

# Bortezomib as a Treatment Option in Patients With Waldenström Macroglobulinemia

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## Abstract

Waldenström macroglobulinemia (WM) is a B-cell lymphoproliferative disorder characterized by lymphoplasmacytic bone marrow infiltration and immunoglobulin M (IgM) monoclonal gammopathy. It remains incurable, with a median survival of 5-10 years in symptomatic WM. Current first-line treatment options include alkylating agents, nucleoside analogues, and rituximab-based therapies. However, primary or secondary resistance invariably develops. Thus, new treatment options are needed. Preclinical studies have shown that the proteasome inhibitor bortezomib targets signaling pathways of relevance in WM. Bortezomib, alone and in combination with rituximab, has demonstrated notable activity in clinical studies in patients with WM, predominantly in phase II trials in the relapsed or refractory setting. In newly diagnosed patients, bortezomib plus rituximab and dexamethasone is highly active (complete response/near-complete response = 22%). Bortezomib-based therapies result in rapid responses, potentially making them suitable treatment options for patients with hyperviscosity-related symptoms who require a rapid reduction in IgM level. In addition, bortezomib appears unique in reducing rituximab-associated IgM flares. Bortezomib is generally well tolerated in WM. However, neurotoxicity is common and might be the cause of dose reduction or treatment discontinuation. Bortezomib has no adverse effect on stem cell harvesting and engraftment, making it a feasible treatment option in transplantation-eligible patients. These encouraging data have led to the inclusion of bortezomib as a salvage treatment option in the recently updated Fourth International Workshop on Waldenström's Macroglobulinemia treatment recommendations.

*Clinical Lymphoma, Myeloma & Leukemia*, Vol. 10, No. 2, 110-117, 2010; DOI: 10.3816/CLML.2010.n.015

**Keywords:** IgM flares, Immunoglobulin M, Nuclear factor- $\kappa$ B, Waldenström's macroglobulinemia

## Introduction

Waldenström macroglobulinemia (WM) is an incurable, relapsing, rare B-cell lymphoproliferative disorder. It is characterized by lymphoplasmacytic bone marrow infiltration and elevated immunoglobulin M (IgM) levels<sup>1-3</sup> and is associated with cytokine and chemokine upregulation, which facilitate survival of the malignant clone.<sup>4</sup> The most common clinical presentations include cytopenias (notably anemia), increased vascular resistance, and serum hyperviscosity.<sup>5,6</sup> The median overall survival is estimated to be

5-10 years, with disease-specific survival of 11.2 years reported in one study<sup>2,3,5,7-10</sup>; however, because of the relapsing nature of the disease, most patients die of disease progression.<sup>4</sup>

Waldenström macroglobulinemia accounts for 1%-2% of all hematologic malignancies, with an overall incidence of approximately 3 per million persons per year.<sup>2,11,12</sup> The median age at diagnosis varies between 63 years and 75 years, and 55%-70% of patients are men.<sup>2,7,10,11,13</sup> The incidence of WM is higher among the white versus black population, with the latter representing only 5% of all patients.<sup>11,12</sup> Genetic factors might have a role in familial clustering of WM, with 19% of the patients in one study having a first-degree relative with a B-cell neoplasm.<sup>14,15</sup>

The predominant risk factor for the development of WM is preexisting monoclonal gammopathy of unknown significance (MGUS), which confers a 46-fold increased risk of disease in comparison with the general population.<sup>16</sup> Increasing IgM level is linked to a progressive increase in risk of transformation from asymptomatic IgM-MGUS to symptomatic WM.<sup>17</sup> However, although elevated serum IgM causes hyperviscosity and other complications, it does not accurately reflect tumor burden or prognosis alone.<sup>4</sup>

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Submitted: Aug 7, 2009; Revised: Sep 13, 2009; Accepted: Sep 21, 2009

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Poor prognosis has also been associated with advanced age, high  $\beta_2$ -microglobulin level, cytopenias, low albumin level, and organomegaly.<sup>9,10,18,19</sup> Indeed, the International Prognostic Scoring System for WM allows patients to be stratified as low, medium, or high risk based on age, hemoglobin concentration, platelet count,  $\beta_2$ -microglobulin, and M-protein.<sup>20</sup> Inactivation of the *TRAF3* and *TNFAIP3* tumor suppressor genes, which are both negative regulators of the nuclear factor (NF)- $\kappa$ B pathway, has been reported, suggesting a therapeutic role for inhibitors of NF- $\kappa$ B.<sup>21</sup>

The proteasome inhibitor bortezomib acts through inhibition of the NF- $\kappa$ B and additional signaling pathways<sup>22-24</sup> and has demonstrated notable activity in frontline<sup>25,26</sup> and relapsed or refractory<sup>25</sup> multiple myeloma (MM), and in relapsed or refractory<sup>27</sup> mantle cell lymphoma (MCL). Thus, bortezomib might also represent a therapeutic option for patients with WM.

