Published in final edited form as:

Br J Haematol. 2009 September ; 146(6): 652–655. doi:10.1111/j.1365-2141.2009.07775.x.

Phase 2 Study of Weekly Bortezomib in Mantle Cell and Follicular Lymphoma

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Abstract

Twice-weekly bortezomib has proven activity in mantle cell (MCL) and indolent lymphomas. This study explored a weekly schedule of bortezomib in follicular lymphoma (FL) and MCL. Although weekly bortezomib was better tolerated, the overall response rate (ORR) was inferior (18% vs. 50%, $p = 0.02$) with no complete remissions (CR) (compared with 18% CR for the twice-weekly schedule). Progression-free survival (PFS) was not different. The weekly schedule of bortezomib was less toxic, but yielded fewer and lower quality responses than twice-weekly bortezomib. Given the similar PFS, the weekly schedule may still be appropriate for some patients.

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Author contributions: John Gerecitano and Owen A O'Connor served as Principal Investigators on this trial and analyzed the data. John Gerecitano wrote the paper. Carol Portlock, Craig Moskowitz, Paul Hamlin, David Straus and Andrew D. Zelenetz cared for patients and monitored for toxicity and response, as well as providing editorial review. Zhigang Zhang performed all statistical analyses, Otilia Dumitrescu and Debra Sarasohn evaluated all restaging studies and served as the official study radiologists, Dorothy Lin, Rachel Hamelers and Ellen Neylon entered all toxicity and response data and helped with statistical analyses and compilation of toxicity tables, Barbara MacGregor Cortelli and Jennifer Papanicholou regularly assessed toxicities and served as the study nurses. Owen A. O'Connor designed the trial, with the help and assistance of John Wright.

Keywords

Bortezomib; Follicular Lymphoma; Mantle cell Lymphoma; Non-Hodgkin Lymphoma; Proteasome inhibitor

Introduction

Bortezomib is the first proteasome inhibitor approved by the US Federal Drug Administration for use in multiple myeloma and relapsed/refractory mantle cell lymphoma (MCL). Several phase II clinical trials (Belch, *et al* 2007, Goy, *et al* 2005, O'Connor *et al* 2005, Strauss, *et al* 2006) have demonstrated activity in non-Hodgkin Lymphoma (NHL). Our original experience with bortezomib in NHL (O'Connor *et al* 2005) demonstrated an overall response rate (ORR) of 58%, with an ORR of 50% in MCL and 77% in follicular lymphoma (FL). The activity in NHL was confirmed by other phase 2 trials (Belch, *et al* 2007, Goy, *et al* 2005, Strauss, *et al* 2006). Although the ORR for several NHL subtypes varied between these studies, the ORR in MCL was remarkably similar, despite the use of different doses of bortezomib (1.5 mg/m² (Goy, *et al* 2005, O'Connor *et al* 2005) versus 1.3 mg/m² (Belch, *et al* 2007, Strauss, *et al* 2006), with all trials employing a conventional day 1, 4, 8, 11 dosing schedule). Based on the results in MCL, the PINNACLE trial treated 141 relapsed/refractory MCL patients with 1.3 mg/m² of bortezomib twice weekly, demonstrating an ORR of 31% with a median duration of response of 9.2 months (Fisher *et al* 2006).

During the conduct of our twice-weekly phase 2 study, outside data emerged suggesting that bortezomib administered with rituximab on a weekly schedule was as effective and less toxic than the same combination given on a twice-weekly basis in patients with indolent NHL (de Vos, *et al* 2005). Although the responses in both arms of this study were promising, the study design did not allow conclusions about the individual contributions of rituximab versus bortezomib. Because of the favorable toxicity profile, once we met our predetermined statistical endpoints, we extended the trial to explore the safety and efficacy of a weekly schedule. A dose of 1.8 mg/m² was selected based on previous phase I data (Papandreou, *et al* 2004). While an experience with a weekly schedule in myeloma has recently been published (Hainsworth *et al* 2008), this is the first reported experience of weekly bortezomib in patients with NHL.

