Bortezomib combined with rituximab and dexamethasone is an active regimen for patients with relapsed and chemotherapy-refractory mantle cell lymphoma

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ABSTRACT

Background
Bortezomib belongs to a new class of anti-cancer agents, the proteasome inhibitors, and has documented activity in multiple myeloma and mantle cell lymphoma. Preclinical studies suggest that bortezomib has synergistic activity with rituximab, which provides a rationale for the exploration of treatment combinations.

Design and Methods
The activity and safety of bortezomib in combination with rituximab and dexamethasone were investigated in patients with relapsed or chemotherapy-refractory mantle cell lymphoma. A treatment cycle consisted of bortezomib (1.3 mg/m^2 on days 1, 4, 8, and 11; six 21-day cycles), rituximab (375 mg/m^2, day 1) and dexamethasone (40 mg orally, days 1 to 4). Responding patients received four consolidating doses of rituximab. Sixteen patients with progressive mantle cell lymphoma after a median of three prior lines of therapy were enrolled.

Results
The overall response rate was 81.3% (13 patients), with seven patients achieving a complete response (43.8%). Six of these patients were also negative for disease activity by positron emission tomography scanning. The median progression-free survival and overall survival were 12.1 and 38.6 months, respectively. In patients achieving a complete response, the median progression-free survival and overall survival have not yet been reached. Adverse events (greater than grade II) included thrombocytopenia (37.5%), fatigue (18.8%) and peripheral neuropathy (12.5%). Two patients discontinued bortezomib because of grade III neuropathy.

Conclusions
Bortezomib combined with rituximab and dexamethasone has promising activity and manageable toxicity in patients with heavily pretreated mantle cell lymphoma. Achievement of complete response emerged as an important factor for sustained disease control.
This trial was registered at *www.clinicaltrials.gov as #NCT00261612*.

Key words: bortezomib, rituximab, mantle cell lymphoma, relapse.

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Introduction

Mantle cell lymphoma (MCL) is an aggressive and difficult to treat subtype of B-cell non-Hodgkin's lymphoma which accounts for approximately 6% of all cases of non-Hodgkin's lymphoma.[1] Historically, MCL had a poor prognosis with a median survival of about 3 years when treated with conventional dose chemotherapy. The administration of the anti-CD20 monoclonal antibody rituximab in combination with conventional chemotherapy was shown to increase responses but it had only a minor impact on survival.[2,3]

Intensified treatment approaches including the hyper-CVAD regimen and high-dose chemotherapy with autologous stem cell support result in an improvement of progression-free and overall survival.[4-6] However, this therapeutic approach is not feasible for the large proportion of patients with MCL presenting at an advanced age or with co-morbidities. Moreover, after first relapse, the prognosis of MCL patients is considered to be very poor with patients having a median survival of approximately 1 to 2 years,[7] which underscores the urgent need for novel therapeutic interventions.

In recent years, inhibition of the proteasome by its specific inhibitor bortezomib has become an emerging antitumor strategy approved by the US Food and Drug Administration first for relapsed multiple myeloma and later for the treatment of relapsed MCL. The proteasome is responsible for the degradation of intracellular proteins, including several proteins involved in cell cycle control and the regulation of apoptosis.[8] Preclinical studies have shown that the proteasome inhibitor bortezomib decreases proliferation, induces apoptosis, enhances the activity of chemotherapy and radiation, and reverses chemoresistance in a variety of *in vitro* and *in vivo* models of hematologic and solid malignancies.[9,10] Proteasome inhibition with bortezomib has specifically promoted apoptosis of tumor cells through the stabilization of p53, p21, p27, Bax, and IκB α, resulting in nuclear factor κB (NF-κB) inhibition. There is strong experimental evidence that the transcription factor NF-κB is active in promoting chemoresistance, cytokine-mediated proliferation, tumor metastasis, and angiogenesis. By blocking proteasomal degradation of IκB, a negative regulator of NF-κB, bortezomib diminishes NF-κB activity, thereby enhancing treatment responses and reversing chemoresistance. For example, bortezomib was approximately two times more potent in inhibiting the growth of chemoresistant multiple myeloma cells compared with chemosensitive cells, in direct correlation with NF-κB activity.[11]

