British Society for Haematology

British Committee for Standards in Haematology

Guidelines on diagnosis and therapy

Waldenström's macroglobulinaemia

guidelines

Abbreviations

ALL	acute lymphoblastic leukaemia
ALT	alanine aminotransferase
AML	acute myelogenous leukaemia
BM	bone marrow
CAP	cyclophosphamide + doxorubicin + prednisolone
2-CDA	2-chlorodeoxyadenosine (cladribine)
CHOP	cyclophosphamide + doxorubicin + vincristine + prednisolone
CLL	chronic lymphocytic leukaemia
CML	chronic myelogenous leukaemia
COP	see CVP
CR	complete remission
CT	computerised tomography
CVP	cyclophosphamide + vincristine + prednisolone
2´-DCF	2´-deoxycoformycin (pentostatin)
DFI	disease-free interval
EFS	event-free survival
G-CSF	granulocyte colony stimulating factor
GM-CSF	granulocyte–macrophage colony stimulating factor
Hb	haemoglobin
HC	haemochromatosis
HCL	hairy cell leukaemia
IFN	interferon
LPL	lymphoplasmacytic lymphoma
McAb	monoclonal antibody
MGUS	monoclonal gammopathy of uncertain significance
MRD	median remission duration / minimal residual disease
MS	median survival
NHL	non-Hodgkin’s lymphoma
PB	peripheral blood
PLL	prolymphocytic leukaemia
PR	partial remission
SLVL	splenic lymphoma with villous lymphocytes
SMZL	splenic marginal zone lymphoma
TRAP	tartrate resistant acid phosphatase
UIBC	unsaturated iron-binding capacity
WBC	white blood cell (count)
WM	Waldenström’s macroglobulinaemia

Waldenström's macroglobulinaemia

A guideline compiled on behalf of the Clinical Task Force of the British Committee for Standards in Haematology by

Drs David Oscier and Stephen Johnson

Methods

- Provided as a solicited draft guideline
- Reviewed by members of the Clinical Task Force
- Presented at Open Forum to attendees at the BSH Annual Meeting, Brighton, April 1999
- Revised as necessary
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Clinical Task Force of BCSH: Prof AK Burnett (Chair), Drs D Milligan, R Marcus, J Apperley, P Ganly, S Johnson, J Davies (Secretary), SE Kinsey

1 Introduction: The diagnostic problem

WM is a chronic B-cell lymphoproliferative disorder characterised by bone marrow infiltration with small lymphocytes, lymphoplasmacytoid cells and plasma cells and a high level of IgM paraprotein[1]. 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[2]. The immunophenotype (IgM+, IgD-, CD19+, CD20+, CD22+, CD5-, CD10- and CD23-) and the presence of somatic mutation of V genes without intraclonal diversity, are consistent with origin from a cell which has traversed the germinal centre[3,4].

There have been few cytogenetic or genetic studies in WM, and no consistent recurring abnormalities have been found[5,6]. A t(9;14) has been associated with a subgroup of small lymphocytic lymphomas with plasmacytoid differentiation, but none of these patients had a serum paraprotein[7]. The differential diagnosis includes other chronic lymphoproliferative disorders associated with an IgM paraprotein, such as chronic lymphocytic leukaemia, and splenic lymphoma with villous lymphocytes (SLVL) / splenic marginal zone lymphoma (SMZL). Differences in the level of serum paraprotein, lymphocytic morphology and degree of marrow involvement in relation to spleen size may help to distinguish WM from SLVL/SMZL. However, these disorders share the same immunophenotype, and WM has been regarded as a 'bone marrow marginal zone lymphoma'[3].

