HOW TO MANAGE...

How to manage Waldenstrom's macroglobulinemia

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Waldenstrom's macroglobulinemia (WM) is very distinct from other indolent lymphoma subtypes: by definition it is accompanied by a monoclonal IgM gammopathy; it presents always with bone marrow infiltration and often with clinical symptoms such as neuropathy or hyperviscosity. These disease characteristics and the frequently advanced age of the WM patient pose a major challenge to the treating clinician even today. Recently, there has been not only substantial progress in our understanding of the biology of WM, but we have also significantly improved our tools to prognostify and to treat patients with this disease. This review summarizes our current knowledge about WM and aims at offering a guideline for the clinical management of patients with this lymphoma subtype, covering questions on how to manage diagnosis, prognostification and treatment based on the most recent data.

INTRODUCTION

Although Waldenström's macroglobulinemia (WM) is classified as an indolent disease, it was and still is a major clinical challenge for the treating physician as it often causes considerable morbidity of the mostly elderly patients. Furthermore, despite substantial progress in treating WM patients, only few patients achieve complete remissions and we are still not able to prevent relapse with all the therapeutic tools we have. Besides treatment aspects, correct diagnosis of WM might be a challenge, in particular with other chronic lymphoproliferative disorders associated with IgM paraproteinemia, such as marginal zone lymphoma.

To this end, we still do not understand the cellular and molecular mechanisms that lead to the development of WM. Taken together, despite significant and undeniable progress with regard to biological insights as well as clinical management of WM patients, many open questions still remain since Jan Waldenström originally reported on two WM patients nearly 70 years ago.[1]

What do we know today?: WM is a rare disease. It accounts for 1–2% of hematological neoplasms, with a reported age-adjusted incidence rate of 3.4 per million among the male population and 1.7 per million among the female population in the United States, and 7.3 and 4.2 per million, respectively, in the European standard population.[2,3] WM is a disease of the elderly with a median age of 63–68 years at diagnosis. Deletion of the long arm of chromosome 6 (6q) is the most frequent cytogenetic abnormality in WM, which is detectable in 7% by conventional cytogenetics and in 34% when analyzed by fluorescence in situ hybridization. Deletion 6q was associated with adverse prognosis features, reflected by higher levels of β_2-microglobulin and monoclonal paraprotein and a greater tendency to display anemia and hypoalbuminemia; however, a more recent study did not detect any impact of 6q deletion on response rate (RR), progression-free survival (PFS) or overall survival (OS) based on a prospective randomized trial of 174 WM patients.[4,5] Of note, 6q deletion is not a WM-specific aberration and is also found in other entities. At the genomic level, copy number alterations were identified in nearly 80% of cases, among them biallelic inactivation of TNFAIP3 and TRAF3, genes involved in the regulation of the nuclear factor-κB signaling pathway.[6] Recently, whole-genome sequencing of 30 patients with WM detected an MYD88 L265P variant in nine of nine patients with WM and positive family history, and in 86% of sporadic cases. Importantly, this variant was very rare or absent in patients with multiple myeloma, monoclonal gammopathy with unknown significance, splenic zone marginal lymphoma and healthy individuals. Incubation of MYD88 variant-positive WM cell lines with an inhibitor of MYD88 homodimerization reduced nuclear factor-κB staining in contrast to cell lines expressing the MYD88 wild type. This mutation was first described in the activated B-cell-like subtype of diffuse large B-cell lymphoma as a gain-of-function mutation, being critical for diffuse large B-cell lymphoma survival, inducing among others interleukin-6 secretion.[7] The association of the MYD88 L265P variant with WM was recently confirmed in an independent study.[8] There are speculations that this mutation might have a role in transforming 'monoclonal gammopathy of undetermined significance' to full-blown WM. However, in another scenario, monoclonal gammopathy with unknown significance might be just a precursor to WM based on a recent series showing frequent MYD88 L265P expression in five of nine monoclonal gammopathy with unknown significance cases, showing all clonal plasma cells as well as clonal lymphocytes in their bone marrow.[9] Taken together, these exciting data at least promise that targeting MYD88 signaling might be a novel approach to impair WM growth.[10] Gene expression profiling demonstrated that WM resembles more chronic lymphocytic lymphoma than multiple myeloma. Interestingly, the most significantly upregulated gene was IL6 and MAPK signaling, indicating that IL6 and its downstream signaling may be of biological importance in WM.[11] Other studies have shown that WM is characterized by a distinct microRNA (miR) pattern with deregulation of a set of seven miRs compared with healthy controls (miR-363*, miR-206, miR-494, miR-155, miR-184, miR-542-3p and miR-9).[12] The impact of genetic

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factors for the development of WM is further underlined by several reports on familiar clustering of individuals with WM and other B-cell lymphoproliferative diseases, with up to 20% of WM patients having a first-degree relative with either a WM or a closely related B-cell disorder.[13,14]

HOW TO DIAGNOSE WM

WM is a distinct clinicopathological entity resulting from the accumulation of clonally related lymphocytes, lymphoplasmacytic cells and plasma cells, which secrete a monoclonal IgM protein, predominantly in the bone marrow. This condition corresponds to the lymphoplasmacytic lymphoma (LPL) as defined by the World Health Organization classification system.[15] Most cases of LPL are WM, with <5% of cases presenting as IgA, IgG and non-secreting LPL. 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.[16] Thus, detection of monoclonal IgM without the histopathological diagnosis of LPL cannot be considered to be WM. Vice versa, diagnosis of LPL without detection of monoclonal IgM does not fulfill the criteria of WM. Morphologically WM is characterized by proliferation of small B cells, plasmacytoid cells and partly plasma cells. The lymphoma cells typically express CD19, CD20, CD22 and CD79a, but lack CD5, CD10 and CD23, which helps to discriminate WM from follicular lymphoma, chronic lymphocytic leukemia and mantle cell lymphoma. It is nearly always possible to document the expression of CD138-positive plasma cells in WM by either immunohistochemistry or flow cytometry.[17] However, expression of CD5, CD10 and CD23 may be found in 10–20% of cases, and does not exclude the diagnosis of WM.[18] According to the WHO classification, WM has to be separated from the CD5 + lymphoplasmocytoid immunocytoma of the former Revised European American Lymphoma Classification (REAL) as these cases are considered to be B-CLL variants today. Furthermore, WM has to be separated from IgM myeloma, which is an extremely rare disease with different clinical characteristics, presenting as a homogenous tumor plasma cell population in the bone marrow. For the diagnosis of IgM myeloma, the patient should fulfill the criteria of having a symptomatic clonal plasma cell proliferative disorder characterized by an IgM monoclonal protein (regardless of size), 10% or more plasma cells on bone marrow biopsy, plus the presence of lytic bone lesions and/or translocation t(11;14).[19] In the future, the presence of the MYDL265 variant might provide additional help to differentiate WM from IgM myeloma.[20]

