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Dutch Physician's Perspectives on Diagnosis and Treatment of Waldenström's Macroglobulinemia Before and After the Implementation of a National Guideline

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ABSTRACT

Waldenström's macroglobulinemia (WM), a rare low-grade B-cell non-Hodgkin lymphoma (NHL), has a distinct clinical presentation and different treatment-related side effects compared with other NHL. Currently, a wide variety of therapeutic agents are available for the treatment of WM but there is no consensus on optimal treatment in first line and/or at relapse. The aim of this survey was to evaluate the current knowledge and perspectives of hematologists on diagnosis and treatment of WM. Also, we compare these results to a similar survey done before the publication of the first Dutch national guideline, in order to evaluate the impact of the implementation of a national guideline. A link to an online survey was sent out to all registered hematologists and hemato-oncologists in the Netherlands with the request to participate. The survey contained questions regarding the preferred diagnostic and treatment methods in patients with WM as well as treatment goals. We also compared physicians preferred treatment goals to those of patients (as studied in a recent nation-wide patient questionnaire). Ninety-five responses (30% response rate) were obtained, out of which 82 (86%) surveys were complete. The respondents most commonly used dexamethasone-rituximab-cyclophosphamide as first-line treatment. For second-line treatment, bendamustine with rituximab and ibrutinib monotherapy were the most frequently applied. Compared with the initial survey, serum IgM M-protein was determined in all cases, MYD88 mutation analysis was currently widely implemented, prevention of an IgM "flare" was uniformly managed by the respondents and use of rituximab-cyclophosphamide-vincristine-prednisone was entirely abandoned. Physicians differed somewhat from patients with regard to most important treatment goals. The approach to diagnostic methods and treatment options in WM was more consistent with international guidelines and was more homogeneous after implementation of the national guideline. These data indicate an increase in knowledge on WM diagnosis and treatment. This may have resulted from implementation of a local guideline or the global rise in awareness and attention for WM.

INTRODUCTION

Waldenström's macroglobulinemia (WM) is a low-grade B-cell non-Hodgkin lymphoma (B-NHL) characterized by infiltration of the bone marrow (BM) with lymphoplasmacytic cells and presence of an IgM M-protein in the serum.[1] WM is rare, with an incidence of 3 patients per million people per year in the west. WM patients are typically managed by hematologist/oncologists in all types of hospitals (small regional, large teaching as well as academic centers).[2,3] The clinical presentation is diverse with symptoms attributable either to BM infiltration by tumor cells or to the immunological properties of the monoclonal IgM, setting it apart from other B-NHL. Also, WM patients experience different side effects of treatments including IgM flares and increased infusion-related reactions associated with rituximab, and higher rates of peripheral neuropathy associated with bortezomib and vincristine compared with their use in other indications.[4–6] Hyperviscosity syndrome is a potentially life-threatening complication seen in up to 13% of WM patients associated with high IgM levels and should prompt the immediate initiation of plasmapheresis.

The highly recurrent somatic mutation in the myeloid differentiation primary response 88 genes (*MYD88 L265P*), present in over 90% of WM patients, was discovered in 2012 and can help to differentiate from other small B-NHLs or IgM multiple myeloma as indicated in the 2016 revision of the World Health Organization (WHO) classification.[1,7] WM can often be managed with a watch & wait strategy, but treatment should be initiated if patients develop symptomatic WM based on international consensus criteria.[8,9] In recent years, the treatment arsenal of WM has greatly expanded with several novel agents for both newly diagnosed and relapsed WM patients. Although

international treatment guidelines are available, there is no consensus on a preferred first-line or relapsed setting treatment.[10–15] Hence, deciding on a therapeutic regimen should be individualized based on patient and disease characteristics. Preferred treatment options include rituximab combined with chemotherapy, of which dexamethasone-rituximab-cyclophosphamide (DRC) is the most frequently applied regimen, followed by rituximab-bendamustine, proteasome inhibitors based combinations such as rituximab-bortezomib-dexamethasone, and the oral Bruton's tyrosine kinase inhibitor ibrutinib.[16]

In 2012, the first Dutch guideline for diagnosis and management of WM was published with the aim of providing physicians guidance in the diagnosis and treatment of this rare malignancy. Before the publication of the first guideline, a survey was conducted among Dutch hematologists and hemato-oncologists to assess knowledge on the strategies used in the diagnosis and treatment of WM patients in the absence of a national guideline.[17] The 2012 survey demonstrated that the main knowledge gaps concerned the differentiation of asymptomatic and symptomatic disease, hyperviscosity syndrome and its relation to IgM levels, and the occurrence and prevention of an IgM flare. An expanded and updated guideline was published in December 2020.[18,19] To evaluate the impact of the first guideline, a follow-up survey was conducted before the publication of this updated version.

