Seventh International
Bone Marrow Failure Disease Scientific Symposium

Collaborating to Transform Treatment and Improve Outcomes

Summary for Patients

Dear Friends,

We are pleased to present this Summary for Patients of the Seventh AAMDSIF International Bone Marrow Failure Scientific Symposium held virtually on July 15, 16 & 17, 2020. Our Symposium brought together many of the world's leading experts on the biology and treatment of aplastic anemia, myelodysplastic syndromes, paroxysmal nocturnal hemoglobinuria, acute myeloid leukemia and related disorders. Despite the virtual format due to the coronavirus pandemic, our registration was higher than ever, with over 750 participants from 38 nations.

The Aplastic Anemia and MDS International Foundation is committed to providing patients and their families with an evolving array of programs and services, while continuing to fund clinical investigators who search for the cures and help improve treatments. We are proud to have awarded more than $5 million in research grants to 94 researchers over the past 31 years to advance the study of bone marrow failure. Several AAMDSIF grantees presented at our Scientific Symposium as recognized leaders in bone marrow failure disease research.

We are most grateful to the co-chairs of this event, Richard Stone, MD and Neal Young, MD, and to the outstanding session co-chairs with whom they worked to plan and organize this Symposium. The presentations by the internationally respected faculty stimulated discussion and provided new insights for future studies. This year the virtual platform enabled hundreds more new investigators and those from distant countries to participate, making it a truly global event.

The Symposium would not have been possible without the generous contributions from our sponsors, listed on the next page. The ongoing collaborative effort of academia, government, private industry and AAMDSIF 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

Neil Horikoshi
CEO & Executive Director

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GENETICS AND GENOMICS OF BONE MARROW FAILURE

HLA Mutations in Aplastic Anemia

Daria Babushok,MD,PhD,
University of Pennsylvania

Normally, T cells in the immune system monitor other cells to detect infections or cancer. To do this, the T cells recognize the human leukocyte antigen (HLA) proteins on cell surfaces. These proteins act as antennas to help the body recognize whether other types of proteins come from the patients' own cells and are therefore safe, or whether they come from foreign invaders, such as viruses and bacteria, and need to be attacked. In aplastic anemia, one of the most common mutations in the diseased bone marrow changes these HLA proteins.

About 15% to 20% of people with aplastic anemia have mutations in the HLA genes that produce the HLA proteins. Cells with these mutations can avoid attack by the immune system. These cells are therefore more likely to survive in the patient's bone marrow than cells without the mutations.

HLA mutations are very diverse, and research has identified thousands of variations in these genes in different people. People might inherit up to six different mutations in HLA genes from their parents, but even members of the same family can have different mutations of these genes.

Identifying the HLA gene variants in a given person with aplastic anemia can help determine what leads to attacks by the immune system on healthy bone marrow cells. By studying HLA gene mutations in 507 adults and children with aplastic anemia, Dr. Babushok identified HLA "risk" variants. She also grouped different forms of the HLA gene into different risk categories, ranging from the highest to the lowest risk.

These findings could have implications for:

- Understanding of the role of the immune system in aplastic anemia
- Diagnosis and prognosis in aplastic anemia
- Choice of haploidentical stem cell transplantation donors for people with aplastic anemia .

New Inherited Syndromes Predisposing to MDS

Marcin Wlodarski, MD, PhD
St. Jude Hospital and University of Freiburg

GATA2 deficiency is caused by inherited mutations in the *GATA2* gene. In patients with this rare disorder, the immune system doesn't work properly, so the body can't fight infections successfully. *GATA2* has an essential role in the early development of the bone marrow stem cells that form blood cells.

GATA2 deficiency can cause problems throughout the body. Just a few examples are inherited deafness, abnormal lymphatic vessels that cause swollen arms or legs, behavioral problems, lung disease, various types of infections, blood clots, and certain types of cancer.

People with *GATA2* deficiency have low blood cell counts, and most eventually develop MDS or acute myelogenous leukemia (AML). Unfortunately, doctors can't predict which people with *GATA2* deficiency will develop MDS and, if so, when.

Dr. Wlodarski led a study of 426 children and teens diagnost over 18 years in Germany who had primary MDS and 82 with secondary MDS. MDS is secondary when it develops from another condition or a cancer treatment, and it is primary otherwise.

