

# Phase I trial of fludarabine, bortezomib and rituximab for relapsed and refractory indolent and mantle cell non-Hodgkin lymphoma

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## Summary

Based on the hypothesis that bortezomib may potentiate fludarabine activity by inhibiting DNA repair, we designed a phase I trial using this combination with rituximab in patients with relapsed and refractory indolent and mantle cell non-Hodgkin lymphoma. Twenty-four patients were enrolled. Non-Hodgkin lymphoma subtypes included 12 patients with follicular lymphoma, four with marginal zone lymphoma, three with lymphoplasmacytic lymphoma, three with mantle cell lymphoma and two with small lymphocytic/chronic lymphocytic leukaemia. Fludarabine and bortezomib were escalated in cohorts of three patients. Rituximab was added to the maximum tolerated dose of fludarabine and bortezomib and added significant dose-limiting myelosuppression. The maximum tolerated dose was fludarabine 25 mg/m<sup>2</sup> on days 1–3, bortezomib 1.3 mg/m<sup>2</sup> on days 1, 4, 8, 11, with rituximab 375 mg/m<sup>2</sup> on day 1 administered every 21 d. Clinical responses were observed in 11 patients, five of whom were refractory to their most recent treatment regimen. Six additional patients had stable disease for a median of 10 months (range 4–30+). Cumulative myelosuppression and neuropathy was observed. The combination of fludarabine, bortezomib, and rituximab appears to be an active regimen with manageable toxicity for relapsed NHL.

**Keywords:** non-Hodgkin lymphoma, bortezomib, proteasome, fludarabine, rituximab.

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The indolent non-Hodgkin lymphomas (NHLs) traditionally include follicular, marginal zone, lymphoplasmacytic and small lymphocytic histological subtypes. They are defined by their chemosensitive nature and slow progressive course (Horning & Rosenberg, 1984). Despite a wide variety of treatment options, most patients ultimately succumb to their disease. In comparison, mantle cell lymphoma is considerably more aggressive than the indolent NHLs and less responsive to currently available therapy (Herrmann *et al*, 2009). As new treatment options with novel targets and non-overlapping toxicities are developed, the armamentarium of effective salvage therapies is steadily increasing. However, the most effective and least toxic of these regimens has yet to be defined.

Bortezomib is a dipeptidyl boronic acid that is a specific and selective inhibitor of the 26S proteasome. It was the first

proteasome inhibitor to be used clinically and has demonstrated considerable efficacy in the treatment of indolent and mantle cell lymphoma (Goy *et al*, 2005; O'Connor *et al*, 2005; Fisher *et al*, 2006; Strauss *et al*, 2006; Belch *et al*, 2007). This data led to the US Food and Drug Administration approval of bortezomib for the treatment of patients with relapsed or refractory mantle cell lymphoma. Bortezomib affects malignant cells through multiple mechanisms including the regulation of proteins involved in cell cycle progression (p21, p27), oncogenesis (p53, I $\kappa$ B) and apoptosis (Bcl-2, cIAP, XIAP, Bax) (Adams *et al*, 1999; Kisselev & Goldberg, 2001; Barr *et al*, 2007). In addition, bortezomib may act by inhibiting DNA repair kinases (DNA-PKcs, ataxia telangiectasia mutated [ATM]) (Hideshima *et al*, 2003; Mitsiades *et al*, 2003). Further, pre-clinical data suggest that the ubiquitin-proteasome

system may serve as a regulator for DNA damage repair (Mu *et al*, 2007), supporting the use of bortezomib in combination with cytotoxic agents.

Fludarabine is a potent cytotoxic agent that acts by inhibiting DNA polymerase and ribonucleotide reductase, thus terminating DNA strand replication. In chronic lymphocytic leukaemia cell line models, synergistic cytotoxicity has been observed with the combination of fludarabine and bortezomib (Duechler *et al*, 2005). Bortezomib may inhibit repair of the fludarabine-induced DNA lesions, thereby enhancing its anti-neoplastic effect. Other potential synergistic mechanisms include down-regulation of XIAP and up-regulation of Bid, resulting in enhanced apoptosis. *In vitro* data suggest that down-regulation of the nuclear factor- $\kappa$ B pathway, a known result of proteasome inhibition, may reverse fludarabine resistance (Hewamana *et al*, 2008).

