Novel Agents in Waldenström Macroglobulinemia

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KEYWORDS

• Waldenström macroglobulinemia • Novel therapies • Targeted therapies
• Immunotherapy

KEY POINTS

- Novel therapies are needed to improve outcomes in patients with Waldenström macroglobulinemia (WM), as WM is incurable with currently available therapies and can severely impact the quality of life of patients with this disease.
- Non-covalent Bruton tyrosine kinase (BTK) inhibitors (eg, pirtobrutinib, nemtabrutinib) seem effective in WM patients who progress on or are intolerant to covalent BTK inhibitors.
- BTK inhibitor-containing regimens (eg, ibrutinib plus venetoclax; acalabrutinib plus bendamustine and rituximab) promise fixed-duration therapy to minimize toxicity and the development of resistance.
- Immunotherapy (eg, antibody-drug conjugates, bispecific antibodies, chimeric antigen receptor T-cell therapy) can potentially achieve deeper and more durable responses in patients with WM.

INTRODUCTION

Waldenström macroglobulinemia (WM) is a rare lymphoplasmacytic lymphoma with specific clinical and pathologic features that distinguish it from other indolent B-cell lymphomas and plasma cell disorders, making the treatment practices unique. Patients with WM typically have a prolonged life expectancy but will require multiple treatments throughout their disease. The current therapeutic landscape for WM includes several treatment options for patients with newly diagnosed WM, such as the Bruton tyrosine kinase (BTK) inhibitors ibrutinib, acalabrutinib, and zanubrutinib, as well as the chemoimmunotherapy regimens bendamustine–rituximab (BR) and cyclophosphamide–rituximab–dexamethasone, and proteasome inhibitor-based regimens. These therapies

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have high response rates and are generally well tolerated. Still, treatment-emergent adverse effects are present with each therapy, and resistance to these therapies occurs even in the first-line setting. In addition, the response rates and duration of response for these therapies decrease in relapsed and refractory disease. Owing to these limiting factors, additional treatments are being explored with a focus on developing more targeted agents, combination therapies, and in some cases fixed duration therapies to bring patients more effective and less toxic therapies. This review discusses multiple novel agents being developed for treating patients with WM.

BRUTON TYROSINE KINASE INHIBITORS

First- and second-generation covalent BTK inhibitors, such as ibrutinib, acalabrutinib, orelabrutinib, tirabrutinib, and zanubrutinib, have an important role in the treatment of newly diagnosed and relapsed/refractory WM and are part of guideline-directed therapy based on multiple previous publications demonstrating the safety and efficacy of these BTK inhibitors in WM.[1–5] Although they are effective, many patients develop side effects, such as cardiac arrhythmia, bleeding, or rheumatologic symptoms that may require dose reduction or medication changes.[6] In addition, resistance may develop in some patients through multiple potential pathways, such as acquiring phospholipase C γ2 and BTK mutations (eg, C481).[7,8] In recent years, reversible, noncovalent BTK inhibitors have been developed as a potential treatment option in patients with resistance or intolerance to earlier BTK inhibitors. The initial data have demonstrated efficacy in WM.

Pirtobrutinib

Pirtobrutinib is a novel non-covalent BTK inhibitor recently Food & Drug Administration (FDA)-approved for treating mantle cell lymphoma that inhibits both wild-type and C481-mutant BTK and has proven efficacy in multiple B-cell malignancies, including WM.[9,10] A recent clinical trial enrolled 323 patients with relapsed or refractory B-cell malignancies, including 78 patients with WM with a median number of 3 prior therapies (range 1–11). All patients were treated with single-agent pirtobrutinib across seven dose levels with 200 mg once daily determined to be the recommended phase 2 dosing. Of those patients with WM, 61 (78%) had been previously treated with a BTK inhibitor, and 40 (66%) had progressed on the prior BTK therapy. The major response rate for the 72 evaluable patients was 68% with 17 (24%) very good partial responses (VGPR) and 32 (44%) partial responses (PR). Of those with prior BTK inhibitor exposure, the major response rate was 64%. The median duration of response in the 49 responding patients was not reached at a short median response follow-up of 7.7 months. The most frequent adverse effects in the trial included fatigue, diarrhea, and contusions with the most frequent grade $\geq$3 adverse event being neutropenia. The discontinuation rate for treatment-related adverse effects was 2%. Owing to these data demonstrating tolerance and efficacy in a heavily pretreated population, additional trials will be pursued, including combination therapies and continued evaluation of the use of pirtobrutinib in patients with prior BTK inhibitor exposure and in patients with treatment naïve disease.

