CHALLENGES WITH CURRENT RESPONSE CRITERIA IN WM.

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The assessment of treatment response in WM has historically relied almost entirely on demonstrating sequential changes in the serum concentration of the IgM M component. It has however become increasingly clear that response assessment is complex in WM with numerous and often competing factors to consider. These include

- Clinical heterogeneity – determining categorical response on the basis of the percentage change in M component is clearly problematical in patients with low levels of M protein. Response assessment based on M protein changes may similarly not be appropriate in those patients with symptomatic IgM related syndromes such as anti-MAG neuropathy and cold agglutinin disease.
- Correlation with clinical benefit – changes in M component are not always associated with clinical benefit in individual patients
- Increasing incidence of high quality categorical responses with newer combinations – complete response rates of up to 20% have been reported with bortezomib containing regimens as well as purine analogue / alkylator / monoclonal antibody combinations.
- Prognostic impact of categorical response – recent data has suggested, at least in terms of PFS and rituximab based combinations that categorical response is predictive of outcome. Patients achieving a VGPR have an outcome similar to those achieving a CR.
- Kinetics of IgM response – this is typically slow with alkylators, purine analogues and rituximab but rapid with bortezomib combinations.
- New serological assays – the serum free light chain assay SFLC appears to be informative in the majority of patients but reported values are relatively low compared to myeloma patients. An additional assay (HLC) which allows quantitation of IgM kappa and IgM lambda has recently been developed and is based on the identification of unique junctional epitopes that exist between heavy and light chains. The routine applicability of these assays has not however been established.
- FDG-PET imaging – this is informative in 80% of patients but further prospective evaluation is required in determining its value in response assessment.
- Discrepancies between IgM and bone marrow / tissue responses – a number of studies have demonstrated an apparent discrepancy between IgM and bone marrow responses, at least in the context of treatment with alkylators, purine analogues and monoclonal antibodies. These appear to selectively deplete the CD20+ B-cell component of the disease with apparent sparing of the CD138+

plasma cell component. In contrast some studies with bortezomib have reported excellent IgM responses but discordant marrow / tissue responses.

Given these complexities detailed response evaluations should be encouraged in all clinical trials and particularly those involving novel agents / combinations. These assessments should ideally include scheduled bone marrow assessments irrespective of the IgM response. As categorical IgM responses continue to improve it is important that flow cytometric and / or molecular methods are developed for the assessment of minimal residual disease.