A survey on diagnostic methods and treatment strategies used in patients with Waldenström’s macroglobulinaemia in the Netherlands

S. Klodzinska¹, J.M.I. Vos², M.J. Kersten³, P. Wijermans⁴, M.C. Minnema⁵

¹Department of Haematology, University Medical Centre Utrecht, Utrecht, the Netherlands,
²Department of Internal Medicine/Haematology, St. Antonius Hospital, Nieuwegein, the Netherlands,
³Department of Haematology, Academic Medical Centre, Amsterdam, the Netherlands,
⁴Department of Hematology, HagaHospital, The Hague, the Netherlands, *corresponding author:
tel: +31 (0) 88-7557230, fax: +31 (0)88-7553741, e-mail: m.c.minnema@umcutrecht.nl

ABSTRACT

Background: Waldenström’s macroglobulinaemia (WM) is defined as a lymphoplasmacytic lymphoma primarily located in the bone marrow, accompanied by an immunoglobulin M (IgM) monoclonal protein in the serum. The symptoms are highly variable, which can sometimes lead to a diagnostic delay. Currently, there is a wide range of therapeutic options used for the management of WM but no approved therapeutic agents are available specifically for this disease.

Methods: An online survey was prepared and sent out to haematologists and haemato-oncologists in the Netherlands, together with an invitational letter to participate. Information was gathered about the preferred methods of diagnosing and treating patients with WM in general, and about the last WM patient diagnosed in their department.

Results: 83 (31.8%) responses were obtained, out of which 68 (81.9%) contained responses to all three parts of the survey. The respondents most commonly used either rituximab-CVP or chlorambucil as first-line treatment, whereas rituximab in combination with purine analogues was the most frequently applied second-line treatment. The prevention of an IgM ‘flare’ was managed by the respondents in various ways, and rituximab maintenance treatment was not commonly used.

Conclusion: This survey indicates that in general the diagnostic methods and treatment options for WM are well known to a representative number of Dutch haematologists. The areas of uncertainty are knowledge about asymptomatic vs symptomatic disease, risk of hyperviscosity in relation to IgM level, and the occurrence and prevention of an IgM ‘flare’. These issues should be addressed in clinical research and guidelines to improve care for WM patients in the Netherlands.

KEYWORDS

Waldenström’s macroglobulinaemia, M-protein, immunochemotherapy

INTRODUCTION

Waldenström’s macroglobulinaemia (WM) is a non-Hodgkin’s lymphoma, characterised by infiltration of the bone marrow with small lymphocytes, lymphoplasmacytic cells and plasma cells, accompanied by secretion of monoclonal immunoglobulin M (IgM) protein in the serum.¹ WM is a rare disease, with an overall incidence of approximately 3 per million people per year and about 75-100 newly diagnosed patients in the Netherlands per year. The clinical presentation is variable among patients, and around 50% of WM patients are asymptomatic and do not require therapy at diagnosis.¹ According to current standards, treatment should be initiated only when lymphoma-related clinical symptoms or at least one of the following parameters are present: haemoglobin <6.2 mmol/l, platelets <100 x 10⁹/l, significant organomegaly or adenopathy, hyperviscosity, cryoglobulinaemia, cold agglutinin disease or amyloidosis.¹ Until recently, no treatment recommendations were available for WM patients in the Netherlands. Even internationally, there is no consensus on the standard of
first-line treatment. Additionally, there are no approved therapeutic agents specifically for this disease. The drugs used most often are alkylating agents, such as chlorambucil and cyclophosphamide, purine analogues, rituximab and corticosteroids. Many aspects must be taken into account when deciding on a certain treatment regimen for a WM patient, which may be recognised as quite a complex process by practising clinicians.

In order to examine the currently used diagnostic and therapeutic management of patients with WM, a survey was carried out amongst Dutch haematologists and haemato-oncologists, investigating the strategies used in general as well as the specific methods used in their last patient diagnosed with WM.

**METHODS**

An online questionnaire in Dutch containing 24 questions was prepared, and a link to this survey was sent out to all known haematologists and haemato-oncologists in the Netherlands (n=261) (see Appendix). A reminder was sent after one month. The questionnaires were answered anonymously.