NF-κB is constitutively activated in MCL cell lines and in biopsy specimens from patients with MCL.[12] Bortezomib produced cell cycle arrest in G1 of the MCL cells and induced apoptosis. Cell death was associated with down-regulation of the anti-apoptotic factors Bcl-xL and bfl/A1 and activation of caspase-3, leading to mitochondrial cytochrome c release. Cell cycle arrest was associated with reduced expression of cyclin D1, which is a molecular genetic marker of MCL. These preclinical data provided the basis for the evaluation of bortezomib in phase II clinical trials among patients with relapsed MCL. Five phase II trials have now documented the activity of bortezomib, as a single agent, in relapsed MCL, with response rates ranging between 30% and 50%: some patients had a complete response.[13-18]

Rituximab has been tested as a single agent for the treatment of previously untreated and relapsed MCL and was shown to induce partial remissions in 27% to 38% of patients.[19-21] In various preclinical studies, evidence was obtained for additive and possibly synergistic tumor cell killing of various combinations of bortezomib, dexamethasone, and rituximab.[22-24] This provided the basis for our investigation to explore bortezomib, rituximab, and dexamethasone (BORID) in patients with relapsed and chemotherapy-refractory MCL.

Design and Methods

Selection of patients

Patients were required to have histologically confirmed, CD20-positive MCL according to the WHO/Revised European-American Lymphoma classification. Patients had to meet the following eligibility requirements for enrollment into the study: have measurable disease (defined as > 1cm by computed tomography scanning); have received at least one prior line of conventional cytotoxic therapy including CHOP (or a CHOP-like regimen); be 19 years of age or older; have a life expectancy of at least 3 months; and have a Karnofsky performance status of more than 60%. Patients were eligible only if they had grade 1 or less sensory neuropathy at baseline. Additional inclusion criteria included a hemoglobin concentration of more than 8.0 g/dL (without transfusion support within 7 days prior to the assessment), a neutrophil count more than $1.0x10^9$/L (>$0.5x10^9$/L in the case of bone marrow involvement), a platelet count more than $50x10^9$/L (without transfusion support within 7 days prior to the assessment), and a creatinine clearance of more than 30 mL/min.

Patients were excluded if signs of severe congestive heart failure (New York Heart Failure Guidelines Class III/IV) or active infection were present. Patients were also excluded if there was evidence that the lymphoma had involved the central nervous system, if they were positive for human immunodeficiency virus, had any psychiatric illness that could limit compliance with study requirements, had another primary malignancy (other than squamous or basal cell skin cancer or *in situ* cervical cancer) diagnosed within 5 years, or were pregnant or breast feeding.

Patients were required to give written informed consent.

Study design

This was a single-center, phase II study of bortezomib combined with rituximab and dexamethasone in patients with relapsed/refractory MCL. The primary endpoint was efficacy of the regimen defined by the response rate. Secondary objectives were tolerability and efficacy defined as progression-free survival and overall survival. The study was approved by the institutional review board of the Medical University of Vienna. A summary of this study was registered at *www.clinicaltrials.gov as #NCT00261612*.

Treatment

Bortezomib was administered at a dose of 1.3 mg/m^2 as an intravenous bolus push over 3 to 5 seconds twice weekly for 2 weeks (days 1, 4, 8 and 11) followed by a 10-day rest period (days 12–21) of a 3-week cycle. Doses were repeated if the absolute neutrophil count was $1.0x10^9$/L or higher and the platelet count was $30x10^9$/L or higher. The protocol included prophylactic intravenous fluids in the form of 500 to 1000 mL of saline, administered before each dose of bortezomib. Rituximab was administered at the dose of 375 mg/m^2 on day 1 of each cycle with a standardized infusion protocol. Premedication included acetaminophen and

diphenhydramine. Pulsed dexamethasone was given orally at a daily dose of 40 mg on days 1–4 of each treatment cycle.

