Original Contribution

Update on Recommendations for Assessing Response from the Third International Workshop on Waldenström's Macroglobulinemia

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Abstract

This report by an international consensus panel updates current recommendations for defining clinical response in Waldenström's macroglobulinemia (WM). The previously published response criteria incorporated parameters for monoclonal protein reduction and/or improvement of marrow and nodal involvement, and included definitions of complete and partial remissions. The criteria have been updated to include minor response and stable disease categories. In addition, the criteria now recognize that delayed responses after treatment with nucleoside analogues and biologic agents and the time point for assessing response in patients with WM should be considered so as to not miss or miscategorize a response. The new criteria should therefore help in better delineating responses to therapy in patients with WM, particularly with the wide use of nucleoside analogues and biologically based agents for this disease.

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Introduction

Waldenström's macroglobulinemia (WM) is a distinct monoclonal B-cell disorder characterized primarily by bone marrow infiltration with lymphoplasmacytic cells, along with demonstration of an immunoglobulin M (IgM) monoclonal gammopathy. This condition is considered to be lymphoplasmacytic lymphoma as defined by the Revised European-American Lymphoma and World Health Organization classification systems.[1] The clinical presentation of WM is heterogeneous. In most patients, the disease is mainly confined to the bone marrow, whereas in < 20% of patients, the presentation is more lymphoma-like.[2] As a result, previously held criteria for evaluating response to therapy in WM varied considerably and borrowed from criteria for other diseases, including chronic lymphocytic leukemia, multiple myeloma, and lymphoma. As part of the Second International Workshop on Waldenström's Macroglobulinemia, uniform response criteria specific to WM were formulated in the context of an international consensus effort.[3] Although these criteria were regarded as specific and uniform, an update was believed to be appropriate, particularly because of the wide use of biologically based therapies for WM.[4-6] Importantly, in some studies, patients exhibiting less than a partial response (PR) had significant clinical benefit, including reversal of anemia and thrombocytopenia and response duration similar to that of patients exhibiting a PR.[7-9] Hence, an update of response categories was deemed necessary to facilitate response evaluation comparisons among different clinical trials and to document clinical benefits in individual patients.

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As part of the Third International Workshop on Waldenström's Macroglobulinemia, held October 7-10, 2004, in Paris, France, an international consensus panel updated the recommendations for assessing response in WM. In formulating its recommendations, the panel recognized the paucity of clinical studies of response evaluation in WM but concluded that it was important to extend the criteria to include the recognition of minor response and stable disease categories.

Definitions of Response

The updated recommendations for assessing response in WM are as follows:

- Complete response (CR): categorized by a disappearance of serum and urine monoclonal protein determined by immunofixation, absence of malignant cells in bone marrow determined by histologic evaluation, resolution of adenopathy/organomegaly (confirmed by computed tomography [CT] scan), and no signs or symptoms attributable to WM. Reconfirmation of the CR status is required ≥ 6 weeks later with a second immunofixation.

- Partial response: categorized by ≥ 50% reduction of serum monoclonal IgM concentration determined by protein electrophoresis, ≥ 50% decrease in adenopathy/organomegaly on physical examination or on CT scan, and no new symptoms or signs of active disease.

- Minor response: categorized by ≥ 25% but < 50% reduction of serum monoclonal IgM determined by protein electrophoresis and no new symptoms or signs of active disease.

- Stable disease: categorized by < 25% reduction and < 25% increase of serum monoclonal IgM determined by electrophoresis without progression of adenopathy/organomegaly, cytopenias, or clinically significant symptoms caused by disease and/or signs of WM.

- Progressive disease: categorized by ≥ 25% increase in serum monoclonal IgM by protein electrophoresis confirmed by a second measurement or progression of clinically significant findings caused by disease (eg, anemia, thrombocytopenia, leukopenia, or bulky adenopathy/organomegaly) or symptoms (eg, unexplained recurrent fever ≥ 38.4°C, drenching night sweats, ≥ 10% weight loss, hyperviscosity, neuropathy, or symptomatic cryoglobulinemia) attributable to WM.

