Best Practice & Research Clinical Haematology 29 (2016) 206–215

Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

journal homepage: www.elsevier.com/locate/beha

Future therapeutic options for patients with Waldenström macroglobulinemia

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Keywords:
BTK
BCL2
CD38
CXCR4
MYD88
Waldenström

A B S T R A C T

Waldenström macroglobulinemia (WM) is a rare lymphoma characterized by the accumulation of IgM-producing lymphoplasmacytic cells. Although WM patients can experience prolonged remissions, the disease invariably recurs. Therefore, novel treatments associated with higher success rates and lower toxicity profiles are needed. The discovery of recurrent mutations in the MYD88 and CXCR4 genes has unraveled potential therapeutic targets in WM patients. As a result of these findings and based on the design and execution of a prospective clinical trial, the FDA granted approval to ibrutinib, an oral Bruton tyrosine kinase (BTK) inhibitor, to treat patients with symptomatic WM. The present review focuses on potential therapies that could change the landscape of treatment of patients with WM, specifically focusing on inhibitors or antagonists or the proteasome, BTK, CD38, BCL2 and the CXCR4 and MYD88 genes themselves. Novel agents with novel mechanisms of action should be evaluated in the context of carefully designed clinical trials.

Introduction

Waldenström macroglobulinemia (WM) is a rare subtype of non-Hodgkin lymphoma, characterized by the malignant accumulation of IgM-secreting lymphocytes, lymphoplasmacytoid cells and plasma

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http://dx.doi.org/10.1016/j.beha.2016.08.021
1521-6926/

cells in the bone marrow and other organs [1]. Patients with WM experienced prolonged survival times with a median overall survival approximating a decade, as shown in recent population-based studies [2,3]. The improved survival of patients with WM is likely associated with improved treatments, supportive therapies and a higher involvement of patients and families in the care of the patient. WM, however, remains incurable and more effective, less toxic therapies are needed.

Recently, a number of advances in the understanding of the genomic landscape of WM have been achieved, including the identification of the MYD88 L265P and the CXCR4 WHIM mutations [4,5]. These findings, coupled with increase knowledge on the biology of the disease, have helped identifying a number of potential therapeutic targets, such as the proteasome, Bruton tyrosine kinase (BTK), CD38, BCL2, and MYD88 and CXCR4 molecules themselves. The purpose of this article is to review and summarize potential therapeutic options for the treatment of patients with WM.

Proteasome inhibition

Proteasome inhibitors are active compounds against WM. One of the most important mechanisms of action of proteasome inhibitors is the targeting of the nuclear factor kappa B (NF-kB) pathway. The NF-kB pathway plays an important role in plasma cell tumorigenesis [6]. In WM, there are higher constitutive levels of NF-kB when compared with healthy donors [7]. Preclinically, bortezomib was highly effective on inhibiting the nuclear translocation of NF-kB, promoting further inhibition of the growth of WM cells by inducing cell cycle arrest and apoptosis. Bortezomib overcomes resistance against WM cell killing induced by the marrow microenvironment. However, bortezomib did not induce cytotoxicity against other mononuclear cells [8–11]. In a multicenter study of the WMCTG, 27 patients received bortezomib twice a week. The overall response rate (ORR) was 85%, and responses occurred at median of 1.4 months. About 20% developed sensory neuropathy, which improved after cessation of therapy. As part of a National Cancer Institute of Canada study, 27 WM patients received bortezomib using the standard schedule. The ORR in this study was 78%. Grade 3 or higher sensory neuropathy occurred in 19% of patients. The combination of bortezomib, dexamethasone, and rituximab (BDR) has been investigated as primary therapy in WM patients. An ORR of 96% and complete response (CR) of 22% was observed. The median PFS was greater than 56 months. The incidence of grade 3 neuropathy was 30% in this study, which used a twice-a-week schedule. An alternative schedule for weekly BDR has been investigated. An ORR of 85%, with VGPR or better in 10% of patients, was observed. The median PFS was 43 months, and patients with VGPR/CR had longer PFS. Grade 2 or higher treatment-related neuropathy occurred in 24% of patients.

