Lymphoplasmacytic Lymphoma/
Waldenström’s Macroglobulinaemia
Guidelines

Approved by Pathway Board for Haematological Malignancies

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These guidelines should be read in conjunction with the latest National Cancer Drug Fund information, and all applicable national/international guidance.

The prescribing information in these guidelines is for health professionals only. It is not intended to replace consultation with the Haematology Consultant at the patient’s specialist centre. For information on cautions, contra-indications and side effects refer to the up-to-date prescribing information. While great care has been taken to see that the information in this section is accurate, the user is advised to check the doses and regimens carefully and if there is any uncertainty about the guidance provided, you should discuss your queries with a Haematology Consultant or Senior Pharmacist. No set of guidelines can cover all variations required for specific patient circumstances. It is the responsibility of the health care practitioners using them to adapt them for safe use within their institutions and for the individual needs of patients.
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1. INTRODUCTION

Waldenström’s macroglobulinaemia (WM) is a chronic B cell lymphoproliferative disorder characterised a classic pentad of features: an M protein on serum electrophoresis, confirmed to be IgM on immunofixation, bone marrow infiltration by lymphoplasmacytic lymphoma, a normocytic anaemia and, in some patients, evidence of hyperviscosity syndrome. Based on SEER data from the United States, the median age at diagnosis of 73 years with an overall annual age-adjusted incidence of 3.8/million persons, ranging from 0.3/million in those <50 years to 28.5/million in persons aged 80 or more. The incidence of WM is higher in men (5.4/million) than women (2.7/million) and in Caucasians (4.1/million) than African-Americans (1.8/million). In the United Kingdom, the annual incidence of the disease is 10.3 per million.

To date the disease remains incurable, but with a wider range of therapeutic options, such as the use of Purine Analogues, anti-CD20 monoclonal antibody therapy, Bendamustine, Bortezomib and the increasing use of high dose therapy with stem cell rescue in selected cases, and novel agents such as BTK and PI3K inhibitors, as well as a better understanding of the pathophysiology of the disease, the outlook for patients with the disease is improving. Recently, using whole genome sequencing, it has been found that >90% of patients with WM or non-IgM LPL have a common mutation, L265P in the myeloid differentiation primary response (MYD) 88 gene and 30% have a mutation in the CXCR4 gene. Somatic mutations in MYD88 and CXCR4 are important determinants of clinical presentation and impact overall survival in WM. Targeted therapies directed against MYD88 and/or CXCR4 signaling may provide a personalized treatment approach to WM in the future.

The most appropriate sequencing and combination of existing and newer therapies in different patients and employment of high dose therapy in first response remain contentious and under evaluation. Small molecules such as the BTK inhibitors and PI3K inhibitors are under evaluation and show promise. In addition, the clinical syndrome of WM presents a series of important clinical issues related to the properties of the IgM paraprotein; hence the detailed discussion of clinical manifestations and non-cytotoxic treatment approaches, including judicious use of interventions such as plasma exchange and blood transfusion.

The aim of treatment, particularly in elderly patients must be to improve duration and quality of life with minimal side effects. However, elderly patients should not miss out on effective novel agents simply due to their age, as a number of newer combinations are well tolerated as well as being effective. For younger patients, who are likely to tolerate more intense treatments, the objective is to prolong life using individualised treatment approaches. Further development and use of the prognostic scoring system for WM (IPSSWM) to guide therapy is a good objective. In doing so, the most appropriate use of newer therapies must be addressed, including the role of maintenance strategies, high dose therapy and utilising prognostic factors in the stratification of intensive treatment.

A characteristic feature of WM/LPL is the slow response to treatment compared to other lymphomas. This has implications for the time frames used for restaging the disease post treatment. The recognition of a good clinical and haematological response to therapy pending the appearance of an objective response by M-protein or degree of infiltration of the BM is important, to avoid premature switching to a new line of therapy. Being an indolent disease, a reduced frequency of drug administration often works just as well as the conventional schedule, with improved tolerance. In most patients a gradual response to treatment is most appropriate and often safer than an attempt to rush to the finishing line. In addition, our experience shows that formal restaging of patients with BM biopsy or cross-sectional imaging is better done at 6 months rather than 3 months after completion of therapy, in order to allow the full therapeutic effects to become apparent.

Ultimately, other than improving the well-being of patients, the judicious use of newer agents may improve progression-free and overall survival, and hence prove to be a cost-effective use of NHS resources in the longer term. Being a rare cancer, appropriate sign-posting to sources of support and information is important, so that patients can empower themselves with useful knowledge.

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## 2. Definition of Waldenström’s Macroglobulinaemia (WM)

The WHO classification of lymphoma considers WM to be a clinical syndrome occurring in most patients with a lymphoplasmacytic lymphoma (LPL), rather than a specific pathological diagnosis. Less than 5% of LPL is made up of IgA, IgG and non-secretory entities. The morphological, immunophenotypic and genetic features are shown below:

| Morphology | BM infiltration has an inter trabecular pattern with sparing of sinuses  
| A significant increase in mast cell numbers has been noted in BM biopsies; these cells over express CD40 ligand (CD154), which is a potent inducer of B cell expansion |
| Surface and/or cytoplasmic Ig (usually IgM)  
| B-cell associated antigens (CD19, CD20, CD22, CD79a)  
| CD25+, FMC7+, PAX5+, CD38+, BCL2+  
| CD10 and CD23 are generally absent, but CD23 may be expressed in 10-35% of cases  
| CD5 is expressed in 5-20% of cases; the presence of CD5 positivity does not rule out the diagnosis of WM |
| Ig heavy and light chains rearranged  
| Del 6q21 (BLIMP-1), found in 40-50% of patients, associated with a complex karyotype, hypoalbuminemia, high B2M levels.  
| MYD88 (myeloid differentiation primary response 88 gene) is found to have the L265P mutation in >90% of cases of WM and non-IgM LPL, a trigger for NFk-B signalling.  
| Mutations in the C terminus of CXCR4 are present in about 30% of patients  
| Treon et al genotyped lymphoplasmacytic cells from 175 WM patients and observed significantly higher bone marrow (BM) disease involvement, serum immunoglobulin-M levels, and symptomatic disease requiring therapy, including hyperviscosity syndrome in those patients with MYD88(L265P)CXCR4(WHIM/NS) mutations (P < .03). Patients with MYD88(L265P)CXCR4(WHIM/FS) or MYD88(L265P)CXCR4(WILDTYPE (WT)) had intermediate BM and serum immunoglobulin-M levels; those with MYD88(WT)CXCR4(WT) showed lowest BM disease burden. Fewer patients with MYD88(L265P) and CXCR4(WHIM/FS or NS) vs MYD88(L265P)CXCR4(WT) presented with adenopathy (P < .01), further delineating differences in disease tropism based on CXCR4 status.  
| <10% of patients have a 17p13 (TP53) deletion or 14q32 (IGH) translocations; Deletion of TP53 are associated with shorter progression-free survival (median 18.7 m versus 30 m without TP53 deletion; P=0.05), and with shorter disease-free survival (median 7.8 m versus 10.1 m without TP53 deletion; P=0.007). |
months versus 28.8 months without TP53 deletion; P=0.001)\(^{11}\)

### 3. Diagnosis & Differential Diagnosis

At present, there are no uniform criteria for diagnosing WM. The extent of BM infiltration required to make the diagnosis varies in reported series from 25-30%\(^{12,13}\). The minimum level of monoclonal IgM ranges from 5 to 30 g/l\(^{12,14}\).

The most widely used diagnostic criteria are:

- **Presence of monoclonal IgM > 30 g/l**
- **BM infiltration with small lymphocytes, plasmacytoid cells and plasma cells accounting for > 30% of nucleated cells, with the following immunophenotype:**
  - sIg\(^+\) (5:1 κ:λ ratio) CD19\(^+\)CD20\(^+\)CD23\(^-\)CD5\(^-\)CD10\(^-\)

A monoclonal IgM may be associated with a variety of disorders other than WM:

- **IgM-MGUS**: Patients with IgM <30 g/l, <10% clonal marrow cells, without anaemia, lymphadenopathy, hepatosplenomegaly and no requirement for chemotherapy for > 6 months.

- **Lymphoma**: Careful histological assessment and review of lymph node or other tissue biopsy is required to exclude other subtypes of lymphoma, including low-grade gastrointestinal MALT lymphoma with BM involvement and IgM production, splenic marginal zone lymphoma (CD22 & CD11c are overexpressed and CD103 may be positive) and nodal monocytoid B cell lymphoma.

- **B-CLL**: Usually characterised by a monoclonal B-lymphocytosis of > 5 x 10\(^9\)/l with co-expression of CD5, CD19, CD20 and CD23, weak surface immunoglobulin, weak/negative CD22 and negative FMC7.

- **Primary amyloidosis**: The deposition of monoclonal light chain as fibrillar amyloid deposits is a rare event in patients with WM. Clinical features and prognosis are similar to other patients with AL amyloidosis, except for a higher relative incidence of cardiac and pulmonary involvement. Confirmation of the diagnosis requires histological assessment and Congo red staining of affected organs or a screening tissue such as a rectal biopsy or fat pad aspirate.

- **IgM myeloma**: Osteolytic lesions and hypercalcaemia are suggestive of IgM myeloma, which follows a more aggressive course than typical WM. The malignant cell infiltrate is plasma cell rather than the admixture seen in WM. IgM-MM cells typically express CD38 and CD138, and are CD20 negative. IgH gene translocations are more common in IgM-MM especially t(11;14)(q13;q32)

- **Cold agglutinin disease**: Monoclonal IgM may possess cold agglutinin activity, i.e. it has specificity for red cell antigens at low temperatures (usually I/i) and causes a chronic haemolytic anaemia. This may be part of the WM clinical entity (10% of WM patients) or occur in the absence of a detectable lymphoproliferative disorder (idiopathic).
4. **CLINICAL FEATURES**

4.1 **RELATED TO THE IG M PARAPROTEIN**

The biological features of the monoclonal IgM often dominate the clinical manifestations:

