Uniform Response Criteria in Waldenstrom’s Macroglobulinemia: Consensus Panel Recommendations From the Second International Workshop on Waldenstrom’s Macroglobulinemia

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Waldenstrom’s macroglobulinemia (WM) is a malignant disorder of lymphoplasmacytic cells that produce a monoclonal immunoglobulin M (IgM). Since the original description by Jan Waldenström of three patients with symptoms of hyperviscosity due to circulating monoclonal IgM, the definition of WM has been controversial. Standardized criteria for diagnosis have now been proposed, including the presence of any IgM monoclonal protein and marrow and/or nodal lymphoplasmacytic cells. Although previous response criteria have generally incorporated parameters for monoclonal protein reduction and/or improvement of marrow/nodal involvement, specific and uniform response criteria are needed to facilitate comparisons of response, remission duration, progression-free survival, and overall survival in clinical trials similar to those previously established for other diseases such as chronic lymphocytic leukemia, lymphoma, and myeloma. This is of particular importance as new agents are developed and evaluated. During the Second International Workshop on Waldenstrom’s Macroglobulinemia (Athens, Greece, 2002) this consensus panel proposed guidelines for standardized response criteria that were subsequently discussed, modified, and then summarized in this report. Presented are recommendations for specific tests to document response, parameters to be followed and subsequently define response, and special considerations specific to WM.

Do IgM Levels Truly Correlate With Disease Burden?

The panel first addressed the issue of how best IgM should be measured and monitored. The panel concurred that the use of nephelometry to determine total serum IgM levels was unreliable, and recommended that serial measurements of IgM monoclonal protein as determined by serum electrophoresis should be used to follow disease burden in a particular patient.

The panel also concurred that among patients with WM, serum IgM monoclonal protein levels

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could not be used as a determinant of disease burden, and therefore cannot be used to compare disease burdens between patients, but once disease burden has been established for a particular-patient serial measurements of IgM monoclonal protein by serum electrophoresis are useful in following disease burden for an individual patient with WM.

The panel also expressed that the presence of cold agglutinins or cryoglobulins may affect determination of IgM levels. Therefore, testing for cold agglutinins and cryoglobulins should be considered as part of the initial evaluation of patients with WM in whom there is a clinical index of suspicion for their presence, and if present, serum samples should be re-evaluated under warm conditions for determination of serum IgM monoclonal protein levels.

**Should IgM Levels per se be the Sole Determinants of Response in Waldenstrom's Macroglobulinemia?**

IgM monoclonal protein levels as determined by serum electrophoresis may be used as a determinant of disease response to therapy in WM. However, increased stringency needs to be employed for the determination of a complete remission response state as further described below.

**Is the Use of Lymph Nodal or Splenic Response Necessary to Determine Response in WM? Can Lymph Node or Splenic Shrinkage Lag Behind IgM and Therefore Complicate Response Determination?**

Decreases in lymph node and spleen size may lag behind IgM responses in certain patients, and conversely IgM decreases may lag in certain patients where lymph nodal and splenic responses have been observed. IgM monoclonal protein levels may also be slow coming with certain therapeutics, particularly nucleoside analogues and biological therapies, and therefore clinicians and clinical investigators should consider following patients until their best overall response so as to not miss a delayed response.

**Should Recovery of Hematological Function be Considered in Response Determinations in WM?**

The panel considered arguments for the inclusion of hematological recovery as part of the response determination in WM. The panel felt that since anemia, as well as thrombocytopenia and leukopenia, could be impacted by many mechanisms related to WM or other non-WM-related disorders, as well as by therapy itself with the notable example of prolonged cytopenias after nucleoside analogue therapy, that hematological recovery ought not be mandated as part of the response criteria for WM. Moreover, the panel considered that since there is such great heterogeneity in the presentation of WM, and that for many patients hematological function is not substantially compromised that inclusion of recovery of hematological function for many WM patients was not appropriate. The panel, however, recommended that since IgM served as a good marker for tracking disease burden in a particular patient with WM, that its use was reasonable as a major determinant for disease response along with evidence of improvement in at least one sign, symptom, or laboratory abnormality for which therapy was initiated for the determination of the partial response (PR) status (as noted below), and resolution of all signs, symptoms, or laboratory evidence associated with disease and normal bone marrow histological examination for demonstration of a complete response (CR) (as is also noted below).

