

# Novel treatment regimens for Waldenström's macroglobulinemia

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Waldenström's macroglobulinemia (WM) is a B-cell lymphoproliferative disorder defined by bone marrow infiltration by lymphoplasmacytic cells as defined by the current classification systems. According to its transition situation between mutated chronic lymphocytic leukemia and multiple myeloma, several new therapeutic alternatives have been proposed for this entity based on the experience with these two well-known conditions together with the highly singular data provided by preclinical models. Thus, in WM two main therapeutic attitudes are possible: the use of conventional therapies based on the administration of single drugs or combinations with alkylating agents, purine analogues and anti-CD20 monoclonal antibodies; or the use of very new combinations that, without rejecting the previously mentioned drugs, include new agents, such as proteasome inhibitors, immunomodulatory agents or even histone deacetylase inhibitors and PI3K/AKT inhibitors, among others. Here we review the most recent results reported for the use of new combinations and new drugs in patients with WM at different stages of the disease.

**KEYWORDS:** bendamustine • bortezomib • cyclophosphamide • dexamethasone • enzastaurin • everolimus • lenalidomide • thalidomide • Waldenström macroglobulinemia

Waldenström's macroglobulinemia (WM) is a B-cell lymphoproliferative disorder defined by bone marrow infiltration by lymphoplasmacytic cells as defined by the Revised European American Lymphoma [1] and WHO classification systems [2], along with the presence of IgM monoclonal gammopathy [3]. From the biological point of view, this condition is very interesting because it is considered a transition from the mature lymphoid B cell after antigenic stimulation in peripheral lymph nodes to the final antibody-secreting plasma cell. In other words, WM is an intermediate disease between mutated chronic lymphocytic leukemia and multiple myeloma (MM), and it shares several characteristics with both entities. Despite this, WM is considerably less frequent than B-cell chronic lymphocytic leukemia (B-CLL) or MM, with an estimated incidence rate of between 3.6 and 5.5 cases per million person-years at risk in the EU and USA [4–7]. This is the reason for the lack of extensive trials to test the efficacy of traditional and novel therapies. Both characteristics of WM (its intermediate nosologic situation and the lack of therapeutic alternatives) have prompted the

use of strategies derived from B-CLL and MM, although the responses have not been as predictable as might have been expected according to previous experience with these two entities.

In this article, we review the most recent results obtained with the use of new drugs and their therapeutic associations in patients with WM at different stages of the disease. Such combinations must be taken with caution, especially if it is considered that the low frequency of WM has not allowed direct comparisons to be made with other more conventional treatment alternatives or between the different novel modalities themselves.

## Current state of the art

Spontaneous remissions do not occur in WM and no placebo effect on response has been noted. However, not all patients require therapy, since those with asymptomatic disease have a similar survival to the general population [6,8]. Accordingly, the Second International Workshop on Waldenström's Macroglobulinemia (IWWM) organized a board of experts, the 'Consensus Panel Two', that clearly identified the symptoms and/or signs that indicate the

need to start therapy [6,9]. The standard therapy for symptomatic patients includes a number of chemotherapeutic agents and monoclonal antibodies; and high-dose chemotherapy and bone marrow transplantation must be considered as feasible possibilities for patients under the age of 65 years. However, the rarity of WM has prevented the development of the well-designed trials that are usually necessary for any drug to achieve formal indication. In fact, some authors have cast doubt on the efficacy of the drugs used most extensively until now, alkylating agents, because a comprehensive meta-analysis failed to demonstrate any clear advantages for these drugs in WM [10].

Accordingly, WM has no formally approved therapy, at least in Europe [10,11]. This reinforces the recommendations of experts, such as those provided by the consensus panel during the fourth IWWM. The panel considered that alkylating agents (chlorambucil, cyclophosphamide or melphalan), nucleoside analogues (cladribine or fludarabine) and the CD20 monoclonal antibody are all reasonable choices for upfront therapy in WM [12,13]. Overall response rates (ORRs) of 30–70%, with complete response (CR) rates of approximately 10%, have been reported with such therapeutic agents in the upfront therapy of WM, with median durations of response averaging 2–3 years. Response rates could be improved by using combinations of the aforementioned drugs, including CR rates up to 20%. Importantly, the presence of cytopenia, the requirement of rapid disease control, young age and in particular candidacy for autologous transplant therapy must be taken into consideration when deciding on first-line therapy. Rituximab has some interesting features that should be taken into account in the clinical setting. First, its use in WM can produce a paradoxical increase in IgM levels during the first weeks of therapy, which does not mean a lack of response; it is known as the Flare phenomenon [14,15]. Second, a late improvement of responses, even weeks or months after the completion of therapy, has also been reported with some rituximab-including regimens [16,17].

