Proteasome Inhibitors in Waldenström Macroglobulinemia

Efstathios Kastritis, MD*, Meletios A. Dimopoulos, MD

KEYWORDS

• Bortezomib • Carfilzomib • Oprozomib • Ixazomib • Unfolded protein response

KEY POINTS

- Proteasome inhibitors (PIs) have become an important part of WM therapy both as primary therapy and as salvage option.
- Bortezomib is the proteasome inhibitor mostly studied and with extensive clinical experience. Bortezomib is active either as a single agent and in combinations with rituximab in all disease settings.
- Bortezomib-associated neuropathy is the most common and challenging toxicity although the use of subcutaneous bortezomib and weekly regimens may reduce its frequency and severity; risk of herpes zoster reactivation is also high if no prophylaxis is given.
- Carfilzomib is a second generation PI and in combination with rituximab and dexamethasone has shown activity in WM; it has low neuropathy risk but has been associated with a potential of cardiotoxicity.
- Ixazomib is an orally available PI, has shown activity in combination with rituximab in newly diagnosed WM and a favorable toxicity profile, with low risk of neurotoxicity or cardiotoxicity. Oprozomib is another oral PI but still in earlier stages of clinical development.

INTRODUCTION

Waldenström macroglobulinemia (WM) is an incurable B-cell lymphoproliferative disorder that is characterized by the infiltration of the bone marrow by clonal lymphoplasmacytic cells and the production of monoclonal immunoglobulin M (IgM) by these cells.[1–4] WM may have a long course, even in symptomatic patients, and during the course of the disease, multiple regimens may be used to control the disease and its

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Department of Clinical Therapeutics, National and Kapodistrian University of Athens School of Medicine, 80 Vassilisis Sofias Avenue, Athens 11528, Greece
* Corresponding author. Department of Clinical Therapeutics, National and Kapodistrian University of Athens School of Medicine, 80 Vassilisis Sofias Avenue, Athens 11528, Greece.
E-mail addresses: ekastritis@gmail.com; ekastritis@med.uoa.gr

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symptoms.[2,5,6] Currently, therapy is considered only for patients with symptomatic disease, and primary options include combinations based on anti-CD20 monoclonal antibodies, mainly rituximab.[2,5,6]

In recent years, proteasome inhibitors (PIs) have become a mainstay of therapy in plasma cell malignancies but also in some specific lymphomas.[7] Regarding the treatment landscape in WM, PIs have also become part of primary and salvage options for patients with WM,[2,5,6] based on the results of several phase 2 studies, mostly with bortezomib, the first in the class of PI. In addition, new PIs have become available and may also find their way into WM therapy, such as carfilzomib, ixazomib, and oprozomib.

In this review, the authors focus on the clinical results of PI-based therapy and the challenges phased in the changing landscape of available therapies for WM.

MECHANISMS OF ACTION

PIs block degradation of ubiquitinated proteins by the proteasome, an organelle found in all cells.[8,9] Blocking proteasome activity results in the accumulation of ubiquitinated proteins and leads to dysregulation of multiple pathways within the cells but also to an increase of endoplasmatic reticulum (ER) stress. Cells that are sensitive cannot cope with the increased ER stress load, and this leads to the activation of apoptotic pathways. Although this schema may be oversimplified, cells that are most sensitive seem to be those that are producing higher amounts of protein, such as plasma cells and other B cells.[10] Different PIs have differences in their affinity for the various proteasome subunits, reversibility or nonreversibility of interaction, and pharmacokinetics. Bortezomib is the first in the class of PI and is a slowly reversible boronated inhibitor of the 26S proteasome, mostly of the chymotryptic unit of the proteasome.[11] Carfilzomib is an irreversible tetrapeptide epoxyketone–based PI (analogue of epoxomicin).[12] Ixazomib is an orally available, boronated, PI, which is metabolized to its active form,[13,14] whereas oprozomib is an oral analogue of carfilzomib.[15]

Preclinical studies have elucidated multiple mechanisms of action for PIs in WM, and bortezomib is the PI mostly studied.[16,17] Bortezomib blockade of the ubiquitin-proteasome degradation pathway affects signaling pathways that also include NF-κB,[16] which has critical function in WM cells' survival and immunoglobulin production. The induction of ER stress has also been implicated as a mechanism for bortezomib activity leading to disruption of the unfolded protein response that prompts WM cell apoptosis,[17,18] which is active in WM cell lines and in primary tumor cells. PIs may also impact the supportive bone marrow microenvironment in WM as has also been implicated for its activity in multiple myeloma.[17,18] Bortezomib has also demonstrated synergistic and/or additive preclinical activity in combination with other agents, including steroids, rituximab, and signaling inhibitors in WM cells.[19,20]

CLINICAL DATA ON THE ACTIVITY OF PROTEASOME INHIBITORS

PIs have undergone extensive clinical investigation in WM, either as a single agent or as part of combination therapies (**Table 1**). The first PI studied in the clinic was bortezomib, initially in patients with relapsed or refractory WM, and was given as a single agent and through an intravenous (IV) route.

Dimopoulos and colleagues[21] investigated the activity of single-agent bortezomib (1.3 mg/m^2 as IV push on days 1, 4, 8, and 11 of a 21-day cycle for up to 6 cycles) in 10 previously treated patients. A major response, that is, at least a partial response