of our programs and services touches all three, research is the program which most inspires hope. In addition to helping secure more than \$9 million in new federal research funding these past three years, we are proud to have awarded nearly \$3 million in research grants to over 40 researchers to advance the study of bone marrow failure. We are very pleased that several of these researchers attended the Scientific Symposium as both panelists and participants.

We are most grateful to the co-chairs of this event, Richard Stone, MD and Neal Young, MD, for their leadership and to the outstanding committee with whom they worked to plan and organize this Symposium. We greatly appreciate the internationally respected group of speakers the committee assembled whose presentations stimulated discussion and provided new insights to enhance bone marrow failure research.

This Symposium would not have been possible without the sponsorship of the National Heart, Lung and Blood Institute and the NIH Office of Rare Diseases Research, and the generous contributions from private industry.

The collaborative effort of government, academia, private industry and AA&MDSIF demonstrates the mutual commitment to the discovery of new treatments for patients, and ultimately, cures for bone marrow failure diseases.

We encourage you to read these summaries to learn more about bone marrow failure diseases and the most promising directions for future research.

Sincerely,

Neil H. Horikoshi, Esq.
Chairman, Board of Directors

John M. Huber
Executive Director

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SYMPOSIUM INFORMATION

Purpose of the Symposium

The AA&MDSIF Bone Marrow Failure Disease Scientific Symposium, "Building a Collaborative Research Community That Saves Lives," was held on March 11-12 in Bethesda, Maryland. The symposium gathered over 120 participants to hear more than 30 of the world's leading researchers on aplastic anemia, myelodysplastic syndromes (MDS) and paroxysmal nocturnal hemoglobinuria (PNH) share the latest findings, discuss current areas of controversy, and propose specific recommendations for the highest priority directions for basic and clinical research needed to advance the field.

Aplastic anemia, MDS, and PNH are rare diseases that all result in bone marrow failure. Once considered distinct, these three diseases are now believed to be linked by similar pathophysiologies. Exploration of current research issues in aplastic anemia, MDS, and PNH would greatly benefit from increased collaboration between basic and clinical scientists and between scientists studying the individual diseases. Increased understanding of the molecular events driving these diseases and of the response to treatment are needed to define at-risk populations and improve current therapies.

The exchange of ideas and opinions on current research that occurred at the symposium is resulting in collaboration among investigators toward new understanding of the diseases, networks to further individual research, and new approaches on how to transform findings into treatments.

Key Findings

Several important clinical and scientific advances made recently in bone marrow failure disease research were identified at the symposium. These included:

- New directions for immune therapy in aplastic anemia and MDS;
- Genetic and epigenetic defects identified in MDS that may lead to novel targeted therapies in the near future;
- Better understanding of the immune and non-immune disease mechanism in aplastic anemia, especially in the field of telomere biology;
- The design and role of stem cell transplantation in aplastic anemia and MDS;
- New pathways for the development of combination therapies for patients with MDS;
- The promising effectiveness of the anti-complement treatment for PNH and the role of stem cell transplantation as a curative option for PNH patients.

These findings and other new insights resulting from the symposium will have an impact on both research and improved patient care for years to come.

Symposium Planning Committee



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GENERAL INFORMATION

Aplastic Anemia & MDS International Foundation



Aplastic Anemia & MDS International Foundation

The Aplastic Anemia & MDS International Foundation is the world's leading non-profit health organization dedicated to supporting patients and their families living with aplastic anemia, MDS, PNH and related bone marrow failure diseases. AA&MDSIF provides answers, support and hope to thousands of patients and their families around the world. Founded in 1983, the Aplastic Anemia & MDS International Foundation is celebrating nearly 30 years of service as a recognized and respected leader in patient education, advocacy and research.

What AA&MDSIF Does

- Provides education and support to patients and their families through news updates and plain language materials, Online Learning Center, Peer Support Network, conferences, community events, and more
- Funds medical research to find better treatments and cures for aplastic anemia, MDS and PNH
- Advocates for increased federal funding of bone marrow failure disease research
- Promotes public awareness of bone marrow failure diseases
- Educates medical professionals on the most up-to-date information about these diseases, their diagnosis and treatment

Dear Patients, Families and Friends,

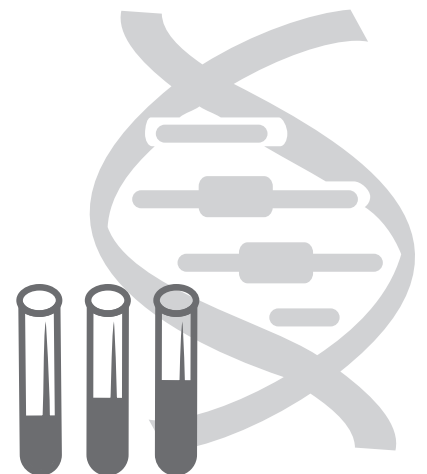
You can help make more research grants and programs possible! Want to help fund research into better treatments and a cure? Consider donating or raising funds to create a named fund to provide a research grant, or to provide patient education, support, advocacy or awareness programs. Please contact me to learn more about making a gift to support the programs of AA&MDSIF which help patients and families fighting bone marrow failure diseases. Thank you, and thanks to everyone who has contributed to make this research possible.

Sandra Walter-Steinberg
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Current and past AA&MDSIF research grant recipients (left to right): Dr. Archibald Perkins, Dr. Lisa Minter, Dr. Monica Bessler, Dr. Jaroslaw Maciejewski, Dr. Kazuhiko Ikeda, and Dr. Antonio Risitano.

answers
support &
hope



Genetics and Epidemiology of MDS

Chair: **Pamela Becker, MD, PhD, University of Washington**

Unfit Stem Cell Pools and Risk of MDS



Grover Bagby, MD
Oregon Health & Sciences University

Hematopoietic, or blood-forming, **stem cells** in the **bone marrow** balance the need to make copies of themselves with the need to develop into red cells, white cells, and platelets. Mutant stem cells that lose some of these capacities can lead to the myelodysplastic syndrome (MDS).

MDS begins when an early genetic change in a bone marrow stem cell enables that cell to grow and survive better than the stem cells around it. As a result, this one mutant stem cell expands and crowds out the normal stem cells. Later on, additional mutations, or changes in genes, occur that can stop stem cells from turning into blood cells.

Until recently, scientists assumed that the non-mutant stem cells in the marrow are otherwise perfectly normal. However, research over the last decade has cast doubt on this theory. Mutations known to be associated with MDS and leukemia can be found in 1% of blood samples from the umbilical cords of newborns, virtually none of which developed MDS or leukemia later in life. These mutations are not enough to cause MDS and AML; something else has to happen. The additional events may be those that damage stem cells. In this case, the initial genetic mutation in the cell is benign, or harmless, until some event occurs in the cell's environment that results in stem cell damage and inflammation. Here the mutant stem cell may be resistant to stem cell damage and as a result it can take over the bone marrow. In effect, stem cell damage and inflammatory response makes it harder for normal cells to grow and survive, but at the same time encourage the expansion of the mutant clone that is resistant to these factors.

Several studies support this view, including a study that exposed hematopoietic stem cells (HSCs) from mice with and without **Fanconi anemia** to **tumor necrosis factor (TNF)**, which causes the HSCs to die more quickly than normal. The cells from the

animals with Fanconi anemia were sensitive to the TNF α for the first three weeks, as expected. However, after three weeks, the small number of cells that survived stopped responding to the TNF α . When the researchers implanted these cells into otherwise normal mice, the mice developed MDS and AML. The researchers concluded that TNF α creates a good environment for the growth of mutant Fanconi anemia stem cells.

This line of research shows that a drug that could reduce the damage inflicted by the inflammatory response should reduce the ability of mutant stem cells to grow (they would have no competitive advantage). This would allow researchers, for the first time, to design strategies to prevent MDS and AML in patients at high risk of these diseases.

The Spectrum of Telomere Biology Disorders: Dyskeratosis Congenita and Beyond



Sharon Savage, MD, National Cancer Institute

Dyskeratosis congenita (DC) is an inherited bone marrow failure and cancer predisposition syndrome characterized by very short telomeres. Telomeres are located at the ends of chromosomes and are required for chromosomal stability. They shorten with each cell division and are a marker of normal aging. When their telomeres become very short, normal cells can no longer divide and they typically die. Some cells overcome this and survive despite having critically short telomeres and chromosomal instability.

To date, researchers have identified six genes that, when mutated, can cause DC. Mutations in the dyskerin gene cause X-linked DC - the X chromosome carries Dyskerin and the person must inherit the gene from both parents to develop the disease. Dyskerin regulates telomerase, an enzyme that maintains telomere length. Dyskerin is an X-linked, **recessive gene**. Researchers have also identified autosomal dominant (TERT, TERC, and TINF2) and recessive genes (NOP10 and NHP2) which can also cause DC that are not located on the X or Y sex chromosomes. In spite of this progress, however, about 40% of all patients with DC do not have one of the genes known to be associated with the disease.

The National Cancer Institute (NCI) is conducting a detailed clinical and genetic study of people with

inherited bone marrow failure syndromes, including DC, and their families (<http://marrowfailure.cancer.gov/>). Researchers used one family with several individuals who had very short telomeres but different clinical features to determine that mutations in the TINF2 gene cause DC. Approximately 25% of people with DC in the study have the TINF2 genetic mutation.

The NCI study also conducted the first detailed analysis of cancer risk in patients with DC. About half of the people with DC in the study develop cancer by age 50. The most common cancers are tongue squamous cell cancer, MDS, and AML. Most (85%) of people with DC in the study have moderate-to-severe bone marrow failure. Ongoing research includes more detailed clinical characterization of patients and gene discovery.

A Snapshot of Myelodysplastic Syndrome in the United States, 2010



Mikkael Sekeres, MD, MS, Cleveland Clinic, Co-Chair, AA&MDSIF Medical Advisory Board

Every year, 3.4 out of every 100,000 people in the United States, or 10,000 people, receive a new MDS diagnosis. These rates are similar to those of England, Germany, and Sweden, but much higher than in Japan. Researchers have not yet identified how many people in the United States currently have MDS. However, assuming that the U.S. rate is similar to that found in a German study, about 60,000 people in the United States are currently living with MDS.