Treatment was repeated every 3 weeks and administered for six cycles unless there was progressive disease, unacceptable toxicity, or the patient wished to discontinue therapy. Support with granulocyte colony-stimulating factor and/or erythropoietin was permitted. In responding patients, rituximab was given as consolidation therapy at a dose of 375 mg/m^2 every 8 weeks for four doses.

Treatment with bortezomib was withheld in patients with grade 3 or higher non-hematologic toxicity or grade 4 hematologic toxicity until the side effects diminished to at least grade 1. After resolution, treatment was resumed at a lower dose (stepwise dose reduction from 1.3 to 1.0 or 0.7 mg/m^2).

Evaluation of response and toxicity

Baseline evaluations included clinical examination, bone marrow aspirate and biopsy, and computed tomography of the chest, abdomen, and pelvis, and head and neck, if indicated. Patients were restaged every three cycles and then every 3 months afterwards until progression. Positron emission tomography was repeated in patients with positive nuclear imaging studies at baseline.

Response criteria for patients enrolled into the study were defined as previously described.[25] All responses were classified as either complete remission, partial remission, stable disease or progressive disease. Patients with measurable gastrointestinal involvement by endoscopy were considered to have a complete remission if all lesions were resolved and multiple random biopsies were negative.

Progression-free survival was calculated from the date of starting BORID treatment until the date of progression or death. Overall survival was calculated from the time of initiation of therapy to death from any cause or last follow-up. Survival curves were plotted using the Kaplan-Meier method.

Toxicity was recorded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0.

Results

Patients

Sixteen patients (13 males, 3 females) with relapsed/refractory MCL were enrolled in this phase II study. Patient had received a median of three prior lines of therapy (range, 1–6) including CHOP-polychemotherapy (100%), rituximab (88%), high-dose chemotherapy followed by autologous stem cell transplantation (31%), a fludarabine-containing regimen (31%), and a thalidomide-combination (50%; combined with either rituximab[26] or rituximab plus chemotherapy). Three patients were refractory to their last line of therapy preceding the study treatment. Additional patients' characteristics and disease-related features are summarized in Table 1. According to International Prognostic Index (IPI) risk group,[27] ten patients (62.5%) were at high-risk. Based on the MCL International Prognostic Index (MIPI),[28] 14 patients (87.5%) were at intermediate or high risk.

Response and survival

A median of 4.4 treatment cycles (range, 2–6) was administered. Applying standard response criteria,[25] we observed an objective response to the BORID treatment combination in 13 of the 16 patients (overall response rate of 81.3%) including complete remission in seven patients (43.8%) and partial remission in six patients (37.5%). Fluorodeoxyglucose positron emission tomography scanning was performed in six of the seven patients who achieved a complete remission and confirmed the remission status by absence of metabolic activity in all six patients. The Ki-67 growth fraction was assessed in only 13 patients, but it appeared that achievement of complete remission was independent of proliferative activity (4 complete remissions among 9 patients with Ki-67 ≥30%; 1 complete remission among 4 patients with Ki-67 <30%). The patients' characteristics, prior therapies, and responses are detailed in Table 2.

The median progression-free survival and overall survival were 12.1 months and 38.7 months, respectively (Figure 1). The association between quality of response and progression-free survival is illustrated in Figure 2. Patients who achieved a complete remission had significantly longer progression-free survival (with 5 patients still being in complete remission beyond 48 months) compared to patients who only reached a partial remission. The median progression-free survival and overall survival of patients who achieved a complete remission have not yet been reached, which is significantly different from the outcome in patients reaching only a partial remission (Figure 3).

