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Lymphoma

Proteasome Inhibition and Combination Therapy for Non-Hodgkin's Lymphoma: From Bench to Bedside

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ABSTRACT

Although patients with B-cell non-Hodgkin's lymphoma (NHL) usually respond to initial conventional chemotherapy, they often relapse and mortality has continued to increase over the last three decades in spite of salvage therapy or high dose therapy and stem cell transplantation. Outcomes vary by subtype, but there continues to be a need for novel options that can help overcome chemotherapy resistance, offer new options as consolidation or maintenance therapy postinduction, and offer potentially less toxic combinations, especially in the elderly population. The bulk of these emerging novel agents for cancer treatment target important biological cellular processes. Bortezomib is the first in the class of proteasome inhibitors (PIs), which target the critical process of intracellular protein degradation or recycling and editing through the proteasome. Bortezomib is approved for the treatment of relapsed or refractory mantle cell lymphoma. The mechanisms of proteasome inhibition are very complex by nature (because they affect many pathways) and not fully understood. However, mechanisms of action shared by bortezomib and investigational PIs such as carfilzomib, marizomib, ONX-0912, and MLN9708 are distinct from those of other NHL treatments, making them attractive options for combination therapy. Preclinical evidence suggests that the PIs have additive and/or synergistic activity with a large number of agents both in vitro and in vivo, from cytotoxics to new biologicals, supporting a growing number of combination studies currently underway in NHL patients, as reviewed in this article. The results of these studies will help our understanding about how to best integrate proteasome inhibition in the management of NHL and continue to improve patient outcomes. ***The Oncologist*** 2012; 17:694–707

OVERVIEW

In the U.S., >70,000 patients are diagnosed with non-Hodgkin's lymphoma (NHL) annually [1], and one in three patients dies within 5 years of diagnosis [2]. Of note, the incidence of NHL has increased dramatically (>80% over the last three decades). The broad spectrum of malignancies comprising NHL can be classified according to cell of origin (B, T, or natural killer cell), as well as mature or immature phenotype, as seen in the World Health Organization classification (Table 1) [3, 4]. The distribution of the different subtypes of NHL varies geographically worldwide.

Response rates to conventional chemotherapy are typically >50%, and many patients achieve a complete response (CR). Even so, most patients eventually relapse [5], and there is no generally accepted therapeutic approach for relapsed or refractory lymphoma [6] outside of Hodgkin's lymphoma and diffuse large B-cell lymphoma (DLBCL) after first relapse. The addition of rituximab to chemotherapy has clearly improved

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Table 1. Major World Health Organization subtypes of B-cell non-Hodgkin's lymphoma in the U. S. [4]

Type	Proportion of B-cell lymphomas
Aggressive	
Diffuse large B-cell lymphoma (DLBCL)	28%
Mantle cell lymphoma (MCL)	6%
Burkitt's lymphoma	1%
Indolent	
Chronic/small lymphocytic leukemia (CLL/SLL)	19%
Follicular lymphoma (FL)	12%
Marginal zone lymphoma (MZL)	4%
Waldenström's macroglobulinemia (WM)	1%
Other B-cell lymphoma	29%

the objective response rate (ORR) and CR rate and has been the main improvement in the treatment of B-cell NHL during the last three decades. Though it varies with B-cell NHL subtype, a significant number of patients relapse with no greatly defined standard therapies. For DLBCL, the combination of high-dose chemotherapy and stem cell transplantation is effective for relapsed NHL [7] but is clearly worse in patients with early relapse or primary failures. Patients with indolent NHL relapse even more frequently, with a subsequent shorter response to chemotherapy and often transformation over time. For mantle cell lymphoma (MCL), dose-intensive approaches have clearly resulted in significantly longer progession-free survival (PFS) intervals, although such approaches are not applicable routinely because the median age at diagnosis is in the mid- to late 60s. Patients with relapsed or refractory MCL are often resistant to chemotherapy and have a poor outcome with conventional therapies or even high-dose therapy with stem cell transplantation.

The need for additional treatment options for NHL has led to the development of novel therapies. The reversible proteasome inhibitor (PI) bortezomib (Velcade®; Millennium Pharmaceuticals, Inc., Cambridge, MA and Johnson & Johnson Pharmaceutical Research & Development, LLC, Titusville, NJ) is an orphan drug approved in the United States and European Union for the treatment of multiple myeloma, and in the United States for the treatment of MCL after one prior therapy.

This review summarizes the clinical evidence supporting PI combination therapy for B-cell NHL. Bortezomib is the only PI currently approved for widespread clinical use and thus is the focus of this review; however, where data are available, studies of other PIs for NHL are also discussed.

Biologic Basis of PI Combination Therapy

Mechanisms of Action

The proteasome is an intracellular, multiunit protease complex responsible for protein modification and degradation. Bortezomib binds to the β-subunits of the core of the proteasome, leading to disruption of intracellular protein degradation/recycling, and induces apoptosis (Fig. 1) [8]. A major mechanism of action for bortezomib is inactivation of nuclear factor (NF)-κB, via stabilization of the NF-κB inhibitor IκB [9–14], which contributes to apoptosis, cell cycle or growth arrest, and stress response. Bortezomib also enhances apoptosis by promoting the release of cytochrome C [15], stimulating generation of reactive oxygen species [16], upregulating the tumor suppressor protein p53 and the two inhibitors of cyclin-dependent kinase (CDK), p21 and p27 [11, 13, 15], and increasing expression of tumor necrosis factor–related apoptosis-inducing ligand (TRAIL) and TRAIL receptors [17]. Bortezomib may also have numerous effects on the B-cell lymphoma 2 (Bcl-2) family of proteins, including activation of proapoptotic Bcl-2 proteins [10, 15, 16, 18] and inhibition of antiapoptotic Bcl-2 proteins [9, 16, 18]. Proteasome inhibition with bortezomib also contributes to cell cycle or growth arrest by interrupting oscillation of cyclins A, B, D, and E, but its cytotoxic activity in NHL may be independent of cyclin D1 levels [19]. In addition to the effects of NF-κB, the stress response can be enhanced through the effects of proteasome inhibition on chemosensitization [20] and radiosensitization, particularly in cell lines that are dependent on NF-κB [21, 22]. Proteasome inhibition may also influence the microenvironment by inhibiting cytokines, growth factors, and adhesion molecules [23]. Additional mechanisms of action of proteasome inhibition are still being elucidated.