Young patients with no important comorbid conditions are candidates for considering high-dose therapy followed by autologous stem cell transplantation (ASCT). For such patients, the panel recommended avoiding or limiting exposure to alkylators and nucleoside analogues. In this setting, non-stem cell toxic agent such as monoclonal antibodies or cyclophosphamide should be considered if stem cells have not been harvested previously. In the case of patients in relapse or with refractory disease, the use of an alternative first-line agent as defined above is considered a reasonable choice. The use of transplant therapy has been explored in the salvage therapy of WM, in which patients received ASCT during various phases of their disease and most of them were heavily pretreated. At this point it should be recalled that in patients for whom autologous transplantation is an option, previous treatment with stem cell-damaging agents should be avoided. This mode is capable of inducing objective responses in most patients, including those refractory to standard chemotherapy. Thus, some patients surviving without progression for at least 5 years have been reported. Prospective studies with larger number of patients are needed to define the role of ASCT in patients with poor prognostic features at diagnosis [18–20].

Some studies have also reported the activity of allogeneic stem cell transplantation in WM, using both conventional and reduced-intensity conditioning [21,22]. This procedure has resulted in good activity, with a 5-year progression-free survival (PFS) of approximately 50–60%, and clear hints of a graft-versus-tumor effect. Nevertheless, the high mortality associated with transplantation (transplant-related mortality of 36% of conventional regimens and between 17 and 27% for reduced-intensity conditioning) means that it should only be considered an investigational approach and hence should only be performed in the context of well-designed clinical trials or in a very selected population of patients.

Considering these expert recommendations critically, it should not be overlooked that they are the result of a consensus in which the participants usually renounce some of their own opinions and accept others to favor an agreement, which remains debatable. In addition, the fast advances in WM therapy sometimes mean that certain opinions rapidly become outdated; in this sense, it is not strange that highly experienced authors have proposed quite different strategies only 6 months after publication of the consensus [23]. In any case, all these data clearly reveal that there is no perfect therapy for WM and that it remains incurable, with a median survival no longer than 8 years from the time of diagnosis. Accordingly, the development and evaluation of novel therapeutics is still mandatory.

#### Last-generation regimens with conventional drugs

Until the advent of the so-called new drugs (immunomodulatory drugs and proteasome inhibitors) in the therapy of monoclonal gammopathies, the most potent therapy for WM consisted of combinations of the three different types of drugs: alkylators, purine analogues and rituximab (TABLE 1).

The most widely used triple combination is cladribine, cyclophosphamide and rituximab, which was initially proposed by the MD Anderson Cancer Center group in 2003 [24], and has recently been updated by Thomas *et al.* [25,26] in 18 previously untreated patients. The ORR (CR plus partial response [PR]) was 94%, including CR in 17%. The median time to response was 2.4 months and the median duration of response was almost 5 years. A less intensive regimen with no cyclophosphamide was used by Laszlo *et al.* in 29 patients (16 previously untreated), with similar responses, a CR plus PR rate of 79%, including an additional 12% of minor responses (MR) [27].

Fludarabine is a very interesting alternative to cladribine in the triple combination, especially in view of the possibility of the oral administration. This possibility was explored by the French group who treated 25 patients (most of them previously treated) with the fludarabine plus cyclophosphamide and rituximab regimen (FCR), in which fludarabine and cyclophosphamide were administered orally. PR was achieved in 69% and MR in 9%, although the median duration of response was only 8 months [28]. However, the most consolidated data for the FCR combination were reported by Tedeschi *et al.*, who treated 43 patients, 28 previously untreated [16]. A total of 91% of them received at least four courses of therapy, achieving an ORR of 82% (CR: 13%;

**Table 1. Last-generation regimens with conventional drugs in Waldenström's macroglobulinemia.**

Study (year)	Patients (n)		Regimen	ORR (%)	HQR (%)	PR (%)	MR (%)	Follow-up (months)	OS (months)	Comments	Ref.
	Untreated	Treated									
Thomas et al. (2007, 2009)	18		R: 375 mg/m <sup>2</sup> iv, day 1 Cy: 40 mg/m <sup>2</sup> /12h p.o., days 1–7 Ci: 1.5 mg/m <sup>2</sup> /8h sc., days 1–7 4–6 courses	94	17	73		DR: 59 TTR: 56 months	+110	DR: 59 months TTR: 56 months	[25,26]
Laszlo et al. (2010)	16	13	R: 375 mg/m <sup>2</sup> iv, day 1 Ci: 0.1 mg/kg sc., days 1–5 4 courses	90	24	55	10	FU: 43; TTP: +48		hCNT1 low expression correlated with poor response	[27]
Vargaffig et al. (2007)	2	23	R: 375 mg/m <sup>2</sup> iv, day 1, F: 40 mg/m <sup>2</sup> p.o. days 1–3, Cy: 250 mg/m <sup>2</sup> p.o. days 1–3 ≥2 courses	90	32	48	10	DR: 8 months	+14	Neutropenia III–IV in 48%	[28]
Tedeschi et al. (2009)	28	15	R: 375 mg/m <sup>2</sup> iv, day 1, F: 25 mg/m <sup>2</sup> p.o. days 2–4, Cy: 250 mg/m <sup>2</sup> p.o. days 2–4 4–6 courses	87	13	69	5	DR: +14 months	+20	Neutropenia in 63%; late improvement of responses was observed	[16]
Dimopoulos et al. (2007)	72		Dx: 20 mg iv., day 1 R: 375 mg/m <sup>2</sup> iv., day 1 Cy: 100 mg/m <sup>2</sup> /12 h, p.o., days 1–5 4–6 courses	83	7	67	9	TTP: 35 months	+60	Grade 3–4 hematological toxicity in 9%	[32]
Abonour et al. (2008, 2009)	47	10	R: 375 mg/m <sup>2</sup> iv., day 0 Cy: 750 mg/m <sup>2</sup> iv., day 1 Dx: 50 mg/m <sup>2</sup> iv., day 1 V: 1.4 mg/m <sup>2</sup> iv. (max 2) day 1 P: 100 mg/m <sup>2</sup> p.o. days 1–5 6–8 courses, every 21 days	95	14	71	10	PFS: +20 months	+36	Neutropenia: 3–4 72%; infections: 6%; alopecia: 84%; nausea/vomiting: 36%; mucositis: 36%	[36–38]