As the bone marrow is always involved in WM, demonstration of bone marrow infiltration by a lymphoplasmacytic cell population, constituted by small lymphocytes with evidence of plasmacytoid/plasma cell differentiation, documented by trephine biopsy and aspiration, is central for the diagnosis of WM. The bone marrow infiltration should routinely be confirmed by immuno-phenotypic studies (flow cytometry and/or immunohistochemistry) showing expression of CD19, CD20, CD22 and CD79a. Routine cytogenetic testing is not advised at this time, except to clarify the diagnosis from IgM myeloma, where 14q32 translocations are a predominant feature in contrast to WM.[21]

Initial staging should include a complete blood count with differential and more detailed serum chemistry. Cytopenia and in particular anemia are common. Serum diagnostics should test for the presence of monoclonal IgM, confirmed by immunofixation. The concentration of the serum monoclonal protein is highly variable, but in most cases lies within the range of 15–45 g/l. Determination of IgM levels can be based on both densitometry and 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 performed with the same methodology, optimally in the same laboratory because of known intralaboratory as well as interlaboratory variations.[22] The presence of cold agglutinins or cryoglobulins may affect determination of IgM levels, and therefore testing for cold agglutinins and cryoglobulins should be performed at diagnosis. The serum-free light-chain testing is not advised in the routine; its relevance for the management of WM patients is currently being evaluated. Furthermore, the β_2-microglobulin and albumin levels should be determined, as these factors have prognostic impact. Serum protein electrophoresis and quantification of immunoglobulin levels (IgM, IgG and IgA) should be performed. Some patients suffer from hyperviscosity caused by exceeding levels of IgM paraprotein. 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, which show, for example, venous engorgement ("sausaging") in the retinal veins, which is an excellent indicator of clinically relevant hyperviscosity.[23] In case of peripheral neuropathy, the evaluation of antimyelin-associated glycoprotein, antiganglio-sides M1 and antisulfatide IgM antibodies may support the diagnosis of IgM-related neuropathy. At diagnosis, ultrasound/computed tomography scan should be performed to document organomegaly/adenopathies. There is no routine role for positron emission tomography scanning unless a large-cell lymphoma transformation is suspected.

HOW TO PROGNOSTIFY WM PATIENTS

In the recent years, a powerful prognostic score has been developed, which categorizes patients into three risk groups with a 5-year survival rate ranging from 86% for the low-risk group to 36% for the high-risk group. This International Prognostic Index (ISSWM) is built on factors that are easy to determine in clinical practice (Table 1).[24] Thus, every patient suffering from WM should be classified according to the International Prognostic Index (ISSWM), as this gives important information about the overall prognosis of a given patient.

HOW TO EVALUATE RESPONSE IN WM

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 monoclonoal IgM affects remission status and that its disappearance is one of the

Table 1. International Prognostic Index (ISSWM)[24]

Risk group	Low	Intermediate	High
Score	0–1 (except age)	Age or 2	⩾3
5-Year OS (%)	87	68	36
Risk factors		Score	
Age ⩾65 years		1	
Other risk factors[a]			
Hb ⩽11.5 g/dl		1	
Thrombo ⩽100 × 10⁹/l		1	
β_2M >3 mg/l		1	
IgM >70 g/l		1	

Abbreviations: β_2M, β_2 microglobulin; Hb, hemoglobin; IgM, monoclonal protein concentration; OS, overall survival; Thrombo, thrombocytes. [a]Each of the risk factors counts as one.

prerequisites for the definition of complete response (CR) in this disease. Fortunately, there is an international consensus on how to define remission status in WM. These response criteria should be used inside and outside of clinical trials to be able to compare treatment results (Table 2).[22] Because of the variability in kinetics of IgM reduction with different treatment modalities and the apparent discrepancy between IgM and the bone marrow/tissue response noted with many regimens, including those containing rituximab and bortezomib, sequential bone marrow assessments are strongly encouraged in clinical trials.

HOW TO MANAGE ASYMPTOMATIC PATIENTS

As WM is an incurable disease and there are no data documenting any benefit for treatment in asymptomatic patients, there is clear consensus that the watch and wait strategy comparable to other indolent lymphomas is still standard today: it means that only patients suffering from lymphoma-related symptoms should start treatment.[25] In the case of WM, this includes symptoms caused by circulating IgM paraprotein, such as hyperviscosity, amyloidosis, symptomatic cryoglobulinemia, cold agglutinin disease, and neuropathy or disease-related hemoglobin level $<10\,$g/dl or platelet count $<100\times10^9$/l. On the other hand, monoclonal IgM

| Table 2.	Response criteria in WM[22]
Response category	Definition
CR	• Absence of serum monoclonal IgM protein by immunofixation • Normal serum IgM level • Complete resolution of lymphadenopathy and splenomegaly if present at baseline • Morphologically normal bone marrow aspirate and trephine biopsy
VGPR	• Monoclonal IgM protein is detectable • ⩾90% reduction in serum IgM level from baseline • Decreased lymphadenopathy/splenomegaly if present at baseline • No new signs or symptoms of active disease
PR	• Monoclonal IgM protein is detectable • ⩾50% but <90% reduction in serum IgM level from baseline • Decreased lymphadenopathy/splenomegaly if present at baseline • No new signs or symptoms of active disease
MR	• Monoclonal IgM protein is detectable • ⩾25% but <50% reduction in serum IgM level from baseline • No new signs or symptoms of active disease
SD	• Monoclonal IgM protein is detectable • <25% reduction and <25% increase in serum IgM level from baseline • No progression in lymphadenopathy/splenomegaly • No new signs or symptoms of active disease
PD	• ⩾25% increase in serum IgM level from lowest nadir and/or • Progression in clinical features attributable to the disease

Abbreviations: CR, complete response; MR, minor response; PD, progressive disease; PR, partial response; SD, stable disease; VGPR, very good partial response.

per se is not a reason to initiate treatment.[26] Close observation is appropriate for these patients.

