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REVIEW

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ABSTRACT

Introduction: Waldenström macroglobulinemia (WM) is a rare subtype of non-Hodgkin lymphoma characterized by the presence of IgM-secreting clonal lymphocytes, plasma cells, and lymphoplasmacytic cells. Many well-established treatment options are available for patients with WM. However, a unique array of side effects may occur in patients during therapy related to the underlying disease, as well as the chosen treatment regimen.

Areas covered: This review summarizes the most common adverse effects that occur during treatment of WM, as well as potential strategies to decrease the risk of toxicity.

Expert opinion: There are multiple highly effective treatment options for patients with WM. All these treatment options, however, can be associated with a variety of adverse events. For example, chemotherapy has been associated with the development of myeloid neoplasms, anti-CD20 monoclonal antibodies with paradoxical IgM flares and infusion reactions, proteasome inhibitors with neuropathy, and BTK inhibitors with bleeding and cardiac arrhythmias. Dose reductions, lower number of cycles and changes in route of administration are some of the tools a clinician has available for managing and minimizing toxicity. Future research will focus on improving patient safety without sacrificing the efficacy of treatment.

1. Introduction

Lymphoplasmacytic lymphoma (LPL) is a rare subtype of non-Hodgkin lymphoma characterized by the presence of clonal B cells, including lymphocytes, plasma cells, and lymphoplasmacytic cells that can accumulate in the bone marrow, lymph nodes, and spleen. More than 90% of LPLs secrete an immunoglobulin M (IgM) paraprotein and are referred to as Waldenström macroglobulinemia (WM) [1]. Approximately 1,500 new cases of LPL/WM are diagnosed in the United States each year. Only a portion of patients requires treatment immediately, as many patients are asymptomatic at the time of diagnosis. However, approximately 30% of asymptomatic patients will need therapy within 2 years of diagnosis and 80% within 10 years [2]. Indications for treatment are varied, but most commonly include the development of anemia, constitutional symptoms, hyperviscosity, neuropathy, or symptomatic extramedullary disease [3].

Due to the rarity of the disease, most treatment recommendations are based on expert consensus, retrospective series, or early-stage prospective clinical trials [4]. Current treatment options for WM patients include alkylating agents, nucleoside analogs, anti-CD20 monoclonal antibodies, proteasome inhibitors, and Bruton tyrosine kinase (BTK) inhibitors. Although these agents are associated with high rates of response, their use can also be associated with the emergence of toxicity. When possible, treatment by an expert in the field is recommended, as treatment choices are dependent on patient-specific characteristics and the distinct toxicity profile of each regimen. This review will focus on manners of reducing toxicity during the treatment of patients with WM.

2. Body

2.1. Reduction in the number of chemotherapy cycles

In the treatment of WM, multiple chemotherapeutic agents such as bendamustine, chlorambucil, and fludarabine are effective and frequently utilized but are often associated with significant side effects, including myelosuppression, immunosuppression, and secondary myeloid neoplasms [5–10]. In recent years, chlorambucil and fludarabine have been less commonly used as first-line therapy due to the development of additional well-tolerated therapies, as well as the substantial risk of myeloid neoplasms associated with these agents [9–11]. Bendamustine, typically in combination with rituximab, remains a widely used treatment option for newly diagnosed patients, as well as those with relapsed and refractory disease [5–8]. Rituximab and bendamustine (Benda-R) are typically given in 28-day cycles for a total of 4–6 cycles. Still, the successful completion of this recommended course may be limited due to treatment toxicities or other complications [5]. This issue has been addressed in previously published data, including a retrospective review of 182 patients, 57 of whom received treatment with bendamustine [12]. A median of four cycles (range, 2–6) were administered. Comparison of the patients who completed six cycles of

Article highlights

- There are several effective and safe options for the treatment of Waldenström macroglobulinemia although patients should be closely monitored during therapy for the emergence of treatment-specific side effects.
- Reduction in the number of rituximab-bendamustine treatment cycles may prevent toxicity without compromising disease outcomes.
- The frequency of bortezomib dosing and the manner of administration can be altered to decrease the risk of peripheral neuropathy in patients with Waldenström macroglobulinemia.
- Patients with Waldenström macroglobulinemia have a unique side effect profile associated with rituximab, including increased risk of rituximab intolerance and IgM flares.
- Ibrutinib is an effective treatment for Waldenström macroglobulinemia with a medically manageable side effect profile that includes atrial fibrillation and bleeding. Newer BTK inhibitors such as zanubrutinib and acalabrutinib show similar activity levels with differences in side-effect profile.

