Guidelines on the management of Waldenström macroglobulinaemia*

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Keywords: Waldenström macroglobulinaemia, diagnosis, treatment.

Key recommendations

Waldenström macroglobulinaemia (WM) is a distinct disorder characterised by a monoclonal immunoglobulin (Ig)M para-protein and morphological evidence of lymphoplasmacytic lymphoma; the cells are IgM+, IgD+, CD19+ and CD20+ but usually CD5+, CD10+ and CD23+

Therapy should currently be reserved for patients who are symptomatic or in whom there is haematological suppression or clear evidence of disease progression.

The aim of treatment should be to improve the quality and duration of life with minimal side-effects in the most cost-effective manner. It is not yet clear that achievement of a complete remission confers clinical benefit, and it is possible that prolonging therapy to maximal response may increase toxicity without extra benefit.

Alkylating agents, purine analogues and rituximab are all appropriate choices for the primary treatment of WM.

Plasma exchange is indicated for the acute management of patients with severe problems because of a circulating para-protein.

Patients who are primarily refractory or acquire resistance to alkylating agents may be candidates for combination therapy, purine analogues or antibody therapy. Data suggest a higher response rate using fludarabine rather than cyclophosphamide, doxorubicin and prednisolone (CAP).

Introduction

Waldenström macroglobulinaemia (WM) is relatively rare, accounting for approximately 2% of all haematological malignancies. In the United States, the annual incidence is 6.1 per million in white males and 2.5 per million in white females although the incidence appears to be lower in non-Caucasians (Herrinton & Weiss, 1993). In the United Kingdom, the annual incidence is 10.3 per million while the median age at presentation is 71 years and the median overall survival 60 months (Owen et al, 2001; Phekoo et al, 2005).

The cause of WM is unknown. The potential role of viral agents, such as hepatitis C and human herpesvirus-8, remains controversial. Inherited genetic factors may play a role in a minority of patients, as, to date, 12 families containing 31 cases have been described (McMaster, 2003).

Methods

The PubMed which contains MEDLINE (1951 to date), Cochrane Library and EMBASE (1974 to date) databases in English language were searched using the key words Waldenström macroglobulinaemia/Waldenström macroglobulinaemia/macroglobulinaemia/macroglobulinemia and further refined by the subsearches plasmapheresis/plasma exchange. Database searches were augmented by checking the reference lists of useful articles identified. No language or publication restrictions were applied. Where important preliminary data exists only in abstract form this has been included but preference has been given throughout to peer-reviewed publications. The authors are experts in their field. Stakeholder involvement was secured through representation from the UK Waldenström Macroglobulinaemia Support Group. Individual authors were responsible for specific sections of the manuscript namely diagnosis and prognostic factors, plasmapheresis and treatment options. The final recommendations were drawn up by consensus using the methods outlined in the AGREE instrument (http://www.agreecollaboration.org) and were further reviewed...
Guideline

by a sounding board of 80 haematologists representing adult practice in both teaching and district hospitals. The levels of evidence used were those of the US Agency for Health Care Policy and Research (summarised in Appendix 1).

**Diagnosis**

**Clinical features**

The presenting clinical features are highly variable in WM. A significant minority of patients are asymptomatic at presentation and have an immunoglobulin (Ig)M paraprotein as a co- incidental finding during unrelated clinical investigations. Patients with symptomatic disease may present with features attributable to tissue infiltration, such as anaemia, systemic symptoms and organomegaly. A proportion of patients present with clinical features directly attributable to physicochemical properties of their paraprotein. These features include hyperviscosity syndrome (HVS), cryoglobulinaemia and autoimmune phenomena, such as peripheral neuropathy and cold agglutinin disease (Dimopoulos et al, 2000). Primary amyloidosis, however, appears to be a rare complication of IgM gammopathies (Gertz et al, 1993).

A haematologist should review all patients with an IgM paraprotein who have features suggesting an underlying lymphoproliferative disorder and also those rare Monoclonal Gammopathy of Undetermined Significance (MGUS) patients who have clinical features attributable to the properties of their paraprotein.

**Laboratory investigations**

The diagnostic criteria for WM have recently been refined and are detailed in Table I (Owen et al, 2003a). WM is, by definition characterised by IgM monoclonal gammopathy and bone marrow infiltration in all patients. IgM paraproteins should be demonstrated by agarose gel electrophoresis and quantified by densitometry (Kyle & Rajkumar, 2003). The concentration of serum IgG and IgA should be determined and quantified by densitometry (Kyle & Rajkumar, 2003). The value of bone marrow examination in asymptomatic patients is however less clear. Differentiating patients with occult WM from those with IgM MGUS is desirable as it provides better diagnostic information to both the patient and clinician. There is, however, no published evidence as yet to suggest that this information will improve the overall outcome of individual patients. Bone marrow examination is not therefore considered essential in asymptomatic patients if there are no clinical or laboratory features to suggest an underlying lymphoproliferative disorder or any paraprotein-related phenomena.

If bone marrow examination is considered necessary it is good practice to obtain a trephine biopsy as the pattern of infiltration is diagnostically important (see below). In addition, it provides a better assessment of the extent of bone marrow infiltration than even the best quality aspirate smears. An adequate trephine biopsy (at least 1 cm in length) also ensures that a diagnosis can be reliably made even when the bone marrow aspirate specimen is of poor quality.

