

Guidelines on the diagnosis and management of Waldenström macroglobulinaemia

Roger G. Owen,¹ Guy Pratt,² Rebecca L. Auer,³ Rita Flatley,⁴ Charalampia Kyriakou,⁵ Michael P. Lunn,⁶ Francis Matthey,⁷ Helen McCarthy,⁸ Feargal P. McNicholl,⁹ Saad M. Rassam,¹⁰ Simon D. Wagner,¹¹ Matthew Streetly,¹² and Shirley D'Sa¹³
British Committee for Standards in Haematology

¹St James's Institute of Oncology, Leeds Teaching Hospitals NHS Trust, Leeds, ²School of Cancer Sciences, University of Birmingham, Birmingham, ³St Bartholomew's Hospital, Barts Health NHS Trust, ⁴Royal Marsden NHS Foundation Trust, ⁵Northwick Park and Royal Free Hospitals, ⁶National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Foundation Trust, ⁷Chelsea and Westminster Hospital NHS Foundation Trust, London, ⁸The Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust, Bournemouth, ⁹Altnagelvin Area Hospital, Western Health and Social Care Trust, Londonderry, ¹⁰Maidstone and Tunbridge Wells NHS Trust, Maidstone, ¹¹Department of Cancer Studies and Molecular Medicine, University of Leicester, Leicester, ¹²Guy's and St Thomas' NHS Foundation Trust, and ¹³University College London Hospitals NHS Foundation Trust, London, UK

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Summary of key recommendations

Diagnosis, staging, prognostication and monitoring

- Sequential monitoring of immunoglobulin (Ig)M should be performed in a single laboratory using a single methodology (Grade A1).
- The value of serum free light chain (SFLC) and Hevylite™ chain (HLC) assays have not been established and are not essential for the routine assessment of Waldenström macroglobulinaemia (WM) patients (Grade C2).
- Anti-myelin-associated glycoprotein (MAG) serology and nerve conduction studies are recommended in patients with symptomatic peripheral neuropathy (Grade A1).
- Screening for hepatitis B and C viruses (HBV, HCV) is required prior to the introduction of rituximab-containing treatments (Grade A1).
- Bone marrow aspirate and trephine biopsy assessment, along with appropriate immunophenotypic studies, are required for a definitive diagnosis of WM (Grade A1).
- In accordance with national guidance on diagnosis in haematological malignancies, all cases should be subject to formal central review (Grade A1).

- Cytogenetic analysis is not required for the routine diagnostic assessment of WM patients (Grade B1).
- Further evaluation of the prognostic significance of del(6q) and deletion of *TP53* are required, ideally in the context of prospective clinical trials (Grade B2).
- Baseline computerized tomography (CT) scans (chest, abdomen, pelvis) are recommended in all symptomatic patients prior to the commencement of chemotherapy (Grade B1).
- The value of fluoro-deoxyglucose positron emission tomography (FDG-PET) remains to be determined and is not recommended outside of a clinical trial (Grade C2).
- Although there is emerging evidence for familial clustering in WM the absolute level of risk for first-degree relatives appears to be low and, in the absence of obvious clinical benefit, systematic screening of family members is not indicated (Grade B1).
- Tissue biopsy is recommended in all patients with suspected histological transformation. Detailed pathological assessment should include assessment of Epstein-Barr virus (EBV) by immunohistochemistry and/or *in situ* hybridization (Grade A1).
- The international prognostic scoring system for WM (ISSWM) should be recorded in all patients at presentation (Grade A1) but there is no evidence to support its use in determining treatment approaches for individual patients (Grade B1).
- Treatment responses should be defined using the uniform response criteria (Grade A1).
- Assessment of SFLC and HLC are not routinely required in the assessment of response (Grade C2).
- Repeat bone marrow aspirate and trephine biopsies are encouraged to refine response assessment in individual patients (Grade A1).

Correspondence: Dr Roger G. Owen, HMDS Laboratory, St James's Institute of Oncology, Beckett Street, Leeds LS9 7TF, UK.
E-mail: rogerowen@nhs.net

Treatment at diagnosis

- 1 Patients with symptomatic WM should receive a rituximab-containing regimen (Grade A1). Appropriate regimens include dexamethasone + rituximab + cyclophosphamide (DRC), bendamustine + rituximab (BR), fludarabine + rituximab (FR), fludarabine + cyclophosphamide + rituximab (FCR) and cladribine + rituximab (Clad-R). The choice of regimen in individual patients will take into consideration performance status, clinical features including renal function, co-morbidities and potential candidacy for stem cell transplantation (SCT) (Grade B1).
- 2 Given the risk of IgM flare, careful monitoring of all patients receiving rituximab is required with monitoring of sequential IgM, clinical assessment for hyperviscosity (HVS) and monitoring of plasma viscosity (PV) if available (Grade A1). The introduction of rituximab should be deferred in patients considered at a higher risk of HVS, this being arbitrarily defined by an IgM M-protein >40 g/l and/or a PV >4 centipoise (cP) (Grade C1).
- 3 Rituximab + cyclophosphamide + doxorubicin + vincristine + prednisolone (CHOP-R) should not be used as primary therapy in WM (Grade B1).
- 4 Chlorambucil remains suitable therapy in elderly frail patients (Grade B1).
- 5 The use of bortezomib is not routinely recommended as primary therapy outside the context of a clinical trial (Grade B2).
- 6 There is insufficient evidence to support the use of maintenance rituximab (Grade C2).

Treatment at relapse

- 1 Repeat bone marrow aspirate and trephine assessment and CT scanning should be performed prior to the re-introduction of treatment (Grade B1).
- 2 Patients who remain asymptomatic despite serological evidence of progression can be observed until clinical symptoms occur (Grade A1).
- 3 Patients should receive a rituximab-containing regimen if CD20 expression is documented. Appropriate regimens include FR, FCR, Clad-R, BR and DRC. The choice of regimen in individual patients will take into consideration performance status, clinical features including renal function, co-morbidities and potential candidacy for SCT (Grade B1).
- 4 Retreatment with primary therapy may be appropriate in some patients (Grade B1).
- 5 Bortezomib-containing regimens are suitable in the relapse setting. Weekly regimens are preferable, given the neurological toxicity associated with the biweekly schedules. Prophylaxis against herpes zoster reactivation is recommended (Grade B1).

- 6 Alemtuzumab is a potential option in refractory disease (Grade B1). Surveillance for cytomegalovirus (CMV) reactivation is recommended.

Treatment for histological transformation

- 1 A diagnosis of transformation requires histological confirmation (Grade A1).
- 2 Patients who are suitable for intensive therapy should receive regimens currently employed for primary diffuse large B-cell lymphoma (DLBCL) (Grade B1).
- 3 Younger responding patients are candidates for a stem cell transplant (SCT) procedure and should be discussed with a transplant centre (Grade B2).

Haemopoietic SCT

- 1 Autologous SCT is a feasible therapeutic option for relapsed WM in younger, fitter patients with aggressive disease [short progression-free survival (PFS), histological transformation] (Grade B2).
- 2 Allogeneic SCT may be considered in selected younger patients with relapsed WM and an aggressive clinical course (short PFS, histological transformation) (Grade B2).
- 3 Autologous and allogeneic SCT should only be performed in the setting of chemosensitive disease with at least a partial response to reinduction therapy (Grade A1).

Hyperviscosity syndrome

- 1 Plasma exchange is recommended for all patients with HVS irrespective of PV (Grade A1).
- 2 As per previous guidance 1–2 procedures, exchanging 1–1.5 calculated plasma volumes, is advised (Grade A1).
- 3 Plasma exchange may be indicated in certain asymptomatic individuals depending on the clinical circumstances, recorded plasma viscosities and co-morbidities (Grade C2).

