



AAMDSIF

Aplastic Anemia Research Summary *from the* 2016 AMERICAN SOCIETY OF HEMATOLOGY ANNUAL MEETING

Summary of Selected Scientific Abstracts for Patients with Aplastic Anemia and Their Caregivers

DIAGNOSIS

1043

***RTEL1* Mutations and Bone Marrow Failure**

Shreyans Gandhi, M.D.; Jie Jiang; Mariam Ibanez; Isabelle Callebaut; Judith C.W.; Marsh, M.D.; Ghulam J Mufti, M.D.

Doctors sometimes have trouble telling whether a patient with bone marrow failure and blood cell shortages has MDS or aplastic anemia.

The investigators screened specimens from patients for mutations in genes that control telomeres and genes that are often mutated in MDS and acute myelogenous leukemia (AML). Telomeres are located at the ends of chromosomes and help keep chromosomes stable. They tend to be short in people with aplastic anemia. The study included 284 patients who had aplastic anemia with an unknown cause or a bone marrow failure syndrome and 172 patients with MDS or AML.

Key findings:

- 20 patients (4%, median age 35 years) had mutations in the *RTEL1* gene. This gene helps keep telomeres long and stable.
- Of these patients, 18 (90%) had short telomeres.
- 15 had low numbers of immature blood cells in the bone marrow.
- 10 years after their symptoms first appeared, 16 patients (80%) were still alive. The others died when their disease progressed or they developed lymphoma.

Conclusions:

- This study provided the first evidence that 4% of patients have an *RTEL1* mutation.
- These mutations are most common in young patients with low counts of immature blood cells in bone marrow.

1044

***RTEL1* Mutations in Patients with Bone Marrow Failure Syndromes Associated with Telomere Dysfunction**

Fernanda Gutierrez-Rodriguez, M.Sc., Pharm.D.; Sachiko Kajigaya, Ph.D.; Xingmin Feng, Ph.D.; Maria del Pilar Fernandez Ibanez, M.S.; Marie J. Desierto; Keyvan Keyvanfar; Zejuan Li, M.D., Ph.D.; Soma Das, Ph.D.; Rodrigo T. Calado, M.D., Ph.D.; Danielle M. Townsley, M.D.; Neal S. Young, M.D.

Telomeres are located at the ends of chromosomes and help keep chromosomes stable. They tend to be short in people with aplastic anemia. The *RTEL1* gene helps keep telomeres long and stable. Some patients with aplastic anemia have mutations in the *RTEL1* gene.

The purpose of this study was to describe *RTEL1* mutations in people with aplastic anemia and their effect on maintaining telomeres. The study tested samples from 63 patients.

Key findings:

- Eight patients had heterozygous mutations in *RTEL1*, meaning that they had two different copies of the gene.
- One patient had the F1262L variant in *RTEL1*. This patient had very short telomeres.
 - This variant seems to be capable of causing aplastic anemia.
- Another patient had the D743N variant in *RTEL1*. This patient had very short telomeres and a family history of diseases associated with short telomeres. These diseases include aplastic anemia, liver cirrhosis, and pulmonary fibrosis.
- Five patients had mutations in genes next to *RTEL1*. Their disease might be due to a more complex combination of genetic mutations.

Conclusions:

- This is the first report of heterozygous *RTEL1* mutations in patients with aplastic anemia.

334 Cancer in Patients with Inherited Bone Marrow Failure Syndromes after 15 Years of Follow-up

Blanche P. Alter, M.D., M.P.H.; Neelam Giri, M.D.; Sharon A Savage, M.D.; Philip S. Rosenberg, Ph.D.

Patients with inherited bone marrow failure syndromes might have aplastic anemia and/or certain physical abnormalities. These syndromes can progress to cancer.

The purpose of this study was to compare the types of bone marrow failure syndromes and assess risk of cancer in 535 patients with Diamond-Blackfan anemia, dyskeratosis congenita, Fanconi anemia, or Shwachman-Diamond syndrome.

Key findings:

- The proportion of patients who developed severe bone marrow failure requiring stem cell transplantation or leading to death was:
 - Diamond-Blackfan anemia: 23%
 - Dyskeratosis congenita: 47%
 - Shwachman-Diamond syndrome: 55%
 - Fanconi anemia: 70%

- Patients with different syndromes tended to develop different types of cancers:
 - Diamond-Blackfan syndrome: cervical, colon, or lung cancer
 - Fanconi anemia and dyskeratosis congenita: head and neck cancer, leukemia, or gynecologic cancer.
 - Shwachman-Diamond syndrome: leukemia or ovarian cancer
- 136 patients underwent stem cell transplantation:
 - 16 of these patients developed cancer after stem cell transplantation.
 - The risk of cancer was 6 times higher in dyskeratosis congenita and 4 times higher in Fanconi anemia after stem cell transplantation than in patients who did not have transplantation.

Conclusions:

- These patients, especially those with dyskeratosis congenita and Fanconi anemia, had a very high risk of leukemia and solid tumors.
- The risk of cancer was particularly high in patients with dyskeratosis congenita and Fanconi anemia after stem cell transplantation.