Toxicity

A summary of adverse events is given in Table 2. Most of the toxicities were grades 1 and 2. Among hematologic toxicities, the most frequent adverse event was thrombo-

Table 1. Patients' characteristics at study entry.

Characteristic	
Number of patients	16
Age (median/range; years)	69 (42-78)
Sex	
Male	13 (81.3%)
Female	3 (18.7%)
Histology of MCL	
Common type	13 (81.3%)
Blastic	3 (18.7%)
ECOG performance status	
0 - 1	9 (56.25%)
≥ 2	7 (43.75%)
Stage	
III + IV	16 (100%)
International Prognostic Index	
Low risk	0
Low intermediate risk	2 (12.5%)
High intermediate risk	4 (25%)
High risk	10 (62.5%)
MCL International Prognostic Index	
Low risk	2 (12.5%)
Intermediate risk	5 (31.2%)
High risk	9 (56.3%)
Number of prior treatment regimens, median (range)	3 (1-6)
Laboratory abnormalities	
Serum LDH elevated (> 240 U/L)	8 (50%)
Ki67 ≥30%	9 of 13 patients (69 %)
Time from diagnosis to first dose of BORID (months), median (range)	43.4 (9.8-98.8)

LDH: lactate dehydrogenase; ECOG: Eastern Cooperative Group.

Table 2. Response, prior therapy, and disease characteristics.

Patients	Response	Prior Therapy	Bulky Disease	IPI	MIPI	Ki-67	Histology
1	PR	CHOP, DHAP, MCP, R-Thal, R-FCM, Radiotherapy	yes	high	high	n.d.	common type
2	CR	CHOP	yes	high	high	100	blastoid
3	CR	CHOP, DHAP, ASCT, Rituximab, R-Thal	no	low-intermediate	low	n.d.	common type
4	PR	CHOP, R-Thal, R-Thal (re-induction), R-FCM	no	high	high	25	common type
5	PR	CHOP, ASCT, Rituximab	no	intermediate-high	intermediate	30	common type
6	CR	CHOP	no	high	intermediate	25	common type
7	CR	CHOP, R-ICE, ASCT, R-Thal	yes	intermediate-high	low	80	blastoid
8	CR	R-CHOP, R-Thal	no	intermediate-high	intermediate	60	common type
9	PR	R-CHOP	no	high	high	40	blastoid
10	PR	R-CHOP, R-FC, R-MCP	yes	high	high	15	common type
11	NR	R-CHOP, R-FCM, R-ICE, ASCT, R-CHOP, Radiotherapy	no	high	high	15	common type
12	PR	R-CHOP + Thal	no	high	high	80	common type
13	NR	R-CHOP + Thal, Radiotherapy	yes	low-intermediate	intermediate	35	common type
14	NR	R-CHOP + Thal, R-FCM	no	high	high	40	common type
15	CR	R-CHOP + Thal	no	high	high	n.d.	common type
16	CR	CHOP, DHAP, ASCT, Rituximab	no	intermediate-high	low	40	common type

IPI: International Prognostic Index; MIPI: Mantle Cell Lymphoma International Prognostic Index; CR: complete remission; PR: partial remission; NR: no remission; n.d.: not determined; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; MCP: mitoxantrone, chlorambucil, prednisolone; R-FCM: rituximab, fludarabine, cyclophosphamide, mitoxantrone; DHAP: cisplatin, cytosine-arabinoside, dexamethasone; R-FC: rituximab, fludarabine, cyclophosphamide; R-ICE: rituximab, ifosfamide, carboplatin, etoposide; R-Thal: ritutixmab, thalidomide; ASCT: autologous stem cell transplantation.