Other PIs are in development—but have not been approved for the treatment of NHL—such as the irreversible PIs carfilzomib [24] and marizomib (salinosporamide A, NPI-0052) [25] and the oral PIs ONX-0912 [26] and MLN9708 [27]. Bortezomib targets both the β_5 subunit of the proteasome, also known as the chymotrypsin-like (CT-L) active site, and the β_1 caspase-like sites, with less affinity for the β_2 trypsin-like sites [28]. Carfilzomib has mechanisms of action that are similar to those of bortezomib but, unlike bortezomib, carfilzomib binds proteasomes irreversibly and is selective for the CT-L active site [29]. Marizomib also binds proteasomes irreversibly [30], leading to activation of caspase-8 [31, 32] and potentiation of apoptosis [23], but it inhibits all three sites for up to 7 days and it may be a more potent inhibitor of NF-κB

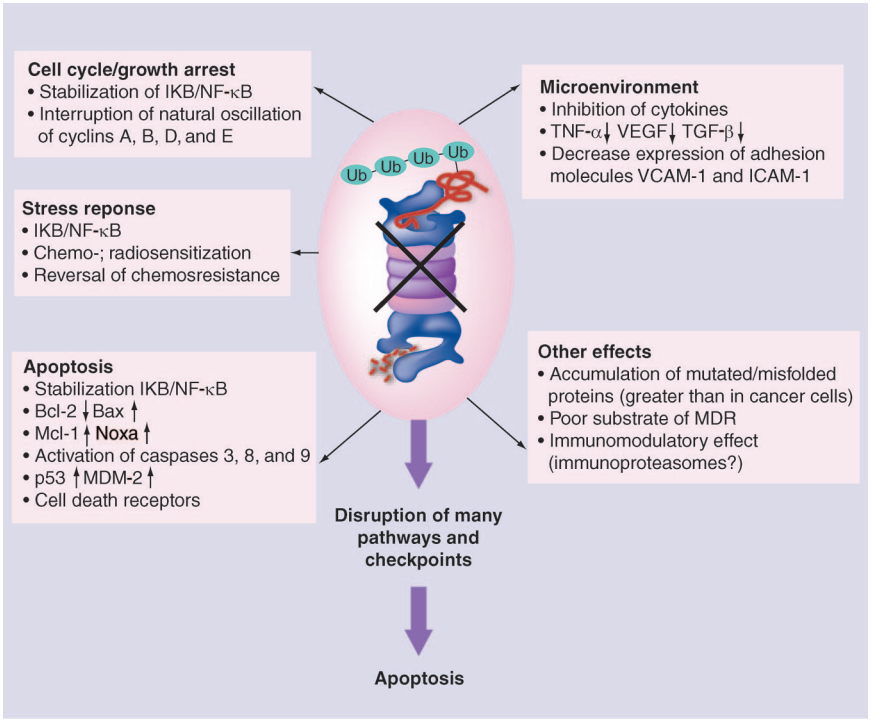

Figure 1. Bortezomib-mediated proteasome inhibition affects multiple signaling pathways.

Abbreviations: ICAM-1, intercellular adhesion molecule 1; IKB, NF-κB inhibitor; MDM-2, murine double minute 2; MDR, multidrug resistance; NF-κB, nuclear factor κB; TNF-α, tumor necrosis factor α; TGF-β, transforming growth factor β; VCAM-1, vascular cell adhesion molecule 1; VEGF, vascular endothelial growth factor.

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than bortezomib [28, 33]. However, it remains to be determined whether or not differences in binding kinetics influence clinical efficacy and safety [34]. ONX-0912 (previously PR-047) has a chemical structure similar to that of carfilzomib and is also selective for the CT-L active site [35] but is orally available. MLN9708 is a boron-containing PI that is also orally available and has better tissue distribution than bortezomib [27].

Rationale for PI Combination Therapy

To maximize antitumor activity, NHL is commonly treated with combination chemotherapy regimens, such as cyclophosphamide, vincristine, and prednisone (CVP), cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), and cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide (EPOCH) [36, 37]. Because they have a distinct mechanisms of action and do not share mechanisms of chemoresistance with conventional chemotherapy or biologicals (Fig. 2), PIs are a rational addition to these agents.

In preclinical studies of NHL, apoptosis was induced synergistically when a PI was combined with established chemotherapeutic agents [38, 39] or immunotherapy (rituximab) [40–42]. Synergy in B-cell NHL was also reported in preclinical studies that combined a PI with several classes of investigational agents, including Bcl-2 inhibitors [20, 43–51], CDK inhibitors (e.g., flavopiridol) [39, 52], mammalian target of rapamycin inhibitors (e.g., everolimus) [53, 54], histone deacetylase inhibitors (e.g., suberoylanilide hydroxamic acid, romidepsin, belinostat, panobinostat, cyproheptadine) [55–64], other PIs [65, 66], protein kinase B (Akt) inhibitors [67], protein kinase C inhibitors [68], an inhibitor of Janus kinase/signal transducer and activation of transcription pathways [69], heat shock protein inhibitors [70], immunomodulation with interferon-γ [71], radioimmunotherapy [72], and TRAIL [73–75].

