RESPONSE ASSESSMENT AND CHALLENGES.

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Uniform response criteria have been developed in most haematological malignancies. Their principle function is to provide a means of meaningfully comparing the outcomes from different clinical trials and to provide reproducible categories of response that are predictive of overall outcome. Similarly they should facilitate the clinical management of individual patients. The current uniform criteria in WM (Kimby *et al,* 2006) identify the following categories

- **Complete response**
  - immunofixation negative, no histological evidence of BM infiltration, resolution of nodes/organomegaly, absence of symptoms. Repeat immunofixation ≥6 weeks.
- **Partial response**
  - ≥50% reduction in monoclonal IgM, nodes and organomegaly
- **Minor response**
  - ≥25% and <50% reduction in monoclonal IgM
- **Stable disease**
  - <25% reduction and <25% increase in monoclonal IgM without progression of nodes/organomegaly and no new symptoms
- **Progressive disease**
  - ≥25% increase in monoclonal IgM and/or new clinical findings

Recent data has for the first time suggested that the quality of categorical response does indeed impact on outcome in WM. Additionally this data has also highlighted the potential value of the VGPR category in which there is a >90% decrease in IgM. There do however remain a number of challenges that should be noted

- Clinical heterogeneity – IgM concentrations are not a measure of disease bulk and vary considerably from patient to patient
- Kinetics of response – this is typically slow with alkylators, purine analogues and monoclonal antibodies but rapid with bortezomib containing regimens
- Discordance between marrow and IgM responses
- Increasing incidence of CR with novel agents and combinations
- Clinically meaningful responses not always reflected in changes in IgM concentration.
- IgM responses do not necessarily imply improvement in symptoms.

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A major concern is the apparent discordance between IgM and bone marrow responses which have been reported by a number of investigators both in the context of conventional and novel therapies. It is clear that routine marrow assessment should be encouraged in the evaluation of novel therapeutic combinations. It seems likely that routine bone marrow assessment will become more relevant now that a substantial proportion of patients are achieving high quality remissions (CR and VGPR) with available combinations. In this context it is interesting to note the value and impact of minimal residual disease assessments in both CLL and myeloma. Defining the "WM phenotype" should facilitate the development of flow cytometric minimal residual disease assays.