Aplastic Anemia & MDS
INTERNATIONAL FOUNDATION



SUMMARY
FOR PATIENTS

INTERNATIONAL BONE MARROW FAILURE DISEASE
SCIENTIFIC SYMPOSIUM 2014

Building a Collaborative Research Community That Saves Lives

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Dear Friends,

It is with great pleasure that we present this Summary for Patients from the 4th AA&MDSIF Bone Marrow Failure Scientific Symposium held March 27 and 28 in Rockville, Maryland. This symposium brought together many of the world's leading 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 & MDS International Foundation (AA&MDSIF) 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. We are proud to have awarded more than $4 million in research grants to over 60 researchers to advance the study of bone marrow failure disease. 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 disease research.

This Symposium would not have been possible without the sponsorship of the National Heart, Lung and Blood Institute (NHLBI), the National Center for Advancing Translational Sciences (NCATS), Office of Rare Diseases Research (ORDR), and generous contributions from the Edward P. Evans Foundation and 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,

Kevin Lyons-Tarr
Chairman, Board of Directors

John M. Huber
Executive Director

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Funding for this conference was made possible in part by 1RI3HL123300-01 from the National Institutes of Health. The views expressed in written conference materials or publications and by speakers or moderators do not necessarily reflect the official policies of the Department of Health and Human Services; nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government.

GENERAL INFORMATION

Purpose of the Symposium

The Fourth AA&MDSIF International Bone Marrow Failure Disease Scientific Symposium, "Building a Collaborative Research Community That Saves Lives," was held on March 27 & 28, 2014 in Rockville, Maryland. The symposium gathered over 160 participants to hear more than 35 of the world's leading researchers on aplastic anemia, MDS and 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, myelodysplastic syndromes (MDS), and paroxysmal nocturnal hemoglobinuria (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:

- Better understanding of the molecular biology of bone marrow failure diseases has resulted in clinical benefit, with many recent therapeutic advances based on genetic research
- The genomic landscape of MDS is a key area of advancement, since 90% of MDS patients have at least one genetic mutation
- Studies of eltrombopag show promising results for aplastic anemia
- Research advances understanding of immunity and immunology in PNH

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.

Interviews were recorded at the symposium with the session co-chairs who explain the highlights of the presentations for patients. These interviews may be viewed at **www.AAMDS.org/2014symposiumvideos.**

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, Support Connection, 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

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SUMMARY FOR PATIENTS

THURSDAY, MARCH 27, 2014

Genetics and Genomics of Bone Marrow Failure

Session Co-Chairs: ***Jaroslaw Maciejewski****, MD, PhD, Cleveland Clinic, and* ***Sharon Savage****, MD, FAAP, National Cancer Institute*

Exome Sequencing in MDS

Hideki Makishima, *MD, PhD, Cleveland Clinic*

Researchers are using state-of-the-art genome sequencing technologies to identify mutations in genes associated with MDS. In a study, whole-exome sequencing, a technique to study the coding regions of all genes, identified more than 2,000 mutations shared by 206 patients with MDS in more than 1,400 genes. About 90% of these patients had at least one of these mutations. On average, patients with MDS had nine of these mutations, and those whose MDS had progressed to acute myelogenous leukemia (AML) had 11 of the mutations. The TET2 mutation was one of the 10 most frequently mutated genes in this study. Patients with mutations in this gene had more mutations than patients without a TET2 mutation.

Dr. Makishima and his colleagues tried to use mutations alone to identify whether patients had MDS or myelodysplastic/myeloproliferative neoplasms (MDS/MPN). The data showed that patients with MDS/MPN might have more uniform genetic mutations than those with MDS.

Dr. Makishima's research showed that some mutations, such as in in TET2 and DNMT3A, tend to occur early in the development of clones, or abnormal copies of cells. These mutations are more common in patients with low-risk MDS. Other mutations, such as in NPM1 and KRAS, tend to occur later in the development of clones. These mutations are more common in patients with high-risk MDS or MDS that has progressed to AML.

Whole-exome sequencing techniques also showed that members of families of several people with MDS or AML often have mutations in the DDX41 gene. Acquired (non-inherited) mutations in DDX41 were much more common in patients with inherited mutations in this gene than those without inherited DDX41 mutations. Acquired DDX41 mutations were also more common in patients with advanced MDS and a poor prognosis. But patients with DDX41 mutations were more likely to respond to treatment with lenalidomide (Revlimid®), a drug that is typically used to treat lower-risk MDS.

Genetics of MDS and Other Bone Marrow Failure Syndromes in Children

Seiji Kojima, *MD, PhD, Nagoya University (presented by* **Hideki Muramatsu***, MD, PhD, Nagoya University)*

When Dr. Kojima studied stored blood samples from several Japanese pediatric institutes, he identified 835 patient samples with congenital blood diseases (present since birth). Of these samples, 49% had no genetic mutations known to be associated with congenital blood diseases.

Dr. Kojima wanted to find out whether whole-exome sequencing (a technique to study the coding regions of all genes) can be used to diagnose congenital blood diseases, including inherited bone marrow failure syndromes. He used this technique with samples from 352 patients with various congenital blood diseases. The results showed that 22% of patients had a mutation associated with a congenital blood disease. Most of these patients had not been diagnosed with one of these diseases using conventional DNA sequencing techniques. Furthermore, the whole-exome sequencing results contradicted the physician's diagnosis in several patients.

Children with juvenile myelomonocytic leukemia (JMML), a rare blood cancer, have too many immature white blood cells that crowd out healthy bone marrow cells. About 80% of children with JMML have mutations in RAS pathway genes. When Dr. Kojima and colleagues used whole-exome sequencing to study specimens from 13 patients with JMML, they found that patients had non-inherited mutations in SETBP1, JAK3, and SH3BP1.

Patients acquire SETBP1 and JAK3 mutations later in the development of the disease than mutations in RAS pathway genes, and SETBP1 and JAK3 mutations contribute to disease

progression. Patients with these mutations and others that develop later in disease progression don't survive as long as patients without these mutations. Patients who undergo bone marrow transplantation are most likely to survive for at least five years after diagnosis.

All of these results show the importance of using whole-exome sequencing in the health-care setting.

Gene Discovery in Inherited BF Syndromes

Marcin Wlodarski, *MD, University of Freiburg*

The prototypical inherited bone marrow failure disease is Fanconi anemia (FA), which results from defective DNA-repair mechanisms. More than 95% of patients with FA have mutations in 15 genes. Most of these mutations involve both copies of the genes. The bone marrow failure in FA gradually gets more severe. The low blood counts associated with FA sometimes respond to treatment with anabolic steroids. Typically, patients develop symptoms of FA before age 10, but some patients are first diagnosed as adults.

Dyskeratosis congenita (DC) is another severe and progressive inherited bone marrow failure syndrome. In at least half of patients with DC, researchers can identify mutations in the genes that help maintain telomeres, which are structures at the ends of chromosomes.

Different genes influence when a patient develops DC symptoms and his or her long-term prognosis. For example, patients with mutations in TINF2 and RTEL1 tend to develop DC symptoms much earlier than patients with mutations in the other DC genes. The risk of problems not related to blood, such as lung and liver fibrosis, is higher in patients with TERT and TERC mutations. A potential explanation is that patients with TERT and TERC mutations tend to live longer.

The GATA2 gene plays an essential role in the early stages of blood cell development. Researchers have recently shown that mutations in GATA2 are associated with several different disorders, such as Emberger syndromes (characterized by swelling, deafness, and warts) and monocytopenia and mycobacterial infection syndrome, an immune system disorder. People with these disorders have a high risk of MDS.

Dr. Wlodarski also found that children with primary MDS (which isn't due to treatment for another disease) had GATA2 mutations. But none of the children who developed secondary MDS (as a result of treatment for another disease) had a GATA2 mutation. Of children with a GATA2 mutation, 80% developed monosomy 7 MDS (associated with only one copy of chromosome 7) or trisomy 8 MDS (an extra copy of chromosome 8). Children with monosomy 7 MDS who were younger than four were less likely to have a GATA2 mutation than those aged 12–18 years. But survival rates were the same in patients with and without the mutation.

GATA2 Mutations in MDS and GATA2 Deficiency

Amy Hsu, *Biologist, National Institute of Allergy and Infectious Diseases*

The GATA2 gene carries the code for the GATA2 protein, which controls many aspects of bone marrow and blood vessel development. A single mutation in the GATA2 gene can cause symptoms of a GATA2 deficiency known by several names, including MonoMAC, familial acute myelogenous leukemia (AML), Emberger syndrome, DCML deficiency, and classical natural killer cell deficiency. Ms. Hsu suggests referring to all disorders involving GATA2 mutations as GATA2 deficiency.

Patients with GATA2 deficiency often have very low levels of monocytes, a type of white blood cell that's part of the immune system. These patients have a high risk of infection and blood diseases, including mycobacterial and viral infections, especially human papillomavirus and Epstein-Barr virus. Patients are often diagnosed with GATA2 deficiency as young adults when they develop certain kinds of infections, aplastic anemia, MDS, or AML.

Patients with MDS caused by GATA2 deficiency are diagnosed much earlier than those with age-related MDS, which is often diagnosed at age 70–80 years. Many patients with GATA2 deficiency have a family history of infections and MDS or leukemia. The best treatment for GATA2 deficiency is bone marrow transplantation.

SUMMARY FOR PATIENTS

Most patients with GATA2 deficiency have mutations in the coding region of GATA2, resulting in a protein that doesn't work correctly. But Ms. Hsu identified patients with GATA2 deficiency who have mutations outside the coding region, in a location that controls the production of GATA2 RNA that is translated into GATA2 protein. These mutations reduce the amount of GATA2 protein made by the mutant copy of the GATA2 gene. In other patients, only one copy of the GATA2 gene makes GATA2 RNA and the other copy produces little or no RNA.

Ms. Hsu showed that GATA2 deficiency is caused by haploinsufficiency, meaning that one good copy of the GATA2 gene can't produce enough GATA2 protein for blood cells to function properly. When she screened 230 patients who had aplastic anemia, 11 had changes in GATA2, including 9 with mutations in non-coding regions of GATA2. When she compared the GATA2 mutations identified at the National Institutes of Health (NIH) to those in the published literature, she noted that 23% of the mutations found at NIH were in non-coding regions, even though the literature had no other reports of non-coding mutations. This finding suggests that GATA2 deficiency might be under-diagnosed.

These results confirm that mutations in GATA2 lead to haploinsufficiency and GATA2 deficiency or other syndromes. This research sheds light on the types of genetic mutations involved in the development of GATA2 deficiency. The results do not mean that physicians should screen every patient who has aplastic anemia for mutations in GATA2. But patients should be screened if they have both aplastic anemia and a history of infections or a family history of bone marrow failure syndromes.