Rituximab, in combination with bortezomib, appears to be well tolerated given non-overlapping toxicities (De Vos *et al*, 2006). Further, synergistic apoptosis has been observed pre-clinically when bortezomib was added to a rituximab-containing combination (Wang *et al*, 2008). We therefore initiated a phase I study of fludarabine, bortezomib and rituximab in relapsed and refractory indolent NHL and mantle cell lymphoma.

## Patients and methods

### Study design

This phase I trial was designed to evaluate the maximum tolerated dose (MTD) and dose limiting toxicities (DLT) of bortezomib in combination with rituximab and fludarabine. Secondary objectives included overall response and clinical benefit rates. The protocol was approved by the institutional review board at University Hospitals Case Medical Center and written informed consent was obtained before enrollment.

### Patient selection

Patients aged 18 years or older with a confirmed indolent NHL (including grade 1 or 2 follicular lymphoma, marginal zone lymphoma, lymphoplasmacytic lymphoma and small lymphocytic/chronic lymphocytic leukaemia) who had relapsed or had been refractory (defined as no response, or progression within 6 months of completing therapy) to at least one standard therapy were candidates for this study. Also included were patients with relapsed or refractory mantle cell lymphoma, aside from those with the blastic variant. Patients were required to have an Eastern Cooperative Group performance status of 0–2 and to have measurable disease. Baseline laboratory parameters included an absolute neutrophil count (ANC)  $\geq 1.5 \times 10^9/l$ , platelet count  $\geq 75 \times 10^9/l$ , and adequate renal and hepatic function.

Patients were excluded for the following conditions: radiation, chemotherapy, or monoclonal antibody therapy within

the previous 4 weeks or radioimmunotherapy within the previous 3 months; previous bortezomib therapy; a history of uncontrolled orthostatic hypotension; grade 2 or higher neuropathy; prior allogeneic transplant; central nervous system lymphoma; serious infection, including human immunodeficiency virus disease; pregnancy or breast feeding.

### Treatment schedule

Bortezomib was supplied by the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI) as a sterile, lyophilized powder in vials with mannitol, which was reconstituted with normal saline to a drug concentration of 1 mg/ml. It was administered by intravenous push over 5 s on days 1, 4, 8 and 11 followed by a 10-d rest period. Fludarabine was handled as directed by the package insert and material safety data sheet and administered at 25 mg/m<sup>2</sup> intravenously as a 30 min infusion daily for 3 or 5 d of each 21 d cycle. Rituximab was handled as directed by the package insert and material safety data sheet and administered at 375 mg/m<sup>2</sup> on day 1 of each cycle per a standardized infusion protocol. Treatment was repeated every 3 weeks until disease progression, unacceptable toxicity or to a maximum of eight cycles. Haematopoietic growth factors were not allowed during cycle one and were administered at the treating physician's discretion thereafter.

Dose escalation is depicted in Table I. Cohorts of 3–6 patients were treated at each dose level. For dose escalation to proceed, three patients had to complete cycle 1 without a DLT. If one DLT was observed, then an additional three patients were accrued, and further escalation occurred if no additional DLTs were seen. If DLT was observed in 2 of 3–6 patients enrolled at a specific dose level during cycle 1, that step was considered the dose-limiting level. A total of six patients were treated at the dose below the DLT level, thus establishing the MTD.

### Response and Toxicity Criteria

Toxicities were assessed using the NCI Common Toxicity Criteria version 3.0 ([http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/ctcae3.pdf](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf)). DLT was defined as

Table I. Study design.