<table>
<thead>
<tr>
<th>Properties of monoclonal IgM</th>
<th>Resulting condition</th>
<th>Clinical manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physicochemical:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viscosity</td>
<td>Hyperviscosity syndrome</td>
<td>Fatigue, headache, blurred vision, mucosal bleeding, impaired cognition, coma</td>
</tr>
<tr>
<td>Precipitation on cooling</td>
<td>Cryoglobulinaemia type I</td>
<td>Raynaud’s phenomenon, acrocyanosis, necrosis, ulcers, purpura, cold urticaria</td>
</tr>
<tr>
<td><strong>Protein-protein Interaction:</strong></td>
<td>Haemostatic abnormalities</td>
<td>Bruising, bleeding, purpura, mucosal bleeding</td>
</tr>
<tr>
<td><strong>Antibody activity against:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nerve constituents</td>
<td>Polyneuropathies</td>
<td>Anti-MAG (myelin-associated glycoprotein)-related: symmetrical, distal, progressive, sensorimotor neuropathy, ataxic gait, bilateral foot drop</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other specificities: symmetrical, distal, progressive painful sensory neuropathy or pure motor neurone disease</td>
</tr>
<tr>
<td>IgG</td>
<td>Cryoglobulinaemia type II mixed</td>
<td>Immune complex disorder causing weakness, purpura, arthralgias, proteinuria, renal failure, progressive, symmetrical distal sensorimotor neuropathy combined with mononeuropathies (e.g. foot drop)</td>
</tr>
<tr>
<td>Red cell antigens</td>
<td>Cold agglutinin haemolytic anaemia</td>
<td>Mild, chronic haemolytic anaemia exacerbated by exposure to cold temperatures, Raynaud’s phenomenon, acrocyanosis and livedo reticularis</td>
</tr>
<tr>
<td><strong>Tissue deposition:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amorphous aggregates in skin, GI tract, kidney</td>
<td>Specific organ dysfunction</td>
<td>Skin: bullous skin disease, papules on extremities GI tract: diarrhoea, malabsorption, bleeding Kidney: mild reversible proteinuria</td>
</tr>
<tr>
<td>Amyloid fibrils</td>
<td>AL amyloidosis</td>
<td>Fatigue, weight loss, periorbital purpura, oedema, hepatomegaly, macroglossia. Organ dysfunction, where affected: renal, cardiac, hepatic, peripheral and autonomic neuropathies.</td>
</tr>
</tbody>
</table>
### 4.2 RELATED TO BM INFILTRATION/ BULK DISEASE

Depending on the degree of marrow infiltration, patients may present with mild anaemia or with severe pancytopenia. Progressive anaemia is the most common indication for initiation of treatment. Approximately one third of patients present with lymphadenopathy, splenomegaly or hepatomegaly.

Rarely, WM may be complicated by:
- Lung involvement (masses, nodules, diffuse infiltration or pleural effusions, resulting in cough, dyspnoea and chest pain)
- Renal involvement (direct infiltration by LPL, or rarely renal or perirenal masses)
- GI involvement (the level of infiltration determines the nature of symptoms, which may include malabsorption, diarrhoea and bleeding)
- CNS involvement (infiltrates or tumours, such as the Bing-Neel syndrome, long-standing hyperviscosity altering vascular permeability and leading to perivascular malignant infiltration, characterised by confusion, memory loss, disorientation and motor dysfunction)
- Ocular involvement (infiltration of peri-orbital structures).
- AL amyloidosis (see Section 8.4.3)

### 5. INVESTIGATIONS AT DIAGNOSIS

<table>
<thead>
<tr>
<th>Test</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC</td>
<td></td>
</tr>
<tr>
<td>Blood film with cell markers as appropriate</td>
<td></td>
</tr>
<tr>
<td>Plasma viscosity (in symptomatic patients and if IgM &gt; 30g/l)</td>
<td></td>
</tr>
<tr>
<td>Direct antoglobulin test (and group and save serum where appropriate)</td>
<td></td>
</tr>
<tr>
<td>Cryoglobulins where appropriate (EDTA and serum samples, kept at 37°C and sent to Chemical Pathology immediately for analysis)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B, C serology, HIV</td>
<td></td>
</tr>
<tr>
<td>U &amp; E, creatinine, LFTs, calcium &amp; phosphate, urate</td>
<td></td>
</tr>
<tr>
<td>β2microglobulin (prognostic evaluation)</td>
<td></td>
</tr>
<tr>
<td>LDH (prognostic evaluation)</td>
<td></td>
</tr>
<tr>
<td>Immunoglobulins</td>
<td></td>
</tr>
<tr>
<td>Serum protein electrophoresis &amp; immunofixation</td>
<td>(to characterise the type of light and heavy chains)</td>
</tr>
<tr>
<td>B12, Folate (to exclude concurrent deficiencies)</td>
<td></td>
</tr>
<tr>
<td>Iron Studies (see Section 7)</td>
<td></td>
</tr>
<tr>
<td>Urine protein excretion and Bence-Jones protein (40-80% have detectable BJP)</td>
<td></td>
</tr>
<tr>
<td>Serum free light chains (prognostic evaluation)</td>
<td></td>
</tr>
<tr>
<td>Bone marrow aspirate and trephine biopsy with immunophenotyping and molecular diagnostics, (optional)</td>
<td></td>
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<tr>
<td>Lymph node or tissue biopsy where appropriate with immunohistochemistry</td>
<td></td>
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<tr>
<td>CT scan: thorax, abdomen and pelvis as well as other sites as indicated</td>
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<tr>
<td>PET-CT may be used in cases of suspected high grade transformation</td>
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</table>
6. IPSSWM and Prognosis

IPSSWM: It is clear from clinical trials and other observations, that WM is a disease that can vary greatly between individuals. To address this question, Morel et al.\textsuperscript{16} looked at various parameters in a series of 587 WM patients that may identify factors that may be predictive of a poorer response to treatment or a shorter remission. These factors were incorporated into the International Prognostic Scoring System for WM (IPSSWM). The IPSSWM was based on analysis of the outcome of initial therapy in symptomatic patients treated with an alkylating agent (63%) or purine analogue (33%) or Rituximab (4%) as first-line therapy. Notably, few patients in this analysis received Rituximab.

The following prognostic factors stand out as being relevant \textit{at the time of the initiation of treatment}:

<table>
<thead>
<tr>
<th>Prognostic Factors</th>
<th>LOW RISK: ≤1 adverse characteristic and age ≤65</th>
<th>INTERMEDIATE RISK: 2 adverse characteristics or &gt; 65 years</th>
<th>HIGH RISK: &gt; 2 adverse characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt; 65 years</td>
<td>27% of patients</td>
<td>38% of patients</td>
<td>35% of patients</td>
</tr>
<tr>
<td>β2-microglobulin &gt; 3g/l</td>
<td>87% 5-yr survival rate</td>
<td>68% 5-yr survival rate</td>
<td>36% 5-yr survival rate</td>
</tr>
<tr>
<td>M-protein &gt; 70 g/l</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb &lt; 11.5 g/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets &lt; 100 x 10^9/l</td>
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</tbody>
</table>

The importance of a prognostic system for the risk stratification of patients with WM and as a tool for study comparisons is important. Results by IPSSWM risk category are increasingly reported and are used for stratification in randomised clinical trials. However, the use of IPSSWM in making treatment decisions remains to be delineated.

Clinical Benefit of treatment and Survival: Patients with minor responses as defined by a reduction of M protein of 25-50% may do just as well as those who have an objective (>50%) response. The recognition of clinical benefit to patients is important in the overall outcome of therapeutic intervention\textsuperscript{17}. Other pertinent features of the disease in assessing outcomes include the characteristically slow response to therapy; up to a fifth of patients may not achieve maximal response for 6 months following completion of therapy. Thus, an underestimation of the true benefit of a drug may occur.

The median survival for patients with WM/LPL is at least 7 years based on various reports. Given the median age of onset of 73 years, co-morbidities are common and it has been calculated that the disease-specific mortality is closer to 12 years\textsuperscript{18,19}. The most common causes of death in WM patients are progression of the lymphoproliferative process, infections and cardiac failure\textsuperscript{14}. In the preterminal stage of the disease, the development of aggressive large cell lymphomas, usually of the immunoblastic type (Richter’s syndrome) have been reported in 6% of patients treated for WM\textsuperscript{20}. 

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7. INDICATIONS FOR INITIATION OF THERAPY

Only patients with symptoms due to the disease need treatment. Those with ‘asymptomatic’ or ‘smouldering’ WM should be monitored every 3-6 months without treatment until treatment is needed. In such patients, the median time from diagnosis to needing treatment is 4.6 years and the risk of progression is 12% per year for first 5 years then 2% per year for the next 5 years. There is no evidence to suggest that patients with smouldering WM benefit from early treatment. Acceptable reasons to start treatment include symptoms due to the disease such as weight loss, progressive fatigue, low blood counts due to bone marrow inadequacy, recurrent infections due to disease-related immune suppression, or paraprotein-related problems such as hyperviscosity or peripheral neuropathy. In addition, there is increasing recognition that a disease-mediated iron utilization defect may occur in some patients. These patients appear to have symptomatic anaemia that is out of keeping with the burden of disease in the BM. Such patients may respond to parenteral iron replacement with a deferral of the need for chemotherapy.21

7.1 Indications Related to paraprotein

- Hyperviscosity syndrome (Section 8.1)
- Cold agglutinin disease (Section 8.2)
- Cryoglobulinaemia (Section 8.2)
- Autoimmune cytopenias (Section 8.3)
- Peripheral neuropathy (Section 8.4)
- Amyloidosis (Section 8.4.3)

7.2 Indications Related to the lymphoma

- Symptomatic BM failure (Guide: Hb< 10 g/dl, neutrophils < 1.5, platelets < 100)
- Bulky/Progressive lymphadenopathy +/- critical organ impingement
- Bulky/Progressive hepatosplenomegaly +/- hypersplenism
- Fever, night sweats, weight loss

7.3 Iron deficiency anaemia in Waldenströms: Consideration of parenteral iron replacement

- Anaemia often prompts therapy in WM, although is not fully explained by bone marrow disease involvement in many patients.
- Hepcidin regulates gut absorption and distribution of iron and is elevated and associated with anaemia in WM.
- An iron reutilisation defect appears to occur in many patients with WM, wherein anaemia results in part from an inadequate release of iron from reticuloendothelial cells despite adequate iron stores.
- For patients with low disease burden, and for whom only symptomatic anaemia is present with low iron saturation level (<10-12%) unexplained by GI blood loss, it is worth considering a trial of parenteral iron first, then if unresponsive move on to chemotherapy.
- Consider a GI workup, for possible sources of Fe loss, depending on clinical findings and likelihood that it is GI vs. WM.
8. **IGM-INDUCED COMPLICATIONS**

8.1 **Hyperviscosity Syndrome**

Symptoms of hyperviscosity develop in some patients when plasma viscosity (PV) exceeds 4 mPa and nearly all when it reaches 10 mPa. Each patient should be carefully assessed for symptoms such as headache, lethargy, confusion, irrational behaviour, visual disturbance, or effects of vascular occlusion, such as seizures, strokes or cardiac ischaemia (angina or congestive cardiac failure). Bleeding manifestations include gum and nosebleeds. Fundoscopic examination is mandatory in all patients in whom HVS is suspected, since retinal changes may be the earliest diagnostic feature. Congested, tortuous retinal veins show sausage-like segmentation, microaneurysms, haemorrhages or exudates as the PV rises.