HOW TO MANAGE WM PATIENTS FIRST LINE

There is still no precise treatment algorithm for WM because of the paucity of larger randomized clinical trials in this disease. Furthermore, treatment decisions have to take into account the individual characteristics of symptomatic patients: half of the WM patients are aged over 70 years and often suffer from non-lymphoma-related comorbidities, so that only well-tolerated low-dose intense treatments will be feasible. On the other hand, young fit patients with an aggressive clinical course might be candidates for high-dose treatments. There are also differences in how quickly a patient needs disease control. Taking this into account, treatment of WM patients has to be individualized and cannot strictly follow treatment algorithm schedules.

SYMPTOMATIC MEDICALLY–FIT WM PATIENTS

Front-line treatments options include alkylating agents, nucleoside analogs, bortezomib (added in the Newport consensus) and monoclonal antibody rituximab (Table 3). However, there is consensus that in symptomatic patients who are medically fit, the combination of rituximab with chemotherapy is among the most effective treatment and the first option to choose. The largest experience is in combining rituximab with alkylating agents or nucleoside analogs. Rituximab can be also combined with bortezomib.

Rituximab in combination with alkylating agents

In a prospective randomized trial the, 'German Low-Grade Lymphoma Group' could demonstrate that R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) is a well-tolerated and effective treatment in the first-line treatment of WM:[27] 48 WM patients were randomly assigned to R-CHOP ($n=23$) or CHOP ($n=25$). In the R-CHOP arm, a significantly higher overall RR (ORR) of 91% (95% confidence interval (CI): 72–99%) versus 60% (95% CI: 39–79%) for CHOP alone was observed ($P=0.0188$), while the CR rates were not statistically different (9% (95% CI: 1–28%) versus 4% (95% CI: 0–20%), $P=0.60$). R-CHOP led to a significantly longer time-to-treatment failure, with a median of 63 months for R-CHOP versus 22 months in the CHOP arm ($P=0.0241$) (Figure 1).

The Eastern Cooperative Oncology Group trial reported about its experience with the R-CHOP combination in the same setting: 91% of the patients achieved a partial response (PR) with a rapid median time to response of 1.6 months; at that time, with a median follow-up time of 18.3 months the median duration of response had not yet been reached. Myelosuppression was the main toxicity.[28] These studies indicate that combinations of rituximab with CHOP are highly effective and well tolerated in medically fit patients. In particular in younger patients in whom stem cell collection for later myeloablative treatment approaches is considered, R-CHOP is an excellent regimen. However, in many patients R-CHOP is considered to be too toxic because of its myelosuppressive effects. In a very interesting non-randomized comparison, it could be demonstrated that omitting doxorubicin (R-CVP; $n=16$) or doxorubicin plus vincristine (R-CP, $n=19$) did not significantly decrease treatment response, while being much less toxic compared with R-CHOP ($n=23$) in patients with WM.[29] Following the same line, Dimopoulos *et al.*[30] introduced a regimen consisting of dexamethasone 20 mg followed by rituximab 375 mg/m² intravenously on day 1 and cyclophosphamide 100 mg/m² orally b.i.d. on days 1–5 (DRC). This regimen was highly effective in a phase II trial in 72 previously untreated patients with symptomatic WM. An objective response was

Table 3. Treatment approaches in WM

Author	No. of patients	Treatment	ORR (%)	Median PFS (months)
(Rituximab)/chemotherapy				
Leblond et al.[43]	339	F (versus Chl)	47.8% (versus 38.6%)	36.3 (versus 27.1)
Treon et al.[81]	43 (75% 1st line)	FR	95.3%	51.2
Weber et al.[82]	17	CCR	94	21+
Hensel et al.[83]	17	PCR	90	12+
Tedeschi et al.[40]	43 (65% 1st line)	FCR	79% (12% CR)	88% at 24 months
Laszlo et al.[37]	29 (55% 1st line)	CDA/rituximab (4 cycles)	89% (22% RC)	Median not reached
Dimopoulos et al.[30]	72	DRC	83%	67% at 2 years
Buske et al.[a27]	72	CHOP/rituximab (versus CHOP)	94%	48+
Rummel et al.[45]	40	R-bendamustin (versus R-CHOP)	96%	Median not reached
Combination regimens including novel compounds				
Treon et al.[38]	23	BDR	96%	30+
Ghobrial et al.[49]	37 (relapsed)	BR	81	19.5
Ghobrial et al.[50]	26 (untreated)	BR	100	12+
Dimopoulos et al.[77]	20 (10 untreated)	T	85%	
Treon et al.[52]	25	TR	72%	34.8
Ghobrial et al.[69]	42	Enzastaurin	38%	10.9
Ghobrial et al.[73]	37	Perifosine	35%	12.6
Ghobrial et al.[84]	36	Panobinostat	47%	6.6

Abbreviations: Chl, chlorambucil; DRC, dexamethasone/rituximab/cyclophosphamide; B(D)R, bortezomib (dexamethasone) rituximab; FCR, fludarabine/(cyclophosphamide)/rituximab; CCR, cladribine/cyclophosphamide/rituximab; PCR, pentostatin/cyclophosphamide/rituximab; T, thalidomide [a]Lymphoplasmacytic lymphoma patients were also included.
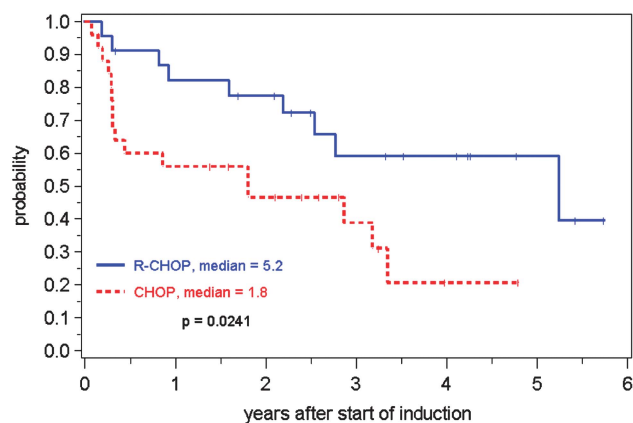
Figure 1. The figure shows the time-to-treatment failure after R-CHOP versus CHOP in patients with WM based on a subgroup analysis of a randomized phase III clinical trial of the German Low-Grade Lymphoma Study Group testing the efficacy of the two regimens in different indolent lymphomas (figure reused from already published material).[27]
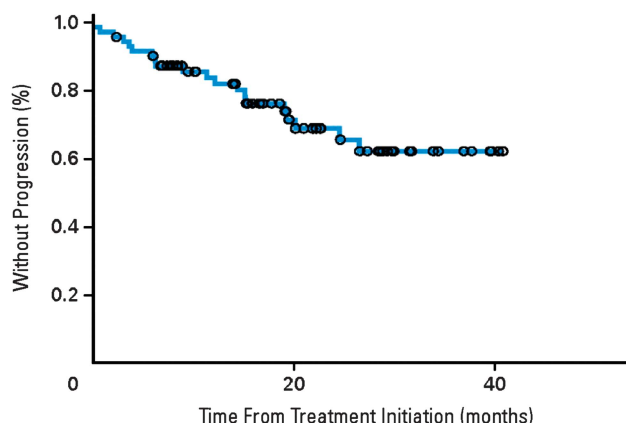