Table 1 Diagnosis

- lymphoplasmacytoid infiltration of marrow
- IgM+, IgD-, CD19+, CD20+, CD22+, CD5-, CD10-, CD23-
- IgM paraprotein

Table 2 Differential diagnosis

- monoclonal gammopathy of uncertain significance (MGUS)
- chronic lymphocytic leukaemia with IgM paraprotein
- splenic lymphoma with villous lymphocytes (SLVL) / splenic marginal zone lymphoma (SMZL)

The distinction between monoclonal gammopathy of uncertain significance (MGUS) and WM is controversial. In a large retrospective study in which MGUS was defined as IgM protein < 30 g/l and no constitutional symptoms, organomegaly or anaemia, 22 of 242 patients developed WM after a median of 8 years[8]. The incidence of WM per million person-years at risk is 3.4 for males and 1.7 for females. WM is predominantly a disease of the elderly, and the incidence over the age of 75 rises to 36.3 for men and 16.4 for women. In the USA the disease is more common in whites than in blacks[9]. Clinical features may be the result of the paraprotein (hyperviscosity, cryoglobulinaemia, cold agglutinin anaemia, peripheral neuropathy) constitutional symptoms, or tumour infiltration, particularly bone marrow failure. Adverse prognostic factors include age > 60 years and cytopenias but not initial tumour burden or IgM levels. WM may remain stable for many years. Disease progression may be due to a rising paraprotein concentration and/or progressive lymphoid infiltration. The overall median survival is approximately 5 years and increases to 7–9 years for patients who respond to treatment. The causes of death are related to infection and marrow failure, particularly in patients who become drug resistant. In a minority of patients WM transforms into a high-grade B-cell lymphoma. Approximately 20% of patients die from an incidental cause.

2 Management

Published studies on the treatment of WM are predominantly small phase II studies which differ considerably in their inclusion criteria and assessment of response. No studies have assessed quality of life or included an economic evaluation. Treatment modalities include the following.

Plasmapheresis

Plasmapheresis is indicated for the acute management of clinically severe complications related to either the level or properties of the paraprotein. A single plasma exchange can result in a reduction in IgM level of 35% with a decrease in plasma viscosity of 50–60%[11]. Since 80% of the IgM paraprotein is intravascular the benefit may last 4–6 weeks. Plasmapheresis is normally a short-term treatment until concomitant chemotherapy becomes effective but rarely may be indicated on a long-term basis in patients with hyperviscosity who are drug resistant[12] or in patients whose only clinical problem is due to the paraprotein (e.g. neuropathy) rather than tumour burden.

Alkylating agents

Chlorambucil with or without prednisolone is frequently used as the initial therapy in WM (Table 3). Responses are usually slow and toxicity is minimal providing the dose is adjusted if cytopenias ensue. The response rate is approximately 60% and the median survival approximately 60 months. 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[13]. The optimal duration of treatment is unknown. There are no data on the use of high-dose chlorambucil in WM. Cyclophosphamide is also effective in WM but there are no comparative data with chlorambucil.

Table 3 Use of chlorambucil as a single agent in the primary treatment of WM

Regimen	Duration of treatment	Median age (years)	Prior treatment	No. of patients	Overall response (%)	CR (%)	Median survival (months)	Ref.
0.1 mg/kg/day	6–12 months after plateau	70	None	117			60	10
8 mg/day + prednisolone 40 mg/day for 10 days every 6 weeks	Until maximum reduction of IgM level	77	None	77	57	10	60	1
0.1 mg/kg/day or 0.3 mg/kg for 7 days every 6 weeks		63	None	24 22	75 64		64 (no difference between regimens)	13

Combination chemotherapy

There are several phase II studies using combination chemotherapy as primary therapy in WM (Table 4). The indications for therapy, patient selection and response criteria are variable but the reported response rate and median survival are higher than those in studies using chlorambucil. There has been no comparative study of chlorambucil versus combination therapy.