MCL

Background

MCL is characterized not only by the reciprocal translocation t(11;14)(q13;q32), which typically results in overexpression of cyclin D1, a key regulator of the cell cycle, but also by a clear genetic heterogeneity among patients, which likely explains the spectrum of disease seen in the clinic (e.g., indolent versus aggressive course).

There is no consensus on the optimal regimen for the treatment of MCL, but patients commonly receive rituximab plus fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (R–hyper-CVAD) [76] or induction chemotherapy followed by autologous stem cell transplantation in the frontline setting [77]. Dose-intensive approaches have clearly resulted in longer PFS intervals, >5 years, which is much

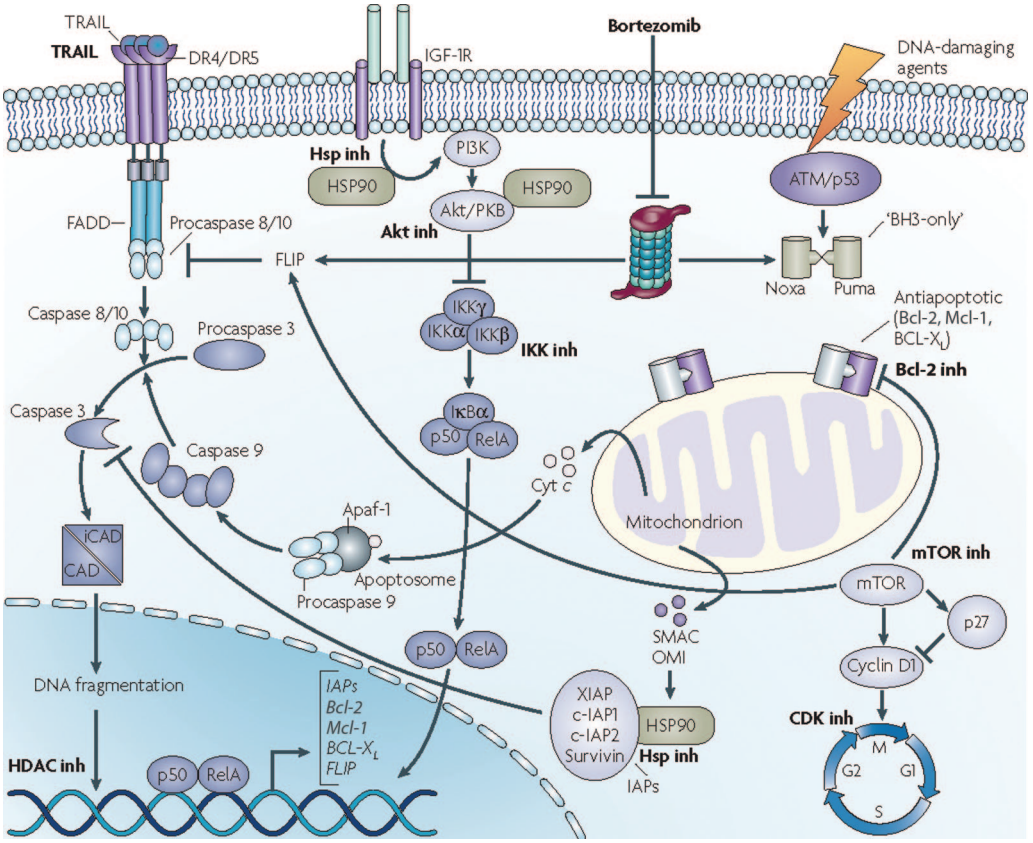

Figure 2. Schematic diagram of programmed cell death and altered pathways in mantle cell lymphoma.

Abbreviations: Bcl-2, B-cell lymphoma 2; CAD, caspase-activated DNase; CDK, cyclin-dependent kinase; Cyt, cytochrome; DR, death receptor; FADD, Fas-associated protein with death domain; FLIP, FLICE-inhibitory protein; HDAC, histone deacetylase; HSP90, heat shock protein 90; IAP, inhibitor of apoptosis protein; iCAD, inhibitor of caspase-activated DNase; IGF-1R, insulin-like growth factor 1 receptor; IKK, IκB kinase; inh, inhibitor; Mcl-1, myeloid leukemia cell differentiation protein 1; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase; PKB, protein kinase B; SMAC, second mitochondria-derived activator of caspase; TRAIL, tumor necrosis factor–related apoptosis-inducing ligand; XIAP, X-linked inhibitor of apoptosis protein.

From Jares P, Colomer D, Campo E. Genetic and molecular pathogenesis of mantle cell lymphoma: Perspectives for new targeted therapeutics. Nat Rev Cancer 2007;7:750–762 [163]. Reprinted by permission from Macmillan Publishers Ltd, © 2007.

better than the 18–22 months seen with rituximab plus CHOP (R-CHOP); however, patients still relapse and the impact on overall survival is debated. Furthermore, given that the median age at diagnosis is in the mid- to late 60s, non-intensive regimens and non-chemotherapy-based regimens are needed.

Although MCL is a largely incurable, aggressive disease with a poor overall prognosis, initial responses may exceed 50%, but most patients relapse and the median survival duration is approximately 3–4 years. The addition of rituximab to high-dose chemotherapy with [78] or without [76] stem cell transplantation lead to longer PFS times in untreated MCL patients. Thus, rituximab has become a standard component of MCL treatment regimens such as R-CHOP [79], R-bendamustine [80, 81], and infusional chemotherapy with R-EPOCH (R-CHOP plus etoposide) [82]. Consolidation with rituximab or radioimmunotherapy may also result in a longer response duration [83, 84]. Nonetheless, additional treatment options are needed to improve outcomes.