Genetic Mutations in Severe Aplastic Anemia

Bogdan Dumitriu, *MD, National Heart, Lung, and Blood Institute*

Dr. Dumitriu evaluated patients with severe aplastic anemia for acquired (non-inherited) mutations in 106 genes associated with primary MDS and acute myelogenous leukemia (AML). The study's goal was to find out whether these mutations were associated with the risk of developing MDS or AML. Ten to fifteen percent of patients with severe aplastic anemia who undergo treatment to suppress their immune system (immunosuppressive therapy) progress to MDS or AML.

The genes that were most often mutated in these patients were PIGA (which causes PNH), ASXL1, BCOR, and DNMT3A. Some patients had mutations in more than one of the genes analyzed. Having one or more acquired mutations at six months after initial diagnosis with severe aplastic anemia didn't affect a patient's chance of survival for the next 14 years or of responding to immunosuppressive treatment. The mutations also had no effect on the likelihood that a patient would have a relapse after responding to treatment or that the disease would progress to MDS or AML. But the mutations did correlate with one patient characteristic—age. Older people were more likely to have mutations (except for mutations in PIGA) than younger people, and the risk of having more than one mutation increased with age.

To understand the risks of developing MDS or AML in patients with severe aplastic anemia, Dr. Dumitriu compared 13 patients with severe aplastic anemia who developed monosomy 7 MDS (which means that they had only one copy of chromosome 7) to 30 patients with stable severe aplastic anemia.

Over the next three years, telomeres (structures at the ends of chromosomes that normally shorten with age) became shorter more quickly in patients whose severe aplastic anemia progressed to MDS or AML than in patients with stable severe aplastic anemia. Less than half the patients whose severe aplastic anemia progressed developed mutations in genes that are associated with MDS and AML. Some patients had these mutations at the beginning of the study, and others acquired the mutations when they developed MDS or AML.

In conclusion, the presence of acquired mutations in patients with severe aplastic anemia seems to be associated with the normal aging process and has no impact on responses to treatment or long-term complications. Acquired mutations don't completely explain the progression to MDS or AML because the risk of progression is related to increased rates of telomere shortening in these patients.

Genetic Mutations in PNH

Naoko Hosono, *MD, PhD, Cleveland Clinic*

Progression to MDS or acute myelogenous leukemia (AML) is a common complication of aplastic anemia.

Dr. Hosono used whole-exome sequencing, a technique to study the coding regions of all genes, to identify genetic mutations on chromosome 7. This study included 18 patients whose aplastic anemia progressed to MDS or AML. Forty percent of these 18 patients had mutations on chromosome 7 at diagnosis, whereas the rate was 28% in those whose disease did not progress. These results show that these genetic mutations might be useful for predicting which patients with aplastic anemia will develop MDS.

Dr. Hosono then studied patients with PNH to see if the findings were similar. Patients with PNH have abnormal clones, or copies, of stem cells in the bone marrow that make blood cells. The disease is caused by a mutation in the PIGA gene that patients acquire (meaning that they don't inherit the mutation from a parent). Like patients with MDS, those with PNH have non-inherited mutations in genes that lead to the formation of abnormal clones, or copies of immature white blood cells. In both diseases, the abnormal clones persist and expand. These patients have low counts of certain blood cells and, often, a history of aplastic anemia.

To learn more about the genetic mutations involved in PNH, Dr. Hosono conducted genomic sequencing in 58 patients with PNH. Most of these patients had one PIGA mutation, and 33% had two PIGA mutations.

The results showed that developing a PIGA mutation is the first step in PNH and is followed by other mutations in PIGA or other genes. But patients who have had bone marrow failure and develop PNH acquire a mutation in another gene before developing a PIGA mutation. Mutations in genes other than PIGA in clones might change the behavior of the PIGA clone. This could explain why different patients with PNH have different symptoms and outcomes.

Mutations in Cohesin Genes

Kenichi Yoshida, *MD, PhD, Kyoto University*

Cohesin is a protein complex that plays an important role in cell division. Mutations in the cohesin components and related genes lead to certain rare congenital diseases (present since birth), such as Cornelia de Lange syndrome and Roberts syndrome.

CTCF is a protein that apparently works with cohesin to control gene expression. Dr. Yoshida and other researchers have shown that acquired (non-inherited) mutations in cohesin genes are involved in MDS and other diseases of the blood and bone marrow. Patients typically have mutations in only one of these genes, suggesting that these mutations might have similar effects to each other on cohesin function.

Dr. Yoshida and colleagues studied 14 genes associated with cohesin function in 944 patients with MDS. Of these patients, 154 (16%) had at least one mutation or deletion in cohesin and related genes.

Eight percent of patients had mutations in the cohesin gene STAG2. In addition, 17 patients (2%) had two, three, or even four STAG2 mutations. Moreover, patients with mutations in STAG2 often had mutations in SRSF2, ASXL1, EZH2, IDH2, RUNX1, and BCOR. But patients with STAG2 mutations did not have mutations in SF3B1. Nineteen patients (2%) had mutations or deletions in CTCF. No patient had mutations in both CTCF and STAG2. Seventeen patients (2%) had mutations or deletions in PDS5B, which is an accessory factor of the cohesin complex. Patients with mutations in a cohesin gene or a related gene had a poorer prognosis than patients without these mutations.

These results show that cohesin mutations could be useful for determining patients' prognosis and selecting appropriate treatments.

New Genetic Targets for Treatment in MDS

Session Co-Chairs: ***Mario Cazzola****, MD, University of Pavia, and* ***Benjamin Ebert****, MD, PhD, Brigham and Women's Hospital*

Targeting Early Genetic Events in MDS

Matthew Walter, *MD, Washington University in St. Louis*

Spliceosome genes form proteins involved in splicing messenger RNA. Messenger RNA contains the coding information that genes need to make proteins. Cells splice together certain sequences in RNA to form messenger RNA molecules that can produce proteins that work properly.

SUMMARY FOR PATIENTS

Most patients with MDS have a mutation in at least one of approximately 20 genes, including several genes involved in RNA splicing. These 20 genes can be grouped into six categories based on their functions in a cell. Patients rarely have mutations in more than one gene within the same category (in other words, these mutations are mutually exclusive). For example, patients with a mutation in the U2AF1 spliceosome gene never have a mutation in the SF3B1 spliceosome gene.

Dr. Walter discussed two possible explanations:

1. Genes in the same category have the same functions. So a patient needs a mutation in only one of these genes to develop MDS.
2. Cells do not tolerate mutations in two members of the same group. If two mutations occur, the cell dies.

In MDS, a founding clone, or abnormal copy of an immature white blood cell, gives rise to many MDS subclones. Each of these subclones carries forward the mutations in the founding clone. The subclones also develop other mutations. Genome sequencing studies show mutations in spliceosome genes tend to occur early in MDS development. If this is true and founding clones tend to have these mutations, targeting mutations in a founding clone with a drug could be an effective strategy to treat MDS.

Mutations in the 20 genes that are most commonly mutated in MDS don't necessarily happen at the same time in MDS development in all patients. A specific gene mutation could happen in a founding clone in one patient and a subclone in another. Dr. Walter therefore focused on mutations that tend to occur in founding clones. For example, mutations in the U2AF1 spliceosome gene tend to occur in founding clones in most patients with this mutation, and the mutation is carried forward in subclones.

Sudemycin is a drug that affects RNA splicing, causing cell death and splicing abnormalities in MDS cells that have a U2AF1 mutation. Studies in cells from mice show that sudemycin blunts the effects of U2AF1mutations. Studies are evaluating the effects of sudemycin on MDS development and progression in mice.

Growth of Abnormal Blood-Forming Cells in MDS

Sten Eirik Jacobsen, *MD, PhD, University of Oxford*

In healthy people, the formation of blood cells is hierarchical, meaning that the earlier steps influence the later steps. In people with leukemia, blood cell formation is not hierarchical because only a small fraction of cells in the early stages can create clones, or copies, of cells in later stages. A possible explanation is that only a few cells—cancer stem cells—can replicate themselves and become other types of cells that can't self-replicate.

MDS stem cells have genetic characteristics and activities that are clearly different from those of healthy blood cells. In patients with low-risk MDS, MDS stem cells are easy to tell apart from other blood-forming cells in the bone marrow, and the number of MDS stem cells is small.

A large proportion of stem cells that form blood cells in the bone marrow of people with MDS are abnormal. This suggests that MDS stem cells can outcompete normal stem cells. The question is whether MDS stem cells are the only ones that can give rise to MDS clones. To answer this question, Dr. Jacobsen and colleagues tracked acquired, or non-inherited, genetic mutations in people with MDS. His rationale was that any stable mutations must occur in cells with the ability to self-replicate.

Dr. Jacobsen analyzed acquired genetic mutations that invariably initiate Lin-CD34+CD38-CD90+ MDS stem cells in patients with low- and intermediate-risk MDS. In these patients, Lin-CD34+CD38-CD90+ MDS stem cells exist only in the stem cell compartment, and the relationship between these MDS and normal stem cells is hierarchical. In addition, acquired mutations seem to give a competitive advantage to Lin-CD34+CD38-CD90+ MDS cells over normal stem cells in the stem cell compartment. But these mutations don't give these early stem cells the ability to self-replicate.

Once a patient develops certain genetic mutations, his or her Lin-CD34+CD38-CD90+ MDS cells develop the ability to self-renew outside the stem cell compartment. The mutations that patients acquire at this later stage, which could be associated with

the development of acute myelogenous leukemia, might allow cells further down in the hierarchy to self-replicate.

Dr. Jacobsen concluded that eliminating the rare Lin-CD34+CD38-CD90+ MDS stem cells might be an effective way to cure MDS.

Non-inherited Genetic Mutations in MDS

Omar Abdel-Wahab, *MD, Memorial Sloan Kettering Cancer Center*

Unlike other bone marrow failure syndromes and blood cancers, MDS is often associated with mutations in epigenetic modifier and splicing genes. Epigenetic modifier genes make changes that do not involve DNA structure. Splicing genes splice together certain DNA sequences in RNA to form messenger RNA molecules that can produce proteins that work properly. Mutations in the SF3B1 and SFRSF2 splicing genes are two of the most common mutations in MDS. Mutations in SRSF2 are associated with poorer survival.

Dr. Abdel-Wahab created a mouse model in which the SRSF2 gene mutation in MDS patients is created (knocked in). To understand whether this mutation results in loss of SRSF2 function or a new SRSF2 function, he also studied a model in which the gene is inactivated (knocked out).

Homozygous mice have two identical copies of the SRF2 gene, whereas heterozygous mice have two different copies. Both homozygous knockout mice and heterozygous knockin mice die before birth, but the heterozygous knockout mice grow normally. Every homozygous knockout mouse has DNA damage, but none of the knockin mice do. These results show that the SFSRF2 mutation doesn't involve complete loss of the gene's function.

Stem cells are immature white blood cells in bone marrow. Stem cells from knockout mice with a homozygous SRSF2 mutation don't form colonies of blood cells as well as heterozygous knockout or knockin mice or mice with a normal SRFS2 gene. This result suggests that stem cells in mice with an SRSF2 mutation can't form different types of blood cells properly.