Table 4 Combination therapy in WM

Regimen	Duration of treatment	Median age (years)	Prior treatment	No. of patients	Overall response (%)	CR (%)	Outcome	Ref.
M2 protocol	Every 5 weeks for 2 years; then every 10 weeks for 1–3 years	70	7 patients had C + P	33	82	18	MRD 40 months; 54% projected alive at 10 years	14
Melphalan 6 mg/m^2 + cyclophosphamide 125 mg/m^2 + prednisone 40 mg/m^2 for 7 days every 4–6 weeks	12 courses; then responders received chlorambucil 3 mg/m^2/day + prednisone 6 mg/m^2/day until relapse	61	None	34	74	23	MRD > 100 months; median EFS 66 months	15
CVP			None	16	44		MS 36 months	1
CHOP			None	20	65		MS 87 months	1

Purine analogues

Initial therapy

Details of studies of fludarabine treatment and of 2-chlorodeoxyadenosine (2-CDA) treatment are given in Tables 5 and 6, respectively. In a single phase II study, reported only in abstract form, an overall response rate of 34% with 15% complete remissions was achieved in patients receiving 4 cycles of fludarabine followed by a further 4 cycles for responding patients[18]. In smaller studies using 2-CDA either by continuous infusion, bolus injection or subcutaneously, the response rate has varied between 85% and 40%. Most patients received between 2 and 4 courses of treatment. The median duration of response to purine analogues has varied between 13 and 36 months, but longer responses are found in patients receiving more cycles of therapy. Responses are rapid and usually evident after 2 cycles of therapy. Toxicity is primarily haematological, with 60% of patients developing grade 3 neutropenia. Infectious and autoimmune complications are reported as in CLL.

Table 5 **Use of fludarabine in WM**

Regimen	Duration of treatment	Median age (years)	Prior treatment	Number of patients	Overall response (%)	CR (%)	Outcome	Ref.
20–30 mg/m^2 i.v. for 5 days	Until maximum response (median 3 cycles)	60	None 1^o refractory Refractory relapse	2 14 12	100 43 17	50	MRD 38 months MS 32 months	16
25 mg/m^2 i.v. for 5 days	6 cycles	56	1^o refractory Refractory relapse	4 8	50 37			17
30 mg/m^2 i.v. for 5 days	4 cycles + 4 additional cycles for responders	66	None None	101 117 (eval) 57	 34 	 15 	MS 42 months MRD 36 months	 18
25 mg/m^2 i.v. for 5 days	Until maximum response (median 6 cycles)	68	1^o refractory Refractory relapse	8 63	30	0	MS 23 months MRD 32 months	19
25 mg/m^2 i.v. for 5 days	6 courses		1^o refractory or 1st relapse	92	28		No difference in MS	20
vs CAP	6 courses				11			

Table 6 **Use of 2-CDA in WM**

Regimen	Duration of treatment	Median age (years)	Prior treatment	Number of patients	Overall response (%)	CR (%)	Outcome	Ref.
0.1 mg/kg c.i.	2 cycles	65 Relapse off R	None 1^o refractory Refractory relapse 4	9 9 7 75	100 44 14 			 21
0.1 mg/kg c.i. for 7 days	2 cycles + 2 additional cycles on relapse	65	None	26	85	11	MRD 13 months	22
0.1 mg/kg c.i. for 7 days	2 cycles	60	1^o refractory Refractory relapse Relapse off R	20 17 9	45 17 78		MS 28 months MRD 12 months	 23
4 mg/m^2/day c.i. for 7 days (5 pts) or 2 h infusion for 5 days (13 pts)	Median of 2 cycles	69	None Refractory relapse Relapse off R	5 9 4	40 33 50			 24
0.5 mg/kg s.c. for 5 days	Median of 3 cycles	65	Refractory relapse Relapse off R	18 6	39 50		MRD 8 months	25
0.12 mg/kg i.v. for 5 days	3 cycles; then 1 cycle if CR or continue until max response if PR	66	None Yes	7 13	57 53	25 0	86% survival at 48 months MRD 28 months	 26

Treatment for refractory or relapsed disease

There are several phase II studies of purine analogues in patients who have received prior therapy, usually with alkylating agents. The response rates vary from 14% to 78% and are highest for patients still sensitive to their primary therapy. 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[18]. The preliminary results of a multicentre randomised study comparing fludarabine with cyclophosphamide, doxorubicin and prednisolone (CAP) in 92 patients in first relapse or with primary refractory disease following treatment with alkylating agents show a higher response rate in the fludarabine arm (28% vs 11%) although there was no difference in overall median survival[20]. There is no consensus on the mode of administration of 2-CDA, the duration of treatment with 2-CDA or fludarabine, or which purine analogue is superior. There are no data on the use of purine analogues in combination with other treatments in WM.

