

# Aplastic Anemia Research Summary *from the* 2015 AMERICAN SOCIETY OF HEMATOLOGY ANNUAL MEETING

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

## DISEASE BIOLOGY

**1213**

### **Pediatric Aplastic Anemia and Refractory Cytopenia of Childhood**

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In 2008, the World Health Organization (WHO) proposed a provisional classification, "refractory cytopenia of childhood (RCC)." RCC features blood cell shortages and small proportions of blasts (abnormal immature white blood cells) in bone marrow and blood. Until now, no studies have addressed whether the current WHO classification reflects clinical outcomes of childhood bone marrow failure syndromes.

A research team analyzed blood and bone marrow specimens from 457 children classified as having aplastic anemia (median age 10 years), RCC (median age 9 years), or refractory cytopenia with multilineage dysplasia (RCMD; median age 7 years). RCMD results in anemia, neutropenia (low counts of neutrophils, a type of white blood cell), and/or platelet shortages that don't respond to treatment.

#### **Key findings:**

- Children with aplastic anemia had lower counts of white blood cells, immature red blood cells, and platelets than those with RCC or RCMD. They also had significantly smaller blood cells.
- 1 patient with aplastic anemia, 6 patients with RCC, and 18 with RCMD had abnormalities in their chromosomes.
- In the 69 patients treated with rabbit antithymocyte globulin and cyclosporine to suppress their immune systems, response rates were similar among patients with aplastic anemia (38%) and RCC (47%) after 6 months. All of the small number of patients with RCMD responded to this treatment.

#### **Conclusions:**

- The authors recommend adding RCMD to the categories of childhood MDS because children with RCMD had specific blood cell characteristics and laboratory test results.
- Further efforts to clarify changes in genes and chromosomes and outcomes in patients are necessary to establish a classification system for childhood bone marrow failure syndromes.

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## Clones and Genetic Mutations at Presentation of Aplastic Anemia

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In about 15% of patients, aplastic anemia progresses to MDS within 10 years. The reasons why this happens aren't fully understood.

A team of researchers studied 36 patients with aplastic anemia or PNH that progressed to MDS or acute myelogenous leukemia within a median of 3.2 years.

### Key findings:

- 17% of patients whose disease progressed to MDS had a PNH clone, or copy of abnormal immature blood cells. 35% of patients whose disease did not progress had a PNH clone.
- Patients whose aplastic anemia or PNH progressed to del(7q) MDS were more likely to have mutations in RUNX1, CBL, SETBP1, and ASXL1 than patients with del(7q) MDS without a prior bone marrow failure syndrome.
- Mutations in TP53 and DMT3A were less common in patients who had PNH or aplastic anemia before developing MDS.
- In a separate analysis, 37 patients with aplastic anemia had somatic (non-inherited) mutations when they first developed symptoms, and 14 of them developed MDS.
- Among 40 of these patients with abnormal clones, 3 developed MDS.
- The patients with mutations in ASXL1, CUX1, TET2, CBL, RUNX1, or SETBP1 did not survive as long as patients without these mutations.

### Conclusions:

- Having non-inherited genetic mutations at the outset predisposes patients with aplastic anemia to develop MDS.
- This finding can be useful for diagnosis and prognosis of patients with aplastic anemia.

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## A Common Biology Between Acquired Aplastic Anemia and Ulcerative Colitis

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Patients with acquired (non-inherited) aplastic anemia sometimes have other autoimmune diseases, such as rheumatoid arthritis and ulcerative colitis. The biological relationships between these diseases are not known.

A team of researchers from Japan analyzed data on 14 patients (median age 55 years) with aplastic anemia who also had ulcerative colitis. Eleven patients developed ulcerative colitis before aplastic anemia, and 3 patients developed ulcerative colitis 1 to 6 years after aplastic anemia.

### Key findings:

- 11 patients had high percentages of types of granulocytes (white blood cells) associated with PNH.
- 6 patients had a variation in the HLA-DRB1 gene that is associated with susceptibility to both ulcerative colitis and aplastic anemia in Japanese patients.
- Of 7 patients treated with either cyclosporine alone or both cyclosporine and antithymocyte globulin, 6 went into remission of aplastic anemia.

### Conclusions:

- The large proportion of patients with PNH-type cells indicates that aplastic anemia complicated by ulcerative colitis is a legitimate bone marrow failure syndrome.
- The high frequency of the HLA-DRB1 variation suggests that the two diseases result from the same disordered biological processes in the body.

**3610**

## **Genetics of Bone Marrow Failure Syndromes in Children**

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Several bone marrow failure syndromes in children can cause shortages of red blood cells, white blood cells, and platelets. Classifying bone marrow failure syndromes in children is challenging.