IgM-related neuropathy

- 1 Neurological examination should be performed in all patients with IgM paraproteins (Grade A1).
- 2 Collaborative working with a neurologist is encouraged. Anti-MAG serology and nerve conduction studies are recommended in patients with symptomatic peripheral neuropathy (Grade A1).
- 3 Chemotherapeutic intervention should be considered in patients with disabling or rapidly progressive anti-MAG neuropathy (Grade B1).
- 4 If chemotherapy is considered appropriate, a rituximab-containing regimen is appropriate with the final choice of regimen being determined by factors such as performance status, co-morbidities and renal function (Grade B1).

Cold haemagglutinin disease (CHAD) and cryoglobulinaemia

- 1 Rituximab-based therapy is recommended for patients with symptomatic CHAD. The addition of fludarabine should be considered for patients with adequate performance status and renal function (Grade B1).
- 2 Cryoglobulinaemia should be considered in patients with IgM monoclonal gammopathy and unexplained purpura, arthralgia, haematuria or peripheral neuropathy (Grade A1).
- 3 Patients with cryoglobulinaemia should be screened for HCV infection (Grade A1).
- 4 Patients with symptomatic cryoglobulinaemia may be treated with corticosteroids and rituximab (Grade B1).
- 5 Patients with symptomatic cryoglobulinaemia and overt WM can be treated with standard therapies (Grade B1).

Supportive care

- 1 Antimicrobial prophylaxis should be considered for patients with hypogammaglobulinaemia who develop recurrent bacterial infections (Grade B1).
- 2 Immunoglobulin replacement therapy should be according to UK Department of Health clinical guidelines (Grade B1).
- 3 Anti-*Pneumocystis jirovecii* prophylaxis is recommended in patients requiring intensive and/or immunosuppressive treatment (Grade B1).
- 4 Anti-herpes simplex virus (HSV) and –herpes zoster virus (HZV) prophylaxis is recommended in patients requiring intensive, immunosuppressive or bortezomib-based therapy (Grade B1).
- 5 Pneumocystis and herpes prophylaxis is not routinely required in patients treated with alkylating agents or bendamustine (Grade B2).
- 6 The duration of anti-pneumocystis and herpes prophylaxis is controversial. Recommendations range from a minimum of 2 months post-therapy to awaiting a rise in CD4 count to $0.2 \times 10^9/l$ (Grade C2).
- 7 Vaccination against *Streptococcus pneumoniae* (using a conjugate vaccine) and *Haemophilus influenzae* type B is encouraged at diagnosis although there is a lack of randomized trials to support vaccination. Patients who respond to vaccination and subsequently develop recurrent bacterial infections should be revaccinated if *S. pneumoniae* and *Haemophilus influenzae* type b (HIB) antibody levels have fallen (Grade C1).
- 8 Annual vaccination against seasonal influenza including novel strains is recommended (Grade C1).
- 9 Live vaccines, such as polio, *H. zoster* and yellow fever, should be avoided (Grade A1).

- 10 Vaccinations should be avoided, if possible, 2 weeks prior to, during and for 6 months after chemo-immunotherapy (Grade B1).

1. Methodology

The guideline group was selected to be representative of UK experts in Waldenström macroglobulinaemia (WM). Recommendations are based on the systematic review of published English language literature up to July 2013 and including data presented in abstract form at the 2012 American Society of Hematology meeting. The writing group produced a draft guideline, which was reviewed and revised by members of the Haemato-Oncology Task Force of the British Committee for Standards in Haematology (BCSH). The guideline was further reviewed by a sounding board of approximately 50 UK haematologists and BCSH and the British Society for Haematology Committee and further consensus amendments were made.

These guidelines have been prepared using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) nomenclature for assessing the quality of evidence and providing strength of recommendations (<http://www.gradeworkinggroup.org/index.htm>).

2. Introduction

Waldenström macroglobulinaemia is a distinct B-cell lymphoproliferative disorder characterized by an immunoglobulin (Ig)M monoclonal gammopathy and bone marrow infiltration by lymphoplasmacytic lymphoma (LPL) (Owen *et al*, 2003). Clinical features are diverse and may relate to overall disease burden, such as peripheral blood cytopenias, organomegaly and constitutional symptoms, or may be directly attributable to the IgM paraprotein. The latter include hyperviscosity syndrome (HVS) and amyloidosis, as well as features attributable to autoantibody specificity, such as peripheral neuropathy, cold haemagglutinin disease (CHAD) and acquired von Willebrand disease (Treon, 2009).

Treatment approaches have traditionally involved the use of alkylating agents and purine analogues, often as single agents. However emerging new data on monoclonal antibody combinations as well as on novel therapies including bortezomib have led to a re-evaluation of the BCSH guidelines published in 2006 (Johnson *et al*, 2006).

A precursor condition IgM monoclonal gammopathy of undetermined significance (MGUS) is defined by having all of the following criteria (i) the presence of an IgM paraprotein of <30 g/l (ii) no evidence of underlying bone marrow infiltration and (iii) absence of signs or symptoms related to WM itself (Table I). The rate of transformation for an individual with IgM MGUS to WM is approximately 1–2% per year (Kyle *et al*, 2003a) The term IgM-related disorders denotes the presence of clinical features attributable to the

Table I. Classification of IgM monoclonal gammopathies.

	IgM paraprotein	BM infiltration	Symptoms
MGUS	Yes	No	No
Asymptomatic WM	Yes	Yes	No
Symptomatic WM	Yes	Yes	Yes
IgM-related disorder	Yes	No	Yes

MGUS, monoclonal gammopathy of undetermined significance; WM, Waldenström macroglobulinaemia; IgM, immunoglobulin M.

IgM paraprotein but the absence of marrow infiltration (Owen *et al*, 2003).

3. Epidemiology

Waldenström macroglobulinaemia is relatively rare with an age standardized incidence rate of 0.55 per 100 000 per year in the UK. There is a male predominance and the incidence appears to be lower in non-Caucasians (Herrinton & Weiss, 1993; Phekoo *et al*, 2008). WM is typically a disease of the elderly with a median age at presentation of >70 years and an overall median survival of approximately 60 months (Owen *et al*, 2001a; Phekoo *et al*, 2008). New epidemiological data have emerged since the last guidance and these have demonstrated an increased risk of WM with a personal or family history of a wide range of autoimmune, inflammatory and infective disorders. This association was particularly strong for Sjogren syndrome and autoimmune haemolytic anaemia, suggesting the potential for a shared susceptibility for these disorders and WM (Koshiol *et al*, 2008; Kristinsson *et al*, 2010a). Further data have also demonstrated an increased risk of WM and other B-cell disorders amongst relatives of patients with WM (Treon *et al*, 2006; Kristinsson *et al*, 2008). In a detailed population-based assessment in Sweden, the estimated relative risk for a first-degree relative of a patient with WM developing WM, MGUS, non-Hodgkin lymphoma or chronic lymphocytic leukaemia (CLL) was 20.0, 5.0, 3.0 and 3.4 respectively (Kristinsson *et al*, 2008).

Recommendation

- 1 **Although there is emerging evidence for familial clustering in WM, the absolute level of risk for first-degree relatives remains low and, in the absence of obvious clinical need, systematic screening of family members is not indicated (Grade B1).**

4. Investigation and diagnosis

4.1. Laboratory assessment

A list of useful laboratory investigations for patients with suspected or established WM is provided in Table II but

Table II. Useful investigations in patients with suspected or established WM.