METHODS

We used the survey conducted in 2012 with some adaptations based on developments in the field (see Suppl. Appendix).[17] Before the publication of the updated Dutch guideline for diagnosis and management of WM in December 2020, a link to the 39 questions containing online questionnaire was sent out to all registered hematologists and hemato-oncologists (including those in training) in the Netherlands via the Dutch Hematology Association (n = 371) using an anonymous survey tool (Qualtrics.com). To increase the response, the survey was also distributed by regular postal mail (n = 100) for those for whom an address was available. A reminder email was sent after 2 months. The surveys were answered in Dutch and anonymously.

The structure of the questionnaire with accompanying annotation was similar to the first version as described previously.[17] The first part contained questions about demographic characteristics and the workplace of the respondent. The second part focused on the preferred diagnostic methods and the preferred treatment regimen and clinical care strategies for newly diagnosed and relapsed WM patients. We added group and rank questions to assess the 3 most important treatment goals from a selection of 11 treatment goals. In addition, we asked the same questions during a nationwide patient survey that was conducted simultaneously, methods were previously published.[20] Also, questions regarding treatment strategy, external consultation regarding newly diagnosed WM patients and need for consultation of a WM expert panel, and questions about their last diagnosed WM patient were included in the second part. Overall, the survey consisted mostly of multiple choice questions with the possibility to select more than 1 answer when appropriate.

Data were analyzed using Qualtrics. Demographic characteristics and answered questions by respondents were summarized by absolute counts and percentages. In the case of questions where multiple choices were allowed, the absolute counts are shown.

RESULTS

Ninety-five surveys (30% response rate) were obtained. A total of 13 (14%) surveys were incomplete due to unanswered questions, primarily in the third part of the survey. The previous version of this survey in 2012 was completed by 83 participants out of 261 (32% response rate). Of the current respondents, 44% participated in the previous survey.

Information about the physician and the hospital

The largest group of respondents was between 40 and 45 years (29%), followed by 26% of respondents younger than 40 years, 17% were aged 51–55 years, and 13% were aged 56–60. Responses came from academic hospitals (34%), large community hospitals (29%), and 37% from smaller peripheral hospitals. The hemato-oncological care in Dutch hospitals is subject to an echelon classification containing 4 levels (A, B, C, and D). For instance, level A on 1 end represents hospitals that can carry out allogeneic and autologous stem cell transplants (mostly academic hospitals) and level D on the other end represents hospitals that provide nonintensive hematological care only.[21] The majority of the responses came from level A (35%) followed by level C (28%) hospitals.

The majority of respondents (n = 29, 36%) stated that they currently have 5–9 WM patients in their practice, followed by 22 (27%) respondents who had 2–4 patients on follow-up or under treatment. Thirteen (16%) and 12 (15%) respondents indicated that they had 10–15 and >15 patients under treatment, respectively. Five (6%) respondents had 1 or no patients under control or treatment.

Subsequently, respondents were asked in how many patients they initiated treatment in the past year. The most frequent response was 2–3 patients or 4–5 patients reported by 43 (53%) and 14 (17%) respondents.

Diagnostic methods used in patients with WM

Diagnostic tools such as computed tomography (CT) scan, protein electrophoresis, positron emission tomography-CT (PET-CT) scan, flow cytometry on BM aspirate, tests for cryoglobulins, and cold agglutinins were readily available in all hospitals. Serum blood viscosity measurement, $MYD88^{L265P}$ and $CXCR4$ mutation analysis were available in 27%, 75%, and 49% of hospitals, respectively.