A research team from Japan studied the genetics of aplastic anemia, refractory cytopenia of childhood, and refractory cytopenia with multilineage dysplasia in children. The analysis included 168 children with one of these diseases, and all of the diseases were idiopathic (had no known cause).

### **Key findings:**

- The only inherited genetic mutation associated with idiopathic bone marrow failure syndrome was in the RTEL1 gene. Children with dyskeratosis congenita had this mutation.
- Some children had non-inherited mutations in BCOR and PIGA.
- Less than 1% of children had mutations in DNMT3A or ASXL1, even though these mutations are common in adults with bone marrow failure syndrome.
- The numbers of non-inherited mutations were similar in children with aplastic anemia, refractory cytopenia of childhood, and refractory cytopenia with multilineage dysplasia.

### **Conclusions:**

- The rate of detectable non-inherited mutations in childhood aplastic anemia was lower than in adult aplastic anemia.
- Idiopathic bone marrow failure syndromes in children were characterized by only a few gene mutations regardless of the type of syndrome.

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## A Phase II Clinical Trial of Cyclophosphamide After Hematopoietic Stem Cell Transplantation from Unrelated Donors to Prevent Graft-Versus-Host Disease

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In haploidentical hematopoietic cell transplantation (HSCT), the donor's HLA markers match half the patient's HLA markers. The introduction of treatment with high-dose cyclophosphamide after HSCT has significantly improved the outcomes of haploidentical HSCT.

This phase II clinical trials included 60 patients who had haploidentical HSCT and 46 patients whose HSCT donors had 9 of 10 of the patient's HLA markers. All patients had advanced-stage blood cancers or aplastic anemia, and none had an unrelated donor whose blood had the same 10 HLA markers as the patient. Patients were treated with cyclophosphamide, tacrolimus, and mycophenolate after HSCT to prevent graft-versus-host disease (GVHD).

### Key findings:

- Counts of neutrophils (the most common type of white blood cells) recovered by day 45 in 95% of patients who underwent haploidentical HSCT and 98% of those in the partially mismatched donor group.
- In 1 patient who had haploidentical HSCT and 1 with a partially mismatched donor, the donated cells did not engraft (reach the bone marrow and start making blood cells).
- 70% of patients in the haploidentical group and 60% of those in the partial mismatch group were still alive 1 year after HSCT.
- Rates of moderate to severe acute GVHD (which started within 3 months of HSCT) were 28% in the haploidentical group and 13% in the partial mismatch group.
- Rates of chronic GVHD (which started more than 3 months after HSCT) were 13% in the haploidentical group and 14% in the partial mismatch group.
- 19% in the haploidentical group and 25% in the partial mismatch group had a relapse within 1 year.

### Conclusions:

- Treatment with cyclophosphamide, tacrolimus, and mycophenolate is effective to prevent GVHD in HSCT from haploidentical and mismatched unrelated donors.

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## Outcomes of Cord Blood Transplantation from an HLA-Identical Sibling

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Hematopoietic stem cell transplantation (HSCT) is the treatment of choice for patients younger than 40 who have a bone marrow failure syndrome and a sibling whose HLA markers (proteins on white blood cells) match theirs. Umbilical cord blood transplantation (CBT) from an HLA-identical sibling is a potentially promising alternative because of its low risk of graft-versus-host disease (GVHD) and of risk to the donor.

This international team analyzed outcomes in 122 children and young adults with a bone marrow failure syndrome who underwent CBT from an HLA-identical relative. Of these patients, 96 had an inherited disorder (including 25 patients with severe aplastic anemia) and 26 did not. The median age at CBT was 6.7 years.

### Key findings:

- 91% of patients recovered their counts of neutrophils (the most common type of white blood cell) within 60 days of CBT, and 89% of patients recovered their platelet counts within 180 days.
- The transplanted cells took a median of 21 days to reach the bone marrow and begin making healthy blood cells (engraftment).
- The transplanted cells did not engraft in 13 patients. 11 of these patients died within a median of 1.9 months after CBT, and the remaining 2 patients survived after a second HSCT.
- 11% of patients developed GVHD within 100 days of CBT, and 12% developed GVHD more than 3 months after CBT.
- 87% of patients survived for at least 5 years after CBT.

### Conclusions:

- In children and young adults with either bone marrow failure syndrome, CBT from an HLA-identical sibling donor has excellent long-term outcomes, including low rates of GVHD.
- The authors recommend the collection of cord blood units at the birth of a new sibling of a patient with an inherited bone marrow failure syndrome.

