

WHEN TO MOVE FROM WATCH AND WAIT TO TREATMENT

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Due to the advanced technologies available for the detection of abnormal proteins, an increasing number of Waldenström patients are found to have monoclonal IgM proteins in their blood and Waldenström cells in the bone marrow but to have no symptoms. When screening is done for patients over the age of 50, approximately 1 person in 200 in the United States will have an IgM protein and, therefore, is at risk for the development of Waldenström macroglobulinemia. Virtually all patients with Waldenström macroglobulinemia have a detectable IgM protein that precedes the diagnosis. In fact, the risk of the development of Waldenström macroglobulinemia in the presence of an IgM protein is nearly 8000 times that of the general population.

Since Waldenström macroglobulinemia is a very slowly progressive process and is currently incurable, there is no advantage to initiating therapy in the absence of symptoms. If the disease were curable, it would be proper to administer the cure and never worry about it again. Unfortunately, this type of early intervention has not been shown to prolong survival. If quality of life could be demonstrated to be better in patients on treatment, this would be a justification for the treatment of asymptomatic individuals. Unfortunately, all of the treatments available for Waldenström macroglobulinemia have potential side effects and late risks. Therefore, treatment is not considered to be associated with an improved quality of life in an otherwise asymptomatic patient. That raises the question, “When is it proper to have treatment?” A similar question concerns those patients who have already received treatment and are back on observation and being monitored: “When is the re-initiation of therapy appropriate and when is it inappropriate.”

It cannot be overemphasized that the level of the IgM protein should not be used as a criterion for the initiation of therapy. In other words, there is something wrong in saying “We’ll begin treatment when your IgM is 2000 or 3000 or 8000, etc.” if the patient is otherwise asymptomatic and there are no other associated risks. That being the case, what are the common symptoms that need to be monitored in patients who are on “watch and wait?”

The answers are not straightforward and require close collaboration with your medical oncologist. Different patients will have a different set of symptoms based on the specifics of their disease, and symptoms manifest differently, so that there is no one right answer that would be applicable to all patients. Although it is not the only criterion for initiating therapy, the most common reason why patients require treatment is a progressive decline in their red blood count. This results in increasing levels of anemia whose symptomatic manifestation is progressive fatigue, shortness of breath with exercise, difficulty climbing stairs, etc. Typically, as Waldenström evolves, the IgM level will climb

over time, and a rise in protein generally means that there is an increase in the number of abnormal Waldenström cells in the bone marrow. As these cells increase in number, they will begin to interfere with the bone marrow's normal function of blood production, leading to a progressive decline in the red blood cell count and resultant anemia. If a patient has a rising IgM level and the blood count is falling and continues to decline – usually at a slow rate but the patient is beginning to develop fatigue, apathy, or shortness of breath – therapy is justified since it will destroy the Waldenström cells in the bone marrow. Destruction of the Waldenström cells allows for improved production of red blood cells and correction of the anemia. Anemia is the most common indication for the initiation of treatment.

In some patients, the platelets that are produced in the bone marrow are also affected. Platelets are the cells that clot the blood. When production of the platelets is impaired, although this is an uncommon development, treatment is justified even if symptoms are absent. If the platelet count falls too far, patients are at risk of bruising or bleeding. Moreover, the treatment of Waldenström with some of the available highly effective agents can further lower the platelet count. And if the platelet count is allowed to drift down excessively before therapy is initiated, it could increase the risk of treatment-related bruising or bleeding. Although there is not a specific cutoff, in my practice I would initiate therapy if the platelet count had fallen to one-half the normal level.

Occasionally patients require treatment because of elevation of the serum viscosity level. One cannot estimate the serum viscosity clinically. It must be measured to confirm hyperviscosity syndrome. The most reliable signs of hyperviscosity syndrome are the presence of nose-bleeding and gum bleeding that are difficult to control. Patients with nosebleed caused by hyperviscosity typically have to undergo multiple episodes of cautery before the problem is recognized. Hyperviscosity can cause risk to vision and can cause serious eye bleeding and, when elevated to extreme levels, can be a trigger for the initiation of therapy.

Occasionally patients will need treatment because of weight loss or night sweats or rapid progression in the enlargement of lymph glands. These are uncommon developments and should raise suspicion in the oncologist's mind that the Waldenström may have converted to a more aggressive form of lymphoma. Nonetheless, there is a small proportion of patients in whom these so-called "constitutional symptoms" have a sufficient impact on patients to justify therapeutic intervention. When Waldenström causes enlargement of the liver and/or spleen, although this occurs but rarely, it can reach a level where patients actually develop abdominal discomfort. If this interferes with their quality of life, therapy would be justified.

There are several manifestations associated with IgM monoclonal proteins that justify therapy, even when there is no problem with anemia, low platelets, enlargement of the liver and spleen, weight loss, etc. A small proportion of patients with an IgM protein can develop systemic amyloidosis. Systemic amyloidosis is, fortunately, a rare complication of IgM proteins and Waldenström. But because it is a serious disorder, most patients require therapy even in the absence of symptoms because the amyloid can cause damage to vital organs. Rare patients with IgM proteins can develop cold agglutinin hemolytic anemia or cryoglobulinemia, which also do not have as benign a course as Waldenström macroglobulinemia and require early intervention to prevent serious end-organ complications.

The management of the “watch and wait” patient is a partnership between the patient and the patient’s physician. Sometimes this is an excellent scenario for a second opinion to provide guidelines in case the oncologist has a limited experience with Waldenström. The input of an experienced medical center often helps to define the monitoring endpoints in order to arrive at an appropriate conclusion.

In summary, some of the signs that indicate the need for treatment of Waldenström macroglobulinemia include: anemia, hyperviscosity, lymph node enlargement and marked enlargement of the liver or spleen. The associated symptoms would be: fatigue, shortness of breath with exertion, palpable lumps, nose or gum bleeding, unexplained weight loss or fevers. Keep in mind that there is no threshold above which the IgM level mandates the initiation of chemotherapy.

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