Methods

This trial is an extension of a twice-weekly trial of bortezomib in NHL, details of which have been presented elsewhere (O'Connor, *et al* 2005). Briefly, eligibility criteria included: measurable disease, follicular lymphoma (FL) or MCL; three or fewer prior chemotherapeutic regimens; no cytotoxic chemotherapy within four weeks of study treatment; more than 3 months since last rituximab; over 18 years of age; Karnofsky Performance Status of at least 60%; absolute neutrophil count (ANC) $1.0 \times 10^9/l$ (if known involvement of the bone marrow, then $ANC > 0.5 \times 10^9/l$); platelet count $> 50 \times 10^9/l$. All patients were required to sign an Institutional Review Board approved informed

consent. Once the twice-weekly portion of the trial reached pre-planned statistical endpoints, patients were enrolled on the weekly schedule described below.

Bortezomib was supplied by Millennium Pharmaceuticals through the Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute, and 1.8 mg/m² was given via IV push over 3-5 s, weekly for four weeks, followed by a two week break (one cycle). Dose reductions to 1.5 mg/m² and 1.3 mg/m² for grade 3 or 4 non-hematological toxicities, or grade 4 hematological toxicities were allowed. Baseline computed tomography scan and a bone marrow biopsy were required, with restaging after every two cycles of treatment. Response criteria followed standard guidelines (Cheson, *et al* 1999). Patients continued on therapy until progression of disease (POD), unacceptable adverse events, or patient preference. Growth factor support was allowed, and patients received prophylactic acyclovir.

Results and Discussion

As this study represents a continuation of our twice-weekly trial (O'Connor *et al* 2005), it affords an opportunity to compare toxicity and efficacy of two distinct dosing schedules in a group of patients with the same enrollment criteria and treatment parameters. A total of 26 patients with MCL (n = 10) and FL (n = 16) received weekly bortezomib. Demographic characteristics (see Table 1) were similar to the 77 patients previously treated on the twice-weekly portion of this study (O'Connor *et al* 2005). Reasons for discontinuing treatment included: POD (n = 13), patient choice (n=7, most often due to prolonged stable disease) and toxicity (n = 3). Two patients were removed due to treatment with steroids (in violation of the protocol) at outside hospitals for disease-related complications. One patient with partial response (PR) after 2 cycles remains on treatment after 7 cycles.

Treatment was well tolerated. A median of 3 cycles was administered (range: 1 to 10), and only one patient required a dose reduction (from 1.8 mg/m² to 1.6 mg/m² for grade 2 fatigue after cycle 2; a further 8 cycles were given with no additional dose reductions). When corrected for baseline, most toxicities were grade 1 and 2 (see Table 2). Grade 3 toxicities included hyperglycaemia (n = 1), thrombocytopenia (n = 2), anaemia (n = 2), leucopenia (n = 3), lymphopenia (n = 9), neutropenia (n = 2), and sensory neuropathy (n = 1). Two grade 4 neutropenic episodes were reported. The most common toxicities occurring in over one third of patients included hyperglycaemia (73%), thrombocytopenia (69%), anaemia (50%), leucopenia (50%), hypocalcemia (46%), hypoalbuminaemia (35%), lymphopenia (35%) and neutropenia (35%). Sensory neuropathy above baseline occurred in 8 (31%) patients (5 were grade 1, 2 grade 2, and 1 was grade 3). When compared with the twice-weekly schedule previously published (O'Connor, *et al* 2005), several toxicities were less common: constipation (15% versus 30%), diarrhoea (15% versus 35%), fatigue (19% versus 39%), nausea (12% versus 29%), and rash (4% versus 14%). Sensory neuropathy was less frequent (31% versus 48%), with one patient (4%) on the weekly schedule (out of 26) and 9 (12%) patients in the twice-weekly schedule (out of 77 total) experiencing a grade 3 neuropathy.

Twenty-two of 26 patients were assessable for response. In contrast to our results with twice weekly bortezomib, no complete remissions were seen. In patients with MCL and FL, the

ORR was significantly lower (18.2%, 95% confidence interval (CI) 4.5% to 36.4% vs. 50.0% 95% CI 37% to 63%, $p = 0.02$). The ORR was 14% in the 14 assessable FL patients and 25% in the 8 assessable MCL patients (all PRs). Eight (36%) had stable disease (SD). Ten patients (45%) progressed on therapy, compared with only 15% on the twice weekly schedule. The median duration of response (DOR) in four patients achieving PR was 6.7 months, and the median progression-free survival (PFS) in all patients was 6.7 months (compared with a median 9 month PFS on their most recent prior therapy).