In the first part of the survey, physicians were asked questions relating to the type of hospital (HOVON level, see http://www.hovon.nl/ziekenhuizen/echelonering.html) they work at and the consultation region it belongs to, as well as the availability of various diagnostic methods. HOVON level A hospitals are academic hospitals equipped to perform both allogeneic and autologous stem cell transplants (SCTs). Level B and C hospitals may administer intensive therapy, for example treatment of acute leukemia, but only level B hospitals perform autologous SCTs, and level D hospitals do not treat patients requiring intensive haematological care.

In the second part the questions were focused on the preferred diagnostic methods for diagnosing WM and the line of treatment preferred for newly diagnosed as well as relapsed patients. In the third part, physicians were asked about their last patient diagnosed with WM, the symptoms that led to the suspicion of WM, the therapeutic management of that patient and the time before a response was detected. Most answers were multiple choice and more than one answer was possible if appropriate.

**RESULTS**

Eighty-three surveys (31.8% of total) were completed, out of which 15 (18.1% of responses) were incomplete, because the questions in the third part of the survey were left unanswered. All of the percentages are given as a percentage of respondents who answered the question.

**Basic information about the physician and the hospital**

The single largest group of respondents was between age 45 and 55 (44.6%), and 62.7% of the respondents were 45 years or older. Most worked at an academic hospital (38.6%) or at a HOVON level C (31.3%) hospital, which represents hospitals equipped to give intensive treatment. Out of the ten referral regions, the responses were mostly gathered from haematologists based in the VU University Medical Center and Isala region (8.1%), University Medical Centre Nijmegen St Radboud region (16.9%), University Hospital Maastricht region (15.7%) and the Erasmus Medical Centre (15.7%). Most of the diagnostic tools, including CT scan, protein electrophoresis and bone marrow morphology and histology were readily available in all Dutch hospitals. Tests for cryoglobulins and cold agglutinins were available to 94% and 92% of respondents respectively. Tests with low availability were serum blood viscosity measurement and anti-MAG antibody titre test, available to 7.5% and 5.6% of respondents respectively.

**Diagnostic methods used in patients with WM**

The most frequently used diagnostic methods are the level of the M-protein in the serum as assessed by protein electrophoresis (88%), bone marrow biopsy with immunohistochemistry (84.3%), bone marrow aspirate morphology (77.1%), serum total IgM level (73.5%) and multiparameter flow cytometry of the bone marrow aspirate (72.3%) (figure 1). Furthermore, 43.4% of respondents reported use of the free light chains (FLC) assay. Imaging techniques were less commonly applied, a CT scan was selected by 60.2% of respondents, followed

![Figure 1. Which diagnostic methods do you use to diagnose WM?](image-url)

Commonly used diagnostic methods in Dutch hospitals for diagnosing WM. More than one answer was possible. Numbers are given as absolute value of the responses received.
by chest X-ray and ultrasound of the abdomen, chosen by 32.5% and 28.9% of respondents, respectively. An FDG-PET scan was used by only 4.8% of respondents. For diagnosing and staging of WM a combination of tests is necessary and the respondents used on average seven diagnostic methods (range 2-9). One respondent chose a combination of only two diagnostic methods but no one opted for only one diagnostic method.

Although demonstrating the presence of monoclonal IgM M-protein is essential for the diagnosis of WM, it was not chosen by 12% of respondents. We looked whether these respondents chose the total IgM level as an alternative test, but this was not the case.

Treatment preferences in patients with WM
Two treatment options were preferred in the first line: rituximab-CVP (cyclophosphamide, vincristine, prednisone) in 26 (36.1%) of the respondents, and rituximab in combination with other alkylating agents in 24 (33.3%) (figure 2). In total, 81.9% of the respondents chose a combination of rituximab and chemotherapy as the preferred first line of treatment. Monotherapy with an alkylating agent was the preferred first-line treatment in only 10 (13.9%) of the respondents. None of the respondents indicated rituximab monotherapy, bortezomib, bendamustine or thalidomide as their recommended first line of treatment.

As preferred second-line treatment, respondents indicated the use of rituximab in combination with purine analogues (55.4%). Additionally, rituximab monotherapy (9.6%), bortezomib (18.1%), bendamustine (21.7%), thalidomide (1.2%) and an autologous stem cell transplant (4.8%) were all indicated as possible second-line treatments (figure 2). Respondents indicated on average two (range 1-8) possible options for second-line treatment.