Plasmapheresis is indicated for

- symptomatic patients irrespective of their PV
- asymptomatic patients with a PV > 5.5 mPa

It should also be considered in asymptomatic patients where the vascular risk is thought to be significant (patients with coronary artery disease, cerebrovascular disease, peripheral vascular disease, and prior or current venous thromboembolic disease) irrespective of the PV. In patients with anaemia that requires transfusion, hyperviscosity may become significant, necessitating prior plasmapheresis with pre and post measurement of PV. In an emergency, pending the commencement of plasmapheresis, a therapeutic venesection may be required, with simultaneous replacement of normal saline or packed red cells, depending on the degree of anaemia that is present. A single plasma exchange can result in a reduction in IgM level of 35% with a decrease in the PV of 50-60%22. Since 80% of IgM is intravascular, the benefit may last for 4-6 weeks. Plasmapheresis is conducted with a continuous blood flow separator with albumin and saline replacement. Plasmapheresis is a bridge to therapy.

8.2 **Cryoglobulinaemia & Cold Agglutinin Disease (CAD)**

Cryoglobulins are antibodies that undergo reversible precipitation at low temperatures. When this occurs, they cause plugging and thrombosis of small arteries and capillaries in the extremities (gangrene) and glomeruli (acute renal failure). This may lead to problems ranging from skin rashes to kidney failure. Circulating large–molecular-weight cryoprotein complexes, even when unprecipitated in vivo, can lead to clinical hyperviscosity syndrome. Cutaneous manifestations include erythematous macules and purpuric papules and ulcerations, livedo reticularis, and Raynaud phenomenon.

There are three main types of the disorder, grouped based on the type of antibody that is produced:

- Cryoglobulinaemia type I
- Cryoglobulinaemia type II
- Cryoglobulinaemia type III

Types II and III are also referred to as mixed cryoglobulinaemia, most often found in people who have a chronic inflammatory condition, such as an autoimmune disease or hepatitis C. Type I cryoglobulinaemia is most often related to cancer of the blood or immune systems.

**TREATMENT:**

- Patients with symptomatic cryoglobulinaemia (such as acrocyanosis, Raynaud’s phenomenon, vasculitis, progressive neuropathy or evidence of glomerulonephritis) may require an intensive series of plasma exchanges, (3 exchanges in one week of each month, particularly during the cold season) in conjunction with Corticosteroids, Cyclophosphamide or Azathioprine to achieve long-term control.
- Patients with hepatitis C associated cryoglobulinaemia should receive appropriate anti-viral measures.
- Cytotoxic medications or corticosteroids may need to be continued to beyond plasma exchange to reduce the risk of rebound.
- It is important to counsel patients to keep warm and wear appropriate clothing.

**CAD** is rare, accounting for 15% of AIHA cases with an incidence of 1 per million people per year23. In 90% of patients CAD is an IgM–mediated process, with rare findings of monoclonal IgG, IgA, or I light chain restriction, whereas warm AIHA is predominantly an IgG-driven disease. The term “cold agglutinin” refers to the finding of agglutination without
antiglobulin antisera in microtitre wells at 4°C. This occurs because IgM is a 1-million-Da molecule capable of spanning the distance between RBCs and overcoming the natural repulsive forces between cells, thus allowing spontaneous in vitro agglutination. In the body core, circulating IgM remains unbound but, as blood shifts toward the cooler peripheral circulation, IgM transiently binds the RBC membrane. Once bound, the IgM molecule activates the complement cascade, binding C3b to the cell surface. As C3b-coated cells return toward the body core, IgM dissociates. C3b-coated cells subsequently lose surface membrane by receptor-specific macrophages present predominantly in the liver (but also to a lesser degree in the spleen), resulting in extravascular haemolysis and perhaps some degree of intravascular haemolysis. The severity of haemolysis depends on the thermal amplitude, rather than the serum concentration of IgM.

Cold agglutinin–mediated haemolysis occurs chronically with resulting anaemia of varying severity, ranging from Hb levels of 8 g/dL and 4.5 g/dL. More than 50% of patients require transfusions, and therapy was considered necessary in 70%. Fatal complications have been reported, with exacerbations of haemolysis triggered by febrile illness, trauma, or surgery. In addition to haemolysis, clinical manifestations include cold-induced circulatory symptoms; livedo reticularis, Raynaud disease, acrocyanosis and, rarely, cutaneous necrosis. Haemoglobinuria tends to be less severe than that seen in paroxysmal cold haemoglobinuria or warm AIHA.

The diagnosis of CAD is established with haemolytic anaemia, reticulocytosis, hyperbilirubinaemia, elevated LDH, and positive Coombs testing for anti-C3 and classically negative anti-IgG.

TREATMENT: Non-pharmacological measures are crucial in the management of CAD, including avoidance of cold exposure, increasing use of warm clothing, and possibly relocating to warm regions. Supportive transfusions may be used in patients with severe anaemia. An in-line blood warmer should be considered to minimize cold agglutinin binding to transfused red cells.

Recurrent episodes of haemolysis unresponsive to non-pharmacological measures merit therapy aimed at suppressing production of the monoclonal IgM protein. Treatments have included corticosteroids, alkylating agents, and purine analogues. Case series of corticosteroid therapy in CAD report response rates no greater than 14%. The need for high doses of corticosteroids limits their viability in the long-term. Alkylating agents produce a poor clinical response and require long term exposure, with clinically significant adverse effects in those who respond. Cladribine has been used and is not efficacious. Although appropriate in refractory warm AIHA, splenectomy should not be used to treat CAD because haemolysis occurs outside the spleen.

Rituximab has been used to treat CAD. Trials of rituximab at a weekly dose of 375 mg/m2 for 4 weeks report response rates of 45% to 58%, with only rare complete responses. Sustained remission is unlikely, and 57% to 89% of responding patients eventually relapse. Therapy with fludarabine and rituximab has been evaluated in CAD. A trial of 29 patients, 10 of whom were unresponsive to rituximab monotherapy, showed a response rate of 76%. Among those refractory to rituximab monotherapy, the response rate was 70%. Eculizumab is a monoclonal antibody used to treat paroxysmal nocturnal haemoglobinuria; it binds to complement protein C5, inhibiting formation of the terminal complement complex. Two case reports described eculizumab use in patients with transfusion-dependent CAD that was refractory to rituximab. Both patients responded to eculizumab alone and achieved transfusion independence. One report described improvement in CAD after treatment with bortezomib.

8.3 AUTOIMMUNE CYTOPENIAS

Depending on the rate of onset and degree of cytopenia, high dose steroids (Prednisolone 1 mg/kg/day with H2 antagonist or PPI, where indicated) in addition to a programme of plasmapheresis and systemic chemotherapy may be indicated. The use of Rituximab may be of benefit in this situation, providing a cytoreductive effect as well as counteracting the autoimmune process. An active autoimmune process is an absolute contraindication to the use of Purine Analogues (especially Fludarabine). The use of Purine Analogues in the presence of a positive DAT without concurrent haemolysis may be undertaken, but with caution and close monitoring. It is worth noting that autoimmune haemolysis has been noted to occur several months after completion of Cladribine therapy.

8.4 IgM-ASSOCIATED PERIPHERAL NEUROPATHIES
Peripheral neuropathies have been reported in 30-70% of patients with IgM-MGUS or WM and may present in varying ways:

- **Chronic inflammatory demyelinating polyneuropathy (CIDP)** is an immune-mediated acquired characterized by an autoimmune activity against peripheral nervous system myelin, by cellular and humoral mechanisms
- **Anti-MAG associated neuropathy**, a neuropathy associated with autoantibodies to myelin-associated glycoprotein (a constituent of normal PN myelin)
- **Amyloidosis** is rare in this context but can develop at any time in a patient with IgM monoclonal gammopathy.

The main features of these disorders are shown below:

### 8.4.1 Anti-MAG NEUROPATHY

#### Anti-MAG Neuropathy

The myelin-associated glycoprotein (MAG) is a transmembrane glycoprotein which is localized in periaxonal Schwann cells and oligodendroglial membranes of myelin sheaths. High titres of IgM anti-MAG antibodies are associated with sensory motor demyelinating peripheral neuropathy. Sensory symptoms tend to dominate early in disease, with motor symptoms occurring later. The possibility of MAG antibody involvement in a suspected neuropathy may be effectively ruled out if a MAG IgM negative result is obtained. High titres of anti-MAG IgM antibodies occur in almost 50% of patients with a IgM paraproteinaemic demyelinating neuropathy (PDN).

Therefore, testing for antibodies to MAG should be considered in patients with an IgM PDN. Patients with sensory neuropathy may have MAG antibodies at low titres.

**NCS:** Absent or reduced sensory action potentials (SAP), reduced motor conduction velocities with a characteristic prolongation of the distal motor latency (DML) due to the greater degree of distal slowing

**CSF** protein is raised in >80% cases

Discuss the need for nerve biopsy with neurologist

#### Treatment

- Indicated if the neuropathy is having a progressive functional impact
- Avoid/minimise neurotoxic agents, such as cytotoxic drugs, alcohol; improve diabetic control if poor

#### Options

- Plasma exchange temporarily effective in 50% cases
- Plasma exchange + CBL no more effective
- Steroids effective in 50%
- IVIG may have limited effect (as measured by NCS > functional perspective)
- **Rituximab:** RCT in 26 patients - R 375 mg/m2 (x 4) vs. placebo
  - In intention-to-treat analysis, the results failed to reach significance
  - B cell depletion for 6 months, 34% reduction in IgM levels, and 50% reduction in anti-MAG titres
  - There was a sustained benefit over 12 months; R was well tolerated

**RiMAG Study:**

- The preliminary results of another randomized controlled trial with Rituximab on 54 patients with anti-MAG neuropathy showed no significant difference in the primary outcome (mean change in sensory score) but there was a 20% absolute difference in the treated patients compared to placebo in the improvement in the Hughes disability scale (20% versus 0%) and in the self-evaluation scale (26% versus 4%) suggesting some functional benefit.

- Both randomized studies showed a 20 to 30% absolute improvement of Rituximab compared to placebo, indicating that we probably have to treat three to four patients to improve one patient.

**Patients with progressive anti-MAG neuropathies will be considered for Rituximab therapy following review in the Joint Neuropathy Clinic.**
### 8.4.2 CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

**Chronic inflammatory demyelinating polyneuropathy**

A typical clinical and electrophysiological presentation of CIDP may accompany IgG, IgM or IgA MGUS. Typically symmetrical proximal and distal weakness of all 4 limbs with sensory involvement and areflexia. Tends to be relapsing or chronically progressive. It has an autoimmune basis. Demyelination affects intermediate rather than distal segments. Raised CSF protein in seen in 70% cases. Nerve biopsy may show features of macrophage-mediated demyelination.