PI Monotherapy for MCL

Single-agent bortezomib was approved for the treatment of relapsed or refractory MCL on the basis of clinical evidence from several studies. The first evidence of clinical activity of bortezomib for NHL came from a phase I study of patients with refractory hematologic malignancies [85]. Two of 10 patients (20%) with NHL (1 of whom had MCL) had a partial response (PR) to bortezomib, 1.38 mg/m^2 twice weekly for 4 weeks in 6-week cycles.

Several subsequent phase I/II trials of single-agent bortezomib for NHL reported responses (comprising all cases of a CR, unconfirmed CR [CRu], or PR) in up to 50% of patients, including a CR or CRu in up to 21% of patients [86–91]. In the pivotal phase II PINNACLE trial [92], 155 patients with relapsed or refractory MCL received single-agent bortezomib, 1.3 mg/m^2 on days 1, 4, 8, and 11 of 21-day cycles, which is the standard dose and schedule for multiple myeloma. The response rate was 33% (CR and CRu rate, 8%), and after an extended follow-up of a median of 26.4 months, the median

duration of response was not reached among patients achieving a CR or CRu and was 9.2 months among all responders [93]. The median overall survival times were 23.5 months in all patients and 35.4 months in responding patients, with an estimated 61.1-month survival duration from diagnosis. Of note, responses were seen even in patients who had failed prior high-dose or dose-intensive therapy or had bulky disease. In another phase II study of 40 heavily pretreated patients with MCL who received bortezomib, 1.5 mg/m^2 on the standard schedule [94], the ORR was 45% (CR and CRu rate, 15%). The most common nonhematologic grade ≥3 adverse events (AEs) in these studies were fatigue, infection, neuropathy, and hyponatremia.

Analyses of biochemical markers in patients with MCL have confirmed that elevated NF-κB predicts better outcomes with bortezomib treatment, whereas bortezomib is not able to overcome the poor risk features of MCL associated with increased cellular proliferation as evidenced by elevated Ki-67 levels [95] or in patients with the blastoid morphologic variant.

A few studies have also reported the activity of investigational PIs as single-agent treatment for MCL. In a phase I study in 37 patients with multiple myeloma or relapsed NHL, carfilzomib (1.2–27 mg/m^2) was given on days 1, 2, 8, 9, 15, and 16 of 28-day cycles; only three patients received the minimum effective dose of 15 mg/m^2 or more, and none of those patients responded [96]. Dose-limiting toxicities included a hypoxic event and grade 4 thrombocytopenia. Another phase I study treated 29 patients with multiple myeloma or relapsed NHL with carfilzomib (1.2–20 mg/m^2) for five consecutive days in 14-day cycles [97]. The minimum effective dose was 11 mg/m^2, above which one of seven patients (14%) with NHL responded. Grade 3 (25%) or grade 4 (8%) AEs were primarily hematologic.

Marizomib (0.0125–0.55 mg/m^2) once weekly for 3 weeks in 4-week cycles was evaluated in a phase I study of 30 patients with solid tumors and five patients with NHL; however, the maximum-tolerated dose was not reached and there were no responses in NHL patients [98].

PI Combination Therapy for MCL

Numerous clinical studies have evaluated combinations of bortezomib with immunotherapy, chemotherapy, and immunochemotherapy in the treatment of MCL (Table 2).

Bortezomib and rituximab are both approved for the treatment of MCL and they have different safety profiles, supporting their combination in MCL treatment. When bortezomib was combined with rituximab in phase II studies [99–101], 29%–64% of patients with relapsed or refractory MCL responded to the combination; neurologic, gastrointestinal, and hematologic toxicities were common but generally reversible. Interim results of another phase II study suggested that the combination of bortezomib with the immunomodulator lenalidomide may also be active and may be well tolerated in the treatment of patients with relapsed or refractory MCL [102]. A phase I study that combined bortezomib with ibritumomab tiuxetan reported responses in 80% of patients with MCL [102a].

Bortezomib may potentiate fludarabine activity by inhibiting DNA repair and inducing apoptosis in Bcl-2–overexpressing cells. A phase I study of this combination [103] reported a PR in one patient with MCL, but two others with MCL discontinued treatment because of cytopenias. In another phase I study of heavily pretreated patients with MCL who received bortezomib, cytarabine, and dexamethasone [104], the ORR was 50%, but all patients had grade 3–4 hematologic toxicity. Among 26 patients with relapsed MCL who received bortezomib plus gemcitabine in a phase II study, the response rate was 60% and the median PFS interval was 11.4 months [105].

Several studies have reported activity with the combination of bortezomib with both immunotherapy (rituximab) and chemotherapy for relapsed or refractory MCL. Bortezomib, rituximab, fludarabine, and liposomal doxorubicin was found to result in an ORR of 73% in patients with relapsed or refractory MCL [106]. The combination of bortezomib, rituximab, and hyperfractionated cyclophosphamide was well tolerated in a phase I study of elderly patients (72–84 years of age) and resulted in an ORR of 75% [107]. Adding prednisone to this combination (i.e., substituting bortezomib for vincristine in the R-CVP regimen) was also active and well tolerated in another phase I study [108]. The combination of rituximab, bortezomib, and bendamustine in six 28-day cycles was evaluated in a phase II study of 30 patients, including seven with MCL [109]. Most patients (83%) had objective responses and the 2-year PFS rate was 47%. Within MCL patients, the overall response rate was 71%. The combination of bortezomib, rituximab, and dexamethasone (BORID) resulted in a 69% response rate in a phase II study of 16 patients with heavily pretreated MCL [110]. In another phase II study, adding doxorubicin and chlorambucil to BORID resulted in an 80% response rate [111].