Carfilzomib is an epoxyketone proteasome inhibitor that has also shown preclinical efficacy in WM cells [12]. Carfilzomib has shown selectivity against the chemotrypsin-like activity of the proteasome, and promoted antitumor activity in WM cells and other IgM-secreting lymphoma cells. Carfilzomib induces WM cell apoptosis by caspase-dependent and independent mechanisms. Carfilzomib has shown to have anti-resorptive and bone-anabolic properties in addition to its anticancer effects [13]. Due to bortezomib-related peripheral neuropathy in WM, carfilzomib, a neuropathy-sparing proteasome-inhibitor, was studied in combination with rituximab and dexamethasone (CaRD) in symptomatic WM patients [14]. The ORR was 87%, and the median PFS was not reached. Declines in serum IgG were common necessitating IVIG therapy in several patients.

More recently, the novel oral proteasome inhibitors oprozomib and ixazomib are undergoing clinical development in WM. Oprozomib is a tripeptide epoxyketone proteasome inhibitor that has shown cell killing activity against bortezomib-resistant MM cells [15]. The antitumor activity of oprozomib is mediated by activation of caspases 3, 8 and 9, poly(ADP) ribose polymerase and inhibition of migration and angiogenesis. As bortezomib, oprozomib inhibits the chemotrypsine-like activity of the proteasome but it is orally bioavailable. In animal tumor models, oprozomib reduced tumor progression and prolonged survival compared with placebo, and showed equivalent antitumor activity than intravenous carfilzomib. Similarly to carfilzomib, oprozomib has shown to have anti-resorptive and bone-anabolic activity [13]. Clinically, oprozomib was administered as single agent in patients with relapsed and/or refractory WM [16]. In this phase 1b/2 study, 36 patients were enrolled of which 17 were included in the phase 2 portion of the study. In the phase 2 portion, in which oprozomib was administered daily for 5 days in 14-day cycles, the ORR was 59%. Grade 3 or higher nausea, vomiting

and diarrhea was seen in >5% of patients exposed to oprozomib. The study is no longer recruiting patients (NCT01416428).

Ixazomib is an orally bioavailable boronic prodrug, and is considered a bortezomib analog [17]. In cell line studies, ixazomib has shown to have anti-myeloma effect equivalent to bortezomib [18]. In animal models, mice treated with ixazomib showed longer survival time than mice treated with bortezomib. Cell killing is mediated by activation of caspases 3, 8 and 9, increase in p53, p31, NOXA, PUMA and E2F, and inhibition of NF-kB. Early phase I studies using twice weekly and once weekly regimens have shown efficacy in patients with relapsed/refractory myeloma with an acceptable safety profile with lower rates of neuropathy than bortezomib [19,20]. Pharmacokinetic studies support a long terminal half-life of 4–11 days supporting once weekly dosing. In November 2015, the US FDA approved ixazomib for the treatment of patients with myeloma who have received at least one prior therapy [21]. Phase 2 studies evaluating weekly ixazomib, dexamethasone and rituximab in WM patients are underway in the US and Europe (NCT02400437; NTR5171).

Other proteasome inhibitors undergoing development are marizomib and delanzomib. Marizomib is an irreversible proteasome inhibitor with a half-life of less than 5 min, and potential penetration into the CNS [22]. Delanzomib is a reversible proteasome inhibitor with oral and intravenous bioavailability. The degree of proteasome inhibition was lower than bortezomib and carfilzomib [23].