This box summarizes key points contained in the article.

bendamustine (n = 24, 42%) with those who received fewer than six cycles (n = 33, 58%) showed no significant difference in major response (OR 2.3, 95% CI 0.2–23.6; p = 0.48), deep response (OR 1.2, 0.4–3.3; p = 0.80), or overall survival (HR 1.01, 95% CI 0.06–16.4, p = 0.99) between the two groups. Similar outcomes were reported in a review of 160 patients treated with either Benda-R or dexamethasone, rituximab, and cyclophosphamide (DRC) [8]. Of the 60 patients treated with Benda-R, 31 patients (52%) received 6 cycles of treatment and 29 (48%) received less than 6 cycles. The major response rate was similar between those who received six cycles (93%) and those who received 4 cycles (90%). Additionally, there was no significant difference in achieving deep responses (46% vs. 20%, p = 0.25) or median progression-free survival (95% CI, 23-NR vs. 95% CI, 14-NR, p = 0.3). These data suggest that the number of planned treatment cycles of bendamustine may be decreased to less than 6 cycles in patients who have achieved an adequate response to reduce short- and long-term toxicity.

2.2. Reducing the risk of bortezomib-related neurotoxicity

The efficacy of the proteasome inhibitor bortezomib in the treatment of WM has been demonstrated in multiple studies. Bortezomib can be administered as a single agent, as well as in combination regimens such as bortezomib, dexamethasone and rituximab (BDR), bortezomib, cyclophosphamide and rituximab (BCR), and cyclophosphamide, bortezomib and dexamethasone (CyBorD) [13–18]. Bortezomib is widely used in multiple hematologic malignancies and is generally well tolerated, but the common side effect of peripheral neuropathy can cause significant complications in patients with WM who may have preexisting neuropathy or are at high risk for development of neuropathy. The increased risk of neuropathy in WM was demonstrated in a study using single-agent bortezomib [14]. In this study, bortezomib was administered at 1.3 mg/m^2 intravenously on days 1, 4, 8, and 11 of a 21-day cycle to 27 patients with WM. A median of six cycles were

administered. Twenty patients (74%) developed peripheral neuropathy that was new or worsening, including 12 patients with sensory changes, 2 with neuropathic pain, and 6 with both sensory changes and pain. Five patients had grade 3 neuropathy. Onset was typically between two and four cycles although in some cases the neuropathy worsened even after bortezomib was stopped. In this trial, neuropathic symptoms led to dose reductions or discontinuation of bortezomib in nine patients (33%). Two additional studies using single agent bortezomib in newly diagnosed or relapsed/refractory WM demonstrated grade ≥3 neuropathy in approximately 20% of patients [15,18]. Combination regimens have also shown elevated rates of neuropathy when using twice-weekly intravenous bortezomib. A prospective trial of BDR in 23 newly diagnosed patients using twice weekly intravenous bortezomib at a dose of 1.3 mg/m^2 followed by a planned maintenance cycle of BDR every 12 weeks for a total of 4 cycles demonstrated grade ≥2 neuropathy in 70% of patients (n = 16) [19]. This led to premature discontinuation of bortezomib in 61% of patients (n = 14).

Due to the high rates of neuropathy with twice-weekly intravenous bortezomib, later clinical trials were designed to allow once-weekly dosing without maintenance bortezomib. A regimen of bortezomib, low-dose dexamethasone, and rituximab was used in a phase 2 multicenter trial treating 59 patients with intravenous bortezomib 1.3 mg/m^2 (days 1, 4, 8, and 11 of a 21-day cycle) during cycle 1 followed by weekly intravenous bortezomib 1.6 mg/m^2 (days 1, 8, 15, and 22 of a 35-day cycle) for additional four cycles [20]. Despite excellent hematologic responses, 46% of patients developed peripheral neuropathy, grade 2 in 17% and grade ≥3 in 7% of patients. Dose reductions of bortezomib due to neuropathy occurred in 37% of patients. Similar results were reported in another trial of 37 patients treated with rituximab in addition to weekly intravenous bortezomib at a dose of 1.6 mg/m^2 (days 1, 8, and 15 of 28-day cycles) [16]. In this study, 46% (n = 17) of patients developed neuropathy, although only 2 patients had grade ≥3 neuropathy and only 6 patients did not complete the 6 cycles of treatment proposed in the clinical trial. Although peripheral neuropathy rates were significantly improved with once-weekly intravenous dosing, peripheral neuropathy remained a concerning side effect for these bortezomib-based regimens.

