Waldenström’s macroglobulinaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

C. Buske1, V. Leblond2, M. Dimopoulos3, E. Kimby4, U. Jäger5 & M. Dreyling6, on behalf of the ESMO Guidelines Working Group⁎

1Comprehensive Cancer Center Ulm, Institute of Experimental Cancer Research, University Hospital Ulm, Ulm, Germany; 2Departement of Hematology Pitié Salpêtrière Hospital, Pierre et Marie Curie University, UPMC IRC11-GRECHY, 75013 Paris, France; 3Department of Clinical Therapeutics, University of Athens School of Medicine, Alexandra Hospital, Athens, Greece; 4Department of Medicine at Huddinge, Division of Hematology, Karolinska Institutet and The Hematology Center, Karolinska University Hospital, Stockholm, Sweden; 5Division of Haematology and Haemostaseology, Department of Medicine I, Medical University of Vienna (MUW), Vienna, Austria; 6Department of Medicine III, University Hospital Grosshadern, LMU Munich, Germany

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incidence

Waldenström’s macroglobulinaemia (WM) is a rare disease. It accounts for 1%–2% of haematological neoplasms with a reported age-adjusted incidence rate of 3.4 per million among males and 1.7 per million among females in the United States and 7.3 and 4.2 per million European standard population [1, 2]. WM is a disease of the elderly with a median age of 63–68 years with a male predominance.

diagnosis

To establish the diagnosis of WM, it is necessary to demonstrate an IgM monoclonal protein, along with histological evidence of infiltration of the bone marrow by lymphoplasmacytic cells in line with the diagnosis of lymphoplasmacytic lymphoma (LPL) [3]. Thus, detection of monoclonal IgM without the histopathological diagnosis of LPL cannot be considered to be WM. Conversely, the diagnosis of LPL without detection of monoclonal IgM does not fulfil the criteria of WM.

Lymphoplasmacytic cell population in the bone marrow should be documented by trephine biopsy and aspiration. The bone marrow infiltration should routinely be confirmed by immunophenotypic studies (flow cytometry and/or immunohistochemistry) showing expression of CD 19, CD 20, CD 22 and CD 79a.

The presence of monoclonal IgM should be confirmed by immunofixation. Determination of IgM levels can be based on either densitometry or total serum IgM quantitation by nephelometry. Because IgM values when assessed by nephelometry are systematically higher than M protein values determined by densitometry, it is essential that sequential response assessments for individual patients are carried out with the same methodology, optimally in the same laboratory because of known intralaboratory as well as interlaboratory variations [4]. To test for IgM-associated coagulopathy and haemolysis, Coombs test and testing for cold agglutinin disease and coagulation parameter are recommended. The presence of cold agglutinins or cryoglobulins may affect the determination of IgM levels; therefore, testing for cold agglutinins and cryoglobulins should be carried out at diagnosis. Serum-free light chain testing is not advised in routine practice as its relevance for the management of WM patients is currently under evaluation. Recent findings documented a strong association between WM and the MYD88 L265P variant, which might serve as an additional tool to diagnose WM and to separate it from other entities such as multiple myeloma, monoclonal gammopathy of undetermined significance, splenic marginal zone lymphoma and MALT lymphoma [5].

staging and risk assessment

Besides documentation of monoclonal IgM gammopathy, as mentioned above, staging should include a complete blood count with differential and more detailed serum chemistry. Furthermore, the beta2 microglobulin and albumin levels should be determined, as these factors have prognostic impact. Serum protein electrophoresis and quantification of immunoglobulin levels (IgM, IgG, IgA) should be carried out. Some patients suffer from hyperviscosity caused by excessive levels of IgM. In this case, quantification of serum viscosity might be helpful. However, serum viscosity does not always correspond well to the clinical severity of hyperviscosity. More important are clinical examinations such as fundoscopy, showing, e.g. venous engorgement (‘sausaging’) in the retinal veins, which is an excellent indicator of clinically relevant hyperviscosity [6]. In the case of peripheral neuropathy, the evaluation of anti-myelin-associated glycoprotein, antigangliosides M1 and anti-sulfatide IgM antibodies may support the diagnosis of IgM-related neuropathy. Also, the possibility of amyloid light-chain
amyloidosis in association with peripheral neuropathy needs to be considered. At diagnosis, an ultrasound or computed tomography (CT) scan should be carried out to document organomegaly/adenopathies. There is no routine role for positron emission tomography (PET) scanning unless a large-cell lymphoma transformation is suspected.

With regard to risk assessment, all patients should be categorised by the international prognostic scoring system for WM (ISSWM), which divides patients into three risk groups with a 5-year survival rate ranging from 86% for the low-risk to 36% for the high-risk group. This is built on factors which are easy to determine in clinical practice (Table 1) [7].