<table>
<thead>
<tr>
<th>Treatment not always necessary: some patients stabilise</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Main treatment options: Steroids, IVIG, plasma exchange</td>
</tr>
<tr>
<td>• 80% of patients respond to one of these options</td>
</tr>
</tbody>
</table>

### 8.4.3 AL AMYLOIDOSIS

**AL Amyloidosis**

• Co-existence of MGUS with axonal neuropathy should raise the possibility of amyloidosis especially if red flag signs are present: pain, weight loss, macroglossia, organomegaly, cardiomegaly
• 20% of patients with systemic AL amyloidosis present with neuropathy
• Mostly symptomatic in the distal lower limbs, predominantly sensory of small fibre and painful type
• Autonomic dysfunction is frequent
• Nerve biopsy is positive in most cases with a clinically symptomatic PN but SAP does not detect peripheral nerve amyloid
• MGUS does not necessarily imply a definite diagnosis of AL amyloidosis- MGUS can be found in 25% of genetic amyloid
• Prognosis is poor with a median OS <18 months despite treatment
• According to the Mayo Clinic experience, IgM patients are older, have a higher prevalence of neuropathy, a lower incidence of cardiac involvement (lower troponin T and NT-proBNP), and a much lower level of the involved immunoglobulin free light chain
• The Royal Free group has reported on the outcomes of 103 consecutive patients with IgM-associated AL amyloidosis. Median age was 65 years (range 46-88), median IgM paraprotein level was 8g/l (range 1F-60), the k:λ ratio was approximately 50:50, with an abnormal SFLC ratio in 88% of patients. There was renal, cardiac and lymph node involvement in 53%, 35% and 21% respectively at presentation and 2 or more organs were involved in 54% of patients. rmal SFLC ratio in 88% of patients.

**TREATMENT**

• Combination alkylator-based or purine analogue-based regimens produced higher responses compared to oral agents, but the numbers were too small to draw absolute conclusions.
• Median overall survival was 49 months.
• Treatment of these patients is complicated by the elderly age and organ involvement.
• Suspected patients should be evaluated at the National Amyloidosis Centre at The Royal Free Hospital.

### 8.5 CNS INVOLVEMENT - BING-NEEL SYNDROME

• BN syndrome is a very rare complication of WM that should be considered in patients with neurological symptoms and a history of WM. The central nervous system (CNS) manifestations of Waldenström’s macroglobulinaemia (WM) are known as the Bing-Neel syndrome (BNS). Patients with BNS can be classified into...
Group A and Group B based on the presence of lymphoplasmacytoid cells within the brain parenchyma, leptomeninges, dura, and/or cerebrospinal fluid (CSF)\(^\text{29}\).

- CNS manifestations (symptoms/signs) are related to the anatomical distribution of CNS involvement.
- When suspected, appropriate neurological testing e.g. imaging studies of affected areas of the central neuraxis, electrophysiological studies and CSF examination for a high CSF protein and cytology is important.
- **CSF analysis** may show lymphocytic pleocytosis, elevated protein, and IgM kappa or lambda light chain restriction; cytology results are variable.
- **Imaging** is frequently abnormal. Biopsy confirms the diagnosis.
- **Treatment data are limited**, but responses are seen with radiation and/or chemotherapy\(^\text{30}\). Treatment should be initiated as responses do occur that may improve quality of life and extend it when limited or no active systemic disease is present.
- At UCLH, the **IDARAM\(^\text{31}\)** regimen has been used successfully in cases of Bing-Neel Syndrome.

- Refer for a neurology opinion if a progressive and/or atypical paraproteinaemic-associated neuropathy or Bing-Neel syndrome is suspected.

**JOINT CLINICS:**
- Shirley D’Sa, Mary Reilly & Michael Lunn (Specialists in Peripheral Neuropathies at the National Hospital for Neurological Diseases, Queen Square) hold a Joint Neuropathy Clinic quarterly at NHNN.
- Michael Lunn & Shirley D’Sa additionally hold a Joint POEMS & Neuropathy Clinic at the UCH Macmillan Cancer Centre or NHNN on a monthly basis
- To refer patients, contact Ysabel Howard, PA to Shirley D’Sa 0203 4567890 x78028 or Ysabel.Howard@UCLH.NHS.UK
8.6 Response Assessment (with thanks to Roger Owen for this section)

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 the M protein is difficult 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 and this should not be overlooked during the course of assessment of response.

- **Increasing incidence of high quality categorical responses with newer combinations** – CR 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.

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### Response (abbreviation) (Third International WM Workshop Criteria6)

- **Complete response (CR)-** Disappearance of monoclonal protein by serum electrophoresis, no histologic evidence of bone marrow involvement, resolution of any adenopathy/organomegaly, or signs no symptoms attributable to Waldenström’s macroglobulinaemia

- **Partial response (PR)-** At least 50% reduction of serum monoclonal IgM concentration on protein electrophoresis and at least 50% decrease in adenopathy/organomegaly; no new symptoms or signs of active disease

- **Minor response (MR)-** At least 25%, but less than 50%, reduction of serum monoclonal IgM by protein electrophoresis; no new symptoms or signs of active disease

- **Stable disease (SD)-** A less than 25% reduction and a less than 25% increase of serum monoclonal IgM by electrophoresis, without progression of adenopathy/organomegaly, cytopenias, or clinically significant symptoms due to disease and/or signs of Waldenström’s macroglobulinaemia

- **Progressive disease (PD)-** At least 25% increase in serum monoclonal IgM by protein electrophoresis, confirmed by second measurement or progression of clinically significant findings due to disease or symptoms attributable to Waldenström’s macroglobulinaemia
9. Initial Treatment Options

Individual patient considerations should be weighed for the choice of therapy, including the need for rapid disease control, age, candidacy for autologous transplantation, co-morbidities, presence of cytopenias, hyperviscosity, lymphadenopathy, IgM-related end-organ damage and patients’ preferences. Recently published treatment recommendations from the 7th International Workshop on WM have stated that DRC remains a primary choice but, combinations such as R-CHOP are no longer considered a first line choice; instead Bendamustine-rituximab (BR) is now a primary treatment option, especially for patients with high tumour bulk. This concurs with the BCSH guidelines.

9.1 Chlorambucil

Chlorambucil (CBL) with or without prednisolone: This has been the mainstay of treatment for patients with symptomatic WM, producing remissions in 50-75% of patients. Responses are usually slow and toxicity minimal if the dose is adjusted for cytopenias. Cyclophosphamide alone or in combination with Prednisolone is also effective but there are no comparative data with CBL. The two main considerations in using CBL include the relatively slow response to treatment, and the stem cell toxicity of this agent in patients who are potential candidates for autologous stem cell transplantation.

The randomized WM1 study (Chlorambucil vs Fludarabine) enrolled 414 eligible patients; on the basis of intent-to-treat analysis, the ORR was 47.8% in the fludarabine arm versus 38.6% in the chlorambucil arm (P = .07). With a median follow-up of 36 months, median PFS, and duration of response (DR) were significantly improved in the fludarabine arm: PFS, 36.3 versus 27.1 months (P = .012) and DR, 38.3 versus 19.9 months (P < .001) and median overall survival (OS) was not reached in the fludarabine arm versus 69.8 months in the chlorambucil arm (95% CI, 61.6 to 79.8 months; P = .014). Grade 3 to 4 neutropenia was significantly higher among patients treated with fludarabine and second malignancies were significantly more frequent in the chlorambucil arm with 6-year cumulative incidence rate of 20.6% versus 3.7% in the fludarabine arm (P = .001). Despite this robust phase III data, the adoption of Fludarabine as standard 1st line therapy for patients with newly diagnosed WM has major limitations. The addition of Rituximab to the treatment of patients with WM has become a standard of care with enhanced responses when combined with purine analogues and Alkylators, without additional toxicity and other agents are showing considerable promise, including Bortezomib and Bendamustine. Nevertheless, this study serves as a useful benchmark for future phase III trials to test novel treatment approaches.

9.2 Alkylators/ Bendamustine and Rituximab

9.2.1 Rituximab

Standard dose (375 mg/m² weekly for 4 weeks) Rituximab produces major responses in 27-35% of previously treated and untreated patients. In some studies, even those who achieved minor responses or stable disease benefited from the cytoreduction achieved in terms of better blood counts and reduction of bulky disease. The median time to treatment failure ranged from 8 to 27 months. Both response rates and response duration can be improved by an extended Rituximab schedule (two 4-weekly courses of 375 mg/m² given 3 months apart).

Time to response after Rituximab is slow, exceeding 3 months on average. A baseline IgM paraprotein level of > 40 g/l, serum albumin <35 g/l and the presence of a λ light chain has been associated with an inferior response. The impact on duration of response for extended over standard-dose Rituximab therapy remains to be clarified, as does the role of maintenance Rituximab. A flare of the serum PP (mechanism remains obscure) in patients with WM who receive Rituximab as a single agent has been well described, but usually subsides within 12 weeks of therapy. This phenomenon is most likely to occur in patients with symptomatic hyperviscosity and/or levels IgM > 40g/l; therefore use Rituximab with caution in these patients; pre-emptive plasmapheresis may be indicated. In the event that the PP rise does not subside or other signs of progressive or persistent disease remain, formal restaging would be indicated before considering further treatment options. Rituximab monotherapy should not be used in patients with symptomatic hyperviscosity. The administration of concurrent chemotherapy may avert the PP flare.
9.2.2 R-CHOP
The addition of Rituximab to CHOP has proved to be superior to CHOP alone in WM patients. A 94% overall response rate with R-CHOP versus 69% for CHOP alone as first-line therapy in a randomised study of 72 patients with WM has been demonstrated, with a significantly prolonged time to treatment failure in the R-CHOP arm, but no increase in toxicity. The use of R-CHOP as up-front therapy for WM is not recommended except for suspected or confirmed (where possible by biopsy) high grade transformation.

9.2.3 R-BENDAMUSTINE
Rummel et al have demonstrated that this regimen produces an increased quality and duration of response compared to R-CHOP. The dose of Bendamustine was 90mg/m² on D1 and 2 every 28 days for 6 cycles with Rituximab given at 375mg/m² with each cycle. In the trial, 514 patients with previously untreated indolent lymphoma were treated including 44 with WM/LPL. BR was better tolerated: no alopecia, less myelotoxicity, fewer infections, less PN and stomatitis. With regard to second primary malignancies, 20 were reported in the BR arm, (including 1 MDS) vs. 23 in R-CHOP arm (including 1 AML). Responses were similar (95% in both arms), but BR was superior in terms of progression-free survival (PFS; median, 69.5 vs 28.1 months; P = .0033) and tolerability. After a median follow-up of 45 months, a difference in overall survival was observed after the fifth year, but further follow-up is needed. Regarding stem cell harvest, after 6 cycles of BR, the CD34 yield was similar to that after R-CHOP.

As part of a large study investigating rituximab maintenance in patients with previously untreated low-grade lymphomas (including WM), BR induction was given in 162 patients with WM (116 were evaluable for response), and 86% achieved at least partial response (PR). Responding patients (at least PR) were randomized to either observation or 2 years of rituximab maintenance; updated results are awaited.