Full blood count*
Plasma viscosity
Serum protein electrophoresis and immunofixation
Quantification of IgM paraprotein by densitometry
Quantification of IgG and IgA
Urea and creatinine
Liver function tests
Lactate dehydrogenase
Beta2 microglobulin
Direct antiglobulin test
Hepatitis B and C status
Anti-myelin-associated glycoprotein titre
Nerve conduction studies
Cold agglutinins
Cryoglobulins

*Flow cytometry is suggested in those patients with a lymphocytosis to confirm peripheral blood involvement.

tests for neuropathy, cryoglobulin and cold agglutinins should be tailored to the clinical scenario. IgM paraproteins should be demonstrated by serum protein electrophoresis and quantitated by densitometry. Assessment of total IgM concentration by nephelometry is a viable alternative to densitometric assessment of paraprotein concentration, although it is important to recognize that the former provides systematically higher values (Riches *et al*, 1991; Murray *et al*, 2009). Concentrations of IgG and IgA should also be determined at diagnosis and at regular intervals during follow up (Hunter *et al*, 2010). It is essential that the sequential assessment of paraprotein concentration be performed by the same method within the same laboratory (Owen *et al*, 2013).

The serum free light chain (SFLC) assay has been evaluated by a number of investigators. Approximately 80% of patients have elevated levels of involved free light chain but the median values reported are relatively low at 48.6–103.5 mg/l and its prognostic significance has not been formally established (Itzykson *et al*, 2008; Leleu *et al*, 2008, 2011a,b). A further assay [Hevylite™ chain assay (HLC)], which allows the quantification of IgM kappa and IgM lambda has recently been developed and is based upon the unique junctional epitopes that exist between heavy and light chains; initial reports have suggested a potential role in WM (Leleu *et al*, 2011a). The routine applicability of these assays in WM has not yet been fully established.

The formal measurement of plasma viscosity (PV) is a useful adjunct in the assessment of WM patients, particularly those with high concentrations of paraprotein. It is however recognized that this assay is not routinely available in all UK laboratories and that the diagnosis of HVS remains a clinical one. Patients with symptomatic neuropathy should be assessed for anti-myelin-associated glycoprotein (MAG) antibodies and undergo nerve conduction studies.

Chemo-immunotherapy regimens containing rituximab can result in reactivation of hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infection. All patients should therefore be screened for evidence of previous HBV or HCV infection prior to the initiation of therapy. Patients positive for hepatitis B surface antigen, hepatitis B core antibody or hepatitis C antibody may require antiviral treatment and should be managed jointly with a specialist in viral hepatitis.

Recommendations

- 1 **Sequential monitoring of IgM should be performed in a single laboratory using a single methodology (Grade A1).**
- 2 **The value of serum free light chain (SFLC) and Hevylite™ chain (HLC) assays have not been established and are not essential for the routine assessment of WM patients (Grade C2).**
- 3 **Anti-MAG serology and nerve conduction studies are recommended in patients with symptomatic peripheral neuropathy (Grade A1).**
- 4 **Screening for HBV and HCV is required prior to the introduction of rituximab-containing treatments (Grade A1).**

4.2. Bone marrow assessment

Central to the diagnosis of WM is the demonstration of marrow infiltration by LPL. Bone marrow assessment should be performed in all symptomatic patients. Its value in the assessment of asymptomatic individuals with an IgM paraprotein is not established but an arbitrary IgM monoclonal protein threshold of 10 g/l has been proposed in some guidelines (Bird *et al*, 2009). Bone marrow examination should however be considered at lower IgM concentrations if the patient has cytopenias, lymphadenopathy or splenomegaly or if the patient is suspected of having an IgM-related syndrome, such as peripheral neuropathy, CHAD or AL amyloidosis.

The presence of an IgM paraprotein is not indicative of a diagnosis of WM as this is demonstrable in a proportion of patients with virtually all of the B-cell lymphoproliferative disorders (Kyle & Garton, 1987; Owen *et al*, 2000; Lin *et al*, 2005) and hence detailed morphological and immunophenotypic assessment are required if a definitive diagnosis of WM is to be made. It is good practice to perform a trephine biopsy in addition to bone marrow aspirate cytology to more accurately assess the degree and pattern of infiltration. LPL is a lymphoproliferative disorder comprised of small lymphocytes in which there is morphological evidence of plasma cell differentiation. This phenomenon is most readily appreciated on trephine biopsy sections and can be definitively demonstrated by immunohistochemistry using plasma cell-specific antibodies such as CD138 and MUM1/IRF4. The pattern of infiltration is typically interstitial, nodular or diffuse whilst a

purely paratrabecular pattern is unusual. Additional morphological clues can be obtained from the trephine biopsy sections and these include the presence of reactive mast cells (readily seen on sections assessed with Giemsa stain or highlighted with CD117 or mast cell tryptase immunohistochemistry) and intranuclear and cytoplasmic immunoglobulin inclusions, termed Dutcher and Russell bodies, respectively.

The overall extent of plasma cell differentiation varies considerably from patient to patient and it appears that this is the major determinant of paraprotein concentration rather than the overall extent of marrow infiltration (Pasricha *et al*, 2011; de Tute *et al*, 2013). In a significant minority (20%) of cases the degree of plasma cell differentiation may be such that plasma cells are the predominant cell type and IgM myeloma becomes part of the differential diagnosis (Morice *et al*, 2009).

Immunophenotypic studies are necessary for a definitive diagnosis of WM and this may be achieved using either flow cytometry or immunohistochemistry, although the former allows for a more extensive assessment of antigenic determinants. In WM it is generally possible to demonstrate both monotypic B cells and monotypic plasma cells but extended phenotyping is usually only performed on the B-cell component (Owen *et al*, 2001a; Ocio *et al*, 2005; Morice *et al*, 2009). This component of the disease shows almost universal expression of the pan B-cell antigens CD19, CD20, CD79a and CD79b while CD5 and CD23 are expressed in a minority of cases only. The germinal centre-associated antigens CD10 and BCL6 are not demonstrable but most cases show expression of the memory B-cell marker CD27 as well as CD52. Distinguishing WM from marginal zone lymphoma (MZL) can be difficult although the expression patterns of CD22, CD25 and CD103 may be helpful, as WM may show a CD25⁺ CD22 weak CD103⁻ pattern whilst MZL may be CD22⁺ CD25⁻ and CD103⁺ (Owen *et al*, 2001a; Ocio *et al*, 2005; Morice *et al*, 2009; Paiva *et al*, 2014).

There are limited data on plasma cell immunophenotyping in WM but the published data suggest that the antigenic patterns seen in myeloma plasma cells (CD19⁻ CD45⁻ CD56⁺) are not seen in WM plasma cells; (San Miguel *et al*, 2003; Ocio *et al*, 2005; Morice *et al*, 2009; Paiva *et al*, 2014). This can be useful in those cases of WM in which plasma cells predominate and plasma cell phenotyping should allow a definitive distinction between WM and the rare entity of IgM myeloma (Feyler *et al*, 2008).