A person's likelihood of developing MDS increases dramatically as he or she gets older, especially after the person reaches age 70. Males are slightly more likely than females and whites are much more likely than blacks to get MDS. Although MDS can be classified into different subtypes, doctors have not identified the subtype in more than half of all patients.

A survey of 101 doctors found that the about half of patients were older than 71 when they received their MDS diagnosis. Approximately 90% of patients with MDS had primary MDS; the remaining 10% had secondary MDS (MDS that happens after the person was exposed to certain poisonous chemicals or to radiation). Most patients with secondary MDS developed the disease after receiving chemotherapy for cancer, but some got the disease after getting

radiation treatment, smoking for several years, or being exposed to certain chemicals. Most patients with MDS have lower risk disease, meaning that the disease is not likely to get worse.

According to the survey, by far the most common treatment for MDS is **erythropoietin-stimulating agents*** (ESA); 58% of doctors reported using ESAs to treat patients who had recently been diagnosed with MDS. Much smaller proportions of doctors used azacitidine (16%), white cell growth factors (10%), Revlimid® (lenalidomide) (8%), Dacogen® (decitabine) (2%), or Thalomid® (thalidomide) (1%). Fewer than 5% of doctors had talked to their patients with MDS about stem cell transplantation and clinical trials.

An email survey of people with MDS found that of the 358 who responded, 55% did not know their International Prognostic Scoring System (IPSS) score (used to assess MDS severity), 42% did not know the percentage of blast cells (immature cells found in high rates in people with high-risk MDS) in their bone marrow, and 28% did not know their cytogenetic status (whether their cytogenetic, or chromosome, abnormalities were complex or simple based on the number of abnormalities). Most patients (80.2%) reported that their doctors had first described their MDS as a bone marrow disorder and/or as anemia (56.4%); only 7.3% of patients had been told they had a cancer and 5.9% reported that their doctor had mentioned leukemia when explaining MDS.

(Note: The results of this MDS Patient Survey will be used by AA&MDSIF to develop a self-advocacy initiative for patients and an outreach campaign to community-based hematologists/oncologists.)

Epidemiology of MDS



Sara Strom, PhD, M.D. Anderson Cancer Center

Myelodysplastic syndromes (MDS) are a group of hematologic conditions common in older populations. However, there is a lack of reliable data concerning the **epidemiology*** and **etiology*** of MDS due to problems with reporting and classification, which have made large-scale population-based studies difficult to conduct.

While chemotherapy and radiation therapy are well-established risk factors for secondary MDS, risk

factors for **de novo MDS**, which account for the majority of cases, have not been fully elucidated. A variety of risk factors have been linked with increased (smoking and exposure to solvents and agrochemicals, obesity) or decreased risk of de novo MDS (wine drinking), but the etiology for the majority of cases remains unknown. The well established association between cigarette smoking and MDS risk seems to be related to intensity and duration of smoking with an effect that persists up to 15 years after smoking cessation.

At MD Anderson Cancer Center, Dr. Strom has conducted a study comparing characteristics on 354 de novo MDS patients to 452 healthy individuals to identify potential risk factors. Of these patients, 69% were male and 94% were white. Results showed that men and women who smoked at the time of the study as well as those men who reported occupational exposure to solvents and agricultural chemicals were at had a significant higher risk of developing MDS. This study also found that drinking up to one and a half glasses of red wine a day significantly reduced MDS risk.

Strom's research also shows that people with MDS who do not smoke live longer than those who do smoke. Interestingly, although people who are obese have a higher risk of getting MDS, they tend to live longer than people who are not obese. Large multi-institutional studies are needed to learn about what causes MDS and the genetic factors that increase susceptibility.

Genetics/Immunobiology of Aplastic Anemia and Paroxysmal Nocturnal Hemoglobinuria (PNH)

Chair: **Neal Young, MD**, National Heart, Lung and Blood Institute

Dysregulated T Cell Hemeostasis in Bone Marrow Failure



P.K. Epling-Burnette, PharmD, PhD,
H. Lee Moffitt Cancer Center

Patients with aplastic anemia, and paroxysmal nocturnal hemoglobinuria (PNH) and some patients with MDS develop bone marrow failure

because of a disturbance in the immune system that protects the body from disease. Researchers currently believe that autoreactive T cells, a type of **white blood cell** that attacks the body's own cells or tissues, cause the bone marrow to produce fewer blood cells in patients with cytopenia (a shortage of blood cells) that results from changes in the immune system. According to this view, reducing the number of these T cells or suppressing the immune system should restore bone marrow function to normal in these patients.

Dr. Epling-Burnette examined samples from 20 patients with MDS who were treated with horse antithymocytic globulin (ATG), which suppresses the immune system. Patients who had a lower ratio between two types of T cells, known as CD4-positive and CD8-positive T cells, before treatment because they had lost many of their CD4-positive cells were more likely to respond to equine ATG.

In another study, Dr. Epling-Burnette treated 23 patients with rabbit ATG, and the blood cell counts in 7 patients returned to normal levels. Dr. Epling-Burnette then used the CD4/CD8 ratio and the presence of Ki67, a marker of cell growth, to identify patients whose MDS would respond to equine or rabbit ATG. Patients with a high CD4/CD8 ratio and the absence of Ki67 had a 10% likelihood of responding, but those with a low ratio and the presence of Ki67 had a 77% chance of responding to the ATG. The percentage of patients that responded to the rabbit and equine forms of ATG were similar.

Knowing a person's T cell characteristics and what happens when the activity of these cells is stimulated might be useful for predicting whether a patient's MDS will respond to therapies that suppress the immune system.

Telomere Dysfunction in Bone Marrow Failure



Rodrigo Calado, MD, PhD, National Heart, Lung and Blood Institute

Telomeres, or regions at the ends of chromosomes, get shorter as people get older. Telomeres are very short in people with aplastic anemia and other bone marrow failure syndromes. Mutations, or changes, in genes, including the telomerase gene, are responsible for the shortening of telomeres. The telomerase gene controls the telomerase enzyme, which plays an important role in cell division and growth. However,

90% of patients with acquired aplastic anemia, whose disease resulted from exposure to certain environmental factors, do not have the telomerase gene mutation.

An analysis of data on 200 patients with acquired aplastic anemia showed that patients with the shortest telomeres did not survive as long as those with longer (or at least less short) telomeres. Patients with shorter telomeres were also much more likely to experience a relapse and the spread of malignant, or unhealthy, cells.

Cells from the bone marrow of patients with a aplastic anemia who have shorter telomeres have more bone marrow cells that lack a specific chromosome. By collecting and growing cells from the bone marrow before these patients are treated, researchers can tell whether the cells have the abnormal chromosomes that people with longer telomeres do not have.

Having short telomeres, regardless of whether the telomerase gene has a mutation, might increase the likelihood that a person's aplastic anemia will turn into cancer. Patients with DC, for example, whose telomeres are very short, have a cancer risk that is 200 times as high as healthy people. This is further evidence that people with short telomeres or whose telomerase does not work properly are more likely to get certain kinds of cancer, including AML.

Telomerase activity explains why treatment with androgen, a male sex hormone, works for some cases of bone marrow failure. Telomerase is more active in the cells that create blood cells when androgen is present. Estradiol, a female sex hormone, also increases telomerase activity in these cells.

Immune Pathophysiology of Myelodysplasia (MDS): Implications for Treatment



Elaine Sloand, MD, National Heart, Lung and Blood Institute

Drugs that suppress the immune system stop activated lymphocytes, a type of white blood cell, from suppressing with the production of healthy blood cells. Studies show that suppressing the immune system improves bone marrow function in about 20–30% of patients with MDS.

Anti-thymocyte globulin (ATG) and **cyclosporine*** are two treatments that doctors inhibit lymphocytes. In a National Institutes of Health (NIH) study, 129 patients with MDS were treated with ATG alone, ATG in combination with cyclosporine, or cyclosporine alone. Overall, 30% of patients responded. Younger patients, those with a low IPSS score, those with the HLA-DR15 gene, and those receiving the combination of ATG and cyclosporine were more likely to respond. When compared to patients in another study treated with supportive care (transfusions and growth factors), patients treated with immunosuppression survived longer.

Many patients required long-term administration cyclosporine in order to maintain their response. In an attempt to produce more long-lasting effect, a study using **Campath® (alemtuzumab)*** an antibody which is more immunosuppressive than horse ATG was initiated. Patients more likely to respond to immunosuppression were enrolled in the study (younger patients and those with HLA-DR15).

Fifteen of 22 (68%) evaluable int-1 patients and two of seven (29%) evaluable int-2 patients responded within 3 months of treatment becoming transfusion independent. Five of seven evaluable responders with chromosomal abnormalities had normal **cytogenetics*** by one year after treatment. Five of eight (62%) responding patients evaluable at 12 months had normal blood counts and seven of eight (89%) were transfusion-independent.

Paroxysmal Nocturnal Hemoglobinuria: Unraveling the Complement Cascade in the Era of Complement Inhibitors



Antonio Risitano, MD, University of Naples, Italy

Soliris® (eculizumab) is the first and only approved therapy for paroxysmal nocturnal hemoglobinuria (PNH) treatment in the United States. Eculizumab blocks complement protein attacks on blood cells and prevents hemolysis (destruction of red blood cells). Complement proteins are part of the immune system, which protects the body from disease. By preventing hemolysis, eculizumab reduces anemia in people with PNH. However, even if the drug inhibits hemolysis in all patients, its clinical benefit is quite heterogeneous among patients.

SUMMARY FOR PATIENTS

Three Phase III clinical trials found that eculizumab decreases patients' need for blood transfusions and decreases anemia in patients with PNH. The drug also reduces fatigue, pain, and shortness of breath. Researchers also believe that the drug might reduce the risk of thromboembolism, or blood clots in the blood stream, in patients with PNH.

Dr. Risitano and colleagues have identified a reason that could explain why some patients with PNH who are treated with eculizumab still have anemia. When patients are treated with eculizumab, they accumulate complement component 3 (C3) fragments on their red blood cells. C3 plays a major role in the immune system and may account for an alternative method of red cell destruction in these patients. The presence of C3 fragments on cells might be an additional target for PNH treatment.

