DIAGNOSIS AND MANAGEMENT OF ANEMIA IN WALDENSTRÖM MACROGLOBULINEMIA

by Morie A. Gertz, MD, MACP

Introduction

Anemia, one of the cardinal findings in Waldenström macroglobulinemia, is present in over 80% of those patients who are not on "watch and wait." In some instances, the severity of anemia is mild and does not require intervention, while in others it is the major reason for designating a patient as being symptomatic and requiring treatment of Waldenström macroglobulinemia.

What is anemia? Anemia represents a reduction in the oxygen-carrying capacity of the blood. The red blood cells provide oxygen to the tissues to enable them to "burn" the nutrients in food and so to generate energy. This "process of burning" cannot occur without oxygen: energy cannot be generated without the delivery of oxygen to tissues provided by red blood cells. As a consequence, a reduction in the number of red blood cells, which is referred to as anemia, is measured by a reduction in the red blood cell count (or by a lower hemoglobin level or a lower hematocrit level), resulting in the inability to deliver inhaled oxygen. Anemia will manifest as fatigue, apathy, and shortness of breath with exertion. Anemia can be identified in individuals as they develop pale skin (pallor) due to the decreased amount of circulating red blood cells.

In Waldenström macroglobulinemia, the most common cause of anemia is a direct reduction in red cell production in the bone marrow due to replacement by Waldenström cells. [Note: Dr. Gertz has famously compared WM in the bone marrow to "weeds in the garden" in several of his Ed Forum talks] In patients with Waldenström macroglobulinemia, the progressive growth of the Waldenström cells (lymphoplasmacytic lymphoma) replaces the normal red blood cell production in the bone marrow, leading to an inability to produce red cells. ["The weeds choke the garden plants."] Impairment of red cell production usually will not occur until the percentage of bone marrow replacement with Waldenström exceeds 40%. Patients who are anemic but have a very small amount of lymphoma in their bone marrow (15% or less) should suspect that the cause of their anemia might be other than Waldenström.

Anemia that is symptomatic and significant (hemoglobin level <11 g/dL) is often the trigger to initiate therapy for Waldenström. Successful treatment of Waldenström is virtually always associated with a rise in the hemoglobin level because the increase in the hemoglobin level reflects the reduction of lymphoma involving the bone marrow. This "recovery of garden plants" (the good cells in the bone marrow) accomplished by "weed destruction" (reduction of the lymphoplasmacytic lymphoma cells) through effective treatment, is the most common reason to treat Waldenström. Thus increased red blood cell counts and increased hemoglobin and hematocrit levels represent key outcome measures of successful therapy.

Are there other causes of anemia in Waldenström?

For Waldenström patients, as for everyone in the general population, there is a possibility of developing anemia unrelated to their Waldenström. Patients with Waldenström are not immune to other causes of anemia that may be related to blood loss, for example anemia generated by stomach ulcers that cause blood loss or by the development of colonic ulcers or polyps that bleed. Patients with Waldenström, like all cancer patients, should have a screening colonoscopy once every ten years as part of their preventive care. Situations where the anemia is out of proportion to the amount of Waldenström in the bone marrow should trigger a search for other causes of anemia. Screening stool specimens for the presence of blood is a very quick and simple way by which to identify blood loss anemia.

The group at Dana-Farber Cancer Institute has identified iron deficiency as an important cause of anemia in Waldenström. Iron is a key component of the hemoglobin molecule found in red blood cells. Iron deficiency does not require treatment of Waldenström but does require replacement of the missing iron to allow for the production of red blood cells. As part of the initial investigation of a patient with Waldenström, it is reasonable to require that screening iron studies be performed to exclude the possibility of unrecognized iron deficiency anemia. The most common tests used to diagnose iron deficiency anemia are the serum iron, total iron binding capacity, and serum ferritin levels. Improvements in the blood count, both hemoglobin and hematocrit, can occur with iron replacement. Taking an iron supplement by mouth may result in improvement; in some instances, however, oral iron replacement is not sufficient, and iron infusions are then given intravenously in order to replace the missing iron.

Rarely, patients with Waldenström macroglobulinemia can have cold agglutinin hemolytic anemia. This is a disorder where the IgM protein results in damage to the red blood cell. Damaged red blood cells are subsequently removed from the circulation in the liver and in the spleen. The mechanism is more complex than direct Waldenström involvement of the bone marrow, and thus the therapy is both more complex and often more frustrating. In many patients, high doses of cortisone or prednisone are required to manage the cold agglutinin hemolytic anemia. Treatment for such patients, however, is often the same as for patients with Waldenström macroglobulinemia, with regimens that include rituximab and/ or fludarabine. For anemic patients who do not have significant Waldenström involvement in the bone marrow, screening should be done for cold agglutinin disease. Screening is extremely simple and requires only two tests: 1) a reticulocyte count and 2) a Coombs test, which is commercially available in every laboratory in the United States.

Screening for B12 deficiency may be appropriate for selected patients.

A very rare cause of anemia is dilutional anemia where high levels of IgM cause movement of fluid into the circulation, diluting the number of red blood cells and causing a decline in the hemoglobin level that does not actually reflect a reduction in oxygen-carrying capacity. This is an extremely rare cause of anemia and is limited to those patients with very high levels of IgM.

It is important to distinguish anemia due to Waldenström from anemia due to the treatment of the Waldenström. Many of the agents that are used in the treatment of Waldenström macroglobulinemia have an effect on normal cellular production in the bone marrow and can actually aggravate anemia. This is simply another way of saying that chemotherapy can damage the good cells as well as the bad (Waldenström) cells. Therefore, in the case of patients under treatment for Waldenström, caution must be exercised to distinguish anemia that is due to progressive Waldenström from anemia due to the treatment of Waldenström. In the latter case, anemia will likely improve after treatment has been completed. Patients who develop progressive anemia while their IgM level declines should be suspected of having therapy-related anemia. Particular attention should be paid when treatment includes lenalidomide because two separate groups have reported that it aggravates the anemia of Waldenström.

Therapy

The best therapy for most patients who have anemia is treatment of the underlying Waldenström. Making the bone marrow healthier will result in better red cell production. As noted above, if iron deficiency is a problem, replacement of iron can improve the hemoglobin.

Finally, there are chemical agents that stimulate the bone marrow to increase red blood cell production and that are particularly useful if patients have impaired kidney function with their Waldenström. These agents, known as erythropoietin and darbepoetin alfa, are no longer used frequently because the FDA has identified these agents as potentially increasing the risk for death, heart attack, and stroke. Therefore, the lowest

possible dose is recommended if these drugs are required. Moreover, in certain cancer types (including breast, lung, head and neck, lymphoma, and cervical cancer), these agents have shortened overall survival. So again, if required, the lowest dose of either erythropoietin or darbepoetin alfa needed to avoid transfusions is recommended.

Summary

In summary, for the majority of Waldenström patients, anemia is directly due to the disease, and effective treatment of Waldenström is the best intervention for anemia. If the level of hemoglobin declines following completion of treatment, it is possible that this anemia results from the treatment. Mild anemia need not be treated. Patients who are anemic but have a low percentage of Waldenström cells in the bone marrow should be screened for blood loss in the colon or stomach, as well as for cold agglutinin disease, iron deficiency, and, rarely, B-12 deficiency.

Dr. Morie A. Gertz is Chair, Internal Medicine, at Mayo Clinic. In his clinical practice he has evaluated and treated patients with Waldenström's macroglobulinemia for more than thirty years.

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