Dose level	Fludarabine 25 mg/m <sup>2</sup>	Bortezomib days 1, 4, 8, 11 (mg/m <sup>2</sup> )	Rituximab 375 mg/m <sup>2</sup>
1	days 1–3	0.7	–
2	days 1–3	1.0	–
3	days 1–3	1.3	–
4	days 1–5	1.3	–
5	days 1–5	1.3	day 1
5a	days 1–3	1.0	day 1
5b	days 1–3	1.3	day 1

any grade 3 or higher treatment-related non-haematological toxicity and grade 4 neutropenia or thrombocytopenia occurring within the first cycle. Grade 4 lymphopenia and anaemia were not considered DLTs. The MTD was defined as one dose level below the level determined to be the DLT.

Assessment of response was performed after every two cycles of treatment. Response was defined using the International Workshop NHL criteria (Cheson *et al*, 1999). For patients with chronic lymphocytic leukaemia, the NCI Working Group guidelines were used to determine a response (Cheson *et al*, 1996). Time to disease progression was calculated as the number of months from the initiation of therapy to the first documentation of disease progression, death regardless of cause or change in therapy, whichever occurred first.

## Results

### Patient characteristics

Twenty-four patients were enrolled onto the study between July 2003 and July 2008. Patient characteristics are listed in Table II. The mean age was 62 (range, 36–87) years and 13 patients were >60 years old. All patients were assessable for toxicity. Patients received an average of 3.5 cycles (range, 1–8) and 20 patients who received two or more cycles were

assessable for clinical response. The mean number of prior chemotherapy regimens was 2 (range, 1–7). Twenty-three patients had previously received rituximab or ibritumomab tiuxetan, eight patients had previously received fludarabine. Twelve patients were refractory to their most recent treatment. Of these, 10 patients were refractory to rituximab or ibritumomab tiuxetan and 2 to fludarabine. Five patients had failed an autologous stem cell transplant.

### Toxicity

Haematological and non-haematological toxicities are depicted in Tables III and IV. No DLTs were observed on dose steps 1–4. With the addition of rituximab at dose level 5, two patients experienced DLTs including neutropenia and thrombocytopenia in one patient as well as neutropenia and neuropathy in another. After independent review and consultation with the Cancer Therapy Evaluation Program, dose steps 5a and 5b were added in which doses of fludarabine and bortezomib were attenuated. Nine additional patients were treated, 3 at level 5a and 6 at 5b. One additional DLT, grade 3 dyspnea, was observed at dose 5b.

Myelosuppression was the most common toxicity, with neutropenia being dose limiting. Grade 3/4 neutropenia and thrombocytopenia were observed in 24% and 17% of cycles, respectively, and appeared to be cumulative in nature. Six patients received filgrastim or pegylated filgrastim support after demonstrating prolonged neutropenia during the first cycle of therapy, four of whom were treated on rituximab-containing dose levels. Five patients were removed from the study due to prolonged myelosuppression, preventing initiation of the subsequent cycle within the protocol-specified 5-week time period. As expected, all patients developed grade 3/4 lymphopenia.

The major non-haematological toxicities were neurological and infectious in aetiology. The peripheral neuropathy was predominately sensory in nature, more prone to develop in patients with previous sensory neuropathies and also appeared to be cumulative. Grade 2 or 3 neuropathy developed in nine patients, six of which had received prior vincristine. This contributed to the decision to discontinue protocol treatment in six cases. It was partially reversible with dose reduction or discontinuation of therapy. One patient treated at dose level 5 experienced an increase in his pre-existing grade 1 peripheral neuropathy to grade 3 during cycle 1. This decreased to baseline with a dose reduction of bortezomib. Two additional patients experienced grade 3 orthostatic hypotension possibly due to drug-induced autonomic neuropathy. Both patients' symptoms resolved with therapy cessation.

The overall incidence of grade 3 infection was 6% (5 of 86 cycles). These included one oropharyngeal infection, one cellulitis, one periodontal abscess and two episodes of culture-negative neutropenic fever. In two instances, patients were removed from the trial following a >5-week period without initiation of the next course of treatment. Other grade 3

Table II. Patient characteristics.