Recommendations

- 1 **Bone marrow aspirate and trephine biopsy assessment along with appropriate immunophenotypic studies are required for a definitive diagnosis of WM (Grade A1).**
- 2 **In accordance with national guidance on diagnosis in haematological malignancies, all cases should be subject to formal central review (Grade A1).**

4.3. Cytogenetic analysis

Conventional karyotyping has limited applicability in WM as it is difficult to obtain tumour metaphases because of the low rate of cell proliferation. There are no disease-defining cytogenetic abnormalities but translocations involving the immunoglobulin heavy chain locus (*IGH*) at 14q32 are characteristically rare (Schop *et al*, 2002; Avet-Loiseau *et al*, 2003; Ackroyd *et al*, 2005; Nguyen-Khac *et al*, 2013). This is of course in contrast to IgM myeloma which is characterized by a high incidence of *IGH* translocations and t(11;14) in particular (Avet-Loiseau *et al*, 2003; Feyler *et al*, 2008). Deletion of chromosome 6q appears to be the commonest cytogenetic abnormality in WM, occurring in up to 50% of patients; it may be associated with adverse clinical and laboratory parameters but its effect on survival remains unclear (Schop *et al*, 2002; Ocio *et al*, 2007; Nguyen-Khac *et al*, 2013). Deletion of *TP53* occurs in a minority of patients and appears to define patients with a poor outcome (Nguyen-Khac *et al*, 2013).

Recent insights into the pathogenesis of WM have been provided by whole genome sequencing, which has demonstrated a single point mutation in the myeloid differentiation primary response gene (*MYD88*) in 90% of patients (Treon *et al*, 2012). This mutation results in a leucine to proline amino acid substitution at position 265 (L265P). Recent studies have also highlighted the potential utility of screening for the L265P mutation in the routine diagnostic setting (Gachard *et al*, 2013; Varettoni *et al*, 2013; Xu *et al*, 2013). In this context it seems most useful in the differential diagnosis of WM from MZL.

Recommendation

- 1 Cytogenetic analysis is not required for the routine diagnostic assessment of WM patients (Grade B1).
- 2 Further evaluation of the prognostic significance of del (6q) and deletion of *TP53* are required, ideally in the context of prospective clinical trials (Grade B2).

4.4. Imaging

Lymphadenopathy and splenomegaly are relatively infrequent in patients with WM, being reported in approximately 15% of patients (Treon, 2009). Baseline computerized tomography (CT) imaging would generally be regarded as standard practice in symptomatic patients prior to commencing therapy. There are limited data on the utility of fluoro-deoxyglucose positron emission tomography (FDG-PET) scanning in WM. A single study (Banwait *et al*, 2011) has demonstrated that this is informative in 80% of patients but there is no convincing rationale for routine use and further prospective study is required. FDG-PET imaging may have a role in the assessment of patients with suspected histological transformation (see below).

Recommendation

- 1 Baseline CT scans (chest, abdomen, pelvis) are recommended in all symptomatic patients prior to the commencement of chemotherapy (Grade B1).
- 2 The value FDG-PET remains to be determined and is not recommended outside a clinical trial (Grade C2).

Histological transformation

Histological transformation, primarily to diffuse large B-cell lymphoma (DLBCL), is a well recognized phenomenon which has been reported to occur in 5–10% of patients with WM (Facon *et al*, 1993; Leblond *et al*, 1998, 2001, 2013; Garcia-Sanz *et al*, 2001; Owen *et al*, 2001a; Lin *et al*, 2003). Clinical features suggestive of histological transformation include bulky and rapidly enlarging lymph node masses, extranodal disease and marked elevation in serum lactate dehydrogenase. Tissue biopsy is essential for a diagnosis of histological transformation and may be directed by PET/CT scanning as has been described in CLL (Bruzzi *et al*, 2006).

The pathobiological events underlying histological transformation events are poorly characterized but recent studies have highlighted a potential role for the purine analogues (Leleu *et al*, 2009). Histological transformation events have been thought traditionally to occur within the original B-cell clone as a consequence of the acquisition of additional genetic events. Recent data however have demonstrated the potentially diverse nature of later events and in particular the role of Epstein-Barr virus (EBV). These latter events include EBV-positive but clonally unrelated DLBCL and spontaneously resolving EBV-positive mucocutaneous ulcer (Varghese *et al*, 2008; Owen *et al*, 2011). These latter disorders should not be considered as transformation events *per se* as they appear to be clonally unrelated to the WM and occur as a consequence of disease and treatment-related immunosuppression.

Recommendation

- 1 Tissue biopsy is recommended in all patients with suspected histological transformation. Detailed pathological assessment should include assessment of EBV by immunohistochemistry and/or *in situ* hybridization (Grade A1).

6. Prognostic assessment

The international prognostic scoring system for WM (ISSWM) is based on the assessment of five key adverse prognostic features namely age >65 years, haemoglobin concentration ≤ 115 g/l, platelet count $\leq 100 \times 10^9/l$, β_2 -microglobulin >3 mg/l and paraprotein concentration >70 g/l. Low risk disease is defined by 0–1 adverse features excluding age, intermediate risk by two adverse factors or age while

high-risk is defined by >2 adverse features. These risk categories each comprise approximately 1/3 of patients and are associated with 5-year survival rates of 87%, 68% and 36% respectively (Morel *et al*, 2009). There is international consensus that this should be recorded in clinical trials but there is no evidence that it should influence treatment decisions for individual patients.

Recommendation

1 The ISSWM should be recorded in all patients at presentation (Grade A1) but there is no evidence to support its use in determining treatment approaches for individual patients (Grade B1).

7. Response assessment

Uniform treatment response criteria have been developed and recently updated with the primary aim of facilitating comparison of clinical trial results (Owen *et al*, 2013). The response categories defined by these criteria can be used in the routine clinical setting and the quality of response does appear to affect outcome (Gertz *et al*, 2009; Treon *et al*, 2011a). However in the management of individual patients it should be recognized that clinical benefit may be seen in some patients without a significant IgM response and, similarly, that reductions in IgM are not always associated with symptomatic improvement.

The SFLC assay appears to be informative in the majority of patients and may provide an earlier indication of both response and progression (Itzykson *et al*, 2008; Leleu *et al*, 2008, 2011b). The HLC assay may also have a potential role in WM response assessment (Leleu *et al*, 2011a). These assays have not however been included in the uniform response criteria and their routine use cannot be recommended at this stage, without further prospective evaluation.

Assessing response prospectively for individual patients can be challenging. It is well known that IgM responses can be slow with alkylators, purine analogues and monoclonal antibodies and that these agents selectively deplete the CD20⁺ B-cell component with sparing of the CD138⁺ plasma cell component of the disease (Varghese *et al*, 2009; Barakat *et al*, 2011). In this context it is possible to demonstrate significant B-cell depletion in the marrow but suboptimal IgM responses, with satisfactory IgM responses being subsequently achieved in the majority of patients. Hence, IgM levels that do not fall for many months into treatment may not necessarily indicate treatment failure and a bone marrow assessment is recommended to assess response. Conversely, bortezomib-containing regimens may demonstrate excellent IgM responses but suboptimal bone marrow responses (Treon *et al*, 2007).

Repeat marrow assessments can provide significant value in the management of individual patients. In order to make

a detailed assessment of residual infiltrates it is recognized that both bone marrow aspirate and trephine biopsies should be obtained and that these should be routinely supplemented by flow cytometric and immunohistochemistry studies. Attempts should be made to characterize residual infiltrates with respect to their B-cell and plasma cell content and immunohistochemical assessment of trephine biopsy sections provides the optimal method. CD138 and/or IRF4 may be used to demonstrate residual plasma cells while CD20 may be used to define residual B-cell infiltration although additional markers, such as PAX5, may be necessary in rituximab-treated patients due to the loss of antigen expression that is sometimes seen in post-treatment specimens (Varghese *et al*, 2009; Barakat *et al*, 2011).

In view of the heterogeneity of clinical response patterns noted in WM, serial bone marrow assessment is encouraged for all patients enrolled in clinical trials, irrespective of their IgM response.