Dr. Risitano has also started to study a novel approach to protect blood cells from complement protein attacks. TT30 is a recombinant fusion protein that can protect blood cells from attacks by complement protein, targeting C3. Dr. Risitano exposed red blood cells from patients with PNH to TT30, showing that TT30 completely prevented hemolysis in this in vitro model. In the same model, eculizumab decreased hemolysis to about 30%, whereas TT30 completely prevented hemolysis. TT30 could play an important role in the development of PNH treatments.

Pathophysiology/Molecular Targets in MDS

Chair: **Jaroslav Maciejewski, MD, PhD, Cleveland Clinic**

Genomics of MDS



Jaroslav Maciejewski, MD, PhD,
Cleveland Clinic, AA&MDSIF Medical
Advisory Board Member and Research
Grant Recipient

Acquired gene mutations, chromosomal breaks, and inherited gene variants may contribute to the development of MDS. In recent years, many modern techniques and instruments have emerged to investigate these changes. Researchers are using these new technologies to better understand the biology of MDS and the reasons why the disease causes such a wide spectrum of different symptoms in different people.

Various inherited genetic variants may play a role in the development of MDS. They can either increase a person's chances of developing MDS or determine the subtype of a person's MDS. Furthermore, different mutations and combinations of mutations acquired by bone marrow stem cells from which MDS can promote development of this disease. By combining technologies to study genetic variants and mutations in patients with MDS, researchers can better define the nature of the underlying defect in MDS. These technologies will be increasingly used as diagnostic tools in the clinic.

Whole Genome Sequencing in MDS



Timothy Graubert, MD, Washington
University in St. Louis

Traditional gene-sequencing technologies allow researchers to examine one gene at a time to find mutations. This approach is very expensive and cumbersome. Dr. Graubert has used whole-genome sequencing to identify new genetic mutations, or changes, that play a role in the development of MDS. Whole-genome sequencing is a laboratory process that maps out the person's entire DNA sequence.

To understand the role of certain genetic mutations in MDS, researchers need to understand the role of changes that the person inherited from his or her parents, as well as those that the person acquired after birth. It is also important to identify these mutations across their entire size spectrum, from single DNA bases to millions of bases.

Whole-genome sequencing lets researchers identify many variants in the patient's genes, but most are just 'bystanders'. Dr. Graubert therefore compares the variants he finds with the frequency of similar variants in samples from other patients to figure out which variants are relevant to MDS.

Characterizing a pair of genomes costs about \$50,000 today, but costs will probably drop to \$10,000 within a year. Given funding limits, Dr. Graubert expects to be able to sequence only about 10 genomes in the current phase of the project. Dr. Graubert therefore had to prioritize which patients with MDS to include in these genome-sequencing studies. He decided to focus on patients whose disease has evolved to AML and those who depend on transfusions.

Dr. Graubert is still analyzing the results of his first genome-sequencing studies. However, he has identified and confirmed 22 variants in genes. The greatest challenge in the future for this research will be figuring out which mutations play an important role.

Hematopoietic Stem Cell Biology



Stephen Nimer, MD, Memorial Sloan-Kettering Cancer Center, AA&MDSIF Medical Advisory Board Member

Researchers have compared MDS cells to normal bone marrow cells to find out which mutations, or changes, in genes play a role in initiating MDS. Because of the uniqueness of all human beings, it is actually necessary to compare the DNA in the MDS cells to normal cells from the same person, in order to determine which mutations are acquired vs. which changes in the gene structure are present at birth. Similar research strategies are being applied to shed light on why some people's MDS is stable for decades, in others the disease quickly progresses to AML.

Another important development in MDS research is the availability of several accurate mouse models of MDS. Dr. Nimer and other researchers are using MDS mouse models to understand how MDS stem cells gain an advantage over normal cells and take over the bone marrow. His research is also focused on how to better eradicate the MDS cells in the bone marrow and spare the normal cells. He has defined the role for one gene, called MEF in this process, as mice that lack the MEF gene are largely spared from the bone marrow toxicity of cancer chemotherapy drugs such as 5-fluorouracil (5-FU). While the normal mice develop a shortage of neutrophils after 5-FU (a type of white blood cell that fights infection) and most do not survive, all of the mice that lack MEF survive. This research suggests that cancer cells that lack the MEF gene can resist chemotherapy, but also that if we can lower the level of MEF in bone marrow cells we can lessen the side effects of cancer chemotherapy.

To investigate why cells that lack MEF are relatively resistant to chemotherapy, the Nimer lab determined that the MEF-knockout mice had high levels of p53, a protein that suppresses tumor formation. So Dr. Nimer created a mouse model where both MEF and p53 were lacking, and under these circumstances, when Dr. Nimer exposed cells from the double-knockout mice to radiation (or chemotherapy), the

cells died at a normal rate, even though cells from the p53-knockout mice were less sensitive to radiation. Dr. Nimer explained that this is because the bone marrow stem cells in the MEF-knockout mice are more quiescent (sleeping) than normal, whereas in the double-knockout mice the percentage of stem cells that are quiescent reverted to normal. This shows that the state of quiescence is largely responsible for determining the response to therapy.

Dr. Nimer is exploring ways to use these findings to figure out how to make bone marrow cells in patients with MDS less quiescent and thus more sensitive to chemotherapy. These strategies could also be used to make the cells more sensitive to radiation therapy.

The Differentiation Context of MDS/AML Self-Renewal May Enable Non-Cytotoxic Epigenetic Therapy that Sparing Normal Stem Cells



Yogen Saunthararajah, MD, Cleveland Clinic

The process by which MDS or AML cells take over the bone marrow is known as self-renewal. An important goal of research is to understand this mechanism of self-renewal in MDS and AML cells and if there are differences between the mechanisms of self-renewal in MDS and AML cells and normal stem cells. Our research together with research, by others suggests that there is indeed a difference between the mechanisms of self-renewal in MDS/AML cells and normal stem cells. Most importantly, this difference can be used to develop treatment that destroys the MDS and AML cells without destroying normal stem cells. Basically, we use the currently available drug decitabine to open the DNA packaging in MDS and AML cells as well as normal stem cells. In the MDS and AML cells, opening DNA packaging makes the cells specialize into more normal blood cells and stop dividing. In contrast, opening the packaging in normal stem cells makes more normal stem cells which continue to divide. The pathway or mechanism used to destroy the MDS and AML cells is called differentiation and does not rely on genes such as p53, which are frequently mutated in MDS and AML cells. So in addition to destroying the MDS and AML cells without destroying normal stem cells, this approach to treatment is different from most standard treatments, suggesting it is an important alternative.

SUMMARY FOR PATIENTS

Although decitabine is currently used to treat MDS and AML, our results suggest a logical basis for using it in a different sort of way that could be less toxic and possibly more effective. Experiments in mice suggest that this may be the case but we need to explore this further with clinical trials. The first clinical trial of the suggested approach will begin at Cleveland Clinic shortly.

The self-renewal of AML cells is different from the self-renewal of normal HSCs, which make blood cells in the bone marrow. Normal self-renewal occurs in stem cells (which can turn into different types of mature blood cells). In contrast, AML cells have trouble differentiating, or becoming a more specialized type of cell. As a result, AML cells renew themselves in lineage-committed cells, or cells that can only develop into one type of blood cell, instead of stem cells. Understanding why and how this happens could help researchers reverse this process to stop the AML cells from self-renewing.

Do Epigenetically Targeted Drugs Target Epigenetics?



Steven D. Gore, MD, Johns Hopkins Medical Center

Researchers have long described the effectiveness of drugs, such as azacitidine, that interfere with the DNA methyltransferase (DNMT) enzyme in patients with MDS. The results of these studies seem to indicate that methylation, a chemical process, plays an important role in the development of MDS.

Several clinical trials have used a DNMT inhibitor and a human histone deacetylase (HDAC) enzyme inhibitor in patients with MDS. The purpose of these studies was to find out whether reversed methylation of four genes during the first treatment cycle indicates that the patient's disease is likely to respond to the treatment. These studies showed that reversed methylation of one of these genes had no association with whether a patient's disease responded to the treatment.

Other research shows that methylation does not completely explain what happens in MDS. The fact that p21, a non-methylated gene, is also involved in MDS means that DNA damage also plays an important role. Additional studies show that DNMT and HDAC inhibitors separately and together damage DNA.

A very recent study using a different approach found that patients who were treated with DNMT and HDAC inhibitors and who responded to the treatment had more methylation activity in the SOCS gene than patients whose disease did not respond. This study and others are leading to the identification of several genes that are active in people whose disease responds to treatment and not in those whose disease does not respond.

Insights into the Molecular Basis of the 5q- Syndrome



Benjamin Ebert, MD, PhD, Harvard Medical School, Brigham and Women's Hospital

Patients with 5q- syndrome, a type of MDS, have a deletion (loss) of the long (q) arm of chromosome 5. Patients with this syndrome tend to have anemia that does not respond to treatment, normal or high levels of platelets, and normal or low levels of neutrophils. The disease is more common in females than males, and it rarely progresses to AML.

Researchers have identified many genes that play a role in 5q- syndrome, including RPS14, a **ribosomal gene**® that plays a role in manufacturing proteins. Studies in mice have shown that having only one copy of a ribosomal gene (so that the gene does not produce enough protein) can increase the activity of the p53 gene. The p53 gene prevents tumors from growing. Increasing p53's activity hampers its ability to function properly, leading to a loss of red blood cells.

Dr. Ebert tested nutlin, a compound that has a similar effect on p53 as a single copy of a ribosomal gene. When he treated mice with nutlin, increasing p53 activity, the mice had fewer red blood cells but not bone marrow cells. This shows that red blood cells are particularly sensitive to p53 activity. Normal bone marrow cells do not have p53 activity. However, cells that form red blood cells from at least some people with 5q- syndrome have quite strong p53 activity.

Dr. Ebert wondered why patients with 5q- syndrome have similar bone marrow characteristics to those of patients with **Diamond-Blackfan anemia**®, but patients with Diamond-Blackfan anemia do not have high **platelet**® counts. He found that when a molecule called miR-145 is too active, this decreases the production of platelets. People with 5q- syndrome have lost a copy of the miR-145 gene, increasing their platelet production.