Waldenström macroglobulinaemia is characterised by bone marrow infiltration by small lymphocytes showing plasma cell differentiation although the extent of this can vary considerably from case to case. Subclassification of cases into lymphoplasmacytoid, lymphoplasmacytic and polymorphous subtypes on this basis is, however, highly subjective and of dubious prognostic value. The pattern of infiltration is diffuse or interstitial in most cases and a solely paratrabecular pattern should raise the possibility of follicular lymphoma (see below).

Immunophenotypic studies are recommended in all cases (Owen et al, 2003a). WM is characterised in most cases by a surface IgM+ slgD+/− CD5− CD10− CD19+ CD20− CD22+ CD23− CD25− CD27− CD75− CD79a− CD103+ CD138− FMC7+ BCL-2+ BCL-6− PAX-5+ immunophenotype (Owen et al, 2001; Owen, 2003; San Miguel et al, 2003). It is not necessary to routinely assess the expression of all these antigens as in practice a slgM+ CD5− CD10− CD19+ CD20+ CD23− immunophenotype in association with a non-paratrabecular pattern of infiltration is diagnostic of WM (Owen et al, 2001; Owen, 2003). In a proportion of patients clonal B cells are identified by flow cytometry without morphologically detectable disease. Such patients are invariably asymptomatic and are best classified as MGUS (Owen et al, 2003a). The immuno-

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Table I. Diagnostic criteria for WM (Owen et al, 2003a).

| IgM monoclonal gammopathy of any concentration |
| Bone marrow infiltration by small lymphocytes showing plasmacytoid/ plasma cell differentiation |
| Intertrabecular pattern of bone marrow infiltration |
| Surface IgM+ CD5− CD10− CD19+ CD20− CD22+ CD23− CD25− CD27− FMC7+ CD103+ CD138− immunophenotype* |

*Variations from this phenotypic profile can occur and care must be taken to satisfactorily exclude other lymphoproliferative disorders. This is particularly relevant in those rare cases that express CD5.
phenotypic profile seen in WM is highly suggestive of derivation from postterminal centre memory B cells. This hypothesis is further supported by IGH sequence analysis, which has demonstrated evidence of somatic hypermutation without intraclonal diversity in most cases (Sahota et al, 2002; Kriangkum et al, 2004; Rollett et al, 2004).

Conventional cytogenetic analysis is of little or no value in the routine diagnostic assessment of patients suspected of having WM. Most patients are karyotypically normal, which may reflect the low-proliferative rate of the clonal B cells. A wide range of numerical and structural abnormalities have however, been described but there are as yet no disease-defining or prognostically relevant abnormalities. Deletions of 6q appear to be the commonest structural abnormality, occurring in up to 50% of patients, although their prognostic significance remains unclear (Schop et al, 2002). Using interphase fluorescence in situ hybridisation (FISH), translocations involving the IGH locus at 14q32 are characteristically absent in WM and FISH studies for the t(14;18) and t(11;14) may therefore be useful in diagnostically difficult cases including those rare cases of IgM myeloma (Schop et al, 2002; Avet-Loiseau et al, 2003a,b; Owen, 2003; Ackroyd et al, 2005a,b).

**Additional investigations**

The following additional investigations are recommended for most patients with WM at presentation:

1. plasma viscosity;
2. renal and hepatic function;
3. direct antiglobulin test and cold agglutinin titre if positive;
4. cryoglobulins;
5. β-2-microglobulin.

Computerised tomography is advised as a baseline for all patients prior to chemotherapy but is not required in asymptomatic patients unless the result would influence the need for chemotherapy. Patients who present with peripheral neuropathy should have nerve conduction studies and anti-myelin-associated glycoprotein (MAG) serology. Additional serological investigations to assess for autoantibody specificity against other neural antigens, such as gangliosides and sulphatides, may be appropriate in those patients with severe neuropathy and negative MAG serology. This is particularly relevant if cytoreductive or monoclonal antibody therapy is contemplated as it is advisable to demonstrate a clear aetiological role for the paraprotein before embarking on such therapies (Owen, 2004).

**Prognostic factors**

Waldenström macroglobulinaemia, in common with all other indolent lymphoproliferative disorders, has a highly variable clinical outcome. A significant minority of patients remain asymptomatic and never require therapy while others have advanced lymphoma-requiring therapy. Several studies have therefore evaluated the effect of standard clinical prognostic factors on overall survival and a number of stratification schema have been developed (Gobbi et al, 1994; Morel et al, 2000; Dhodapkar et al, 2001; Merlini et al, 2003). These are detailed in Table II. Age, haemoglobin concentration, serum albumin and β-2-microglobulin were consistently identified as very strong predictors of outcome in these studies. An international collaboration is underway to develop a WM-specific prognostic index. Interestingly in most studies the paraprotein concentration had no prognostic value, which further confirms the pathological data of Bartl et al (1983) who failed to demonstrate a relationship between the extent of bone marrow infiltration and paraprotein concentration.

**Communicating with patients**

The International Waldenström Macroglobulinemia Foundation web site at http://www.iwmf.com provides a directory of

![Table II. Prognostic factors in WM.](link)
information for sufferers of WM, their families and carers. Information is also provided for healthcare professionals, scientists and others interested in learning about WM. The Foundation operates a talk list specifically set up for WM patients that enables them to ask questions and give answers to one another; the process is started by sending an e-mail to iwmf-talksubscribe-request@home.ease.lsoft.com (do not sign or put anything in the subject or message area); once approved, comments and questions can be posted by sending an e-mail to iwmf-talk@home.ease.lsoft.com. To contact the UK WM Support Group for an information pack, advice or support, patients should send an e-mail to info@september-services.com. Research information on WM and information on clinical trials is available at http://www.waldenstromresearch.org.