BTK inhibition

With the approval of ibrutinib by the US FDA for the treatment of patients with WM [24], BTK inhibition has become an important therapeutic approaches in WM. The MYD88 L265P gene mutation is present in over 90% of patients with WM [5]. The occurrence of this mutation in WM has since been validated in several independent cohorts [25–28]. In WM cell lines, more robust MYD88 co-immunoprecipitation was observed with phospho-BTK in MYD88 L265P expressing cells versus MYD88 wild type cells [29]. In MYD88 expressing cells, exposure to ibrutinib reduced binding of BTK and MYD88. Furthermore, phospho-BTK expression was significantly decreased when WM cells were treated with an inhibitor of MYD88 signaling. Conversely, MYD88 L265P overexpression stimulated BTK activation in WM cells. Pre-clinically, the down stream effects of ibrutinib included inhibition of IkB-alpha phosphorylation, thereby blocking NFKB signaling. Ibrutinib also induced higher levels of killing in MYD88 L265P expressing cells than in wild type cells.

A phase 2 study evaluated the BTK inhibitor ibrutinib at a dose of 420 mg PO daily in 63 patients with previously treated WM [30]. Ibrutinib therapy was associated with an ORR of 91%, a major response of 73%, and a median time to response of 4 weeks. The response rates depended on the genomic profile of WM patients. The major responses rate among patients with MYD88 L265P and no CXCR4 mutation was 92%, versus 62% in MYD88 and CXCR4 mutated patients. Among MYD88 wild-type patients, no major responses were observed [31]. Based on these results, ibrutinib was approved by the US FDA to treat patients with WM in April 2015. A study evaluating ibrutinib in previously untreated WM patient is undergoing accrual (NCT02604511). Important adverse events associated with ibrutinib included bleeding diathesis and a trial fibrillation, particularly among patients with a prior history of arrhythmia.

Acalabrutinib (ACP-196) is an irreversible second-generation BTK inhibitor undergoing clinical development in WM. Acalabrutinib appears to have greater selectivity to BTK than ibrutinib [32]. Additionally, acalabrutinib did not inhibit EGFR, ITK, TEC or HCK [33]. HCK is regulated by MYD88, seems to mediate WM cell survival, and is a relevant target of ibrutinib [34]. It is unclear of this difference between ibrutinib and acalabrutinib has any clinical implication. In vivo studies have shown that thrombus formation is unaffected in mice exposed to acalabrutinib while thrombus formation was inhibited with ibrutinib. Preclinically, acalabrutinib has shown to be effective in animal models of non-Hodgkin lymphoma and CLL [35,36]. Clinically, acalabrutinib has shown an ORR of 95% in previously treated CLL patients. The ORR was 100% in patients with 17p deletion [33]. No bleeding or atrial fibrillation was observed although follow-up is short. A phase 1b/2 study in previously treated patients with WM is ongoing (NCT02180724).

Other BTK inhibitors undergoing clinical development in hematologic malignancies are CC-292 (AVL-292), BGB-3111 and ONO-4059 (GS-4059). CC-292 has shown anti-BTK activity in kinase

assays, and anti-BCR signaling in lymphoma and myeloma cell lines. In humans, CC-292 has a terminal half-life of 2 h but analysis of BTK activity indicated the drug remained active after its plasma levels had become undetectable [37]. BGB-3111 has demonstrated nanomolar BTK inhibition with a more restricted off-target activity than ibrutinib [38]. Specifically, BGB-3111 did not inhibit rituximab-induced NK cell interferon secretion, unlike ibrutinib, consistent with weak ITK inhibition. The survival of mouse models was longer on BGB-311 than on ibrutinib. BGB-3111 has shown to be safe in a phase I study in patients with relapsed/refractory B-cell malignancies, including observed responses in 5 of 6 WM patients [39]. ONO-4059 (ONO-WG-307) has also shown activity against BTK and BCR signaling with an IC50 of 2.2 nM [40]. A phase I dose escalation study evaluated ONO-4059 in patients with B-cell malignancies including 3 patients with WM, and showed efficacy and a favorable toxicity profile [41].