Non-Transplant Treatments for Aplastic Anemia & PNH

Chair: **Peter Hillmen**, MB, ChB, PhD, Leeds Teaching Hospital, United Kingdom


Hereditary Marrow Failure Syndromes: Presentation, Diagnosis, and Treatment Options




Richard Harris, MD, Cincinnati Children's Hospital

Many hereditary marrow failure syndromes exist. The most common are listed below. A person who inherits a marrow failure syndrome from the parents may develop aplastic anemia or may fail to produce adequate numbers of one or more of the blood cell lines (neutropenia, thrombocytopenia, or anemia). These patients may eventually develop abnormal "clones" of marrow stem cells that cannot become healthy blood cells. They might also develop MDS or leukemia.

The most common hereditary marrow failure syndromes include the following:

Fanconi anemia  (FA): Patients with Fanconi anemia are often short and have a small head and small eyes. They may have missing or abnormal thumbs or radii (one of the forearm bones), heart defects, endocrine abnormalities (diabetes, hypothyroidism, or growth hormone deficiency), abnormalities of the GI tract or kidneys. On average, children with FA develop marrow failure by age 7 and many progress to MDS or leukemia with time. Many children with FA require a stem cell transplant to treat the marrow failure or the MDS/leukemia.

Schwachman Diamond syndrome (SDS): Patients with SDS are often short and have a narrow rib cage, problems with their teeth, low white blood cell counts, and developmental delays or attention deficit-hyperactivity disorder. Their pancreas does not produce enough enzymes, which help break down the nutrients in food. About 15 to 30% of patients with SDS develop MDS or leukemia. Treatments include growth factors to stimulate the bone marrow to make more white blood cells; blood or bone marrow transfusions; pancreatic enzyme replacement; and orthopedic, psychological, and dental follow-up.

Dyskeratosis congenita (DC): People with DC typically have small, ridged finger and toe nails and white patches inside the mouth. They usually have low white blood cell counts but they can have low counts of all types of blood cells. Patients with DC have a high risk of developing MDS or leukemia, especially if they develop **monosomy 7**  in their marrow. Some patients with DC develop liver fibrosis or pulmonary fibrosis (scarred lung tissue). DC treatments include bone marrow transplant, growth factors, and blood transfusions. Patients with DC need to have their liver and lung function monitored on a regular basis.

Congenital amegakaryocytic thrombocytopenia (CAMT): Patients with CAMT usually have a severe platelet shortage when they are born and some develop a shortage of all blood cell types. Doctors should consider bone marrow transplant for patients with CAMT at an early age to prevent the disease from progressing to MDS or AML. Other treatments are platelet transfusions and monitoring the bone marrow.

Diamond Blackfan anemia (DBA): In patients with DBA, the bone marrow does not make red blood cells, producing severe anemia within a few months of birth. These patients are usually short, may have heart and kidney defects, and might have a cleft lip and palate. DBA responds to steroids in more than half of patients. Doctors also use blood transfusions and, sometimes, bone marrow transplants to treat DBA.

The Non-Transplant Treatment of Aplastic Anemia



Phillip Scheinberg, MD, National Heart, Lung and Blood Institute

The bone marrow of people with aplastic anemia cannot make blood cells. As a result, people with aplastic anemia have low counts of red, white blood cells and platelets. Most people with aplastic anemia receive their diagnosis before they turn 40.

Forty years ago, survival rates for this disease were dismal, and most patients died within one or two years of diagnosis. The picture is much brighter today because of bone marrow transplant and immunosuppressive therapy. Immunosuppressive drugs reduce the activity of the body's immune system. This allows bone marrow cells to grow and make new blood cells.

SUMMARY FOR PATIENTS

The most common types of immunosuppressive therapy used for people with aplastic anemia are horse or rabbit ATG and **cyclosporine**®. In Dr. Scheinberg's experience, about 60-70% of people with aplastic anemia who are treated with horse ATG and cyclosporine benefit from the treatment. Patients whose aplastic anemia responds to immunosuppressive therapy tend to survive much longer than people whose disease did not respond to the treatment.

However, in about 30-40% of patients, the disease does not respond to horse ATG with cyclosporine. Furthermore, in about one-third of people whose disease does respond to horse ATG and cyclosporine, the aplastic anemia comes back at a later time. Dr. Scheinberg has studied treatments for these patients.

Campath® (**alemtuzumab**)® is a very powerful immunosuppressive treatment that has Food and Drug Administration (FDA) approval for chronic lymphocytic leukemia (CLL). Specifically, Dr. Scheinberg has compared Campath to rabbit ATG in patients whose aplastic anemia did not respond at first to horse ATG. In about one third of both groups, the disease responded to the treatment. Many patients whose disease responded stopped needing blood transfusions. Furthermore, in about two-thirds of patients whose aplastic anemia responded to horse ATG and cyclosporine at first, but whose disease came back, the aplastic anemia responded to Campath in about two-thirds of cases. Several of these patients had normal blood counts. However, results of Campath in patients whose aplastic anemia had never been treated were not as good—less than one-third responded.

PNH: Overview and Key Issues



Régis Peffault de Latour, MD, PhD,
*Hospital Saint Louis, Paris, AA&MDSIF
Research Grant Recipient*

PNH is usually classified into two categories: classic PNH (red blood cells break down but the bone marrow is normal) and aplastic anemia/PNH syndrome (the bone marrow does not make new blood cells properly but the red blood cells are much less likely to break down).

Dr. Peffault de Latour wanted to find out whether this classification made sense, so he studied 460 patients diagnosed with PNH between 1950 and

2005 in France (on the behalf of the French society of hematology). Of these patients, 113 met the definition for classic PNH and 224 for aplastic anemia/PNH syndrome. However, Dr. Peffault de Latour decided not to classify 93 patients with PNH (so-called intermediate PNH) in order to keep stringent criteria for the analysis.

Patients with aplastic anemia/PNH syndrome or the intermediate type of PNH tended to survive longer than those with classic PNH. Survival was longest in patients treated with immunosuppressive drugs. These drugs reduce immune system activity and allow the bone marrow to make red blood cells. The researchers concluded that the classic PNH and aplastic anemia/PNH syndrome classification system makes sense for predicting the disease course.

About 20% of patients with intermediate or classic PNH in the study developed aplastic anemia. About 30% to 40% of patients with all three types of PNH developed thrombosis (blood clots in blood vessels), which is a life-threatening complication. Patients were more likely to develop thrombosis if they already presented this complication, were older than 55, had received blood transfusions, or had been treated with warfarin or immunosuppressive therapy.

To treat patients with classic PNH and to try to prevent thrombosis in people with PNH, Dr. Peffault de Latour and colleagues gave Soliris® (eculizumab), to 23 patients. Eculizumab reduced the activation of the coagulation cascade and the reactional fibrinolysis. In other words, Eculizumab reduced the capacity of PNH patients to clot. These results indicate that eculizumab might be able to prevent thrombosis. However, further research is needed before eculizumab can be used for this purpose.

Dr. Peffault de Latour studied 211 patients with classic PNH or aplastic anemia/PNH syndrome who had received a stem cell transplant in Europe. The transplant was successful in 188 patients, and 70% were still alive five years later. At the moment, Dr. Peffault de Latour is trying to isolate which patients could benefit from transplant and notably if patients with thrombosis should be transplanted upfront. This work is now underway and should be available soon.

The Treatment of PNH: The Advent of Complement Inhibition



Petra Muus, MD, Radboud University Nijmegen, Medical Centre, Nijmegen, The Netherlands

A survey of members of a PNH patient association found that their major quality-of-life issues include lack of energy, exhaustion, unpredictability of episodes with increased hemolysis, interference with school or work, and relationship problems. The effects of thrombosis, or blood clots in the blood vessels, can be very difficult to live with. Few patients with PNH report no major quality-of-life problems.

People with PNH have a high risk of thrombosis. Studies have shown that Soliris® (eculizumab) treatment increases levels of hemoglobin in patients with PNH who depend heavily on blood transfusions. Eculizumab decreased the likelihood that patients would need blood transfusions. These patients also reported less fatigue and better quality of life.

An analysis of data on 195 patients with PNH found that before treatment with eculizumab, 39 patients had experienced thrombosis. In contrast, only three patients had thrombosis during eculizumab treatment. Eculizumab was also effective in PNH patients who were not dependent on red cell transfusion. In these patients, too, the hemoglobin level rose, the risk of thrombosis was reduced and they had a better quality of life during treatment with eculizumab.

Dr. Muus recommends eculizumab for any patient with PNH who already had PNH-related thrombosis. The treatment is also indicated for patients with classic PNH who depend on blood transfusions and those whose symptoms interfere with their life, even if they don't depend on transfusion. Researchers do not yet know whether eculizumab is appropriate for pregnant women with PNH or for patients with both PNH and aplastic anemia or MDS.

Management of PNH: Optimizing Therapy and Avoiding Complications



Richard Kelly, MD, St. James University Hospital, United Kingdom

Dr. Kelly analyzed data on 70 patients with PNH who had been treated with Soliris® (eculizumab) for at least two months. Almost two thirds had a complete response to the treatment defined as no longer needed blood transfusions. The 25 patients who did not have a complete response were slightly older, had a lower **platelet*** count before therapy, required more transfused blood each year, and were more likely to have had aplastic anemia than those that became transfusion independent. Although these patients did not have a complete response, many experienced dramatic improvements in their quality of life.

Meningitis is a rare, but very serious complication of eculizumab treatment in patients with PNH. Two patients at the Leeds PNH Center developed this complication. Both were treated with antibiotics and are doing well now. To prevent meningitis, the United Kingdom changed its guidelines to require penicillin treatment and meningitis vaccination for patients on eculizumab. Patients and their doctors now receive information about eculizumab's risks and patients get safety cards advising them to see their doctor immediately if they have a temperature or are unwell.