In this study, 7% of patients with primary MDS had inherited *GATA2* mutations, but none of the children with secondary MDS had a *GATA2* mutation. Of patients with primary MDS who had advanced-stage disease, 15% had a *GATA2* mutation. Also, 37% of patients with monosomy 7 (one copy, instead of two, of chromosome 7) had a *GATA2* mutation, and this proportion increased with age. For example, two thirds of adolescents with MDS and monosomy 7 carried a mutation in this gene.

Dr. Wlodarski believes that patients with *GATA2* deficiency are born with normal bone marrow function. Over time, some of these patients lose healthy stem cells and develop unhealthy ones. Eventually, these patients develop MDS or AML.

Two other recently identified inherited forms of MDS are *SAMD9* and *SAMD9L* syndromes. Published reports have found these new syndromes in about 130 patients so far. These patients can have abnormal bone marrow stem cells, a high risk of infection, poor growth, genitals with both male and female features, a malfunctioning adrenal gland, and disease in their intestines. As in patients with *GATA2* deficiency, people with *SAMD9* or *SAMD9L* syndromes have a high risk of MDS with monosomy 7.

Dr. Wlodarski's group analyzed a large number of children with MDS and monosomy 7 enrolled in the European Working Group of MDS in Childhood studies. They found that half the patients have either *GATA2*, *SAMD9*, or *SAMD9L* mutations.

Fortunately, survival rates overall and after bone marrow transplantation are similar in patients with *GATA2* deficiency, *SAMD9* or *SAMD9L* syndromes, or MDS if these patients don't have a known inherited mutation.

Genes That Predispose Adults to Develop Bone Marrow Failure

Jaroslaw Maciejewski, MD, PhD
Cleveland Clinic

One way to study inherited mutations that increase the risk of MDS is to study families that have many members with a bone marrow failure syndrome. This approach works with children because those who develop MDS often have inherited mutations.

But the inherited mutations that can lead to aplastic anemia or MDS in adults are rare in patients with low blood cell counts and bone marrow failure. And these mutations are even rarer in adults with acute myelogenous leukemia (AML). But they might play an important role in the development of bone marrow failure.

Dr. Maciejewski and colleagues analyzed the genomes of almost 3,000 people with aplastic anemia, paroxysmal nocturnal hemoglobinuria, or MDS. About 3% of patients with Fanconi anemia had a mutation in a Tier 1 gene (one with strong evidence showing that it plays a role in cancer) or in a Tier 2 gene (one suspected of playing a role in cancer). Fanconi anemia is a rare inherited disease in which the bone marrow does not make enough red blood cells, white blood cells, or platelets. As expected, most of these genes are associated with Fanconi anemia or telomerase. Telomerase is an enzyme that maintains the telomeres at the ends of chromosomes. Chromosomes with very short telomeres let cells keep dividing, resulting in more gene mutations and DNA damage.

About 3% of a large group of patients with MDS or aplastic anemia had a mutation in a myeloperoxidase gene. These genes help certain types of white blood cells fight infection, so patients with these mutations had a high risk of infection. Most of these patients had no evidence of a myeloperoxidase deficiency. This newly discovered mutation that is associated with bone marrow failure in adulthood could lead to DNA damage and mutations in other genes.

Dr. Maciejewski also discussed acquired (not inherited) TET2 mutations in clonal hematopoiesis of indeterminate potential and MDS. Inhibiting TET2 leads to the expansion of abnormal stem cells in the bone marrow, leading to the formation of unhealthy blood cells.

In conclusion, inhibiting mutant TET2 might prevent unhealthy bone marrow cells in people with MDS from expanding and allow normal cells to form healthy blood cells. One such TET2 inhibitor, eltrombopag (Promacta), might be an effective treatment for patients with MDS and a TET2 mutation.

Impact of Acquired Gene Mutations in Shwachman-Diamond Syndrome and progression to MDS/AML

R. Coleman Lindsley, MD, PhD
Dana-Farber Cancer Institute

Shwachman-Diamond syndrome (SDS) is a rare inherited disease that affects the bone marrow and other organs. People with SDS tend to be short, their pancreas might not work properly, and they have a very high risk of MDS and acute myelogenous leukemia (AML). Patients with SDS who develop AML rarely survive more than a year.

A major goal of SDS treatment is therefore to identify patients before their SDS progresses to AML. These patients can then undergo stem cell transplantation to cure their disease. But the current methods for monitoring these patients aren't very sensitive, and they don't detect the earliest signs of progression to AML.