**Treatment**

**Indications for treatment**

The usual criteria for starting patients with WM on active treatment consist of clinical evidence of adverse effects of the paraprotein, e.g. hyperviscosity with neurological or ocular disturbance, peripheral neuropathy, amyloidosis, symptomatic cryoglobulinaemia; haematological suppression (haemoglobin <10 g/dl, or platelet count <100 x 10^9/l); progression to high-grade lymphoma or development of constitutional symptoms (Kyle et al., 2003).

Published studies on the treatment of WM are predominantly small phase II studies, which differ considerably in their inclusion criteria and assessment of response; consequently direct comparisons of the response rates and durations of response between studies are likely to be very unreliable. Treatment modalities may include those described in the following sections. Therapy-related myelodysplasia or acute myeloid leukaemia is reported in WM, usually in patients who have been exposed to alkylating agents.

**Plasma exchange**

Plasma exchange is used in the management of clinically severe complications caused by the paraprotein. The effect is temporary and intervention, usually in the form of chemotherapy, is used to prevent the paraprotein from re-accumulating.

**Hyperviscosity syndrome (HVS)**

Symptoms and signs of hyperviscosity include spontaneous bleeding, neurological symptoms and retinopathy. Patients with HVS have an expanded plasma volume and cardiac failure may also occur (MacKenzie et al., 1970; McGrath & Penny, 1976). There are several published reports demonstrating the efficacy of plasmapheresis in HVS although randomised data are lacking (Skoog & Adams, 1959; Schwab & Fahey, 1960; Lawson et al., 1968; Powles et al., 1971; Buskard et al., 1977; Busnach et al., 1983; Avnstorp et al., 1985; Reinhart et al., 1992). There is not, however, a simple linear relationship between paraprotein concentration and either plasma viscosity, whole blood viscosity or symptoms. An increase in IgM concentration from 20 to 30 g/l results in an increase in plasma viscosity of <2 centipoise (cP) but an increase from 40 to 50 g/l increases the plasma viscosity by around 5 cP (Fahey, 1965). Indeed, a 1-volume plasma exchange results in a 35–41% decrease in IgM concentration but in up to a 60% reduction in plasma viscosity (Busnach et al., 1983; Avnstorp et al., 1985; Reinhart et al., 1992). In patients with WM the actual plasma volume may exceed that calculated and, given the data above, a 1–1.5 volume exchange is therefore advisable. 1–2 procedures appear to reduce the plasma viscosity to near normal levels and prevents return of the paraprotein to pretreatment levels for several weeks (Buskard et al., 1977).

**Statement.** 1–2 procedures, exchanging 1–1.5 calculated plasma volumes, is advised for the treatment of HVS in WM. In patients who are drug-resistant this may be indicated as long-term management – Level of evidence III, grade of recommendation B.

**Neuropathy**

Peripheral neuropathy may be associated with an IgM paraprotein. Symptoms are predominantly sensory, affect the lower limbs and electromyography usually demonstrates demyelination (Ropper & Gorson, 1998). Plasma exchange was associated with improvement in several uncontrolled studies in the 1980s (Ernerudh et al., 1986; Haas & Tatum, 1988). There were two prospective randomised trials in the 1990s, one double-blind the other a comparative open trial (Dyck et al., 1991; Oksenhendler et al., 1995). Neither showed any benefit from plasma exchange but only small numbers of patients with IgM gammopathy were reported. More recently in a retrospective, non-randomised, non-blinded report of 19 patients with IgM paraproteinemia polyneuropathy, plasma exchange was reported to be beneficial (Simovic et al., 1998).

**Statement.** The evidence supporting plasma exchange for the treatment of peripheral neuropathy associated with an IgM paraprotein is weak – Level of evidence III–IV, grade of recommendation C.

**Cryoglobulinemia**

Cryoglobulins are immunoglobulins that precipitate at temperatures below 37°C and redissolve on warming. Cryoglobulins are frequently monoclonal IgM. Type I cryoglobulins consist of monoclonal immunoglobulin only while type II cryoglobulins consist of a complex of polyclonal IgG and monoclonal IgM with rheumatoid factor activity. The latter is
typically associated with hepatitis C infection and is characterised by skin purpura, arthralgia, Raynaud phenomenon and vasculitis affecting the skin, liver, kidneys and peripheral nerves. Type I cryoglobulins are generally an in vitro phenomenon without clinical sequelae. Symptomatic cryoglobulinaemia is a rare complication of WM and, while there are no randomised-controlled trials that assess the value of plasma exchange in this condition and evidence of benefit is limited to case reports and uncontrolled studies, the use of apheresis to remove easily accessible cryoglobulin from the circulation would seem logical and there is a general consensus that plasma exchange is useful in the management of acute severe disease (Koo, 2000; Kaplan, 2001; Drew, 2002).

Statement. Although there are few studies that consider the role of plasma exchange in the treatment of cryoglobulinaemia, there is a clear rationale for its use – Level of evidence III–IV, grade of recommendation C. The treatment room should be warm and blood warmers used in the cell separator circuit to prevent precipitation during the procedure.

Alkylating agents

Chlorambucil with or without prednisolone is frequently used as the initial therapy in WM (Table III). Responses are usually slow and toxicity is minimal providing the dose is adjusted if cytopenias ensue. The response rate is approximately 60%, depending on the criteria used, and the median survival approximately 60 months (Facon et al, 1993; Dimopoulos & Alexanian, 1994; Kyle et al, 2000; Garcia-Sanz et al, 2001). A recent study showed no difference in response rate or survival when chlorambucil was administered either daily or intermittently for 1 week every 6 weeks (Kyle et al, 2000). The optimal duration of treatment is unknown. There are no data on the use of high-dose chlorambucil in WM. Cyclophosphamide alone or in combination is also effective in WM but there are no comparative data with chlorambucil (Garcia-Sanz et al, 2001).