Bendamustine is also active in patients with relapsed or refractory WM, either with rituximab, Ofatumumab, or as monotherapy (very good partial response [VGPR] in 17%, PR in 67%; median PFS, 13.2 months), but prior purine analogue exposure was associated with prolonged myelosuppression.

Thus, available data indicate that BR is at least as effective as R-CHOP, may be associated with longer PFS and less toxicity, and probably does not compromise stem cell collection. However, R-CHOP is not a standard first-line regimen for WM; less intensive and less toxic regimens like DRC are more often used. No increased incidence of secondary malignancies after BR was observed but longer follow-up is needed. BR is a primary option for patients with newly diagnosed WM, especially those in need for rapid disease control or with bulky disease.

9.2.4 DRC
Dimopoulos et al have reported on 72 previously untreated patients who received Dexamethasone 20 mg iv on day 1, Rituximab 375 mg/m² on day 1 and Cyclophosphamide 100 mg/m² bd orally on days 1-5 given on a 21 day cycle for 6 courses. An objective response (> 50% reduction in PP) was seen in 83% of patients including 7% with CR, 67% with PR and 9% with MR. The median time to response was 4.1 months and the 2 year progression-free survival rate was 90%. Only 9% of patients experienced grade 3 or 4 haematological toxicity. It is not toxic to stem cells, so can be used prior to stem cell transplantation.

Dimopoulos et al updated the results of the DRC regimen phase 3 study with a minimum follow-up of >6 years. Median PFS was 35 months, and median time to next treatment was 51 months. Forty patients received second-line treatment, 28 (70%) patients were retreated with either rituximab alone or rituximab-based regimens, and 82% achieved at least MR. Thirty-five (49%) patients died (including 15 patients from unrelated causes). One patient, who received further therapy with fludarabine, developed myelodysplastic syndrome, and 2 patients developed diffuse large B-cell lymphoma. Five-year OS was 62%, and median OS was 95 months.

9.2.5 RITUXIMAB MAINTENANCE
This approach has been rigorously assessed in the setting of follicular lymphoma, including extended treatment with Rituximab every two months for up to two years. This was found to almost halve the risk of relapse after three years, compared with the routine practice of observation alone. Importantly, the maintenance approach is not unduly problematic in terms of on-going side effects or impact on quality of life.
WM shares many parallels with follicular lymphoma, but is a distinct disease entity. Treon et al analysed 248 WM patients who had received Rituximab + chemotherapy, of which 35% went on to receive maintenance Rituximab\(^\text{47}\). There was a significant improvement in the median PFS of 56.3 months in the maintenance group vs. 28.6 months in those who did not receive maintenance. In addition, lower IgM levels were seen and deeper remissions noted in the maintenance group. However, those on maintenance had hypogammaglobulinaemia and higher rates of infections, mainly respiratory. At present, maintenance Rituximab is not recommended due to insufficient evidence for benefit.

### 9.3 PURINE ANALOGUES

#### 9.3.1 Fludarabine and Cladribine +/- Alkylators and Rituximab

In younger patients who might be candidates for high dose therapy, prolonged use of Purine Analogues may result in depletion of the stem cell compartment and should be avoided.

These agents have been widely used in the treatment of WM\(^\text{48}\). Most of the initial experience came from studies in relapsed disease, where the response rate varies from 30-78%. There is evidence also of high RR in previously untreated patients with both agents, ranging from 34-90%, with evidence for a response generally occurring within 3-6 months of commencement of therapy, but occasionally taking up to 1 year\(^\text{15, 49}\). CR rates remain <10% with single agent Purine Analogues\(^\text{50}\).

Their main disadvantage is the prolonged lymphopenia that results, with consequent risk of opportunistic infections. Myelosuppression can also be problematic, more so for Cladribine than for Fludarabine on a per-cycle basis. Treatment-related deaths (usually due to infection) are not rare and have been reported to be as high as 3% in a previously untreated patient group\(^\text{49}\). There are no comparative efficacy data for Fludarabine vs. Cladribine as single agents. Reported response rates for Fludarabine range from 40-86%; median time to response of 2.8 months and durable responses (40-50 months)\(^\text{39, 51, 52}\). Cladribine has shown objective response rates of 64-90% with varying numbers of cycles\(^\text{53-56}\).

#### 9.3.2 Fludarabine with Rituximab

In a report in patients who had received up to 2 prior therapies not including Purine Analogues or Rituximab\(^\text{57}\), delays due to neutropenia were common and therapy was truncated in several patients despite delays or G-CSF support. The response rate on an intention-to-treat basis was 90% (though only 3 CRs were seen) and at a follow up of 17 months, 36 of 39 responders remain in remission. Thus, although an effective combination, the myelosuppressive toxicity was quite high, suggesting that the optimum dosing regimen of these two agents remains to be found.

#### 9.3.3 Cladribine & Cyclophosphamide Alone or in Combination with Rituximab

62 newly diagnosed patients received Cladribine (1.5 mg/m\(^2\) sc tds for 7d) plus Cyclophosphamide (40 mg/m\(^2\) po bd for 7d) with or without Rituximab (375 mg/m\(^2\)/week for 4 weeks) repeated once after 6 weeks. Overall response rate was 89% for Cladribine/ Cyclophosphamide and 93% for Cladribine/Cyclophosphamide/Rituximab. Median time to achieve remission was similar in both groups (2.5 months), but time to treatment failure was significantly longer in the Rituximab arm (64.2m vs. 31.4m). Toxicity was reported as minimal\(^\text{56}\).

#### 9.3.4 Fludarabine & Cyclophosphamide

FC was explored in 11 patients with primary refractory or relapsed disease and observed a partial response in 55%\(^\text{58}\). Another study found a median time to treatment failure of 27 months in the 78% of 49 patients who achieved a response to the same regimen\(^\text{59}\).

#### 9.3.5 FCR

Fludarabine (25mg/m\(^2\) iv on days 2-4), Cyclophosphamide (250mg/m\(^2\) iv on days 2-4) and Rituximab (375 mg/m\(^2\) on day 1) every 4 weeks for 6 courses have been administered to 19 patients (including 5 previously untreated). At least a PR was achieved in 79% of patients, 10 patients showed a delayed response with a progressive response after a median of 10 months and 9 patients had an IgM flare\(^\text{60}\).

Purine analogue, Alkylator and Rituximab combinations clearly have significant efficacy in WM, both in the first line as well as relapsed settings. The significant haematological and immunosuppressive toxicities of these combinations must be carefully weighed against the likely benefits for individual patients. Of note are recent reports of Richter’s
transformation and secondary MDS/AML in WM patients treated with Purine Analogue combinations\textsuperscript{61}, which favour limiting their use in younger patients.

\textbf{9.4 Bortezomib}

Trials of Bortezomib in WM, have shown that Bortezomib, produces a high rate of response (78% responded overall, 25% rate of PR) when given as a single agent at diagnosis or at relapse to patients with WM\textsuperscript{62}. The main side effects encountered include peripheral neuropathy (which is reversible in the majority), low blood counts and dizziness (due autonomic neuropathy). Also noted was that although the IgM level fell briskly in most patients, the degree of marrow infiltration often fell less precipitously; there was a discrepancy between IgM levels and clearance of the bone marrow. The rapidity in the reduction in IgM makes this agent potentially useful for patients with intractable HVS.

When given in combination with Dexamethasone and Rituximab (Bortezomib administered iv twice a week) in previously untreated WM, the median time to response is 1.4m, there was a flare in 2 of 12 patients and the response rates were as follows: ORR 96%, PR 83%, CR 22%. At 2 years, 18/23 remain progression free; neurotoxicity major reason for stopping\textsuperscript{63}. In another trial of Bortezomib (iv/biw) x1 then Bortezomib (iv/w) DR in 60 patients, the response rates were: CR 4%, PR 65%, MR80%. Sensory PN occurred in 35%, with grade 3 PN in 5%; no IgM flares were reported\textsuperscript{64}. With subcutaneous administration and no evidence of reduced efficacy, it is expected that the rate and depth of peripheral neuropathy will fall and the treatment become more tolerable.

\textbf{9.5 R2W Trial}

This is a randomised, non-comparative, phase II trial of subcutaneous bortezomib, cyclophosphamide, rituximab (BCR, experimental arm) versus fludarabine, cyclophosphamide, rituximab (FCR, control arm) for initial therapy of WM. 50 patients will be randomised between BCR and FCR (2:1). Patients will receive 3 cycles of treatment and then be reassessed. Those with evidence of progression will stop trial treatment. All other patients will continue with a further 3 cycles (to a total of 6) unless there is a clear clinical contraindication to further treatment. (Chief Investigator is Dr Rebecca Auer, Barts Cancer Institute, London).

- **Experimental:**
  - Bortezomib: 1.6 mg/m\textsuperscript{2} s.c; days 1, 8, 15 of each cycle.
  - Cyclophosphamide: 250 mg/m\textsuperscript{2} oral; days 1, 8, 15 of each cycle.
  - Rituximab: 375 mg/m\textsuperscript{2} i.v. infusion; days 1, 8, 15 and 22 of cycles 2 and 5 only.

- **Active Comparator**
  - Fludarabine: 40 mg/m\textsuperscript{2} oral, days 1, 2 and 3 of each cycle
  - Cyclophosphamide: 250 mg/m\textsuperscript{2}; oral, days 1, 2 and 3 of each cycle.
  - Rituximab: 375 mg/m\textsuperscript{2} i.v. infusion days 1, 8, 15 and 22 of cycles 2 and 5 only.

\textbf{9.6 Stem Cell Transplantation}

\textbf{9.6.1 Autografting}

There are few published papers and variety of preparative regimens have been used, including Cy/TBI, Mel/TBI and BEAM\textsuperscript{65} and the impact of this approach on long term survival is not known. An analysis of 158 adult patients with WM reported to the European Group for Blood and Marrow Transplantation (EBMT) between 1991 and 2005 has been published\textsuperscript{66}. Median time from diagnosis to ASCT was 1.7 years (range, 0.3 to 20.3 years), 32% of the patients experienced treatment failure with at least three lines of therapy, and 93% had sensitive disease at the time of ASCT.

Median follow-up for surviving patients was 4.2 years (range, 0.5 to 14.8 years). Non-relapse mortality was 3.8% at 1 year. Ten patients developed a secondary malignancy, with a cumulative incidence of 8.4% at 5 years. Relapse rate was 52.1% at 5 years. Progression-free survival (PFS) and overall survival were 39.7% and 68.5%, respectively, at 5 years and were significantly influenced by number of lines of therapy and chemorefractoriness at ASCT. When used as consolidation at first response, ASCT provided a PFS of 44% at 5 years. ASCT was concluded to be a feasible procedure in young patients with advanced WM. ASCT should not be offered to patients with chemoresistant disease and to those who received more than three lines of therapy.

