CLL SOCIETY
Resource Library

AUTOIMMUNE HEMOLYTIC ANEMIA

WHAT IS AUTOIMMUNE HEMOLYTIC ANEMIA?

Autoimmune hemolytic anemia (AIHA) is the most common autoimmune condition associated with chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL). AIHA is a potentially life-threatening condition where the immune system attacks and destroys the body's red blood cells. Red blood cells contain a protein called hemoglobin, which is responsible for picking up oxygen in the lungs and delivering it throughout the rest of the body. Those with CLL and SLL are at increased risk of developing AIHA, but it is difficult to estimate exactly how often AIHA occurs. Some estimates range from 4 to 30%, but it is likely closer to 4-10%. AIHA occurs more often in those with poor prognostic biomarkers (such as unmutated IGHV, 17p deletion, and TP53 mutation), becomes more common with age, and has a higher chance of occurring as the cancer progresses.

WHAT IS THE DIFFERENCE BETWEEN WARM AND COLD AUTOIMMUNE HEMOLYTIC ANEMIA?

There are two types of AIHA, warm and cold. The type of AIHA is determined by the type of antibody that the immune system uses to attack and destroy healthy red blood cells.

It is estimated that more than 80% of those with CLL and SLL who develop AIHA will have the warm type (also called wAIHA). In warm AIHA, a type of antibody called IgG is produced by the immune system and attaches to red blood cells at warm (normal) body temperatures causing them to be prematurely destroyed.

It is estimated that less than 20% of those with CLL and SLL who develop AIHA will have the cold type. In cold AIHA, a type of antibody called IgM is produced by the immune system and attaches to red blood cells at cold body temperatures causing them to be prematurely destroyed.

WHAT ARE THE SYMPTOMS OF AUTOIMMUNE HEMOLYTIC ANEMIA?

The symptoms of AIHA are caused by the low red blood cell count and the resulting reduced delivery of oxygen to tissues. Common symptoms may include:

- Fast heartbeat
- Chest pain
- Breathlessness or difficulty breathing with activity
- Unusual and extreme fatigue or weakness
- Lightheadedness, dizziness, or feeling faint
- Paleness of the skin or inner eyelids
- Enlarged spleen
- Dark brown urine
- Yellowing of the skin or whites of the eyes (jaundice)

WHY DOES AUTOIMMUNE HEMOLYTIC ANEMIA OCCUR?

The connection to CLL and SLL is not yet fully understood, but it is known that the dysfunctional immune system of those with the disease has an increased tendency to produce abnormal antibodies that attack healthy blood cells (such as red blood cells). It is suspected that dysfunctional T-cells, which help regulate the immune response, also play a role.

When the immune system attacks other healthy cells within the body, the condition is classified as an autoimmune disease. AIHA can occur alongside another autoimmune disease known as immune thrombocytic purpura (ITP). When these two conditions occur together (or when combined with another rare autoimmune disease that causes a decrease in the type of white blood cells called neutrophils), it is called Evans Syndrome.

HOW IS AUTOIMMUNE HEMOLYTIC ANEMIA DIAGNOSED?

There is no one specific test to definitively diagnose AIHA, and the common tests used are less reliable in CLL. It is diagnosed by excluding all other causes, meaning once a low red blood cell count has been discovered, more tests are used to rule out any other causes. A low red blood cell count will be compared to previous results to determine how quickly the red blood cells have been decreasing.

Additional blood tests or a bone marrow evaluation may be necessary to determine if the low red blood cell count is due to AIHA or some other cause (such as progression of the cancer, medication side effects, infection, or other blood disorders). When a red blood cell count is discovered, it is critical that autoimmune disease be ruled out as the cause before considering what the treatment should be. This is because both progression of the cancer and autoimmune disease can result in low red blood cell counts, but treatments can be very different.