Combination chemotherapy

There are several phase II studies using combination chemotherapy as primary treatment in WM (Table III). The indications for therapy, patient selection and response criteria are variable but there is no evidence that combination chemotherapy is superior to alkylating agents (Case et al, 1991; Dimopoulos & Alexanian, 1994; Garcia-Sanz et al, 2001 and Petrucci et al, 1989 updated by Annibali et al, 2005). Indeed there has been no comparative study of chlorambucil versus combination therapy.

Statement. Alkylating agent-based therapy is appropriate for the initial and subsequent treatment of WM – Level of evidence IIa, grade of recommendation B.

Purine analogues

Details of studies of treatment with fludarabine and cladribine [2-chlorodeoxyadenosine (2-CDA)] are given in Tables IV and V.

Response rates to fludarabine as initial therapy range from 38% to 100% (Dimopoulos et al, 1993a; Foran et al, 1999; Thalhammer-Scherrer et al, 2000; Dhodapkar et al, 2001, 2003). In a single phase II study of fludarabine an overall response rate (ORR) of 38% with 3% complete remissions was achieved in patients receiving an initial four cycles followed by a further four cycles for responding patients (Dhodapkar et al, 2001, 2003); survival data in this study were reported from registration not the initiation of treatment so the impact of therapy cannot be assessed. As has been observed with the treatment of chronic lymphocytic leukaemia (CLL), patients who achieve a response of >1 year to fludarabine may respond again at progression (Maloisel et al, 2000). In smaller studies using cladribine, either by continuous infusion, bolus injection or subcutaneously, the response rate has varied between 55% and 100% (Dimopoulos et al, 1993b, 1994a; Liu et al, 1998; Delannoy et al, 1999; Lewandowski et al, 2000). There is no pharmacological necessity to administer cladribine by continuous infusion and no advantage in response rates compared with administration as 2-h intravenous infusions. Most patients had received between two and four courses of treatment.

The median duration of response to purine analogues has varied between 13 and 41 months. Toxicity is primarily haematological, with 60% of patients developing grade 3 neutropenia. Infectious and autoimmune complications are reported as in CLL. A small series of patients has been reported in which response or disease control was obtained with fludarabine after failure of treatment with cladribine (Lewandowski et al, 2002) but previous experience of the use of cladribine to treat fludarabine-resistant patients was disappointing (Dimopoulos et al, 1994b).

Both fludarabine and cladribine are effective therapy for patients who are primarily resistant or who relapse after alkylating agents. There are several phase II studies of purine analogues in patients who have received prior therapy; the response rates vary from 14% to 78% and are highest for patients still sensitive to their primary therapy (Kantarjian et al, 1990; Dimopoulos et al, 1993a,b, 1995; Zinzani et al, 1995; Betticher et al, 1997; Leblond et al, 1998, 2001; Liu et al, 1998; Delannoy et al, 1999; Lewandowski et al, 2000; Dhodapkar et al, 2001, 2003). Some, but not all studies have found higher response rates in patients with primary refractory disease than in those with refractory relapse. The largest single study, which evaluated the role of fludarabine in both untreated and previously treated patients, showed no significant difference in outcome between the two groups (Dhodapkar et al, 2001, 2003). Accelerated responses occurring as early as 1 month from the start of therapy have been observed after cladribine (Dimopoulos et al, 1994a); however, delayed responses
Table III. Alkylator-based therapy for WM.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration of treatment</th>
<th>Median age (years)</th>
<th>Prior treatments</th>
<th>Number of patients</th>
<th>Overall response (CR + PR)%</th>
<th>Median survival/response duration (months)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cb 0.1 mg/kg/d</td>
<td>6–12 months after plateau</td>
<td>70</td>
<td>None</td>
<td>128</td>
<td>31</td>
<td>60</td>
<td>Facon et al (1993)</td>
</tr>
<tr>
<td>Cb 8 mg/m² + pred 40 mg/m² daily for 10 d every 6 weeks</td>
<td>Until maximum reduction of IgM</td>
<td>NS</td>
<td>None</td>
<td>77</td>
<td>57 (CR = 10)</td>
<td>60</td>
<td>Dimopoulos and Alexanian (1994)</td>
</tr>
<tr>
<td>Cb 0.1 mg/kg/d or 0.3 mg/kg/d for 7 d every 6 weeks</td>
<td>NS</td>
<td>63</td>
<td>None</td>
<td>24</td>
<td>75</td>
<td>64 (no difference between regimens)</td>
<td>Kyle et al (2000)</td>
</tr>
<tr>
<td>Cb 0.4 mg/kg/d on 2 d q14 ± pred 60 mg/m² for 4 d or 2–5 mg/d continuous M2 protocol</td>
<td>Minimum 6 months, maximum 12 months</td>
<td>69</td>
<td>None</td>
<td>145</td>
<td>57 (CR = 2)</td>
<td>MRD = 53</td>
<td>Garcia-Sanz et al (2001)</td>
</tr>
<tr>
<td>Every 5 weeks for 2 years then every 7–10 weeks for 1–3 years</td>
<td>70</td>
<td>7 patients prior to Cb + pred</td>
<td>33</td>
<td>82 (CR = 18)</td>
<td>MRD = 43 for CR and 39 for PR</td>
<td>Case et al (1991)</td>
<td></td>
</tr>
<tr>
<td>Melphalan 6 mg/m² + cyclo 125 mg/m² + pred 40 mg/m² daily for 7 d every 4–6 weeks</td>
<td>12 courses then responders Cb + pred maintenance</td>
<td>61</td>
<td>None</td>
<td>34</td>
<td>74 (CR = 26)</td>
<td>EFS = 66</td>
<td>Petrucci et al (1989)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>71</td>
<td>77</td>
<td>EFS = 47</td>
<td>Annibali et al (2005)</td>
<td></td>
</tr>
<tr>
<td>CVP</td>
<td>NS</td>
<td>NS</td>
<td>None</td>
<td>16</td>
<td>44</td>
<td>36</td>
<td>Dimopoulos and Alexanian (1994)</td>
</tr>
<tr>
<td>CVP</td>
<td>Minimum 6 cycles</td>
<td>69</td>
<td>None</td>
<td>22</td>
<td>41</td>
<td>MRD = 22</td>
<td>Garcia-Sanz et al (2001)</td>
</tr>
<tr>
<td>CHOP</td>
<td>NS</td>
<td>NS</td>
<td>None</td>
<td>20</td>
<td>65</td>
<td>88</td>
<td>Dimopoulos and Alexanian (1994)</td>
</tr>
</tbody>
</table>