Ci: Cladribine; Cy: Cyclophosphamide; Dox: Doxorubicin; DR: Duration of response; Dx: Dexamethasone; F: Fludarabine; HCN1: Human concentrative nucleoside transporter-1; HQR: High-quality response (which includes complete response, near complete response and very good partial response); iv.: Intravenous; MR: Minor response; ORR: Overall response rate; OS: Overall survival; P: Prednisone; p.o.: per os (orally); PR: Partial response; R: Rituximab, sc.: Subcutaneous; TTP: Time to tumor progression; V: Vincristine.

PR: 69%) and an additional 5% of MR. Of note, nine patients in PR fulfilled the criteria for CR except for the persistence of a positive immunofixation, indicating that 31% of the patients achieved a response qualified as CR plus near CR (nCR). In this latter study, neutropenia with long-lasting neutropenic episodes caused a limitation to the number of courses planned in the therapy. Similar results were reported by the Australian group, although in a more heterogeneous series of 22 patients treated with fludarabine combinations, including 14 cases treated with FCR, where they obtained an 84% ORR [29].

The major disadvantage of triple combinations, including purine analogues is their hematologic toxicity [13,16,30,31]. Since hematologic and immunosuppressive complications of nucleoside analogues are well established, it is possible to manage them with reductions in dosage, limitations to the number of courses and the use of growth factors. However, some recent reports have indicated an increased incidence of Richter's transformation and the development of myelodysplastic syndromes/secondary acute myelogenous leukemia in WM and CLL patients treated with nucleoside analogue-containing therapy [30,31]. These data suggest that the use of nucleoside analogues should be avoided in WM, particularly in younger patients. Accordingly, Dimopoulos *et al.* proposed the combination of dexamethasone, rituximab and cyclophosphamide (DRC) as a reasonable alternative for previously untreated WM patients (TABLE 1) [32]. This regimen was administered to 72 previously untreated patients, and in a recent update of this series, the ORR was 83%, including 7% CR, 67% PR and 9% MR; the median time to response was 4 months and the median time to progression was 35 months, with the good advantage that only 9% of patients underwent grade 3 or 4 hematologic toxicity [33]. Interestingly, in long-term follow-up, 30 patients remained free of progression, and of 42 patients fulfilling criteria for progressive disease (PD), 14 did not require additional therapy at the time of the update [34]. Moreover, 19 out of 28 patients were re-treated with rituximab-based rescue therapy (alone:  $n = 7$ ; DRC:  $n = 8$ ; with other agents:  $n = 4$ ) and most of them responded again (84% MR or better). No patient developed myelodysplastic syndrome or secondary acute myeloid lymphoma, and only one patient developed diffuse large B-cell lymphoma. The probability for 5-year overall survival (OS) and cause-specific survival is 59 and 74%, respectively. These findings strongly support the use of the DRC regimen as an active and safe treatment choice for patients with symptomatic WM.

An intriguing question in WM concerns therapy with the cyclophosphamide, adriamycin, vincristine and prednisone, plus rituximab (CHOP-R) regimen. The use of anthracyclines has sparked much debate within the context of in WM. In fact, CHOP has never been considered standard of care in WM [6,12,13,35], and some reports have provided similar efficacy for CHOP-R, COP-R and CP-R in this disease, but with clearly lower toxicity in the case of the latter protocol [36]. However, the data derived from some reports using CHOP-R are sufficient for this therapy to be considered an interesting possibility, especially in young patients, who can be considered for harvesting stem cells after induction therapy [36–39]. Pooling all four

reports, 57 evaluable patients were treated with a conventional CHOP regimen planned for administration every 3 weeks for six courses, together with six infusions of rituximab at standard doses. Some patients also received maintenance therapy with extended rituximab therapy or with interferon. The ORR was as high as 95%, with only two cases of stabilization and one case of disease progression. In addition, at least a PR rate was observed in more than 85% of patients, including a CR rate of 14%. The PFS is estimated at around 80% at 2 years, which is not much higher than with other less intensive protocols without anthracyclines. Nevertheless, these findings merit consideration for R-CHOP in young WM patients.

### New drugs for Waldenström's macroglobulinemia

Over the last decade, we have witnessed considerable improvement in the outcome of two entities close to WM: MM and CLL. In the case of MM, this is mainly due to recently approved drugs, such as thalidomide, lenalidomide and bortezomib. In the case of CLL, the reason can be found in the use of different monoclonal antibodies. Investigators in WM have been very quick to attempt to translate such experiences to WM patients, providing new schemes of that may be found useful in this disease.