The most frequently applied diagnostic methods were quantitative assessment of M-protein level (100%), histologic evaluation of BM biopsy (96%), morphologic evaluation of BM aspirate (94%), and quantitative assessment of IgM level (93%). Flow cytometry of BM aspirate was selected by 80% of the respondents. Mutation analysis of $MYD88$ and $CXCR4$ were reported in 78% and 16% of the respondents, respectively. Of all the imaging techniques, CT scan (74%) was the most applied, followed by ultrasound of the abdomen (16%), radiograph of the chest (14%), and PET-CT scan (9%). A cryoglobulin test (33%) and serum blood viscosity measurement (4%) were among the least applied diagnostic methods (Figure 1). Since the diagnosis and staging of WM require a combination of tests, the respondents used an average of 8 diagnostic tests (range, 2–13). Demonstrating the presence of monoclonal IgM M-protein is imperative for the diagnosis of WM, and indeed all respondents selected this option. Measurement of total IgM level was selected by 93%. Presence of lymphoplasmacytic cells in the BM is also a prerequisite for the diagnosis of WM, and 96% of respondents performed a BM biopsy for histologic evaluation. Two definitions currently exist side by side with regard to IgM monoclonal gammopathy of undetermined significance (MGUS); the WHO maintains IgM paraproteinemia with <10% BM infiltration, while the International Workshop on WM defines MGUS as IgM paraproteinemia of any level without evident BM infiltration and without related symptoms. When the respondents were asked which percentage of BM infiltration they used to distinguish between IgM MGUS and WM, 71% selected at least 10%, while the remaining respondents selected 0% (any amount of BM infiltration indicates WM diagnosis). IgM-related disorders were diagnosed less than once a year
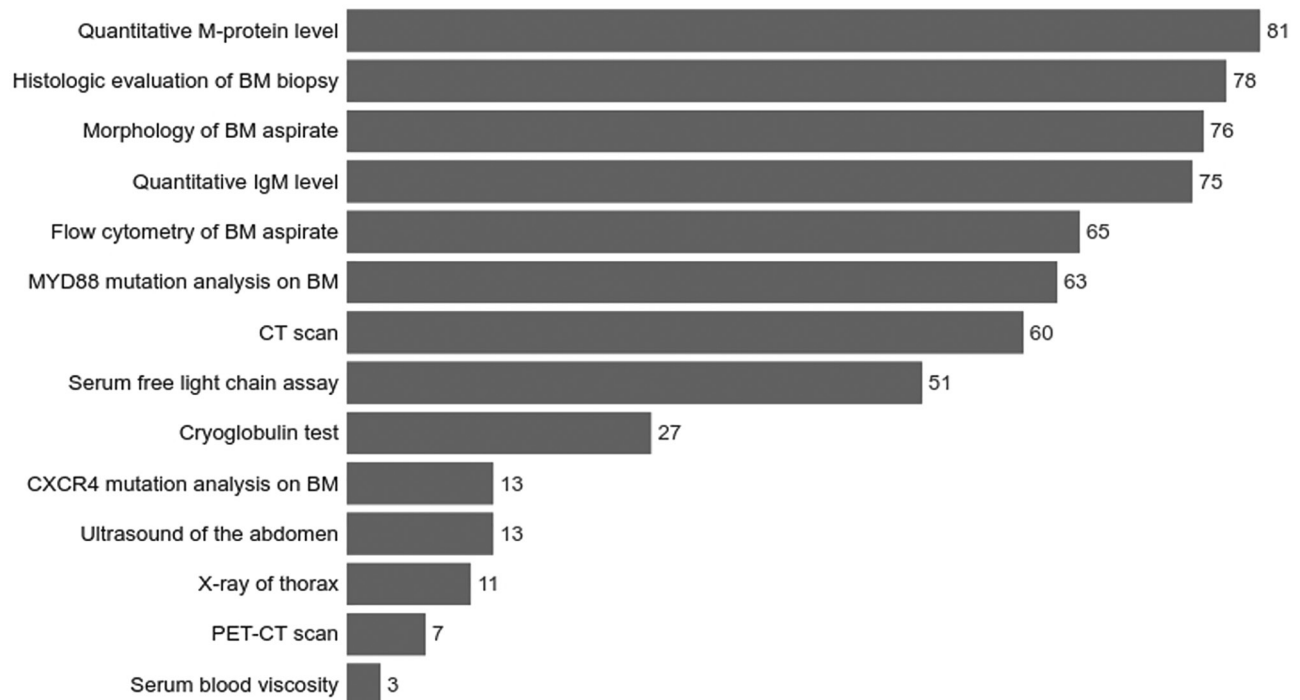
Figure 1. Commonly used diagnostic methods in Dutch hospital for the diagnosis of WM. Selection of multiple answers was possible. The numbers represent absolute counts of the responses received. BM = bone marrow; CT = computed tomography; PET-CT = positron emission tomography and computed tomography; WM = Waldenström's macroglobulinemia.