Data from multiple myeloma regimens have demonstrated equivalent efficacy but lessened neurotoxicity with the use of subcutaneous bortezomib [21,22]. Initial data confirming the efficacy and decreased neurotoxicity with subcutaneous bortezomib in WM were recently published in a Phase II randomized study in which 59 treatment-naive patients with WM were treated with BCR [13]. BCR was administered in 28-day cycles with bortezomib 1.6 mg/m^2 subcutaneous on days 1, 8, and 15 and was compared to fludarabine, cyclophosphamide, and rituximab (FCR). Both regimens were given for six cycles. The overall response rate with BCR remained high, comparable to previous trials, with no cases of grade ≥3 neuropathy reported. Additional data regarding the neurotoxicity of subcutaneous bortezomib from an ongoing Phase II clinical trial evaluating the use of dexamethasone, rituximab, and cyclophosphamide (DRC) with or without subcutaneous bortezomib in patients with WM were recently presented at the 62nd

American Society of Hematology Annual Meeting [23]. In this study, the addition of weekly, subcutaneous bortezomib to DRC did not improve PFS over DRC alone and was associated with a 20% rate of neuropathy with only 2% rate of grade 3 neuropathy. These data support the use of subcutaneous over intravenous bortezomib although one should still be mindful of potential neurotoxicity.

Additionally, in patients with underlying neuropathy or those otherwise unable to tolerate bortezomib, alternative proteasome inhibitors can be utilized to carefully consider their unique toxicity profiles. Ixazomib is a second-generation proteasome inhibitor that is administered orally. Ixazomib has been used in combination with dexamethasone and rituximab (IDR) and was recently demonstrated as a safe and effective regimen in a prospective trial of 26 treatment-naive patients with WM [24,25]. The overall response rate was 96% with a major response rate of 77% and very good partial response achieved in 19% of patients. The side effect profile was different from that seen in previous bortezomib trials, and although neuropathy was limited to grade 1 neuropathy (except for one patient with neuropathy related to underlying diabetes), gastrointestinal toxicity was reported, with 19% of patients having diarrhea, 35% with nausea, and 15% with vomiting. Similar findings were reported in a phase II study of IDR in previously treated WM patients in which an overall response rate of 88% was reported with minimal neurotoxicity [26]. Carfilzomib is an alternative second-generation proteasome inhibitor that also has a low rate of peripheral neuropathy. Carfilzomib safety and efficacy were demonstrated in a prospective study of 31 patients with WM treated with carfilzomib, rituximab, and dexamethasone (CaRD) [27]. In this trial, the overall response rate was 87% with a major response rate of 68% and peripheral neuropathy was limited to 6 patients (19%). Based on these results, this is a reasonable alternative regimen to use in WM, but with close monitoring for cardiotoxicity, which has been demonstrated in patients with multiple myeloma and was seen in one patient in this WM trial [28]. Fewer data support the use of these second-generation proteasome inhibitors, but their use can be considered in select patients.

2.3. Rituximab: IgM flare, intolerance, and subcutaneous administration

Rituximab has been used in the treatment of WM for many years. It can be administered as part of combination therapy or as a single agent albeit with lower response rates in the latter setting [29,30]. Although rituximab offers significant benefits as part of WM treatment, there are specific risks, including IgM flare, infusion reactions, and rituximab intolerance, which occur more frequently in patients with WM compared to other hematologic malignancies. Paradoxical IgM flare is defined as an increase in serum IgM level of ≥25% above the baseline level, and it occurs in approximately 50% of patients with WM treated with single-agent rituximab. The time to onset is about 4 weeks after rituximab initiation and IgM levels may remain elevated for many months [31,32]. This increase can lead to exacerbation or worsening of neuropathy, increase in cryoglobulins and cold agglutinins, and

symptomatic hyperviscosity requiring plasmapheresis [31–34]. The risk of symptomatic complications secondary to IgM flare increases significantly above an IgM level of 4,000 mg/dL. For this reason, it is recommended that before single-agent rituximab treatment, patients undergo prophylactic plasmapheresis to decrease the IgM below this level.