- Not evaluable/delayed response: in some cases, there is insufficient data and/or time for a determination of response to treatment. A delayed response might be seen particularly after purine analogue or monoclonal antibody therapy. The panel recommended that patients must have been followed for ≥ 3 months after treatment initiation to be considered unresponsive to therapy. In addition, the best response is often exhibited several months after treatment discontinuation.

Special Considerations in Response Evaluation in Waldenström's Macroglobulinemia

Time Point for Evaluation of Response

Clinical response should not be assessed prematurely because reduction of monoclonal IgM and improvement of associated disease features might be slowly evolving and occur over many months or years, particularly after treatment with nucleoside analogues and biologically based therapies. Patients should therefore be followed serially, and responses should be based on "best response" at disease nadir to avoid missing a delayed response and categorizing such a response inaccurately. Responses should be confirmed with a second immunofixation (for CR) or electrophoresis (for all other categories of response) ≥ 6 weeks after the initial determination of response. Sometimes the lymph node or splenic shrinkage might lag behind the serum M-protein decrease, therefore resulting in an underestimation of response. Clinicians should be aware of this possibility so as to not miss a delayed response. Paradoxic increases in serum IgM levels that might last for many weeks have been reported in patients with WM while they are actively receiving rituximab therapy.[10-12] Marked increases in serum IgM levels have also been observed in patients with WM receiving cladribine.[13] In addition, discordant bone marrow responses have been observed in patients with WM after treatment with bortezomib[14,15] despite reductions in serum IgM. Treon et al described a patient whose IgM decreased by 72% but whose tumor involvement increased from 25% to 48% of the intrabecular space.[14] Similarly, IgM levels in some patients even surged to pretreatment levels after the cessation of therapy, indicating that, in some cases, bortezomib can suppress the paraprotein without affecting disease burden.[14,15] In such circumstances, when a patient's underlying clinical status remains unclear, a bone marrow biopsy and/or CT scans might be beneficial in clarifying the patient's underlying disease burden.

Hematologic Response

Recovery of hematologic function is a clinically important feature of response to therapy in patients with WM. However, the panel believed that anemia, thrombocytopenia, and leukopenia could be impacted not only by mechanisms related to active WM but also by therapy itself. In fact, treatment with nucleoside analogues might produce prolonged cytopenias even in patients fulfilling all the response criteria. Consequently, the panel noted that the major determinants of response should be reduction of monoclonal IgM and/or tumor bulk and that hematologic recovery should not be mandatory in the response criteria for WM.

Relapse and Progression Criteria

Although strict criteria are necessary to define relapse or progression of disease for comparisons of data in clinical trials, the demonstration of relapsed or progressive disease defined only by the reappearance or an increase in monoclonal IgM protein does not necessarily indicate an immediate need for retreatment, particularly in the absence of clinically significant

signs and symptoms attributable to WM. Recommendations proposed by the Consensus Panel for Prognostic Markers and Criteria to Initiate Therapy should be consulted for specific treatment criteria.[2] The time to the requirement of a new treatment might also be a valuable marker for evaluation of the efficacy of therapy. The updated recommendations for relapse and progression criteria are as follows:

- Relapse from CR: categorized by the appearance of the monoclonal protein in serum or urine by immunofixation confirmed by a second determination, recurrence of bone marrow involvement by lymphoplasmacytic cells, recurrence/development of lymphadenopathies/splenomegaly, or symptoms/signs attributable to WM.

- Progression from PR: categorized by ≥ 25% increase in serum monoclonal IgM from the lowest attained response value determined by protein electrophoresis, confirmed by a second measurement or progression of clinically significant signs (eg, anemia, thrombocytopenia, leukopenia, or bulky adenopathy/organomegaly) or symptoms (eg, unexplained recurrent fever ≥ 38.4°C, drenching night sweats, ≥ 10% weight loss, hyperviscosity, neuropathy, or symptomatic cryoglobulinemia) attributable to WM. An absolute increase of 5 g/L (confirmed on a second determination) is required in order to define disease progression when the only criterion for progressive disease is the increase of M-protein size. In a patient with a localized large mass and/or a high level of lactic dehydrogenase at relapse or progression, a biopsy should be considered to assess the possibility that transformation into a diffuse large B-cell lymphoma has occurred.