Women with PNH who become pregnant are more likely to have symptoms due to PNH than when they are not pregnant. They are at increased risk of falling blood counts, developing blood clots, and of premature births occurring. Very little data is available on eculizumab use in pregnant women. However, one woman who was treated with eculizumab during her pregnancy gave birth to a healthy, full-term baby and is currently pregnant again and still on eculizumab. Physicians should prescribe **low-molecular-weight heparin*** to all pregnant women with PNH as soon as the pregnancy is confirmed. Physicians should also consider eculizumab for their pregnant patients with PNH. However, these women might need higher doses of the drug or more frequent doses if they experience a recurrence of their PNH symptoms.

In some people with PNH, the disease can spontaneously remit. Of 53 patients treated at the

Leeds PNH Center with eculizumab for at least 12 months, nine experienced a steady decline in the size of their white blood cell PNH clones. Patients who experienced a decline tended to have smaller clones before starting the treatment but these changes can occur in people with large PNH clones too. Clone size decreased enough in two patients that they were able to stop taking eculizumab without any damage to their health.

Transplant Treatments for Aplastic Anemia, MDS, and PNH

Chair: **John Barrett, MD**, National Heart, Lung and Blood Institute

Allogeneic Stem Cell Transplants for Aplastic Anemia



John Barrett, MD, National Heart, Lung and Blood Institute

Dr. Barrett summarized a presentation that Andrea Bacigalupo, MD, of the Ospedale San Martino Genova had been scheduled to give. Dr. Bacigalupo has analyzed data from 2,037 stem cell transplants from genetically matched siblings and 1,071 transplants from unrelated donors in patients with aplastic anemia since 1999. A stem cell transplant replaces the immature and unhealthy cells that form blood cells in the bone marrow.

These data show that survival rates for transplants from genetically matched siblings have increased dramatically, from 44% of patients in the 1970s to almost 80% in the last decade. The chance of survival decreases with age. Patients who are younger than 20 are twice as likely to survive after a stem cell transplant as those older than 50.

Transplants are most successful when they are done within three months of aplastic anemia diagnosis. Immune suppression therapy lowers the body's immune response (the body's defense system against foreign substances, such as cells from another person), allowing the bone marrow stem cells to grow and make new blood cells. However, immune suppression treatment before transplant does not affect the likelihood of survival.

Transplants of stem cells from bone marrow have better outcomes than transplants of stem cells from peripheral blood (blood that circulates in the body instead of the bone marrow). This is mostly because peripheral stem cell transplants are much more likely to produce **graft-versus-host disease (GVHD)**[®], which can damage the patient's skin, intestines, or liver. When a patient has GVHD, the donor's immune cells that have been transplanted to the patient mount an immune response against the patient's body.

Survival rates from transplants involving stem cells from unrelated donors have also improved dramatically, from 0% in the 1970s to 67% in the last decade. As with stem cell transplants from genetically matched siblings, transplants of cells from the bone marrow unmatched donors have better outcomes than transplants of cells from peripheral blood.


Unrelated Hematopoietic Progenitor Cell Transplant for Acquired SAA in Children and Young Adults



David Margolis, MD, PhD, Medical College of Wisconsin, AA&MDSIF Medical Advisory Board Member

One of the reasons why stem cell transplants from unrelated donors are less successful than transplants from genetically matched donors is GVHD. GVHD starts when the donor's cells are transplanted into the patient and begin to attack the patient's cells. Another problem with stem cell transplants from unrelated donors is that the patient's T cells, a type of white blood cell that organizes attacks on foreign substances, identify the donor's cells as foreign and attack the donated cells. This is known as "rejection."

A major goal of transplant surgeons like Dr. Margolis is to prevent GVHD and rejection and avoid the need for a second transplant. Dr. Margolis has prevented rejection of transplants from unrelated donors using high doses of radiation. He has prevented GVHD by reducing the number of T cells in the patient's body. As a result, more than 90% of his patients who undergo a stem cell transplant survive. Unfortunately, radiation has serious side effects, especially in younger children. These side effects can include skin problems, nausea, vomiting, and diarrhea. In rare cases, radiation therapy can cause a new cancer to form in the part of the body that received the radiation.

Dr. Margolis recently adopted the European Group for Blood and Bone Marrow Transplantation Approach to avoid giving large doses of radiation to young children. This approach calls for the administration of three drugs—**Fludara® (fludarabine)** , cyclosporine, and Thymoglobulin® (rabbit ATG)—instead of radiation before the transplant. Dr. Margolis only uses radiation in patients older than 14. Dr. Margolis has used this approach in 15 patients aged 4-22 years. About half received their transplant within 24 months of their aplastic anemia diagnosis.

Transplants in 11 of 12 of Dr. Margolis's patients with well-matched donors were successful. Two of these patients developed mild or moderate GVHD, but they recovered. These patients are doing well and none has had any long-lasting side effects. One of the patients with a well-matched donor and all three patients with genetically mismatched, unrelated donors rejected their stem cell grafts. However, all four are still alive.

Hematopoietic Stem Cell Transplantation for Severe Aplastic Anemia in Japan



Seiji Kojima, MD, Nagoya University, Japan

Human leukocyte antigens (HLAs) are proteins on most cells of the body. The immune system uses these proteins to recognize the cells that belong in the body and those that are foreign. Doctors use HLA typing to match patients and donors for bone marrow or cord blood transplants. When the donor's HLA markers closely match those of the patient, the patient's immune cells aren't likely to attack the donor's cells and the donor's immune cells are less likely to attack the patient's body.

Dr. Kojima explored how many HLA markers need to match between an unrelated donor and patient with aplastic anemia. He analyzed the outcomes of 301 patients with aplastic anemia who had received a bone marrow transplant from an unrelated donor in Japan between 1993 and 2005. Three quarters of patients whose donated bone marrow cells matched 10 key HLA markers survived for at least 10 years. Only 54% of those whose donated bone marrow matched seven or fewer key HLA markers survived for 10 years.

Dr. Kojima also examined the impact of mismatches in different HLA alleles. An allele is one of several forms of a gene at the same location on a given

chromosome. He found that mismatches in the HLA-C or DQB1 allele combined with a mismatch in the HLA-A or HLA-B allele led to a much lower likelihood of survival.

Dr. Kojima therefore developed an algorithm, or rule, for choosing donors based on HLA matching. According to this system, the following are acceptable:

- Matching on all 10 key HLA markers
- A mismatch in 1 of the 10 key HLA markers
- Mismatches in both the HLA-C and DRB1/DQB1 alleles

However, the following are not acceptable:

- Mismatches in three or more of the 10 key HLA markers
- A mismatch in the HLA-C or DQB1 allele combined with a mismatch in the HLA-A or HLA-B allele

Nonmyeloablative Allogeneic Hematopoietic Stem Cell Transplantation as Immunotherapy to Eradicate PNH



Richard Childs, MD, National Heart, Lung and Blood Institute

Doctors have used stem cell transplants from genetically matched donors for about 25 years to treat and cure PNH. Until recently, most transplants for PNH used myeloablative conditioning to kill as many PNH stem cells as possible before the transplant and prevent the disease from coming back. Myeloablative conditioning uses high doses of chemotherapy and sometimes radiation therapy to destroy the patient's bone marrow and, thus, the bone marrow's ability to make blood cells. This approach can cause serious side effects, including infections, bleeding, and organ failure

More recently, doctors have started using non-myeloablative, or reduced-intensity, transplants in patients with certain bone marrow failure syndromes to avoid the major side effects of myeloablative conditioning. Reduced-intensity conditioning uses drugs that are less toxic than chemotherapy, but can still stop the patient's immune system from rejecting the transplanted cells.

The literature suggest that about 60% of patients who have undergone a myeloablative transplants for

PNH will have had long term survival. The published literature has very little information on the outcomes of reduced-intensity transplants in patients with PNH. Experiments conducted in the lab have shown that PNH cells are sensitive to immune attack and can be killed of by donor T-cells.

Dr. Childs decided to use Fludara® (fludarabine) to reduce, but not eliminate, the bone marrow's ability to make blood cells. He wanted to find out whether the donor's transplanted cells could then kill the rest of the patient's abnormal PNH stem cells. This study focused on patients with severe PNH who were receiving a stem cell transplantation from a genetically matched related donor.

Fifteen of the first 17 patients in this study survived for at least four years after the transplant, and their unhealthy PNH cells disappeared, with all patient's PNH cells disappearing by four months after the transplant. Ten patients developed acute GVHD (which started within the first 100 days) and 11 developed chronic GVHD (which started after the first 100 days). GVHD is a serious side effect of stem cell transplants that can cause rashes, nausea, diarrhea, and stomach pains. Nine of the 11 patients with chronic GVHD have had their GVHD burn out and no longer need treatment for this condition. Most patients have been able to return to work full time within 6-8 months after the transplant.

Transplantation for Genomic Instability: Fanconi Anemia and Seckel Syndrome



Stella Davies, MBBS, PhD, Cincinnati Children's Hospital

People with **Fanconi anemia**® have different genetic and physical features. Researchers have identified more than 13 gene variants that are associated with Fanconi anemia. Siblings with the same genetic variants often have very different Fanconi anemia symptoms. Most children with Fanconi anemia survive for at least 10 years after a bone marrow transplant from a genetically matched sibling.

At birth, children with Fanconi anemia have normal stem cells. In early childhood, their healthy stem cells die quickly. As a result, they don't have enough healthy stem cells to make blood cells, resulting in shortages of all types of blood cells. By late childhood, children with Fanconi anemia tend

to develop MDS. It is therefore critical to intervene as early as possible.

Because Fanconi anemia is caused by an inherited genetic disorder, most children with the disease do not have a healthy, genetically matched sibling who can donate bone marrow. Children with Fanconi anemia have a poor likelihood of surviving after a bone marrow transplant from an unrelated donor. But using Fludara® (fludarabine, a chemotherapy drug) to kill the Fanconi anemia cells before the transplant dramatically increases the likelihood of survival. Fludarabine also improves engraftment, or growth of the transplanted cells in the patient's bone marrow.

Dr. Davies has studied an experimental gene therapy in two children with Fanconi anemia. The study involved collecting stem cells, correcting the mutant genes in these cells, and readministering the cells to the children. The studies found evidence of the corrected gene in only one child. Both children had higher healthy stem cell counts shortly after the transfusion, but their blood counts dropped over time. Dr. Davies believes that this study did not give enough healthy cells to the children. She is therefore working to improve the technique.