Bortezomib has also been evaluated in combination with intense immunochemotherapy for untreated MCL. A phase I study that alternated hyper-CVAD with bortezomib plus high-dose rituximab, methotrexate, and cytarabine (R-M/A) reported objective responses in all 15 patients [112]. Adding bortezomib to both the R–hyper-CVAD and R-M/A cycles was well tolerated when the dose of bortezomib that was added to R-M/A was increased from 0.7 mg/m^2 to 1.0–1.3 mg/m^2 [113]. Toxicities with the addition of bortezomib were similar to the toxicities that would be expected without bortezomib. A phase II study that added bortezomib and rituximab to modified hyper-CVAD resulted in a response rate of 90% [114]. In that study, sensory neuropathy required the doses of bortezomib and vincristine to be decreased from 1.5 mg/m^2 and 2 mg, respectively, to 1.3 mg/m^2 and 2 mg, respectively, and then to 1.3 mg/m^2 and 1 mg, respectively, in subsequent cohorts to improve tolerability [114]. On the basis of these studies, the standard bortezomib dose of 1.3 mg/m^2 appears to be appropriate for further evaluation in combination with rituximab and hyper-CVAD regimens. Several studies are under way to evaluate the activity and tolerability of bortezomib with these and other widely used treatments for untreated MCL. Other studies are evaluating the use of bortezomib maintenance or consolidation therapy after remission with bortezomib plus R-CHOP, but data from those studies are not yet available.

Table 2. Proteasome inhibitor combination regimens evaluated in the treatment of mantle cell lymphoma

Proteasome inhibitor plus . . .	Evidence
Published data on relapsed or refractory mantle cell lymphoma	
Immunotherapy	29%–64% response rate in phase II studies of bortezomib plus rituximab [99–101]
	Good tolerability in a phase I study of bortezomib plus lenalidomide [102]
	80% response in a phase I study of bortezomib plus ibritumomab tiuxetan [102a]
Chemotherapy	Response in one patient in a phase I study of bortezomib plus fludarabine [103]
	50% response rate in a phase I study of bortezomib, cytarabine, and dexamethasone [104]
	60% response rate in a phase II study of bortezomib plus gemcitabine [105]
Immunochemotherapy	73% response rate in a phase II study of bortezomib, rituximab, fludarabine, and liposomal doxorubicin [106]
	75% response rate in a phase I study of bortezomib, rituximab, and hyperfractionated cyclophosphamide in elderly patients [107]
	Activity and good tolerability in a phase I study of bortezomib, rituximab, cyclophosphamide, and prednisone [108]
	71% response rate in a phase II study of bortezomib, rituximab, and bendamustine [109]
	69% response rate in a phase II study of bortezomib, rituximab, and dexamethasone (BORID) [110]
Published data on untreated mantle cell lymphoma	
Immunochemotherapy	80% response rate in a phase II study of bortezomib, rituximab, dexamethasone, adriblastine, and chlorambucil (RiPAD+C) [111]
	100% response rate in a phase I study of R–hyper-CVAD alternating with bortezomib plus R-M/A [112]
	Good tolerability when bortezomib (up to 1.3 mg/m^2) was added to both R–hyper-CVAD and R-M/A in a phase I study [113]
	90% response rate but high toxicity in a phase II study of bortezomib plus modified R–hyper-CVAD when bortezomib doses were $>$1.3 mg/m^2 [114]
Investigational Agents	25% response rate in a phase I study of bortezomib plus obatoclax [115]

Abbreviations: R–hyper-CVAD, rituximab plus fractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; R-M/A, high-dose rituximab, methotrexate, and cytarabine.

Obatoclax is a small-molecule inhibitor of all members of the Bcl-2 family of prosurvival proteins. Bortezomib increases levels of Mcl-1, which is a Bcl-2 family member, and the combination of bortezomib and obatoclax was synergistic in a preclinical study [45]. A dose-finding phase I study of bortezomib plus obatoclax reported an ORR of 33% in patients with relapsed or refractory MCL [115]. Many other clinical studies are under way to evaluate the addition of bortezomib or an investigational PI to conventional chemotherapy or investigational agents for MCL (supplemental online Table A). Results of those studies are eagerly awaited.

Follicular Lymphoma

Background

Follicular lymphoma (FL) is a common type of indolent NHL that is associated with translocation of chromosomes 14 and 18, resulting in constitutive activation of the *BCL2* oncogene and inhibition of apoptosis [116]. Because FL is also associated with constitutive activation of NF-κB [117], bortezomib is a rational treatment choice on the basis of its inhibition of NF-κB. The indolent types of B-cell NHL, including FL, are not considered curable. The addition of immunotherapy to conventional chemotherapy has improved overall survival significantly in FL [116]. The addition of maintenance therapy has continued to extend PFS; nevertheless, a large number of patients still relapse, illustrating the need for novel therapies in this setting [83].

Single-Agent PI Therapy for FL

Single-agent PI treatment has only modest activity for FL. In a phase II study, the standard bortezomib dose (1.3 mg/m^2 twice weekly) resulted in objective responses in only six of 36 patients (17%) with relapsed or refractory FL [118]. A randomized, phase II study that compared two dosing schedules of

single-agent bortezomib for FL reported response rates of 30% (15 of 50 patients) with twice-weekly dosing and 22% (eight of 37 patients) with once-weekly dosing [119]. Two other phase II studies demonstrated higher response rates of 55%–77% following twice-weekly bortezomib, 1.3–1.5 mg/m^2, but those studies each included only nine to 11 evaluable patients [87, 99], and dose-limiting neurologic toxicity was seen at the higher dose [99]. It may be necessary to continue treatment for FL longer before a response to PI therapy is seen. A phase II study in patients with various types of relapsed or refractory NHL reported that 50% of patients with FL responded to single-agent bortezomib after a median of 11–12 weeks, compared with a median time to treatment response of only 4 weeks for MCL [120].