### treatment plan

#### asymptomatic patients

Comparable with other indolent lymphomas, a watch and wait approach is standard for asymptomatic patients, meaning that only patients suffering from lymphoma-related symptoms should start treatment [8]. In the case of WM, this includes symptoms caused by circulating IgM such as hyperviscosity, amyloidosis, symptomatic cryoglobulinaemia, cold agglutinin disease, neuropathy or disease-related haemoglobin level <10 g/dl or platelet count <100 × 10⁹/l. On the other hand, monoclonal IgM per se is not a reason to initiate treatment [9]. A close observation is appropriate for these patients.

#### first line

Frontline treatment options include alkylating agents, nucleoside analogues, bortezomib and the monoclonal antibody rituximab. Fludarabine as a single agent is more effective than chlorambucil [I, B] [10]. The combination of rituximab with chemotherapy is among the most effective treatments and the first option to choose and should be considered in medically fit patients and, in particular, in patients who need rapid response.

Options for rituximab in combination with alkylating agents are DCR (dexamethasone, cyclophosphamide and rituximab) [III, B] [11] or rituximab–CHOP [II, B] [12].

Rituximab can be combined with purine analogues such as cladribine or fludarabine [II, B]. Bendamustine, which carries characteristics of both alkylating agents and purine analogues, in combination with rituximab is highly effective in WM [II, B] [13].

Bortezomib has shown considerable activity in combination with rituximab in the first-line treatment of WM with or without dexamethasone [III, B] [14, 15]. In medically non–fit patients (e.g. patients who do not tolerate chemotherapy because of non-lymphoma related co-morbidities), single-agent rituximab is a treatment option, which avoids chemotherapy-related toxic effects [III, B] [16]. However, responses are delayed and, particularly in patients with signs of hyperviscosity or patients with high IgM values, there is the danger of so-called ‘IgM flare’, a transient increase of serum IgM immediately following initiation of rituximab treatment [17, 18]. In these patients, plasmapheresis should precede rituximab application. Figure 1a summarises the treatment algorithm for first-line therapy.

Rituximab maintenance treatment outside of clinical trials is not considered standard today. There are retrospective data suggesting clinical benefit for rituximab maintenance also in WM, but prospectively randomised data are still missing [19].

#### relapsed disease

There is a consensus that an alternative rituximab/chemotherapy regimen should be used if the relapse occurs within the first year [8, 20]. The choice of the rituximab/chemotherapy depends on the prior regimen. If the patient was treated initially with rituximab plus alkylating agents, the salvage regimen could be switched to rituximab in combination with nucleoside analogues, rituximab/bendamustine or bortezomib and vice versa.

If patients are chemosensitive and eligible for autologous stem cell transplantation, myeloablative chemotherapy followed by reinfusion of autologous stem cells is a valid option in these clinically aggressive cases [III, B] [21]. Allogeneic transplantation may be considered in young relapsed patients with aggressive clinical course, but preferably within clinical trials [22]. Figure 1b summarises the treatment algorithm for therapy in relapsed patients.

#### response evaluation

WM is distinct with regard to response criteria and differs in this respect from other lymphomas. This is in particular due to the fact that the level of reduction of the monoclonal IgM affects remission status, and that its disappearance is one of the prerequisites for the definition of complete response in this disease. There is an international consensus on how to define the remission status in WM. These response criteria should be used in and outside of clinical trials to be able to compare treatment results (Table 2) [4]. Because of the variability in kinetics of IgM reduction with different treatment modalities and the apparent discrepancy between IgM and bone marrow/tissue response noted with many regimens, sequential bone marrow trephine biopsies are strongly encouraged and mandatory inside clinical trials. Ultrasound or CT should only be carried out in the case of initial splenomegaly/lymph node enlargements. A PET–CT scan is not indicated in WM.

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**Table 1.** International prognostic scoring system for Waldenström’s macroglobulinaemia (ISSWM) adapted from [7]

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
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<tr>
<td>Score</td>
<td>0–1 (except age)</td>
<td>≥ 2</td>
<td>≥ 3</td>
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<tr>
<td>5-year OS* (%)</td>
<td>87</td>
<td>68</td>
<td>36</td>
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<tr>
<th>Risk Factors</th>
<th>Score</th>
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<tbody>
<tr>
<td>Age ≥ 65 years</td>
<td>1</td>
</tr>
<tr>
<td>Other risk factors b</td>
<td>1</td>
</tr>
<tr>
<td>HB ≥ 11.5 g/dl</td>
<td>1</td>
</tr>
<tr>
<td>Thrombo ≤ 100,000 × 10⁹/l</td>
<td>1</td>
</tr>
<tr>
<td>Beta-2 M ≥ 3 mg/l</td>
<td>1</td>
</tr>
<tr>
<td>IgM &gt; 70 g/l</td>
<td>1</td>
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*OS, overall survival.

bEach of the risk factors is counted as one.

βHb, haemoglobin.