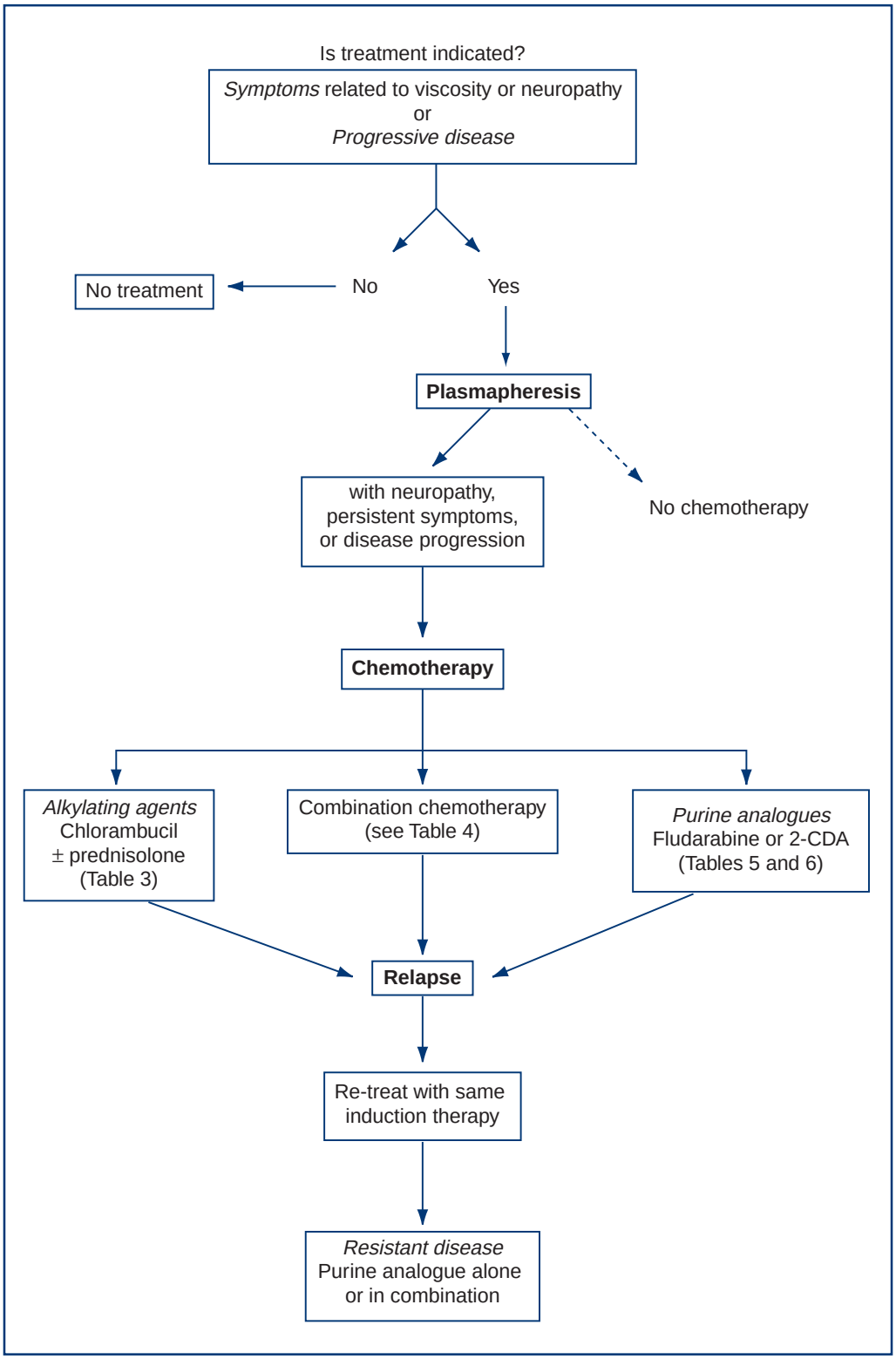

Figure 1 Management of WM

Other treatments

There are two small studies using anti-CD20 (rituximab) in heavily pretreated patients with WM or LPL (Table 7). The response rate varied between 23% and 57%, and in one study the median duration of response was 8 months. There are no data on the use of CAMPATH-1H in WM. A study of interferon-alpha 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. There are no confirmatory studies.