BCL2 antagonism

The B-cell lymphoma-2 (BCL2) family of proteins is central to the regulation of apoptosis. Apoptosis occurs via activation of two pathways, the extrinsic pathway, triggered by activation of cell surface death receptors, and the intrinsic pathway, followed by the perturbation of mitochondrial membrane integrity. Studies have shown that the intrinsic pathway is tightly controlled by BCL2 family proteins [42]. Gene expression analysis demonstrated that BCL2 was overexpressed in both B-cell and plasma cell compartments in WM patients in comparison to healthy donors [43]. By flow cytometric analysis, the overexpression of BCL2 protein has been confirmed in a Spanish study on 60 cases meeting pathologic criteria for WM [44]. More recently, transcriptome sequencing has revealed overexpression of BCL2 in samples of patients with WM, regardless of MYD88 or CXCR4 mutational status, suggesting an independent pathohysiologic mechanism [45]. Previous BCL2 inhibitors, although active, caused dose-dependent thrombocytopenia that limited further clinical development [46,47].

To circumvent this challenge, a unique BCL2 small molecule co-crystal structure was used to design venetoclax (ABT-199), a first-in-class BCL2 selective inhibitor. In addition to showing preclinical efficacy in BCL2–dependent cell lines and tumor xenograft models, venetoclax demonstrated immediate activity in patients with refractory lymphoid malignancies while causing only minor changes in platelet counts [48]. In WM cell lines, venetoclax was able to induce a higher level of apoptosis than ibrutinib [49]. Venetoclax not only induced higher apoptosis in CXCR4-mutated cell lines but the level of apoptosis appeared similar in wild-type as well as cells engineered to express the CXCR4 S338X nonsense mutation. Venetoclax has shown synergy against WM cells when combined with ibrutinib [49,50]. Clinically, venetoclax has shown activity in CLL and induced tumor lysis syndrome in 3 of 56 patients during the dose escalation phase of the study [51]. After adjustments to dose escalation, no tumor lysis syndrome was observed in 60 patients during the expansion phase. The ORR was 79%, with responses in patients with high-risk features such as 17p deletion. Complete remissions were seen in 20% of patients. Venetoclax recently gained FDA approval for the treatment of patients with CLL with 17p deletion who have received at least one prior therapy [52]. In a phase I study I patients with NHL, 3 of 4 patients with WM experienced a response, including a CR in 1 patient [53]. A phase II study on venetoclax in patients with relapsed/refractory WM is ongoing (NCT02677324).

The BCL2 targeted single-stranded DNA oligonucleotide PNT2258 is complementary to a region upstream of the BCL2 gene, and has been encapsulated in amphoteric liposomes, and has shown activity against BCL2-driven solid and hematologic malignant cells [54]. PNT2258 is undergoing clinical trials in lymphoma (NCT02226965).

Anti-CD38 therapy

CD38 surface expression is present on many cell types in different tissues including subsets of B and T-lymphocytes. Marked expression of CD38 has been demonstrated on plasma cells. Interestingly, no CD38 expression has been detected on pluripotent (early) CD34+ stem cells, while more mature (intermediate) CD34+ cells do express CD38. In WM, a substantial component of the malignant clone (40–70%) expresses CD38 [44,55,56]. Daratumumab is an IgG1κ human monoclonal antibody that targets CD38. Potential mechanisms of action have been investigated in both in vitro and in vivo

studies. The results denote that complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC) are major mechanisms of action for daratumumab. Half-maximal killing of myeloma cells in vitro by CDC and ADCC occurred at antibody levels of approximately 0.1 μg/mL and 0.03 μg/mL, respectively. Trials in the xenograft lymphoma model in severe combined immunodeficiency mice have shown that daratumumab potently inhibits the in vivo growth of CD38-expressing tumor cells at concentrations from 0.5 mg/kg. Recent data supports that daratumumab therapy was associated with expansion of CD4+ T-helper as well as CD8+ cytotoxic cells, and increase in clonality of the T-cell receptor repertoire, which could enhance cytotoxic T-cell responses [57]. Such finding is supported by the observation than responders to daratumumab have increased T-cell responses to viral and alloantigens suggesting an up-regulation of antitumor immune response. Such changes in T-cell expansion were more evident in responders than in non-responders to daratumumab.