Subsequently, respondents were asked about any precautionary actions used to reduce the risk of hyperviscosity syndrome due to an IgM ‘flare’ reaction when treating patients with rituximab. Twenty-one of the respondents (29.6%) did not use any preventive actions, whereas 22 (31%) stated that as a precautionary measure they avoided using rituximab in the first treatment cycle. The remaining 28 (39.4%) of the respondents stated that in some cases they would use plasmapheresis before starting treatment or do not use rituximab in the first treatment cycle. As a follow-up question respondents were asked at which level of M-protein or IgM they would apply this strategy. The mean reported level was 40 g/l with a range from 20 g/l up to >90 g/l (n=15).

When asked about the use of maintenance therapy 52 (74.3%) of the respondents answered that maintenance therapy is not indicated, whereas 16 (22.9%) of the respondents indicated rituximab as best maintenance therapy. One respondent indicated bortezomib and one respondent indicated thalidomide as best option.

The next series of questions concerned the symptoms which prompted the start of treatment in patients previously diagnosed as asymptomatic. Multiple answers were possible and the most frequent were anaemia (85.5%), symptoms of hyperviscosity (84.3%) and occurrence of B symptoms (79.5%) (figure 3). Nineteen respondents (22.9%) reported that a specific level of M-protein or IgM was the

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**Figure 2.** Which of the given treatment options do you prefer as a first and second line of treatment?

![Graph showing treatment preferences](image)

Preferred first and second line of treatment for WM. More than one answer was possible. Numbers are given as absolute value of the responses received.
main reason to start treatment, at a median M-protein level of 30 g/l (range 20 - >60g/l).

Most recent experience with diagnosis and treatment of a WM patient
To this section 68 responses (81.9% of all responses) were gathered. The questions concerned the number of patients the respondents currently have under observation or treatment, and the diagnostic and treatment methods which were used on their last patient with WM.

Twenty-five (36.8%) respondents stated that they currently have 5-8 patients with WM on follow-up or under treatment, whereas 20 (29.4%) stated that they have more than 8 patients. Twenty respondents (29.4%) have between 2 and 4 patients and the remaining 3 (4.4%) respondents stated that they have 1 or no patients under control or treatment. When asked about the number of patients actively being treated the most frequent response was 0-1 patient (48.5%) or 2-4 patients (45.6%). The age of the last treated patient was ‘between 60 and 70’ in 39.7% and ‘more than 70 years of age’ in 38.2% of the respondents. Only 4 respondents (5.6%) indicated that the age of the last patient was less than 50 years.

The most common symptoms leading to the diagnosis of WM in their last treated patient were anaemia (51.8%) and weakness and fatigue (15.9%) and many respondents selected both answers.

Anaemia was also the most frequently indicated reason to start treatment in 43 (52.9%) of cases. Other indications for the start of therapy included ‘evidence of problems caused by the M-protein’ (29.4%) as well as ‘evidence of disease progression by increase in the level of IgM or M-protein’ (16.2%) and ‘development of B symptoms’ (9.9%). Ten respondents (15.4%) stated that they began treatment as soon as the patient was diagnosed.

The most commonly used first-line therapy to treat the last patient with WM was R-CVP (33.3%). Alkylating agents such as chlorambucil were also commonly used (30.3%). In total, 56% of respondents used rituximab in combination with any chemotherapy, while 4 (6%) gave rituximab monotherapy as first-line treatment to their last patient. Furthermore, respondents choosing a combination of rituximab and chemotherapy as first-line treatment also more often reported (59.3%) that the patient responded to the treatment (defined as a >25% decrease in the M-protein level) within three months of the initiation of treatment, compared with the other first-line treatment options (41.7%). In general, the maximum response was reported to occur in the first part of treatment (cycle 1 to 3-4) in 17 patients (30.4%), in the last part of treatment (cycles 3-4 to 6-8) in 27 patients (48.2%), and after stopping treatment in 12 patients (21.4%). In 38 patients (64.4%) second-line treatment had not yet been necessary, in 14 (23.7%) second-line therapy was started between 1 and 4 years after first-line therapy and in 4 (6%) patients after 4 years. Three patients (5.1%) needed second line of treatment within one year of the last dose of the first-line treatment. Five respondents (8.5%) reported that they used rituximab maintenance therapy for their last patient.