Figure 2. The graph illustrates the time to progression (defined as the time from start of treatment with DRC to disease progression) after DRC in patients with symptomatic treatment-naïve WM (figure reused from already published material).[30]

Rituximab in combination with purine nucleoside analogs

Cladribine (2-chlorodeoxyadenosin, 2-CdA) and in particular fludarabine are commonly used chemotherapeutics in WM. In smaller phase II studies, even pretreated patients achieved high RRs between 30 and 50% with fludarabine in relapsed/refractory patients and between 55 and 90% in treatment-naive patients.[31–34] In a large phase II trial of first-line single-agent fludarabine, the ORR was 38% (CR rate 3%) among 118 patients. The median event-free survival and OS were 3.0 and 6.8 years, respectively.[35] In a phase II trial it could be demonstrated that in relapsed patients, the efficacy of fludarabine can be further improved by adding cyclophosphamide (FC regimen).[36] Side effects include myelosuppression and T-cell depletion with subsequent immunosuppression and the danger of treatment-related infections. Furthermore, fludarabine might be stem cell toxic and impair stem cell collection later on.

Combination therapy of rituximab with nucleoside analogs has been investigated as both first-line and salvage therapy by Laszlo

documented in 83% of patients, including 7% with CR and 67% with PR. Furthermore, the median time to response was 4.1 months. The 2-year PFS (defined as the time from start of treatment with DRC to disease progression) for the total patient group was 67% and for responding patients 80%. This remarkable activity was paralleled by only moderate myelotoxicity, with only 9% of patients experiencing grade 3 or 4 neutropenia and none experiencing grade 3 or 4 thrombocytopenia. Thus, the DRC regimen is a very attractive regimen for the treatment of WM, avoiding unnecessary toxicity in a palliative situation[30] (Figure 2).

et al.,[37] who recently evaluated the combination of subcutaneous cladribine with rituximab in 29 WM patients with either untreated or previously treated disease. Intended therapy consisted of rituximab on day 1 followed by subcutaneous cladribine 0.1 mg/kg for 5 consecutive days, administered monthly for four cycles. With a median follow-up of 43 months, the ORR observed was 89.6%, with 7 CRs, 16 PRs and 3 minor responses. Response activity was similar between untreated and previously treated patients. In a study by the Waldenstrom's Macroglobulinemia Clinical Trials Group (WMCTG), the combination of rituximab and fludarabine was administered to 43 WM patients, 32 (75%) of whom were previously untreated.[38] The ORR was 95.3%, and 83% of patients achieved a major response (MR). The median time to progression was 51.2 months in this series, and was longer for those patients who were previously untreated and for those achieving at least a very good partial response.

In WM larger data sets are still missing regarding fludarabine/ (cyclophosphamide)/rituximab (FCR) combination; in a report on five patients with WM, FCR induced responses in all patients, with no unexpected toxicity.[39] In a more recent report, 43 patients with symptomatic WM were treated with up to six cycles of FCR: the ORR was 79%, with 11.6% of the patients achieving a CR, 20% a very good partial response (VGPR) and 41.8% a PR. Importantly, the best response was partly delayed and addition of rituximab induced later on a VGPR in 33% of the patients. However, long-lasting neutropenia was observed in 44% of the patients mostly after six cycles of FCR for a median duration of 7 months and up to 24 months. Thus, although FCR seems to be an effective regimen also in WM, myelosuppression is of concern and six cycles of FCR should be avoided.[40]

The long-term safety of nucleoside analogs in WM was examined by Leleu et al.[41] in a large series of WM patients. A sevenfold increase in transformation to an aggressive lymphoma and a threefold increase in the development of acute myelogenous leukemia (AML)/myelodysplasia (MDS) were observed among patients who received a nucleoside analog versus other therapies for their WM. A metanalysis by Leleu et al.[41,42] of several trials utilizing nucleoside analogs in WM patients, which included patients who had previously received an alkylator agent, showed a crude incidence of 6.6–10% for the development of disease transformation, and an incidence of 1.4–8.9% for the development of MDS or AML. These results were not confirmed in a large randomized study comparing the efficacy of fludarabine alone with that of chlorambucil, with a 6-year cumulative incidence of disease transformation of 7.7% in the fludarabine arm versus 11.1% in the chlorambucil arm. Three MDS/AMLs were observed during the follow-up, all cases in the chlorambucil arm. However, there is some evidence to suggest that this complication may be more frequent in patients treated with fludarabine–alkylator combinations than with fludarabine monotherapy.[43]

Bendamustine is a chemotherapeutic drug that chemically displays the characteristics both of a purine nucleoside analog and of an alkylating agent. Developed in the sixties of the last century in the post-war communist Eastern part of Germany as a competitor to established alkylating drugs such as cylopho-sphamide, it has just recently experienced a re-birth based on its high efficacy in follicular lymphoma and its excellent toxicity profile. A subgroup analysis comprising 40 evaluable patients with WM of a large randomized clinical trial, which compared BR with R-CHOP, was presented recently: both immunochemotherapies induced high RRs with 96% for BR and 94% for R-CHOP. Again both treatments were not able to induce complete remissions. However, the duration of response was longer for BR, with the median not reached compared with a median of <42 months for R-CHOP after a median observation of 26 months.[44,45] Although this was a subgroup analysis with a limited number of patients, these early results point to a remarkable activity of BR also in WM

and indicate that BR is another highly attractive treatment option in this often elderly group of patients. However, the long-term safety of BR is unknown in WM patients and the risk of solid tumors and/or MDS/AML must be assessed in prospective trials.