In a phase I/II study, patients with relapsed/refractory myeloma were exposed to increasing doses of daratumumab [58]. Patients received a median of 4 prior therapies, and 80% of patients had disease that was refractory to the last therapy received. Over 60% of patients were refractory to bortezomib and lenalidomide, and 76% had received autologous stem cell transplant (ASCT). The ORR in this study was 36% in patients who received 16 mg/kg doses with median PFS of 5.6 months. Infusion-related reactions (IRRs) were experience by 70% of patients but 1% had grade 3 IRRs. Pneumonia and thrombocytopenia were grade 3 or 4 AEs seen in >5% of patients. A multicenter phase II study reported on 106 myeloma patients who received 16 mg/kg doses of daratumumab [59]. Patients received a median of 5 prior lines of therapy, 95% were refractory to proteasome inhibitors and immunomodulatory drugs, and 80% had previously received ASCT. ORR was 29% with 3% complete response. The median PFS and OS were 3.7 months and 17.5 months, respectively. Anemia and fatigue were the most common AEs. No drug-related AEs led to treatment discontinuation. Based on these data, the FDA granted accelerated approval for daratumumab to treat patients with myeloma who have received at least 3 prior treatments. Daratumumab is the first monoclonal antibody approved for treating myeloma.

Other anti-CD38 monoclonal antibodies undergoing development are isatuximab (NCT01084252) and MOR202 (NCT01421186). In preclinical studies, isatuximab has shown to exert direct cytotoxicity against myeloma cells via multiple mechanisms of action, including caspase mediated and lysosome dependent cell death [60]. In first-in-human studies, the maximum tolerated dose of isatuximab was not reached [82]. Partial response or better were seen in 33% of patients. Infusion reactions were seen in 39% of patients, even after premedication, although reactions were grade 1 and 2 and occurred only during the first infusion. MOR202 has shown to mediate cell killing through ADCC and ADCP. An ongoing study in myeloma has shown that MOR202 was well tolerated [61]. The maximum tolerated dose was not reached. Infusion reactions were seen in 31% of patients when MOR202 was administered without dexamethasone but not seen when administered with dexamethasone.

Anti-CXCR4 therapy

Whole genome sequencing studies have reported the occurrence of recurrent somatic CXCR4 gene mutations in approximately 30–40% of WM patients [4]. These findings have been validated in additional studies [62,63]. Mutations in CXCR4 are the second most common somatic variant identified after MYD88 L265P. The somatic mutations occur in the C-terminal domain, and are similar to those observed in patients with WHIM (Warts, Hypogammaglobulinemia, Infections, and Myelokathexis) syndrome [64]. These mutations regulate signaling of CXCR4 by its ligand CXCL12 (SDF-1a) [65]. In WM patients, two classes of CXCR4 mutations occur: non-sense and frameshift mutations [4,66]. Over 30 different types of CXCR4 mutations have been described, and in about 30% of WM patients, multiple CXCR4 mutations were identified [67]. Preclinical studies with the most common CXCR4 S338X mutation in WM have shown sustained signaling of AKT, ERK and BTK following CXCL12 binding in comparison with wild-type CXCR4, as well increased cell growth and survival of WM cells [68]. CXCR4 mutations are primarily subclonal to MYD88, with highly variable clonal distribution in WM patients [67]. CXCR4 mutations have also been identified in a small proportion of individuals with IgM MGUS.

Additional preclinical studies have shown that WM cells have increased expression of CXCR4 as well as its ligand CXCL12 [69]. Inhibition of CXCR4 by plerixafor (AMD3100) abrogates transendothelial

migration of WM cells and inhibits adhesion of WM cells to fibronectin. In December 2008, plerixafor was approved by the FDA for use in combination with granulocyte-colony stimulating factor to mobilize hematopoietic stem cells for collection and subsequent autologous transplantation in patients with lymphoma and myeloma [70]. Plerixafor has been tried in patients with WHIM syndrome [71]. In this study, 3 patients injected plerixafor twice daily for 6 months resulting in an increase in circulating leukocytes, although immunoglobulin levels were not fully restored. No drug-related adverse events were observed.