Nemtabrutinib

Nemtabrutinib is another non-covalent BTK inhibitor with efficacy against wild-type and C481-mutated BTK. Early data with this therapy were reported from a clinical trial that enrolled 112 patients, the majority of which had chronic lymphocytic leukemia (CLL) or small lymphocytic lymphoma (SLL) and six patients with WM (NCT03162536).[11]

Individual responses in the patients with WM are not yet available, but of the 57 patients with CLL/SLL, 95% had prior BTK inhibitor exposure, and 63% had a BTK C481 mutation. The overall response rate (ORR) was 56%. The most common drug-related adverse effects were similar to other BTK inhibitors; fatigue, thrombocytopenia, diarrhea, hypertension, and neutropenia, in addition to nausea and the unique effect of dysgeusia in 21% of patients. Grade $\geq$3 adverse effects occurred in 40% of patients, the most common being neutropenia, thrombocytopenia, and lymphocytosis. Additional studies evaluating the continued use of nemtabrutinib (NCT04728893, NCT05347225, and NCT05673460) and another non-covalent BTK inhibitor AS-1763 (NCT05602363) are underway in hopes of developing better tolerated and more effective BTK inhibitors.

BRUTON TYROSINE KINASE DEGRADERS

Additional manners of targeting BTK are also being explored, including BTK degradation, which can potentially overcome intrinsic and acquired BTK resistance in patients with lymphoma. The initial data with DD-03-171, a degrader of BTK inhibitor (BTK), IKFZ1, and IKFZ3, showed the ability to prevent the proliferation of lymphoma cells in vitro and in patient-derived xenografts also demonstrated reduced lymphoma burden and improved overall survival in murine models.[12] Currently, the BTK degraders NX-2127, NX-5948, and BGB-16673 are being explored in patients. NK-2127 degrades BTK and IKZF3 and has immunomodulatory activity with the potential to overcome resistance to currently available covalent and non-covalent BTK inhibitors, as demonstrated in a first-in-human phase 1 trial that has treated 28 patients with relapsed or refractory CLL or B-cell malignancies with NX-2127 at 100 mg daily.[13] All 17 patients with CLL had prior BTKi exposure, and of the 14 CLL samples tested, BTK mutations were found in C481 (29%), L528 (29%), T474 (14%), and V416 (7%). A mean BTK degradation of 86% was seen in all patients, and of the 12 evaluable patients with CLL, the ORR was 33% with evidence that the hematologic response deepens over time (up to 50% at 6 months). Grade $\geq$3 treatment-related adverse effects included neutropenia, anemia, and hypertension. The clinical trial exploring the use of NX-2127 (NCT04830137) continues to recruit and includes patients with CLL and other B-cell malignancies such as WM. NX-5948, a selective degrader of BTK without immunomodulatory activity, has demonstrated in vitro activity and in vivo effects in murine models.[14] Initial studies have also demonstrated central nervous system penetration. Clinical evaluation of this compound is ongoing in patients with relapsed or refractory B-cell malignancies (NCT05131022). Future studies will potentially include patients with central nervous system lymphoma, such as Bing–Neel syndrome. Two phase 1 open-label dose escalation and expansion trials are also ongoing with the BTK degrader BGB-16673 in patients with relapsed or refractory B-cell malignancies (NCT05006716 and NCT05294731). The outcome of this trial will determine the appropriate dose level to use in future phase 2 clinical trials.

BRUTON TYROSINE KINASE INHIBITOR COMBINATIONS

Although BTK inhibitors are effective and generally well-tolerated in WM, the potential for cumulative toxicities and indefinite therapy can be burdensome for patients. Clinical trials are ongoing to evaluate combination and fixed-duration treatment strategies with BTK inhibitors in combination with other therapies.