When rituximab is given in combination with or sequentially with other select agents, the risk of IgM flare decreases substantially. This was seen when rituximab was used in combination with bortezomib in multiple studies, such as a recent phase 2 multicenter trial of BDR in which rituximab was not initiated until cycle 2 [20]. In this trial, there was a median reduction in IgM of 18% after 1 cycle of bortezomib and only 11% of patients developed an IgM flare with no patient requiring plasmapheresis for symptomatic complications. Another phase 2 trial of weekly bortezomib 1.6 mg/m^2 administered to 37 patients with relapsed or refractory WM reported an IgM flare occurring in 22% of patients [16]. These studies confirm a lower risk of IgM flare when rituximab is given in combination with bortezomib although patients still require close monitoring. Bendamustine may also reduce the risk of IgM flare when given in combination with rituximab, as seen in a retrospective review of 71 patients treated with rituximab 375 mg/m^2 on day 1 with bendamustine 50 to 90 mg/m^2 on days 1 and 2 [7]. In this series, no patients experienced an IgM flare with treatment.

A reduction in IgM flare has also been demonstrated in recent trials combining the BTK inhibitor ibrutinib with rituximab. In a Phase III randomized trial of ibrutinib 420 mg once daily in combination with rituximab 375 mg/m^2 intravenously once weekly on weeks 1 to 4 and 17 to 20 [35], IgM flare occurred in 47% of patients receiving placebo in combination with rituximab, and only in 8% of patients receiving ibrutinib in combination with rituximab. None of the patients who experienced an IgM flare required plasmapheresis.

Another complication that occurs more frequently in WM compared with other malignancies is rituximab intolerance, which occurs in approximately 10% of WM patients [36]. Intolerance generally occurs at a median of 1 year from the first rituximab exposure and can occur in treatment-naive or relapsed patients receiving rituximab as either monotherapy or in combination with other therapies. Rituximab intolerance can occur even in patients who have received rituximab previously. Rituximab intolerance should initially be managed with a slower infusion rate and a more intensive pre-medication regimen, including acetaminophen, H1 and H2 antagonists, and steroids. If these precautions do not improve rituximab tolerance, then an alternative anti-CD20 monoclonal antibody such as ofatumumab may be utilized. The response rate of ofatumumab given as a monotherapy has been reported in a phase II trial of 37 patients with newly diagnosed or relapsed WM and is similar to that of rituximab with IgM flare occurring in only 9% of patients [37]. The use of ofatumumab in patients with rituximab intolerance is supported by a retrospective review reporting tolerance and response to ofatumumab in 82% of patients initiating this treatment in the setting of rituximab intolerance. It is also recommended by the National Comprehensive Cancer Network (NCCN) guidelines [36,38]. There are no single-agent data on

obinutuzumab activity and tolerance after rituximab in WM patients although obinutuzumab was used in combination with idelalisib in relapsed/refractory WM patients in whom adverse events were primarily associated with idelalisib [39].

Additional benefits in quality of life and overall patient satisfaction, while maintaining the efficacy of rituximab, can also be achieved in some patients by transitioning from the intravenous to the subcutaneous formulation, as now recommended in the NCCN guidelines [38]. This change in administration route is supported by multiple prospective studies in patients with other subtypes of non-Hodgkin lymphoma [40--40–42]. Due to the risk of an infusion reaction, intravenous rituximab is given as the first infusion, but if there are no issues with tolerance, subsequent rituximab doses can be administered by subcutaneous administration while maintaining efficacy and decreasing infusion time. Although data are still limited, the safety and efficacy of this transition were recently reported in a prospective trial utilizing IRD in previously treated WM patients and a prospective trial of DRC in WM [23,26].