\textbf{9.6.2 Allografting}

Information regarding alloSCT in WM is limited. A total of 86 patients who received an allograft for WM were reported to the EBMT\textsuperscript{67}. Conditioning was either myeloablative (MAC; n = 37) or reduced-intensity (RIC; n = 49) and were
retrospectively studied. The median age was 49 years (range, 23 to 64 years); 47 patients had received three or more previous lines of therapy, and 8 patients had experienced failure of a prior ASCT. A total of 59 patients (68.6%) had chemotherapy-sensitive disease at the time of alloSCT. Median follow-up was 50 months (7 to 142 months). Non-relapse mortality (NRM) at 3 years was 33% for MAC and 23% for RIC. The overall response rate was 75.6%. The relapse rates (RRs) at 3 years were 11% for MAC and 25% for RIC. AlloSCT can induce durable remissions in a selected population of young and heavily pre-treated patients with WM.

The role of this treatment intervention remains unclear due to the considerable morbidity and mortality associated with the procedure. At present, allogeneic stem cell transplantation could be considered for younger, fitter patients who have relapsed following autologous stem cell transplantation.

10. Treatment Recommendations

The following factors should be taken into account when choosing the most appropriate primary therapy for patients with WM:

- Age
- Co-morbidities
- Cytopenias
- Symptoms of hyperviscosity
- The need for rapid disease control due to symptoms
- Significant bulk disease (splenomegaly or lymphadenopathy)
- Symptomatic peripheral neuropathy
- Whether or not the patient is a candidate for an autologous stem cell transplant

10.1 Initial Cyto-reductive Therapy (Algorithms 1 & 2)

All patients should be considered for the R2W Trial if eligible.

10.2.1 Patients > 65 Years.

- Off trial, older, frailer patients with gradual progression of their disease but sufficient marrow reserve. Chiorambucil +/- Prednisolone. It is worth proceeding slowly (every 6-8 weeks) to allow for marrow recovery between cycles if needed. Treatment duration generally spans 8 to 12 cycles to produce an adequate depth of response.
- Patients with cytopenias should be offered DRC x8
- Rituximab (375mg/m² weekly for 4 weeks possibly repeated after 3 months) is a suitable alternative

10.2.2 Patients <65 Years

- Off trial, R-Bendamustine x6 or DRC x8 are preferable in younger good risk patients, to keep the option for stem cell harvest open.
- Responders will be monitored following completion of therapy
- Patients who have failed first line treatment should be considered for high dose therapy.
10.2 Treatment in Special Situations

10.2.1 Transformation to High Grade Lymphoma
- If high grade transformation is suspected, PET-CT scanning is useful for identifying FDG-avid disease and guiding biopsy.
- R-CHOP or R-ESHAP is appropriate therapy in this setting, depending on prior anthracycline use, consolidated by ASCT if performance status allows.

10.2.2 WM Complicated by CNS Involvement (Bing-Neel Syndrome)
- If CNS involvement is suspected, appropriate investigations should be carried out to confirm the diagnosis.
- Imaging is frequently abnormal. Biopsy confirms the diagnosis.
- Treatment data are limited, but responses are seen with radiation and/or chemotherapy.
- Treatment should be initiated as responses do occur that may improve quality of life and extend it when limited or no active systemic disease is present.
- At UCLH, the IDARAM regimen has been used successfully in a few cases of Bing-Neel Syndrome.
- Consideration should be given for a consolidative ASCT, conditioned with either Thiotep/BCNU or Cyclophosphamide/TBI where appropriate.

10.2.3 WM Complicated by AL Amyloidosis
- Rarely, WM may be complicated by AL amyloidosis. In this situation, the need for a brisk response is critical to stopping amyloidotic organ progression especially in the heart and kidneys. Inducing a clonal response and hence a lowering the paraprotein and light chain production is the key to improving the function of any organ affected by amyloidosis.
- Bortezomib, used as a single agent, has been shown to be an effective agent for treating myeloma and amyloidosis and combining it with other drugs appears to increase the rapidity and completeness of response. Bortezomib has also been demonstrated to be highly effective in WM/LPL (see below) and in patients with AL amyloidosis associated with WM/LPL. In a recent European collaborative analysis of patients with AL amyloidosis due to WM/LPL, treatment with bortezomib combinations, Bendamustine combinations or autologous stem cell transplantation were associated with best outcomes.
- The combination of this evidence as assessed by expert opinion has led to the following recommendation in this very rare subset of patients: the preferred option for initial therapy is Bortezomib (1 or 1.3 mg/m²) combined with Dexamethasone (20-40mg) on days 1, 4, 8 and 11 and Rituximab (375 mg/m² on day 11) for 4-8 cycles or Bortezomib (1.6 mg/m2) combined with Dexamethasone (20-40mg) on days 1, 8,15 and 22 and Rituximab (375 mg/m2 on day 8) for 4-8 cycles. An alternative regimen would be Bendamustine 90mg/m² on D1 and 2 every 28 days for 6 cycles with Dexamethasone (20-40mg) on days 1-4 with Rituximab given at 375mg/m² with each cycle. Patients who satisfy criteria for ASCT in amyloidosis should be considered for ASCT as consolidation or, in selected cases, upfront. However, there is little data in the setting of amyloidosis and the response to therapy is likely to be slower.

10.2.4 WM Complicated by a High Light Chain Load
- Patients with a given diagnosis of WM may rarely be affected by an unexpectedly high level of light chain production or high levels of BJP excretion. In this situation, careful consideration should be given to the possibility of IgM myeloma as an alternative explanation. A skeletal survey should be carried out in these patients and appropriate review of the diagnostic bone marrow biopsy for evidence of IgM myeloma cells, which typically express CD38, CD138, CD56 and cyclin D1, all of which are absent in WM. IgH gene translocations are more common in IgM-myeloma especially t(11;14)(q13;q32). There is a similar rationale as for AL amyloidosis for inducing a brisk response to initial therapy in these patients, who appear to have an overlap clinical syndrome. As such a Bortezomib-containing schedule should be considered for front-line therapy in those patients who are deemed, following review to have WM/LPL with a high FLC excretion rather than myeloma. Patients concluded to have IgM myeloma should receive therapy according to the myeloma protocol.
10.2.5 WM Complicated by Bone Lesions

- Patients with a diagnosis of WM/LPL who present with evidence of lytic bone disease and/or hypercalcaemia should also be carefully reviewed for the possibility of IgM myeloma as above.

10.3 Relapse & Refractory Disease: Options

- The choice of therapy depends on prior therapies, the timing and nature of the relapse and the principal clinical problem (prior autologous stem cell transplant, presence of cytopenias and degree of marrow reserve, presence of HVS, and presence of peripheral neuropathy).
- For patients in relapse who demonstrated a durable response of >1 year following cessation of initial therapy, the re-use of the same agent/s may be reasonable.
- Patients who fail to respond to second line therapy according to the treatment algorithm (primary refractory disease) should be considered for novel therapies if available.

10.3.1 Thalidomide and Lenalidomide

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. Therefore, neither agent is recommended in the setting of WM.

10.3.2 Bortezomib

Bortezomib (1.3 mg/m² twice weekly for 2 weeks on a 21 day cycle until PD or 2 cycles beyond CR or stable PR) has been evaluated in a phase II study of 27 patients with either untreated or previously treated disease. The ORR was 78% with major responses seen in 44% of patients. Main toxicities were predictable: neuropathy (which later resolved in two-thirds of affected patients) & fatigue. More recently, in a WMCTG multicentre trial, 27 patients (all but one has relapsed/refractory disease) received up to 8 cycles of Bortezomib. The ORR was 85% and occurred within a median of 1.4 months. Most common grade 3 or 4 toxicities were sensory neuropathy, cytopenias and dizziness, all of which improved or resolved once therapy stopped. Bortezomib (1.3 mg/m²) has been combined with Dexamethasone (40mg) on days 1, 4, 8 and 11 and Rituximab (375 mg/m² on day 11) for 4 cycles followed by 4 maintenance cycles from 3 months every 3 months as initial therapy. An ORR of 96% was seen in the 23 patients treated, including 4 patients who achieved a CR. Median time to response was 1.1 month. One-third of patients developed grade 3 peripheral neuropathy.

To reduce neurotoxicity, Ghobrial et al used weekly bortezomib with rituximab (6 cycles, no maintenance) in 26 patients (58% achieved at least PR, 8% CR/nCR, and 1-year event-free survival was 79%). IgM flare developed in 40% and 54% of patients who developed peripheral neuropathy, but in none was the grade ≥3.

Dimopoulos et al46, to avoid IgM flare, used a bi-weekly induction cycle of bortezomib (intravenous 1.3 mg/m² on days 1, 4, 8, and 11), followed by 4 cycles of weekly bortezomib (intravenous 1.6 mg/m² for 4 weeks) with rituximab and dexamethasone on cycles 2 and 5. Among 59 previously untreated patients, 68% achieved at least PR (3% CR, 7% VGPR); IgM flare occurred in 11%, but plasmapheresis was not required, probably due to the initial bortezomib induction. After a median follow-up of 42 months, responses were durable (median PFS was 42 months and 3-year PFS for those with at least PR was 70%), despite the lack of maintenance. Peripheral neuropathy was observed in 46% (grade ≥ 3 in 7%), but only 5 (8%) patients discontinued bortezomib due to neuropathy. Discordance between serum IgM levels and bone marrow responses has been noted in a subset of Bortezomib-treated patients, for incompletely understood reasons.

The recommendation from the Seventh International Workshop is that Bortezomib combinations should be strongly considered for patients with high levels of IgM, with symptoms of, or at risk of developing, hyperviscosity syndrome, symptomatic cryoglobulinemia or CAD, amyloidosis, and renal impairment. At present, Bortezomib is not funded beyond exceptional use for WM in the UK.

10.43 Alemtuzumab

Alemtuzumab Owen et al have shown that CD52 expression is demonstrable in WM patients. Owen et al treated 28 patients (5 untreated, 23 previously treated) with LPL/WM with Alemtuzumab (test doses were followed by 30mg iv 3
times per week for 12 weeks). Among 25 assessable patients, the ORR was 76% (32% PRs, 44% MRs). Haematological toxicities were common in previously treated patients (including grade 3 or 4 neutropenia, thrombocytopenia or anaemia) and CMV reactivation and infection were also seen. There were 3 treatment-related deaths. With a median follow up of 8.5 months, 11 out of 19 responders remain progression free \(^72\). More recently, another series of patients showed a 32% PR rate \(^73\).