Pre- and Post-Transplant Treatment Strategies to Improve Outcome after SCT for MDS



Uwe Platzbecker, MD, University of Dresden, Germany

About half of all patients with MDS get their diagnosis at age 70 or later. By this age, many have other diseases and medical conditions. Doctors can figure out whether a bone marrow transplant from a genetically matched donor is likely to be successful in a patient with MDS based on whether the patient has kidney disease or lung disease, as well as other medical conditions, and how serious these diseases or conditions are.

Approximately 60% of all patients with MDS survive for at least five years after a bone marrow transplant from a genetically matched relative. Almost as many survive if the transplant comes from an unrelated but genetically matched donor. However, survival is worse when using a transplant from a donor who is not genetically matched to the patient.

Another factor to consider in deciding whether a patient should have a bone marrow transplant is whether the patient needs red blood cell transfusions. Patients who receive many red blood cell transfusions have high iron levels. These patients do more poorly after a bone marrow transplant than patients who have had fewer transfusions. However, these patients might do more poorly because their transplants are delayed due to their poor health condition. Thus, needing red blood cell transfusions and having a high iron level might not affect the likelihood that a transplant will succeed.

Many options are now available to improve bone marrow transplant outcomes. These include:

- Induction chemotherapy, or chemotherapy, to kill the unhealthy cells before the transplant. This is a good option in patients with more diseased cells if they are younger, especially if they are otherwise healthy and if the treatment takes place shortly before the transplant.
- Reduced-intensity conditioning, which involves drugs that have fewer side effects than chemotherapy to stop the patient's immune system from rejecting the transplanted cells. Reduced-intensity conditioning is appropriate for older patients and patients with other diseases or medical conditions.
- Demethylating agents, which help the bone marrow function normally and kill unhealthy cells, are a good option for preparing patients for bone marrow transplant.
- No conditioning treatment, which has no negative side effects. However, the patient's disease might get worse while he or she waits for a transplant. This option is best for patients who aren't waiting long for their transplant and who have a low number of immature cells in the bone marrow.

Non-Transplant Treatment for MDS

Chair: **Richard M. Stone**, MD, Dana-Farber Cancer Institute

What Classification and Prognostic Factors Have Taught Us About the Approach to Patients with MDS



Luca Malcovati, MD, University of Pavia, Italy

Doctors use the International Prognosis Scoring System to classify a patient's MDS as low, intermediate 1, intermediate 2, or high risk. The category of a patient's disease is based on the percentage of blasts, or immature cells in the bone marrow; the type and number of chromosome abnormalities in bone marrow cells, and whether the patient has low levels of blood cells. Doctors and researchers use the IPSS to make treatment decisions, design clinical trials, and define for which patients the new drugs undergoing regulatory approval for MDS can be used.

In 2001, the World Health Organization (WHO) developed a new classification system for MDS, which was then updated in 2008. This system classifies MDS into different types based on whether the bone marrow cells look abnormal. This classification system is useful for predicting the progress of MDS in different patients and how likely these patients are to survive.

Dr. Malcovati has created the WHO classification-based prognostic scoring system (WPSS). This system uses information on cell abnormality, chromosome changes in blasts, and whether the patient depends on red blood cell transfusions. Dependence on blood transfusions is important because patients with MDS who need regular transfusions have a high risk of dying and developing leukemia. The WPSS classifies MDS into five risk groups: very low, low, intermediate, high, and very high risk.

When Dr. Malcovati tested the WPSS in more than 700 patients, he found that patients in each category have significantly different chances of surviving and of developing leukemia. Another study in more than 1,000 patients confirmed that the WPSS can be used to accurately predict how long the patient is likely

to survive and whether the patient would develop leukemia. Adding information on bone marrow fibrosis (growth of scar tissue in the bone marrow) to the WPSS resulted in even more accurate predictions of how patient with MDS will do.

Physicians can use the WPSS to choose the most appropriate treatment for their patient. For example, WPSS gives more accurate information than the IPSS on whether a patient is likely to need immediate stem cell transplantation or whether the patient's disease is not likely to get worse if the transplant is delayed.

MDS: Pathophysiology, Therapy, and Some Speculations



H. Joachim Deeg, MD., Fred Hutchinson Cancer Research Center, AA&MDSIF Medical Advisory Board Member

In patients with advanced MDS, contact between immature bone marrow cells, known as clonal hematopoietic precursor cells, and the stroma, or the supporting tissue that surrounds the cells, can determine whether the cell will die or survive. Survival of the cells is likely to lead to expansion of those (abnormal) cells and eventually to the development of leukemia. Patients with MDS have high levels of tumor necrosis factor α (TNF α) in their bone marrow. TNF α is a cytokine, or messenger protein, that plays a key role in the immune response by helping cells heal themselves. In addition, the bone marrow of patients with MDS has TNF α receptors (structures on the cell that receive chemical signals) that do not work properly.

Studies have shown that treatment with Enbrel® (etanercept), which removes TNF α , helps improve the responses of low-grade MDS to ATG, which suppresses the immune system. In a study published in 2010, etanercept also increased the responsiveness of more advanced MDS to Vidaza® (azacitidine), which helps the bone marrow function normally. In this more recent study, 80% of patients experienced some response to the treatment, and many continue to do well, more than three years after the start of treatment.

Supportive Approaches in the Lower-Risk MDS Patients: Growth Factors and Iron Chelation



David P. Steensma, MD, FACP, Dana-Farber Cancer Institute, AA&MDSIF Medical Advisory Board Member

Many patients with MDS receive supportive care only. Supportive care is designed to improve quality of life, but does not cure the disease. Since the early 1970s, there has been no improvement in the survival of patients with MDS who received only supportive care, emphasizing the need for drugs that delay disease progression or help patients live longer.

Erythropoiesis-stimulating agents (ESAs)—red blood cell growth factors that increase the number of red blood cells that the patient's bone marrow makes—are a form of supportive care, and this class of drugs is the most commonly prescribed treatment for MDS. However, the FDA-approved label for these agents does not include MDS, and clinicians do not know how safe ESAs are for patients with MDS.

ESA safety is a concern because prospective research involving 14,000 patients with different types of non-bone marrow cancer showed that ESAs could actually decrease a patient's chances of survival. However, several retrospective studies of ESAs in patients with MDS showed that patients who received ESAs lived longer than patients who didn't. However, it is possible that these retrospective results are misleading; for instance, doctors might have treated patients with MDS who were likely to do better with ESAs, and reserved more intense treatments for sicker patients, skewing results. There have been no prospective studies of ESAs in MDS that are large enough to be able to answer the important questions about ESA safety.

More than two thirds of patients with MDS experience thrombocytopenia, or a shortage of platelets in the bloodstream, at some point during the course of the disease. Thrombocytopenia is severe in about 20% of these patients. Bleeding due to thrombocytopenia is the second leading cause of death, after infection, in patients with MDS. **Platelet*** transfusions can be helpful, but they often stop working after a while. New platelet growth factors, romiplostim and eltrombopag, are currently being studied in patients with MDS.

Patients with high iron levels, including patients with MDS who have received many blood transfusions, seem to do more poorly than those with more normal levels. Iron chelators are drugs that remove extra iron from the body. Iron chelation might reduce the risk of infection and improve the bone marrow's ability to make healthy blood cells in patients with MDS and might also decrease certain iron-related complications, such as heart failure or diabetes. However, more research is needed to determine how many patients with MDS have high iron levels and whether iron chelation helps patients live longer.

Immunomodulatory Agents in MDS: 5q- and Beyond



Aristotle Giagounidis, MD, St. Joannes Hospital, Duisberg, Germany, AA&MDSIF Medical Advisory Board Member

Patients with 5q- syndrome, a type of MDS, have a deletion (loss) of the long (q) arm of chromosome 5. Patients with this syndrome tend to have anemia that does not respond to treatment, normal or high levels of platelets (a type of blood cell), and normal or low levels of neutrophils (a type of white blood cell). In 2005, the FDA approved Revlimid® (lenalidomide) to treat anemia, or shortage of red blood cells, in people with 5q- syndrome who need red blood cell transfusions.

The first study (completed in 2005) to show that lenalidomide was effective in patients with MDS included 12 patients with 5q- syndrome. Most (83%) of the patients responded to the treatment.

A more recent study randomly assigned 205 patients with 5q- syndrome to receive 10 mg of lenalidomide for 21 days, 5 mg of lenalidomide for 28 days, or placebo (medicine with no active ingredients). By 12 weeks, 95% of patients experienced a response to the lenalidomide and, regardless of the lenalidomide dose, no longer needed red blood cell transfusions. However, more than half of the patients on lenalidomide experienced serious thrombocytopenia (shortage of platelets in the bloodstream) or neutropenia (shortage of neutrophils in the bloodstream). Doctors treated these side effects successfully in most cases, so these patients were able to stay on lenalidomide.

Studies have shown that 17% to 26% of patients with 5- syndrome on lenalidomide eventually develop AML. However, research data also show that patients with 5q- syndrome who achieve cytogenetic remission, or have no sign of abnormal chromosomes, after lenalidomide treatment are much less likely to develop AML than patients who do not achieve cytogenetic remission.

Doctors using lenalidomide over the long term in patients with 5q- syndrome should check their bone marrow every six months. If the patient experiences a complete cytogenetic response, then the patient can stay on lenalidomide and perhaps stop the treatment after 12 to 18 months. If the patient has no cytogenetic response or the MDS comes back, then the patient should stop the lenalidomide because he or she has a high likelihood of developing AML.

Lenalidomide might be helpful for patients with high-risk, or very severe, 5q- syndrome that is likely to get worse. In a study of 47 patients with high-risk or intermediate-2 risk MDS, disease symptoms disappeared in 67% on lenalidomide.

The Future of Hypomethylating Agents in MDS



Pierre Fenaux, MD, PhD, University Paris, Hôpital Avicenne, France

Hypomethylating agents, also known as demethylating agents, help the bone marrow of patients with MDS function normally and kill unhealthy cells. When used for a long time, these drugs can lengthen survival and improve quality of life in patients with more advanced MDS.