In recent years, preclinical studies have demonstrated the activity of a broad array of small-molecule inhibitors and monoclonal antibodies in this disease. This group of drugs with activity in WM includes compounds with very different mechanisms of action, such as inhibitors of the PI3K/AKT/mTOR pathway, proteasome inhibitors, inhibitors of several kinases (e.g., PKC or tyrosine-kinases), histone-deacetylase inhibitors, sildenafil, resveratrol and others (reviewed in [40]).

In the following sections we focus on the growing body of clinical evidence showing the effectiveness of these new combinations in WM, characterized by high ORR and longer PFS. For this, we shall classify the new options for WM patients in three different groups based on the mechanism of action and the clinical evidence gained from these patients.

### Bortezomib-based schemes

Bortezomib, a first-in-class proteasome inhibitor, was first approved in the USA and EU for the treatment of MM patients who have received at least one prior therapy, but it has recently been demonstrated to be highly efficient in first-line therapy too [41]; this has led to its approval for previously untreated MM patients in the USA and EU. In WM, bortezomib also exhibits potent *in vitro* activity against primary WM cells and cell lines [42–44]. In clinical practice, single-drug bortezomib provides 46–60% of major responses in refractory/relapsing patients, showing a clinical benefit in at least 60–80% [45–48]. These responses can be further improved by adding rituximab; Ghobrial *et al.* treated 37 patients with relapsed/refractory WM with bortezomib only once a week but higher doses (1.6 mg/m<sup>2</sup>), on days 1, 8, 15, every 28 days for six cycles, together with rituximab 375 mg/m<sup>2</sup> weekly during courses 1 and 4 [49]. They observed a MR or better in 81% of patients, including two patients (5%) who achieved CR/nCR and 17 (46%) PR.

These findings have stimulated the use of bortezomib in untreated patients. Based on the above results, the Waldenström's Macroglobulinemia Clinical Trials Group (WMCTG) designed a study to evaluate the combination of bortezomib, dexamethasone and rituximab (BDR) in 23 previously untreated WM patients [50]. The patients received intravenous bortezomib at 1.3 mg/m<sup>2</sup> and dexamethasone at 40 mg on days 1, 4, 8, 11, along with rituximab at 375 mg/m<sup>2</sup> on day 11 for four consecutive courses followed by four maintenance courses of rituximab given every 3 months. Among the 23 treated patients, the response rate was as follows: CR: n = 3; nCR: n = 2; very good PR: n = 3; PR: n = 11; and MR: n = 3 (for an ORR, and a major response rate of 96 and 83%, respectively), with a commendable 22% of patients achieving CR/nCR. The time to at least a minimum response was 1.1 months and, with a median follow-up of 2 years, 80% of patients remained free of disease progression, including all those achieving a very good PR or better in that study. Such excellent results have led some experts to recommend BDR in first-line therapy in current clinical practice [23].

The development of grade 3 peripheral neuropathy (PNP) continues to be of concern when using BDR as scheduled above, and may occur in up to a third of patients or more. In fact, PNP was the cause of premature discontinuation of bortezomib in 14 patients (61%) [50]. This is why other BDR schemes were developed, with substantial modifications to prevent complications leading to discontinuations. Thus, the most logical change is the use of bortezomib in weekly doses, which has been shown to be highly effective in reducing the appearance of PNP in MM [51], indolent lymphomas [52] and WM [49], even allowing dose increases of up to 1.6 mg/m<sup>2</sup>. Another modification stems from concern about the rituximab-related IgM flare, aggravating serum viscosity levels or IgM-related morbidity. This problem could be prevented by the omission of rituximab in the first course of treatment. Bearing in mind these two ideas, the European Myeloma Network is currently conducting a Phase II multicenter study with the BDR combination in previously untreated WM patients. A total of 61 patients are scheduled for treatment with BDR, which will be administered in one 21-day treatment course followed by four 35-day treatment courses. Bortezomib will be administered at a dose of 1.3 mg/m<sup>2</sup> on days 1, 4, 8 and 11 of course 1, whereas, in courses 2–5, bortezomib will be given at a dose of 1.6 mg/m<sup>2</sup> on days 1, 8, 15 and 22 of each cycle. In addition, only during courses 2 and 5 will dexamethasone 40 mg intravenous and rituximab 375 mg/m<sup>2</sup> intravenous be administered following the administration of bortezomib, accounting for a total of eight infusions of rituximab. The trial is still ongoing, but some initial data were reported during the last ASH-2009 meeting [53]. A total of 38 patients had been recruited and 31 were evaluable for response, which included CR in one (3%), PR in 16 (52%), MR in five (16%), stable disease (SD) in four (13%) and PD in five (16%) patients. Plasmapheresis was not required in any of the patients either before or after treatment with BDR, and the IgM flare phenomenon was not seen in any of them. Toxicities of at least grade 3 included neutropenia in 26% of patients, thrombocytopenia in 11% and PNP in only 7%. One patient died of septic shock in the

absence of neutropenia and three patients underwent pulmonary toxicity of at least grade 3, which was attributed to bortezomib. Since antiviral prophylaxis was included in the protocol, only one patient developed herpes zoster after discontinuing it. No bortezomib discontinuations were noted, although the initial dose was reduced in 30% of patients, primarily because of PNP. Although these results seem to be poorer than with the other aforementioned BDR protocol, it is still too soon to reject possible modifications since responses can improve with a longer follow-up. All these findings underscore the promising perspectives for the protocol, which is to be updated in November 2010.