Based on the data from a phase 2 study of the B-cell leukemia/lymphoma 2 (BCL2) antagonist venetoclax in WM demonstrating an 84% ORR as well as the safety of venetoclax and ibrutinib combination in CLL and mantle cell lymphoma, a clinical trial was

designed to evaluate the combination of venetoclax with ibrutinib for a 2-year duration in WM.[15–17] The initial data from this trial show an ORR of 100% with a major response rate of 93% and a median time to minor response of 1.9 months.[18] Eighteen patients (40%) achieved a VGPR and 24 (53%) achieved a PR. The 12-month progression-free survival (PFS) in this trial was 92%. Grade ≥3 adverse events in at least two patients included neutropenia, oral mucositis, tumor lysis, and cardiac arrhythmias. Despite the high hematologic response rates and the previous success of this regimen in other hematologic malignancies, the trial was stopped early due to a high rate of ventricular arrhythmias with four patients (9%) experiencing ventricular arrhythmia and/or cardiac arrest. The exact etiology for the increased risk of arrhythmias in this population compared with patients with other malignancies is unknown. Despite the early cessation of this trial due to toxicity, the trial demonstrated the potential to achieve deep hematologic responses with a finite duration combination of BTK inhibitor and BCL-2 inhibitor, and therefore, additional trials using novel BTK inhibitors, such as pirtobrutinib with venetoclax (NCT05734495), are ongoing.

Another combination therapy with promising early results is the combination of a BTK inhibitor and chemoimmunotherapy, as seen in an ongoing single-arm trial combining six cycles of BR with 12 months of acalabrutinib (NCT04624906).[19] Interim data from this trial reported that eight of the first ten patients had completed all six cycles of BR. All patients had achieved a VGPR at cycle 7. The most common grade ≥3 toxicities were cytopenias with one case each of transaminitis, atrial fibrillation, and infection. Future investigations in this trial will evaluate the rates of minimal residual disease negativity, treatment tolerance, and PFS.

The combination of zanubrutinib, the proteasome inhibitor ixazomib and dexamethasone is being investigated in a phase 2 single-arm study (NCT04463953), and the preliminary results were recently reported.[20] This regimen includes ixazomib and dexamethasone administered for up to six cycles, followed by maintenance therapy every 3 months. Zanubrutinib was administered orally twice daily with all treatment ending after a maximum of 24 months. At the time of data presentation, 20 patients had enrolled in the study and 19 were evaluable for response. Eight patients had achieved a VGPR (42%), ten had a PR (53%), and one had a minor response (5%) for an ORR of 100% and a major response rate of 95%. The median time to minor response was 1.1 months. Two patients achieved minimal residual disease negativity. Grade ≥3 serious adverse events of rash and neutropenia were observed in two patients. Additional results from this trial will be reported in the future. Another proteasome inhibitor-based clinical trial is ongoing to explore the use of carfilzomib in combination with ibrutinib compared with ibrutinib alone in WM (NCT04263480). These combination trials offer the potential for a fixed-duration therapy with deep hematologic responses.

C-X-C CHEMOKINE RECEPTOR TYPE 4 TARGETING AGENTS

C-X-C chemokine receptor type 4 (CXCR4) mutations are present in approximately 40% of patients with WM and may serve as another potential therapeutic target.[21] This additional mutation is associated with a longer time to hematologic response, decreased rates of major responses, and shorter PFS in patients treated with BTK inhibitors.[4,22] One CXCR4 antagonist, ulocuplumab, was initially explored in combination with ibrutinib.[23] Ulocuplumab was administered every other week during cycles 2 to 6. Ibrutinib was given daily with the intention of continuing ibrutinib indefinitely in the setting of continued disease response and tolerance of therapy. In this study, 12 patients were evaluable for response with 100% overall and major response

rate. The time to minor and major responses were 0.9 and 1.2 months, respectively. Compared with historical data, the time to response, depth of response, and PFS compared favorably to single-agent ibrutinib in patients without CXCR4 mutations. Following this trial, an additional trial investigating the use of the CXCR4 antagonist mavorixafor was initiated.[24] Mavorixafor 200 to 600 mg orally once daily was given with ibrutinib, and preliminary data after 10 patients were enrolled showed an ORR of 100%, with four of eight patients achieving a major response. This clinical trial is now closed to enrollment, and outcome data are expected in the near future. Despite the efficacy and safety of these agents in combination with ibrutinib, the additional development of these agents is not currently being pursued, but CXCR4 antagonists may still play a role in the future therapy for WM.