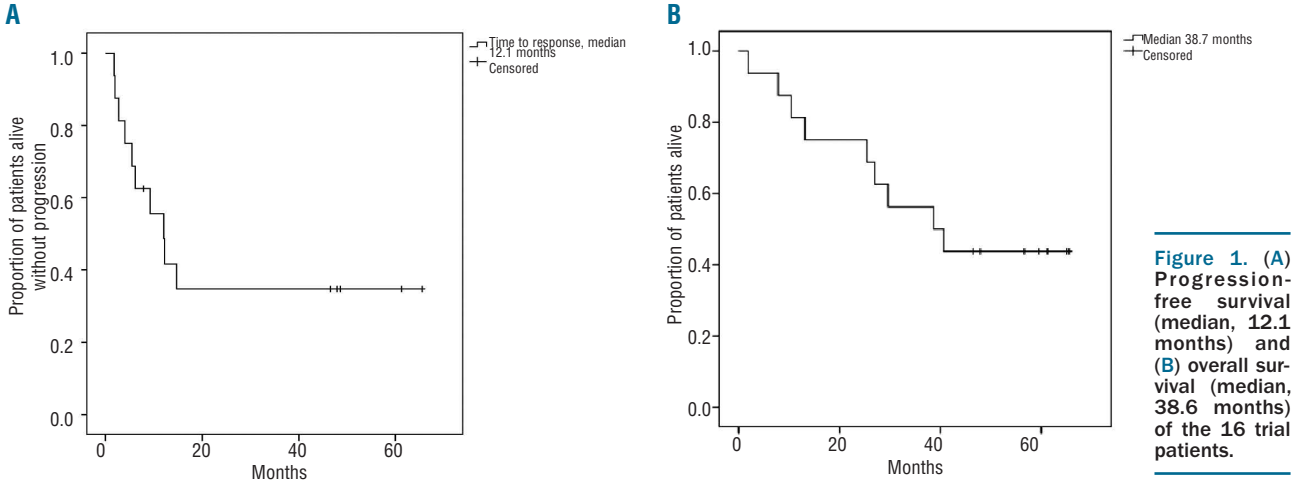

Figure 1. (A) Progression-free survival (median, 12.1 months) and (B) overall survival (median, 38.6 months) of the 16 trial patients.

cytopenia following the typical cyclic pattern of bortezomib-induced thrombocytopenia[29] (grade 3 thrombocytopenia in 6 patients, corresponding to 37.5% of patients). No bleeding events were recorded. Frequent grade 3 and 4 non-hematologic toxicities were fatigue (18.8%), peripheral neuropathy (12.5%), and hyponatremia (12.5%). Bortezomib treatment was discontinued because of toxicity in two patients: both patients developed grade 3 peripheral neuropathy, and bortezomib was discontinued after cycles 3 and 5.

Grade 1 and 2 toxicities observed at high frequencies included infections (7 patients, 43.8%), peripheral neuropathy (43.8%), fatigue (25%), diarrhea (25%), and skin toxicity (18.8%). These cutaneous reactions were consistent with the vasculitic rash known to be associated with bortezomib;[30] biopsies performed in two patients confirmed the presence of T-cell infiltrates consistent with a drug reaction. Interestingly, all three patients with a rash had a response to the BORID treatment (2 complete remissions, 1 partial remission).

Discussion

This phase II study evaluated the combination of bortezomib, rituximab, and dexamethasone in the setting of relapsed/refractory MCL and demonstrated promising activity of the regimen with respect to response rate (overall response rate 81.3%; complete remission 43.8%), progression-free survival (median, 12.1 months) and overall survival (median, 38.7 months). It needs to be pointed out that these treatment results were obtained in a predomi-