Recommendation

- 1 Treatment responses should be defined using the uniform response criteria (Grade A1).**
- 2 Assessment of SFLC and HLC are not routinely required in the assessment of response (Grade C2).**
- 3 Repeat bone marrow aspirate and trephine biopsies are encouraged to refine response assessment in individual patients (Grade A1).**

8. Therapy for Waldenström macroglobulinaemia

8.1. Indications for therapy

A significant proportion of WM patients are asymptomatic at presentation and can be safely observed at 3–6 monthly intervals. The risk of progression to symptomatic disease is 59% at 5 years (Kyle *et al*, 2012). The indications for the introduction of treatment are unchanged from the previous guidance (Johnson *et al*, 2006) and include constitutional symptoms, symptomatic lymphadenopathy or splenomegaly, HVS, haematological suppression due to marrow infiltration and IgM-related syndromes, such as peripheral neuropathy and CHAD (Kyle *et al*, 2003b).

8.2. Choice of primary therapy in symptomatic individuals

Developing evidence-based treatment algorithms in WM is hindered by a lack of randomized data. The majority of published studies are non-randomized, often single institution-based, phase II studies that typically include both *de novo* and relapsed patients. Patients with WM are usually elderly and often have multiple co-morbidities and functional impairments. The use of risk assessments, such as comprehensive

geriatric assessments, is being increasingly recommended in haematological malignancies in the elderly to provide guidance when deciding on the appropriate treatment regimen and in identifying support needs. Dose reductions to avoid toxicity should be considered, particularly with the first course of treatment, with potential to increase the dose if well tolerated in some patients. Severely frail patients with a very poor performance status are unlikely to benefit from treatment.

The role of rituximab in the primary therapy of WM has not been formally established in dedicated randomized controlled trials. There is however extensive literature of single agent activity with response rates of up to 50% being reported (Byrd *et al*, 1999; Foran *et al*, 2000; Treon *et al*, 2001, 2005; Dimopoulos *et al*, 2002; Gertz *et al*, 2004). The addition of rituximab has, of course, produced considerable benefit in DLBCL, follicular lymphoma, CLL and mantle cell lymphoma (Coiffier *et al*, 2002; Marcus *et al*, 2008; Hallek *et al*, 2010; Griffiths *et al*, 2011). Subgroup analysis of a larger German study suggested that CHOP-R (rituximab + cyclophosphamide + doxorubicin + vincristine + prednisolone) was superior to CHOP (cyclophosphamide + doxorubicin + vincristine + prednisolone) in LPL and WM in terms of overall response rate (ORR) and time to treatment failure (Buske *et al*, 2009) while single centre experience from the US suggests an improvement in overall survival (OS) since the introduction of rituximab-based therapies (Thomas *et al*, 2012). Rituximab is generally well tolerated but can be associated with a paradoxical rise in IgM, the so-called 'IgM flare' phenomenon. Studies of single agent rituximab have suggested that 26% of patients have a $\geq 25\%$ increase in IgM levels and that this can rarely result in hyperviscosity and exacerbation of clinical symptoms (Dimopoulos *et al*, 2002; Ghobrial *et al*, 2004). The risk of IgM flare is likely to be lower with combination therapy. IgM flare cannot be predicted by presenting IgM concentration but clinically significant sequelae are more likely at higher starting values. There is therefore an argument for deferring the introduction of rituximab and this seems most relevant to those with higher presenting IgM and/or PV.

In the previous guidelines treatment with alkylating agents and purine analogues were considered appropriate primary therapy options (Johnson *et al*, 2006). The recently completed phase III multicentre European study comparing chlorambucil and fludarabine has, however, shown the latter to be superior in terms of response rates, progression-free survival (PFS) and OS (Leblond *et al*, 2013). Similarly, single agent fludarabine appeared to be superior to a CHOP-like anthracycline-containing regimen (CAP; cyclophosphamide + doxorubicin + prednisone) in patients with relapsed disease (Leblond *et al*, 2001).

Rituximab combinations have been studied in WM cohorts although randomized data are lacking. Treon and colleagues demonstrated a major response rate [MRR; complete response (CR) + partial response (PR)] of 86% and

median time to progression of 51 months with fludarabine and rituximab (FR) (Treon *et al*, 2009a). Similarly, Tedeschi *et al* (2012) reported a MRR of 74% with the FCR (FR + rituximab) combination. Cladribine combinations also appear efficacious in WM. For instance, a MRR of 79% has recently been reported with the cladribine-rituximab (Clad-R) regimen (Laszlo *et al*, 2010). In this study the median time to treatment failure was not reached with a median follow up of 34 months (Laszlo *et al*, 2010). It is also clear that high quality remissions are seen in a significant minority of patients, as the CR rate was 19% with FCR and 24% with Clad-R.

Despite the reported efficacy of the purine analogue combinations, doubts remain regarding their overall suitability in certain patients. There are concerns regarding their suitability in patients who may be potential candidates for autologous transplantation whilst concerns regarding myelotoxicity and infection are pertinent in elderly patients, particularly those with suboptimal renal function. For instance, 44% of patients had persistent neutropenia with the FCR regimen whilst \geq grade 3 neutropenia was demonstrated in 63% of patients treated with FR (Treon *et al*, 2009a; Tedeschi *et al*, 2012). Concerns regarding the long-term risk of histological transformation and myelodysplasia/acute myeloid leukaemia have also been raised by some authors (Leleu *et al*, 2009).

Alternative rituximab-containing regimens may be more appropriate in some patients. The DRC regimen, comprising of dexamethasone, rituximab and cyclophosphamide, appears a less toxic regimen with a reported MRR of 74% along with a 2-year PFS of 67% with only 9% of patients experiencing grade 3 neutropenia (Dimopoulos *et al*, 2007, 2012). Similarly, the combination of bendamustine and rituximab (BR) appears to be promising in WM. Rummel *et al* (2012) have recently demonstrated an ORR of 86% amongst 116 patients treated in an ongoing clinical trial. Similarly, the same group suggested that the BR combination was superior to CHOP-R with regards to CR rate, toxicity and response duration in subgroup analysis of a large trial in indolent lymphoma (Rummel *et al*, 2013).

Despite its widespread use, the role of CHOP with or without rituximab is questionable. The randomized data available would suggest inferiority to both fludarabine- and bendamustine-based therapy. Similarly, there are concerns regarding the neurotoxicity of vinca alkaloids in this patient group. Single agent chlorambucil may still be suitable therapy for very frail patients in whom combination therapy is considered inappropriate, as the MRR is approximately 40% and the PFS 27 months (Leblond *et al*, 2013).

Bortezomib combinations have been evaluated as upfront therapy in two relatively small phase II studies. Treon *et al* (2009b) demonstrated a MRR of 83% with biweekly intravenous bortezomib in conjunction with dexamethasone and rituximab. Responses were rapid, occurring at a median of 1.4 months but treatment was discontinued because of

neuropathy in 61% of patients. In a subsequent study, a weekly bortezomib regimen in conjunction with rituximab produced a MRR of 65% but no grade 3 or 4 neuropathy (Ghobrial *et al*, 2010a). The durability of response remains uncertain with these regimens and it is not clear whether they provide advantages over more conventional rituximab-containing chemotherapy regimens. A randomized comparison of FCR and a similar bortezomib-containing regimen (BCR) using subcutaneous bortezomib is currently recruiting in the UK.