Bortezomib and immunomodulatory agents
Among the novel therapeutic compounds, bortezomib has been tested the most in WM (Table 3). Several phase II trials have confirmed the efficacy of bortezomib used as a single agent in WM.[46–48] More recently, the combination of bortezomib with rituximab was analyzed in a phase II trial: 37 patients with relapsed or refractory WM were treated with bortezomib 1.6 mg/m^2 on days 1, 8 and 15 in a 28-day cycle for six cycles combined with rituximab 375 mg/m^2 on days 1, 8, 15 and 22 for cycles 1 and 4. The median number of treatments was 3 and 78% of the patients completed the treatment. This combination induced an OR of 81%, with 5% CR and 46% PR. Grade 3 or 4 toxicity was acceptable, with 16% leucocytopenia, 11% anemia and 5% neuropathy. One patient died of pneumonia, emphasizing that severe infectious complications might occur in this patient population.[49] The same regimen was tested in 26 untreated WM patients, with 88% minor responses, 58% partial response and 8% CR or near-CR. The 1-year event-free survival was 79% and importantly no grade 3/4 neuropathy was documented.[50] A lower incidence of peripheral neuropathy was observed using once a week bortezomib as compared with the incidence of grade 3 neuropathy (30%) in a study that utilized a twice a week schedule for bortezomib administration at 1.3 mg/m^2.[38] The impact of once versus twice weekly bortezomib administration on PFS remains to be clarified. Taken together, bortezomib is the most promising compound for first-line treatment in WM patients beside standard rituximab/chemotherapy. It is still an open question, however, whether adding bortezomib to rituximab/chemotherapy increases efficacy without enhancing toxicity. This important question has to be addressed in future clinical trials.

Thalidomide is among the standard treatment options in multiple myeloma and was tested earlier for its activity in WM: Dimopoulos et al.[51] reported on 20 patients (10 untreated and 10 previously treated) who received between 200 and 600 mg orally. RRs were high, with an OR of 85 with 25% PR. The time to response was short (0.8–2.2 months) and median PFS was 11 months. However, many patients had difficulties in tolerating higher thalidomide doses and only five patients in this trial succeeded in getting the maximum dose of 600 mg.[51] Treon et al.[52,53] combined thalidomide with rituximab. The intended schedule was 200 mg thalidomide for 2 weeks, followed by 50 weeks of 400 mg thalidomide combined with rituximab 375 mg/m^2 intravenously from weeks 2 to 5 and 13 to 16. On an intent-to-treat basis, overall response and MR were encouraging (72 and 64%, respectively). For the evaluable patients, the median time to treatment failure was 34.8 months. However, dose reduction had to be done in all patients and 14 patients discontinued treatment, and so the authors recommended the 200 mg dosing of thalidomide outside clinical trials. Furthermore, adding thalidomide to rituximab did not prevent the paradoxical increase of serum IgM known from rituximab single-agent therapy in WM. Therefore, prophylactic plasmapheresis should be considered in patients with highly elevated IgM before treatment. Lenalidomide is another potentially attractive drug in WM. However, in a recent publication it was reported that it induces—at least in a dose of 25 mg orally—sudden drops in the hematocrit in 13 of 16 patients with WM, with a median decrease of 4.8% in the first 2 weeks. This anemia without any obvious signs of hemolysis or general myelosuppression persisted in affected patients even after dose reduction to 5 mg lenalidomide per day.[53] The underlying mechanism for this is not completely known. Thus, lenalidomide should not be given outside of clinical trials in WM at the moment.

HOW TO MANAGE WM PATIENTS WITH CO-MORBIDITIES

WM is a disease of the elderly and many patients suffer from non-lymphoma-related comorbidities. Unfortunately, there are no larger clinical trials testing the optimal therapeutic approaches for medically non-fit patients with WM. Thus, this subgroup of patients, which will dramatically grow in the future years, is clearly under-represented in clinical trials. Owing to the lack of guidelines as to how to treat this patient group, the management of unfit patients remains a primary unmet clinical need. Today, treatment of these patients has to be based on individual decisions, depending on many factors, in particular on the degree of individual comorbidities, geriatric syndromes and frailty. There are several treatment approaches that have antilymphoma activity, but avoid major toxicity. One potential approach is plasmapheresis. This approach avoids chemotherapy and is normally well tolerated. In particular, for patients with hyperviscosity plasmapheresis is an accepted treatment option. Its disadvantage is its transient effect, so that it should be followed by systemic treatment. Rituximab/chemotherapy is the treatment of choice in medically fit patients, but can be toxic in the elderly. In non-fit patients single-agent chlorambucil is a valid option and induces an objective improvement between 70 and 80%.[54] However, time to response can take months, so that for patients who need rapid disease control chlorambucil might be not appropriate. In a large randomized study of 339 treatment-naive WM patients, the efficacy of chlorambucil was compared with that of fludarabine: in this study, the median age was 68 years, thus close to the median age of patients with WM in the general population. The ORR was higher in the fludarabine arm with 47.8% compared with 38.6% for chlorambucil ($P = 0.07$). The median duration of response was 38.5 versus 21.3 months for fludarabine and chlorambucil, respectively ($P = 0.0024$). The median PFS was 37.8 months and the OS not reached in the fludarabine arm compared with 27.1 months PFS and 69.8 months OS in the chlorambucil arm ($P \leqslant 0.015$; 95% CI: 61.6–79.8), respectively. Taken together, this randomized study has demonstrated a significant advantage in favor of fludarabine with a manageable toxicity.[43]

Rituximab single-agent therapy is less effective in WM than in follicular lymphoma and 4 weekly infusions of rituximab achieve ORRs of about 20 to 30%. However, extended rituximab applications enhance RRs to up to 50%.[55] Response is often slow after rituximab single-agent therapy, and in particular in patients with signs of hyperviscosity or patients with high IgM values, there is the danger of the so-called 'IgM flare', a transient increase of serum IgM immediately following initiation of rituximab treatment.[56] Patients with baseline serum IgM levels of >50 g/dl or serum viscosity of >3.5 cp may be particularly at risk for a hyperviscosity-related event and in such patients plasmapheresis should be considered. Importantly, the IgM flare in response to rituximab does not predict treatment failure with most patients returning to baseline serum IgM level by 12 weeks.