**Definitions of Complete and Partial Responses**

The panel recommended the following criteria for use in determining clinical responses in WM.

Morphologic evaluation should be confined for determination of CR. Although phenotypic analysis by flow cytometry or immunohistochemistry may prove useful in defining diagnostic and response criteria in the future, the panel felt that was insufficient evidence to currently require the use of these tests for response determination.

**Complete Response (CR)**

Complete disappearance of serum and urine monoclonal IgM by immunofixation, resolution of adenopathy/organomegaly, and no signs or symptoms that are directly attributable to Waldenstrom's macroglobulinemia (unexplained recurrent fever ≥38.4°C, drenching night sweats, ≥10% body weight loss, hyperviscosity, or symptomatic cryoglobulinemia). Absence of malignant cells by bone marrow histologic evaluation is required. Reconfirmation of the CR status is required at least 6 weeks later.
Partial Response (PR)

A ≥50% reduction of serum monoclonal IgM concentration on protein electrophoresis and ≥50% improvement in bulky adenopathy/organomegaly on computed tomography (CT) scan. No new signs, symptoms, or other evidence of disease.

Not Evaluable (NE)

Insufficient data/time for a determination of response to treatment.

When Should a Patient be Considered as Having Progressive Disease or Relapsing From a Complete Remission?

The panel recommended the following criteria for use in determining identifying patients who did not attain a response, or who demonstrate progressive disease after a response.

Progressive Disease (PD)

A greater than 25% increase in serum IgM monoclonal protein levels from the lowest attained response value as determined by serum electrophoresis, confirmed by at least one other investigation, or progression of clinically significant disease related symptom(s).

Relapse From CR

Reappearance of serum IgM monoclonal protein levels as determined by immunofixation studies, confirmed by at least one other investigation, or progression of clinically significant signs or symptoms attributable to disease, or development of any other clinically significant disease related symptom(s).

The panel also recommended that evidence of PD or relapse from CR should not necessarily indicate that at this juncture therapy needs to be reinitiated, and that the criteria proposed by Consensus Panel 2 with regard to criteria for initiation of therapy should apply in these circumstances.

Use of Imaging Modalities in WM to Determine Response: CT Scans, Magnetic Resonance Imaging, PET Scans

The panel affirmed the use of CT scans as part of the response determination for CR and PR status as noted above, but felt that insufficient evidence existed at this time to recommend the routine usage of magnetic resonance imaging (MRI) or positron emission tomography (PET) scans in the management of WM.

DISCUSSION

Quantification of Monoclonal IgM

In patients with WM, accurate measurement of monoclonal IgM is paramount. Total immunoglobulin quantification by nephelometry is frequently unreliable, particularly at higher levels, because of distorted elevation due to polymerization. This is in addition to overestimation at low levels of paraprotein because of the inclusion of normal IgM. Therefore, for response evaluation, serial measurements of monoclonal paraprotein should be performed using precise densitometry measurements on standard serum protein electrophoresis. However, when the monoclonal protein is either less than 0.5 g/dL 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 paraprotein is no longer detectable by routine electrophoresis.

Although initial measurement of the monoclonal IgM establishes a baseline for comparison of subsequent serial measurements of paraprotein and response determination in an individual patient, a particular level of monoclonal IgM does not consistently relate to disease burden and, therefore, monoclonal IgM cannot be used to determine tumor mass between patients.

Since the presence of cryoglobulins can effect the quantification of monoclonal IgM, testing for these at baseline should be considered, particularly if the clinical index of suspicion for their presence is high. If cryoglobulins are present, subsequent samples for quantification of monoclonal IgM should always be collected and transported at 37°C to insure accurate and consistent determination of the paraprotein level.

Quantification of Bence Jones Protein

Bence Jones protein (BJP) excretion in a sample collected over 24 hours should be quantitated by protein electrophoresis. Although small quantities of BJP are noted in approximately 50% of patients with WM, BJP rarely, if ever, impacts the clinical course of disease. Therefore, no specific recommendations are necessary for reduction of BJP in
defining PR. CR, however, reflects complete disappearance of disease and should be confirmed by negative studies on urine immunofixation if an abnormality had been present at diagnosis.

Documentation of Bone Marrow Involvement

Because of the macrofocal nature of bone marrow infiltration in WM, the panel recommended that bone marrow aspirate and biopsy not be required for confirmation of PR, but absence of malignant cells by morphologic evaluation should be confirmed for determination of CR. Although phenotypic analysis by flow cytometry or immunohistochemistry may prove useful in defining diagnostic and response criteria in the future, the panel felt there was insufficient evidence to currently require the use of these tests for response determination.