Mice with a homozygous mutation have a low white blood cell count and some have a low red blood cell count. The reason for these low blood cell counts is that a properly functioning SRSF2 gene is necessary for forming healthy blood cells.

Genes that Determine Responses to Treatment with Lenalidomide

Benjamin Ebert, *MD, PhD, Brigham and Women's Hospital*

Thalidomide was used in the 1950s to treat nausea in pregnancy. The drug caused birth defects and was eventually taken off the market. However, the drug had some remarkable biological properties. For example, thalidomide stopped the bone marrow from forming unhealthy blood cells in people with cancer. A derivative of thalidomide eventually received approval from the U.S. Food and Drug Administration for the treatment of multiple myeloma.

Lenalidomide (Revlimid®) is another derivative of thalidomide. Lenalidomide is a particularly powerful drug for treating patients with 5q-deletion MDS, which involves a deletion (loss) of the long (q) arm of chromosome 5. In many ways, lenalidomide is the best drug for MDS because of its effect on blood cell formation and its ability to help patients achieve remission.

Dr. Ebert found that lenalidomide decreases levels of IKZF1 and IKZF3 proteins, which regulate the formation of white blood cells. This effect happens within just three hours of treatment. The amount of the ubiquitinated protein (marked for transportation or degradation) that attaches to these proteins increases as the lenalidomide dose rises.

Another target of lenalidomide is the CSNK1A1 gene, located in the middle of the region of chromosome 5 that is deleted in 5q-deletion MDS. The CSNK1A1 gene has haploinsufficient expression, meaning that patients have only one healthy copy of this gene. Lenalidomide decreases the abundance and activity of CSNK1A1.

Inhibiting the Csnk1a1 protein produced by the CSNK1A1 gene results in the elimination of both MDS and leukemia cells. Therefore, the Csnk1a1 protein might be a treatment target in acute myelogenous leukemia (AML). Dr. Ebert is currently developing a mouse model to study the effect of targeting Csnk1a1 in 5q-deletion MDS.

SUMMARY FOR PATIENTS

Immune System Biology of Aplastic Anemia and PNH

Session Co-Chairs: ***Régis Peffault de Latour****, MD, PhD, Hôpital Saint-Louis, Paris, and* ***Antonio Risitano****, MD, PhD, University of Naples*

Biology of Aplastic Anemia: Beyond the Immune System

Rodrigo Calado*, MD, PhD, University of São Paulo*

Dr. Calado presented two cases of severe aplastic anemia to show the importance of understanding the disease's biology for choosing the appropriate treatment for each patient.

Telomeres are structured at the ends of chromosomes that help keep chromosomes stable. As people age, their telomeres become shorter. Patients with short telomeres at diagnosis with aplastic anemia are more likely to develop MDS or acute myelogenous leukemia than those with longer telomeres. Those with mutations in the telomerase genes TERT or TERC, which help maintain telomere length, tend to develop moderate aplastic anemia. However, a significant minority have severe aplastic anemia at diagnosis.

For several decades, the main treatment for severe aplastic anemia has been to suppress the immune system with various drugs. At least half of patients with TERT or TERC mutations respond to immune-suppressive therapy. But other patients don't respond to this treatment.

Case 1: A 28-year-old man with a shortage of platelets and large, fragile red blood cells was treated with a corticosteroid (an immune-suppressive treatment), but did not respond. His disease seemed to be in between aplastic anemia and MDS. Five years later, he had low counts of all blood cells and needed regular blood transfusions. He had a strikingly good response to treatment with two immune-suppressive drugs, rabbit antithymocyte globulin (ATG) and cyclosporin. The patient had short telomeres, which are structures that protect the ends of chromosomes and that normally get shorter with age. Six months later, the patient developed a cough, breathing problems, and fever, which are common in patients with telomerase mutations. Three months later, he died.

Although patients with aplastic anemia who have telomerase mutations might benefit from ATG and cyclosporin, these responses are sometimes temporary. Eltrombopag (Promacta®) is a treatment option for patients whose severe aplastic anemia does not respond to immune-suppressive treatment. This drug stimulates thrombopoietin, a hormone that controls platelet production in the bone marrow. In a study in 25 patients with aplastic anemia that did not respond to immune-suppressive treatment, eltrombopag increased blood cell counts in 11 patients (44%).

Case 2: A 26-year old woman had low counts of all blood cell types starting at age 16. Two of her brothers had died of aplastic anemia. Eleven other siblings were healthy but one had anemia. The family's telomere lengths were normal. Several family members had mutations in the THPO gene that makes thrombopoietin.

This case shows that THPO gene mutations cause inherited aplastic anemia in families. The THPO mutation might be a good treatment target for severe aplastic anemia.

Autoimmunity in Aplastic Anemia

Shahram Kordasti*, MD, PhD, King's College London and King's College Hospital*

In autoimmunity, the patient's immune system regards his or her own tissues as foreign invaders and attacks them. About 60–70% of patients with aplastic anemia respond to treatments with antithymocyte globulin and cyclosporin, which suppress the immune system. This shows that autoimmunity might play a role in aplastic anemia.

The immune-suppressive drug cyclosporin is an important component of aplastic anemia treatment, suggesting that T cells are important in aplastic anemia. T cells are a type of white blood cell that help protect the body from harmful substances. Removing T cells can help patients recover from aplastic anemia.

Patients with aplastic anemia have fewer T regulatory (Treg) cells, which control the activity of other T cells, than people without aplastic anemia. Patients with fewer Treg cells have more severe aplastic anemia, and those with more Treg cells are more likely to respond to treatment.

There are different types of Treg cells, and Treg cells can change from one type to another. Treg cells can be identified by their genetics and behaviors.

When a patient with aplastic anemia responds to treatment with an increase in Treg cells, where do those additional Treg cells come from? The Treg cells that remain in these patients expand very little after treatment, so they don't explain the extra Treg cells that show up after treatment. Instead, these additional Treg cells are already present in the patient before treatment. But before treatment, the FOXP3 gene, which regulates the immune system, does not work properly in these cells. The gene only starts working properly after treatment.

Treg cells and their ability to change characteristics are critical players in aplastic anemia autoimmunity. Expanding the number of Treg cells that maintain their forms could be an effective treatment approach for aplastic anemia.

Autoimmunity in PNH

Anastasios Karadimitris, *MD, PhD, Imperial College London*

Patients with PNH have abnormal clones, or copies, of hematopoietic stem cells (HSCs) in the bone marrow. HSCs can turn into all types of blood cells. Because of a mutation, or change, in the PIGA gene, HSCs in patients with PNH lack glycosyl phosphatidylinositol (GPI)-anchored proteins. These proteins protect red blood cells from being destroyed, help blood form clots, and defend the body from infections.

Patients with PNH have abnormal red blood cells that don't have two important complement-regulating proteins, CD55 and CD59. When a person is injured or attacked by a virus, the complement system recruits enzymes and other mediators to fight the invader. The CD55 and CD59 complement proteins normally protect red blood cells from destruction by complement. Without these proteins, the complement system destroys red blood cells prematurely. However, the cause of bone marrow failure in PNH has not been determined.

In autoimmunity, the patient's immune system regards his or her own tissues as foreign invaders and attacks them. Aplastic anemia involves autoimmunity and has a lot in common with PNH. For example, patients with both diseases have low counts of HSCs. The bone marrow failure in PNH might also be the result of an autoimmune attack.

In people with PNH, the autoimmune process seems be selective. These patients have many more T cells that attack HSCs with GPI-anchored proteins than HSCs lacking these proteins because of the PIGA mutation. T cells are a type of white blood cell that help protect the body from harmful substances. But the T cells in PNH only attack HSCs with GPI-anchored proteins when these cells are bound to CD1d protein. These T cells could be responsible for the bone marrow failure in PNH.

A Novel Treatment Target for PNH

John Lambris, *PhD, University of Pennsylvania*

Patients with PNH have abnormal red blood cells that don't have two important complement-regulating proteins. When a person's body is attacked by foreign pathogens (biological agents, such as viruses or bacteria, that cause disease), the complement system recruits its enzymes and other mediators to fight the invader. The complement proteins that are lacking in PNH normally protect red blood cells from destruction by complement. Without these proteins, the complement system destroys red blood cells prematurely.

Eculizumab (Soliris®) is a drug that blocks complement protein attacks on blood cells and prevents premature destruction of red blood cells in people with PNH. Eculizumab has dramatically improved PNH treatment. But this treatment costs more than $400,000 a year per patient, and the drug doesn't prevent premature destruction (breakdown) of red blood cells outside the veins and arteries.

Dr. Lambris described three experimental treatments to attack the complement component 3 (C3) protein. One of these approaches might offer an effective treatment for PNH.

The first treatment, compstatin (also known as Cp40), protects tissue from ongoing complement attacks and prevents tissue damage. The compound is stable in plasma and has a long half-life—it takes 12 hours for the body to eliminate half the drug's concentration. The drug could be injected under the skin every 12 hours, and it would be very cheap

to manufacture. Dr. Lambris hopes to start a Phase I clinical trial of compstatin in January 2015.

Factor H, is a protein that naturally helps control complement. To create the second treatment, Dr. Lambris engineered a version of Factor H known as "mini-FH." Mini-FH is 10 times more active than the natural Factor H and helps PNH red blood cells protect themselves from complement attack.

Dr. Lambris is developing the third strategy, a Factor-H-binding peptide that uses the body's natural complement inhibitors to inhibit complement attacks. This compound could protect cells and organs from complement attack. He hopes to test this peptide in a clinical trial the next few years.

Aplastic Anemia in the Developing World

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

Severe Aplastic Anemia in India

Professor Maitreyee Bhattacharyya, *Nilratan Sarkar Medical College, Kolkata, India*

Aplastic anemia is two to four times more common in Asia than in Western countries. Explanations could be exposures to infections or chemicals in the environment or differences in genetic factors. The actual rate of aplastic anemia in India and its causes in Asia need to be determined through scientific research.

Dr. Bhattacharya's institution has 450 registered patients with aplastic anemia. More patients are 11–20 years old at diagnosis than any other age range. This age at diagnosis is much younger than in developed countries. Although aplastic anemia is equally common in males and females in general, about two-thirds of patients in India are male. Reasons could be that males are more likely to be exposed to chemicals and females are less likely to see a health-care provider to get a diagnosis.

Slightly more than half of all patients at Dr. Bhattacharya's institution have severe aplastic anemia, and the remainder have non-severe or very severe aplastic anemia. The most common symptoms at diagnosis are anemia (low red blood cell count), bleeding, and fever.

Patients in India pay for treatment out of their own pockets. Very few hospitals offer bone marrow transplantation, and patient wait for a year, on average, for a transplant. Some patients are treated with a locally developed antithymocyte globulin (ATG; a treatment that suppresses the patient's immune system). Whether the local ATG is as effective as the ATG used in other countries is not known. The most common treatments for aplastic anemia in India are cyclosporin and androgens to suppress the immune system, which are cheaper than ATG. But many patients can't afford even these drugs.