2.4. Adverse effect profile of ibrutinib and other BTK inhibitors

The discovery of the MYD88 L265P mutation and the resulting tumor-cell growth through BTK in patients with WM led to the development and FDA approval of the first BTK inhibitor ibrutinib to treat WM. Since its development, ibrutinib has become an important treatment option for WM, with an overall response rate of 91% as monotherapy [43]. The side effect profile from the initial study of patients with relapsed or refractory disease demonstrated grade ≥2 adverse events that included neutropenia (22%), thrombocytopenia (14%), bleeding events (6%), and atrial fibrillation (5%). A similar side-effect profile was demonstrated in a subsequent study using ibrutinib monotherapy in treatment-naive as well as rituximab-refractory WM patients [44,45]. Additionally, in the phase 3 trial that randomized patients to rituximab with or without ibrutinib, similar ibrutinib-related adverse effects were seen. Both hypertension and atrial fibrillation were seen more commonly as grade ≥3 adverse events in the ibrutinib arm, as well as an increase in serious adverse events, including pneumonia, atrial fibrillation, and respiratory tract infections. To prevent these common complications related to adverse effects of the BTK inhibitors, it is essential to thoroughly assess patients prior to initiation of treatment with the knowledge that preexisting cardiac conditions or concurrent anticoagulation can increase the risk of adverse events. After treatment initiation, patients require close monitoring for toxicity.

Atrial fibrillation, one of the most concerning side effects with ibrutinib, has a time to onset that ranges from a few months to more than a year. Although atrial fibrillation risk persists throughout treatment, the variation in time of onset is likely related to the individual patient's preexisting cardiac conditions [46,47]. As previously reported, the median time of onset was 4 months in patients with a history of atrial fibrillation but 33 months in those with no history of atrial fibrillation [47]. If atrial fibrillation develops, the patient's stroke risk should be determined. If anticoagulation is required, a thorough assessment of bleeding risk should be completed before starting anticoagulation due to the increased risk of bleeding associated with BTK inhibitors. If it is deemed safe to initiate anticoagulation or if the patient is already on anticoagulation at the time of ibrutinib initiation, direct oral anticoagulants should be preferentially chosen. Concurrent use of vitamin K antagonists was an exclusion criterion in prior trials, so safety data are not available. Despite the paucity of evidence, warfarin may potentially be used in combination with ibrutinib if other treatment options do not exist, a discussion of risks and benefits is performed, and the patient is very closely monitored. Although new atrial fibrillation does not necessitate cessation of therapy, a dose reduction or temporary hold in therapy may occur, while initial treatment of the arrhythmia is facilitated. If clinically indicated, cardiac amyloidosis should be exonerated.

Another well-reported side effect of BTK inhibitors is an increased risk of bleeding. A recent systematic review reported a relative risk of bleeding of 2.72 (95% CI, 1.62–6.58) in patients on ibrutinib across multiple indications [48]. This risk has been confirmed in trials specific to WM, including the risk of easy bruising and minor bleeding with grade 1 or 2 events occurring in up to 39% of patients with WM on ibrutinib monotherapy [44,45,49]. Although it is uncommon, a small risk of major life-threatening hemorrhage also exists, so close monitoring of bleeding is necessary. If patients experience major bleeding or hemorrhage, ibrutinib should be held and platelet transfusion can be administered as needed to counteract the effects of ibrutinib on platelet aggregation [50]. Close attention should be paid to patients concurrently on marine oils, antiplatelet agents, and anticoagulants, as the risk of bleeding with ibrutinib could be further increased on these agents. For those with mild bleeding, although a temporary hold in ibrutinib may be necessary, the patient may benefit from re-initiation of the drug at a lower dose per prescribing information [51]. Additionally, the risk of bleeding with ibrutinib may be decreased by close monitoring of concomitant medications to avoid the use of medications that are moderate and strong CYP3A inhibitors and Seville oranges and grapefruit, which are also CYP3A inhibitors [51,52]. Fish oil and vitamin E have also been reported to increase the bleeding risk in patients on ibrutinib and should be avoided when possible [49,53]. In patients taking concomitant anticoagulants or antiplatelet agents, the risk of bleeding is increased and close monitoring is required. Vitamin K antagonists are not generally recommended for anticoagulation and direct oral anticoagulants should be used when possible.