Another well-tolerated regimen avoiding conventional chemotherapy is the bortezomib/rituximab combination, when bortezomib is given on a weekly basis. This regimen did not cause any major neurotoxicity in treatment-naive patients, thereby avoiding a side effect that would substantially affect quality of life in elderly patients.[50] With regard to rituximab/chemotherapy particularly, the DRC regimen described above is highly attractive as it combines high antilymphoma activity with virtual no major hematologic toxicity in patients with WM.[30]

Rituximab/bendamustine is considered to be an excellent choice for the treatment of elderly patients with other chronic B-cell lymphoproliferative disorders because of its excellent toxicity profile (for example, in patients with renal insufficiency) and high antilymphoma activity. A subgroup analysis just recently presented at the 2012 ASCO plenary session confirmed that also for patients with WM this combination regimen is well tolerated and is superior to R-CHOP (hazard ratio: 0.33; $P = 0.0033$).[45] However, prospective trials testing bendamustine in the group of medically non-fit WM patients are missing, defining precisely the role of this chemotherapy in this patient group.

HOW TO MANAGE IGM-ASSOCIATED CLINICAL SYMPTOMS IN WM

Antimyelin-associated glycoprotein neuropathy

Treatment options should be adapted to the aggressiveness of the neuropathy and the dynamics of progression. Watch and wait is recommended for non-disabling neuropathy, rituximab monotherapy can be used in disabling, but slowly progressive neuropathy, as rituximab single-agent-induced improvements develop slowly with a median clinical response time of 9 months, observed in 30–80% of patients. In rapidly progressive and disabling neuropathy, rapid control of the disease is needed. In this case, the combination of rituximab/chemotherapy (for example, cyclophosphamide, purine analogs) is recommended.[57,58]

Cold agglutinin disease

The hemolysis is usually extravascular (removal of C3b-opsonized cells by the reticuloendotelial system, primarily in the liver) and rarely intravascular from complement destruction of red blood cell membranes. Corticosteroids and splenectomy are not effective to control hemolysis in cold agglutinin disease. Rituximab alone, or in combination with chemotherapy, is recommended, such as fludarabine–rituximab combinations, resulting in 75% RRs and 20% complete remissions.[59]

HOW TO MANAGE WM WITH AGGRESSIVE CLINICAL COURSE

In case of hyperviscosity or interaction of the monoclonal protein with coagulation factors, mainly factor VIII Willebrand and fibrinogen, plasmapheresis should be started, followed by rituximab/chemotherapy regimens, such as R-CHOP, R-bendamustine, rituximab/purine analogs or R-bortezomib, ensuring rapid clinical response. Few patients have a high tumor burden with bulky disease and/or extramedullary aggressive disease. In those patients, the treatment of choice is similar to the one used in other advanced-stage low-grade lymphomas, such as R-CHOP, R-bendamustine or R-FC.

HOW TO MANAGE REFRACTORY/RELAPSED WM PATIENTS

When discussing the management of relapsed or refractory patients with WM, we have to be aware that there is no common standard approach. Therefore, these patients should be included into clinical trials, testing novel strategies and compounds, whenever possible. Outside of clinical trials, rituximab/chemotherapy is still the backbone also for relapsed WM in many cases and autologous stem cell transplantation (ASCT) is considered to be an important tool in eligible patients by many centers.

Rituximab/chemotherapy

Similar to the guidelines in follicular lymphoma, rituximab/chemotherapy is one of the cornerstones in the treatment in relapsed patients with WM, if the relapse after prior rituximab treatment does not occur within the first half year. There is consent that an alternate rituximab/chemotherapy regimen should be used if the relapse occurs within the first (recommendations of the 'International Workshop on Waldenstrom's macroglobulinemia) or the first 2 years (mSMART Mayo clinical consensus recommendations).[25,60] 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 analogs, rituximab/bendamustine or bortezomib, and *vice versa*. Another important aspect is whether ASCT is considered. In that case potentially stem cell toxic regimens should be avoided, such as repetitive applications of nucleoside analogs. There are no general guidelines for patients who relapse within 6 months after initial rituximab/chemotherapy. In follicular lymphoma, bendamustine single-agent therapy has shown high activity in this situation.[61] If patients are chemosensitive and eligible for ASCT, myeloablative chemotherapy followed by reinfusion of autologous stem cells is a valid option in these clinically aggressive cases.

Autologous stem cell transplantation

There are several reports documenting that myeloablative chemotherapy followed by ASCT is feasible and highly effective in patients with WM.[62] The largest report was published by the European Group of Blood and Bone Marrow Transplantation (EBMT), retrospectively analyzing the outcome of 158 patients with WM undergoing ASCT between 1991 and 2005. The vast majority of patients (93%) had chemosensitive disease at the time point of transplant. The PFS and OS were 39.7% and 68.5%, respectively, at 5 years. Multivariate analyses showed that chemorefractory disease at ASCT and at least three treatment lines were the most important independent prognostic factors for a significantly shorter PFS. With regard to OS, three or more treatment lines, chemorefractory disease at ASCT, male sex and age >50 years, were associated with a significantly inferior OS. ASCT was well tolerated with a low 1-year non-relapse mortality (3.8%). However, the cumulative rate of secondary neoplasms was 8.4% at 5 years including three patients with AML and four patients with MDS.[63] On the basis of these experiences, high-dose therapy followed by ASCT in chemosensitive relapsed WM is an important treatment option for medically fit patients, in particular in clinically more aggressive cases or cases with a high IWMSS. ASCT is actually inducing substantially higher CR rates than conventional chemotherapy in WM and was shown to be highly active in IgM amyloidosis.[64]

Allogeneic transplantation

There are several clinical reports indicating that also allogeneic transplantation is feasible and effective in WM. The largest series was again reported by the EBMT, reporting on the long-term outcome of 86 WM patients.[65] The patients received allograft by either myeloablative (n = 37) or reduced-intensity (n = 49) conditioning. The patient population was highly selected with a median age of 49 years, and 47 patients had three or more previous lines of therapy (8 patiens failed prior autologous transplantation). A total of 59 patients (68.6%) had chemotherapy-sensitive disease at the time of allogeneic SCT. The relapse rates at 3 years were 11% for myeloablative and 25% for reduced-intensity conditioning recipients. The 5-year PFS and OS for WM patients who received a myeloablative allogeneic SCT were 56% and 62%, and for patients who received reduced-intensity conditioning 49% and 64%, respectively. The occurrence of chronic graft-versus-host disease was associated with improved PFS, and suggested the existence of a clinically relevant graft-versus-WM effect in this study. However, non-relapse mortality was substantial, with 33% at 3 years for patients receiving a myeloablative transplant, and 23% for those who received reduced-intensity conditioning. This is in line with smaller series reported by other groups,[66–67] so that there is common sense that allogeneic transplantation should be considered in young relapsed patients with aggressive clinical course, but preferably within clinical trials.