To identify genetic mutations that are early signs of AML progression in people with SDS, Dr. Lindsley analyzed acquired mutations (meaning that they developed after birth) in 55 genes of 139 people with SDS who had SBDS mutations.

More than 70% of patients with MDS or AML had abnormal clones, or copies, of bone marrow cells that make blood cells. So it might be possible to identify abnormal clones that will become leukemia cells before the transformation to MDS or AML.

Most abnormal clones in people with SDS have a mutation in one of four genes, EIF6, TP53, PRPF8, or CSNK1A1. These people rarely have the mutations associated with abnormal bone marrow clones in people without SDS. They also tend to have mutations in several genes, particularly in EIF6 and TP53.

Monitoring of acquired gene mutations could help doctors identify the formation of abnormal bone marrow clones in patients with SDS at an early stage. This information could help doctors figure out which patients need more frequent monitoring or interventions to prevent AML.

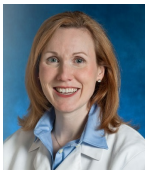
To show how this strategy might work, Dr. Lindsley described the genetic findings from a patient with SDS who had no signs of transformation to AML for 6 years based on complete blood cell counts and bone marrow biopsies. The patient developed AML in the 7th year without having any clinical signs of progression. The typical monitoring strategy could not tell which clones are likely to become AML clones and which ones are likely not to make this change.

Using single-cell DNA sequencing, the investigators showed that in the patient's sample before AML developed, the patient had 13 mutations in 13 different clones. Only the clone with mutated TP53 showed signs of progression toward AML. This clone was detectable 4.5 years before the patient developed AML. The clone was rare at first but became more common over time.

Dr. Lindsley concluded that single-cell DNA analysis might be a valuable addition to the current methods of monitoring patients with SDS for the earliest signs of AML.

TRANSPLANTATION FOR BONE MARROW FAILURE

Haploidentical Bone Marrow Transplantation for Severe Aplastic Anemia



Amy DeZern, MD, MHS
Johns Hopkins University

In 2020, treatment for severe aplastic anemia often still depends on the person's age and whether they have a matched sibling donor. But this paradigm is now changing.

For patients older than 40 and those who don't have a matched sibling stem cell donor, the conventional first treatment is typically immunosuppressive therapy (IST). IST stops the immune system from attacking bone marrow stem cells. About 70% of patients can respond to this treatment.

The first treatment for younger patients has long been bone marrow transplant (BMT) with a matched sibling donor. In most cases, the conditioning regimen for BMT includes cyclophosphamide and antithymocyte globulin (ATG). This treatment helps the donorÊ¼s stem cells replace those of the patient so that the patientÊ¼s bone marrow can start making new blood cells.

A treatment option for patients who don't respond to IST or who have a relapse with this treatment is haploidentical BMT. In this procedure, the donor's HLA markers (a set of proteins on white blood cells) only match half the patient's HLA markers. The results are very similar to those with matched sibling donors, opening the possibility of BMT for more patients. In addition, haploidentical BMT can be considered as a first treatment for certain patients.

Dr. DeZern presented the results of two separate Phase II clinical trials of haploidentical BMT for patients with severe aplastic anemia. One trial included 20 patients (average age 29 years, 69% male) who had relapsed or refractory disease, meaning that they either had a relapse or their bone marrow function hadn't improved within 3 months of starting IST. In the second trial, 17 patients had severe aplastic anemia that hadn't been treated.

In both trials, the investigators used similar conditioning regimens: rabbit ATG, followed by fludarabine and cyclophosphamide. Patients also had total body irradiation the day before the BMT. Also, several medications, including high-dose cyclophosphamide, were given after BMT for up to 6 to 12 months year to prevent graft-versus-host disease. In graft-versus-host disease, the transplanted cells attack the patient's body and lead to inflammation of some healthy tissues.

The transplanted cells engrafted in the vast majority of patients in both trials. Engraftment means that the donor cells grow in the patient's marrow and making new blood cells.

At the time of this presentation, all of the patients treated for relapsed or refractory disease are alive. Two patients in the group that hadn't had aplastic anemia treatment before died before the total body irradiation dose was increased, but none died once this change was made. One patient in each of the two groups had a graft failure, meaning that the transplanted cells didn't reach the bone marrow and start making healthy bone marrow cells. Both of these patients had a second BMT from a different donor and are doing well. Graft-versus-host disease rates were very low, and most cases were mild.