**2031**

## **High-Dose Cyclophosphamide After Bone Marrow Transplantation from Haploidentical Stem Cell Donors for Severe Aplastic Anemia**

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Bone marrow transplantation (BMT) is the treatment of choice for young patients who have severe aplastic anemia and a sibling whose HLA markers match theirs. Those who don't have a matched sibling donor and those older than 40 usually have immunosuppressive treatment because up to 40% of these patients have a relapse or develop PNH or MDS.

This study at Johns Hopkins University aimed to find out whether treatment with high-dose cyclophosphamide after BMT would improve outcomes. The study included 10 patients (median age 34 years) with severe aplastic anemia that had not responded to previous immunosuppressive treatment or that had relapsed after treatment. Nine patients underwent haploidentical BMT, meaning that the donor's HLA markers matched half of the patient's HLA markers. One patient had BMT from a mismatched, unrelated donor. All patients were treated with cyclophosphamide on days 3 and 4 after BMT.

### **Key findings:**

- At the time of BMT, 6 patients had PNH clones (copies of abnormal immature blood cells), but all of the PNH clones were gone after BMT.
- The transplanted blood cells reached the bone marrow and began to make healthy blood cells, in the blood and bone marrow of all patients (engraftment).
- After a median of 17.5 months, all patients were alive and well.
- 2 patients developed mild to moderate graft-versus-host disease of the skin and mouth and had to be treated with steroids.
- 2 patients were able to stop immunosuppressive treatment within 15–17 months of BMT.

### **Conclusions:**

- BMT followed by cyclophosphamide seems to be promising in patients with severe aplastic anemia that has not responded to previous treatment.
- This treatment has acceptable rates of engraftment, eradication of preexisting diseases involving clones (copies of abnormal immature blood cells), and expansion of the donated blood cells.

## LBA-2

### Addition of Eltrombopag to Standard Immune-Suppression Treatment for Aplastic Anemia

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About 10% of patients with severe aplastic anemia have a complete response (meaning they have no signs of aplastic anemia), and 60–65% have a hematologic response (normalization of blood cell counts) to immunosuppressive treatment with horse antithymocyte globulin (hATG) and cyclosporine. These rates have been stable over the last three decades in spite of attempts to improve them.

This phase II clinical trial tested the efficacy of adding eltrombopag (Promacta®) to hATG and cyclosporine in 88 patients (median age 31 years) with severe aplastic anemia. All patients were treated with hATG and cyclosporine. Eltrombopag was added after or at the same time as hATG, and this treatment continued for 6 months.

#### Key findings:

- Patients tolerated the combination of eltrombopag, hATG, and cyclosporine well.
- Two patients stopped taking eltrombopag because of severe skin reactions
- 6 patients dropped out the of the trial early because their disease did not respond to treatment or they developed MDS.
- After 6 months of treatment, 92% had some kind of response and 54% had a complete response.
- Response rates were higher at 3 months and 6 months in patients treated with the combination treatment than patients treated with just cyclosporine and hATG.

#### Conclusions:

- Adding eltrombopag to standard immunosuppressive treatment markedly increases response rates for severe aplastic anemia that has not been treated before.
- Starting eltrombopag at the same time as standard immunosuppression could accelerate the rate and quality of blood cell recovery.



# ELTROMBOPAG OUTCOMES

## 300 Impact of Eltrombopag on Expansion of Clones with Genetic Mutations in Aplastic Anemia

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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 in patients with aplastic anemia. But eltrombopag could also promote the evolution or expansion of mutant clones (copies of abnormal blood cells) and increase the rate of progression to MDS, a serious complication of aplastic anemia.

This study assessed outcomes in 13 patients treated at the Cleveland Clinic with eltrombopag for aplastic anemia that had not responded to immunosuppressive treatment. The treatment lasted a median of 85 weeks.

### Key findings:

- 6 patients (46%) responded to eltrombopag treatment, meaning that their blood counts improved and they stopped needing blood transfusions.
- 5 patients (38%) had stable disease and needed only occasional blood transfusions.
- 1 of the 2 non-responders developed a PNH clone, and the other developed acute myelogenous leukemia.
- 2 patients had expanded PNH granulocytes (types of white blood cells) after eltrombopag treatment.
- 3 patients had a mutation in the CEBPA, EZH2, or BCOR genes in abnormal clones.
- 5 patients (38%) acquired new mutations in CEBPA, EZH2, RUNX1, 2AF1, or BCOR after eltrombopag treatment.

### Conclusions:

- A few patients had expansions of abnormal clones with mutations potentially associated with progression to leukemia during eltrombopag treatment.
- Eltrombopag might not be treatment for patients with aplastic anemia who have mutations in CBL, SETBP1 and RUNX1. These genes are associated with progression to MDS.