Thrombo, thrombocytes.

β-2 M, beta-2 microglobulin.

IgM, monoclonal protein concentration.
**personalised medicine**

In this disease setting, more research is needed to identify molecular markers which could lead to advances in personalised medicine.

**follow-up**

Follow-up should include history, physical examination, blood count, routine chemistry and quantification of IgM every 3 months for 2 years, every 4–6 months for an additional 3 years, and
subsequently once a year with special attention to transformation and secondary malignancies, including secondary leukaemia. Minimal adequate radiological or ultrasound examinations every 6 months for 2 years are recommended, and annually thereafter only in cases of initial splenomegaly or lymph node enlargement. Regular CT scans are not necessary outside clinical trials.

Table 2. Response criteria in Waldenström’s macroglobulinaemia (WM) [4]

<table>
<thead>
<tr>
<th>Response category</th>
<th>Definition</th>
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| Complete response (CR)         | (i) Absence of serum monoclonal IgM protein by immunofixation  
(ii) Normal serum IgM level  
(iii) Complete resolution of lymphadenopathy and splenomegaly if present at baseline  
(iv) Morphologically normal bone marrow aspirate and trephine biopsy |
| Very good partial response (VGPR) | (i) Monoclonal IgM protein is detectable  
(ii) ≥90% reduction in serum IgM level from baseline*  
(iii) Decreased lymphadenopathy/splenomegaly if present at baseline  
(iv) No new signs or symptoms of active disease |
| Partial response (PR)          | (i) Monoclonal IgM protein is detectable  
(ii) ≥50% but <90% reduction in serum IgM level from baseline  
(iii) Decreased lymphadenopathy/splenomegaly if present at baseline  
(iv) No new signs or symptoms of active disease |
| Minor response (MR)            | (i) Monoclonal IgM protein is detectable  
(ii) ≥25% but <50% reduction in serum IgM level from baseline  
(iii) No new signs or symptoms of active disease |
| Stable disease (SD)            | (i) Monoclonal IgM protein is detectable  
(ii) <25% reduction and <25% increase in serum IgM level from baseline  
(iii) No progression in lymphadenopathy/splenomegaly  
(iv) No new signs or symptoms of active disease |
| Progressive disease (PD)       | (i) ≥25% increase in serum IgM levels from lowest nadir and/or  
(ii) Progression in clinical features attributable to the disease |

*Sequential changes in IgM levels may be determined either by M protein quantitation by densitometry or total serum IgM quantitation by nephelometry ([4]. ©2012 Blackwell Publishing Ltd. Reprinted with permission).

Table 3. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System*)

<table>
<thead>
<tr>
<th>Levels of evidence</th>
<th>Definition</th>
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<tbody>
<tr>
<td>I</td>
<td>Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted, randomised trials without heterogeneity</td>
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<tr>
<td>II</td>
<td>Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity</td>
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<td>III</td>
<td>Prospective cohort studies</td>
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<td>IV</td>
<td>Retrospective cohort studies or case–control studies</td>
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<tr>
<td>V</td>
<td>Studies without the control group, case reports, experts opinions</td>
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<th>Grades of recommendation</th>
<th>Definition</th>
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<tr>
<td>A</td>
<td>Strong evidence for efficacy with a substantial clinical benefit, strongly recommended</td>
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<tr>
<td>B</td>
<td>Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended</td>
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<tr>
<td>C</td>
<td>Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs...), optional</td>
</tr>
<tr>
<td>D</td>
<td>Moderate evidence against efficacy or for adverse outcome, generally not recommended</td>
</tr>
<tr>
<td>E</td>
<td>Strong evidence against efficacy or for adverse outcome, never recommended</td>
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</table>


subsequently once a year with special attention to transformation and secondary malignancies, including secondary leukaemia. Minimal adequate radiological or ultrasound examinations every 6 months for 2 years are recommended, and annually thereafter only in cases of initial splenomegaly or lymph node enlargement. Regular CT scans are not necessary outside clinical trials.

note

Levels of evidence and grades of recommendation have been applied using the system shown in Table 3. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.
conflict of interest

Prof. Buske has reported consultancy/honoraria from Celgene, Pfizer and Roche. Prof. Leblond has reported speaker’s bureau for Roche, Mundipharma, GlaxoSmithKline; advisory board for Roche, Janssen. Dr Dimopoulos has reported honoraria from Celgene, OrthoBiotech, Onyx. Prof. Kimby has reported research support from Roche; advisory board for Teva and Janssen. Prof. Jäger has reported speaker’s honoraria and research support from Roche, Janssen-Cilag, Celgene. Prof. Dreyling has reported: scientific advisory board for Celgene, Janssen, Pfizer, Roche; speaker’s honoraria for Celgene, Janssen, Pfizer, Roche; research funding to the institution from Celgene, Janssen, Mundipharma, Pfizer, Roche.

references