PI Combination Therapy for FL

Table 3 summarizes published results of PI combinations for FL. Adding bortezomib to rituximab may improve treatment outcomes in FL patients. Among patients with relapsed FL, a phase II study of once-weekly or twice-weekly bortezomib dosing in combination with rituximab reported response rates of 43% and 49%, respectively [121]. In another randomized, phase II study of once-weekly or twice-weekly bortezomib combined with rituximab, the response rate was 53% among patients with recurrent FL, but neurologic, gastrointestinal, and hematologic toxicities were common [100]. Data from a randomized, phase III study of 676 patients with relapsed FL suggested that the combination of bortezomib and rituximab was significantly more effective than rituximab alone [122] in terms of the response rate (63% versus 49%; $p < .001$) and median PFS interval (389 days versus 334 days; $p = .039$), and the median overall survival time was not reached in either group after a median follow-up of 33.9 months. Although the absolute 1.8-month longer PFS duration overall did not achieve the prespecified goal of a 33% improvement, there were statistically significant improvements in patients with high-risk FL by Follicular Lymphoma International Prognostic Index score (11.4 months versus 7.9 months; $p = .013$) or by tumor burden (11.3 months versus 8.4 months; $p = .019$). Further analysis of the data identified individual biomarkers and pairs of biomarkers that may aid identification of subgroups deriving maximal benefit from the addition of bortezomib to rituximab therapy [123]. An ongoing, phase II study is comparing the activity of bortezomib and fludarabine with rituximab and fludarabine among patients with FL who have received previous rituximab treatment [124].

An emerging treatment strategy for NHL involves administration of radioimmunotherapy, and the addition of a PI may improve the response to these treatments. Ibritumomab tiuxetan combines a monoclonal antibody with a linker-chelator that has high affinity for radioactive yttrium-90 or indium-111. Like rituximab, ibritumomab binds to the CD20 antigen on the surface of normal and malignant B cells, allowing radiation from the attached isotope to kill the B cells, and ibritumomab itself may also trigger cell death. Response rates of 40%–89% were reported in phase II studies that combined bortezomib and ibritumomab tiuxetan [102a, 125].

Several studies have reported activity for the combination of bortezomib with immunochemotherapy. A response rate of 58% (seven of 12 patients) was reported among patients with relapsed or refractory FL who received bortezomib, rituximab, and fludarabine in a phase I dose-finding study [126]. Bortezomib, rituximab, and bendamustine was associated with excellent response rates of 88%–100% in phase II studies of 49 patients and 11 patients, respectively, with relapsed or refractory FL [127, 128]. In a phase II, nonrandomized, two-arm study of 55 patients with relapsed or refractory FL, bortezomib, rituximab, cyclophosphamide, and prednisone led to a 78% response rate, and the addition of doxorubicin resulted in a 75% response rate [129].

Less is known about the activity of PI combination therapy in patients with previously untreated FL. In this patient population, the addition of bortezomib to R-CVP was effective and very well tolerated in a phase II study [130]. That study and one of the studies of relapsed or refractory FL [128], which were published concurrently, did not meet their primary endpoint of higher CR rates than in historical controls. An accompanying editorial examined the limitations of these studies, questioned whether or not selected groups of patients should be evaluated for benefits from bortezomib-containing combination immunochemotherapy for FL and highlighted the importance of randomized data in clinical decision making [131].

In another phase II study, the addition of bortezomib to rituximab, cyclophosphamide, and dexamethasone also had an acceptable safety profile in elderly patients with untreated, predominantly indolent subtypes of NHL, and the combination was associated with a response rate of 90% [132].

Consolidation with PI therapy may also be beneficial for patients with indolent NHL, but this has not been studied extensively. Consolidation therapy for FL with bortezomib, 1.6 mg/m^2 once weekly for 3 weeks in 4-week cycles, has been reported after combination treatment with bortezomib and ibritumomab tiuxetan [125].

DLBCL

Background

DLBCL is the most common subtype of NHL (almost one third of patients [4]) and is typically treated with rituximab plus anthracycline-based chemotherapy (R-CHOP or R-EPOCH). The addition of rituximab has dramatically improved outcomes of DLBCL, though patients who fail R-CHOP chemotherapy usually do poorly with salvage chemotherapy, especially if they relapse within 12 months. Eighty percent of relapses in DLBCL after R-CHOP occur within the first 2 years, representing therefore a difficult challenge in practice. Multiple prognostic factors have been identified, including IPI, proliferation index (high Ki-67), and molecular subtype (activated B-cell origin [ABC] and germinal center B cell-like [GCB]) [133, 134]. Though the outcomes of both GCB and ABC subtypes have been improved by chemoimmunotherapy [135], the ABC subtype continues to have a significantly worse outcome than GCB [136, 137]. A better understanding of the biology of DLBCL has shown that NF-κB and activation of the B-cell receptor pathway are critical in the ABC subtype. Thus,

Table 3. Proteasome inhibitor combination regimens evaluated in the treatment of follicular lymphoma