Treon *et al* (2011b) also evaluated the role of maintenance rituximab in WM patients and demonstrated improved PFS (56.3 vs. 28.6 months) and OS (not reached *versus* 116 months). This was however a non-randomized study and further confirmation should be forthcoming on the completion of an on-going randomized trial (Rummel *et al*, 2012).

Recommendations

- 1 **Patients with symptomatic WM should receive a rituximab-containing regimen (Grade A1). Appropriate regimens include dexamethasone + rituximab + cyclophosphamide (DRC), bendamustine + rituximab (BR), fludarabine + rituximab (FR), fludarabine + cyclophosphamide + rituximab (FCR) and cladribine + rituximab (Clad-R). The choice of regimen in individual patients will take into consideration performance status, clinical features including renal function, co-morbidities and potential candidacy for stem cell transplantation (SCT) (Grade B1).**
- 2 **Given the risk of IgM flare, careful monitoring of all patients receiving rituximab is required with monitoring of sequential IgM, clinical assessment for HVS and monitoring of PV if available (Grade A1). The introduction of rituximab should be deferred in patients considered at a higher risk of hyperviscosity, this being arbitrarily defined by an IgM M-protein >40 g/l and/or a PV >4 centipoise (cP) (Grade C1).**
- 3 **Rituximab + cyclophosphamide + doxorubicin + vincristine + prednisolone (CHOP-R) should not be used as primary therapy in WM (Grade B1).**
- 4 **Chlorambucil remains suitable therapy in elderly frail patients (Grade B1).**
- 5 **The use of bortezomib is not routinely recommended as primary therapy outside the context of a clinical trial (Grade B2).**
- 6 **There is insufficient evidence to support the use of maintenance rituximab (Grade C2).**

8.3 Choice of therapy at relapse

The criteria for the reintroduction of treatment at relapse are broadly similar to those used at presentation. Treatment

should only be introduced when clinical symptoms develop and not at the time of progression, as defined by changes in paraprotein concentration. A caveat would be the reintroduction of treatment in patients with previous HVS in whom the symptomatic threshold is already known. Repeat bone marrow assessment is generally recommended prior to each therapy in order to determine the extent of marrow infiltration and reaffirm CD20 antigen expression, which may be lost in patients previously treated with rituximab. Patients with durable responses to their initial therapy may be retreated with the same regimen and some authors suggest a minimum response duration of 2 years in this context (Ansell *et al*, 2010). The choice of regimen at relapse includes regimens discussed in the primary therapy section. Decisions around treatment at relapse will depend on patient wishes, availability of clinical trials, duration of previous responses, tolerability to previous treatment, performance status, co-morbidities and potential for stem cell transplantation (SCT).

Bortezomib has been studied by a number of investigators in the relapsed setting. Initial studies evaluated bortezomib as a single agent in the conventional biweekly intravenous schedule and demonstrated a MRR of 44–60% but neurotoxicity was common. Additionally it was noted that some patients demonstrated a discrepancy between their IgM and lymph node/bone marrow responses (Dimopoulos *et al*, 2005; Chen *et al*, 2007; Treon *et al*, 2007). Subsequent studies have incorporated rituximab and have also given bortezomib in a weekly schedule. These schedules appear effective, with a MRR of approximately 50% and a lower incidence of neurotoxicity (Agathocleous *et al*, 2010; Ghobrial *et al*, 2010b). Additionally, the routine subcutaneous administration of bortezomib should reduce this risk further.

Treon *et al* (2011c) also evaluated the BR combination in patients with relapsed disease and demonstrated an ORR of 83% and an estimated PFS of 13 months. In this cohort, myelotoxicity was most significant in those patients previously treated with purine analogues (Treon *et al*, 2011c). Alemtuzumab has also been evaluated in WM, with one study demonstrating an ORR of 75% and MRR of 36% while the median time to progression was 16.8 months in responding patients (Treon *et al*, 2011d). Infectious complications including cytomegalovirus (CMV) reactivation were common while late onset immune thrombocytopenia was demonstrated in a significant minority of patients (Treon *et al*, 2011d).

The immunomodulatory drugs thalidomide and lenalidomide have, in conjunction with rituximab, been evaluated in small phase II studies. While clinical efficacy is evident their use appears limited by significant neurotoxicity with thalidomide and the development of significant anaemia in lenalidomide-treated patients (Treon *et al*, 2008, 2009c). Alternative anti-CD20 monoclonal antibodies, such as ofatumumab and obinutuzumab, are likely to have clinical

activity in WM but cannot be recommended outside of a clinical trial.

Recommendations

- 1 Repeat bone marrow aspirate and trephine assessment and CT scanning should be performed prior to the reintroduction of treatment (Grade B1).
- 2 Patients who remain asymptomatic despite serological evidence of progression can be observed until clinical symptoms occur (Grade A1).
- 3 Patients should receive a rituximab-containing regimen if CD20 is expressed. Appropriate regimens include FR, FCR, Clad-R, BR and DRC. The choice of regimen in individual patients will take into consideration performance status, clinical features including renal function, co-morbidities and potential candidacy for SCT (Grade B1).
- 4 Retreatment with primary therapy may be appropriate in some patients (Grade B1).
- 5 Bortezomib-containing regimens are suitable in the relapse setting. Weekly regimens are preferable, given the neurological toxicity associated with the biweekly schedules. Prophylaxis against herpes zoster virus (HZV) reactivation is recommended (Grade B1).
- 6 Alemtuzumab is a potential option in refractory disease (Grade B1). Surveillance for CMV reactivation is recommended.

8.4. Treatment for histological transformation

The natural history of patients who undergo histological transformation has not been formally established in WM but is anticipated to be poor given the experience in other B-cell disorders, such as CLL. Central to the management of patients with suspected transformation is detailed pathological evaluation, which should include the assessment of EBV in pathogenesis. In this context it should be noted that spontaneous resolution of EBV-related disorders can occur (Dojcinov *et al*, 2010, 2011; Owen *et al*, 2011). In line with recently published guidance in CLL (Oscier *et al*, 2012). WM patients with biopsy-proven DLBCL should receive intensive chemotherapy regimens used in patients with primary DLBCL. It is recognized that this approach may not be applicable in many patients and that palliation may be achieved with high-dose steroids or in some instances local radiotherapy. Younger patients who achieve satisfactory responses may be candidates for either autologous or allogeneic SCT and should be discussed with a transplant centre.

Recommendations

- 1 A diagnosis of transformation requires histological confirmation (Grade A1).

- 2 Patients who are suitable for intensive therapy should receive regimens currently employed for primary DLBCL (Grade B1).
- 3 Younger responding patients are candidates for a stem cell transplant procedure and should be discussed with a transplant centre (Grade B2).

9. Transplantation

Several studies, predominantly in the relapsed setting, have shown that autologous SCT (autoSCT) in WM is feasible, safe (5% 1-year non-relapse mortality), often leading to prolonged disease control but with no evidence of cure (Kyriakou *et al*, 2010a; Bachanova & Burns, 2012). Chemosensitivity at the time of transplant is the most important predictor of response and transplantation should be avoided in refractory disease. Only a selected minority of relapsed WM patients are suitable for autoSCT given the older median age, frequent comorbidities and the indolent nature of many patients' disease. Given the selective nature and small numbers of patients transplanted there are no data to support a survival benefit but it is expected to prolong PFS over conventional treatments with a reported median PFS of about 4 years and a 60% survival after 5 years (Kyriakou *et al*, 2010a; Gertz *et al*, 2012). Alkylating agents and purine analogues deplete stem cell numbers and therefore should be used cautiously or avoided in patients who are potential candidates for autoSCT (Bachanova & Burns, 2012). AutoSCT is felt to be most beneficial for younger, fitter patients with a chemosensitive relapse who have had a short duration of first remission (<2 years). Although autoSCT may be appropriate in the case of relapsed chemosensitive disease, there is a lack of evidence to indicate precise eligibility criteria, optimal timing and conditioning regimen (Bachanova & Burns, 2012). The frequency of longer term adverse effects, such as secondary malignancies (particularly myelodysplasia), are not known but clearly relevant for a disease with a long median survival.