Response rates to immune-suppressive treatments are much lower in India than in other countries. Moreover, responses are often delayed, and achieving a complete response (meaning that the patient has no signs of aplastic anemia) takes as long as a year. The reasons why are not known. Many patients receive only treatments designed to control their symptoms and not to cure their disease.

Aplastic Anemia in Thailand

Surapol Issaragrisil, *MD, Mahidol University, Thailand*

According to a study by Dr. Issaragrisil, about four per million people have aplastic anemia in Thailand. This rate is higher than in Europe or the United States. In Thailand, aplastic anemia is probably caused by such factors as drinking non-bottled water and being exposed to ducks, geese, and fertilizers made from animal products. Drug use is not a major cause of aplastic anemia in Thailand.

The guidelines for managing severe aplastic anemia in Thailand call for bone marrow transplantation in patients younger than 40 who have a matched sibling donor. But many patients can't afford bone marrow transplantation or drugs to suppress their immune system. So patients are often treated with anabolic steroids.

A study in 95 patients who were treated with horse or rabbit antilymphocyte globulin (ALG), rabbit antithymocyte globulin (ATG), or ATG-Fresenius® showed that patients treated with horse ALG had

better survival than those treated with ATG-Fresenius or rabbit ATG. About a fifth of patients treated with ALG or ATG had a complete response (meaning no signs of aplastic anemia) and a third had a partial response at 12 months. The most common treatment complications were infection and bleeding.

About a fifth of patients treated with anabolic steroids for at least six months had a complete response and half had a partial response at 12 months. None of the patients with very severe aplastic anemia survived with anabolic steroid treatment. The main complications of steroid treatment were high levels of certain liver enzymes, breast enlargement in men, and abnormal hair growth. In patients with severe aplastic anemia, survival was similar in those treated with ALG, ATG, and anabolic steroids.

The Thai study confirmed previous reports of an association between mutations in the HLA-DB1 gene and aplastic anemia.

Treatment of Severe and Very Severe Aplastic Anemia in a Chinese Hospital: First Perspective

Fengkui Zhang, MD, *Institute of Hematology and Blood Diseases Hospital, China*

Chinese doctors follow the guidelines of the British Committee for Standards in Haematology when they treat severe and very severe aplastic anemia. This treatment usually consists of antithymocyte globulin (ATG) and cyclosporin, which suppress the patient's immune system. Horse ATG is at least as effective as rabbit ATG. But horse ATG is not available in China, so Chinese providers use rabbit or pig ATG.

The Blood Diseases Hospital in Tianjin, China, recommends bone marrow transplantation in patients who are 40 or younger and have a matched sibling donor. For other patients, clinicians prefer antithymocyte globulin (ATG) and cyclosporin. If a patient cannot afford this treatment, the next choice is pig ATG and cyclosporin. The treatment for patients who can't afford pig ATG, which costs about a third as much as rabbit ATG, is high doses of cyclophosphamide (Cytoxan®).

Of 292 patients with severe or very severe aplastic anemia treated with rabbit ATG and cyclosporin at the Blood Diseases Hospital, 37% had a complete response (no signs of aplastic anemia) at 12 months and 14% had a partial response. About 84% survived for at least five years after treatment. Survival rates were highest in children and adults younger than 40, and patients with severe aplastic anemia survived longer than those with very severe aplastic anemia.

A study in 48 patients treated with pig ATG and cyclosporin found that about 83% responded. In a study comparing pig to rabbit ATG, about 20% of 56 patients treated with pig ATG had a complete response at 6 months, compared to 16% of 107 patients treated with rabbit ATG.

Among 48 adults treated with high doses of cyclophosphamide, response rates were similar to those in 73 patients treated with rabbit ATG. About 80% of patients in both groups survived for at last 5 years, and two-thirds didn't have a relapse in that time. When 22 children with severe or very severe aplastic anemia were treated with high-dose cyclophosphamide and cyclosporin, almost three quarters responded within 12 months. This response rate is similar to the rate with rabbit ATG. One reason why responses to cyclophosphamide treatment in China are so much better than in other countries could be that Chinese and Caucasian patients process this drug differently.

Treatment of Aplastic Anemia in a Chinese Hospital: Second Perspective

Yizhou Zheng, *MD, PhD, Institute of Hematology and Hospital of Blood Diseases, China*

Horse antithymocyte globulin (ATG) is not available in China, and most patients with aplastic anemia do not have a suitable sibling donor for bone marrow transplantation. Rabbit ATG is the best choice for most patients with aplastic anemia in China.

Dr. Zheng's team uses rabbit ATG as its first treatment. When the standard dose of rabbit ATG was used in 51 patients, only about 41% of patients responded by six months. But when Dr. Zheng changed the dosing schedule, the response rate at 6 months in 124 patients was 62%. This rate was almost as good as with horse ATG, which many studies have shown to be more effective than rabbit ATG. Furthermore, survival rates at five years in 55 patients aged 20 or younger were similar to rates in those older than

20 after treatment with the new rabbit ATG dosing schedule. But only half as many older patients survived for at least five years after treatment with the standard ATG as younger patients. Ethnicity might explain the different response rates for ATG found in different studies.

Cyclosporin has many side effects, including seizures, burning sensations in hands and feet, infections, and headaches. Ways to prevent these side effects include treatment with azithromycin (an antibiotic) or certain types of diuretics (to increase urination rates) with cyclosporin or lower cyclosporin doses. Dr. Zheng uses levamisole, which stimulates the immune system, in combination with cyclosporin to treat moderate aplastic anemia.

In 118 patients with moderate aplastic anemia, 87% of newly diagnosed patients and 57% of those with chronic (ongoing) aplastic anemia survived without a relapse for at least two years after this treatment, which had no major side effects. Eight of 16 patients with severe aplastic anemia that has relapsed or not responded to an earlier treatment responded to this combination treatment. Dr. Zheng is now trying to understand why the combination of levamisole and cyclosporin had these effects in different types of aplastic anemia.

FRIDAY, MARCH 28, 2014

Transplant Treatments for Bone Marrow Failure

Session Co-Chairs: ***Richard Childs****, MD, National Heart, Lung, and Blood Institute, and* ***David Margolis****, MD, Medical College of Wisconsin*

Sibling and Matched Unrelated Donors

David Margolis, *MD, Medical College of Wisconsin*

In hematopoietic stem cell transplantation (HSCT), stem cells are infused from a healthy donor into a patient. Before HSCT, patients typically undergo a conditioning treatment to prevent their immune system from attacking the transplanted cells and increase their likelihood of survival.

A recent study compared conditioning treatments involving a combination of cyclophosphamide (Cytoxan®) with antithymocyte globulin (ATG) with or without alemtuzumab (Campath®) before HSCT. The study included 155 patients (median age 21 years) with severe acquired (non-inherited) aplastic anemia. About half of the patients received transplanted cells from a matched sibling donor and the others had a matched unrelated donor, matched non-sibling related donor, or mismatched and unrelated donor.

Rates of severe graft-versus-host disease were similarly low in patients conditioned with alemtuzumab or ATG. The donor cells reached the bone marrow and began producing new blood cells in about 90% of patients conditioned with ATG or alemtuzumab. The overall survival rate at five years was 90% in the alemtuzumab group and 79% in the ATG group, but this difference was not statistically significant.

In a study of outcomes after HSCT in 84 African Americans and 215 caucasians with severe aplastic anemia, 58% of African Americans and 73% of caucasians survived for at least five years. Survival rates were also higher for caucasians with a matched sibling donor than for African Americans with a matched sibling donor.

A recent review of research compared HSCT from matched sibling donors to immune-suppressive therapy for severe plastic anemia. All three studies that met the criteria for this review had problems with their methods. As a result, the review's authors couldn't draw firm conclusions about whether HSCT or immune-suppressive treatment is better for severe aplastic anemia.

Transplantation of Umbilical Cord Blood from Unrelated Donors

Régis Peffault de Latour, *MD, PhD, Hôpital Saint-Louis, Paris*

Hematopoietic stem cells in the bone marrow can turn into any type of blood cell. HSC transplantation (HSCT) involves the infusion of stem cells from a healthy donor into a patient.

Transplanted HSCs from the umbilical cord blood of unrelated donors sometimes fail to engraft, meaning that they don't travel to the bone marrow and begin producing healthy blood cells. Also, patients often develop an infection after transplantation of these

stem cells. But unrelated cord blood transplantation might be the only option for young patients with very severe aplastic anemia who don't respond to immune-suppressive treatment.

In one study, 14 patients with advanced bone marrow failure syndromes, including six with severe aplastic anemia, received a double unrelated cord blood transplantation (two units of cord blood). The transplanted cells engrafted (were accepted by the patient's body) in 60% of patients. About 80% of those with severe aplastic anemia survived for at least two years. Patients with Fanconi anemia didn't do well in this study, but most patients with severe aplastic anemia did improve. In a second study, unrelated cord blood transplantation in 31 patients with severe aplastic anemia also had a 60% engraftment rate. Fewer patients developed graft-versus-host disease (GVHD; attack by transplanted cells on the recipient's body), but only 41% survived for at least two years. In a third study in 71 patients, results were similar for double and simple unrelated cord transplantation, and the rate of GVHD was low. At three years, 38% of patients were still alive.

A Phase II clinical trial, APCORD, is currently evaluating unrelated cord blood transplantation in patients with severe aplastic anemia in France. Before transplantation, the patients undergo a conditioning treatment to prevent their immune system from attacking the transplanted cells and increase the likelihood of survival. APCORD uses a lower-intensity conditioning regimen that involves a lower dose than usual and might make the transplantation safer. The results to date are promising.

French physicians now offer unrelated cord blood transplantation to patients younger than 40 with severe aplastic anemia that hasn't responded to immune-suppressive treatment and who don't have a matched donor.

Bone Marrow Transplantation from Partially Matched Donors for Severe Aplastic Anemia and PNH

Amy DeZern, *MD, MHS, The Johns Hopkins University School of Medicine*

Hematopoietic stem cell transplantation (HSCT), which can potentially cure aplastic anemia, involves the infusion of stem cells from a healthy donor into a patient. Transplant physicians use HLA markers, which are proteins on white blood cells, to match bone marrow donors and recipients. Ideally, all of the donor's HLA markers match those of the patients. But in a haploidentical HSCT, the donor's HLA markers match half the patient's HLA markers.

The main concern with haploidentical HSCT is the risk of graft-versus-host disease (GVHD), in which the transplanted cells attack the recipient's body. More than half of haploidentical HSCT recipients developed life-altering GVHD 10 years ago, but rates have dropped steadily since then.

Dr. DeZern's hospital currently uses haploidentical HSCT in patients who haven't responded to treatment for aplastic anemia to suppress their immune system (immunosuppressant treatment) and don't have an HLA-matched sibling.