10. 3. 4 EVEROLIMUS

Everolimus (RAD001): An inhibitor of MTORC1 (component of Akt-MTOR pathway which regulates the growth and survival of LPL cells), this agent has activity in relapsed/refractory setting \(^74\). A prospective study of upfront treatment of 10mg oral Everolimus daily (sequential de-escalation to 7.5mg, 5mg then 5mg alt die allowed). Oral Dexamethasone solution was administered for prevention of stomatitis. 33 patients with standard disease characteristics were treated. At best response, the median total IgM level of 44 g/l fell to 19 g/l, and median IgG PP 26 g/l fell to 15g/l. 11/33 stopped due to disease progression. The median time to best response was 3 months but there was discordance between IgM and BM response; the main toxicities were myelosuppression and oral ulceration. Additionally, 5% to 15% developed pulmonary toxicity, frequently resulting in interruption or discontinuation of therapy. Everolimus may therefore be considered for selected patients with relapsed or refractory disease and limited options.

10. 3. 5 CARFILZOMIB

Carfilzomib: Carfilzomib a second-generation proteasome inhibitor, has activity in WM \(^75\). In a Phase II trial (n=20):16 were previously untreated, 4 had prior Everolimus. The CaRD schedule was given \(^76\). Carfilzomib 20 mg/m\(^2\) x1, then 27 mg/m\(^2\) on D1,2, D8,9; Dexamethasone 20 mg iv on D1,2, D8,9; Rituximab 375 mg/m\(^2\) on D2,9; Q 21 d x 6 cycles. After 8 weeks responding patients were eligible for maintenance (q8 w): Carfilzomib 27 mg/m\(^2\) on D1,2; Dexamethasone 20 mg iv on D1,2; Rituximab 375 mg/m\(^2\) on D2. A median of 6 (3-8) cycles were administered including maintenance. The median total IgM fell from 33g/l to 13g/l, Hct 30.7% to 34.1%, median BM disease: 60% to 27%; ORR 75%; 1 VGPR, 9 PR, 1 MR; median time to best response was 4m. There were varying toxicities, all reversible; no >grade 2 PN. CaRD therefore represents a novel neuropathy-sparing option for proteasome inhibitor-based therapy for WM.

10. 3. 6 POMALIDOMIDE

Pomalidomide: In a Phase I trial in relapsed/refractory WM (n=6, median age 71, prior lines 2 [1-4]) at the MDACC \(^77\), Pomalidomide was given continuously at a dose of 1mg daily with plan to increase the dose by 1mg increments to the MTD. At 1mg, there were no dose limiting toxicities and a median of 4 cycles were administered, but at the 2mg dose level, there were reports of dizziness, syncope, neutropenia and acute IgM rise in 1 needing plasma exchange. These preliminary data suggest that the MTD is 1mg for patients with WM.

10. 3. 7 OFATUMUMAB

Ofatumumab: Ofatumumab (OFA) is a fully human monoclonal anti-CD20 antibody approved for the treatment of fludarabine and Alemtuzumab-refractory CLL and has demonstrated activity in indolent B-NHL. Experience in 37 patients with WM has been reported \(^78\). Median age was 63 years (range 43–85); 22 were male. Median IgM level was 31.1 g/l (range 8.1–86.4); median Hb was 9.8 g/dl (range 5.3–13.2). Nine were treatment naïve; 28 had received a median of 3 prior therapies (range 1–5) including R (25) and purine analogue (14). OFA is clinically active in patients with WM, with an acceptable toxicity profile and a lower incidence (5%) of IgM flare. The ORR to OFA was 59% including a 50% ORR in patients with IgM ≥ 40 g/l. Anaemia responded to OFA with 58% of patients with baseline Hb < 11.0 g/dl experiencing ≥ 3.0 g/dl increase. A higher dose of OFA appeared to be more effective in patients previously exposed to R or with baseline IgM ≥ 40 g/l.

Infusion-related reactions were common, especially during the first dose; mild infections were also common, and IgM flare was observed. Ofatumumab has promising activity, may be active in patients with prior exposure to rituximab, and may be considered for patients intolerant to rituximab; however, more data are needed in rituximab-refractory disease. Combinations of Ofatumumab with other agents in WM are under investigation.

10. 43 8 IBRUTINIB

Ibrutinib: BTK is a critical signalling molecule positioned early in this signalling cascade in close proximity to Syk and PI3Kδ. BCR signalling whether constitutive or following antigen binding, leads to activation of several downstream pathways that connect the BCR to proteins involved in cell survival, proliferation and migration (probably via NF-κB and MAPK). Emerging evidence suggests that BTK activation is facilitated by MYD88 pathway signalling in L265P expressing
WM cells. Hence BTK inhibition is a promising approach to the treatment of WM. Major responses to ibrutinib therapy are higher in MYD88L265P and CXCR4WT patients, the latter being highly associated with ibrutinib response. In preclinical studies, WM cells engineered to express the S338X CXCR4 non-sense mutation show resistance to the suppressive effects of ibrutinib on AKT and ERK 1/2 signalling, which could be restored by use of the CXCR4 specific inhibitor Plerixafor. These studies highlight the importance of understanding both MYD88 and CXCR4 mutation status in WM, and may provide the basis for a more personalized treatment approach including the use of relevant inhibitors for MYD88 mutated patients, and the use of CXCR4 inhibitors in CXCR4 mutated WM patients.

10.4 ROLE OF HIGH DOSE TREATMENT WITH STEM CELL SUPPORT

10.4.1 AUTOGRAPHING

- Patients should be considered for HDT/SCT if they have
  (i) failed to respond to > 1 line of treatment or
  (ii) relapsed from plateau phase within 1 year.

10.4.2. ALLOGENEIC TRANSPLANTATION

- Fitter patients <60 years with an HLA-identical match and who have multiply relapsed disease or fail to respond to >2 lines of therapy may be considered for a reduced intensity conditioned allogeneic transplant provided they achieve a PR/CR. However, such a procedure should be approached with caution given the associated high mortality and morbidity.
Waldenström’s Macroglobulinaemia

**Algorithm for Patients > 65 or Not Suitable for Stem Cell Transplant: Upfront**

- **Fitter patients:** taking into account indications for Rx: Cytopenias, high M-protein, need for quick response, presence/absence of peripheral neuropathy.

- **Chlorambucil + / - prednisolone**
  - + / - Rituximab or Rituximab alone
  - Avoid/Defer Rituximab for 2 cycles if baseline paraprotein >40 g/l

- **R2W Trial or R-Bendamustine or DRC or Rituximab alone**
  - Avoid/Defer Rituximab for 2 cycles if baseline paraprotein >40 g/l

- Patients with low disease burden, with symptomatic anaemia and low iron saturation level (<10-12%) unexplained by GI blood loss (investigated as appropriate).

- **Reassess @ 3-6 months post Rx to allow for maximal response**
  - Or as per trial protocol

- **>PR + Adequate clinical response**
  - Watchful waiting until relapse

- **<PR + Adequate clinical response**
  - Continue therapy

- **<PR No clinical response**
  - Consider trial of parenteral iron first, and then if unresponsive proceed to chemotherapy.

- **Adequate response**
  - Y

- **>Watchful waiting until relapse**

- **Y**

- **N**

- **See Relapse/Refractory Algorithm**

* Adequate clinical response = improved well-being, less fatigue, reduction/cessation of B symptoms, improvement in blood counts as evidence for improved BM reserve regardless of degree of fall in paraprotein level
Waldenström’s Macroglobulinaemia

**Algorithm for Patients < 65, Suitable for Stem Cell Transplant: Upfront**

1. **Patients with low disease burden,** with symptomatic anaemia and low iron saturation level (<10-12%) unexplained by GI blood loss (investigated as appropriate)

   Consider trial of parenteral iron first, and then if unresponsive proceed to chemotherapy.

2. **Younger fitter patients** eligible for future ASCT: (Choice of therapy depends speed of response, disease bulk, performance status; presence/absence of peripheral neuropathy

   - **R2W Trial** or **R-Benda x6-8 or DRC x8**
   - Defer Rituximab for 2 cycles if baseline paraprotein >40 g/l

3. Restage @ 3-6 months post Rx to allow for maximal response
   - Or as per trial protocol

4. **<PR + inadequate clinical response**
   - Watch off therapy for 3-6 months to allow for maximal response before considering therapy change

   - **PR or CR**

5. **Consider stem cell transplantation:**
   - High-dose therapy with ASCT is an option for salvage therapy in selected patients with chemosensitive disease
   - Salvage treatment options depend on the duration and response to prior therapies, the patient’s overall condition and age, and candidacy for ASCT

   - **Y**
     - R-ESHAP x 2 Or Cyclo-G-CSF + PBSCH depending on degree of BM clearance post salvage

   - **N**
     - See Relapsed/Refractory Algorithm

   - Restage @ 3-6 months
     - PR or CR

   - Watchful waiting

   - **Progression**

---

1. In general, R-CHOP is reserved for treatment of high grade transformation but selected patients with bulky disease who need a rapid response to treatment may be considered for R-CHOP as first line therapy

2. Adequate clinical response = improved well-being, less fatigue, reduction/cessation of B symptoms, improvement in blood counts as evidence for improved BM reserve irrespective of change in paraprotein level

3. Salvage treatment options: Retreat with initial agent if sufficient duration of response; switch to alternative agent; options include DRC, BR, purine analogues, BortDR, R-ESHAP

4. Younger patients with slowly progressing disease may be better candidates for allo-SCT. However, in view of the increasing treatment options and the high morbidity and mortality associated with allo-SCT, this therapy should preferably be considered in the context of a clinical trial.