In vitro studies with the fully human IgG4 anti-CXCR4 monoclonal antibody ulocuplumab (BMS-936564) have shown that it binds at low nanomolar affinity with CXCR4-expressing cells, blocks SDF-1 binding to CXCR4 and inhibits migration [72]. As monotherapy, ulocuplumab exhibited antitumor activity against leukemia, lymphoma and myeloma xenograft models. Ulocuplumab, but not plerixafor, induced apoptosis in CLL cells at nanomolar concentrations in the presence or absence of stromal cell support [73]. Ulocuplumab, similar to plerixafor, inhibited SDF-1 mediated CXCR4 activation and migration in CLL cells. The effect of ulocuplumab does not require caspase activation. Other anti-CXCR4 compounds under clinical development include BKT140 (NCT01010880) and LY2624587 (NCT01139788) [74,75].

IRAK1/4 inhibition

MYD88 L265P activates multiple downstream signaling pathways including BTK and IRAK1/IRAK4 that support malignant cell growth and survival [29,76]. Ibrutinib targets BTK, and shows high overall and major clinical response rates, though no complete responses are observed, indicating alternative survival signaling. Phosphoflow analysis of bone marrow lymphoplasmacytic cells taken from WM patients following >6 months of continued ibrutinib treatment demonstrated highly active IRAK1 and IRAK4, but not BTK. These findings prompted further investigation of the relative impact of IRAK1 and IRAK4 in supporting WM cell survival [77]. Using lentiviral transduction, we identified shRNAs that produced similar levels of protein reduction by western blot analysis for both IRAK1 and IRAK4. Compared to scrambled control vector, knockdown of IRAK1 or IRAK4 both produced decreased tumor cell survival in MYD88 mutated cells. Treatment of primary WM cells taken from untreated patients, patients on ibrutinib therapy, as well as MYD88 mutated WM cells lines with ibrutinib and IRAK4/IRAK1 inhibitor resulted in more robust reductions in NF-kB signaling. The IRAK4 inhibitor PF-06650833 is being evaluated in healthy subjects (NCT02485769).

TLR antagonism

Toll-like receptors (TLRs) are pathogen-associated molecular pattern recognition receptors of the innate immune system. TLR7/9, which are expressed in human B-cells, respond to DNA- and RNA-based ligands by initiating a signaling cascade mediated through NF-κB, IRAK1/4, BTK, and JAK/STAT. DNA- and RNA-based ligands for TLR7/9 also are generated as damage-associated molecular patterns in certain autoimmune diseases and malignancies. MYD88 is a key adaptor molecule in TLR signaling. MYD88 L265P drives over-expression of TLR7/9 signaling, promoting cancer cell survival and proliferation. Preclinical data showed that IMO-8400 inhibits cell signaling and reduces tumor growth in WM and DLBCL models harboring the MYD88 L265P mutation. In a Phase 1 trial in healthy subjects, subcutaneous administration of IMO-8400, a TLR/9 antagonist, showed safety and tolerability through single- and multiple-dose escalation [78]. A randomized, placebo-controlled Phase 2 trial was conducted with IMO-8400 in patients with psoriasis [78]. IMO-8400 was well tolerated in both studies, with no treatment-related severe adverse events or drug-related treatment discontinuations. The only treatment-related adverse events were injection site reactions. In both trials, laboratory parameters were similar to placebo treatment. A dose-escalation phase 1/2 study in patients with previously treated WM is undergoing accrual (NCT02092909). Preliminary results in WM patients have shown good tolerability with adverse events such as transient flu-like symptoms and injection site reactions [79]. One case of grade 3 arthritis was reported in a patient with previous history of arthritis. There was preliminary evidence of clinical activity.