Cyclophosphamide (Cytoxan®) is a strong immunosuppressant that can be used to treat severe aplastic anemia. Research has therefore explored the use of cyclophosphamide to prevent GVHD after HSCT. At Dr. DeZern's institution, cyclophosphamide is given on the third and fourth days after haploidentical HSCT to prevent GVHD with very good success.

Dr. DeZern's hospital used this GVHD prevention approach in several patients with severe aplastic anemia that hadn't responded to a previous treatment in combination with a very strong conditioning chemotherapy regimen before HSCT. Two of these patients had haploidentical donors. The first patient did well and didn't develop GVHD. The second patient's donated cells also engrafted quickly and this patient did not develop GVHD. But the patient got a severe infection and died. The hospital decided not to use such a strong chemotherapy before HSCT.

Dr. DeZern's hospital now uses a different transplant approach with lower doses of chemotherapy before HSCT. This approach includes administrations of antithymocyte globulin (an immunosuppressant drug), fludarabine (a chemotherapy drug), and radiation before HSCT and high doses of cyclophosphamide to prevent GVHD after HSCT. This approach minimizes the risk of GVHD and speeds up recovery. It's especially good for patients with non-malignant bone marrow failure disorders like severe aplastic anemia or PNH.

This approach has been used in three patients undergoing haploidentical HSCT for severe aplastic anemia who hadn't responded to immunosuppressant treatment. The transplanted cells engrafted successfully, and the patients had little to no GVHD. A similar approach also had good engraftment outcomes and no GVHD in five patients with PNH who had not responded to treatment with eculizumab (Soliris®). An ongoing clinical trial continues to evaluate this approach for patients with severe aplastic anemia who haven't responded to immunosuppressant treatment at Dr. DeZern's hospital and others.

Combined Haploidentical and Umbilical Cord Transplantation for Severe Aplastic Anemia

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

Hematopoietic stem cell transplantation (HSCT), which can potentially cure aplastic anemia, involves the infusion of stem cells from a healthy donor into a patient. HLA markers are proteins on white blood cells used to match bone marrow donors and recipients. Ideally, all of the stem cell donor's HLA markers match those of the patients. But in a haploidentical HSCT, the donor's HLA markers match half the patient's HLA markers.

Units of umbilical cord blood from unrelated donors that match enough HLA markers are available for about 80% of adults. But HSCT using umbilical cord blood from unrelated donors in adults with aplastic anemia to date have had poor rates of engraftment (when the donated cells reach the bone marrow and start forming healthy blood cells) and a high risk of death.

HSCT with a combination of cord blood and haploidentical bone marrow cells might speed up engraftment and reduce the risk of infection after HSCT. Dr. Childs and his colleagues at the National Heart, Lung, and Blood Institute are testing this approach in patients with severe aplastic anemia who don't have a matched related or unrelated bone marrow donor.

The first 19 patients (median age 19 years) treated using this approach had not responded to or had had a relapse after several different treatments to suppress their immune system. All had severely low white blood counts and were at risk of or had suffered repeated infections. These patients had also had many blood transfusions. As a result, their iron levels were very high.

The donated cells engrafted in all 19 patients. The graft later failed in 1 patient, but the patient did well after a double cord transplant (two units of cord blood). Eighteen patients stopped needing regular blood transfusions. After two years, 17 patients were still alive, for an 85% survival rate. This rate is much better than the historical 50% survival rate for cord blood transplantation. About 40% of patients developed mostly mild graft-versus-host disease (GVHD), meaning that their transplanted cells caused inflammation in some of their normal tissues. Most of these cases of GVHD resolved completely with a brief course of steroid treatment.

HSCT with both haploidentical bone marrow cells and umbilical cord blood seems to be a viable option for patients with severe aplastic anemia who don't have an HLA-matched donor. This procedure dramatically shortens the time to increase white blood cell counts, has a low risk of graft failure, and has promising survival rates. Also, the stem cells from the haploidentical relative provide a backup source of stem cells if the cord blood unit doesn't engraft.

Non-Transplant Therapy of Severe Aplastic Anemia

*Session Co-Chairs:**Judith Marsh**, MD, Kings College Hospital, and **Phil Scheinberg**, MD, Hospital Sao Jose - Hospital Beneficencia Portuguesa del Sao Paolo*

Horse Vs. Rabbit Antithymocyte Globulin (ATG): Is the Debate Over?

Immunosuppressive treatment with antithymocyte globulin (ATG) weakens the immune system and stops it from attacking the bone marrow in patients with aplastic anemia. ATG can be made from horses or rabbits.

The Debate Is Over

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

About 60 to 65% of patients with severe aplastic anemia respond to horse ATG treatment, and this rate has not improved over the last two decades. Many researchers have tried to improve the standard immunosuppressive treatment for severe aplastic anemia by adding other drugs to ATG or replacing ATG with another drug. But these approaches haven't increased response rates or prolonged survival, and many patients have had unacceptable side effects.

Rabbit ATG should be better than horse ATG in theory. But a randomized trial at the National Institutes of Health (NIH) found that twice as many patients with severe aplastic anemia have higher blood counts after treatment with horse ATG than with rabbit ATG. Also, more patients treated with horse ATG survive for at least five years. However, Dr. Young cautioned that this study had some important limitations. So whether the results reflect what will happen to other patients in other health-care settings isn't clear.

Several other studies have had similar results to the NIH study, and very few studies have found rabbit ATG to be better than horse ATG. But most these studies were retrospective, meaning that the researchers collected data after patients were treated.

The best type of evidence to compare different treatments comes from a randomized, controlled trial in which the researchers assign patients randomly to the different treatments. But the NIH study is the only randomized controlled trial to date that compared horse and rabbit ATG.

The Debate Is Not Over

Régis Peffault de Latour, *MD, PhD, Hôpital Saint-Louis, Paris*

Experts expected rabbit ATG to be better than horse ATG because rabbit ATG killed more unhealthy immune cells in patients with advanced aplastic anemia who hadn't responded to another immunosuppressive treatment. Rabbit ATG can also expand the cells that regulate the immune system in patients with severe aplastic anemia. But research has not borne out these expectations, so studies need to explain why patients do better with horse ATG than rabbit ATG.

The most common cause of death in patients treated with 3.5 mg/kg of rabbit ATG for five years is infections. But a smaller dose, 2.5 mg/kg, of rabbit ATG for 5 days, had a higher response rate in one study than the usual dose. An ongoing study in Japan is comparing the effects of these two doses.

Many studies have shown that rabbit ATG works in about 30 to 40% of patients who haven't responded to another type of immunosuppressive treatment. Horse ATG in these patients isn't any more effective than rabbit ATG. A European study is combining a new treatment, eltrombopag (Promacta® in the United States) with rabbit ATG in patients who haven't responded to a previous immunosuppressive treatment. A combination of horse ATG and eltrombopag was not effective, but perhaps eltrombopag and rabbit ATG will do better.

The manufacturer withdrew horse ATG from the market in many countries 2007. Some people worry that rabbit ATG might also be taken off the market (although this hasn't happened yet). Both of these treatments need to be available so that doctors have more than one option for patients with severe aplastic anemia.

Studying Other Ways to Treat Aplastic Anemia—a Dead End?

Antonio Risitano, *MD, PhD, University of Naples*

About a third of patients with aplastic anemia don't respond to available immunosuppressive (IST) treatments, designed to suppress the patient's immune system, or respond only partly. Even in those who do respond, the disease sometimes comes back or, more rarely, progresses to acute myelogenous leukemia (AML).

Researchers have tried a third drug, such as mycophenolate mofetil, with IST consisting of

antithymocyte globulin (ATG) and cyclosporin. Mycophenolate mofetil helps prevent the rejection of a transplanted kidney, heart, or liver. But a National Institutes of Health (NIH) study showed that response rates with mycophenolate, mofetil ATG, and cyclosporin were no better than with ATG and cyclosporin alone. Also, similar numbers of patients developed AML after the triple treatment and the double treatment. The results of adding rapamycin (used to stop rejection of transplanted bone marrow cells and organs) as a third drug to ATG and cyclosporin were similarly disappointing.

Researchers have tested IST strategies that don't include ATG, including two agents proven to be biologically active for the treatment of aplastic anemia. About 70% of patients who had never been treated and almost half of those who hadn't responded to an earlier treatment responded to high doses of cyclophosphamide (Cytoxan®) in a study in 67 patients. But between 20% and 40% of patients developed severe infections. Another study of cyclophosphamide had to end early because the drug had major side effects. Cyclophosphamide is a great drug but its complications are a major barrier to its use.

Alemtuzumab (Campath®) kills all lymphocytes (a type of white blood cell). An NIH study found that alemtuzumab was effective, with responses at six months in 56% of patients whose disease had come back after previous IST and 37% in those who hadn't responded to previous IST. But only 19% of patients who hadn't been treated with IST before responded to alemtuzumab. Another study found that almost 60% of patients with severe aplastic anemia, including those never treated and those treated before, responded to alemtuzumab and the drug had no major side effects. But this study didn't randomly assign patients to different treatments, so it can't be used to draw any firm conclusions.

A potentially promising strategy is to target different types of white blood cells. Researchers are studying several drugs that inhibit tumor necrosis factor, a protein produced by white blood cells. These drugs include etanercept (Enbrel®), infliximab (Remicade®), and adalimumab (Humira®).

Dr. Risitano concluded that although alternative IST is a narrow path, it isn't a dead end.

Agents that Stimulate Blood Clot Formation in Aplastic Anemia: Progress at Last?

Judith Marsh, *MD, Kings College Hospital, and* **Danielle Townsley**, *MD, National Heart, Lung, and Blood Institute*

Growth factors stimulate the bone marrow to produce blood cells. Studies in the 1980s and 1990s used different growth factors alone or in combination to treat aplastic anemia. These treatments had no significant or prolonged effects on blood cell production and most had side effects. Also, these growth factors delayed the use of more effective treatments, which increased the risk of infections and rejection of transplanted bone marrow cells.

Four prospective randomized clinical trials have studied the use of the growth factor granulocyte colony-stimulating factor (G-CSF) in combination with antithymocyte globulin (ATG) and cyclosporin, which suppress the immune system (immunosuppressive treatment [IST]), to treat aplastic anemia. Adding G-CSF to ATG plus cyclosporin did not prolong survival or improve responses compared to ATG and cyclosporin alone (without G-CSF) or reduce the risk of relapse, except in one study. Therefore, professional societies don't recommend using traditional growth factors routinely with ATG plus cyclosporin for aplastic anemia.

Dr. Townsley reported on the use of eltrombopag (Promacta®), a second-generation platelet growth factor, in aplastic anemia. At higher doses, eltrombopag might expand stem cells in people with bone marrow failure. Using this treatment early in the disease course might increase a patient's chances of responding to ATG plus cyclosporin.