Proteasome inhibitor plus . . .	Evidence
Published data on relapsed or refractory follicular lymphoma	
Immunotherapy	43%–53% response rate in phase II studies of once- and twice-weekly dosing of bortezomib with rituximab, respectively [100, 121]
	63% and 49% response rates in a phase III comparison of bortezomib plus rituximab versus rituximab alone, respectively [122]
Radioimmunotherapy	40%–89% response rate in phase I studies of bortezomib plus ibritumomab tiuxetan [102a, 125]
Immunochemotherapy	58% response rate in a phase I study of bortezomib, rituximab, and fludarabine [126]
	88%–100% response rate in phase II studies of bortezomib, rituximab, and bendamustine [127, 128]
	77% response rate in a phase II study of bortezomib, rituximab, cyclophosphamide, and prednisone, with and without doxorubicin [129]
Published data on untreated follicular lymphoma	
Immunochemotherapy	83% response rate and good tolerability in a phase II study of bortezomib plus R-CVP [130]
	90% response rate in a phase II study of bortezomib, rituximab, cyclophosphamide, and dexamethasone [132]

Abbreviation: R-CVP, rituximab plus cyclophosphamide, vincristine, and prednisone.

investigators are looking at strategies to improve outcomes of DLBCL, especially by combining novel therapies with R-CHOP, in the hope of decreasing the incidence of early failures.

Single-Agent PI Therapy for DLBCL

Preclinical data and the understanding of the biology of DLBCL provided a rationale for proteasome inhibition in DLBCL [138]. Despite its inhibition of the NF-κB pathway, single-agent PI therapy appears to have little clinical utility in this patient population. In a phase I/II study of patients with relapsed or refractory DLBCL, bortezomib monotherapy had minimal activity (1 PR) [139]. To our knowledge, single-agent studies of carfilzomib, marizomib, or ONX-0912 in patients with DLBCL have not been published.

PI Combination Therapy for DLBCL

Table 4 summarizes published results of PI combinations for DLBCL. In patients with untreated DLBCL, the addition of bortezomib to CHOP resulted in an ORR of 89% [140], whereas in another phase I study that included 40 patients with untreated DLBCL, the addition of bortezomib to R-CHOP resulted in objective response in all patients with DLBCL, including CRs in 86% of patients [141]. In a randomized, phase II study of 49 patients with aggressive or indolent NHL (including nine with DLBCL and 11 with FL, among others), bortezomib—either once-weekly (1.3 mg/m^2 or 1.6 mg/m^2) or twice-weekly (1.0 mg/m^2 or 1.3 mg/m^2)—was administered with R-CHOP for up to six cycles [142]. Most patients (92%) responded to the combination, including CRs in 83% of patients with aggressive NHL, but severe neuropathy was seen among patients who received the higher doses of bortezomib.

A study of bortezomib combined with EPOCH in patients with relapsed or refractory DLBCL showed modest activity overall [139]. Subtype analysis in DLBCL patients may help to identify appropriate candidates for combination treatment with a PI. Data suggest that the combination of bortezomib with R-EPOCH shows a dramatic response in the ABC subtype and only 13% in the GCB subtype [143]. A large, randomized study (PYRAMID) is under way to evaluate R-CHOP with and without bortezomib in patients with newly diagnosed DLBCL, and all patients will be screened to identify only those patients with non-GCB subtypes for treatment [144]. The results of that study and other ongoing studies of PI combinations should aid the understanding of the role of these combinations for DLBCL.

Other Types of NHL

Many of the early studies that predominantly evaluated patients with MCL, FL, or DLBCL included a few patients with other types of NHL as well, but the sample sizes generally were too small to draw conclusions about the activity of PI therapy for these NHL subtypes. Activity with PI combination regimens was observed in patients with marginal zone lymphoma or Waldenström's macroglobulinemia (WM). Among patients with WM, the overall response rates were 96% with BORID [145] and 90% with bortezomib plus rituximab [146], and the combination of bortezomib and rituximab plus dexamethasone may be particularly effective for WM, with greater activity than in other types of NHL [100]. Bortezomib combinations

Table 4. Proteasome inhibitor combination regimens evaluated in the treatment of DLBCL

Proteasome inhibitor plus . . .	Evidence
Published data on relapsed or refractory DLBCL	
Chemotherapy	25% response rate in a phase I/II study of bortezomib plus EPOCH [139]
Published data on untreated DLBCL	
Chemotherapy	89% response rate in phase I study of bortezomib plus CHOP [140]
Immunochemotherapy	100% response rate in a phase I study of bortezomib plus R-CHOP [141]
	92% response rate in a phase II study of bortezomib plus R-CHOP[142]

Abbreviations: CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; DLBCL, diffuse large B-cell lymphoma; EPOCH, cyclophosphamide, doxorubicin, vincristine, prednisone, and etoposide; R-CHOP, rituximab plus CHOP.

appear to have limited activity for chronic or small lymphocytic leukemia; preclinical data suggest that marizomib may be even more effective for this tumor type [25]. Among patients with marginal zone lymphoma, twice-weekly bortezomib plus once-weekly rituximab was associated with response in approximately half of the patients [121].

Bortezomib also induces apoptosis in peripheral T-cell lymphoma (PTCL) cells [13], and phase I studies reported activity in PTCL patients when bortezomib was combined with pegylated liposomal doxorubicin [86], CHOP [147], gemcitabine [148], and both liposomal doxorubicin and gemcitabine [149]. A phase II study of bortezomib with ACVBP resulted in an ORR of 45% in patients with PTCL, but the investigators reported that this was similar to previously reported rates with ACVBP alone [150]. Bortezomib also has single-agent activity in patients with cutaneous T-cell lymphoma (CTCL) [151] and preclinical data suggest that it is synergistic with pralatrexate [152] for CTCL.

Rituximab has been shown to improve outcomes in post-transplant lymphoproliferative disorder caused by Epstein-Barr virus (EBV) [153], and bortezomib has shown activity in EBV-transformed B cells [154]. The combination of bortezomib and rituximab is being evaluated for this condition.