727

Mutations in Patients with Severe Aplastic Anemia Treated with Eltrombopag and Standard Immunosuppression

Danielle M. Townsley, M.D.; James N. Cooper, M.D.; Thomas Winkler, M.D.; Phillip Scheinberg, M.D.; Olga Rios; Barbara Weinstein; Janet Valdez; Jennifer Lotter; Marie J. Desierto; Maria del Pilar Fernandez Ibanez, M.S.; Colin Wu, Ph.D.; Cynthia E. Dunbar, M.D.; Wanlong Ma; Maher Albitar, M.D.; Neal S. Young, M.D.

The standard immunosuppressive treatment (IST) for severe aplastic anemia consists of horse antithymocyte globulin and cyclosporine. Eltrombopag (Promacta®) stimulates thrombopoietin, a hormone that controls platelet production in the bone marrow. This process increases the number of platelets and decreases bleeding risk. Adding eltrombopag to standard IST increases response rates in patients with severe aplastic anemia compared to IST alone.

The purpose of this study was to use next-generation sequencing to assess 54 genes that are often mutated in bone marrow cancers. The study included samples from 90 patients who had been treated with IST and eltrombopag.

Key findings:

- The analyses identified at least one mutation in 21 patients (23%).
- All 21 patients had higher blood counts after treatment.
- Of the 19 patients with a somatic mutation (one that they did not inherit and will not pass on to their children), 14 had a complete hematologic response (meaning that their blood cell counts rose).
- In comparison, of the 69 patients without a mutation, 20 (29%) had a complete hematologic response.
- Patients with a *BCOR* mutation had better responses to treatment and tended to be younger (age 12–49 years).
- After a median of 21 months, 7 patients (8%) developed new chromosomal abnormalities. Three of these patients had a mutation in a gene associated with bone marrow failure disease.

Conclusions:

- Adding eltrombopag to IST increases response rates and improves responses in patients with severe aplastic anemia.
- The combination treatment does not increase the risk of progression to MDS or acute myelogenous leukemia.

1505

Alemtuzumab as a Rescue Therapy in Bone Marrow Failure Diseases

Swapna Thota, M.D.; Srinivasa Reddy Sanikommu, M.D.; Bhumika Patel, M.D.; Meena Sadaps; Cassandra M. Hirsch; Michael J. Clemente, M.S.; Serena Marotta, M.D.; Antonio M Risitano, M.D., Ph.D.; Mikkael A. Sekeres, M.D., M.S.; Jaroslaw P. Maciejewski, M.D., Ph.D.

In aplastic anemia, the immune system doesn't work properly, leading to blood cell shortages. Alemtuzumab (Campath®) is a drug that reduces the number of abnormal lymphocytes (type of white blood cell) in the blood. Up to 58% of patients with relapsed aplastic anemia respond to this treatment. But the dosing is based on evidence from patients with chronic lymphocytic leukemia.

The authors summarize their experience with alemtuzumab at the maximum dose of 100 mg in 22 patients with aplastic anemia, 22 with pure red cell aplasia, 18 with T cell large granular lymphocytic leukemia, and 3 with idiopathic neutropenia and pure white cell aplasia. All patients (median age 58 years) were seen at the Cleveland Clinic or the University of Naples in 2002–2015. At the Cleveland Clinic, alemtuzumab was used in patients who had not responded to another treatment. The drug was given to patients whose disease had never been treated at the University of Naples.

Key findings:

- 92% of patients tolerated the treatment well.
- The main side effects were related to infections.
- 54% of patients with aplastic anemia responded to the treatment.
- In patients with aplastic anemia, responses lasted a median of 6 months.
- Among patients with aplastic anemia, 72% of those whose disease had never been treated responded, as did 45% of those whose disease had relapsed after a previous treatment or who had not responded to a previous treatment.

Conclusions:

- Low-dose alemtuzumab is a reasonable alternative for patients with bone marrow failure diseases, especially in those whose disease did not respond to a previous treatment or who had a relapse.
- After treatment, patients need to be monitored for infections and disease recurrence.

2673

Potential Use of Expanded Regulatory T-Cells to Treat Aplastic Anemia

Benedetta Costantini, M.D. M.Phil.; Shahram Kordasti, M.D., Ph.D.; Marc Martinez-Llordella, Ph.D.; Giovanni Povoleri, M.Phil.; Judith C. W. Marsh, M.D.; Frederic Toulza, Ph.D.; Ghulam J. Mufti, D.M.

T cells are a type of white blood cell that helps protect the body from infection. Patients with aplastic anemia have low numbers of T cells, and the T cells they do have don't function properly. T regulatory (Treg) cells control the activity of other T cells.

The aim of this study was to investigate a way to expand Treg cells outside the human body. The investigators also assessed the function and characteristics of the expanded Treg cells.

Key findings:

- Aplastic anemia T-regulatory cells that are expanded through incubation in a special culture for 4 weeks behave like regular Treg cells.
- Expanded Treg cells express the *IL-7* and *CD80* genes. These genes are important for Treg movement and stability.
- The expanded Treg cells are more similar to Treg B than Treg A cells. Patients with aplastic anemia tend to lack Treg B cells.

