

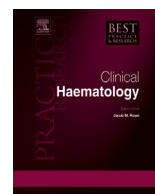


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Contents lists available at ScienceDirect

Best Practice & Research Clinical Haematology

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



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Future therapeutic options for patients with Waldenström macroglobulinemia

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ABSTRACT

Keywords:

BTK
BCL2
CD38
CXCR4
MYD88
Waldenström

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.

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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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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- κ B) pathway. The NF- κ B pathway plays an important role in plasma cell tumorigenesis [6]. In WM, there are higher constitutive levels of NF- κ B when compared with healthy donors [7]. Preclinically, bortezomib was highly effective on inhibiting the nuclear translocation of NF- κ B, 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 chemotrypsin-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

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