In a study in 43 patients with aplastic anemia who hadn't responded to IST, 17 patients (40%) responded in that counts of at least one type of blood cell increased. Many patients had higher counts of two or three types of blood cells (red blood cells, white blood cells, and platelets). The treatment also eliminated the need for blood transfusions in some patients. The researchers gradually stopped giving the drug to a few patients who had robust and stable responses in all three types of blood cells. These patients continued to do well and haven't needed eltrombopag again. Among the 26 patients who didn't respond within the first three or four months, two responded later, eight developed

chromosome abnormalities in the bone marrow, one died of blood cell shortages, and three died of infection. Patients tolerated eltrombopag well and didn't have any major side effects.

The next step is to give eltrombopag in combination with standard IST (horse ATG and cyclosporin) to patients with aplastic anemia who had never been treated. In an ongoing pilot study at the National Institutes of Health, early results suggest that more patients respond with the addition of eltrombopag, and the response happens sooner than with standard IST alone. The results suggest that patients stop needing transfusion support sooner after treatment with eltrombopag and standard IST. Patients have had few serious side effects. But more time is needed to find out whether any serious events, such as development of MDS, happen over the long term.

This study is now evaluating whether use of eltrombopag for less time with standard IST is enough to minimize chromosome changes in bone marrow. Several other studies are evaluating eltrombopag in patients with aplastic anemia or MDS who have or haven't been treated with IST before.

Non-Transplant Therapies in Developed and Developing Countries: A Roundtable Discussion

Phil Scheinberg, *MD, Hospital São Jose - Beneficência Portuguesa de Sao Paulo,* **Judith Marsh**, *MD, Kings College Hospital,* **Neal Young**, *MD, National Heart, Lung, and Blood Institute,* **Antonio Risitano**, *MD, PhD, University of Naples, and* **Régis Peffault de Latour**, *MD, PhD, Hôpital Saint-Louis, Paris*

Dr. Risitano described a new European Society for Blood and Marrow Transplantation (EBMT) multicenter study. This study is evaluating horse antithymocyte globulin (ATG) and cyclosporin with or without eltrombopag (Promacta®) as first-line therapy in 200 patients with severe or very severe aplastic anemia. In addition, the EBMT EMAA study will compare cyclosporin alone to cyclosporin and eltrombopag in patients with untreated moderate aplastic anemia. Patient enrollment for both of these studies will begin in the summer of 2014.

Dr. Scheinberg reported that data on rabbit ATG in Latin American countries are very similar to data from studies in the United States and Europe, where outcomes with rabbit ATG are worse than with horse ATG. The challenges to successful treatment for aplastic anemia in developing countries include the difficulty of obtaining ATG for patients who can't afford it, the long time between diagnosis and treatment with immune suppression or bone marrow transplantation, and the lack of experience administering ATG and monitoring cyclosporin in many health-care institutions.

Dr. Scheinberg reviewed some studies of aplastic anemia in different countries. For example, studies in China, Pakistan, and Japan are evaluating different doses of rabbit ATG in severe aplastic anemia. A study in South Korea is evaluating AMG431, an experimental agent that's similar to eltrombopag and might stimulate bone marrow cells in aplastic anemia that hasn't responded to previous immune-suppression treatment.

Dr. Young commented that some ethnic groups might respond different to horse or rabbit ATG, eltrombopag, and other treatments for severe aplastic anemia. The Asian studies that Dr. Scheinberg mentioned will provide much-needed data on the ideal dose of rabbit ATG.

Another concern in developing countries is lack of access to treatment because of the expense. Even a 50% response rate to an available treatment would make a big difference to patients in developing countries. In these countries, more effective treatments based on horse ATG or bone marrow transplantation are available at only a few centers. As more people in developing countries benefit from the improving economic environment, they are likely to get better treatments.

One potential concern with eltrombopag is that if it's used for too long, it could lead to changes in the bone marrow that are associated with MDS, leukemia, or both. Clinical studies are determining the ideal dose and duration of eltrombopag treatment.

SUMMARY FOR PATIENTS

Non-Transplant Therapy of MDS

Session Co-Chairs: ***Elihu Estey****, MD, Fred Hutchinson Cancer Research Center, and*
Valeria Santini*, MD, University of Florence*

How Different Is MDS from Acute Myelogenous Leukemia?

Elihu Estey, *MD, Fred Hutchinson Cancer Research Center*

Doctors usually decide whether a patient has MDS or acute myelogenous leukemia (AML) based on the proportion of blasts, or immature white blood cells, in the patient's bone marrow. Patients with at least 20% immature blasts have AML, and those with fewer blasts have MDS.

But the development of high-risk MDS with 10 to 20% blasts is more like the development of AML than low-risk MDS with less than 10% blasts. Moreover, whether patients respond to a given treatment doesn't depend on whether they have MDS or AML.

The Revised International Prognostic Scoring System (IPSS-R) classifies a patient's MDS into five risk groups that are associated with different average lengths of survival and likelihood of developing AML. According to the IPSS-R, the average length of survival is 1.4 years in patients with 20–30% blasts and 1.3 years in those with 10–20% blasts. In contrast, survival ranges from 2.3 to 5.9 years in patients with less than 10% blasts.

Studies in the 1980s showed that patients with certain abnormalities in their chromosomes tended to survive for only a short time and those with normal chromosomes survived longer, regardless of whether they had MDS or AML. A study in the 1990s found that patient responses to treatment depended on chromosomes, not whether they had MDS or AML.

Researchers are measuring the effects of blast proportion before treatment on outcomes. If people with 20–30% blasts do more poorly with AML treatment than those with more than 30% blasts, patients with 20–30% blasts should get MDS treatments, such as azacitidine (Vidaza®) or decitabine (Dacogen®). If patients with 10–20% blasts have similar outcomes to patients with 20–30% blasts, then treatments for the two groups should be similar.

In conclusion, the data suggest that a 20% cut-point for deciding whether a patient has MDS or AML might not be justified. A 10% cut-point might make more sense.

Lack of Response to MDS Treatment

Hetty Carraway, *MD, MBA, Cleveland Clinic*

Azacitidine (Vidaza®) and decitabine (Dacogen®) are hypomethylating agents. Experts think that these drugs reverse epigenetic marks on tumor-suppressor genes and genomic DNA. These agents can also regulate DNA damage responses mediated by the immune system.

Not all patients with MDS respond to treatment with hypomethylating agents. The current options for treating patients who don't respond to hypomethylating agents or who have a relapse after treatment include:

- A different hypomethylating agent
- An agent or agents that modulate the immune system
- Intensive chemotherapy
- Bone marrow transplantation
- Experimental drug as part of a clinical trial

Ways to improve outcomes of MDS treatment might include:

- Identifying which patients might respond best to a given treatment
- Increasing the activity of hypomethylating agents
- Decreasing the metabolism of hypomethylating agents
- Optimizing the ability of hypomethylating agents to reach their target in the body

Another strategy is to increase the amount of drug transported into cells. SGI-110 is an experimental hypomethylating agent that increases exposure to decitabine in cells. A Phase II clinical trial included 90 patients with acute myelogenous leukemia (AML) that hadn't responded to treatment or who were older than 65 and had developed AML as a result of another disease or treatment. In this study, 16% of patients responded to the experimental drug even though they hadn't responded to hypomethylating agents before or their AML had returned after treatment. Among those older than 65 with untreated AML, 43% had a remission.

A different way to increase response rates is to use different dosing schedules of hypomethylating agents (such as lower doses over longer periods of time) than the standard dosing schedule. Finally, a strategy to consider is combining hypomethylating agents with other drugs. Researchers have combined azacitidine with entinostat, vorinostat, or tefinostat. These drugs interfere with other modifications (such as acetylation, a type of chemical reaction) involved in MDS.

Biology and Treatment of 5q-deletion MDS

David Steensma, *MD,*
Dana-Farber Cancer Institute

About 10% of patients with MDS have a deletion (loss) of the long (q) arm of chromosome 5 in their bone marrow cells, sometimes called "del(5q)." The prognosis of patients with this chromosome abnormality varies. In patients with del(5q) MDS, the combination of anemia, a normal or high platelet count, no excess blasts (abnormal young white blood cells), and no other chromosome abnormalities is known as 5q-minus syndrome. Some patients with del(5q) MDS, especially those with 5q-minus syndrome, can survive for a long time and have a low risk of developing acute myelogenous leukemia (AML).

Lenalidomide (Revlimid®) is a drug with many different biological effects, such as changing immune system responses to abnormal cells and killing abnormal cells directly. Lenalidomide is very effective for 5q-minus MDS and has approval from the U.S. Food and Drug Administration for this indication.

Among patients with MDS who have del(5q), those with a larger chromosomal deletion that includes certain chromosome regions (commonly retained regions 1 and 2 [CRR1 and CRR2]) of chromosome 5 tend to have poorer outcomes than patients with MDS whose bone marrow cells have a smaller deletion and retain these regions. Patients with del(5q) MDS whose deletions are large and include CRR1 or CRR2 have a higher risk of AML progression and tend not to live as long.

Patients with del(5q) MDS are most likely to respond to lenalidomide if they have a normal, unmutated TP53 gene; a platelet count higher than 280 x 109 per liter; less than 5% blasts; and del(5q) alone or del(5q) with only one other abnormality in a chromosome.

Even though lenalidomide works best in del(5q) MDS, doctors sometimes prescribe this drug for anemic patients with MDS who lack del(5q) when other therapies don't work. It's hard to predict which of these patients will respond well to the drug.

A Phase II clinical trial designed to help answer this question compared lenalidomide alone to lenalidomide plus epoetin (a synthetic version of the hormone erythropoietin, which helps the bone marrow form red blood cells). The study included 132 patients with lower-risk MDS who didn't have del(5q).

The combination of lenalidomide and epoetin raised red blood cell counts to higher levels than lenalidomide alone. Also, more patients in the lenalidomide/epoetin group stopped needing regular red blood cell transfusions than in the lenalidomide group. The investigators identified a gene expression signature (pattern of genes that are turned on and turned off in blood cells) and a change in the gene encoding cereblon that predicted a higher likelihood of response to lenalidomide. But the effect of these changes was not strong and neither of these tests are currently available for routine patient care. Therefore, experts still don't understand which patients with non-del(5q) MDS are likely to respond to lenalidomide.

All patients stop responding to lenalidomide eventually, and the biology of del(5q) MDS needs to be better understood. An early-phase study is evaluating the use of cenersen (Aezea®) in patients with 5q-deletion MDS who need regular red blood cell transfusions. Cenersen blocks the effects of the p53 protein, which might make unhealthy bone marrow cells more sensitive to lenalidomide. Other studies are being designed for such patients for whom lenalidomide has failed. Patients who are treated off-study with azacitidine (Vidaza®), decitabine (Dacogen®), or stem cell transplantation sometimes benefit from those approaches.

SUMMARY FOR PATIENTS

Prognosis and Treatment in Lower-Risk MDS

Valeria Santini, *MD,*
University of Florence

More patients with MDS have low-risk disease than intermediate- or high-risk MDS according to the International Prognostic Scoring System (IPSS). In the IPSS, low-risk MDS has only a small chance of progressing to acute myelogenous leukemia (AML). Nevertheless, in some cases, low-risk MDS progresses rapidly to AML, and doctors don't know why.

