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## Updates to the guidelines for the diagnosis and management of multiple myeloma

The guideline on the diagnosis and management of multiple myeloma was published in 2011 (Bird *et al*, 2011). Subsequently, addendums have been made and an updated electronic version of the guideline is available on the British Committee for Standards in Haematology website ([http://www.bcsghguidelines.com/4\\_HAEMATOLOGY\\_GUIDELINES.html](http://www.bcsghguidelines.com/4_HAEMATOLOGY_GUIDELINES.html)). The purpose of this letter is to highlight three major changes made to the guideline published in 2011.

1. Fluorescence *in situ* hybridization (FISH) studies are now recommended for all patients at diagnosis, as they provide important prognostic information, but their role in directing therapy needs further evaluation in prospective clinical trials. The International Staging System (ISS) is the accepted staging system in multiple myeloma, defining three risk categories based on the serum concentrations of  $\beta_2$ -microglobulin and albumin, but alone is not useful in directing

therapy. Certain cytogenetic and molecular genetic abnormalities have been shown to predict outcome in myeloma. The immunoglobulin heavy chain gene translocations t(4;14), t(14;16) and t(14;20) and the copy number changes 1q gain and 17p deletion, demonstrated by FISH, confer an adverse outcome in myeloma. It has therefore been proposed that these abnormalities define 'high-risk' myeloma and should be specifically sought at diagnosis in all patients. Chromosome 13 deletion is not an independent prognostic marker and the adverse effect relates to its close association with high-risk abnormalities, particularly the t(4;14). The European Myeloma Network have outlined the technical aspects of FISH testing in myeloma and related disorders and recommended the essential abnormalities to be tested for are t(4;14), t(14;16) and 17p13 deletions as well as 1p and 1q abnormalities, where possible (Ross *et al*, 2012). Data from the Medical

Research Council Myeloma IX trial has been used to define risk groups based on the presence or absence of multiple adverse FISH lesions and to combine these with the ISS. This is able to identify an ultra-high-risk group defined by ISS II or III and >1 adverse lesion, associated with a short progression-free survival (PFS) (Boyd *et al*, 2012). This information is helpful to inform clinical discussions with patients about anticipated longer term outcome. There is increasing data to suggest that the adverse effect of genetic factors may at least in part be overcome by newer agents (Sonneveld *et al*, 2012) and some centres propose a treatment approach based on genetic risk stratification with an emphasis on bortezomib-based induction for high risk myeloma (Kumar *et al*, 2009). Whilst there is now international consensus about the need to undertake FISH analysis at diagnosis there is not yet international consensus as to the optimal treatment approach for different risk groups and further studies for high risk myeloma are required. Nonetheless, using cytogenetics as a biological risk assessment is likely to assist in treatment decisions in the future as further evidence is generated about the optimal treatment for a given group of patients. Next generation sequencing is able to identify copy number alterations, translocations and somatic mutation and is likely to succeed FISH testing in the future. A number of groups have used gene expression profiling to define risk in both newly diagnosed and relapsed patients and DNA arrays to identify copy number abnormalities in newly diagnosed myeloma but their role in determining treatment decisions in routine clinical practice is yet to be defined. Other prognostic indicators include the serum free light chain concentrations, the immunoglobulin heavy/light chain ratios and the presence or absence of neoplastic plasma cells identified by multiparameter flow cytometry following treatment. It is essential that new prognostic indicators continue to be evaluated in prospective clinical trials to determine the role for these in the future stratification of myeloma treatment.

2. A second autologous stem cell transplant (ASCT) should be strongly considered in patients with >12 months response to the first ASCT although its impact on overall survival is currently unclear. A second ASCT is considered 'standard' by the British Society of Blood and Marrow Transplantation (BSBMT) Indications Committee, and is fully commissioned by National Health Service (NHS) England. There is a need for improved biomarkers to help predict the likelihood of benefit from a second ASCT.

A planned double (tandem) ASCT cannot be recommended on the current evidence. However, it is recommended that enough stem cells are collected to support two high dose procedures in patients with good performance status. Individuals with the best outcome following a 'deferred' second ASCT are those achieving a first progression-free interval of at least 2 years following their first transplant (Mikhael *et al*, 2004).

Until recently, the body of evidence has been retrospective but did demonstrate a clinical utility of a second ASCT,

particularly in those who achieved a minimum PFS of 12–18 months after the first ASCT (Cook *et al*, 2011). The UK Myeloma Forum/BSBMT Myeloma X trial, a randomized phase III study, demonstrated superiority of a second ASCT over low-dose alkylating agent (cyclophosphamide weekly) in terms of durability of disease response after a bortezomib-containing regimen at first relapse in patients with at least >12 months PFS from first transplant (Cook *et al*, 2013). No differential effect was demonstrated in patients with high-risk genetics, though full analysis of the randomized interventions was hampered by limited data. Follow-up is too short currently to determine the effect on overall survival.

3. Bortezomib should be given by subcutaneous injection rather than intravenously. Bortezomib is best given by subcutaneous administration. Historically, it was initially given by intravenous administration until Moreau *et al* (2011) demonstrated that subcutaneous administration was equally effective but, importantly, was associated with significantly reduced incidence and severity of peripheral neuropathy compared to bortezomib delivered by intravenous administration (Arnulf *et al*, 2012; Moreau *et al*, 2011). Bortezomib may still be given intravenously in patients with severe fluid overload where there is a concern about adequacy of absorption.

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## Defining the best cut-off value for lymphopenia in diffuse large B cell lymphoma treated with immuno-chemotherapy

In the last decade a number of investigations have been performed to identify clinical, laboratory or molecular parameters, predictive of response to therapy, prognosis and survival in malignant lymphoma. These studies attempted to define risk groups and tailor therapy more effectively. Patients with diffuse large B cell lymphoma (DLBCL) have a heterogeneous clinical course and therapeutic response but,

despite advances in immuno-chemotherapy, not all patients are cured.

In this context, evaluation of the prognostic and predictive value of a simple laboratory parameter at diagnosis, such as the absolute lymphocyte count (ALC), could provide useful additional information in addition to the International Prognostic Index (IPI) score. The prognostic power of an