Dr. DeZern concluded that alternative approaches to matched-donor BMT, including haploidentical BMT, offer a safe potential cure for severe aplastic anemia that has yet to respond to previous treatment or that relapsed after treatment. In addition, up-front haploidentical BMT is increasingly a treatment option for newly diagnosed severe aplastic anemia in people without matched related donors.

Transplantation for Inherited Bone Marrow Failure Disorders and Fanconi Anemia

Carmem Bonfim, MD, PhD
University of Parana

In most patients with inherited bone marrow failure syndromes, the bone marrow becomes increasingly abnormal and unable to make healthy blood cells. These patients have a higher risk of cancer. Stem cell transplantation (SCT) can cure the bone marrow complications of the disease.

Diamond Blackfan Anemia

Diamond Blackfan anemia is a rare inherited bone marrow failure syndrome. These patients typically have anemia and low counts of certain immature red blood cells. The usual treatment is a combination of steroids and regular blood transfusions. SCT is used for patients who don't respond to steroids or who develop aplastic anemia or another bone marrow failure disease.

A study in Germany and France of 70 patients with Diamond Blackfan anemia found that survival rates with SCT have been excellent since 2000, especially for patients with matched-sibling donors. In Brazil, 44 patients in another study had excellent survival rates with matched related or unrelated donor transplants. But survival rates were poor for patients with mismatched donors. A donor is mismatched when some of their HLA markers (a set of proteins on white blood cells) don't match all of the patient's HLA markers.

Dyskeratosis Congenita

Patients with dyskeratosis congenita have very short telomeres. Telomeres at the ends of chromosomes help keep chromosomes stable. These patients have abnormal skin patterns, weak nails, and white patches inside the mouth. Treatments with androgens, a male hormone, improve bone marrow function in most patients. But SCT is only the cure.

Survival rates are improving for patients with dyskeratosis congenita who undergo SCT before age 20 and for those with a matched donor. To decrease the complications of SCT, a recent clinical trial in patients with dyskeratosis congenita or other telomere diseases used fludarabine (Fludara) and alemtuzumab (Campath) for conditioning. Conditioning treatment helps make room in the patient's bone marrow for the transplanted blood cells to grow. In this study, the donated stem cells reached the bone marrow and began making healthy blood cells in 19 of 20 patients.

Fanconi Anemia

In Fanconi anemia, the bone marrow doesn't make enough red blood cells, white blood cells, or platelets. SCT is the only cure. Results are best when SCT is done before the patient needs regular blood transfusions or develops severe infections. Outcomes are also better when the stem cells come from a matched sibling who doesn't have Fanconi anemia or a matched unrelated donor.

Results of SCT with Fanconi anemia from 2009 to 2017 in Brazil were excellent in 91 patients (average age 9 years) who had a matched related donor. Six years after the procedure, 95% were still alive. Another study of 53 patients with Fanconi anemia in Brazil found that with haploidentical SCT, where half the donor's HLA markers match those of the patient, adding antithymocyte globulin to the conditioning treatment doubled survival rates. This treatment also increased the likelihood that the donated cells would reach the bone marrow and make healthy blood cells.

Conclusions

Dr. Bonfim concluded that international collaboration is needed to advance the care of patients with inherited bone marrow failure diseases. In particular, studies are needed on diagnosis of these diseases, transplant and nontransplant treatments, and long-term outcomes.

NON-TRANSPLANT THERAPIES

Immunosuppressive therapy (IST) weakens the patient's immune system and stops it from attacking the bone marrow. With the addition of eltrombopag (Promacta) to standard IST, most patients have higher blood counts. But about a third have a relapse later, and the disease can progress to MDS or acute myelogenous leukemia (AML) in about 10 to 15% of cases.

RACE Study Update

Antonio Risitano, MD, PhD
University of Naples

One possible explanation for the limited success of IST for aplastic anemia is the lack of healthy stem cells in these patients. For this reason, researchers are interested in combining IST with treatments that promote the expansion of healthy bone marrow cells that can form healthy blood cells.

A nonrandomized study published in 2017 showed that adding eltrombopag (Promacta) to IST as the first treatment for severe aplastic anemia had a much higher response rate than IST alone. Eltrombopag stimulates thrombopoietin, a hormone that controls platelet production in the bone marrow. This treatment increases the number of healthy platelets and decreases bleeding risk.