When using the BDR protocol, it is important to bear in mind that herpes zoster prophylaxis is mandatory, since the frequency of this complication is increased by up to 11–13% in patients treated with bortezomib [54,55], a risk that may increase further when another two immunosuppressive drugs, such as dexamethasone and rituximab, are added to the therapy [56]. In addition, prophylaxis for *Pneumocystis jirovecii* pneumonia should also be considered, since treatment with rituximab has also been associated with this complication [57,58]. In any case, close attention to infectious complications should be exercised in WM patients undergoing BDR treatment, because although bortezomib, rituximab and dexamethasone do not seem to have contributed to a very high risk of opportunistic infections separately, their use in combination may be associated with a high risk of non-neutropenic infections [50], and some of these may be very serious in this frail population of patients [53].

In summary, BDR seems to be an efficient protocol in patients with WM and produces rapid and durable high-quality responses. The use of BDR allows stem-cell collection, which may be of particular interest for young patients and for those in whom rapid remissions are needed. Herpes zoster prophylaxis and prevention of infections are necessary with BDR, and reversible PNP is the most problematic toxicity observed, while other secondary effects are usually non-threatening, reversible and manageable.

### Immunomodulatory drugs

Immunomodulatory drugs represent a new class of antineoplastic drugs with anti-inflammatory, antiangiogenic and immunomodulatory properties, and they target tumor cells through direct cytotoxicity and indirect interference with several components of the bone marrow microenvironment [59]. Since they have been especially effective in certain hematologic malignancies, especially in MM, immunomodulatory drugs have also been tested in WM, although only to a limited extent.

Thalidomide in monotherapy was evaluated by the Greek group in 20 symptomatic WM patients (50% previously treated), using relatively high doses (up to 600 mg/day). Activity was modest, affording a PR rate of 25% [60], with manageable toxicity, but constipation, somnolence, fatigue and mood changes were secondary effects that prevented the maximum dose from being reached in most patients (only five) and forced discontinuation in seven. These results were followed up with combinations of clarithromycin, low-dose thalidomide and dexamethasone (BLT-D), with excellent results, similar to those reported by Coleman in

an initial heterogeneous series with 50 MM and WM patients, in which 93% of evaluable patients responded to this scheme [61]. The series was updated in 2003 with 12 WM patients who were treated with clarithromycin at 500 mg twice daily, thalidomide 50–200 mg daily and dexamethasone 40 mg weekly until disease progression [62]. In this specific population, ten patients (83%) had a significant response, consisting of three nCR, three major responses, four PR, and two MR. However, toxicity was relatively high: gastrointestinal (primarily constipation): 42%; neurological: 100%; endocrine: 42%; and thrombotic: 8%. Dimopoulos *et al.* reported another 12 patients treated with this combination, but only three of them achieved PR and toxicity was also high [63]. This is why the experience has not been extended up to now, and BLT-D has been relegated to heavily pretreated patients with refractory macroglobulinemia.

Based on previous *in vitro* findings that suggested a synergistic effect of rituximab with thalidomide, the WMCTG conducted a Phase II clinical trial in symptomatic patients with WM combining rituximab with thalidomide [64]. The intended therapy for patients in the Phase II study of rituximab with thalidomide consisted of thalidomide administered at 200 mg daily for 2 weeks, followed by 400 mg daily thereafter for 1 year. Patients received four weekly infusions of rituximab at 375 mg/m<sup>2</sup> beginning 1 week after the initiation of thalidomide administration, followed by four additional weekly infusions of rituximab at 375 mg/m<sup>2</sup> beginning at week 13. Of the 25 cases included in this study, most of them were previously untreated (n = 20). Among 23 evaluable patients, the responses were: CR (n = 1); PR (n = 15); MR (n = 2); SD (n = 1) for an ORR and a major response rate of 78 and 70%, respectively. For responding patients, the median time to best response was (as slow as) 19 months. There were 17 patients not requiring prophylactic plasmapheresis; among them, an increase in serum IgM was observed in nine (53%) patients, with a more than 25% increase in serum IgM in five out of 17 (29%) patients. With a median follow-up longer than 42 months, the median time to progression was 35 months. The thalidomide dose was reduced in all patients and was withdrawn prematurely in 14 patients. PNP was the most limiting toxicity, because it was seen in 44% of patients with grade 2 or above. Other toxicities at this level involved somnolence (12%), confusion (12%), rash (8%), tremors (8%), bradycardia (8%) and palpitations (4%). Among the patients with serious PNP, the symptoms were first reported at a median of 6 months (range: 0.6–12 months) after the initiation of thalidomide, and resolution to at least grade 1 occurred in ten out of 11 (91%) patients at a median time of 5 months after the onset of the neuropathy. Accordingly, rituximab with thalidomide also represents an alternative choice in the management of previously untreated WM patients not requiring immediate disease control, particularly for those presenting with significant myelosuppression since no myelotoxic drugs are used in this combination.