OTHER TARGETED AGENTS

Continued exploration of the B-cell receptor and nuclear factor kappa B (NF-κB) pathways has led to the development of additional targeted therapies. Mucosa-associated lymphoid tissue translocation protein 1 (MALT1), when dysregulated, is known to contribute to the development of lymphoid malignancies and has emerged as a potential target in lymphomas such as WM which rely on NF-κB pathway upregulation.[25]

JNJ-67856633, a potent, selective MALT-1 inhibitor showing preclinical activity in activated B-cell diffuse large B-cell lymphoma, is being explored in combination with ibrutinib (NCT04876092) and in combination with a novel BTK inhibitor JNJ-6426481 (NCT04657224) in patients with non-Hodgkin lymphomas.[26] SGR-1505 and ONO-7018, additional MALT1 inhibitors, are also actively being studied in phase 1 open-label clinical trials evaluating these drugs' safety and pharmacologic characteristics in patients with relapsed or refractory B-cell malignancies (NCT05544019 and NCT05515406).

Another small molecule inhibitor currently in development is emavusertib (CA-4948), an inhibitor of interleukin-1 receptor-associated kinase 4 (IRAK4). IRAK4 is part of the myddosome signaling pathway known to be dysregulated in WM. Hence, an ongoing phase 1 clinical trial (NCT03328078) enrolling patients with relapsed or refractory hematologic malignancies, including WM. Preliminary data have reported three patients with WM enrolled in the trial with two of the three patients achieving a PR.[27] Recruitment for this trial is ongoing. Future studies may also be pursued in Bing–Neel syndrome, as early data have shown that emavusertib crosses the blood-brain barrier, and some central nervous system tumors, such as primary central nervous system lymphoma, have demonstrated susceptibility to this compound in laboratory testing.[28]

IMMUNOTHERAPIES

Chimeric Antigen Receptor T Cells

Several new therapies in the immunotherapy field have been approved for multiple myeloma and lymphoma. One of these therapies, chimeric antigen receptor (CAR) T-cell therapy, is actively being investigated in WM. The initial preclinical data with a CAR T-cell therapy targeted against the CD19 antigen demonstrated activity in WM cells in vitro and in vivo murine models of WM.[29] These data were followed by a report of three patients with relapsed and refractory WM treated with CD19-directed CAR T-cell therapy in clinical trials (NCT03085173 and NCT00466531). All three patients responded to CAR T-cell treatment with one attaining a minimal residual disease-negative complete response. However, these responses had limited durability as all patients relapsed between 3 and 26 months. Additional data from these two clinical trials are not yet available, but the studies are ongoing.

A large clinical trial using brexucabtagene autoleucel, a cluster of differentiation 19 (CD19) CAR T-cell construct, has FDA approval for treating relapsed or refractory mantle cell lymphoma, and B-cell precursor adult lymphocytic leukemia is currently recruiting patients with WM. It will provide additional data on the safety of this construct in WM (NCT05537766). In the initial trials that led to the approval of brexucabtagene autoleucel, the most common non-hematologic grade $\geq$3 adverse effects included fever/febrile neutropenia, hypotension, infection, hypoxia, cytokine release syndrome, and neurologic toxicity with the latter two adverse effects being frequently associated with CAR T-cell therapy.[30,31] Most patients also developed leukopenia, neutropenia, lymphopenia, thrombocytopenia, and anemia.

An additional CAR T-cell product with preliminary data in non-Hodgkin lymphoma is MB-106, a cluster of differentiation 20 (CD20)-targeted CAR T with M-1BB, and CD28 costimulatory domains. An ORR of 94% was reported in the initial 16 patients with relapsed or refractory B-cell non-Hodgkin lymphoma treated with this construct. Less than half of patients (n = 7, 44%) developed cytokine release syndrome with all cases being grade 1 or 2 and immune effector cell-associated neurotoxicity syndrome in only one patient (6%), which compares favorably to other CAR T-cell constructs. A large clinical trial with MB-106 is ongoing (NCT05360238) and will include patients with WM. Data from the first two patients with WM treated with this construct were previously presented and showed a hematologic response in both patients.[32]

Antibody-Drug Conjugates

Another novel immunotherapy being investigated in WM is loncastuximab tesirine, a CD19-directed antibody-drug conjugate. Loncastuximab tesirine has been FDA-approved for use in patients with relapsed or refractory diffuse large B-cell lymphoma based on phase 1 data demonstrating an ORR of 43%, 47%, and 79% in diffuse large B-cell lymphoma, mantle cell lymphoma, and follicular lymphoma, respectively.[33] Additional phase 2 data in diffuse large B-cell lymphoma reported a response rate of 48% and a complete response rate of 24% with the most common grade $\geq$3 treatment-related adverse events in these trials being neutropenia, thrombocytopenia, and elevation in gamma-glutamyltransferase. Based on response rates and tolerance of this therapy in both aggressive and indolent B-cell lymphomas with CD19 expression, it was thought that the CD19 expression seen on lymphocytes and plasma cells in WM might make this disease susceptible to treatment with loncastuximab tesirine.[34,35] An ongoing clinical trial (NCT05190705) should provide information on the efficacy and safety of this drug in WM.