Vidaza® (azacitidine), a hypomethylating agent, takes some time to produce a response (fewer unhealthy blood cells) in the patient's disease. Every four weeks, patients receive an injection every day for seven days. Most patients respond by six of these treatment cycles. Patients should probably try the drug for at least six cycles before their doctor concludes that the drug is not working. Once the disease responds to the drug, the patient should stay on the drug for some time because their response could continue to improve.

A European study found that Dacogen® (decitabine), another hypomethylating agent, stopped the disease from getting worse for longer, but did not lengthen survival in patients with severe MDS

SUMMARY FOR PATIENTS

compared to supportive care (treatment designed to make the patient more comfortable, but not to cure the disease). It is not clear why decitabine did not improve survival in this study. One reason might be that patients only received on the average four cycles of the drug. Furthermore, a study at MD Anderson Cancer Center found that decitabine prolonged survival in more patients than intensive chemotherapy.

Some other important research findings on hypomethylating agents include the following:

- Azacitidine is as effective in patients older than 75 as in younger patients.
- A low dose of azacitidine after intensive chemotherapy can help prevent MDS from getting worse.
- Azacitidine can reverse the progression of myeloproliferative disorders into MDS or AML.
- Azacitidine and decitabine can benefit some patients with less severe MDS
- Combinations between azacitidine or decitabine and other drugs, that may further improve their results (compared to their use as single agents) are actively tested in clinical trials

HDAC inhibitors show much more promise for treating AML or MDS when they are combined with other treatment. Dr. Garcia-Manero has studied combinations of valproic acid, an HDAC inhibitor, and Dacogen® (decitabine) or Vidaza® (azacitidine), drugs that help the bone marrow function normally and kill unhealthy bone marrow cells. From 22% to 44% of patients with leukemia or MDS experienced a response to the combinations. Responses were often very rapid. In some cases, patients showed signs of responding after a single cycle of the drug combination. However, complete cytogenetic response (no leukemia or MDS cells in the blood or bone marrow) might take several months.

The only good way to predict which patients will respond to the drug combination is to measure valproic acid levels. Patients who had the highest valproic acid levels before treatment were the most likely to respond to the combination treatment.

This finding could lead to research on how to create high levels of valproic acid in patients. However, high doses of the drug can cause serious side effects. Another approach to test is HDAC inhibitor combinations.

Incorporating HDAC Inhibitors in MDS



Guillermo Garcia-Manero, MD, M.D.
Anderson Cancer Center

HDAC inhibitors can stop cancer cells from proliferating, or dividing, help **stem cells*** mature into healthy cells, and cause unhealthy cells to die. However, the best dose to use is not clear. Also, most of the studies of HDAC inhibitors in bone marrow failure diseases have focused on leukemia, and about 10-15% of patients typically experience a response.

A study of three doses of suberoylanilide hydroxamic acid (SAHA), an HDAC inhibitor, in 35 patients with leukemia found that 15% of patients with AML responded to the drug. However, the level of response did not depend on the dose. For example, some patients whose disease had not responded to any other treatment achieved a complete response (the disappearance of all signs of leukemia) after receiving a low dose of SAHA.

GLOSSARY

alemtuzumab (Campath) - A monoclonal antibody - a medicine that is engineered to look for a specific substance in the body. Alemtuzumab attaches to and kills white blood cells called lymphocytes. In certain types of aplastic anemia, lymphocytes are responsible for attacking the bone marrow **stem cells**. Alemtuzumab is in clinical trials for treating aplastic anemia. It is approved by the U.S. Food and Drug Administration (FDA) for treating certain types of leukemia and is helpful in other conditions that require immunosuppressive therapy.

androgen therapy - An approach to treating bone marrow failure using natural male hormones. Androgen therapy can help the bone marrow make more blood cells. This is an older treatment for bone marrow failure that is rarely used because of the side effects. Scientists are studying these medicines to try to better understand why they work in some cases of acquired and genetic bone marrow failure.

antithymocyte globulin (ATG, Atgam, Thymoglobulin) - ATG is an immunosuppressant, a drug that lowers the body's immune response. Scientists believe that aplastic anemia happens when the immune system attacks and destroys bone marrow **stem cells**. ATG kills the specific cells that are attacking the bone marrow **stem cells**. This allows the bone marrow to grow and make new blood cells. ATG may be used to treat other bone marrow failure diseases in some cases. ATG is approved by the U.S. Food and Drug Administration (FDA) for treating moderate and severe aplastic anemia. ATG is commonly used with another drug called cyclosporine.

autosomal dominant - One of several ways that a trait or disorder can be passed down through families. If a disease is autosomal dominant, it means you only need to get the abnormal gene from one parent in order for you to inherit the disease.

bone marrow - The soft, spongy tissue inside most bones. Blood cells are formed in the bone marrow.

Campath - See alemtuzumab

cord blood transplant - A procedure where umbilical cord **stem cells** are given to the patient through an intravenous (IV) line. **Stem cells** are collected from an umbilical cord right after the birth of a baby. They are kept frozen until needed. In time, donated **stem cells** given to the patient begin making new, healthy blood cells.

cyclosporine (Neoral, Sandimmune) - An immunosuppressant, this drug that lowers the body's immune response. Cyclosporine is used along with antithymocyte globulin (ATG), another immunosuppressant, for treating aplastic anemia and some other forms of bone marrow failure.

cytogenetics - (sie-toe-juh-NEH-tiks) - The study of chromosomes (DNA), the part of the cell that contains genetic information. Some cytogenetic abnormalities are linked to different forms of myelodysplastic syndroms (MDS).

de novo - (di-NO-vo) - Brand new, referring to the first time something occurs. MDS that is untreated or that has no known cause is called de novo MDS.

Diamond-Blackfan Anemia - A rare form of pure red cell aplasia that can be passed down from parent to child. Diamond-Blackfan anemia (DBA) is characterized by low **red blood cell** counts detected in the first year of life. Some people with DBA have physical abnormalities such as small head size, low frontal hairline, wide-set eyes, low-set ears. Genetic testing is used to diagnose DBA.

epidemiology - The study of patterns and causes of disease in groups of people. Epidemiology researchers study how many people have a disease, how many new cases are diagnosed each year, where patients are located, and environmental or other factors that influence disease.

epoetin alfa (Epoen, Procrit) - Epoetin alfa can help improve red blood cell counts in bone marrow failure disease patients whose natural **erythropoietin** levels are low. It is given by injection under the skin (subcutaneous) or in the vein (intravenous). Epoetin alfa is approved by the U.S. Food and Drug Administration (FDA) for treating anemia. It is in a class of drugs called growth factors (cytokines).

erythropoietin-stimulating agents (ESA) - A man-made version of a naturally occurring substance in the body (erythropoietin) that encourages the bone marrow to make more red blood cells.

erythropoietin - (i-rith-row-POY-uh-tun) - A protein made by the kidneys. Erythropoietin, also called EPO, is created in response to low oxygen levels in the body (anemia). EPO causes the bone marrow to make more red blood cells. A shortage of EPO can also cause anemia.

Estradiol - The most predominant sex hormone in females (and present in males). Estradiol is a form of estrogen and is involved in many body functions beyond the reproductive system.

Etiology - The study of the cause or origin of a disease.

Fanconi anemia - A rare inherited disorder that happens when the bone marrow does not make enough blood cells: red cells, white cells, and platelets. Fanconi anemia is diagnosed early in life. People with Fanconi anemia have a high likelihood of developing cancer. Genetic testing is used to diagnose Fanconi anemia.

fludarabine (Fludara) - A chemotherapy drug that interferes with the growth of cancer cells. It is usually used to treat chronic lymphocytic leukemia (CLL).

graft-versus-host disease (GVHD) - Also called GVHD, it is a common complication of bone marrow/stem cell transplantation. It is caused when the donor's immune cells, now in the patient, begin to see the the patient's body as foreign and mount an immune response. GVHD most commonly affects the recipient's skin, intestines, or liver. Severity can range from mild to very severe. In some cases, GVHD can be prevented or treated with immunosuppressive drug therapy.

hematopoiesis - (hi-mat-uh-poy-EE-suss) The process of making blood cells in the bone marrow.

low-molecular-weight heparin - A class of medication used as an anticoagulant in diseases that feature thrombosis, as well as for prevention of situations that lead to a high risk of thrombosis.

monosomy 7 - A rare chromosomal disorder characterized by deletion of a portion of chromosome 7 that is seen in a variety of hematologic disorders.

platelet - The smallest type of blood cell. Platelets help the blood to clot and stop bleeding. Also called a thrombocyte.

recessive gene - A gene that has its expression masked in the presence of a dominant gene.

red blood cell - The most numerous type of blood cell in healthy people. Red blood cells contain hemoglobin, a protein that picks up oxygen in the lungs and brings it to cells in all parts of the body. Also called erythrocyte, RBC.

ribosomal gene - A gene that develops ribosomes, which build or synthesize proteins to support cell functions.

secondary MDS - A type of MDS that is caused by a previous treatment for another disorder or disease. Treatments typically associated with secondary MDS include radiation therapy and chemotherapy used to treat cancer. Also called therapy-related MDS, T-MDS.

stem cells - Cells in the body that develop into other cells. There are two main sources of stem cells. Embryonic stem cells come from human embryos and are used in medical research. Adult stem cells in the body repair and maintain the organ or tissue in which they are found. Blood-forming (hemapoietic) stem cells are found in the bone marrow. These cells make copies of themselves and develop into red cells, white cells, and platelets.

T cells - A principal type of white blood cell that completes maturation in the thymus and that has various roles in the immune system, including the identification of specific foreign antigens in the body and the activation and deactivation of other immune cells.

GLOSSARY

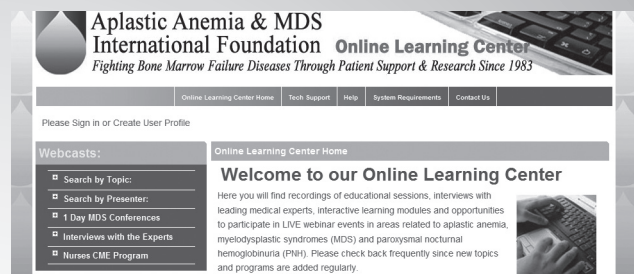
Tumor necrosis factor (TNF) - A protein that mediates inflammation and that induces the destruction of some tumor cells and the activation of white blood cells

Warfarin (Coumadin) - Blood thinner or anticoagulation drug, used to treat blood clots. It decreases the ability of blood to clot.

white blood cell - Cells in the body that fight disease and infection by attacking and killing germs. There are several types of white blood cells including neutrophils, eosinophils, basophils, lymphocytes and monocytes. Each type of cell fights a different kind of germ. Also called WBC, leukocyte.

