

WHO NEEDS TREATMENT FOR WALDENSTROM'S MACROGLOBULINEMIA AND WHEN?

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Receiving a diagnosis of Waldenstrom's macroglobulinemia is life changing, and what to do next is often very confusing for the patient and for those offering support as well. The first issue is to try to understand the diagnosis you have received. At the simplest level, you learn that lymphoplasmacytic lymphoma cells are growing in your bone marrow and that these cancerous cells may be limiting the growth of healthy blood cells. You also are told that lymphoplasmacytic lymphoma produces a monoclonal IgM protein that can thicken your blood and clog your circulation.

Once you understand the diagnosis, you are assured that, although the disease is incurable, it can be managed successfully. You are then presented with a wide variety of treatment options. Treatment can be anything from a watchful-waiting observation approach, to treatment with chemotherapy in combination with rituximab, to possibly treatment with rituximab alone. Often, discussions related to the need for plasmapheresis also enter the conversation. All of this can be extremely confusing for patients, and a clear understanding of who should be treated and when treatment should be initiated is really important.

Patients diagnosed with Waldenstrom's macroglobulinemia can present with a wide spectrum of findings. To illustrate the spectrum of presentation that I see among patients in my practice at Mayo Clinic, I will highlight two groups of patients on opposite ends of the symptom spectrum. The first group consists of patients diagnosed almost by accident when they undergo laboratory testing as part of an annual physical examination and are found to be mildly anemic. Follow-up testing to investigate the cause of their anemia often includes a serum protein electrophoresis test on the blood. A monoclonal IgM protein may be detected. The blood level, however, may show that the total serum IgM

protein (that is, IgM present in the circulating blood) in these patients is actually only slightly higher than normal. When further testing, including a bone marrow biopsy, is done, the bone marrow does confirm low-level involvement by lymphoplasmacytic lymphoma. The presence of a serum IgM monoclonal protein and bone marrow involvement by lymphoplasmacytic lymphoma therefore confirms the diagnosis of Waldenstrom's macroglobulinemia. However, these patients often have no other symptoms and no other findings of significance. Patients in this group may not require immediate treatment.

In contrast, other patients can present with a far more complicated picture. Some patients in this second group can present with significant tiredness and nausea, sometimes with visual difficulties, confusion, sleepiness, and easy bleeding. Some patients can present with severe neuropathy, ankle ulcers, and possible organ compromise. Lab testing in such patients often shows the patients to be very anemic with low platelets, and there may be evidence of hyperviscosity (thickening of the blood due to high IgM levels). For such patients, bone marrow testing often shows much more extensive involvement by lymphoplasmacytic lymphoma, and a very high level of IgM in the blood is also identified. Patients in this second group also fit the diagnosis of Waldenstrom's macroglobulinemia but are far more ill than the first group of patients, and they need urgent treatment. Clearly, initial treatment of the two groups of patients will be quite different.

Overall the predominant decision regarding the optimal time to initiate treatment and the choice of treatment is determined by two main issues. The first is clinical symptoms associated with the extent of the disease and the second is complications related to deposition of the serum IgM. While it is tempting to consider treating everybody once the diagnosis is certain, it is important to note that some patients with very little disease at the time of diagnosis may remain without symptoms or complications for years. Immediately starting treatment in these patients would result in more side effects and toxicities and significantly more risks than observing the patients without initiating treatment. At the same time, a further goal of management is to monitor a patient under observation to avoid this patient becoming as ill as the patients in the second group outlined above.

The following are agreed-upon symptoms and clinical findings for starting treatment. The first set of symptoms is what are called 'constitutional symptoms' that would suggest that the disease is very active and progressing more rapidly. These include weight loss, fevers, and drenching sweats at night. Each of these is carefully defined – weight loss is significant when more than 10% of one's body weight; fevers

require the temperatures to be 101.5°F and higher; and night sweats need to be drenching to the point of soaking one's clothing, requiring you to change your clothes or the bedding. Other evidence that the disease is very active and requires treatment is enlarging lymph nodes and an enlarging spleen or a decrease in blood counts because of involvement of the bone marrow. This would include blood counts with a low hemoglobin (less than 11g/dL) or low platelet count (less than 120,000/dL).

The second major factor contributing to a decision to initiate treatment is evidence for complications due to the serum IgM levels. These complications would include hyperviscosity, which usually presents with easy bleeding, confusion, visual changes, and also significant fatigue. Further symptoms associated with the serum monoclonal IgM can be peripheral neuropathy, protein deposition in the skin and organs resulting in systemic amyloidosis, and renal insufficiency.

What is notable, however, is that the absolute IgM level is on its own not usually a criterion to initiate treatment. Although high IgM levels are often associated with some of the symptoms listed above, and the IgM is expected to increase over time if the disease slowly progresses, it is important to know that the IgM level itself may not necessarily require treatment. It is more important to consider these other factors at the time of initiating treatment.

The decision to select treatment based on the criteria above is often associated with what symptoms a patient has and how quickly a response is needed. In patients who have significant symptoms, treatment with chemotherapy plus rituximab is usually recommended. In our practice, the combination of dexamethasone, cyclophosphamide, and rituximab (DRC) is often selected. Treatment with bendamustine plus rituximab is an alternative if a more rapid response is needed. Additional choices could be treatment with a combination that would include bortezomib; however patients with neuropathy can have increased neuropathic symptoms with this agent. Some patients who have anemia secondary due to red cell breakdown or peripheral neuropathy due to IgM depositing in the nerves, could be treated just with rituximab alone. There are also other effective drugs to use in initial treatment. While these other treatment options are also reasonable, the combinations mentioned above are less toxic to bone marrow stem cells and allow for stem cell collection for future stem cell transplantation if necessary.

As outlined in this article, the choice of initial treatment for Waldenstrom's macroglobulinemia and when to start treatment is often more complicated than simply noting changes in the blood test results. It is therefore very important to discuss all of the treatment options, as well as the decision to start treatment, with your treating physician and to be part of the decision-making process. Active participation in your care is a critical part of receiving good management of Waldenstrom's macroglobulinemia and maintaining good quality of life.

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Dr. Ansell is Chair of the Mayo Clinic Lymphoma Group as well as Chair of the Faculty Development and Recruitment for Hematology at Mayo Clinic. He has been honored with various awards during his training and career, including the Department of Medicine New Investigator at Mayo Clinic and Medical Honoree at the Lymphoma Research Foundation, Minnesota Chapter. Dr. Ansell has held memberships with organizations including the American Association for Cancer Research, the American Medical Association, the American Society of Clinical Oncology, and the Eastern Cooperative Oncology Group, and he has served on the editorial boards of the American Journal of Hematology, Journal of Clinical Oncology, Blood Cancer Journal, and Clinical Lymphoma and Myeloma. Dr. Ansell is the co-author of more than 234 articles in peer-reviewed journals.

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