Diagnosis and response assessment: what are the outstanding issues?

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Waldenström macroglobulinaemia(WM) is a B-cell lymphoproliferative disorder characterized by IgM monoclonal gammopathy and bone marrow (BM) infiltration by lymphoplasmacytic lymphoma (LPL). Historically LPL has been considered a poorly reproducible diagnostic category and largely a diagnosis of exclusion as a consequence of a lack of disease defining immunophenotypic and genotypic features. Considerable advances have been made recently with the demonstration of a WM specific ($CD22^{weak}$ $CD25^{+}$) immunophenotype and the MYD88 L265P mutation in the vast majority of patients. These developments have resulted in significant advances in diagnosis and prognostic assessments but challenges remain. These include

- Cases wild type for MYD88 L265P – how should such cases be considered? Should alternative mutations be sought in the routine diagnosticsetting?

- IgG and IgA LPL – what are the phenotypic and genotypic characteristics?

- IgM related syndromes – do these have the same underlying cellular features as WM?

- Do new diagnostic modalities allow for a more specific definition of IgM MGUS?

- What are the biological events underlying progression and transformation events?

- What is the significance of the MYD88 L265P mutation in other B cell LPD such as primary CNS lymphoma? Are there common aetiological factors?

Criteria for the assessment of post treatment response have been developed to promote uniform reporting of clinical trial data. The response categories are predominantly based upon percentage reduction in IgM as this appears to predict progression free survival at least in the context of rituximab-containing regimens. It has however become clear that there may be discrepancies between serum IgM and BM / tissue responses. Studies in myeloma and CLL have shown the value of quantitative assessment of residual BM disease as there are demonstrable improvements in outcome with each log depletion. Furthermore, it

is noted that conventional complete response fails to retain prognostic significance in multivariate models for both progression free and overall survival when considered along with quantitative residual BM disease assessment by flow cytometry. Accurate and reproducible quantitative methods are clearly desirable in WM and planned sequential BM assessments are encouraged in clinical trials. The most appropriate methodologies have not been established in WM. Flow cytometry can be used to quantitate residual B-cells and is applicable to most patients on the basis of the WM-specific $CD22^{weak}$ $CD25^{+}$immunophenotype. Given the heterogeneity of cellular responses in the BM it is important to assess residual plasma cells as well B-cells and to correlate this with quantitative changes in IgM. It is also possible to quantitatively assess residual disease with molecular methods based either on the presence of the MYD88 L265P mutation or unique immunoglobulin sequence. Molecular methods are likely to offer greater sensitivity compared to flow cytometry but they will not be able to demonstrate any heterogeneity within B-cell and plasma cell responses. Ideally studies should evaluate the peripheral blood in parallel with the BM as non-invasive methods are clearly desirable.