	No. of patients
Enrolled	24
Sex	
Male	14
Female	10
Age > 60 years	13
Race	
African-American	6
Caucasian	18
Performance status	
0	19
1	4
2	1
Lymphoma subtype	
Follicular	12
Marginal zone	4
Lymphoplasmacytic	3
Small lymphocytic/chronic lymphocytic leukaemia	2
Mantle cell	3
Stage at enrollment	
II	2
III	3
IV	19
Bone marrow involvement	15
Bulky disease	1
Refractory to prior therapy	12
Refractory to rituximab or ibritumomab tiuxetan	10
Refractory to fludarabine	2

Table III. Haematological toxicity.

Dose level	Cycle 1					All cycles				
	No. of patients	Neutropenia		Thrombocytopenia		No. of cycles	Neutropenia		Thrombocytopenia	
		Grade 3	Grade 4	Grade 3	Grade 4		Grade 3	Grade 4	Grade 3	Grade 4
1	3					14	1		1	
2	3					9	1			
3	3					10	1		1	
4	3	2				7	3	1	1	
5	3		2*		1*	11	3	5		7
5a	3					14	1	1	3	
5b	6					21	3	1	1	1

\*Dose limiting toxicity.

Table IV. Non-haematological toxicity.

Dose level	Cycle 1					All cycles							
	No. of patient	Neurological*		Pulmonary		No. of cycles	Fever/infection		Neurological*		Pulmonary		
		Grade 3	Grade 4	Grade 3	Grade 4		Grade 3	Grade 4	Grade 3	Grade 4	Grade 3	Grade 4	
1	3					14							
2	3					9	1						
3	3					10							
4	3					7			1				
5	3	1†				11	1		1				
5a	3					14	1						
5b	6			1†		21	2		3		1		

\*Includes peripheral neuropathy and orthostasis/syncope.

†Dose limiting toxicity.

toxicities included grade 3 dyspnea potentially related to bortezomib in a patient treated at dose level 5b, grade 3 diarrhoea in two patients, and one episode each of fatigue, hypoglycaemia, and an infusion-related rituximab reaction. One patient experienced grade 3 pain related to progressive disease, not believed to be neurological in aetiology. The only grade 4 non-haematological toxicities included five episodes of hyperglycaemia, all occurring in a single patient with diabetes mellitus after receiving glucocorticoids as part of her anti-emetic regime.

Dose modifications or delays in therapy occurred in 34 of the 86 cycles (40%). Bortezomib was dose reduced in 16 cycles and individual doses were held 26 times for a delivered dose intensity of 88%. In addition, there were a total of 17 weekly delays in therapy. The most common reasons for interruptions in therapy were neutropenia or thrombocytopenia (55% of cases) as well as peripheral neuropathy (32%).

### Clinical responses

Objective responses were observed in 11 patients (Tables V and VI) for an overall response rate of 45% (95% confidence

interval [CI]: 0.28 – 0.65) with a clinical benefit rate (complete remissions + partial remissions + stable disease) of 71% (17/24) with 95% CI: 0.51–0.86. Two of the three patients achieving a complete response have no signs of relapsed disease at 1 and 3 years, respectively, despite both having been heavily pre-treated including receiving high-dose chemotherapy with autologous stem cell rescue. Six of the responding patients went on to receive additional therapy. One patient underwent high-dose chemotherapy and autologous stem transplantation and another patient received an umbilical cord blood transplant. Both remain in remission for >5 years. Two patients received additional immuno-chemotherapy, including fludarabine + rituximab and rituximab + EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin), respectively, and two patients received further rituximab given in maintenance fashion. Six patients were classified as having stable disease with a median time of 10 months (range 4–30+). Of the 12 patients with disease refractory to their most recent regimen, one complete response, four partial responses, and three patients with stable disease (of 4, 5 and 6 months, respectively) were observed.

Table V. Clinical responses.