A Prospective Randomized Multicentre Study Comparing Horse Antithymocyte globuline (hATG) + Cyclosporine A ± Eltrombopag (RACE) randomly assigned patients (average age 53 years) with severe or very severe aplastic anemia to standard IST of hATG plus cyclosporine as well as eltrombopag or to hATG and cyclosporine only. This study did not use any placebo. The initial plan was to give the treatment for 6 months, but the trial was designed to be stopped at 3 months if participants showed early signs of response.

All patients in this Phase III randomized clinical trial received the same dose of eltrombopag, 150 mg a day. If patients were in remission after 3 months, they stopped taking the eltrombopag. Those who weren't in remission continued taking the eltrombopag for 3 more months. The study had sites in several European countries.

At 3 months, 10% of patients in the IST group and 22% in the eltrombopag and IST group responded. However, survival rates at 18 months were similar in both groups (83% for IST alone and 86% for IST and eltrombopag).

Long-Term Outcomes of Immunosuppression and Eltrombopag for Severe Aplastic Anemia

Bhavisha Patel, MD
National Heart, Lung, and Blood Institute

Patients with a new diagnosis of severe aplastic anemia are treated with either IST or, depending on their age and availability of a suitable donor, a stem cell transplant. The goal of both treatments is to restore normal bone marrow function and decrease the risk of long-term complications.

A Phase 1/2 clinical trial funded by the National Institutes of Health treated 92 patients with severe aplastic anemia with IST plus eltrombopag. Group 1 was treated with eltrombopag starting on Day 14 for 6 months, Group 2 from Day 14 for 3 months, and Group 3 from Day 1 for 6 months. The study was designed to evaluate complete responses in the bone marrow at 6 months. Group 3 had the best responses, so the Group 3 treatment regimen was used for an extension study.

After the first 44 patients enrolled in this trial, analyses showed that relapse rates were higher than expected after 6 months, when both the IST and eltrombopag treatment ended. The investigators therefore decided to keep patients on lower doses of cyclosporine for up to 2 more years.

Dr. Patel reported the long-term findings from 176 patients—the original 92 as well as 84 from the extension study. Half the patients had very severe aplastic anemia. On average, the initial group of patients were followed for 4 years, and the extension group for about a year.

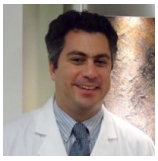
Of 143 participants who responded to the combination treatment at 6 months, about 40% had a relapse within an average of 2 years. Relapses were most common at the time that the first cyclosporine dose was lowered and eltrombopag was stopped, and again when the lower cyclosporine dose was stopped at 2 years. Relapses were also more common in older patients.

The investigators treated 57 participants who had a relapse with a full dose of cyclosporine, and if they did not respond, with eltrombopag as well. Seventy percent of these patients responded to either cyclosporine alone or cyclosporine combined with eltrombopag.

The relapse rates with the combination of eltrombopag and IST were the same as for IST alone. Relapses tended to occur when treatments are changed, but most patients with a relapse responded to cyclosporine with or without eltrombopag retreatment. Progression to MDS or AML occurred in less than 10% of patients treated. This rate was no different than that for patients treated with IST alone.

Future Directions in Non-Transplant Therapies






Bhavisha Patel, MD, National Heart, Lung, and Blood Institute
Antonio Risitano, MD, PhD, University of Naples
Phillip Scheinberg, MD, Hospital A Beneficência Portuguesa
Neal Young, MD, National Heart, Lung, and Blood Institute

Triple Therapy—Eltrombopag, Antithymocyte Globulin, and Cyclosporine—for Severe Aplastic Anemia

At this time, triple therapy for severe aplastic anemia with eltrombopag, cyclosporine, and antithymocyte globulin (ATG) provides the best responses for severe aplastic anemia. The panel members said that this combination should be used as the standard first treatment whenever possible. In younger patients, stem cell transplantation (SCT) with a matched related donor remains the standard of care because the benefits of eltrombopag in children are not yet clear.

The progression rate to MDS with ATG, cyclosporine, and eltrombopag to date has been similar to that with ATG and cyclosporine alone. When disease progresses after triple therapy, it tends to happen early in the treatment course, usually within the first 6 months. When severe aplastic anemia progresses to MDS, SCT remains an important option for patients who are eligible for it.

Eltrombopag and Cyclosporine Without ATG for Severe Aplastic Anemia

Triple therapy has many advantages, but ATG has some disadvantages. ATG has to be administered through a central line (a tube inserted into a vein) in experienced centers and can cause side effects. Also, it's not readily available in most places. For these reasons, treatments, including some that don't use ATG, that can be started promptly are being studied.