Due to the increased bleeding risk with ibrutinib, it is also essential to hold the medication before and after invasive procedures to prevent bleeding complications as procedural bleeding has been reported in WM [45]. Current guidelines recommend cessation of ibrutinib 3 to 7 days before a planned procedure, depending on the bleeding risk of the procedure. Approximately 20% of patients may develop withdrawal symptoms during the time of temporary ibrutinib cessation, characterized by fever, body aches, night sweats, arthralgias, chills, headache, or fatigue. The median time to onset of withdrawal symptoms is 2 days, and symptoms

rapidly resolve on re-initiation of ibrutinib. However, the IgM level may take many months to return to baseline if the patient has disease progression while the drug is held [54].

Regarding other side effects, such as hypertension, rash, cytopenias, and gastrointestinal toxicity, dose reductions in ibrutinib can be made from a full dose of 420 mg once daily to 280 mg, if necessary, based on the prescribing directions. Dose reductions have been reported in previous trials with no significant effects on disease outcomes [45,49]. Additionally, some patients may benefit from the use of a novel BTK inhibitor, such as zanubrutinib or acalabrutinib. A recent open-label randomized phase 3 trial comparing ibrutinib and zanubrutinib demonstrated similar efficacy with both medications, but a lower rate of atrial fibrillation, contusion, diarrhea, peripheral edema, hemorrhage, muscle spasms, and pneumonia in patients taking zanubrutinib [55]. Although zanubrutinib is not yet FDA approved for WM, this treatment can be considered in patients at high-risk for ibrutinib-related adverse effects. A trial directly comparing acalabrutinib and ibrutinib has not been performed, but recent data with acalabrutinib report atrial fibrillation and hypertension in 5% of patients with a low rate of grade 3–4 bleeding. However, the follow-up time is limited to 2 years [56]. In a small phase II study, about two-thirds of patients with chronic lymphocytic leukemia who were intolerant to ibrutinib switched to acalabrutinib and experienced responses without recurrence of the adverse event that initially prompted the switch [57]. A prospective study evaluating zanubrutinib in patients with B-cell lymphomas who are intolerant to ibrutinib or acalabrutinib is ongoing (NCT04116437). Based on the data available to date, acalabrutinib or zanubrutinib may be potential treatment options in WM patients with toxicities that develop while on ibrutinib or with preexisting conditions that portend an increased risk of adverse events. The non-covalent, reversible BTK-inhibitors LOXO-305 and ARQ531 are currently in clinical development, and preliminary trial results have shown efficacy in B-cell non-Hodgkin lymphomas with no signs of atrial fibrillation or bleeding risk [58,59]. Additional data are necessary to elucidate the specific roles these new BTK inhibitors will play in treating WM.

3. Conclusion

WM is a rare, indolent B-cell malignancy with multiple effective therapies available for the treatment of newly diagnosed and relapsed or refractory disease. Despite the efficacy of these available therapies, each treatment option has specific adverse effects, which in many cases are unique to patients with WM. Diligence is required during these patients' treatment to recognize these particular toxicities and adjust therapy to provide each patient with an effective treatment regimen while minimizing toxicity.

4. Expert Opinion

There have been great strides in the treatment of WM over the last two decades, and more so in the previous 5 years, driven explicitly by the advent of BTK inhibitors. The approval of ibrutinib in 2015 for the treatment of symptomatic patients represented a landmark for WM, particularly since it was based on targeted treatment approach that directly resulted from genomic insights made possible by whole-genome sequencing [60,61]. In 2018, the combination of ibrutinib and rituximab was approved for WM patients based on the results of a relatively large, for a rare disease, randomized controlled prospective study [35]. These events show that understanding the biology of the disease can lead to better treatments and that large studies can be done on rare diseases.

The purpose of this review was to delve into toxicity issues related to WM-directed regimens. As examples, rituximab can be associated with IgM flares and intolerance, alkylating agents and nucleoside analogs with secondary myeloid neoplasms, bortezomib with peripheral neuropathy, and BTK inhibitors with atrial arrhythmia and bleeding. Additonally, the risk of infections may be increased, particularly with chemoimmunotherapy and anti-CD20 monoclonal antibodies. As a summary, selected general and disease-centric adverse events associated with WM-directed therapy and the recommended management are shown in Table 1. However, several tools are available to better manage the adverse events related to WM-directed treatment, including switching agents, decreasing the number of cycles or the dose of the agent causing the event, or changing the route of administration, to cite a few.