Several blood tests look for evidence of destroyed red blood cells and may help confirm the diagnosis of AIHA. These tests include:

- **Complete Blood Cell Count (CBC):** The most important value on the CBC when looking for AIHA is hemoglobin, which is typically low.
- **Reticulocyte Count:** Reticulocytes are immature red blood cells. In AIHA, the reticulocyte count is typically high. This occurs because the bone marrow

AUTOIMMUNE HEMOLYTIC ANEMIA (continued)

is trying to produce new red blood cells to replace the ones destroyed by AIHA. Occasionally, the reticulocyte count may be inappropriately normal or low if other factors such as nutritional deficiencies or decreased production of healthy cells in the bone marrow are also present.

- **Bilirubin:** When red blood cells are destroyed, they produce bilirubin. Bilirubin is stored in the liver and normally excreted in the stool. It is yellow and brown in color and is what gives feces the brown color. When bilirubin is produced faster than it can be excreted (as in AIHA), it builds up in the blood causing the skin and whites of the eyes to appear yellow.
- **Haptoglobin:** As the body attacks its own red blood cells, they die off and release hemoglobin into the bloodstream, called free hemoglobin. Haptoglobin is a protein in the blood that binds to free hemoglobin to help remove it from the blood. In AIHA, haptoglobin levels are typically low or undetectable.
- **Peripheral Blood Smear:** This test examines a sample of blood under a microscope looking for the appearance of abnormal blood cells. In AIHA, there may be the presence of red blood cell fragments called "schistocytes."
- **Coombs Test/Direct Antiglobulin Test (DAT):** This test looks for the presence of certain antibodies (IgG and IgM) or proteins called complement that are attached to red blood cells. In AIHA, it is typically positive.
- **Lactate Dehydrogenase (LDH):** This test looks for signs of cell damage. In AIHA, the destruction of red blood cells, and the resulting production of new red blood cells in the bone marrow, typically results in a high LDH.

WHEN IS TREATMENT NEEDED FOR AUTOIMMUNE HEMOLYTIC ANEMIA?

AIHA may not require treatment if symptoms remain mild. Treatment may be necessary when the red blood cell count drops too rapidly, when the hemoglobin drops too low, or when symptoms become severe or intolerable.

HOW IS AUTOIMMUNE HEMOLYTIC ANEMIA TREATED?

There are currently no FDA-approved treatments for AIHA. However, treatments including several that suppress the immune system may be effective at controlling AIHA. Commonly used options include:

- **Steroids:** Initial treatment for AIHA usually includes steroids taken by mouth to help control the immune system's overactivity. However, high-dose steroids can also be administered intravenously through a vein. If effective, steroids will typically result in an increase in red blood cell counts within 2 to 3 weeks.
- **Rituximab:** If steroids are not enough to help, a medication called rituximab may be given intravenously through a vein to further calm down the immune system and keep it from attacking healthy red blood cells. Rituximab works by preventing the overproduction of antibodies (made by the dysfunctional immune system) that destroy healthy red blood cells. It also may help treat the underlying CLL or SLL.
- **Intravenous Immunoglobulin:** If the red blood cell count drops dangerously low, a treatment called intravenous immune globulin (IVIG) may be given to slow the destruction of red blood cells and provide rapid improvement (within 24-48 hours). IVIG is also an available option for those who do not respond to steroid therapy.
- **Blood Transfusion:** If the red blood cell count drops to critically low levels, an infusion of packed red blood cells may be necessary to quickly restore the red blood cell count to a normal level.
- **Splenectomy:** In some severe cases, surgical removal of the spleen may be necessary when other treatments do not stop the rapid destruction of red blood cells.
- **Other Treatment Options:** Medications given less often to treat AIHA can include drugs that suppress the immune system such as cyclophosphamide, cyclosporine, mycophenolate, and danazol. It is common to combine different medications to increase the red blood cell count when the disease is not well controlled using just one medication alone. An example of this treatment approach is combining steroids with rituximab. Another successful approach can be to treat the underlying CLL or SLL to better control the AIHA.

DOES AUTOIMMUNE HEMOLYTIC ANEMIA IMPACT SURVIVAL IN THOSE WITH CLL AND SLL?

If left untreated, AIHA can become life-threatening. However, most studies have found no reduction in overall survival of those living with CLL and SLL. AIHA does tend to recur and can become a chronic condition that will need to be treated promptly if it does come back. Fortunately, AIHA can usually be well-controlled with appropriate treatment and careful monitoring.