A trial of the combination of eltrombopag and cyclosporine without ATG in just over 50 patients with severe aplastic anemia enrolled its last participant on April 30, 2020. The trial's aim is to determine whether this treatment had better response rates than the typical 35 or 40% with a combination of rabbit ATG and cyclosporine. The study will follow patients for 6 months after enrollment.

A new National Institutes of Health clinical trial is giving eltrombopag and cyclosporine to patients with severe aplastic anemia and then moving them to the triple therapy as soon as possible if they don't respond to the two-drug combination. This study will show whether delaying ATG treatment is effective.

Cyclosporine is good for preventing relapse, and eltrombopag helps boost the healthy stem cells left in the patient's bone marrow. If patients respond to eltrombopag and cyclosporine alone, they might do well without horse ATG, but this depends on what types of blood cell shortages they have. Patients are more likely to die sooner or have complications with eltrombopag and cyclosporine if they have very low counts of neutrophils, a type of white blood cell. These patients are likely to do better with the addition of horse ATG.

What the Future Holds

A new era is coming in which age will be the deciding factor for severe aplastic anemia treatment. For very young patients, the goal is to schedule SCT as soon as possible, regardless of the type of donor available. Even unrelated donors whose HLA markers match those of the patient can be used successfully in children if the procedure happens within two months of diagnosis. A less than 100% match increases the risk of complications after SCT. Stem cells from a sibling or parent whose HLA markers match half those of the patient (haploidentical donor) have been used when patients didnÊ¼t respond to IST. Although the results are still preliminary, childrenÊ¼s outcomes look promising. For most adults, triple therapy is the best option. If this treatment doesnÊ¼t work, other ISTs are less likely to help, and SCT should be considered.

TREATMENT FOR MDS AND SECONDARY AML

Acute myelogenous leukemia (AML) is secondary when it develops in a patient who has had MDS or has been treated for another disease.

New Treatment Strategies for Patients with AML or MDS and TP53 Mutations

David Sallman, MD
Moffitt Cancer Center

The TP53 gene provides instructions for making the p53 protein. This protein suppresses tumors by preventing cells from growing and dividing too quickly or in an uncontrolled way.

People who have MDS or secondary AML and a TP53 mutation don't tend to survive as long as people without these mutations. The prognosis is even poorer in patients with MDS who have TP53 mutations and several abnormalities in their chromosomes.

In patients with MDS, a chemical process known as "methylation" blocks DNA's ability to control cell growth. The hypomethylating agents (HMAs) azacitidine (Vidaza) and decitabine (Dacogen) remove the methyl groups that attach to DNA so that DNA sequences can act normally.

Response rates to HMAs are similar, at 30% to 50%, in patients with MDS who do or do not have a TP53 mutation. But people with a TP53 mutation don't usually survive as long after treatment as those without a mutation, and less than 20% of patients have a complete remission. Patients with TP53 also don't tend to do well with stem cell transplantation.

APR-246 is an experimental drug that can reactivate the p53 protein. A clinical trial at the Moffitt Cancer Center in Florida is evaluating the combination of APR-246 and azacitidine in patients with MDS and the TP53 mutation. These patients have not been treated with an HMA before. This study is assessing the response rate as well as side effects and impact on survival.

As of November 15, 2019, the most common side effects in the first 55 patients in the trial were nausea and vomiting. At that time, 39 patients (71%) had responded to the treatment. A Phase III clinical trial is now studying the combination of azacitidine and APR-246 in patients with intermediate-risk, high-risk, or very-high-risk MDS who have TP53 mutations.

Dr. Sallman also discussed a study that combined magrolimab , another experimental drug, with azacitidine. The CD47 molecule tells immune cells to not to eat cancer cells. By blocking this signal, magrolimab lets immune cells recognize and destroy cancer cells. Response rates to this combination are high in patients with AML or MDS who have a TP53 mutation.

Inhibiting the Activity of TGF-Beta in MDS

Amit Verma, MD
Albert Einstein College of Medicine

Transforming growth factor beta (TGF-beta) is a type of protein. TGF-beta sends out signals that control various cell activities. These activities include growth and division, maturation to carry of certain functions, and controlled cell death.

Several members of the TGF-beta family control the formation of blood cells in the bone marrow. When TGF-beta doesn't work properly in a person with MDS, the bone marrow can start forming unhealthy immature blood cells that become unhealthy white blood cells, red blood cells, and platelets.