DISCUSSION

The survey had a response rate of 31.8%. Responses were evenly spread among all of the ten haematological consultation regions in the Netherlands. The majority of respondents were experienced haematologists, but selection bias is of course always present in this type of research. Respondents may be haematologists with a specific interest in WM and answers may be partly guessed due to lack of memory of details or answers may be given that are the ‘expected correct’ answers instead of reflecting daily practice.

Many of the diagnostic methods important for the diagnosis of WM are easily accessible in Dutch hospitals. As expected, most respondents use a combination of tests to confirm the diagnosis. The five methods used most frequently were blood tests assessing the M-protein and total IgM levels, bone marrow biopsy with immunohistochemistry, as well as multiparameter flow cytometry and morphology of the bone marrow aspirate. Surprisingly, many respondents (72.3%) chose multiparameter flow cytometry as one of the diagnostic methods, which is indeed very helpful but is not mentioned in international guidelines as a required test. The FLC assay was chosen...
by 43.4% of the respondents, although this method has not shown to have additive value in patients with WM. The preferred first line of treatment according to most respondents (81.5%) was immunochemotherapy. Although rituximab is registered for treatment of non-Hodgkin lymphomas (NHL), it is not registered specifically for WM treatment. Since WM is considered a type of NHL, and effectiveness has been shown in one randomised trial, its use has become common practice. However, when asked for first-line treatment used in their last diagnosed patient only 56% had prescribed immunochemotherapy, and chlorambucil monotherapy was still used in 30% of the patients. This discrepancy might reflect transition of treatment preferences in the last years, comorbidity of the last treated patient, difference between daily practice and given ‘expected’ answers or it may be due to the fact that less haematologists responded to the last part of the survey. When deciding on a second-line treatment, many respondents indicated that several options were possible. Rituximab in combination with purine analogues was the preferred second line of treatment (55.4%), and additionally R-CVP, bendamustine, bortezomib and rituximab monotherapy were chosen. Rituximab maintenance therapy is seldom applied but a recent retrospective analysis suggests that it may also be beneficial in WM patients. Results of an ongoing randomised trial performed by the Studiengruppe Indolente Lymphome in Germany are eagerly awaited. Subsequently, the respondents were asked about the precautions taken to prevent an IgM ‘flare’ reaction when a rituximab-containing treatment was started. The IgM ‘flare’ is the occurrence of an initial increase in the IgM level that usually occurs within 15-30 days after initiation of treatment which can cause hyperviscosity syndrome in patients who already had a high IgM level. The increased level of IgM can remain elevated for three to four months and is not an indication of treatment failure. The IgM ‘flare’ arises in approximately half of the WM patients treated with rituximab monotherapy, and is generally seen less frequently when rituximab is combined with fast-acting chemotherapy such as fludarabine or bortezomib. In the DRC (Dexamethasone-Cyclophosphamide-Rituximab) trial, in which no preventive actions were taken, an IgM ‘flare’ was observed in 32% of patients, and 11% experienced an >25% IgM increase. However, this did not lead to signs or symptoms of hyperviscosity syndrome in any of the patients. Respondents were given three possible options and had a slight preference to select patients in whom they would omit rituximab in the first cycle and/or use plasmapheresis. As a follow-up question, the last group of respondents were asked at which level of IgM they would take preventive measures, which varied from >20g/l up to >90g/l. This disparity in the responses might be an indication of uncertainty and the need for more defined guidelines to prevent an IgM ‘flare’. Indications for starting treatment were mostly anaemia, symptoms of hyperviscosity and B symptoms, such as weakness, fatigue, weight loss and anorexia. Nineteen (22.9%) of the respondents stated that they initiate treatment when a certain level of IgM or M-protein is present, usually between 30g/l and 50 g/l. In general, the level of IgM or M-protein itself is not an indication for treatment initiation, unless symptoms of hyperviscosity are present. The last part of the survey asked about personal experience with WM patients. As expected for an indolent disease, most patients were not receiving active treatment (‘wait and see’ policy) and were older than 60 years. The majority of respondents did not have many patients in their practice which may imply they have limited experience in treating WM patients. When deciding on treatment initiation, the most important symptoms were anaemia, development of symptoms of hyperviscosity and progression of disease although an increase in IgM or M-protein levels was also mentioned. Because WM is a disease in which treatment responses are often delayed, respondents were asked what their experience was with time to first response. Combinations of rituximab and chemotherapy seem to induce the fastest responses. In about 20% of patients responses were only obtained after treatment was stopped. This is also a well-known phenomenon: responses occurring until one year after the end of treatment have been reported and this may be due to longer survival of the clonal plasma cells, which produce the M-protein, after anti B-cell directed therapy.