The Revised IPSS (IPSS-R) is based on the same factors as the IPSS, but it takes more information into account and categorizes patients into five risk groups instead of four. Each group has a different length of survival and likelihood of AML. The IPSS-R and other tools to predict the course of MDS assign very different survival probabilities to patients who have low-risk MDS according to the IPSS. Outcomes are even more diverse in patients with intermediate-1 MDS.

In addition to genetic mutations, other tools for prognosis in low-risk MDS are being studied. A recently proposed model predicts outcomes in patients with low-risk MDS based on how quickly platelet or white blood cell counts drop and how much these counts decline. Patients whose blood cell counts drop more quickly tend not to do as well as those whose blood counts decline more slowly. This tool seems to offer a good way to predict outcomes for patients with low-risk MDS.

Erythropoietin-stimulating agents (ESAs) are used to treat anemia (low levels of hemoglobin, a protein in red blood cells that transports oxygen) in patients with lower-risk MDS and delay the need for red blood cell transfusions. Some evidence shows that ESAs might also prevent MDS from progressing to AML. The IPSS-R, especially when used with other information (such as blood levels of the hormone erythropoietin, which instructs bone marrow cells to make red blood cells), is useful for identifying which patients with low-risk MDS are least likely to respond to ESAs and might survive longer with other kinds of treatment.

Patients with 5q-deletion MDS respond poorly and only briefly to ESAs, so they're usually treated with lenalidomide (Revlimid®). Some patients with low-risk MDS who don't have 5q-deletion MDS don't respond to ESAs, but they might respond to the azacitidine (Vidaza®) or decitabine (Dacogen®), which attacks unhealthy cells in bone marrow. These drugs seem to prolong survival in these patients with low-risk MDS, just as they do in those with high-risk MDS, but this effect needs to be confirmed in clinical trials.

GLOSSARY

5q deletion MDS: a type of myelodysplastic syndrome (MDS) involving a deletion (loss) of the long (q) arm of chromosome 5

5q-minus MDS: in patients with del(5q) MDS, the combination of anemia, a normal or high platelet count, no excess blasts (abnormal young white blood cells), and no other chromosome abnormalities

Acquired: resulting from exposure to certain environmental factors

Acute myelogenous leukemia (AML): a blood cell cancer

Alemtuzumab (Campath®): drug that reduces the number of lymphocytes (type of white blood cell) in the blood that works in other autoimmune diseases

Amino acid: protein "building block"

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

Anticoagulant medications: used to prevent thrombosis

Antithymocyte globulin (ATG): weakens the patient's immune system and stops it from attacking the bone marrow

Aplastic anemia: the bone marrow does not make enough blood cells

Auto-antibodies: immune system proteins that fight the person's own proteins

Autoimmunity: the patient's immune system regards his or her own tissues as foreign invaders and attacks them

Autologous recovery: bone marrow was able to make healthy blood cells

Azacitidine (Vidaza®): the first drug approved by the U.S. Food and Drug Administration to treat myelodysplastic syndromes (MDS), is usually given on seven consecutive days of each 28-day cycle. The typical dose is 75 mg per square meter each day

Blasts: (abnormal) young white blood cells

Bone marrow failure: bone marrow stops making enough healthy blood cells

Chromosomes: parts of cells containing genetic information)

Chronic myelomonocytic leukemia (CMML)

Clones: copies of immature white blood cells

Coagulation system: forms blood clots

Cohesin: a protein that plays an important role in cell division

Comorbidities: health problems (or diseases or conditions) other than MDS

Compassionate use: a treatment's use outside of a clinical trial before the treatment has received approval from a country's regulatory agency

Complement proteins: Patients with PNH have abnormal red blood cells that don't have two important complement-regulating proteins, CD55 and CD59. When a person's body is attacked by foreign pathogens, the complement system recruits its enzymes and other mediators to fight the invader. The CD55 and CD59 complement proteins normally protect red blood cells from destruction by complement. Because people with PNH don't have these proteins, their complement system destroys their red blood cells prematurely

Complete marrow response: bone marrow had less than 5% abnormal blasts, or abnormal, immature cells

Complete response: disappearance of all (no) signs of MDS; normal or near normal blood counts

Conditioning: treatment to prevent the patient's immune system from attacking the transplanted cells also increases the likelihood of survival

Congenital: present since birth

Constitutional: inherited

Cyclophosphamide (Cytoxan®): drug used before the transplant to prevent the patient's immune system from rejecting the donated cells, can prevent GVHD in patients who have undergone HSCT from a haploidentical, related donor

Cyclosporine: an immunosuppressant drug

Cytogenetics: abnormalities in chromosomes; are good in patients with low levels of abnormalities in their chromosomes

Cytopenia: shortage of certain types of blood cells

Deep sequencing: a lab process that measures the DNA sequence of the same region of the genome several times, can identify rare mutations

Del(5q): About 10% of patients with MDS have a deletion (loss) of the long (q) arm of chromosome 5 in their bone marrow

Double umbilical cord transplantation: two units of cord blood

GLOSSARY

DNA methylation: a chemical process that helps control gene activity

Eculizumab (Soliris®): a drug that blocks complement protein attacks on blood cells and prevents premature destruction of red blood cells in people with PNH

Eltrombopag (Promacta®): offers an alternative to immunosuppressive therapy in patients with aplastic anemia. This drug stimulates thrombopoietin, a hormone that controls platelet production in the bone marrow. This process increases the number of platelets and decreases bleeding risk. Patients take the drug by mouth, and most tolerate the drug well

Engraftment: transplanted cells reach the bone marrow and begin to make healthy blood cells

Enzymes: proteins that carry out important functions in cells

Epigenetic changes: changes that are not due to changes in DNA structure

Epitopes: parts of proteins that are immune system targets

Epoetin: a synthetic version of the hormone erythropoietin, which helps the bone marrow form red blood cells

Erythropoiesis: process of forming red blood cells in bone marrow

Erythropoietin: helps the bone marrow form red blood cells

Erythropoietin-stimulating agents (ESAs): used to treat anemia in patients with lower-risk MDS and delay the need for red blood cell transfusions; used as first-line treatment for anemia in patients with lower-risk MDS who do not have 5q- syndrome

Event-free survival: survival time without relapse

Exome: coding regions of all genes

Extravascular hemolysis: premature destruction (breakdown) of red blood cells outside the veins and arteries

Fanconi anemia: a rare inherited disease, in which the bone marrow does not make enough red blood cells, white blood cells, or platelets

Gene expression profile: a pattern of genes that are turned on and turned off in blood cells

Genomic techniques: used to study all of the hereditary information (all of the person's DNA, including all genes) in patients; whole-genome sequencing: is a laboratory process that maps out the person's entire DNA sequence

Germline mutation: inherited

Glycosyl phosphatidylinositol (GPI): Cells with PIG-A don't have the glycosyl phosphatidylinositol (GPI)-anchored proteins. Some of these proteins protect red blood cells from being destroyed, help blood form clots, and defend the body from infections.

Graft: donor's stem cells

Graft-versus-host disease (GVHD): attack by transplanted cells on the recipient's body; transplanted cells cause inflammation of some normal tissues. Acute: within three months of transplantation; chronic: starting more than three months after transplantation

Granulocyte colony-stimulating factor (G-CSF): drug that might help the bone marrow form new blood cells

Growth factors: stimulate the bone marrow to produce blood cells

Haploidentical stem cell transplant: the donor's HLA markers match half of the patient's HLA markers

Haploinsufficient: have lost one of their two alleles (copies)

Hematopoiesis: formation of healthy blood cells in the bone marrow

Hematopoietic stem cell transplant (HSCT): can potentially cure aplastic anemia, MDS (only cure for MDS), and paroxysmal nocturnal hemoglobinuria (PNH). This procedure involves the infusion of healthy blood-forming (hematopoietic) stem cells from a healthy donor with the same HLA (immune system) markers as the patient. The donor's stem cells (known as a graft) enter the bone marrow, where they form healthy blood cells. the infusion of stem cells from a healthy donor into a patient

Hematopoietic stem cells: make (can turn into all types of) blood cells in bone marrow

Hemoglobinuria: red blood cells in the urine

Hemolysis: premature complete or partial destruction (breakdown) of red blood cells; intravascular hemolysis: breakdown of red blood cells in the veins and arteries

Heterozygous: having two different copies of a gene

Histone deacetylase (HDAC) inhibitors: interfere with the genetic changes involved in MDS

HLA markers: a set of proteins on white blood cells used to match bone marrow donors and recipients

GLOSSARY

Homozygous: having two identical copies of a gene

Hypocellular MDS: have too few cells in the bone marrow, but they also have abnormal clones, or copies, of bone marrow cells that turn into abnormal blood cells

Hypomethylating agents: kill unhealthy cells in the bone marrow, e.g., azacitidine (Vidaza®) and decitabine (Dacogen®)

Hypoplasia: low blood cell count

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

Immunoglobulin: antibody used by the immune system to fight foreign objects

Immunosuppressive therapy: drugs to weaken the patient's immune system and stop it from attacking the bone marrow. Helps the bone marrow make more healthy blood cells. Standard first treatment for aplastic anemia. Usually involves a combination of horse antithymocyte globulin (ATG) and cyclosporine

Initiation factors: proteins that bind to part of a ribosome when it starts forming proteins). This helps control the ability of ribosome subunits (components) to join together

International Prognostic Scoring System (IPSS): system that doctors often use to choose treatments for their patients with MDS; to evaluate each patient's MDS and select appropriate therapy. Classifies a patient's MDS into four risk categories: low, intermediate-, intermediate-2, and high-risk based on three factors: the percentage of blasts, or immature white cells, in the bone marrow, number and severity of chromosome changes in bone marrow cells, and number of low blood counts, also called cytopenias. The IPSS uses information that doctors can easily collect, but does not account for many factors that can affect the patient's outcomes, such as age, fibrosis (scarring of bone), ferritin (iron marker) levels, genetic mutations, comorbid conditions, or severity of low blood counts. Patients with the same IPSS score can have very different risks of progression to AML and survival. Also, the IPSS was developed and tested with patients prior to MDS treatment, so it is not designed to provide an accurate prognosis after treatment has begun. The IPSS can only be used at the time of diagnosis and is not a dynamic prognostic tool

Intravascular hemolysis: breakdown of red blood cells in the veins and arteries

Iron chelation therapy: used to remove extra iron from their bodies

Iron overload: can damage the body's tissues and organs

Lenalidomide (Revlimid®): a biologic agent that slows down the growth of blood vessels that feed abnormal cells; can eliminate the need for red blood cell transfusions in patients with 5q-deletion MDS

Lesions: injuries to genes

Lymphocyte: type of white blood cell

Macrocytic anemia: red blood cells are fragile and larger than normal

Messenger RNA: contains the genetic coding information needed to make proteins

Methylation and deacetylation: chemical processes that stop genes in patients with myelodysplastic syndromes (MDS) from carrying out their normal activities