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*Please note Rituximab with or without chemo is funded by NHS England PbR exclusion in the 1st line treatment of WM in patients. Bendamustine for low grade is available via the Cancer Drugs fund for 1st line treatment if the patient fulfils the criteria.*
Waldenström’s Macroglobulinaemia

**RELAPSED AND REFRACTORY ALGORITHM**

Options, depending on prior therapy, timing and nature of relapse and principal clinical problem*:
- R-Bendamustine, R-Purine analogue +/- Cyclophosphamide, R-Velcade-Dexamethasone, DRC
- R-CHOP (high grade transformation)

**NB MabCute Study, Gilead 0125 Study (Chemo-Idelalisib)**

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**PR or CR following salvage**

- Prior ASCT
  - <60 with HLA match & fit for RIC allo
    - RIC allo HSCT
  - <PR following Rx:
    - Benda/Bortezomib/R Alemtuzumab Ofatumumab

- No prior ASCT
  - Not fit for SCT
    - <65 & fit for auto HSCT: Cyclo-G OR ESHAP + PBSC harvest
    - ASCT
  - <65 & fit for auto HSCT: Cyclo-G OR ESHAP + PBSC harvest
  - ASCT

- Watchful waiting

---

*Bendamustine is more myelosuppressive than Bortezomib but less inclined to cause peripheral neuropathy. Bortezomib can produce a brisk response in terms of IgM levels, useful in HVS setting. Both can be used in AKI/CKD.*

Purine analogues to be avoided if ASCT remains a possibility

*Please note Rituximab with or without chemo is funded by NHS England PbR exclusion in the treatment of relapsed WM in patients who have not received prior rituximab treatment. It is also funded by PbR exclusion in the treatment of 2nd or 3rd treatment of low grade B cell lymphomas.*

*Bendamustine is funded by the Cancer Drugs Fund in relapsed disease if the patient fulfills the criteria.*
## APPENDIX A: CHEMOTHERAPY REGIMENS

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Regimen Details</th>
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| CHOP-RITUXIMAB                       | **Cyclophosphamide 750 mg/m² i.v., day 1**  
|                                      | **Doxorubicin 50 mg/m² slow i.v. bolus, day 1**  
|                                      | **Vincristine 1.4 mg/m² (max 2 mg) i.v. bolus, day 1**  
|                                      | **Rituximab 375mg/m² i.v. infusion, day 1**  
|                                      | **Prednisolone 100 mg po once daily, days 1-5**  
|                                      | Repeat every 21 days up to 6 cycles  
| Supportive Care:                     | Lansoprazole 30mg orally daily or ranitidine 150mg orally twice daily or equivalent, allopurinol 300mg orally daily,  
| Tests:                               | FBC, Urea and Electrolytes, LFT’s on Day 1  

| Chlorambucil with or without Prednisolone | **Chlorambucil 8 mg/m² po once daily, days 1-10**  
|                                          | **Prednisolone 40 mg po once daily, days 1-10**  
|                                          | Repeat every 4-6 weeks according to marrow tolerance  
| Supportive Care:                        | Allopurinol 300mg orally daily,  
| Tests:                                 | FBC, Urea and Electrolytes, LFT’s on Day 1  

| DRC                                   | **Dexamethasone 20 mg iv on day 1**  
|                                      | **Rituximab 375 mg/m² iv on day 1**  
|                                      | **Cyclophosphamide 100 mg/m² bd orally on days 1-5**  
|                                      | Repeat every 21 day cycle for 6 courses  
| Supportive Care:                      | Aciclovir 400mg orally twice daily or equivalent, co-trimoxazole 960mg orally once daily 3x week or equivalent, allopurinol 300mg orally daily  
| Tests:                                | FBC, Urea and Electrolytes, LFT’s on Day 1  

| Cladribine +/- Rituximab              | **Cladribine 0.12 mg/kg sc on days 1-5**  
|                                      | ** +/- Rituximab 375 mg/m² iv weekly x 4**  
|                                      | **Repeated after 8 weeks (up to 2 courses)**  
| Supportive Care:                      | Aciclovir 400mg orally twice daily or equivalent, Co-trimoxazole 960mg orally once daily 3x weekly or equivalent, allopurinol 300mg orally daily  
| Tests:                                | FBC, Urea and Electrolytes, LFT’s on Day 1  

| Fludarabine                           | **Fludarabine 40 mg/m² p.o. once daily, days 1-5**  
|                                      | **OR**  
|                                      | **Fludarabine 25 mg/m² i.v. once daily, days 1-5**  
|                                      | Repeat every 28 days up to 6 cycles  
| Supportive Care:                      | Aciclovir 400mg twice daily or equivalent, co-trimoxazole 960mg orally once daily 3x weekly or equivalent, allopurinol 300mg orally daily  
| Tests:                                | FBC, Urea and Electrolytes, LFT’s on Day 1  

London Cancer LPL/WM Guidelines 2015-16 v1.0
<table>
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<tr>
<th>Regimen</th>
<th>FBC, Urea and Electrolytes, LFT’s on Day 1</th>
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<td><strong>BR</strong></td>
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<td><strong>Regimen:</strong></td>
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<tr>
<td>Bendamustine 90 mg/m² iv days 1-2</td>
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<td><strong>BDR</strong></td>
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<td><strong>Regimen:</strong></td>
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<td>Bortezomib 1.3 mg/m² sc + Dexamethasone 40 mg p.o. days 1, 4, 8, and 11</td>
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<td>Rituximab 375 mg/m² iv day 11</td>
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<td>or Bortezomib (1.6 mg/m²) sc + Dexamethasone (20-40mg) on days 1, 8,15 and 22</td>
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<td>FBC on D4, D8 and D11</td>
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<td>Alemtuzumab 30 mg sc 3x week (e.g. Mondays, Wednesdays, Fridays) for weeks 1-12</td>
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<td><strong>Supportive Care:</strong></td>
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<td>Pethidine 25-50mg if required for rigors, Paracetamol 1000mg if required, Chlorphenamine 10mg iv if required, Prednisolone 20mg if required for reactions.</td>
<td></td>
</tr>
<tr>
<td>Aciclovir 400mg orally twice daily or equivalent, Co-trimoxazole</td>
<td></td>
</tr>
<tr>
<td>960mg once daily 3x weekly or equivalent, allopurinol 300mg daily</td>
<td></td>
</tr>
<tr>
<td><strong>FCR</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Regimen:</strong></td>
<td></td>
</tr>
<tr>
<td>Fludarabine 40 mg/m2 p.o. once daily, days 1-3</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide 250 mg/m2 p.o. once daily, days 1-3</td>
<td></td>
</tr>
<tr>
<td>Rituximab 375mg/m2 iv day 1</td>
<td></td>
</tr>
<tr>
<td>OR Fludarabine 25 mg/m2 i.v. once daily, days 1-3</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide 250 mg/m2 i.v. once daily, days 1-3</td>
<td></td>
</tr>
<tr>
<td>Rituximab 375mg/m2 iv day 1</td>
<td></td>
</tr>
<tr>
<td>Repeat every 28 days up to 6 cycles</td>
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</tr>
<tr>
<td><strong>Supportive Care:</strong></td>
<td></td>
</tr>
<tr>
<td>Aciclovir 400mg orally twice daily or equivalent, co-trimoxazole</td>
<td></td>
</tr>
<tr>
<td>960mg once daily 3x weekly or equivalent, allopurinol 300mg daily</td>
<td></td>
</tr>
<tr>
<td><strong>Tests:</strong></td>
<td></td>
</tr>
<tr>
<td>FBC, Urea and Electrolytes, LFT’s on Day 1</td>
<td></td>
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<tr>
<td><strong>Rituximab</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Regimen:</strong></td>
<td></td>
</tr>
<tr>
<td>Rituximab 375 mg/m² weekly x 4</td>
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<tr>
<td><strong>ESHAP</strong></td>
<td></td>
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<tr>
<td><strong>Regimen:</strong></td>
<td></td>
</tr>
<tr>
<td>Etoposide: 40mg/m2 i.v. once daily in 250ml N/Saline over 1 hour, days 1-4</td>
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<tr>
<td>Methyldaprednisolone: 500mg i.v. once daily in 100ml N/Saline</td>
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</tr>
<tr>
<td>IDARAM</td>
<td>Regimen:</td>
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<tr>
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</tr>
<tr>
<td>Methotrexate 12.5mg intrathecal day 1 (Routine in course 1 only. see below)</td>
<td></td>
</tr>
<tr>
<td>Idarubicin daily 10mg/m2 IV days 1 and 2</td>
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</tr>
<tr>
<td>Dexamethasone 100mg daily IV infusions of 12h duration days 1-3</td>
<td></td>
</tr>
<tr>
<td>Cytarabine daily 1000mg/m2 IV over 1 hour days 1 and 2</td>
<td></td>
</tr>
<tr>
<td>Methotrexate 2000mg/m2 IV over 2 hours day 3 (For folinic acid rescue; methotrexate levels; hydration and urinary alkalinisation schedules follow local protocol)</td>
<td></td>
</tr>
</tbody>
</table>

**Intrathecal Therapy:**
All patients will receive intrathecal chemotherapy on day 1. CSF will be analysed for lymphomatous involvement by flow cytometry. Further intrathecal injections are not recommended unless the disease is largely leptomeningeal as the IDARAM chemotherapy will cross into the CSF. In the case of LM disease intrathecal methotrexate can be repeated with each course. Patients who have a clear CSF from the outset will therefore receive only one intrathecal injection on day 1.

**Concomitant Medication:** Patients should receive pegfilgrastim 6mg s.c. on day 5 of each cycle or G-CSF from D7. Supportive care as per HD MTX protocol i.e. urinary alkalinisation, Aciclovir 400mg orally twice daily or equivalent

<table>
<thead>
<tr>
<th>Cyclo-G</th>
<th>Regimen:</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLEASE CHECK LOCAL PROTOCOL</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide 1500mg/m2 IV infusion in 0.9% Saline over 2 hours at t=0, day 1</td>
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<tr>
<td>Mesna 300mg/m2 IV bolus at t=0, day 1</td>
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<tr>
<td>Mesna 600mg/m2 po at t=+2h and t=+6h, day +1</td>
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<tr>
<td>GCSF SC daily (at a dose of 5mcg/kg/day), from day +2 until harvesting completed</td>
<td></td>
</tr>
</tbody>
</table>

**Preparation Patient weight Daily dose**
- Lenograstim < 85kg 263mcg SC
- > 85kg 526mcg SC
- OR
- Filgrastim
  - <48kg 5mcg/kg SC
  - 48-60kg 300mcg SC
  - 61-96kg 480mcg SC
  - >96kg 780mcg SC

**Supportive care**
- Mesna - available as 400mg and 600mg tablets (round up the dose to the nearest whole tablet).
- Anti-emetics
Please note - Dose reductions to chemotherapy drugs in the protocols will be applied as described in the North London Cancer Network “Dosage Adjustment for Cytotoxics in Hepatic Impairment-January 2009” and “Dose Adjustment for Cytotoxics in Renal Impairment-January 2009”. Anti-emetics are prescribed as in the “Pan London Antiemetic Guidelines for Adult Patients Receiving Chemotherapy and Radiotherapy”.

**APPENDIX B: SOURCES OF SUPPORT FOR PATIENTS**

WMUK: A UK charity for patients with WM and related disorders: [www.wmuk.org.uk](http://www.wmuk.org.uk)

The Lymphoma Association: WM Patient Information Sheet available on line: [www.lymphoma.org.uk](http://www.lymphoma.org.uk)

Macmillan Cancer Support: WM Patient Information Sheet available on line: [www.macmillan.org.uk](http://www.macmillan.org.uk)


56. Weber DM, Wang M, Delasalle KB, Gavino M, Alexanian R. 2-Chlorodeoxyadenosine (2-CdA) and Cyclophosphamide (Cy) Alone or in Combination with Rituximab (Rit) for Previously Untreated Waldenstrom’s Macroglobulinemia (WM). ASH Annual Meeting Abstracts. 2004;104: 1476-.


79. PRNewswire. Ibrutinib Monotherapy Clinical Trial Data in Patients with Waldenstrom’s Macroglobulinemia Presented at the International Conference on Malignant Lymphoma in Lugano, Switzerland2013.