LY-2157299 (also known as galunisertib) is an experimental drug that inhibits the activity of TGF-beta. A Phase II clinical trial gave LY-2157299 twice daily to 38 patients with MDS. Of 24 participants who needed regular transfusions of at least 4 units of red blood cells, 9 (38%) stopped needing transfusions or had increases in hemoglobin for at least 8 weeks. In patients who responded to the treatment, their immature blood cells formed more healthy blood cells.

TGF-beta works by activating the SMAD2 protein, which is overly active in the bone marrows of people with MDS. ALK kinases are proteins that send signals from cell surfaces into cells. Inhibiting ALK kinases reduces SMAD2 activation and leads to increased blood cell formation in specimens from people with MDS.

Luspatercept (Reblozyl) is a drug that reduces the ability of SMAD2 to send out signals. In this way, luspatercept help immature red blood cells in the bone marrow form healthy mature red blood cells.

MEDALIST was a Phase III clinical trial (NCT02631070) that evaluated the safety and efficacy of luspatercept in 229 adults (median age 71 years, 63% male) with low-risk or intermediate-risk MDS who had anemia with ring sideroblasts. Two-thirds of the patients were randomly assigned to luspatercept treatment, and one-third to placebo. All patients were treated every 3 weeks for at least 24 weeks.

Of 153 patients in the luspatercept group, 58 (38%) stopped needing red blood cell transfusions for at least 8 weeks. In addition, the bone marrows of 81 patients (53%) in the luspatercept group showed increases in numbers of healthy red blood cells. Responses lasted an average of 30 weeks.

Some remaining research questions are whether luspatercept works in other forms of MDS and whether it's more effective when combined with other drugs.

Targeting Splicing to Treat MDS

Timothy Graubert, MD
Massachusetts General Hospital

Splicing factors are proteins that control the splicing together of certain RNA sequences to form messenger RNA molecules. Messenger RNA contains the genetic coding information needed to make proteins, the building blocks of cells.

Most people with MDS have mutations in the genes that form splicing factors. Because these mutations are so common in MDS, a treatment that targeted them could potentially help a large number of patients.

Also, splicing mutations are often some of the first gene mutations that patients with MDS acquire as their disease develops. As a result, all the abnormal cells in a patient with MDS who has a splicing mutation could potentially be eliminated if this pathway could be targeted effectively.

A way to target the activity of mutated splicing genes could be to "poison" their splicing process. The abnormal cells containing these mutated genes might be more sensitive to this poisoning than healthy cells containing normal splicing genes.

One reason to think that this approach might work is that patients almost never have more than one splicing mutation. In general, cells can't survive with mutations in more than one of these genes. Also, MDS cells require at least one normal copy of a splicing gene to have enough healthy splicing activity to survive.

H3B-8800 is an experimental medicine that changes the way RNA is spliced and could therefore kill cells with mutated splicing genes. A Phase I clinical trial (NCT02841540) evaluated the responses of 84 patients with MDS and other bone marrow failure diseases to H3B-8800.

The results of this study were disappointing because none of the patients had a complete or even a partial response to the treatment. But these findings are preliminary and not enough to dismiss the potential that this treatment could be effective.

Another idea is that interfering with the DNA damage response caused by the mutant splicing genes could kill cells with these mutations.

A Phase Ib/II clinical trial is evaluating AZD6738 in patients with MDS or chronic myelomonocytic leukemia (NCT03770429). This experimental drug targets a pathway in cells that repairs DNA damage by blocking the ATR protein. Inhibiting ATR with AZD6738 could cause cells with mutant splicing factors to accumulate DNA damage and die while sparing cells that have normal splicing genes.

New Combination Treatments for Higher-Risk MDS

Olatoyosi Odenike, MD
University of Chicago

In patients with MDS, a chemical process known as "methylation" blocks DNA's ability to control cell growth. The hypomethylating agents (HMAs) azacitidine (Vidaza) and decitabine (Dacogen) remove the methyl groups that attach to DNA so that DNA sequences can act normally.

HMAs are the main treatment for higher-risk MDS. But only about 30% to 50% of patients in clinical trials respond to these drugs, and 10% to 20% have a complete response. Also, responses last only about 10 to 13 months.

HMAs have to be injected several times a month as long as the drugs are working, which makes these treatments inconvenient for patients. Versions of HMAs that patients could take by mouth would be more convenient for patients and might let patients take these drugs longer. These drugs might be more effective than current HMAs.