Inhibition of Myddosome assembly

MYD88 dimerization is necessary for assembly of the Myddosome, a structure composed of MYD88 dimers that recruits and activates IRAK1/2/4. The MYD88:IRAK4:IRAK1/2 complex can then trigger canonical NF-kB growth and survival signaling [29,67,76]. The Myddosome can also activate BTK, which can promote canonical NF-kB signaling in mutated MYD88 WM cells [29]. The MYD88 protein is composed of an N-terminal death domain (DD) spanning amino acids 40–119, an intermediate linker domain (ID) that spans amino acids 120–173, and a C-terminal Toll/IL1 receptor (TIR) domain that encompasses amino acids 174–309. Upon ligand binding to TLR/IL1R, the TIR domain facilitates binding to the receptor complex, and promotes MYD88 dimerization. In contrast to native MYD88, mutated MYD88 protein can assemble without external stimuli, and trigger constitutive NFKB activation [5,29,76]. Previous studies in human monocytes have shown that mutations on Glu^{196} in the TIR domain interfered with TIR-mediated MYD88 dimerization, IRAK recruitment, and reduced NF-kB activation [80]. Recent preclinical studies have evaluated the vector-mediated transduction of mini-peptides targeting Glu^{196} to WM cells [81]. Expression of $MYD88^{181-202}$ blocked growth of MYD88 mutated WM cells, but did not impact growth of MYD88 WT cells. Other mini-peptides targeting Ser^{257} and Arg^{301} coding for $MYD88^{256-292}$ and $MYD88^{295-302}$ were also evaluated, but showed weak induction of apoptosis and reduction of pro-survival signaling without meaningful growth inhibitory effect. Interestingly, the transduction of $MYD88^{40-85}$ mini-peptides was associated with increased apoptosis, sustained growth inhibition as well as reduced IRAK1 and NF-kB activation. Efforts to develop stapled peptides and peptidomimimetics to block Myddosome assembly based on these findings are underway.

Conclusion

The approval of ibrutinib for the treatment of symptomatic WM patients has marked the beginning of a very interesting scientific period in the treatment of this disease. Not only it allows the use of effective therapies with a well-tolerated adverse event profile, but it has also taught us that the genomic profiling of WM patients can help to direct treatment decisions. In this light, the advent of novel drugs and novel mechanisms of action is warmly welcomed. Compared with current options, the novel proteasome inhibitors are administered orally and do not seem to be associated with neuropathy, and the novel BTK inhibitors might have lower rates of bleeding and atrial fibrillation. TLR7/9 antagonism is under clinical development, and anti-BCL2, anti-CD38 and anti-CXCR4 drugs have recently or will shortly enter clinical trials in WM. Drugs targeting IRAK1/4 and the Myddosome are exciting molecules for a near future. In all, the clinical development of new treatments in WM is the result of tireless basic and translational research. However, such development cannot happen without patients' participation in clinical trials. One of the objectives of this review is to emphasize the importance of the referral of patients as well as the development of thoughtful clinical trials. Given the rarity of this disease, multi-institutional collaboration is highly encouraged.

Practice points and research agenda

1. Waldenstrom macroglobulinemia is an incurable lymphoma and more effective, less toxic treatment options are needed.
2. Treatment should be personalized and would depend on the patient's clinical presentations, co-morbidities, genomic profile, treatment toxicity and preferences, among other factors.
3. Current treatment options include alkylating agents, proteasome inhibitors, nucleoside analogues, anti-CD20 monoclonal antibodies and Bruton tyrosine kinase (BTK) inhibitors.
4. Future treatment options might include novel anti-CD20 antibodies, proteasome and BTK inhibitors as well as BCL2 inhibitors, anti-CD38 antibodies, anti-CXCR4 molecules, and anti-MYD88 signaling agents.

Disclosures

JJC received honoraria from Alexion, Biogen, Celgene and Otsuka, and research funding from Abbvie, Gilead, Millennium and Pharmacyclics. SPT received research funding and/or honoraria from Gilead, Janssen, Onyx and Pharmacyclics. MLP has received honoraria from Pharmacyclics.

Conflict of interest

ZRH, GY and KA have no conflicts of interest to disclose.

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