Over the next 5 years, we will see the rise of second generation and non-covalent BTK inhibitors, BCL2 inhibitors, CXCR4 targeting agents, and several immunotherapeutic options. Although the efficacy rates of these compounds could be high, one thing is sure that these agents will also have adverse events, and we will need to familiarize ourselves with them to provide the best balance between efficacy and toxicity. For this purpose, we foresee that most prospective clinical trials and population-based studies will evaluate and use quality of life markers to better understand treatment decisions.

A recent population-based study using the National Cancer Database has suggested that WM patients treated at center with a large WM patient volume might have an improved survival after adjustment for age, disease severity, education level, and year of diagnosis [62]. The authors suggest that patients treated in large volume centers may have access to services to help manage comorbidities and other complications related to the disease and its treatment. These data support WM patients seeking evaluation by a WM specialist who could then coordinate with the treating physician and help with the management.

The world of WM therapy is a state of constant dichotomy. On the one hand, we thrive for deeper responses, even at the cost of increased toxicity, which we believe in turn could translate into longer responses. On the other hand, we aim at improving the quality of life, even at the cost of lower efficacy, as no specific therapy has shown to increase overall survival in WM patients. However, we need to further increase our understanding of the disease from genetic, biological, and pathophysiological perspectives to reach the Holy Grail of maximum efficacy with minimum toxicity in WM patients. The careful design of meaningful clinical trials, in addition to patient participation, will be the two columns in which the balance between efficacy and toxicity will finally rest.

Table 1. Selected adverse events associated with Waldenström macroglobulinemia-directed therapy.

Agent	Adverse event	Management
Rituximab	Paradoxical IgM flare (40–50% with monotherapy; 10–20% with combination)	• Plasmapheresis prior to rituximab monotherapy if IgM >4000 mg/dL • Delay starting rituximab in patients receiving combination therapy
	Intolerance with repeated IV infusions (5–10%)	• Pre-medication with acetaminophen, H1 and H2 blockers, and steroids • Slower infusions • Switch to ofatumumab
	Hypogammaglobulinemia	• IVIG if serum IgG <400 mg/dl and recurrent respiratory infections
Nucleoside analogs (fludarabine and cladribine)	Myeloid neoplasms (5–10%)	• Bone marrow aspiration and biopsy if persistent or refractory cytopenias
	DLBCL transformation	• PET/CT and biopsy if clinically suspicious
	Hypogammaglobulinemia	• IVIG if serum IgG <400 mg/dl and recurrent respiratory infections
Alkylating agents (cyclophosphamide and bendamustine)	Myeloid neoplasms (1–5%)	• Bone marrow aspiration and biopsy if persistent or refractory cytopenias
	Hypogammaglobulinemia	• IVIG if serum IgG <400 mg/dl and recurrent respiratory infections
Proteasome inhibitors (bortezomib, carfilzomib, and ixazomib)	Neuropathy (bortezomib IV twice a week)	• Subcutaneous formulation • Weekly administration • Dose decrease
	Cardiopulmonary adverse events (carfilzomib)	• Avoid use in elderly patients or those with significant cardiac disease • Weekly administration
	GI adverse events (ixazomib)	• Weekly administration • Dose decrease
	Herpes zoster reactivation	• Prophylactic acyclovir or valacyclovir throughout therapy
	Hypogammaglobulinemia	• IVIG if serum IgG <400 mg/dl and recurrent respiratory infections
BTK inhibitors (ibrutinib, acalabrutinib, and zanubrutinib)	Atrial arrhythmia (10%)	• Zanubrutinib has lower risk than ibrutinib • Pretreatment cardiac risk assessment can help predict risk
	Neutropenia	• Ibrutinib has lower risk than zanubrutinib
	Perioperative bleeding	• Hold BTK inhibitor 3–7 days before and after a surgical procedure
	Withdrawal symptoms (20%, when holding temporarily)	• Minimize holding • Prednisone on holding days
	Severe hypertension, cutaneous or GI adverse events	• Switch to a different BTK inhibitor or alternative therapy

BTK: Bruton tyrosine kinase; DLBCL: diffuse large B-cell lymphoma; IVIG: intravenous immunoglobulin; GI: gastrointestinal; PET/CT: positron emission tomography and computed tomography

Funding

Declaration of interest

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