But it's hard to make oral forms of azacitidine and decitabine. Cytidine deaminase (CDA), an enzyme in the gut and liver, rapidly clears these drugs from the bloodstream.

ASTX727 is a combination of oral decitabine with a new drug, E7727, that inhibits CDA. A Phase III clinical trial, the ASCERTAIN study (NCT03306264), randomly assigned 133 patients with MDS or chronic myelomonocytic leukemia to ASTX727 for the first cycle and decitabine for the second cycle, or to one cycle of decitabine and then a cycle of ASTX727. All patients were then treated with ASXTX727 for the remaining cycles. Drug levels in the bloodstream were equivalent with oral ASTX727 and intravenous decitabine.

The most common serious side effects were low blood cell counts and low white blood cell counts with fever. Of the 101 patients whose responses could be analyzed after an average of 5 months, 65 (64%) responded to the treatment. In July 2020, the U.S. Food and Drug Administration approved the use of ASTX727 (now known as venetoclax) for higher-risk MDS.

CC-486 is a version of azacitidine that patients take by mouth. QUAZAR AML-001 is a Phase III clinical trial of CC-486 in 486 patients with AML that had not responded completely to previous treatment and who were not eligible for stem cell transplantation. Survival rates in patients treated with CC-486 were 73% after a year and 51% after 2 years.

Other treatments under investigation for higher-risk MDS that could be combined with HMAs include:

- Venetoclax (VENCLEXTA) dampens the activity of the BCL-2 protein. Overexpression of this protein can prevent patients with MDS from responding well to MDS treatment.
- Cancer cells use the CD47 signal to prevent the macrophage cells in the body's immune system from attacking the cancer cells. Magrolimab blocks the CD47 "don't eat me" signals and boosts the "eat-me" signals. In this way, magrolimab helps the immune system attack and kill cancer cells.
- Pevonedistat inhibits the NEDD8-activating enzyme. Therefore, pevonedistat might prevent MDS cells from surviving.

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YOUR GIFT IS IMPORTANT

81% of AAMDSIF funding is used for patient and health professional programs

Individual and private foundation funding is critical to our ability to provide quality education, engage the top experts in the field and utilize the best of technology

Pharmaceutical and biotech companies with drugs and treatments for bone marrow failure disease provide educational grants that help support our publications, webinars and conferences

MAXIMIZE YOUR GIVING

MONTHLY GIVING SUPPORTS OUR SERVICES EFFICIENTLY AND EASILY:

$45 per month
helps support a leading expert to present an educational webinar for patients

$100 per month
helps support one disease specific session at a Patient & Family or Health Professional Conference

$200 per month
helps support between 20-25 hours of one-on-one patient support with patient advocacy team

OPPORTUNITIES FOR MAJOR IMPACT

Organize or participate in a local event such as March for Marrow

Designate AAMDSIF in your workplace giving or state giving campaign.

Designate AAMDSIF as a beneficiary in your estate planning or IRA account in your yearly distribution.

Contact Julie Lowe at
(301) 279-7202 x103 or Lowe@aamds.org

How AAMDSIF Can Help You …

Many FREE services and programs are available to anyone impacted by, or just interested in, bone marrow failure diseases:

- Personalized Support available online at www.aamds.org/support, at help@aamds.org or from information specialists at (800) 747-2820 x2
- Educational Materials
  Disease and treatment information:
  www.aamds.org/education/patient-guides-and-fact-sheets
- Webinars
  Free webinars, classes, expert interviews:
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- Patient and Family Conferences
  Connecting our community with leading experts:
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  Call (800) 747-2820 x2 or online at
  www.aamds.org/find-a-specialist
- Clinical Trials Information
  How they work, how to join:
  www.aamds.org/clinicaltrials
- Peer Support Network
  Trained patient and family volunteers:
  www.aamds.org/support
- Support Groups
  In person and online volunteer-led support and awareness groups:
  www.aamds.org/support

Looking for a way to help? Volunteer and help raise awareness for bone marrow failure diseases!

Your work can directly help patients and their families. Call 301-279-7202 or email lowe@aamds.org to learn more about how you can get involved.

- Hold digital fundraisers in your community or in your workplace
- Plan a "March for Marrow" fundraising walk or other events
- Create awareness in your community about bone marrow failure
- Coordinate local patient support groups

Learn more about volunteering by contacting Julie Lowe at lowe@aamds.org or (301) 279-7202 x103.

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