**CONCLUSION**

Most oncologists and haematologists participating in this survey showed excellent understanding of the diagnostic methods and treatment options in WM. The level of M-protein at which symptoms may be expected is always a subjective clinical judgement and some physicians wait until symptoms occur while others start treatment if IgM levels increase. The areas of uncertainty mostly concern the risk of hyperviscosity and its relationship with IgM levels, and the occurrence and prevention of IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare’. These issues, among others, are addressed in the Dutch guidelines to prevent an IgM ‘flare'.

Grants or conflict of interest: none reported
REFERENCES


APPENDIX

A survey on diagnostic methods and treatment strategies used in patients with Waldenström’s macroglobulinaemia

Basic information about the haematologist and the type of work facility

1. What is your age?
   a. Younger than 25
   b. Between 25 and 30
   c. Between 30 and 35
   d. Between 35 and 45
   e. Between 40 and 45
   f. Between 45 and 50
   g. Between 50 and 55
   h. Older than 55

2. What is the HOVON level (‘Echelon’) of your hospital?
   a. Level A
   b. Level B
   c. Level C
   d. Level D
   e. Level E
   f. Level F
   g. Level G
   h. Level H
   i. Level I
   j. Level J

3. In the Netherlands the haematological care is organised around 10 consultation centres. Which one is your consultation centre?
   a. UMCG
   b. UMCN St Radboud
   c. MST
   d. AZM
   e. ErasmusMC
   f. LUMC
   g. Haga Hospital
   h. UMCG
   i. AMC
   j. VUmc/Isala

4. Which diagnostic methods are available in your hospital? (multiple answers possible)
   a. CT scan
   b. PET scan
   c. Multiparameter flow cytometry
   d. Total IgM levels
   e. Total M protein levels
   f. Serum free light chain assay
   g. Viscosity measurement (centipoise)
   h. Cryoglobulin analysis
   i. Cold agglutinin test
   j. Anti-MAG antibodies test
   k. Other, namely...

5. Which diagnostic tools do you use to diagnose WM? (multiple answers possible)
   a. Ultrasound of the abdomen
   b. X-ray
   c. CT scan
   d. PET scan
   e. Bone marrow biopsy with immunohistochemistry
   f. Morphology of bone marrow aspirate
   g. Multiparameter flow cytometry of bone marrow aspirate
   h. Blood tests to determine IgM levels
   i. Blood tests to determine M-protein levels
   j. Serum free light chain assay
   k. Other, namely...

6. What is, in your opinion, the preferred first-line treatment for symptomatic WM patients?
   a. Rituximab
   b. Alkylating agents such as chlorambucil
c. Purine analogues such as fludarabine and cladribine
d. Rituximab in combination with alkylating agents
   e. Rituximab in combination with purine analogues
   f. R-COP (R-CVP)
g. DRC regimen (dexamethasone, rituximab, cyclophosphamide)
h. Bortezomib (in combination)
i. Bendamustine (in combination)
j. Thalidomide (in combination)
k. Other, namely...

7. The administration of rituximab is associated with an ‘IgM flare’ in 50% of the patients. Do you take precautionary measures?
   a. No, the IgM flare rarely causes problems
   b. Yes, in the first cycle I do not give rituximab
   c. In some cases I take precautionary measures such as plasmapheresis or I give the first cycle without rituximab
8. If your answer to question 7 was ‘In some cases I take precau-
tionary measures such as plasmapheresis or I give the first
cycle without rituximab’: at what level of IgM or protein do you
decide to take precautionary measures? (give your answer in
g/l)...