Subtype	Dose level	Time to disease progression	Prior therapies
Complete response			
Marginal zone	5	36+ months	CHOP, DHAP, HDC + PBSCT, bryostatin/vincristine, rituximab*
Follicular	5A	7 months†	FND, rituximab, rituximab maintenance
Follicular	5B	12+ months	CHOP, rituximab, DHAP, HDC + PBSCT
Partial response			
Mantle cell	1	8 months†	CHOP, rituximab, FND, rituximab maintenance*
Follicular	2	5 months†	Fludarabine, CVP, fludarabine*, rituximab*
Follicular	3	9 months	CHOP, rituximab
Follicular	4	4 months	Rituximab*
Follicular	5	8 months†	CVP, rituximab, rituximab maintenance
Marginal zone	5	3 months†	CVP, rituximab, rituximab maintenance
Marginal zone	5B	7 months†	CVP*, rituximab*
Follicular	5B	3+ months	CHOP, rituximab
Stable disease			
Marginal zone	1	6 months†	CHOP, rituximab*, zevalin*
SLL/CLL	2	4 months†	Fludarabine, CVP, fludarabine*, rituximab*
Follicular	3	5 months	CHOP, rituximab, DHAP, HDC + PBSCT, bryostatin/vincristine*
Lymphoplasmacytic	4	30+ months	Melphalan/prednisone
Lymphoplasmacytic	5A	10 months	Fludarabine, melphalan/prednisone, thalidomide, rituximab
Follicular	5B	7 months†	Rituximab, idiotype vaccine

CHOP, cyclophosphamide, adriamycin, vincristine prednisone; CVP, cyclophosphamide, vincristine prednisone; DHAP, dexamethasone, cytarabine, cisplatin; FND, fludarabine, mitoxantrone, dexamethasone; HDC + PBSCT, high-dose chemotherapy and peripheral blood stem cell transplantation.

\*Refractory disease.

†Censored for consolidative therapy.

Table VI. Clinical responses by histological subtype.

	n	CR	PR
Follicular	12	2	5
Marginal zone	4	1	2
Lymphoplasmacytic	3		
SLL/CLL	2		
Mantle cell	3		1

CR, complete response; PR, partial response; SLL/CLL, small lymphocytic lymphoma/chronic lymphocytic leukaemia.

## Discussion

Proteasome inhibition affects a variety of cell-signalling pathways via inhibition of proteolysis. Among its pro-apoptotic effects, bortezomib may increase the sensitivity of tumour cells to the cytotoxic effects of chemotherapy through the inhibition of DNA repair. Induction of c-Jun NH<sub>2</sub>-terminal kinase activity, resulting in activation of caspase-3, led to cleavage of the DNA repair enzymes DNA-PKcs and ATM (Hideshima *et al*, 2003). Further, clinical and laboratory investigations have demonstrated that bortezomib sensitized lymphoma and multiple myeloma cells to DNA-damaging chemotherapeutics, reversing drug resistance in some cases (Mitsiades *et al*, 2003; O'Connor *et al*, 2006; Dunleavy *et al*, 2009). Based on the previously demonstrated efficacy of

bortezomib in indolent and mantle cell NHL as well as the potential for bortezomib to inhibit repair of fludarabine-induced DNA strand breaks, we conducted this phase I study in NHL patients with relapsed or refractory disease and determined the MTD to be fludarabine 25 mg/m<sup>2</sup> on days 1–3, bortezomib 1.3 mg/m<sup>2</sup> on days 1, 4, 8 and 11 and rituximab 375 mg/m<sup>2</sup> on day 1.