(28%) and once or twice a year (59%) by the respondents and were managed with rituximab monotherapy (48%) or rituximab combined with chemotherapy (43%).

Treatment preferences in patients with WM

The great majority of respondents preferred the combination regimen DRC as first-line treatment (77 [95%] of respondents [Figure 2]). Rituximab monotherapy was the second preferred first-line treatment by 11 (14%) respondents, followed by rituximab in combination with bendamustine in 9 (11%), and rituximab in combination with chlorambucil in 8 (10%). Ibrutinib monotherapy was preferred as first-line treatment in 4 (5%) respondents. None of the respondents selected chlorambucil monotherapy and lenalidomide (± steroids) as their preferred first-line treatment. Thirteen (15%) of respondents chose rituximab as maintenance therapy, whereas 69 (85%) respondents answered that maintenance therapy is not indicated. As second-line treatment, bendamustine (± rituximab) and ibrutinib monotherapy were the 2 most preferred treatments selected by 55 (68%) and 47 (58%) respondents. Additionally, bortezomib (± rituximab), DRC, and ibrutinib in combination with rituximab were all selected as possible second-line therapies (Figure 2). On average, respondents provided 2 options (range, 1–8) for the preferred second-line treatment. Regarding the potential risk of hyperviscosity due to an IgM "flare" reaction that could occur in patients treated with rituximab, respondents were asked whether they used precautionary actions to reduce this risk. Two (2%) respondents did not use precautionary measures, while 76 (94%) respondents avoided the administration of rituximab in the first or subsequent cycles, and 12 (15%) respondents indicated using plasmapheresis when IgM levels are high. When asked at which IgM level they would use precautionary measures, a median level of 34 g/L (range, 10–50 g/L; only 1 respondent chose IgM level >40 g/L) was reported (n = 11).

Symptoms that prompted treatment in asymptomatic patients were anemia (98%) with hemoglobin level <6.2 mmol/L, symptoms of hyperviscosity (95%), and presence of B-symptoms (88%) (Figure 3). The 27 (33%) respondents who selected that

a specific level of M-protein or IgM was the main reason to initiate treatment would have started at a median level of 40 g/L (range, 3–75 g/L).

Regarding the setting in which they discuss a newly diagnosed WM patient, respondents chose a local medical team meeting or a multidisciplinary team meeting (MDT) (n = 37 [46%]) and regional MDT with at least 1 pathologist and an external expert (n = 39 [48%]). When asked if they felt a need for a national consultation platform for complicated WM cases, 50 (62%) respondents answered that the regional multidisciplinary consultation suffices and/or they would consult an expert themselves. Only 12 (15%) of respondents were interested in a national consultation platform and would consult it 2–3 times a year.

Comparison with the 2012 survey

We then compared the results of the current survey with those from the 2012 survey. The current survey had a similar response rate (n = 95; 30% of all hemato(-oncologists) versus n = 83; 32%) and most respondents were slightly younger in age (55% <45 y versus 63% >45 y). Regarding diagnostic methods, the most commonly used methods remained similar to 2012, albeit assessment of an IgM M-protein in the serum was currently selected by all respondents compared with 88% in 2012.

Symptoms prompting treatment initiation in asymptomatic patients were also similar to the ones selected in 2012. However, current respondents who selected the height of the IgM level or M-protein would initiate treatment at a median level of 40 g/L compared with respondents in 2012 that would start at a level of 30 g/L.

Treatment preference shifted from rituximab-cyclophosphamide-vincristine-prednisone (R-CVP) (n = 26; 36%) and rituximab combined with an alkylating agent (n = 24; 33%) in 2012 to the DRC regimen in the majority (n = 77; 94%) of current respondents. Rituximab monotherapy was also a preferred first-line treatment option (n = 11; 13%) while in 2012 none of the respondents preferred it in the first-line. For second-line treatment, preferences differed greatly as rituximab in combination with purine analogs was preferred by a majority (n = 46; 55%)