Novel compounds

There are several drugs with promising activity and tolerable side effects in clinical testing, preclinical as well as first clinical data documented clinical activity for enzastaurin, an oral serine/threonine kinase inhibitor that targets the protein kinase C and phosphatidylinositol 3-kinase/AKT pathways, in WM patients (Table 3).[68] In a first multicenter trial, 42 partly heavily pre-treated patients were treated with oral enzastaurin 250 mg two times daily (500 mg total) after a loading dose (day 1, cycle 1) of 375 mg three times daily (1125 mg total) for eight cycles of 28 days each or until progressive disease. The objective RR was 38.1% (2 PRs and 14 minor responses). In general enzastaurin was well tolerated. There was one patient with grade 3 leukopenia and one patient died during the study from septic shock.[69]

Another pathway on which growth of WM cell lines depends is the mammalian target of rapamycin pathway. Everolimus is an oral inhibitor of this pathway and inhibition of this pathway leads to apoptosis of primary WM cells, and WM cell lines.[70] In a phase II trial Ghobrial *et al.*[71] treated 50 patients with a median of three prior therapies with everolimus: they achieved an OR of 70%, with 42% of patients attaining an MR. The PFS at 12 months was estimated to be 62%. Grade 3 or higher related toxicities were observed in 56% of patients, with cytopenias constituting the most common toxicity. Pulmonary toxicity occurred in 10% of patients. Dose reductions due to toxicity occurred in 52% of patients. In previously untreated patients with WM everolimus induced a minor response in 67% of the patients. Side effects were mainly cytopenias, particularly anemia and thrombocytopenia. In addition, pneumonitis occurred in 15% of patients.[72]

An important pathway linked to tumor growth is the Akt pathway: perifosine is a novel Akt inhibitor that belongs to a class of lipid-related compounds called alkyl-phospholipids. A phase II clinical trial was conducted in 37 patients. Of the patients, 11% achieved a PR and MR was observed in 24%. Stable disease occurred in 54% of the patients, and PFS was 12.6 months.[73]

Histone-deacetylase inhibitors follow a completely different mode of action and interfere with the chromatin topology and gene regulation machinery. Preclinical studies have demonstrated that primary WM cells exhibit a higher level of histone-deacetylases, thus providing the rational for testing histone-deacetylase inhibitors. The activity of panobinostat was demonstrated *in vitro* in tumor cells and cell lines.[74,75] First data from a phase II study enrolling 36 previously treated patients documented activity of this therapeutic approach in WM patients: the compound induced an ORR of 47% (PR: 22%; MR: 25%), and the median PFS was 6.6 months. Major side effects were hematological with grade 3 and 4 anemia, neutropenia and thrombocytopenia in 15%, 26%, and 52%, respectively.[76]

DEVELOPING TREATMENT ALGORITHMS IN WM

There is no standard treatment carved in stone for patients with WM. This is due to the fact that patient characteristics differ substantially and that fortunately we have many treatment options at hand that induce remissions in a palliative situation. Outside a clinical trial, several factors should be taken into account in choosing the most appropriate primary treatment. These include the age of the patient and possible comorbidity, the presence of cytopenias, especially thrombocytopenia, the presence of symptoms and signs indicative of hyperviscosity, the need for rapid disease control due to severe symptoms, significant splenomegaly or lymphadenopathy, symptomatic peripheral neuropathy and the eligibility for ASCT. Despite this there is consensus that the four main agents for systemic primary treatment of patients with WM include: (1) alkylating agents (chlorambucil, cyclophosphamide), (2) nucleoside analogs (fludarabine, cladribine) and bendamustine, (3) bortezomib and (4) the monoclonal anti-CD20 antibody rituximab. Furthermore, it is

generally accepted that combining rituximab with the chemotherapeutic agents listed above increases RRs and the duration of the response, so that rituximab/chemotherapy is considered to be the backbone of treatment in medically fit patients with WM. In addition, outside of clinical trials one should follow the following recommendations:

- for patients who present with symptoms and signs of hyperviscosity, plasma exchange should precede any systemic treatment.
- rituximab monotherapy is associated with sudden increase in IgM levels and should be avoided in patients with hyperviscosity.
- for patients who are candidates for high-dose therapy (or may be candidates at some point of their disease), every effort should be made to avoid exposure to nucleoside analogs.
- for patients with refractory or relapsing disease, the use of an alternate first-line agent is reasonable (for example, alkylating agents, bortezomib after primary therapy with nucleosides and vice versa).
- for patients who are resistant to alkylating agents, a nucleoside analog plus rituximab will be effective in 30–40% of cases.

- for patients who develop resistance to all four classes of agents, few valid options are available. Such patients are best served when treated within the context of a phase II trial testing novel compounds.

On the basis of these treatment principles, the following treatment algorithms as depicted in Figure 3 for first-line and salvage therapy can be suggested, implying that changes due to individual patient characteristics might be necessary. As illustrated schematically, the watch and wait strategy is still standard for asymptomatic patients. In symptomatic patients, rituximab/chemotherapy is one key approach in both the medically fit and the compromised patient. Among the novel compounds, bortezomib is already widely accepted by its incorporation into treatment algorithms, whereas other emerging drugs, such as enzastaurin, are still in their early clinical development.

'QUO VADIS' IN WM IN THE NEXT 5 YEARS?