Documentation of Lymphadenopathy/Organomegaly

CT scans of the chest, abdomen, and pelvis should be performed at baseline to establish the presence of lymphadenopathy and/or organomegaly. Improvement of significant bulky adenopathy/organomegaly should be confirmed by CT scan if treatment was initiated solely on this basis (bulky adenopathy/organomegaly). Resolution of all adenopathy/organomegaly, and no new sites of disease, by CT scan is necessary to confirm CR and evaluation should not be limited to sites of previous disease. In the rare patient with bulky disease, as in other forms of lymphoma, there may be difficulty interpreting response because of residual masses after chemotherapy. For these rare patients the panel recommended following the complete response unconfirmed (Cru) criteria previously described by Cheson et al. There is currently insufficient evidence to recommend routine use of MRI or PET.

Hematologic Response

Determination of remission based on hematologic criteria is difficult since anemia and other cytopenias may be due to etiologies other than WM. Therapy with nucleoside analogues may also produce prolonged cytopenias even in patients considered to be in remission by other criteria. Because of these special considerations the panel noted that the major determinant of partial response should be reduction of monoclonal IgM and that no specific criteria for hematologic response were recommended.

Response Criteria/Special Considerations

This consensus panel recommended the following criteria as definitions of response/remission. Should future testing of additional studies (i.e., MRI, PET scan, free light chain assays, Ig k/l light chain, etc) demonstrate confirmed predictive value, these criteria may be revised. Clinical response should not be assessed prematurely since reduction of monoclonal IgM and improvement of associated disease features may be slow (months to a year), particularly after treatment with nucleoside analogue or biologic therapies. Reductions in adenopathy/organomegaly and hematologic recovery may follow monoclonal protein response, or vice versa; therefore, determination of best response should be assessed at disease nadir to avoid missing a delayed response. To insure stability of remission, response should be confirmed with a second electrophoresis no earlier than 6 weeks after the initial determination of response and CR should be confirmed by immunofixation no earlier than 6 weeks after the initial negative immunofixation. The panel recommended that for patients to be considered evaluable for lack of response to treatment they must have been monitored for at least 3 months after treatment initiation. Specific definitions for response follow.

Relapse and Disease Progression/Special Considerations

Although strict criteria are necessary to define relapse/PD for comparisons of data in clinical trials, PD defined only by a small increment in paraprotein does not necessarily indicate a need for re-treatment 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.

Relapse From CR

Reappearance of monoclonal serum IgM by immunofixation confirmed by a second measurement and/or progression of clinically significant signs (anemia, thrombocytopenia, leukopenia, bulky adenopathy/organomegaly) or symptoms (unexplained recurrent fever ≥38.4°C, drenching night
sweats, ≥10% body weight loss, or hyperviscosity, nephropathy, symptomatic cryoglobulinemia, or amyloidosis) directly attributable to WM:

Relapse From PR

A >25% increase in serum monoclonal IgM by protein electrophoresis confirmed by a second measurement or progression of clinically significant signs (anemia, thrombocytopenia, leukopenia, bulky adenopathy/organomegaly) or symptoms (unexplained recurrent fever ≥38.4°C, drenching night sweats, ≥10% body weight loss, or hyperviscosity, neuropathy, nephropathy, symptomatic cryoglobulinemia, or amyloidosis) directly attributable to WM. For monoclonal protein nadir ≤2 g/dL, an absolute increase of 0.5 g/dL is required to determine disease progression.

At relapse, reevaluation by CT scan, particularly in patients with a high lactate dehydrogenase value, should be performed. Any large masses should be biopsied to confirm that transformation to an intermediate- or high-grade lymphoma has not occurred.

Future Considerations

These criteria serve as initial 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 may be appropriate as treatment improves and if prospective analyses of other modalities to assess disease, such as MRI, PET scans, β₂-microglobulin, and free light chain assays, indicate that one or more of these supplement current criteria or more accurately determine response and impact survival. In addition, to promote timely evaluation of novel agents for the treatment of WM, investigators are also encouraged to report endpoints such as time to treatment since progression-free survival may not de-

fine the point at which clinically significant relapse has occurred.

REFERENCES