Since the rituximab and thalidomide regimen represents a good therapeutic option for WM with the appearance of PNP as a major disadvantage, the use of more potent immunomodulatory drugs without neurotoxicity represents the logical evolution

of this regimen. Lenalidomide is a thalidomide derivative that has been shown to possess greater immunomodulatory capacity than thalidomide [59,65,66], and it has not been associated with neurotoxicity in large clinical trials [67,68]. Accordingly, the WMCTG performed a Phase II study with lenalidomide and rituximab in symptomatic WM patients naive to both agents [69]. In this trial, the intended therapy consisted of lenalidomide (25 mg/day for 3 weeks and then 1 week off) along with rituximab (375 mg/m<sup>2</sup>/week) dosed through weeks 2–5 and 13–16. Of the 16 patients enrolled, 12 were previously untreated. Unexpectedly, an acute decrease in hematocrit was observed in 13 out of the 16 patients (median hematocrit decrease: 4.8%), which was attributed to the use of lenalidomide and led to the study being closed down. On an intent-to-treat basis, the ORR and major response rates were 50 and 25%, respectively. With a median follow-up of 31 months, four of eight responding patients have progressed, with a median time to progression of 19 months. Accordingly, the final low number of patients did not allow any reasonable interpretation to be made.

Despite these poor results, the lenalidomide and rituximab combination remains an attractive alternative. The onset of lenalidomide-related anemia could not be explained. It was observed even when the lenalidomide doses were reduced, and the anemia occurred in the absence of hemolysis or other types of cytopenia. Thus, the only logical explanation would involve a special sensitivity of red cell progenitors in WM or a poor response to therapy by the disease, which usually causes anemia. However, both problems could be solved with additional measures. First, the use of programmed erythroid-stimulating agents could help to improve the erythroid progenitors. Second, the use of dexamethasone should improve the response rate to lenalidomide, since dexamethasone has been reported to exert a potent synergistic effect with lenalidomide [70]. In fact, initial trials with lenalidomide alone in MM afforded very modest results (~25% responses), which were substantially increased with the addition of dexamethasone [71]. In addition, the optimum dosage of lenalidomide has not been yet established in indolent chronic lymphoproliferative disorders, especially in the case of very elderly populations, as is the case in WM. Current ongoing trials in chronic lymphocytic leukemia are still being carried out to test the optimal dose and schedule for lenalidomide, which ranges from 5 mg/day continuously to 25 mg/day, 21 days every 4 weeks [72]. Evidently, these data require future trials using lower start doses of lenalidomide or alternative schedules for WM patients. In particular, the inclusion of a Phase I dose escalation should be mandatory in order to determine the best dose schedule.

#### **Other drugs under investigation in Waldenström's macroglobulinemia** **Alemtuzumab**

CD52 is an antigen that is widely expressed on bone marrow lymphoplasmacytic cells in WM patients [73–75], as well as on mast cells [76], which are increased in the bone marrow of patients with WM and provide growth and survival signals to WM cells through several TNF family ligands. This makes alemtuzumab,

a humanized monoclonal antibody that targets CD52, potentially useful for WM therapy. However, experience with alemtuzumab is very short. The WMCTG treated 28 patients suffering from lymphoplasmocytic lymphoma, including 27 IgM patients and one with an IgA M-component [77]. A total of 23 patients had been treated previously, all of them with at least one rituximab-containing regimen. The protocol included three daily test doses of alemtuzumab (3, 10 and 30 mg intravenously), followed by 30 mg alemtuzumab intravenously three-times a week for up to 12 weeks. A total of 25 patients were evaluable for response and included eight PRs (32%) and 11 MR (44%), with an ORR of 76%. The median time to tumor progression was more than 12 months. Hematologic toxicity was frequent, with grade 3–4 neutropenia in 39% of patients, thrombocytopenia in 18% and anemia in 7%. Cytomegalovirus reactivation and infection were also frequent, especially in the previously treated patients and this circumstance was related to one death in the study. Another two patients died from treatment-related causes. Despite these interesting data concerning efficacy, treatment-related toxicity has relegated the use of alemtuzumab in WM to backstage in favor of other, less toxic approaches.

#### **PI3K/AKT inhibitors**

The PI3K/AKT and mTOR pathway is important in the control of cell proliferation and survival in cancer [78]. In WM in particular, this pathway has been shown to be strongly involved, since it regulates survival and the homing of tumor lymphoplasmacytic cells [79], which provides an excellent background for a target-based therapy with specific inhibitors.

The AKT inhibitor perifosine inhibits proliferation and induces apoptosis in WM cells *in vitro*, leading to cytotoxicity in the context of a bone marrow microenvironment [79]. Thus, in animal models, perifosine induces a significant reduction in WM tumor growth. When used in a clinical context in 37 patients, the drug afforded an ORR of 36%, with only 6% PR, although the disease was stabilized in 58% of the patients [80].