Cb: chlorambucil; pred: prednisolone; cyclo: cyclophosphamide; M2 protocol: carmustine (BCNU), cyclophosphamide, vincristine, melphalan, prednisolone; CVP: cyclophosphamide, vincristine, prednisolone; CHOP: cyclophosphamide, doxorubicin, vincristine, prednisolone; MRD: median response duration; CR: complete response; PR: partial response; EFS: event-free survival; NS: not stated; IgM: immunoglobulin M.
<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration of treatment</th>
<th>Median age (years)</th>
<th>Prior treatment</th>
<th>Number of patients</th>
<th>Overall response (CR + PR)</th>
<th>Median survival/response duration (months)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>F 30 mg/m² i.v. for 5 d</td>
<td>4 cycles + 4 additional cycles for responders</td>
<td>66</td>
<td>None</td>
<td>118</td>
<td>38 (CR = 3)</td>
<td>N/A</td>
<td>Dhodapkar et al (2001, 2003)</td>
</tr>
<tr>
<td>F 30 mg/m² i.v. for 5 d</td>
<td>NS</td>
<td>57</td>
<td>Relapse/refractory</td>
<td>10</td>
<td>40</td>
<td>MRD = 10</td>
<td>Kantarjian et al (1990)</td>
</tr>
<tr>
<td>F 20–30 mg/m² i.v. for 5 d or 30 mg/m² for 3 d</td>
<td>Until maximum response (median three cycles)</td>
<td>60</td>
<td>None</td>
<td>2</td>
<td>100</td>
<td>MRD = 38</td>
<td>Dimopoulos et al (1993a)</td>
</tr>
<tr>
<td>F 25 mg/m² i.v. 5 d</td>
<td>6 cycles</td>
<td>56</td>
<td>Primary refractory</td>
<td>4</td>
<td>50</td>
<td>N/S</td>
<td>Zinzani et al (1995)</td>
</tr>
<tr>
<td>F 25 mg/m² i.v. 5 d</td>
<td>Until maximum response (median six cycles)</td>
<td>68</td>
<td>Primary refractory</td>
<td>8</td>
<td>30</td>
<td>MRD = 32</td>
<td>Leblond et al (1998)</td>
</tr>
<tr>
<td>F 25 mg/m² i.v. 5 d</td>
<td>6 cycles</td>
<td>64</td>
<td>Relapse/refractory</td>
<td>45</td>
<td>30</td>
<td>OS = 41, MRD = 19</td>
<td>Leblond et al (2001)</td>
</tr>
<tr>
<td>F 25 mg/m² i.v. 5 d</td>
<td>Maximum response + 2 cycles</td>
<td>64</td>
<td>None</td>
<td>19</td>
<td>79 (CR = 5)</td>
<td>MRD = 41</td>
<td>Foran et al (1999)</td>
</tr>
<tr>
<td>F 25 mg/m² i.v. 5 d</td>
<td>6 cycles</td>
<td>58</td>
<td>None</td>
<td>7</td>
<td>85</td>
<td>MRD = 21+</td>
<td>Thalhammer-Scherrer et al (2000)</td>
</tr>
<tr>
<td>F 25 mg/m² i.v. 3 d</td>
<td>4 cycles</td>
<td>73</td>
<td>None</td>
<td>2</td>
<td>55</td>
<td>MRD = 24</td>
<td>Dimopoulos et al (2003a)</td>
</tr>
<tr>
<td>Cyclo 250 mg/m² i.v. 3 d</td>
<td>Median 4 cycles</td>
<td>64</td>
<td>None</td>
<td>14</td>
<td>85% (CR = 0)</td>
<td>MRD = 27</td>
<td>Tamburini et al (2005)</td>
</tr>
<tr>
<td>Cyclo 300 mg/m² i.v. 3 d</td>
<td>Median 4 cycles</td>
<td>58</td>
<td>None</td>
<td>35</td>
<td>70% (CR = 0)</td>
<td>MRD = 38</td>
<td>Tam et al (2005)</td>
</tr>
<tr>
<td>F 25 mg/m² i.v. 3 d</td>
<td>Median 4 cycles</td>
<td>58</td>
<td>None</td>
<td>1</td>
<td>89% (CR = 0)</td>
<td>MRD = 38</td>
<td></td>
</tr>
</tbody>
</table>