A

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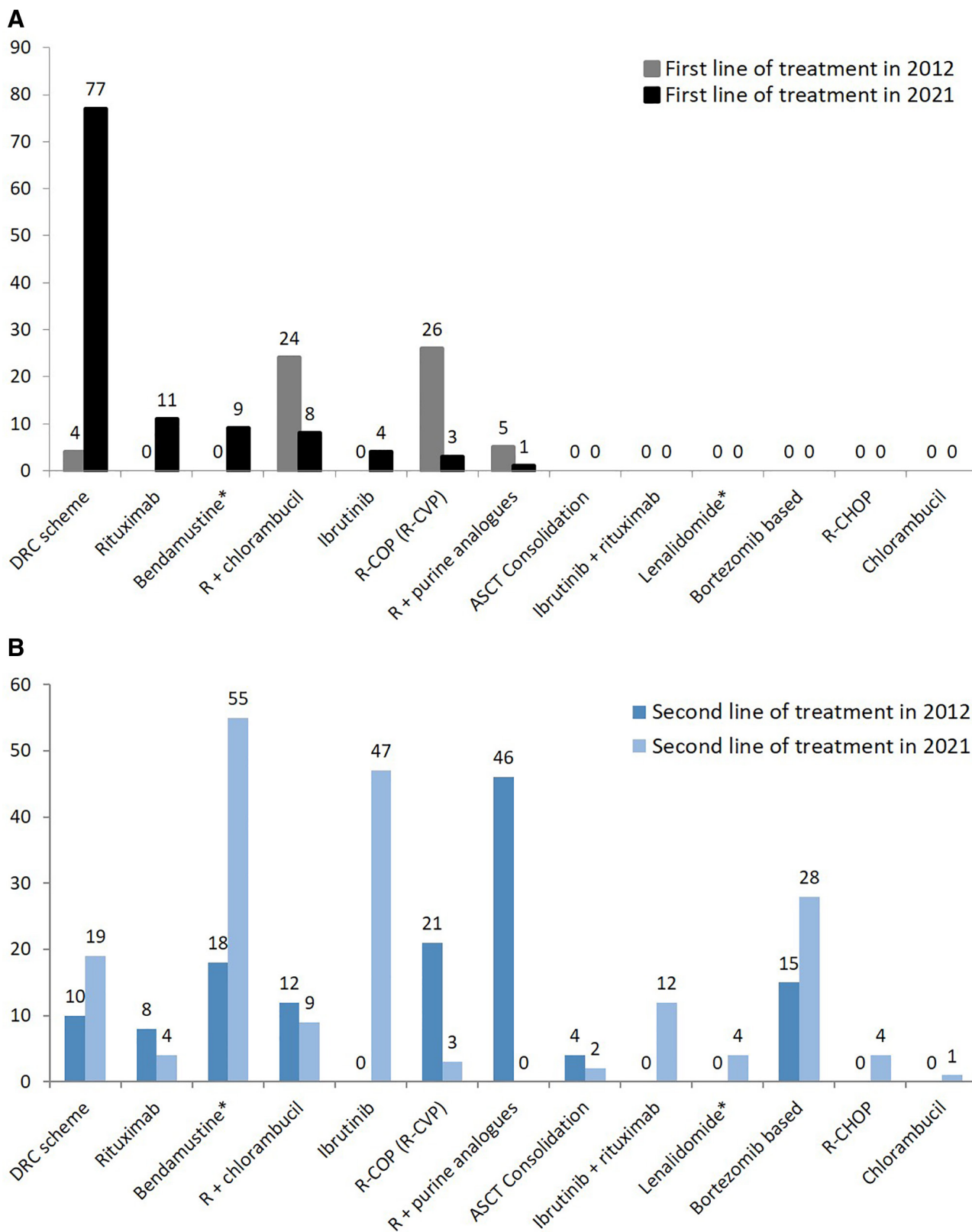
Figure 2. Preferred first- and second-line treatment for WM. (A), First-line treatment results from the 2012 and current survey. (B), Second-line treatment results from the 2012 and current survey. More than 1 answer was possible. Numbers are absolute counts of received responses. ASCT = autologous stem cell transplant; DRC = dexamethasone-rituximab-cyclophosphamide; R = rituximab; R-CHOP = rituximab-cyclophosphamide-hydroxydaunorubicin-Oncovin-prednisone; R-COP = rituximab-cyclophosphamide-vincristine-prednisone; R-CVP = rituximab-cyclophosphamide-vincristine-prednisone; WM = Waldenström's macroglobulinemia.