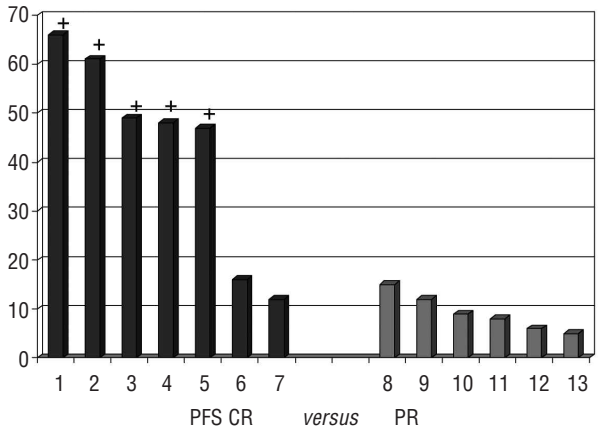

Figure 2. Progression-free survival (months, y-axis) in patients achieving a complete remission (black bars, 1 to 7) compared to patients in partial remission (gray bars, 8 to 13). A + denotes patients in ongoing complete remission.

Table 3. Adverse events

Adverse event	Grades 1 + 2	Grades 3 + 4
Non-hematologic toxicities		
Neurotoxicity (sensory neuropathy)	7 (43.8%)	2 (12.5%)
Fatigue	4 (25%)	3 (18.8%)
Diarrhea	4 (25%)	1 (6.3%)
Infection	7 (43.8%)	0
Pneumonia	3 (18.8%)	0
Herpes Zoster	2 (12.5%)	0
Candidiasis	1 (6.2%)	0
Conjunctivitis	1 (6.2%)	0
Skin (vasculitic rash)	3 (18.8%)	0
Nausea	1 (6.2%)	0
Hyponatremia	0	2 (12.5%)
Other	5 (31.3%)	0
Hematologic toxicities		
Anemia	13 (81.3%)	0
Thrombocytopenia	10 (62.5%)	6 (37.5%)
Leukopenia	5 (31.3%)	1 (6.2%)

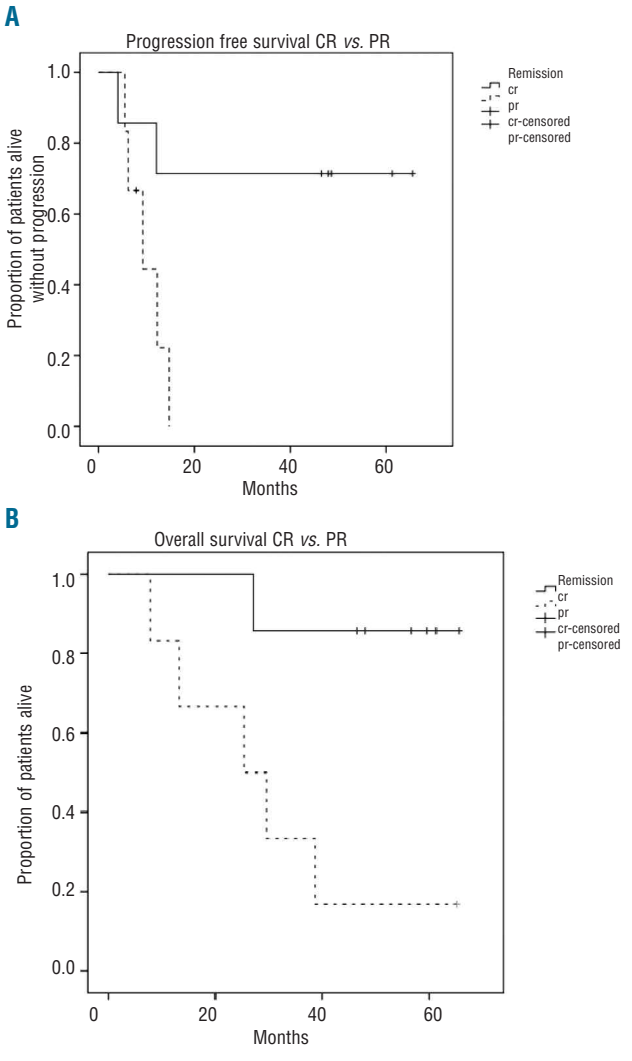

Figure 3. (A) Progression-free survival for patients in complete remission (solid line) *versus* patients in partial remission (dotted line), log rank: *P*=0.037; (B) Overall survival for patients in complete remission (solid line) *versus* patients in partial remission (dotted line), log rank: *P*=0.013.