Conclusions:

- Aplastic anemia Treg cells can be expanded outside the human body.
- The expanded Treg cells are likely to control the immune system's response in aplastic anemia.
- These expanded cells might be part of a new cell therapy for severe aplastic anemia.

2682

Eltrombopag Treatment for Diamond-Blackfan Anemia

Thomas Winkler, M.D.; Danielle Townsley, M.D.; Ronan Desmond, M.D.; Bogdan Dumitriu, M.D.; Sophia Grasmeder; Neal S. Young, M.D.; Cynthia E. Dunbar, M.D.

Diamond Blackfan anemia is a rare bone marrow failure syndrome. In patients with this syndrome, the bone marrow doesn't make enough red blood cells, which carry oxygen to the body's tissues. Patients usually develop anemia (red blood cell shortage) during the first year of life. As they get older, many patients develop shortages of all types of blood cells along with a high risk of leukemia. Although regular blood transfusions and corticosteroids can reduce the anemia, these treatments both have serious long-term effects.

The authors report on a 28-year-old woman diagnosed with Diamond-Blackfan anemia at age 1 month. She had not responded to corticosteroids and was treated with regular blood transfusions. In 2012, she developed shortages of all types of blood cells and abnormal immature blood cells in her bone marrow. The patient was treated with eltrombopag (Promacta®), which stimulates thrombopoietin. Thrombopoietin is a hormone that controls platelet production in the bone marrow.

Key findings:

- The patient's hemoglobin count rose from 7.0g/dl to 11.9g/dl and her platelet count rose from 112K/ul to 251k/ul.
- She did not require any more blood cell transfusions.
- After she stopped the eltrombopag treatment, her hemoglobin dropped steadily over 8 months.
- When eltrombopag was restarted, her blood cell counts rapidly improved.
- As of the writing of this abstract, the patient was being treated with 50 mg eltrombopag daily and had normal blood cell counts.
- She had no treatment-related side effects.

Conclusions:

- The investigators believe that this is the first report showing that eltrombopag is effective for Diamond-Blackfan anemia.

HEMATOPOIETIC STEM CELL TRANSPLANTATION

1500 Stem Cell Transplantation for Patients with *GATA2* Deficiency

Dennis D. Hickstein, M.D.; Nirali N Shah, M.D.; Alexandra Freeman, M.D.; Christa Zerbe, M.D.; Steven M. Holland, M.D.

GATA2 deficiency is a genetic disease that can cause severe infectious, breathing problems, and inherited MDS/acute myelogenous leukemia (AML). The only effective treatment is hematopoietic stem cell transplant (HSCT).

The investigators assessed the outcomes of HSCT in 24 patients (average age 25 years) with *GATA2* mutations. Patients received different treatments before the procedure to reduce the number of cancerous cells as well as different treatments after HSCT to prevent graft-versus-host disease (GVHD).

Key findings:

- Twenty-two of the 24 patients were alive and disease free after an average of 13 months.
- Two patients who received a transplant from an unmatched related donor died of AML or GVHD.
- Four of 13 patients who received stem cells from a related donor developed serious GVHD.
- Abnormalities in chromosomes disappeared in 13 patients with MDS.
- In 23 patients, white blood cell counts were in the normal range.

Conclusions:

- HSCT reverses the signs and symptoms of *GATA2* deficiency with few serious side effects, even in patients with other serious medical concerns.

HEMATOPOIETIC STEM CELL TRANSPLANTATION

2679

Stem Cell Transplantation for Diamond Blackfan Anemia

Farah O'Boyle, Ph.D.; Anne Bradshaw; Richard M. Szydlo; Josu de la Fuente, Ph.D.

Hematopoietic stem cell transplantation (HSCT) can restore normal blood cell formation in the bone marrow of patients with Diamond Blackfan anemia. But the outcomes of HSCT from unrelated or mismatched donors have been poor.

The investigators report on 17 patients with Diamond Blackfan anemia (median age 8 years) who underwent HSCT between 2006 and 2015. Ten patients received transplanted cells from siblings whose 10 blood markers matched the patient's. Two patients received transplanted cells from unrelated donors, and one patient received cord blood cells with 5 of 6 matching markers.

Key findings:

- The donated cells engrafted in all patients, meaning that the cells reached the bone marrow and began making healthy blood cells.
- On average, patients survived for 31 months after HSCT.
- One patient died on the 53rd day due to pneumonia.
- Four patients developed severe graft-versus-host disease (GVHD) within 3 months of HSCT.
- Four patient developed GVHD more than 3 months after HSCT. This HSCT complication went away in all 4 patients by 18 months.

Conclusions:

- HSCT from related and unrelated donors leads to early and sustained engraftment with a low rate of graft failure and death.
- However, patients have a risk of serious side effects in the digestive system and lungs.
- These side effects can be reduced by decreasing the intensity of treatments given to prevent GVHD.