Monocytes: a type of white blood cell that destroys bacteria

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

Mutations: change or alteration in a gene

Myelodysplastic/myeloproliferative neoplasms (MDS/MPN): disease of the blood and bone marrow with features of both MDS and myeloproliferative diseases, in which blood cell counts slowly rise

Myeloid: myeloid cells white blood cells that normally become different types of blood cells

Neutropenia: shortage of certain white blood cells

p53 protein: normally suppresses tumor development

Parenteral administration: through the vein or by injection

Paroxysmal nocturnal hemoglobinuria (PNH): have abnormal clones, or copies, of stem cells in the bone marrow that make blood cells. Because of a mutation, or change, in the PIG-A gene, these clones don't have proteins that would normally be attached by glycosyl phosphatidylinositol (GPI), a fat found on many blood cells that anchors proteins to cell surfaces. In addition to cells that lack GPI, patients with PNH don't have normal hematopoiesis, or formation of healthy blood cells in the bone marrow

GLOSSARY

Pathogen: biological agents, such as viruses or bacteria, that cause disease

Peripheral blood: bloodstream

Primary MDS: did not result from a prior treatment for another disease

Proteases: enzymes that break down proteins

Reduced intensity conditioning regimen: uses a lower dose than typical conditioning treatments and might make the transplantation safer

Refractory anemia with ring sideroblasts (RARS): type of myelodysplastic syndrome (MDS). In patients with this disease, more than 15% of red blood cells in the bone marrow contain ring- shaped iron deposits known as ring sideroblasts. These patients have a low red blood cell count that can't be treated with iron or vitamins

Revised IPSS (IPSS-R): based on the same factors as the IPSS, but takes more information into account than the IPSS and categorizes patients into five risk groups instead of four, associated with a different average length of survival and likelihood of developing AML. Patients in the very good group tend to survive longest (nine years, on average) and are least likely to develop AML. These averages might not apply to patients who have had treatment that could improve their survival

Ribosomes: cell structures that process the cell's genetic instructions to create proteins

Rigosertib (Estybon®): a small-molecule inhibitor of pathways that play important roles in the growth and proliferation of cancerous cells

Romiplostim (Nplate®): a protein used to treat low platelet counts

Secondary MDS: results from treatment (such as radiation or chemotherapy) for another disease

Shwachman-Diamond syndrome (SDS): a rare inherited disease that affects the bone marrow and other organs. In these patients, the bone marrow doesn't make one or more types of blood cells. Once they reach their 30s, more than a third of patients with SDS develop myelodysplastic syndromes or acute myelogenous leukemia

Somatic mutation: not inherited, acquired after birth

Spliceosomes: groups of proteins involved in splicing messenger RNA. Messenger RNA contains the genetic coding information needed to make proteins. Cells splice together certain sequences in RNA to form messenger RNA molecules that can produce proteins that work properly

Stem cells: immature cells in bone marrow that make blood cells

Subcutaneously: under the skin

T cells: type of white blood cell that helps protect the body from infection

T helper cells: help other immune cells carry out their functions

T regulatory (Treg) cells: control the activity of other T cells

Telomerase: an enzyme that maintains telomere length

Telomeres: located at the ends of chromosomes and help keep chromosomes stable. As people age, their telomeres become shorter, and this shortening is fastest in the first 20 years of life

Thrombocytopenia: shortage of platelets in the bloodstream

Thromboembolisms: clots that block blood vessels

Thrombopoiesis: blood clot formation

Thrombopoietin: a hormone that controls platelet production in the bone marrow

Thrombosis: blood clot in a vein or artery

Ubiquitinated protein: marked for transportation or degradation

Vorinostat (Zolinza®): an HDAC inhibitor

Whole-genome sequencing: a laboratory process that maps out the person's entire DNA sequence

World Health Organization (WHO): revised its classification system for MDS in 2008. The WHO Classification System places patients into seven different MDS subtypes. These subtypes are based on the number of low blood counts, proportion (less than 5% or 5–10%) of immature cells in the bone marrow (blast cells), whether the new red blood cells in the bone marrow have rings of iron deposits around the nucleus, which types of marrow cells look abnormal, and whether the bone marrow chromosomes are missing part of chromosome 5

Visit the AA&MDSIF Online Learning Center: www.AAMDS.org/Learn

View pre-recorded webcasts and participate in live webinars conducted by the nation's leading experts on bone marrow failure diseases and their treatment. All content is free and available to anyone with access to a computer and internet connection. You can also view our innovative interactive education modules and see a variety of interviews with experts on aplastic anemia, MDS, and PNH. We have a variety of topics and more are being added all the time, so be sure to visit often for the latest updates.

Don't have Internet access? Go to your public library or local community center; or ask a friend or family member to help you the next time you visit.

PROGRAMS PRESENTED BY SYMPOSIUM SPEAKERS INCLUDE:

David Araten, MD	• PNH FAQ: Living Well Forum for Patients and Families • Advanced Understanding of PNH: Hemolytic Anemia, Pancytopenia, and Thrombosis • PNH Clinical Update for Patients: Important Findings from the 2011 American Society of Hematology Annual Meeting • Basic PNH for the Newly Diagnosed • Blood Cell Production vs. Blood Cell Destruction: PNH and Other Bone Marrow Failures • Advanced Understanding of PNH: Hemolytic Anemia, Pancytopenia, and Thrombosis
Amy DeZern, MD	• Aplastic Anemia: What You Need to Know
David Margolis, MD	• Teaching Children about Bone Marrow Failure with the Bone Marrow Garden • The Bone Marrow Garden • Bone Marrow Transplantation for Pediatric Aplastic Anemia Patients
David Steensma, MD	• What We've Learned about MDS at the American Society of Hematology (ASH) Meeting: Existing and Emerging Treatments • MDS: Current Thinking on the Disease, Diagnosis, and Treatment • New Directions in MDS: What's on the Horizon? • Treating Lower-Risk MDS in 2012: Applying the Most Current Clinical Research to Patient Care *(do we want to include this?) • Emerging Treatments and New Protocols for MDS Therapy in 2012 MDS
Danielle Townsley, MD	• Aplastic Anemia: Current Thinking on the Disease, Diagnosis, and Non-Transplant Treatment • New Directions in Aplastic Anemia Treatment: What's on the Horizon?
Neal Young, MD	• Frequently Asked Questions about Aplastic Anemia

Interviews were also recorded at the symposium with the session co-chairs who explain the highlights of the presentations for patients. These interviews may be viewed at www.AAMDS.org/2014symposiumvideos.

AA&MDSIF RESEARCH GRANT PROGRAM

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 an 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 C-MPL Defects fo 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. Jarolslaw 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-y 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 Unversity: *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 Famly**) 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

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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 Eculizamab* **2008** **Dr. Benjamin Braun** (*Harold Spielberg**) University of California, San Francisco: *Mechanisms and Therapy of Anemia Caused by Activating K-ras Mutuation* **2008** **Dr. Jarolslaw 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* **2011** **Dr. Kim-Hien T. Dao** *(Torry Yahn*)* Oregon Health & Science University: *Beta-catenin is a molecular target of the Fanconi anemia core complex.* **2011** **Dr. Keith R. McCrae** *(PNH Research and Support Foundation*)* Cleveland Clinic: *Circulating microparticles in PNH* **2011** **Dr. Parinda Mehta** *(Trinity Ewert Research Fund*)* Cincinnati Children's Hospital Medical Center: Quercetin in patients with Fanconi Anemia, a pilot study. **2011** **Dr. Mridul Mukherji** *(Harold Spielberg Research Fund*)* University of Missouri - Kansas City: Rescue of TET2 Mutations from MDS Patients **2012** **Dr. David Araten** *(PNH Research and Support Foundation*)* New York University for his study of *Secondary Mutations and Thrombosis in PNH.* **2012** **Dr. Lisa Minter** *(Caitlyn Langley Research Fund, Holly Cataldo Research Fund*)* University of Massachusetts of Amherst: *Cell-penetrating Antibodies as a Novel Treatment for Aplastic Anemia.* **2012** **Dr. Jeffrey Pu** *(PNH Research and Support Foundation*)* Pennsylvania State University: *Relevance of PIG-A Mutations in acquired Bone Marrow Failure Diseases.* **2012** **Dr. Matthew J. Walter** *(Research is Hope Fund*)* Washington University in St. Louis :*The Role of U2AF1 Mutations in the pathogenesis of Myelodyplastic Syndromes.* **2012** **Dr. Zhe Yang Wayne** *(Harold Spielberg Research Fund*)* State University, Detroit: *Structural Insights into Deregulated Epigenetic Mechanisms and DNA Demethylation in MDS.* **2013** **Dr. Andrew Dancis** *(Research is Hope Fund*)* University of Pennsylvania: *SF3B1 Mitochondrial Phenotype In Myelodysplasia as a Therapeutic Target.* **2013** **Dr. Hideki Makishima** *(PNH Research and Support Foundation*)* Cleveland Clinic : *Clonal Architecture in PNH: Somatic Genetic Defects Facilitating Clonal Expansion.* **2013** **Dr. Rosario Notaro** *(Amber Lynn Wakefield Research Fund*)* Fondazione dell' Istituto Toscano: *The Role of GPI-reactive T cells in the Pathogenesis of Acquired Aplastic Anemia.* **2013** **Dr. Eirini Papapetrou** *(Research is Hope Fund*)* University of Washington: *Modeling 7q-MDS with Human Induced Pluripotent Stem Cells.* **2013** **Dr. Akiko Shimamura** *(Torry Yahn Research Fund*)* Fred Hutchinson Cancer Research Center: *Genetic Predictors of Response to Immunosuppressive Therapy for Aplastic Anemia* **2014** **Dr. Daria Babushok** *(Yahn, Jordan and Janowiak Funds*)* Hospital of the University of Pennsylvania: *Clonal Hematopoiesis in Pediatric Aplastic Anemia* **2014** **Dr. Luis Batista** *(Research Is Hope Fund*) Washington University: Improving the Self-Renewal Capability of Stem Cells Derived from Bone Marrow Failure Patients.* **2014** **Dr. Rosannah Cameron** *(Minelli and Fernandez Funds*) Albert Einstein College of Medicine: The Role of the Spliceosome in Regulating DNA Methylation in MDS* **2014** **Dr. Youmna Kfoury** *(Lancaster Trust*)* Massachusetts General Hospital: *Phenotypic and Molecular Characterization of Osteolineage Cells in Patients with MDS* **2014** **Dr. Patrizia Ricci** *(PNH Research and Support Foundation*)* Federico II University of Naples: *Small Peptide C3-Inhibitors for the Treatment of PNH: Moving Towards the Bedside* **2014** **Dr. Chao Yie-Yang** *(PNH Research and Support Foundation*)* University of Michigan: *Discovery of Small Molecule Complement Inhibitor as the Treatment for PNH*

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