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| Steven Gore, MD | • Bone Marrow and Stem Cell Transplantation for MDS |
| Jaroslawn Maciejewski, MD, PhD | • Advances in MDS Treatment: What's on the Horizon
• PNH: Frequently Asked Questions |
| David Margolis, MD | • Issues for Parents of Pediatric Bone Marrow Failure Patients
• Issues for Pediatric Bone Marrow Failure Patients |
| Phillip Scheinberg, MD | • Aplastic Anemia 101
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• MDS: Current Thinking on the Disease, Diagnosis, and Treatment
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• Treating Higher-Risk MDS
• Understanding FDA Approved Drug Treatments for MDS |
| • David Steensma, MD | • Fundamentals of Hematology and Bone Marrow Failure Diseases
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1989 • Dr. Winald Gerritsen Memorial Sloan-Kettering Inst. for Cancer Research **1990 • Dr. Hildegard Greinix** Fred Hutchinson Cancer Research Center: *Late Failure of Autologous Marrow Grafts in Lethally Irradiated Dogs Given Anti-Class II Monoclonal Antibody* **1990 • Dr. Stephen R. Paul** Dana-Farber Cancer Institute: *Role of FAC in a Genetic Model of AA* **1991 • Dr. Jeffrey P. Novack** Fred Hutchinson Cancer Research Center: *Signal Transduction of the C-kit Tyrosine Kinase Receptor* **1992 • Dr. Leslie G. Biesecker** University of Michigan Medical Center: *Embryonic Protein Kinase Receptor Cloning* **1994 • Dr. Ronald L. Paquette** UCLA School of Medicine: *Mutations of Interleukin-1 and Stem Cell Factor Receptor Genes in AA; Absence of c-kit Point Mutations in Acquired AA: I.D. of New Polymorphisms in Exons 10 and 18* **1994 • Dr. Surapol Issaragrisil** Mahidol University, Thailand **1995 • Dr. Hagop Youssoufian** Bingham and Women's Hospital and Harvard Medical School: *Role of FAC (fanconi anemia) in a Genetic Model of AA* **1995 • Dr. Chaker Nadim Adra** (Mary Elizabeth Clancy*) Beth Israel Hospital: *Molecular and Cellular Biology of a Novel Hematopoietic-Specific Multispanning Protein* **1996 • Dr. David Araten** (Vernille Family*) Memorial Sloan-Kettering Inst. for Cancer Research: *PNH Cells and PID-A Gene Mutations in Normal Donors, Chromosomal abnormalities in PNH* **1998 • Dr. Richard Carter** Emory University: *Irradiated Donor Lymphocyte Transfusion, a Novel Approach to Prevent Graft Failure During Allogeneic Bone Marrow Transplantation* **1998 • Dr. Tatiana Zorina** (Alexandra Jane Greenberg & Tyler David Fica*) Philadelphia & Children's Hospital of Pittsburgh: *Treatment of AA w/Bone Marrow Chimerism Achieved by Facilitating Cell-Mediated Allogeneic Allegheny University Health Sciences, Stem Cell Engraftment* **1999 • Dr. Sherilyn Gross** (Mark Jeska Family*) *Ex Vivo Expansion of Bone Marrow Cells from AA Patients* **1999 • Dr. Sujit S. Sheth** (**Betsy Lakie*) Columbia University: *Hbed Chelation Therapy for Iron Overload in AA & MDS* **2000 • Jen Chin Wang** (Harold Spielberg*) Maimonides Medical Center, Bookdale University Hospital: *Studies on CMPL Defects for the Elevated TPO and Fibrosis in MDS* **2001 • Dr. Marianne Greene** (Torry Yahn*) University of Chicago: *Knockout of the GATTA-1-FOG-1 Interaction: Implications for MDS* **2002 • Michael Boosalis** (Donny Schmidt*) Boston University School Medicine: *Molecular Mechanisms of Cell Proliferation Induced by Short Chain Fatty Acid Derivatives* **2003 • Dr. Archibald Perkins** (Harold Spielberg*) Yale University School of Medicine: *Role of the MDS/Evi 1 Locus in MDS* **2003 • Dr. Jaroslaw Maciejewski** (David Homza*) Cleveland Clinic Taussig Cancer Center: *Immune Pathophysiology of MDS-Lessons from the Molecular Analysis of T Cell Receptor Repertoire in AA* **2003 • Dr. Russell Ware** (Deb Valchik*) Duke University School of Medicine: *Genetic Analysis of Growth Advantage and Thrombosis in PNH* **2004 • Dr. Jaroslaw Maciejewski** (Pursuing New Hope/Papernick Family*) Clinic Taussig Cancer Center: *Differential Inhibition of Normal Stem Cells in PNH* **2004 • Dr. Monica Bessler** (Florentine Caminisch*) Washington University in St. Louis: *Genes, Chromosomes, and Bone Marrow Failure* **2005 • Dr. Catriona H.M. Jamieson** (Virginia Stephenson*) Stanford University School of Medicine: *Progenitor Profiling in MDS* **2005 • Dr. Elena Solomou** NIH, National Heart, Lung & Blood Institute: *Transcriptional Control of Increased Express of IL-2 and IFN-γ in T cells from Patients with AA* **2005 • Dr. Eva Guinan** (Mary-Pat Madden Grieshaber Family*) Dana-Farber Cancer Institute: *Strategies to Improve Immune Reconstitution after Allogeneic Transplant: Development of Class II Tetramers for CMV Epitopes* **2005 • Dr. Gabrielle Meyers** (PNH Group Research Study*) Utah University: *Clonal Evolution and Dominance in PNH* **2005 • Dr. Jane L. Liesveld** University of Rochester Medical Center: *Proteasome Inhibition in MDS* (Julia Anderson & Gordon Forgash*) **2005 • Dr. Matthew Walter** (Malama Collingsworth*) Washington University in St. Louis: *Genomics of MDS* **2005 • Dr. Seth Joel Corey** University of Texas-MD Anderson Cancer Center: *Signaling Defects in the MDS of Severe Chronic Neutropenia* **2006 • Dr. Hinh Ly** (Holly Cataldo & Jennifer Walsh-Hawes*) Emory University School of Medicine: *Telomere Maintenance in Patients with AA* **2006 • Dr. Lisa Minter** (Marissa Marie Amuso & Jack Byrne*) University of Massachusetts - Amherst: *Gamma-Secretase Inhibitors as Therapeutic Intervention in Bone Marrow Failure Syndromes* **2006 • Dr. Lukasz Gondek** (PNH Foundation/ Sarah Higgins Family*) Cleveland Clinic Taussig Cancer Center: *A Novel Approach for the Study of Genetic Predisposition in AA and PNH Using High-Density Arrays* **2006 • Dr. Christine O'Keefe** (Lindsay Minelli*) Cleveland Clinic Taussig Cancer Center: *Genome Stability in MDS* **2007 • Dr. Hiromi Gunshin** (Trinity Ewert*) University of Massachusetts - Amherst: *Studies Toward Alternative Therapies for Iron Overload in Patients* **2007 • Dr. Kay Macleod** (Erwin Umbach/MacGillivray Family*) Ben May Inst. Cancer Research Center: *Oxidative Stress in Etiology of MDS* **2007 • Dr. Lubomire Sokol** (Harold Spielberg*) H.Lee Moffitt Cancer Center: *Studying Microarray Profiling of Micro RNA in 5Q Minus Syndrome* **2008 • Dr. Antonio Maria Risitano** (PNH Foundation) University of Naples (Italy): *Genetic Fingerprint of Complement and Complement-related Genes in PNH: Relationship with Pathophysiology, Clinical Manifestations (including Thrombosis) and Response to Eculizumab* **2008 • Dr. Benjamin Braun** (Harold Spielberg*) University of California, San Francisco: *Mechanisms and Therapy of Anemia Caused by Activating Kras Mutation* **2008 • Dr. Jaroslaw Maciejewski** Cleveland Clinic Taussig Cancer Center: *Identification of Mutations in C-Cbl as Pathogenetic Factors in Patients with MDS* **2008 • Dr. Lisa Minter** (Torry Yahn*) University of Massachusetts-Amherst: *Evaluating PKC-0 as a Therapeutic Target in a Mouse Model of Severe AA* **2009 • Dr. Archibald Perkins** (Harold Spielberg*) University of Rochester: *Development of Targeted Therapies for 3q26-positive MDS* **2009 • Dr. Kazuhiko Ikeda** (PNH Foundation*) Washington University School of Medicine: *The Mechanism of Clonal Dominance of PNH Cells* **2009 • Dr. Regis Peffault de Latour** (PNH Foundation*) Hospital Saint Louis, Paris: *The Role of Unfolded Protein Response in PNH* **2010 • Dr. Gregory Abel** (MacGillivray*, Madden* & AAMDSIF General Research Fund) Dana-Farber Cancer Institute: *Developing a Disease-Specific Measure for Quality of Life in Patients with MDS* **2010 • Dr. Cristian Bellodi** (Emily Kass*) University of California, San Francisco: *Emerging Role of p53 Translation Control in Hematopoietic Stem Cell Quiescence and Differentiation* **2010 • Dr. Muneoshi Futami** (Harold Spielberg*) Northwestern University: *Molecular Basis for Disordered Myeloid Growth in Monosomy 7* **2010 • Dr. Ramon Tiu** (Torry Yahn*) Cleveland Clinic: *LFA-3/CD2 Pathway: Potential Target for Immunosuppressive Therapy in AA*

Key * Supported by a Named Tribute Fund; AA= aplastic anemia; MDS= myelodysplastic syndromes; PNH= paroxysmal nocturnal hemoglobinuria.



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