F, fludarabine; cyclo, cyclophosphamide; CR, complete response; PR, partial response; OS, overall survival; MRD, median response duration; N/A, not applicable; N/S, not stated.
Table V. Cladribine therapy in WM.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration of treatment</th>
<th>Median age (years)</th>
<th>Prior treatment</th>
<th>Number of patients</th>
<th>Overall response (CR + PR)</th>
<th>Median survival/response duration (months)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>C 0.1 mg/kg/d ci for 7 d</td>
<td>2 cycles</td>
<td>65</td>
<td>None</td>
<td>9</td>
<td>100</td>
<td>N/S</td>
<td>Dimopoulos et al (1993b)</td>
</tr>
<tr>
<td>C 0.1 mg/kg/d ci for 7 d</td>
<td>2 cycles</td>
<td>65</td>
<td>None</td>
<td>9</td>
<td>44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C 0.1 mg/kg/d ci for 7 d</td>
<td>2 cycles</td>
<td>65</td>
<td>None</td>
<td>7</td>
<td>14</td>
<td></td>
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<tr>
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<td>2 cycles</td>
<td>65</td>
<td>None</td>
<td>4</td>
<td>75</td>
<td></td>
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<tr>
<td>C 0.1 mg/kg/d ci for 7 d</td>
<td>2 cycles</td>
<td>65</td>
<td>None</td>
<td>26</td>
<td>85 (CR = 12)</td>
<td>MRD = 13+</td>
<td>Dimopoulos et al (1994a)</td>
</tr>
<tr>
<td>C 0.1 mg/kg/d ci for 7 d</td>
<td>2 cycles</td>
<td>65</td>
<td>None</td>
<td>20</td>
<td>45</td>
<td>OS = 28</td>
<td>Dimopoulos et al (1995)</td>
</tr>
<tr>
<td>C 0.1 mg/kg/d ci for 7 d</td>
<td>2 cycles</td>
<td>65</td>
<td>None</td>
<td>17</td>
<td>24</td>
<td>MRD = 12</td>
<td></td>
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<tr>
<td>C 0.1 mg/kg/d ci for 7 d</td>
<td>2 cycles</td>
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<td>None</td>
<td>9</td>
<td>78</td>
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<tr>
<td>C 0.1 mg/kg/d ci for 7 d</td>
<td>2 cycles</td>
<td>65</td>
<td>None</td>
<td>11</td>
<td>73</td>
<td>18% relapse at 3 years</td>
<td>Delannoy et al (1999)</td>
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<tr>
<td>C 0.1 mg/kg/d ci for 7 d</td>
<td>2 cycles</td>
<td>65</td>
<td>None</td>
<td>16</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C 0.1 mg/kg/d ci for 7 d</td>
<td>2 cycles</td>
<td>65</td>
<td>None</td>
<td>20</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C 0.1 mg/kg/d ci for 7 d</td>
<td>2 cycles</td>
<td>65</td>
<td>None</td>
<td>37</td>
<td>84</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C 0.1 mg/kg/d ci for 7 d</td>
<td>2 cycles</td>
<td>65</td>
<td>None</td>
<td>27</td>
<td>93</td>
<td>MRD = 60</td>
<td></td>
</tr>
<tr>
<td>C 0.1 mg/kg/d ci for 7 d</td>
<td>2 cycles</td>
<td>65</td>
<td>None</td>
<td>20</td>
<td>60</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C 0.1 mg/kg/d ci for 7 d</td>
<td>2 cycles</td>
<td>65</td>
<td>None</td>
<td>16</td>
<td>94</td>
<td>MRD = 23</td>
<td>Weber et al (2003, 2004)</td>
</tr>
<tr>
<td>C 0.1 mg/kg/d ci for 7 d</td>
<td>2 cycles</td>
<td>65</td>
<td>None</td>
<td>20</td>
<td>60</td>
<td>MRD = 9</td>
<td></td>
</tr>
<tr>
<td>C 0.1 mg/kg/d ci for 7 d</td>
<td>2 cycles</td>
<td>65</td>
<td>None</td>
<td>37</td>
<td>84</td>
<td>MRD = 36</td>
<td></td>
</tr>
<tr>
<td>C + cyclo as above + rituximab 375 mg/m² weekly x 4</td>
<td>2 cycles</td>
<td>65</td>
<td>None</td>
<td>27</td>
<td>93</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

C, cladribine; cyclo, cyclophosphamide; pred, prednisolone; ci, continuous infusion; CR, complete response; PR, partial response; OS, overall survival; MRD, median response duration; N/S, not stated.
recommandation A

CAP as salvage therapy – Level of evidence Ib, grade of recommendation B. Fludarabine is more active than on which purine analogue is superior – Level of evidence IIa, and subsequent treatment of WM. There is no consensus on Statement rituximab (ORR ¼ 93%) or without rituximab (ORR ¼ 89%; Weber et al, 2003, 2004).

Purine analogues and alkylating agents are known to be synergistic. Response rates of 85% and 55–89% have recently been reported with the fludarabine–cyclophosphamide combination in previously treated and relapsed/refractory patients respectively (Dimopoulos et al, 2003a; Tam et al, 2005; Tamburini et al, 2005). Limited data also suggest that the fludarabine–cyclophosphamide–rituximab combination has some activity and is worthy of further study (Tam et al, 2005). High rates of response have also been reported in previously untreated patients receiving combinations of cladribine and cyclophosphamide with (ORR ¼ 93%) or without rituximab (ORR ¼ 89%; Weber et al, 2003, 2004).