The addition of rituximab added significantly to the myelotoxicity of this regimen. Rituximab-related neutropenia is a rare complication associated with single agent use and may occur months after administration (Chaiwatanatorn *et al*, 2003; Voog *et al*, 2003; Tesfa *et al*, 2008). Delayed onset neutropenia has also been well described when administered in conjunction with chemotherapy and appears to correlate with the intensity of the regimen (Cairolì *et al*, 2004; Lemieux *et al*, 2004; Nitta *et al*, 2007). In addition, its ability to potentiate mid-cycle chemotherapy-related granulocytopenia has been observed in randomized clinical trials with CHOP (cyclophosphamide, adriamycin, vincristine prednisone) and fludarabine-based regimens, a finding that did not translate into increased infectious complications (Byrd *et al*, 2003; Hiddemann *et al*, 2005). In our study, the patients treated at dose level 5 developed grade 4 neutropenia or thrombocytopenia in 8 of 11 cycles of therapy. The severe myelosuppression occurred more often and earlier in the treatment course compared to patients treated at the identical doses of fludarabine and bortezomib without rituximab. This potentiation of granulocytopenia may



be related more to an undetermined interaction of rituximab with fludarabine than with bortezomib given the similar myelosuppression between dose levels 5a and 5b. However, it is possible that rituximab may have potentiated bortezomib-related thrombocytopenia, a common toxicity of the proteasome inhibitor that has not been otherwise observed with only fludarabine and rituximab (Czuczman *et al*, 2005). However, further investigation to validate these observations is needed given the small numbers treated at each dose level.

Haematological toxicity also appeared to be related to prior therapy. Patients who had dose intensive treatment or a greater number of prior regimens containing cytotoxic agents appeared to have a higher incidence of Grade 3 or 4 haematological toxicity. This was more pronounced at higher dose levels. As such, this regimen may not be ideal for patients with poor bone marrow reserve, such as those who have undergone previous stem cell transplantation.

Neuropathy resulted in 11 dosing adjustments or delays and resulted in a DLT in one patient. All three episodes of grade 3 neuropathy occurred at dose levels where 1.3 mg/m<sup>2</sup> of bortezomib was used. While the effects were reversible, this complication was predictable with the combination of fludarabine and bortezomib. Patients with pre-existing peripheral or autonomic neuropathy as well as those with lymphoplasma-cytic lymphoma should be monitored closely. However, treatment is feasible as the symptoms typically improve after therapy discontinuation, consistent with previous observations (Chaudhry *et al*, 2008).

Despite the adverse effects, considerable efficacy was also demonstrated with fludarabine bortezomib and rituximab. Although the primary goal of a phase I study is not to determine efficacy, it is encouraging that 11 of 20 evaluable patients achieved a complete or partial remission. Durable responses were observed at a variety of dose levels and were observed even in the patients who did not receive rituximab, suggesting that bortezomib added significantly to the regimen. This effect was noted despite the previous use of fludarabine in eight patients and anti-CD20 immunotherapy in 23 patients.

Treatment options are limited for patients with chemotherapy or rituximab-refractory disease. Response rates between 61% and 74% have been observed with other salvage strategies, including bendamustine and radioimmunoconjugates, in treatment-refractory patients (Witzig *et al*, 2002; Horning *et al*, 2005; Friedberg *et al*, 2008). Further, response rates with other bortezomib-containing chemotherapeutic regimens used to treat patients with relapsed indolent NHL are comparable (Gerecitano *et al*, 2008; Moosmann *et al*, 2008). In our study, 5 of 12 patients who were refractory to their last treatment regimen attained an objective response. Further, 4 of 11 patients who attained an objective response were treated at dose levels not containing rituximab suggesting notable activity of the fludarabine bortezomib combination. With this encouraging efficacy, further study using this combination in patients with refractory disease is warranted.

In conclusion, we found the toxicity of fludarabine, bortezomib and rituximab to be predictable and tolerable with the major DLT being neutropenia. Further, neutropenia and thrombocytopenia resulted in a significant number of treatment interruptions and delays. Given the observed myelosuppression, administration of this regimen at 4-week intervals with haematopoietic growth factor support is recommended for further study in the phase II setting. Future correlates will quantify fludarabine induced DNA stand breaks and test the ability of bortezomib to inhibit repair of these lesions.

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## Disclosures

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