### Current Treatment Options for Waldenström Macroglobulinemia

In accordance with current guidelines, treatment is initiated only when WM patients become symptomatic.<sup>2,3,11,28</sup> Criteria for starting treatment are hemoglobin < 100 g/L, platelets <  $100 \times 10^9/L$ , clinically significant adenopathy or organomegaly, symptomatic hyperviscosity, severe neuropathy, amyloidosis, cryoglobulinemia, cold agglutinin disease, or evidence of large-cell transformation.<sup>1,2,28</sup> Patients with asymptomatic WM should be followed without treatment until  $\geq 1$  of the above criteria are met.<sup>29,30</sup>

Most WM therapies were originally derived from those for other lymphoproliferative diseases presenting with elevated immunoglobulin levels, such as MM or chronic lymphocytic leukemia.<sup>4</sup> However, because of the low incidence of WM, clinical trials in this disease have small sample sizes, and no large comparative studies have been performed. Subsequently, there is no US Food and Drug Administration- or European Medicines Agency-approved regimen for frontline or relapsed or refractory WM.<sup>1</sup> Current treatment regimens include alkylating agents, nucleoside analogues, and rituximab.<sup>1,31</sup>

Recommendations from the Fourth International Workshop on Waldenström's Macroglobulinemia have recently been published.<sup>28</sup> Treatment options for WM in the front-line setting include single-agent chlorambucil, cladribine, fludarabine, or rituximab and combination treatment comprising doublets of cladribine or fludarabine plus cyclophosphamide or rituximab, or triplets of cladribine, fludarabine or pentostatin plus cyclophosphamide and rituximab.<sup>28</sup> Other recommended therapies include rituximab plus thalidomide (RT), R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone), and cyclophosphamide, dexamethasone, and rituximab (CDR).<sup>28</sup> Treatment options in the relapsed or refractory setting are similar to those in the frontline setting, with the omission of the CDR regimen and the inclusion of single-agent alemtuzumab or thalidomide, or these agents in combination with dexamethasone.<sup>28</sup> High-dose therapy plus autologous stem-cell transplantation (HDT-ASCT) is also considered a treatment option in various settings.<sup>28</sup>

Unfortunately, response rates for these various regimens are low, with approximately 50% of patients achieving a partial response (PR;  $\geq 50\%$  M-protein reduction) and few achieving a complete

response (CR; 100% M-protein reduction).<sup>5,32</sup> For example, CR rates in the frontline setting using alkylating agents, nucleoside analogues, and monoclonal antibodies, alone or in combination, are  $\leq 10\%$ .<sup>1</sup> Major response rates ( $\geq$  PR) in WM are 31%-85% in frontline and 20%-54% in relapsed or refractory settings with single agents and 74%-94% in both settings using combination therapies.<sup>2,7,8,18,33-49</sup>

The choice of treatment for WM depends on several factors, including candidacy for ASCT, the presence of cytopenias, and the need for rapid disease control. Recommendations from the Fourth International Workshop on Waldenström's Macroglobulinemia relate to each of these factors.<sup>28</sup> The prolonged use of alkylating agents and nucleoside analogues is unsuitable in patients undergoing ASCT because these therapies can adversely affect bone marrow function,<sup>6</sup> thereby impairing stem-cell mobilization and potentially preventing the harvesting of sufficient stem cells for patients to undergo ASCT. However, cyclophosphamide is an alkylating agent that has no adverse effect on stem cell collection. Rituximab plus thalidomide, R-CHOP, and CDR regimens are therefore appropriate in ASCT candidates.<sup>28</sup> Other alkylating agents can induce myelodysplasia and acute nonlymphocytic leukemia, and nucleoside analogues might induce bone marrow suppression and immunosuppression.<sup>50</sup> The use of these agents is further limited in patients with cytopenias, particularly thrombocytopenia; such patients might benefit from therapies with low myelotoxicity; RT and CDR regimens are suggested as options in these patients, even in non-ASCT patients.<sup>28</sup> A rapid response to therapy is important in WM, particularly for patients presenting with hyperviscosity symptoms. R-CHOP and CDR are recommended for these patients.<sup>28</sup>

Standard therapies typically have slow response rates; for example, with chlorambucil, several months are required to determine the chemosensitivity of the disease, and rituximab has a median time to response of 3.3 months.<sup>5,38,51</sup> Rituximab is also associated with transient increases in IgM titers, known as 'IgM flares.' Flares can lead to hyperviscosity-associated events, including epistaxis, headaches and, in one case, a subdural hemorrhage.<sup>52</sup> In one study, flares occurred in 54% of the patients and were associated with lower response rates (28% vs. 80% for patients with and without flares, respectively).<sup>53</sup>

Because of the limitations of standard therapies in certain patient groups and the relapsing nature of WM, additional treatment options are required for this disease.<sup>4,28</sup> Consequently, novel agents and new approaches continue to be investigated. These include treatment options effective in MM, such as lenalidomide and allogeneic/mini-allogeneic SCT as well as novel agents targeting pathways of relevance in WM, such as Akt and mammalian target of rapamycin inhibitors.<sup>1,2,11,54-57</sup> Bortezomib, effective in MM and MCL, also targets signaling pathways of relevance in WM.<sup>25-27,58,59</sup> Therefore, bortezomib appears a highly suitable treatment option for WM and, as reviewed in the next section, has demonstrated notable activity as a single and combination agent in clinical studies.

### Bortezomib as a Treatment Option in Waldenström Macroglobulinemia Preclinical Studies

Preclinical studies have elucidated the mechanism of action of bortezomib in a number of tumor types. Bortezomib blocks the