of the 2012 respondents compared with practically none of the current respondents. Instead, the majority of current respondents

(n = 55; 67%) preferred bendamustine (± rituximab) or ibrutinib monotherapy (n = 47; 57%) as second-line treatment. A
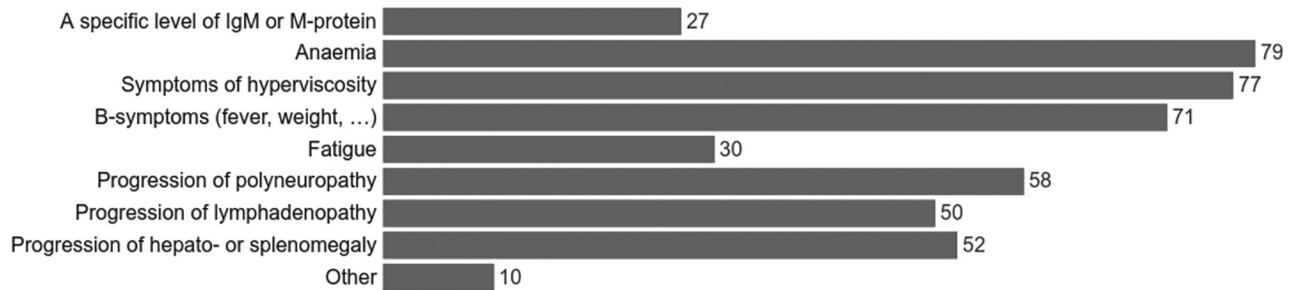
Figure 3. Variables that prompted the start of treatment in asymptomatic patients after a Watch & Wait policy. More than 1 answer was possible. Numbers are given as absolute counts of the responses received.
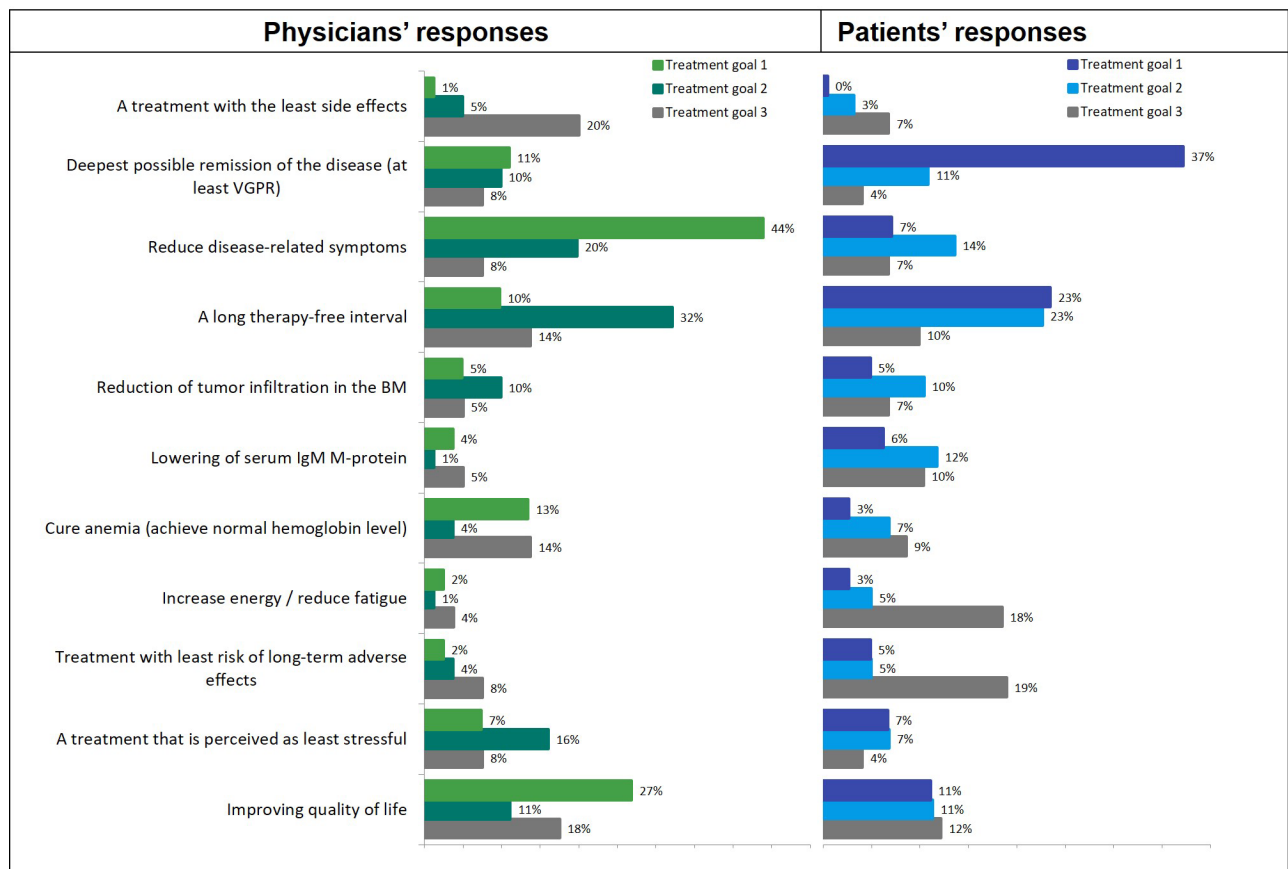
Figure 4. Selection of the 3 most important treatment goals according to the physicians (depicted in green and gray) and patients (depicted in blue and gray) when therapy for WM is initiated. The treatment goals 1 with the most responses is selected as most important treatment goal. The same is done for treatment goal 2 and treatment goal 3 to obtain the 3 most important treatment goals. BM = bone marrow; VGPR = very good partial response; WM = Waldenström's macroglobulinemia.