nantly heavily pretreated population of patients with features of advanced disease and poor prognosis (Table 1). This is reflected by a median of three prior lines of therapy, risk scores (IPI, MIPI)[28] suggesting intermediate and high risk in the majority of patients, as well as a high proliferative activity[31] (Ki-67 index >30% in 9 of the 13 patients tested). The observed efficacy of this treatment combination clearly exceeds the activity of each single agent in the BORID regimen. Bortezomib by itself may induce a remission in 29%-45% of previously treated MCL patients as reported in five phase II studies.[13-18]

A complete remission following bortezomib treatment may be achieved in up to 8% of patients.[16,18] In these trials with bortezomib used as a single agent, the median progression-free survival was reported to range between 5.3 and 6.7 months. The remission rate among patients with MCL treated with single-agent rituximab is about 30–35%, and virtually all responses are partial remissions.[19-21] It is difficult to assess the contribution of pulsed dexamethasone to the activity of the BORID regimen. Based on observations in multiple myeloma, we can assume that dexamethasone may enhance the activity of bortezomib in inducing apoptosis in malignant cells.[25,32,33]

The achievement of durable responses among patients who reached a complete remission after treatment with the BORID regimen is of particular interest. With five out of seven patients who had a complete response still in complete remission beyond 48 months, the median progression-free survival and overall survival have not yet been reached in complete remission patients. These clinical results are in agreement with recent data demonstrating the importance of good quality remissions in MCL as a crucial factor for sustained disease control.[34] A favorable outcome for patients in complete remission after treatment with single-agent bortezomib was also reported in the PINNACLE-trial.[16,18] Consolidation treatment with rituximab may have contributed to these favorable results,

although we did not observe a clinically detectable improvement in the remission status during rituximab consolidation. The toxicity of the BORID regimen was limited in the series of patients in this study, and adverse events were manageable with routine clinical care. Notably, it was safe to combine bortezomib with rituximab and dexamethasone, and the side effects of bortezomib were similar to those reported in MCL[13-18] and multiple myeloma.[35,36] Besides hematologic side effects, including thrombocytopenia, peripheral neuropathy needs to be carefully monitored during treatment with bortezomib. We observed bortezomib-induced grade 3 sensory neuropathy in two patients with MCL and this side effect eventually resulted in treatment discontinuation. This frequency of grade 3 or more neuropathy appears to be in the range that was also reported in previous trials with bortezomib using a twice-weekly schedule of administration. A recent trial of bortezomib with rituximab in relapsed follicular lymphoma and MCL, however, reported grade 3 neurotoxicity in 13 of 25 patients (52%) limiting the use of this treatment combination.[37] This high rate of neurotoxicity may be related to the dose of bortezomib (1.5 mg/m^2 twice weekly) used in the trial by Baiocchi *et al.*; the bortezomib dose used in our study was 1.3 mg/m^2. Neuropathy also developed frequently in a recent trial of bortezomib in MALT lymphoma, in which the dose of bortezomib was 1.5 mg/m^2 administered twice weekly.[38] Besides the early dose modification of bortezomib, alternative doses and schedules of bortezomib should be considered in lymphoma patients,[39] in particular if bortezomib is used after prior administration of neurotoxic agents.

Thus far, several bortezomib combinations have been evaluated in patients with relapsed/refractory MCL. Bortezomib may not only be combined with rituximab,[37,39] but also with cytarabine,[40] fludarabine,[41] and even polychemotherapy.[42] Although the actual numbers of MCL patients in trials of such combinations are very small, the combinations do appear to have greater efficacy compared to bortezomib alone. We believe that our trial adds important information to these reports because of the long-term follow-up demonstrating a durable benefit, particularly for those patients achieving a complete remission.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

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