Bispecific Antibodies

In recent years, bispecific antibodies, particularly those with the B-cell specific surface antigen CD20 and the T-cell surface antigen CD3 binding sites, have been successfully explored in non-Hodgkin lymphoma. Mosunetuzumab, a CD20 and CD3 bispecific antibody, was recently granted FDA approval for treating advanced follicular lymphoma. Ongoing trials are exploring the use of this bispecific as well as glofitamab, epcoritamab, and odronextamab in non-Hodgkin lymphoma.[36] To date, data are not available for the use of these products in WM. However, additional evaluation of these therapies in WM is warranted and the development of these clinical trials is underway.

Phospholipid-Drug Conjugates

Iopofosine I-131 (previously known as CLR131) is a small-molecule phospholipid-drug conjugate. This radiopharmaceutical is designed to deliver a radioisotope, iodine-131, directly to cancer cells. This drug has been granted Fast Track Designation and

Table 1
Selected prospective clinical trials evaluating novel agents in Waldenström macroglobulinemia

ClinicalTrials.Gov ID	Agents	Phase	Setting
NCT02952508	Iopofosine 131	II	RR
NCT03620903	Ibrutinib, bortezomib, rituximab	II	TN
NCT04061512	Ibrutinib, rituximab vs DRC	III	TN
NCT04263480	Ibrutinib, carfilzomib vs ibrutinib	III	TN
NCT04463953	Zanubrutinib, ixazomib, dexamethasone	II	TN
NCT04624906	Acalabrutinib, bendamustine, rituximab	II	TN
NCT04728893	Nemtabrutinib	II	RR
NCT05099471	Venetoclax, rituximab vs. DRC	II	TN
NCT05190705	Loncastuximab tesirine	II	RR
NCT05360238	MB-106	II	RR
NCT05537766	Brexucabtagene autoleucel	II	RR
NCT05734495	Pirtobrutinib, venetoclax	II	RR

Abbreviations: DRC, dexamethasone, rituximab, cyclophosphamide; RR, relapsed or refractory; TN, treatment-naïve.

Orphan Drug Designation by the US Food and Drug Administration based on data from the CLOVER-1 phase 2 trial. This initial trial enrolled patients with multiple indolent lymphomas, including six patients with WM.[37] The ORR in these patients was 100% with 83% major responses, including one complete response. The median time to initial response was 48 days. The median duration of response has yet to be reached. The primary treatment-emergent adverse events were cytopenias and fatigue. A trial dedicated to WM is now ongoing (NCT02952508).

Table 1 lists selected clinical trials with novel agents in patients with WM.

SUMMARY

There are several safe and effective options to treat patients with WM. However, WM remains incurable using standard therapies; therefore, agents with novel and non-cross-resistant mechanisms of action are needed. A wide variety of targeted agents and immunotherapies are undergoing clinical development in patients with WM aimed at improving the response and survival of these patients while minimizing adverse events. These newer agents are likely to chisel the treatment landscape of WM. Multi-institutional efforts and energetic patient participation are needed to complete these clinical trials.

CLINICS CARE POINTS

- Multiple effective therapies for WM exist, but novel therapies are needed due to the long life expectancy of patients with WM, as well as the risk of disease relapse and development of treatment resistance.

CONTRIBUTIONS

S. Sarosiek and J.J. Castillo: Conception, writing, and final approval of the article.

DISCLOSURES

J.J. Castillo received research funds and/or honoraria from Abbvie, United States, AstraZeneca, BeiGene, China, Cellectar, Janssen, United States, Kite, LOXO, Pharmacyclics, United States, Roche, Switzerland, and TG Therapeutics, United States. S. Sarosiek received research funds and/or honoraria from Beigene, Cellectar, and ADC Therapeutics.

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