similar majority of the respondents (n = 69; 84% versus n = 52; 74%) still refrained from using maintenance therapy.

In 2012, 30% of the respondents did not consider the IgM "flare" a clinically significant complication compared with 2% of the current respondents. The use of precautionary measures to avoid an IgM "flare" increased greatly (30% versus 94%). The use of plasmapheresis as a preventative measure decreased from 39% to 13%. In the current survey, 76 (93%) respondents would rather omit rituximab in the first 1 or 2 cycles compared with 22 (31%) respondents in 2012.

Ranking exercise physicians versus patients

Finally, respondents performed a ranking exercise on their prioritization of treatment goals. Respondents ranked "reduce disease-related symptoms" as the most important treatment

goal (n = 36, 44%), followed by "a long therapy-free interval" (n = 26, 32%), and "a treatment with the least side effects" (n = 16, 20%). Sixty-six (81%) respondents stated that treatment goals were dependent on the age and condition of the patient. For a fit patient younger than 65 years, the 3 most important goals were "a long therapy-free interval" (n = 25, 31%), "the deepest possible remission of the disease (at least very good partial response [>90% reduction in IgM/M-protein])" (n = 19, 23%), and "a treatment with the lowest risk of long-term adverse events (eg, secondary malignancies)" (n = 17, 21%). For a less fit patient, older than 65 years, the 3 most important goals were "improving quality of life" (n = 27, 33%), "reducing disease-related symptoms" (n = 17, 21%), and "a treatment that is perceived as least burdensome by the patient" (n = 15, 19%). The same question was presented to WM patients (n =

227) in a separate survey conducted in the same year.[20] WM patients selected "the deepest possible remission of the disease" (n = 84) as most important treatment goal, followed by "a long therapy-free interval" (n = 50) and "a treatment with the lowest risk of long-term adverse events (eg, secondary malignancies)" (n = 42) (Figure 4).

DISCUSSION

We surveyed physicians knowledge and perspectives on WM diagnosis and treatment in 2020 and compared these to the results of a similar survey conducted before publication of the first Dutch WM guideline 8 years earlier. Our survey had a 30% response rate representing about 26% of all hematologists in the Netherlands. We believe that the respondents are a good representation of all hemato(-oncologists) in the Netherlands since the responses were evenly distributed regarding region and type of hospital. We found a significant shift in some diagnostic methods and treatment preferences since 2012.