Immunoproteasome Inhibitors

The immunoproteasome is a variant found predominantly in cells of hematopoietic origin. Thus, selectively targeting the immunoproteasome may improve the ratio between antitumor activity and side effects [155]. Immunoproteasome inhibition is being evaluated for multiple myeloma and NHL [26, 156]. This approach is still in the early stages of development and clinical studies of combination treatment with immunoproteasome inhibitors for NHL are not yet available.

Tolerability

The tolerability of bortezomib in combination with other agents (supplemental online Table A) is generally consistent with the most common toxicities of bortezomib monotherapy for NHL (neuropathy, neutropenia, thrombocytopenia, gastrointestinal events, and fatigue) [5, 157, 158] and the toxicities commonly associated with the other agents that are combined with bortezomib. Some studies have suggested that weekly dosing of bortezomib (instead of twice weekly) in combination regimens may improve tolerability [108, 121, 159, 160].

Peripheral sensory neuropathy is a known toxicity of bortezomib, but it is usually reversible [161]. The prescribing information for bortezomib includes detailed instructions about dose reduction, withholding, and discontinuation in patients with moderate-to-severe peripheral neuropathy and/or neuropathic pain. In addition, a recent phase III noninferiority trial comparing i.v. with s.c. administration of bortezomib in patients with multiple myeloma revealed similar efficacies with significantly lower rates of grade $\geq$3 peripheral neuropathy (16% versus 6%, respectively) and all grade peripheral neuropathy (53% versus 38%, respectively) [162].

Because the other PIs have not been studied as extensively as bortezomib, and because they are not yet available for widespread clinical use, their safety profiles are not as well known. However, as a result of their different chemical properties, it is likely that carfilzomib, marizomib, ONX-0912, and other investigational PIs will have different efficacy and safety profiles from those of bortezomib [34].

Dosing

The recommended dose of bortezomib for relapsed MCL is in 3-week cycles, with an i.v. bolus of bortezomib administered over 3–5 seconds on days 1, 4, 8, and 11 (i.e., twice weekly). Additionally, the s.c. formulation of bortezomib was recently approved with the same dosing guidelines as the i.v. formulation. After the first eight doses, extended therapy can be administered in 5-week cycles on days 1, 8, 15, and 22 (i.e., once weekly). Many different once-weekly and twice-weekly dosing schedules have been evaluated in clinical studies of bortezomib for NHL, as discussed in the sections above. Randomized comparisons generally reported similar efficacies for the twice-weekly schedule and the once-weekly schedule [100, 108, 119, 121, 159, 160]. But, as noted above, weekly dosing of bortezomib in combination regimens led to better tolerability than with the twice-weekly dosing schedule in some of those studies [108, 121, 159, 160]. In our practice, we typically administer bortezomib as a single agent, either i.v. or s.c., using the twice-weekly approved dosing schedule.

Conclusions

Single-agent bortezomib is approved for use for MCL in many countries and has been shown to have activity for other forms of NHL as well. Early clinical studies of other PIs such as carfilzomib and marizomib have not yet provided compelling support for their use as single agents for NHL, but more mature data are needed before their single-agent safety and activity can be determined. The mechanisms of action of PIs are distinct from those of other treatments for NHL, and preclinical evidence suggests that they can be additive or synergistic with many standard treatments for NHL, including biologicals, with an acceptable safety profile.

Early clinical evidence supports the activity of bortezomib combinations for B-cell NHL, particularly when combined with standard treatments such as rituximab and R-CHOP. Controlled clinical trials and long-term data are anticipated to confirm the safety and efficacy of these combinations and PI combinations with other standard treatments for NHL. Combinations of PIs with other novel or targeted agents also have demonstrated additive or synergistic activity in early studies.

Numerous single-arm and controlled studies are under way (supplemental online Table A) that are likely to provide additional evidence to support combinations of bortezomib or other PIs with both standard and emerging treatments for NHL. The results of those studies should serve to guide future research toward finding the best combination therapies for each of these B-cell lymphomas and ultimately extend lives and improve the quality of life of patients.

Recommendations

1. MCL. Bortezomib is the only single agent approved by the U.S. Food and Drug Administration for the treatment of relapsed or refractory MCL, and it remains part of the standard of care in patients with MCL in first or subsequent relapse. Multiple ongoing studies have already shown the feasibility of combining bortezomib with conventional regimens for MCL (including R–hyper-CVAD), and ongoing studies will help refine how to best integrate bortezomib into the management of MCL patients, in both the frontline and salvage settings.

2. FL. Recent data exploring the use of bortezomib as a single agent or in combination therapy with rituximab for FL does not support a change in clinical practice. However, studies of bendamustine-based combinations are still ongoing, with promising preliminary results (a high CR rate).

3. DLBCL. Recent research suggests that preferential inhibition of the NF-κB pathway by bortezomib explains the higher activity seen in combination with immunochemotherapy in patients with the ABC subtype of DLBCL (which is more dependent on NF-κB than the GCB subtype of DLBCL). This might provide a venue for improvement in the outcomes of patients with ABC DLBCL (still worse than those of patients with the GCB subtype treated with R-CHOP), which is currently being tested in a large randomized study (PYRAMID trial).

4. WM. The combination of bortezomib plus rituximab is highly active in patients with WM. This combination should be considered in clinical practice in the relapsed or refractory setting and frontline setting, as shown, for example, in a study that looked at maintenance with bortezomib, dexamethasone, and rituximab every 3 months after induction [145].

5. An s.c. formulation of bortezomib was recently approved with the same dosing guidelines as the i.v. formulation to facilitate administration.

6. Given the number of ongoing trials and options currently available, we highly encourage ***The Oncologist*** readership to consider enrollment in clinical trials examining the role of PIs across the spectrum of NHL subtypes to continue to improve patient outcomes.

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