Other treatments

As with other CD20⁺ lymphoid malignancies, the therapeutic anti-CD20 monoclonal antibody rituximab is active in the treatment of WM (Table VI). Response rates vary between 20% and 50% irrespective of whether patients have been previously exposed to chemotherapy; however, the median duration of response is greater for previously untreated patients and may be extended by continuing treatment in responding patients (Byrd et al, 1999; Foran et al, 2000; Treon et al, 2001, 2005; Dimopoulos et al, 2002a,b; Gertz et al, 2004). There is some evidence that rituximab may be helpful in the management of WM-associated peripheral neuropathy, a complication which may be difficult to treat even with extended plasmapheresis (Weide et al, 2000; Pestronk et al, 2003). Although the use of rituximab in the management of WM may reduce exposure to chemotherapy and benefit patients in the long-term, its timing is important as there appears to be a clinically significant risk of ‘flare’ in the levels of IgM paraprotein, which may result in hyperviscosity and a resulting need for plasmapheresis with the inevitable loss of therapeutic antibody (Dimopoulos et al, 2002b; Gobrial et al, 2004; Treon et al, 2004). Although there has been a single case report of a similar phenomenon after cladribine therapy (Krishna et al, 2003) this event appears to be a particular risk with single agent rituximab and was not noted when the agent is administered in conjunction with chemotherapy (Nichols & Savage, 2004). There is also preliminary data showing evidence of activity for alemtuzumab (CAMPATH-1H) in WM (Owen et al, 2003b).

Statement. Rituximab is active in the treatment of WM but associated with the risk of transient exacerbation of clinical effects of the disease and should be used with caution in patients with symptoms of hyperviscosity and/or IgM levels >40 g/l – Level of evidence IIb, grade of recommendation B.

Thalidomide has been recently utilised in many disease states including plasma cell dyscrasias because of its multiple actions including immunomodulation, antiangiogenesis and altered expression of adhesion molecules. In WM, small cohorts of patients including both those with newly diagnosed and relapsed/refractory disease treated with thalidomide alone achieved response rates of approximately 25% (Dimopoulos et al, 2001). Thalidomide has also been administered at lower doses in combination with clarithromycin and dexamethasone to patients with WM, with evidence of activity (Dimopoulos et al, 2003b; Coleman et al, 2003).

A study of interferon-α given for 6 months to a mixture of untreated and pretreated patients produced a response rate of 50% with a median duration of response of 27 months (Rotoli et al, 1994). In another small study, interferon-α was used with chlorambucil and prednisolone for induction therapy and continued for maintenance in responders but its contribution to the efficacy of the schedule was difficult to assess (Vela-Ojeda et al, 2002).

Preliminary data exist for the use of radioimmunotherapy with 131I-tositumomab (Tsai et al, 2004), oblimersen sodium (G3139 BCL-2 antisense oligonucleotide; Frankel, 2003) and bortezomib (Strauss et al, 2004; Dimopoulos et al, 2005) in the treatment of WM.

Statement. Thalidomide is of potential use in the treatment of patients who have previously received alkylating agents, purine analogues and antibody therapy. Other agents are currently only recommended in the context of clinical trials – Level of evidence III, grade of recommendation B.

High-dose therapy

Recently, autologous peripheral blood stem cell transplantation has been performed in patients with WM. High doses of alkylating agent, especially melphalan alone or in combination with total body irradiation, have been employed in small cohorts of WM patients. The number of patients is too small and the follow up too short to evaluate the role of this treatment in WM...
Table VI. Rituximab monotherapy and thalidomide in WM.

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Duration of treatment</th>
<th>Median age (years)</th>
<th>Prior treatment</th>
<th>Number of patients</th>
<th>Overall response (CR + PR)%</th>
<th>Response duration (months)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rituximab 375 mg/m² weekly</td>
<td>4 or 8 cycles</td>
<td>60</td>
<td>Yes</td>
<td>7</td>
<td>43</td>
<td>MRD = 7</td>
<td>Byrd et al (1999)</td>
</tr>
<tr>
<td>Rituximab 375 mg/m² weekly</td>
<td>4 cycles</td>
<td>59</td>
<td>Yes</td>
<td>7</td>
<td>29</td>
<td>N/S</td>
<td>Foran et al (2000)</td>
</tr>
<tr>
<td>Rituximab 375 mg/m² weekly</td>
<td>8 cycles (weeks 1–4 and 12–15)</td>
<td>72</td>
<td>Yes</td>
<td>12</td>
<td>50</td>
<td>MRD = 16</td>
<td>Dimopoulos et al (2002b)</td>
</tr>
<tr>
<td>Rituximab 375 mg/m² weekly</td>
<td>4 cycles</td>
<td>60</td>
<td>Yes</td>
<td>23</td>
<td>27</td>
<td>MRD = 8</td>
<td>Treon et al (2001)</td>
</tr>
<tr>
<td>Rituximab 375 mg/m² weekly</td>
<td>8 cycles (weeks 1–4 and 12–15)</td>
<td>74</td>
<td>None</td>
<td>17</td>
<td>35</td>
<td>MRD = 13</td>
<td>Dimopoulos et al (2002a)</td>
</tr>
<tr>
<td>Rituximab 375 mg/m² weekly</td>
<td>4 cycles</td>
<td>66</td>
<td>None</td>
<td>34</td>
<td>35</td>
<td>MRD = 27</td>
<td>Gertz et al (2004)</td>
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<tr>
<td>Rituximab 375 mg/m² weekly</td>
<td>8 cycles (weeks 1–4 and 12–15)</td>
<td>70</td>
<td>Yes</td>
<td>35</td>
<td>20</td>
<td>MRD = 29+</td>
<td>Treon et al (2005)</td>
</tr>
<tr>
<td>Thalidomide 100–600 mg/d</td>
<td>N/S</td>
<td>74</td>
<td>None</td>
<td>17</td>
<td>48</td>
<td>MRD = 11</td>
<td>Dimopoulos et al (2001)</td>
</tr>
<tr>
<td>Thalidomide 50–200 mg/d + clarithromycin 1000 mg/d + Dex 40 mg/week</td>
<td>N/S</td>
<td>62</td>
<td>Yes</td>
<td>12</td>
<td>83</td>
<td>N/S</td>
<td>Coleman et al (2003)</td>
</tr>
<tr>
<td>Thalidomide 200 mg/d + clarithromycin 1000 mg/d + Dex 40 mg/week</td>
<td>N/S</td>
<td>71</td>
<td>Yes</td>
<td>12</td>
<td>25</td>
<td>N/S</td>
<td>Dimopoulos et al (2003b)</td>
</tr>
</tbody>
</table>