9. If you decide to follow a wait-and-see policy (no treatment),
which of these diagnostic results are an indication for you to
start treatment? (multiple answers possible)
a. A certain level of IgM or M
protein  
b. Anaemia or other

c. Symptoms of hyperviscosity
d. B-symptoms  
e. Progression of
polyneuropathy  

10. If your answer to question 9 was: ‘A certain level of IgM or M
protein’: what level of IgM or M protein is important for you to
start the treatment? (give your answer in g/l)...

11. What do you think are preferred second-line treatments?
(multiple answers possible)
a. Rituximab  
b. Alkylating agents such as
cyclophosphamide and
chlorambucil  
c. Purine analogues such as
dfluorarabine and cladribine
d. Rituximab in combination
with alkylating agents  
e. Rituximab in combination
with purine analogues  
f. R-COP (R-CVP)

12. What do you think is the best maintenance therapy?
a. None  
b. Rituximab  
c. Bortezomib

Most recent experience with the diagnosis and treatment of a patient
with Waldenström’s macroglobulinaemia

13. Do you treat patients with WM in your clinic?
a. Yes  
b. No

14. How many patients are you currently seeing (follow-up and in
treatment)?
a. 0-1  
b. 2-4  
c. >8

15. How many patients are you currently treating?
a. 0-1  
b. 2-4  
c. >8

16. What was the age of the last patient with WM that you treated?
a. Less than 50 years  
b. Between 50 and 60 years  
c. More than 70 years

17. What was/were the first symptom(s) of this patient, which
resulted in the diagnosis of WM? (multiple answers possible)
a. None, patient was
asymptomatic  
b. Weakness and fatigue
c. Bleeding  
d. Weight loss and/or anorexia
e. Anaemia  
f. Elevated erythrocyte sedi-
mentation rate  
g. Lymphadenopathy
h. Hepatomegaly  
i. Splenomegaly
j. Neuropathy  
k. Vasculitis/skin lesions
l. Haemolysis
m. Other, namely...

18. When did you start treatment? (multiple answers possible)
a. As soon as the patient was
diagnosed  
b. As soon as there was
evidence of problems caused
by the M protein (hypervis-
cosity, neuropathy, amyloido-
sis, cryoglobulinaemia)  
c. As soon as there was
evidence of disease progres-
sion caused by a rise in the M
protein or IgM levels

19. What was the first-line treatment that you used in this patient?
a. Rituximab  
b. Alkylating agents such as
cyclophosphamide and
chlorambucil  
c. Purine analogues such as
dfluorarabine and cladribine
d. Rituximab in combination
with alkylating agents  
e. Rituximab in combination
with purine analogues  
f. R-COP (R-CVP)

20. How soon after the start of treatment did the patients show a
response (defined as >25% reduction in M-protein levels)?
a. Less than 3 months  
b. Between 3 and 6 months  
c. Between 6 months and 1 year  
d. No response to first line of
treatment

21. When was the maximum (best) response achieved?
a. In the first part of the
treatment (cycle 1 to 3-4)  
b. In the last part of the
treatment (cycles 3-4 to 6-8)  
c. After the treatment was
stopped  
d. Insufficient or no response,
switched to another
treatment, namely...

22. How long after the last dose of the first-line treatment did you
begin with second-line treatment?
a. Second line of treatment was
not needed  
b. Between 2-4 years  
c. Between 1 and 2 years  
d. More than 4 years

23. If applicable, what was the second line of treatment that you
used?
a. Not applicable  
b. Rituximab  
c. Alkylating agents such as
cyclophosphamide and
chlorambucil  
d. Purine analogues such as
dfluorarabine and cladribine
e. Rituximab in combination
with alkylating agents  
f. Rituximab in combination
with purine analogues  
g. R-COP (R-CVP)

24. Did you use maintenance treatment in this patient?
a. Yes, in the first line, and I
used rituximab  
b. Yes, in the second line, and I
used bortezomib  
c. Yes, in the first line, and I
used bortezomib  
d. Yes, in the second line, and I
used rituximab  
e. Yes, in the second line, and I
used thalidomide  
g. No  
h. Other, namely...

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