Everolimus is an oral agent targeting raptor mTOR (mTORC1). Its activity in 50 relapsed/refractory WM patients has recently been reported, with a promising ORR (CR, PR and MR) of 70%, including 42% PR and 28% MR [81]. Although the median duration of response and median PFS has not been achieved, the estimated PFS at 6 and 12 months are 75 and 62%, respectively. The main toxicity was hematological, with some pulmonary toxic events.

Enzastaurin is another serine/threonine kinase inhibitor that targets not only the PI3K/AKT, but also the PKC pathways. Enzastaurin has been shown to possess activity in preclinical models of MM [82,83] and WM [84], leading to a clinical trial in previously treated WM [85]. A total of 29 patients were treated with 250 mg oral enzastaurin twice daily (1125-mg loading dose on day 1) in a 28-day course. Eight courses were planned until PD or toxicity. In cases of PD, dexamethasone (20–40 mg p.o. daily, days 1–4, 9–12 and 17–20 for four courses; days 1–4 of each course thereafter) was allowed. After a median of four courses, 20 patients remained in the study, with no drug-related discontinuations. One

patient achieved PR and seven MR, accounting for an ORR of 28%. Grade 3 was only seen in one patient, although there was one death due to infection unrelated to enzastaurin administration. These results (especially the low toxicity) have led to an expansion of the cohort up to 50 patients for definitive evaluation.

#### **Histone deacetylase inhibitors**

Many tumors, including MM [86] and WM [87], show an increased HDAC activity that results in a decrease in DNA transcription, with special relevance in the expression of tumor-suppressor genes. This leads to a pro-oncogenic condition. Treatment with HDAC inhibitors could normalize this deacetylated pattern, which lead (through different mechanisms) to the final differentiation or apoptosis of tumor cells. This possibility has been confirmed for several HDAC inhibitors available in preclinical WM models [88].

Suberoylanilide hydroxamic acid (SAHA), also known as vorinostat, is a HDAC inhibitor [89] that targets the histone deacetylases HDAC1, HDAC2 and HDAC3 (Class I) and HDAC6 (Class II) at nanomolar concentrations (IC<sub>50</sub><86 nM) in murine erythroleukemic cells [90], although it requires a higher concentration in WM cells (3.5 μM) [88]. Vorinostat has been approved for the treatment of T-cell cutaneous lymphoproliferative disorders, because it provides 24% PR and clinical benefits in more than half heavily pretreated patients [91]. Vorinostat has also shown activity in MM, which has led to its use in clinical trials [92], but little is known about its effect in WM. It is able to interrupt the cell cycle and to stimulate apoptosis in the WSU-WM cell line, and in freshly isolated cells from patients (n = 3) [93]. The cell cycle interruption could be mediated through an intracellular increase in p21 and p53 [94], while apoptosis would be induced through a cellular stress that would disrupt the balance between the p38 MAPK and Erk pathways [95]. Despite these interesting data, apart from some unpublished anecdotal responses in pretreated WM patients, there are no studies in clinical use, even in clinical trials, in which WM is treated jointly with other B-cell lymphoproliferative disorders.

NVP-LBH589 (panobinostat) is another HDAC inhibitor with *in vitro* anti-tumor activity in WM models [87,88]. The basis for using panobinostat in MM has allowed the development of clinical trials that have shown clinical benefits [96–98], but in WM clinical development is still immature and a specific clinical Phase II trial is currently recruiting patients, although no relevant data are available yet [201].

#### **Resveratrol**

The polyphenolic phytoalexin **trans-resveratrol (3,4',5-trihydroxy-trans-stilbene)** is an antioxidant present at high concentrations in grapes and their derivatives, and has attracted considerable attention owing to its anticancer properties [99,100]. Some reports have shown that resveratrol induces apoptosis and inhibits the proliferation of cell lines from Burkitt's lymphoma (HSSultan), promyelocytic leukemia (HL-60) and MM, and highly consistent data have been shown for WM [101]. Resveratrol inhibited proliferation and induced cytotoxicity against WM

cells, IgM-secreting cells and primary WM cells, without affecting peripheral blood mononuclear cells. These effects were due to a downregulation of several kinase pathways and an activation of intrinsic and extrinsic caspase pathways. Based on these data, four patients with IgM monoclonal gammopathies without criteria for treatment were treated with a combination of resveratrol and simvastatin [102]. Although the results must be considered very preliminary, it is intriguing that in all patients the size of the M-spike was reduced after 3 months of therapy, which should be considered for the development of future trials in WM, as is currently being performed for MM (clinical trial NCT00920556).

### **Bendamustine**

Bendamustine in a compound with mixed features of alkylating agents and purine analogs have demonstrated great activity in indolent lymphomas. The final results of a multicenter randomized Phase III study confirmed the better profile of the bendamustine plus rituximab combination versus CHOP-R as first-line therapy for patients with follicular, indolent and mantle cell lymphomas [103]. In this study evaluating 513 follicular and mantle cell lymphoma patients, the CR rate was significantly higher for bendamustine plus rituximab (40.1%) than for CHOP-R (30.8%;  $p = 0.0323$ ), as well as the median PFS (54.8 vs 34.8 months;  $p = 0.0002$ ). In this study, at least 42 patients with WM were also included, and the results of 40 (bendamustine plus rituximab:  $n = 23$ ; CHOP-R:  $n = 17$ ) were anticipated at the fifth IWWM held in Stockholm [104]. The ORR for bendamustine plus rituximab was similar to CHOP-R (96 vs 94%, respectively), and the median PFS was not reached with bendamustine plus rituximab was 40 months for CHOP-R, with no statistical significant differences. The toxicity profile was better for bendamustine plus rituximab, since it had a lower rate of total alopecia (0% with bendamustine plus rituximab vs 89% CHOP-R) and a lower number of infectious complications (infections of any grade 9% for bendamustine plus rituximab and 47% for CHOP-R). The overall results concerning efficacy and toxicity were very impressive, in favor of the bendamustine plus rituximab combination in all histological subtypes, but, more specific analyses are necessary in WM patients, in whom a long follow-up is required.