General Considerations in Response Evaluation in Waldenström's Macroglobulinemia

Uniform disease response assessment is essential in evaluating the efficacy of any treatment approach. Immunoglobulin M monoclonal protein levels, as determined by serum electrophoresis, are considered the most important determinant of disease response to therapy for most patients with WM. In patients with a more lymphoma-like disease, anatomic definition of response is required with assessment of enlarged lymph nodes and bone marrow tumor involvement.

Immunoglobulin M Evaluation

In its first recommendations, the panel addressed the issue of how IgM should be measured and monitored. The panel concurred that, among patients with WM, the relative concentration of serum IgM monoclonal protein should not be used. However, for an individual patient with WM, serial measurements of IgM monoclonal protein by serum electrophoresis are useful in following tumor burden. Initial measurement of the monoclonal IgM establishes a baseline for comparison of subsequent measurements and response determination in an individual patient.

The presence of cold agglutinins or cryoglobulins might affect determination of IgM levels. Therefore, testing for cold agglutinins and cryoglobulins should be part of the initial evaluation of patients with WM if there is a clinical suspicion of their presence, and, if present, serum samples should be reevaluated under warm conditions for determination of serum IgM monoclonal protein levels during response evaluation. Samples should always be collected and transported at 37°C to insure accuracy and consistency in the determination of paraprotein levels.[16]

For response evaluation, measurements of monoclonal immunoglobulin should be performed using precise densitometry measurements on standard serum protein electrophoresis. However, when the monoclonal protein is < 5 g/L or not quantifiable, determination of IgM levels by nephelometry is acceptable. Because serum immunofixation is more sensitive than serum protein electrophoresis, CR should be confirmed by immunofixation after the M-component is no longer detectable by routine electrophoresis.

Quantification of Bence Jones Protein

Excess Bence Jones protein (BJP) excretion should be considered in patients with WM with abnormal renal function. In this regard, the 24-hour urine protein excretion, urine electrophoresis, and urine immunofixation should be done. Although small quantities of BJP, particularly those of the κ type, are noted in approximately 50% of patients with WM, BJP rarely causes significant nephropathy and usually has no impact on the clinical course of disease.[5] Therefore, no specific recommendations are necessary for reduction of BJP in defining PR. Complete remission, however, reflects complete disappearance of disease and should be confirmed by negative study results on urine immunofixation if an abnormality had been present at diagnosis. The role of assays for serum-free κ and λ levels and their ratio remains to be defined in patients with WM.

Bone Marrow Evaluation

For determination of CR, absence of malignant cells by morphologic evaluation should be confirmed. Because of the heterogeneous nature of bone marrow infiltration in WM, bone marrow aspirate and biopsy are not required in order to confirm PR. Although phenotypic analysis by flow cytometry or immunohistochemistry might prove useful in defining diagnostic and response criteria in the future, the panel believed that there was still insufficient evidence to currently require the use of these tests for response determination outside clinical trials.

Computed Tomography Scans

The panel affirmed the use of CT scans as part of the response determination for CR and PR status but believed that insufficient evidence existed to recommend the routine use of magnetic resonance imaging or positron emission tomography scans in the management of WM. Computed tomography scans of the chest, abdomen, and pelvis should be performed at baseline to investigate the presence of lymphadenopathy and/or organomegaly. Regression or resolution of adenopathy and/or

organomegaly, if present at baseline, should be confirmed by CT scan after treatment. In a patient with bulky disease, which is rare in WM, there might be difficulty in interpreting response because of residual masses after chemotherapy (as seen in lymphoma). For these patients, the panel recommended use of the CR unconfirmed criteria previously described by Cheson et al.[17]

Future Considerations

These criteria serve as guidelines for determination of response in WM. The value of these criteria should be evaluated in large clinical trials using cause-specific survival as the endpoint. Modification of these guidelines might be appropriate as treatment improves and if prospective analyses of other modalities, such as magnetic resonance imaging, positron emission tomography scans, free light-chain assays, immunophenotyping, or molecular biology prove to be clinically useful. Other endpoints, such as the time to requirement of new treatment, might define the point at which clinically significant relapse has occurred and might provide an additional endpoint to the current standard of progression-free survival.

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