Our 'traditional' overall goal regarding indolent lymphoma is to cure patients with this disease. However, there is no established curative therapeutic approach for this group of diseases, which
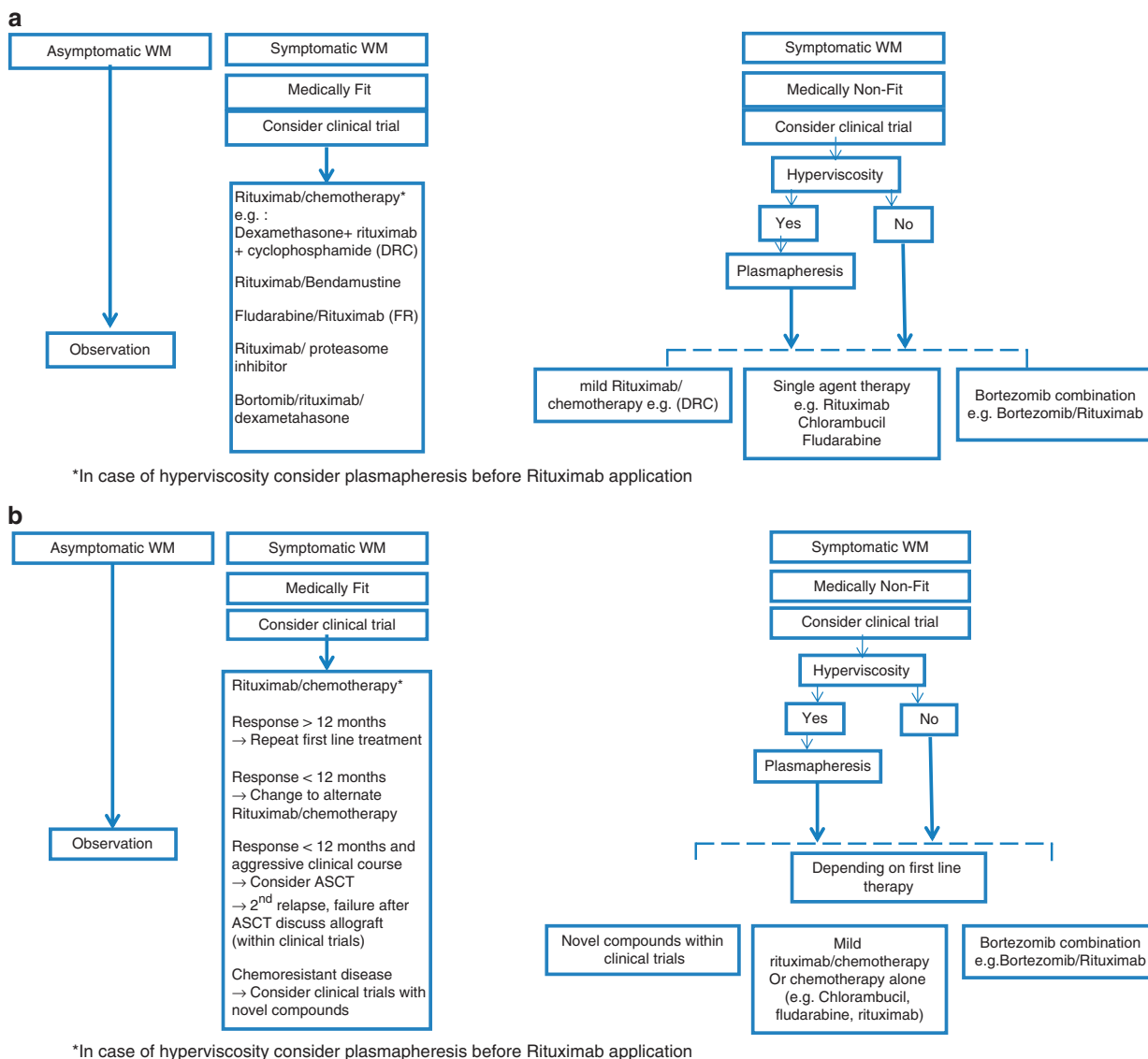

Figure 3. Treatment algorithms for newly diagnosed (a) and relapsed (b) patients with WM.

also holds true for WM. One could argue that allogeneic transplantation is curative in a subset of patients, but one has to admit that this approach is not feasible for the large group of elderly patients and is even not widely accepted for young and fit patients with WM. On the other side, we see a development towards a growing number of effective treatments associated with low toxicity. Thus, we are more and more able to control the disease without major limitations in the quality of life of these patients. In the elderly patient population this means that quite often the indolent lymphoma is not anymore the cause of death. In this view we should pursue a more realistic vision of our therapeutic goals in WM and probably other indolent lymphoma subtypes: it should be our aim to develop treatment strategies that are effective in not only controlling the disease but also minimizing toxicity and avoiding long-term complications. Furthermore, these treatment strategies should be manageable on an outpatient basis and should not depend on intravenous application. There are already developments in this direction, such as the before-mentioned DRC regimen, in which all the components can be given orally or subcutaneously.[30] The same is true for the combination rituximab/bortezomib.[49] Oral drugs such as thalidomide and lenalidomide are appealing, but thalidomide is quite toxic in WM patients[52,77] and lenalidomide induced unexpected acute drops in hematocrit in 81% of patients, which persisted after dose reduction.[53]

Another class of compounds with great potential are monoclonal antibodies as exemplified by rituximab: ofatumumab is a fully humanized CD20-directed monoclonal antibody that targets the small loop of CD20, a target that is different from that of rituximab. In all, 59% ORR was observed in a series of 37 symptomatic WM patients. Of note, in two patients an IgM flare with subsequent symptomatic hyperviscosity was observed.[78] However, so far it is not clear whether ofatumumab has any advantage compared with rituximab in WM. Alemtuzumab has also been investigated in WM patients given the broad expression of CD52. Recently, the long-term results of alemtuzumab were reported. However, the antibody was associated with major toxicities, mainly hematologic and infectious complications, including CMV reactivation, with three treatment-associated deaths in 27 symptomatic WM patients and one IgA-positive LPL patient.[79] Another concept that is already standard in follicular lymphoma and that might become integral part of WM treatment in the near future is maintenance. Surprisingly, data are scarce and there is actually no prospective study published so far for patients with WM. There is, however, a retrospective study examining the outcome of 248 WM rituximab-naïve patients who were either observed or received maintenance rituximab.[80] In this retrospective study, categorical responses improved in 16/162 (10%) of observed patients compared with 36/86 (41.8%) of patients who received maintenance rituximab following induction therapy. Both PFS (56.3 versus 28.6 months) and OS (>120 versus 116 months) were longer in patients who received maintenance rituximab. There were more infections in the maintenance arm, but mostly of grade 1 or 2. The superiority of rituximab maintenance has to be confirmed in a randomized study, before it can be recommended outside of clinical trials. In the future, it is very likely that novel compounds that might be suitable for maintenance treatment will show up—for example, compounds that can be given orally and have favorable toxicity profile, such as enzastaurin.[69] MYD88 mutation and its interaction with the Bruton tyrosine kinase pathway could offer new treatment targets.[10]

In summary, we still do not have the 'magic bullet' for WM, but there is a continuous development of therapeutic approaches, which are well tolerated, control disease symptoms and, at the end, keep the patient mobile. Our progress in the management of WM was based on controlled clinical trials, so that we should continue to include patients, whenever possible, in clinical studies. This will finally pave the way to treatment concepts that are able to achieve long-term control of the disease without compromising the quality of life of the mostly elderly patients.

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