### **Conclusion**

Increasing knowledge of the pathogenesis of WM has led to the investigation of new drugs with more specific mechanisms of action. *In vitro* studies using cell lines and fresh cells obtained from patients clearly support the translation of these drugs to the clinical setting. However, the most successful strategy is the one that uses drugs or schemes that are highly active in CLL or MM. Taking advantage of borderline characteristics, investigators have selected the most active drugs with the lowest toxicity. This has led to the development of two new potent and safe chemotherapeutic combinations, DRC and BDR, which have provided the best results with very few secondary effects. Although they have not been compared directly with other strategies in randomized

trials, their proven efficacy makes it crucial to consider them in patients with WM. In any case, it should be recalled that the results of these regimens are considered good mainly because of the higher quality of response (higher percentages of CR and PR) than those provided with other schemes, but that this did not translate into a better PFS and/or OS. Thus, the Mayo Clinic Group has recently shown good survival curves (24 months of PFS) in 69 patients treated with only four courses of rituximab, with the particularity that patients achieving a MR appeared to do as well as those achieving a PR, which would suggest that more aggressive or intensive therapy for minor responders is not required [17]. On the other hand, the CR rate of approximately 20% observed with the new strategies is something completely new in WM. As in MM, the debate about the best way to define the response in WM is opened again.

### **Expert commentary**

Current therapy for WM mainly includes the use of a combination with an alkylator and rituximab, with or without an additional nucleoside analogue, and perhaps with some steroid. In addition, in certain specific cases (e.g., in very elderly patients), some concurrent pathological conditions and the presence of high amounts of M-component, a conservative attitude is adopted, using long-term administration of low doses of chlorambucil. However, the efficacy of new drugs, together with an acceptable toxicity profile, is now changing this picture, and bortezomib and thalidomide should be considered as new partners for the above treatments, especially in young patients. Other alternatives are also being incorporated to the clinical arsenal used to treat this disease so that resistant and relapsing patients can be treated not only with repeats of previous therapies, but also undergo transplantation and receive new inhibitors of recently explored key pathways.

### **Five-year view**

In a speculative exercise, although with a realistic viewpoint, it is estimated that in 5 years time most patients with newly diagnosed WM will be treated with combinations, such as DRC or BDR. It is clear that the absence of rituximab in any therapeutic program in WM will have to be very well justified. We anticipate that nucleoside analogues will be shelved, owing to their toxicity, and that the alkylators conventionally used in WM, such as chlorambucil and melphalan, will be reserved for specific patients in whom the use of the other regimens is precluded. For some specific patients, R-CHOP could also be used, especially in very young patients susceptible to transplantation. However, the decision between DRC/BDR or R-CHOP will depend more on the viewpoint of the group treating the patient, depending on whether WM is considered an immunosecretory disorder (first option) or a non-Hodgkin's lymphoma (second option).

Finally, the most promising drug for the future in WM is everolimus, which has shown promising results in relapsing/refractory patients, although bendamustine also afforded very interesting results in the first trial that used this drug in WM.

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**Key issues**

- Current regimens with nucleoside analogues in Waldenström's macroglobulinemia (WM) are very efficient, but acute and long-term toxicity will require a change in the view of regimens with such drugs.
- The use of anti-CD20 is now mandatory in WM unless specific circumstances preclude.
- New monoclonal antibodies, such as alemtuzumab, ofatumumab or GA101, are interesting options in WM, and should be tested in the future.
- Among the different combinations with conventional drugs in WM, dexamethasone plus cyclophosphamide plus rituximab is the regimen with the best efficacy and the lowest toxicity.
- Several combinations with new drugs are possible, but bortezomib, dexamethasone and rituximab is emerging as the one with the greatest efficacy. Nevertheless, modifications aimed at improving its neurotoxicity profile will have to be explored in the future.
- The PI3K/AKT pathway seems to play a key role in WM. Thus, inhibitors of this pathway are expected to provide good results, and this indeed seems to be the case.
- Immunomodulatory drugs such as lenalidomide are very promising in WM, but trials including a Phase I step are required to ensure the safety profile of combinations with this drug.
- To date, high-quality responses (complete response, near complete response and very good partial response) have been rare in WM. However, new drug combinations are now affording almost 30–40% of such responses. In addition, even responses considered poor in MM, such as stabilization of the disease and minor responses, are of worth in many patients with WM. This is why the results are so heterogeneous and, as in MM, why a new consensus to report responses in WM must be achieved.

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