Dex, dexamethasone; CR, complete response; PR, partial response; MRD, median response duration; NS, not stated.
(Desikan et al., 1999; Dreger et al., 1999; Yang et al., 1999; Anagnostopoulos et al., 2001, 2003; Munshi & Barlogie, 2003; Tournilhac et al., 2003). Small numbers of allogeneic transplants have also been performed in this setting (Martino et al., 1999; Anagnostopoulos et al., 2001, 2003; Tournilhac et al., 2003) with complete response achieved in some patients. Most WM patients are too old to tolerate the high-dose chemoradiotherapy associated with the conventional transplantation procedure but non-myeloablative allogeneic peripheral blood stem cell transplantation might prove to be a promising alternative treatment in refractory patients (Ueda et al., 2001).

Statement. High-dose therapy supported by autologous stem cell transplantation has a role in the management of selected patients with WM with primary refractory or relapsed disease – Level of evidence III, grade of recommendation B.

Future developments

The definition of the best initial therapy for patients with a wide range of chronic lymphoproliferative disorders requiring treatment is unclear because of the high likelihood of obtaining a further response when patients relapse or progress at a later time. The results of second- and third-line therapies have an inevitable impact on the overall clinical course and so analysis of the effect of initial therapy on survival is profoundly affected. The use of careful immunophenotypic criteria can now define a more homogenous population of patients with WM, which will reduce the risk of including other distinct lymphoid malignancies.

A prospective randomised trial has opened to compare the effect of initial therapy with fludarabine or chlorambucil. The study is projected to require a total of 400 patients and currently involves collaborative groups of clinicians in the UK, France, Austria, Germany and Australia; it will assess the effect of treatment in terms of response to therapy, duration of response, improvement in haematological parameters, comparative toxicity of therapy, quality of life and survival; randomisation and data collection are entirely Internet-based and the trial site can be accessed at http://www.waldenstrom.org. Evaluation of treatments with activity for patients at later stages in the disease, particularly those who are refractory to chemotherapy, is an important priority. More detailed studies of the activity of therapeutic antibodies, such as rituximab, both alone and in combination with chemotherapy, are needed in this setting. The scope for high-dose therapy and allogeneic transplantation may be limited by the age of many patients with WM; however, procedures such as non-myeloablative transplantation may prove to be of benefit to selected patients.

Disclaimer

While the advice and information in these guidelines is believed to be true and accurate at the time of going to press, neither the authors, the British Society for Haematology nor the publishers accept any legal responsibility for the content of these guidelines.

Declarations/conflicts of interest

SAJ has received support to travel to meetings and fees for speaking at satellite symposia from Schering and Roche and has served on the advisory boards of Schering, Roche and Janssen-Cilag. RGO has received support to attend meetings and fees for lectures and organising educational events from Roche and support for research from Roche, Amgen and Schering. DGO has received support to attend meetings from Schering and Roche. The WM1 trial is supported by an unrestricted grant from Schering Healthcare.

References


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### Appendix 1

#### Levels of evidence

<table>
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<tr>
<th>Level</th>
<th>Type of evidence</th>
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<tbody>
<tr>
<td>Ia</td>
<td>Evidence obtained from meta-analysis of randomised-controlled trials</td>
</tr>
<tr>
<td>Ib</td>
<td>Evidence obtained from at least one randomised-controlled trial</td>
</tr>
<tr>
<td>Iia</td>
<td>Evidence obtained from at least one well-designed controlled study without randomisation</td>
</tr>
<tr>
<td>Iib</td>
<td>Evidence obtained from at least one other type of well designed quasi-experimental study</td>
</tr>
<tr>
<td>III</td>
<td>Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies.</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence obtained from expert committee reports or opinions and/or clinical experiences of respected authorities</td>
</tr>
</tbody>
</table>

#### Grades of recommendation

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<th>Evidence</th>
<th>Level recommendation</th>
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<tr>
<td>A</td>
<td>Ia, Ib</td>
<td>Required – at least one randomised-controlled trial as part of the body of literature of overall good quality and consistency addressing specific recommendation</td>
</tr>
<tr>
<td>B</td>
<td>Iia, Iib, III</td>
<td>Required – availability of well-conducted clinical studies but no randomised-controlled trials on the topic of recommendation</td>
</tr>
<tr>
<td>C</td>
<td>IV</td>
<td>Required – evidence obtained from expert committee reports or opinions and/or clinical experiences of respects authorities Indicate absence of directly applicable clinical studies of good quality</td>
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</table>