The preferred first-line treatment according to the majority (95%) of the respondents was DRC, while in 2012, the majority of the respondents (36%) opted for the combination rituximab-cyclophosphamide-vincristine-prednisone (R-COP)/R-CVP. This switch in preferred treatment was confirmed in a nationwide Dutch patient registry, showing decrease of R-COP/CVP from 12% to 2% and increased use of DRC from 14% to 39% (between 2014 and 2018).[22] We suspect that this switch is mostly related to the publication of the first Dutch WM guideline, which suggested DRC as a preferred first-line treatment strategy in contrast to international guidelines at that time that suggested a range of first-line therapies without a preferred option.[16] The use of vincristine was discouraged considering the high rates of peripheral neuropathy without clearly added efficacy.[16,18,23,24]

Regarding second-line treatment, the shift from R-CVP as preferred second-line treatment in 2012 to bendamustine can be explained by the 2013 publication of a positive clinical trial that demonstrated superiority of R-bendamustine over rituximab-cyclophosphamide-hydroxydaunorubicin-Oncovin-prednisone in (22 versus 19) WM patients. In addition, R-bendamustine was already mentioned in the 2012 guideline as an option in the relapsed setting based on conference abstracts and retrospective data.[25] Ibrutinib was not mentioned in the 2012 guideline since the pivotal trial was only published in 2015.[13]

The IgM "flare" phenomenon (the initial increase in IgM levels after initiation of rituximab that occurs in approximately half of WM patients) can be a risk in patients who already have high levels of IgM, potentially causing hyperviscosity syndrome and is quite unique for WM.[16] The awareness of this phenomenon rose from 70% to 98% between 2012 and 2021. Also, measures to prevent IgM flare rose from 31% to 93%. Again, this demonstrates an increased awareness of this WM-specific disease complication, even when this phenomenon has been known in the international literature since 2004.[26]

MYD88 mutation analysis on the other hand, was not mentioned in the 2012 survey nor in the 2012 national guideline since its existence was only published in the second half of 2012.[27] Still, our data show that the *MYD88* mutation analysis became available in most Dutch hospitals and was widely implemented in routine clinical practice. We suspect this was picked up from the literature by Dutch hematologists/pathologist, aided by the inclusion of *MYD88* mutations in the revised WHO book chapter on WM.[1]

To summarize, knowledge regarding diagnosis and treatment of WM increased between 2012 and 2021 among Dutch hematologists. This may be related to the implementation of the first Dutch guideline 2012 or to a global increase in awareness and attention for WM. WM has gained increasing attention, which has been boosted by the discovery of the *MYD88* mutation

and the registration of ibrutinib as the first drug specifically for WM.[28–30] Several international guidelines have been published since 2012.[10,15,16] In addition, the international WM workshop was held in Amsterdam in 2016, which may have further triggered Dutch practitioners.

With regards to treatment goals, patients prioritized treatment with a high efficacy while physicians prioritized the effect on disease-related symptoms. These are interesting differences that would merit further investigation. Also, these differences highlight the importance of a dialogue between physician and patients regarding individual prioritized treatment goals, especially in the setting of WM, where there is not one preferred treatment regimen.

Our study has some limitations. The main limitation is that it is unclear what the contribution was of the multiple sources of information that became available in The Netherlands to the increased awareness of WM. It would be interesting to repeat this survey with adapted questions regarding sources that are used to direct WM practice to determine the causes of this phenomenon. Another major limitation inherent in quantitative surveys is the potential for biased responses due to the limited set of response options provided to the participants. Also, the possibility of selection bias is present since physicians with an interest and/or more experience in WM might be more willing to complete the survey. However, we see that >50% of respondents have less than 10 WM patients under their care. The respondents were however younger in age compared with 2012; this indicates the recent completion of their training, but on the other hand, this also means little experience, and it is therefore unclear how the younger age influenced the results. Finally, we did not assess the impact of treatment costs and drug access on physicians treatment choices since within the Dutch health system, only accessible drugs that are approved and reimbursed can be prescribed, and universal insurance coverage is equal for all inhabitants. Repeating this survey on an international level would be interesting and should include the aforementioned additions.

CONCLUSIONS

Preferred diagnostic methods and treatment options in WM were more in line with international guidelines and were more homogeneous among hematologists and oncologists in the Netherlands compared with 2012. This increase in knowledge resulted in the abandonment of regimens that were already discouraged in the international literature and guidelines and the increased awareness of WM-specific disease complications such as IgM flare. These improvements may be due to the implementation of the first national guideline in 2012. Alternatively, the increase in knowledge may be explained by a global rise in awareness and attention for WM. Also, we identified interesting differences in treatment goal perspectives between physicians and patients that deserve further exploration.

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