There are limited data for allogeneic SCT (alloSCT) in WM but there is evidence for a graft-*versus*-WM effect with some patients having long-term disease control. Treatment-related mortality is significant at 23% for reduced-intensity conditioned (RIC) alloSCT compared to 33% with fully myeloablative conditioning. In the European Group for Blood and Marrow Transplantation series, the 5-year PFS was 45–50% and the OS 50–60% (Kyriakou *et al*, 2010b). Given the significant morbidity and mortality of the procedure, allogeneic transplantation can only be considered in selected younger, fitter patients with a good performance status and an aggressive but chemosensitive disease course. Given the age range of WM, it is likely that a RIC-alloSCT rather than a fully myeloablative procedure would be more appropriate except for the exceptionally young patient. There is insufficient data to indicate the optimal timing and conditioning regimen for alloSCT.

Recommendations

- 1 Autologous SCT is a feasible therapeutic option for relapsed WM in younger, fitter patients with aggressive disease (short PFS, histological transformation) (Grade B2).
- 2 Allogeneic SCT may be considered in selected younger patients with relapsed WM and aggressive clinical course (short PFS, histological transformation) (Grade B2).
- 3 Autologous and allogeneic SCT should only be performed in the setting of chemosensitive disease and at least a PR to reinduction therapy (Grade A1).

10. Hyperviscosity syndrome

The symptoms of hyperviscosity syndrome (HVS) include skin and mucosal bleeding, visual disturbance secondary to retinopathy, neurological symptoms and rarely cardiac failure (Stone, 2009; Stone & Bogen, 2012). Central to the diagnosis of HVS is the demonstration of central retinal changes by fundoscopy, which include retinal venous engorgement and retinal haemorrhages. It has been long established that there is not a linear relationship between PV and IgM concentration above a threshold level of approximately 30 g/l. Similarly it is also well established that the recorded PVs in patients with HVS vary considerably but remain constant in individual patients (Fahey *et al*, 1965). Knowledge of the symptomatic threshold for individual patients is extremely useful as it allows a meaningful discussion regarding the reintroduction of therapy before symptoms recur. The majority of studies have demonstrated that HVS rarely occurs below 4 centipoise (cP) but there is some data to suggest that peripheral retinal changes can occur at lower viscosities (Rosencranz & Bogen, 2006; Menke *et al*, 2009; Stone, 2009). The measurement of PV is a very useful adjunct to the clinical assessment of patients although it is recognized that it is not universally available in UK laboratories.

Therapeutic plasma exchange is highly effective at reducing PV, lowering IgM concentrations and reversing the clinical effects of HVS. This is primarily due to the fact that 80% of IgM is intravascular and estimates suggest that a 1-volume plasma exchange results in an approximately 40% reduction in IgM and 60% reduction in PV [see Johnson *et al* (2006) for references and recent guideline (Schwartz *et al*, 2013)]. Isovolumetric venesection is a potentially useful technique in emergency situations when access to formal plasma exchange is not readily available.

Although it is accepted that plasma exchange should largely be reserved for patients with HVS it is recognized that in certain circumstances plasma exchange may be warranted in asymptomatic individuals, such as those with multiple vascular co-morbidities. There is a risk of precipitating HVS with transfusion of red cells and so plasma exchange should be considered in patients with a high PV (PV >4cP) prior to transfusion of red cells. Similarly, there is anecdotal evidence

to support pre-operative exchange in some patients as it may improve wound healing and reduce the risk of venous thromboembolism. In patients not responding to, or too frail for disease-modifying treatment, ongoing plasma exchange may be useful to control HVS and improve quality of life.

Recommendation

- 1 Plasma exchange is recommended for all patients with HVS, irrespective of PV (Grade A1).
- 2 As per previous guidance, 1–2 procedures, exchanging 1–1.5 calculated plasma volumes, is advised (Grade A1).
- 3 Plasma exchange may be indicated in certain asymptomatic individuals, depending on the clinical circumstances, recorded plasma viscosities and co-morbidities (Grade C2).

11. IgM-related syndromes

11.1. Peripheral neuropathy

Neuropathies are particularly common in WM, being demonstrable in almost 50% of patients (Levine *et al*, 2006) and clinical neurological assessment should therefore be performed in all patients with IgM paraproteins. It should be recognized that not all neuropathies are directly attributable to the IgM and collaborative working with a neurologist is desirable to facilitate appropriate investigation and confirmation of any aetiological role for the IgM.

Peripheral neuropathy attributable to activity of the monoclonal IgM to MAG is a well recognized entity and the clinical presentation is typically one of unsteadiness, tremor and prominent vibratory sensory dysfunction but little motor involvement (Steck *et al*, 2006). Nerve conduction studies show a characteristic demyelinating pattern while high titre anti-MAG antibodies are typically demonstrable in the serum (Kaku *et al*, 1994; Kuijf *et al*, 2009). Conservative treatment approaches are often adequate as the neuropathy is only slowly progressive but anti-WM treatment may be indicated for patients with disabling or rapidly progressive symptoms (Joint Task Force of the European Federation of Neurological Societies & the Peripheral Nerve Society, 2010). Determining the most appropriate therapy is difficult given the limited evidence available as well as the fact that many clinical trials have utilized inadequate outcome measures (Merkies & Lauria, 2006). There are published data on rituximab, purine analogues and alkylating agents as well as on intravenous immunoglobulin and plasma exchange (Lunn & Nobile-Orazio, 2012). A pragmatic approach at this stage would be to apply a similar treatment algorithm to that used in patients with symptomatic WM and consider that rituximab, either alone or in combination, provides suitable treatment for those patients in whom chemotherapeutic intervention is considered appropriate. It should however be noted that the

anti-MAG titre has little or no value in determining the severity of the neuropathy and no value in determining response to therapy.

IgM reactivity to other neural antigens, including sulphatide, gangliosides and trisulphated heparin disaccharide, have been described in WM but their pathogenetic relevance remains unclear and specific treatment recommendations cannot be made. Other pathogenetic mechanisms for WM neuropathy include amyloidosis, cryoglobulinaemia and direct infiltration.

Recommendations

- 1 Neurological examination should be performed in all patients with an IgM paraprotein (Grade A1).**
- 2 Collaborative working with a neurologist is encouraged. Anti-MAG serology and nerve conduction studies are recommended in patients with symptomatic peripheral neuropathy (Grade A1).**
- 3 Chemotherapeutic intervention should be considered in those patients with disabling or rapidly progressive anti-MAG neuropathy (Grade B1).**
- 4 If chemotherapy is considered appropriate, a rituximab-containing regimen is appropriate with the final choice of regimen being determined by factors such as performance status, co-morbidities and renal function (Grade B1).**

11.2. Cold haemagglutinin disease

Cold haemagglutinin disease (CHAD) is a rare autoimmune haemolytic anaemia due to a cold reactive autoantibody typically directed against I/i red cell antigens, this antibody agglutinating red cells at low temperatures. It is considered to be a clonal B-cell lymphoproliferative disorder as the vast majority of patients will have an IgM paraprotein and many will fulfill the diagnostic criteria for WM (Berentsen, 2011). The clinical features include chronic anaemia and cold-induced symptoms such as acrocyanosis and Raynaud phenomenon.