Very small studies using high-dose steroids[31] and single-agent anthracyclines[32] have been reported, but the data are not evaluable. Paclitaxel appears ineffective in WM[33]. Recently, autologous peripheral blood stem cell transplantation has been performed in 6 patients with WM, 4 of whom had relapsed after prior therapy. All responded, including 1 CR. The number of patients is too small and the follow-up too short to evaluate the role of this treatment in WM[34].

Table 7 Miscellaneous treatments for WM

Regimen	Duration of treatment	Median age (years)	Prior treatment	Number of patients	Overall response (%)	CR (%)	Outcome	Ref.
Interferon-alpha 3 MU daily for 1 month; then 3 times/week	6 months	66	15/36	36	50	8	MRD 27 months	27
Interferon-gamma 0.25 mg/m^2/day		62	Yes	5	20			28
Anti-CD20 (rituximab) 375 mg/m^2 weekly	4 or 8 cycles	60	Yes	7	57		MRD 8 months	29
Anti-CD20 (rituximab) 375 mg/m^2 weekly	4 cycles	64	Yes	26	23			30

Recommendations

1. There are no data to suggest that patients with MGUS or stable WM benefit from treatment. Therapy should currently be reserved for symptomatic patients or where there is clear evidence of disease progression such that clinical problems are likely to ensue in the near future.

2. WM is currently incurable. The aim of treatment should be to improve the quality and duration of life with minimal side effects in the most cost effective manner. There is evidence that the survival of patients who respond to therapy is better than for those with resistant disease. 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.

3. Options for the primary therapy of WM include a single alkylating agent, an alkylating agent in combination with an anthracycline or anthracinedione ± steroids, or a purine analogue. *The evidence supporting activity of these treatments consists entirely of level III or IV reports but is sufficiently extensive that these choices can all be recommended at grade B*. There are no comparative data but combination therapy or alkylating agents may be more suitable for younger patients with aggressive disease. Those patients who achieve a CR may be suitable for stem cell collection and subsequent autologous transplantation. *However, the evidence for this approach is very limited (level IV) and the confidence with which it can be recommended is grade C.* As discussed above, plasmapheresis is indicated for the acute management of patients with severe problems due to a circulating paraprotein. *Although the evidence is only at level IV, the recommendation can be made at grade B*.

4. Patients who relapse after responding to primary therapy are likely to respond again to the initial regimen. Patients who are primarily refractory or acquire resistance to alkylating agents may be candidates for combination therapy such as CAP, purine analogues, or antibody therapy. Preliminary data suggest a higher response rate using fludarabine rather than CAP, but it is unclear whether the activity was similar in both the primary refractory and relapsed groups of patients. Patients with resistance to purine analogues may be considered for CAP, combination regimens which include a purine analogue, or antibody treatment. There are no data which compare the effectiveness of these approaches.

Table 8
Key recommendations

1. Reserve treatment for symptomatic patients or those with progressive disease
2. Relieve symptoms in the short term by plasmapheresis
3. Chemotherapy with a single alkylating agent alone *or* in combination with an anthracycline or anthracinedione with or without prednisolone, *or* a purine analogue
4. Treat relapse with same initial treatment. For refractory disease, combination therapy, a purine analogue, or experimental therapy (e.g. a monoclonal antibody) may induce a response

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PR	partial remission
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SMZL	splenic marginal zone lymphoma
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WM	Waldenström’s macroglobulinaemia

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