Not all patients require treatment but those with symptomatic and transfusion-dependent anaemia and/or disabling cold-induced symptoms should be considered for therapeutic intervention. Treatment with corticosteroids, alkylating agents, azathioprine, interferon and splenectomy are largely ineffective (Berentsen, 2011). Two trials have demonstrated the efficacy of single agent rituximab (375 mg/m² weekly for 4 weeks) with ORRs of approximately 50% and a median duration of response of 11 months (Berentsen *et al*, 2004; Schollkopf *et al*, 2006). A recent study of fludarabine in combination with rituximab showed a response rate of 76% including 21% CR and an estimated median response duration of 66 months. Responses were also noted in patients refractory to single agent rituximab (Berentsen *et al*, 2010).

Recommendation

- 1 Rituximab-based therapy is recommended for patients with symptomatic CHAD. The addition of fludarabine should be considered for patients with adequate performance status and renal function (Grade B1).**

11.3. Cryoglobulinaemia

Cryoglobulins, immunoglobulins that precipitate on cooling, are demonstrable in approximately 1% of individuals with monoclonal proteins (Bryce *et al*, 2006). Type I cryoglobulins consist entirely of monoclonal immunoglobulin and very rarely have clinical sequelae. Type II cryoglobulins comprise a mix of monoclonal Ig, almost always of IgM kappa type and polyclonal IgG and typically have rheumatoid factor activity. All patients with type II cryoglobulinaemia have, by definition, a clonal B-cell disorder but overt WM is only demonstrable in a minority of patients. Underlying HCV infection is demonstrable in some patients. Type II cryoglobulinaemia is clinically characterized by purpura, cutaneous ulceration, peripheral neuropathy, arthralgia and glomerulonephritis (Bryce *et al*, 2006; Gertz, 2012; Terrier *et al*, 2012). There are limited published data on the treatment of patients with cryoglobulinaemia. Patients with proven HCV infection should be referred to a hepatologist for definitive treatment. Historically, most patients with symptomatic cryoglobulinaemia have received corticosteroids and/or alkylating agents but a recent multicentre study has suggested that rituximab (typically in the standard schedule of 375 mg/m² × 4 weeks) and corticosteroids provide better disease control (Terrier *et al*, 2012). It may also be appropriate to treat those patients with overt WM with standard immuno-chemotherapy regimens as detailed above.

Recommendations

- 1 Cryoglobulinaemia should be considered in patients with IgM monoclonal gammopathy and unexplained purpura, arthralgia, haematuria or peripheral neuropathy (Grade A1).**
- 2 Patients with cryoglobulinaemia should be screened for HCV infection (Grade A1).**
- 3 Patients with symptomatic cryoglobulinaemia may be treated with corticosteroids and rituximab (Grade B1).**
- 4 Patients with symptomatic cryoglobulinaemia and overt WM can be treated with standard therapies (Grade B1).**

11.4. Primary amyloidosis

Amyloidosis (AL) is a rare complication of IgM paraproteinemia. Several studies have suggested that amyloidosis occurs less frequently in patients with IgM paraproteins than with other monoclonal proteins, as it accounts for only 5–7% of

all cases of AL amyloidosis (Gertz *et al*, 1993; Wechalekar *et al*, 2008; Palladini *et al*, 2009). Given that IgM paraproteins may be demonstrable in many B-cell lymphoproliferative disorders, there is a clear need for detailed assessment of the underlying B-cell clone in IgM-associated amyloid as it may influence treatment decisions (Wechalekar *et al*, 2008).

12. Autoimmune cytopenias

Immune-mediated haemolytic anaemia of warm type, immune thrombocytopenia and red cell aplasia can all occur in WM patients. They may be presenting features or occur later in the disease course (Owen *et al*, 2001b; Aslan *et al*, 2006; Poulain *et al*, 2006; Treon *et al*, 2011d). Data from CLL suggests that these complications are less common with chemo-immunotherapy regimens than with single agent alkylators or purine analogues and the treatment algorithms proposed in the recent BCSH guidelines on CLL (Oscier *et al*, 2012) are broadly applicable in WM patients.

13. Supportive care

Infective complications are common in WM. They are more likely in patients with advanced disease, advanced age, multiple lines of therapy, refractory disease, severe neutropenia, hypogammaglobulinaemia and multiple comorbidities. Detailed guidance on antimicrobial prophylaxis and immunization is beyond the scope of this guideline and there is a lack of data specifically relating to WM. Given the similarities in supportive practices with CLL it is reasonable to follow the BCSH guidelines relating to supportive care of CLL patients that are listed below (see Oscier *et al*, 2012 for full details) with the caveat that there is a lack of specific evidence in WM.

Hypogammaglobulinaemia is frequently seen in WM and does not appear to correct despite adequate response to currently available therapies (Hunter *et al*, 2010). A minority of patients will have recurrent bacterial infection as a consequence of this and may be suitable for immunoglobulin replacement therapy according to UK Department of Health clinical guidelines (http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_085235).

In a recent large population-based study an increased risk of venous thromboembolism (VTE) was noted in patients with WM (Hultcrantz *et al*, 2012). The greatest risk was noted during the first year following diagnosis but an excess risk was also documented at 5 and 10 years. In contrast to myeloma, there was no apparent excess risk of arterial thrombosis. In addition, patients with IgM MGUS (in contrast to those with IgG and IgA MGUS) do not appear to be at greater risk of VTE nor arterial thrombosis (Kristinsson *et al*, 2010b; Hultcrantz *et al*, 2012). Further prospective data

is required before definitive statements on VTE prophylaxis can be made. This data should however be considered when WM patients encounter periods of additional risk, such as surgery.

Patients receiving purine analogues, alemtuzumab and bendamustine should receive irradiated blood products for life (Treleaven *et al*, 2011).

Recommendations

- 1 Antimicrobial prophylaxis should be considered for patients with hypogammaglobulinaemia who develop recurrent bacterial infections (Grade B1).
- 2 Immunoglobulin replacement therapy should be according to UK Department of Health clinical guidelines (Grade B1).
- 3 Anti-*Pneumocystis jirovecii* prophylaxis is recommended in patients requiring intensive and/or immunosuppressive treatment (Grade B1).
- 4 Anti-herpes simplex virus (HSV) and -HZV prophylaxis is recommended in patients requiring intensive, immunosuppressive or bortezomib-based therapy (Grade B1).
- 5 Pneumocystis and herpes prophylaxis is not routinely required in patients treated with alkylating agents or bendamustine (Grade B2).
- 6 The duration of anti-pneumocystis and herpes prophylaxis is controversial. Recommendations range from a minimum of 2 months post-therapy to awaiting a rise in CD4 count to $0.2 \times 10^9/l$ (Grade C2).
- 7 Vaccination against *Streptococcus pneumoniae* (using a conjugate vaccine) and *Haemophilus influenzae* type B (HIB) is encouraged at diagnosis although there is a lack of randomized trials to support vaccination. Patients who respond to vaccination and subsequently develop recurrent bacterial infections should be revaccinated if *S. pneumoniae* and HIB antibody levels have fallen (Grade C1).
- 8 Annual vaccination against seasonal influenza including novel strains is recommended (Grade C1).
- 9 Live vaccines, such as polio, herpes zoster and yellow fever, should be avoided (Grade A1).
- 10 Vaccinations should be avoided, if possible, 2 weeks prior to, during and for 6 months after chemo-immunotherapy (Grade B1).

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