Compared with the twice-weekly schedule (O'Connor, *et al* 2005), weekly dosing was associated with fewer adverse events (Table 2). Although haematological toxicities were common in both treatment groups, there was a higher incidence of grade 3 thrombocytopenia in the twice-weekly group (19%, vs. 8%). The incidence of neuropathy (48% versus 31%), particularly grade 3 neuropathy (12% versus 4%), also favored the weekly treatment group. Fatigue was also more common (39% versus 19%) and severe (0 versus 5 cases of grade 3-4 reported) in the twice-weekly group. This supports the argument that certain bortezomib-related toxicities correlate with schedule.

While weekly dosing was better tolerated, it also appeared less efficacious. Only 4 of 22 (18%) evaluable patients on the weekly schedule achieved a response of any kind (all PR), compared with an ORR of 50%, including 10 complete remissions, in 54 evaluable patients with FL and MCL in the twice-weekly group [O'Connor et al., in press]. This difference was statistically significant ($p=0.02$). Despite these differences in response rate, median PFS was similar between the two groups (4.5 months for twice-weekly patients, 5.3 months for weekly patients).

In preclinical studies, bortezomib has shown at least additive, if not synergistic activity when combined with several other agents (De Vos, *et al* 2004, Heider, *et al* 2008, Paoluzzi, *et al* 2008, Wang, *et al* 2008). What remains less clear is whether the best single agent schedule (twice weekly) is necessary to optimize complementary activity in combinations, or whether alternative schedules (e.g. weekly) will be equally as active. Clearly, the only way to answer the question is to conduct randomized studies. We are currently exploring the efficacy of weekly and twice weekly schedules of bortezomib in combination with rituximab, cyclophosphamide, and prednisone (Gerecitano, *et al* 2008).

Acknowledgments

This trial was supported under an NCI Phase II grant (UO1 CA 69913) and supervised by CTEP, and the study drug was obtained through CTEP.

References

- Belch A, Kouroukis C, Crump M, Sehn L, Gascoyne RD, Klasa R, Powers J, Wright J, Eisenhauer EA. A phase II study of bortezomib in mantle cell lymphoma: the National Cancer Institute of Canada Clinical Trials Group trial IND.150. *Annals of Oncology*. 2007; 18:116–121. [PubMed: 16971665]
- Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, Lister TA, Vose J, Grillo-Lopez A, Hagenbeek A, Cabanillas F, Klippensten D, Hiddemann W, Castellino R, Harris NL, Armitage JO, Carter W, Hoppe R, Canellos GP. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *Journal of Clinical Oncology*. 1999; 17:1244–1253. [PubMed: 10561185]

- de Vos S, Dakhil S, McLaughlin P, Saleh M, Belt R, Flowers C, Knapp M, Hart L, Patel-Donnelly D, Glenn M, Gregory SA, Holladay C, Boral A, Zhang T, Goy A. Bortezomib Plus Rituximab in Patients with Indolent Non-Hodgkin's Lymphoma (NHL): A Phase 2 Study. *Blood*. 2005; 106:17. Abstract.
- de Vos S, McBride WH, Calimlim J, Koeffler PH, Said JW, Perwan M. Active combination therapy of Bortezomib and Rituximab in an in vitro and in vivo DLBCL model. *Proceedings of the American Association for Cancer Research*. 2004; 45:546. Abstract.
- Fisher RI, Bernstein SH, Kahl BS, Djulbegovic B, Robertson MJ, de Vos S, Epner E, Krishnan A, Leonard JP, Lonial S, Stadtmauer EA, O'Connor OA, Shi H, Boral AL, Goy A. Multicenter Phase II Study of Bortezomib in Patients With Relapsed or Refractory Mantle Cell Lymphoma. *Journal of Clinical Oncology*. 2006; 24:4867–4874. [PubMed: 17001068]
- Gerecitano J, Portlock C, Hamlin P, Moskowitz C, Noy A, Straus D, Zelenetz A, Schulman P, Dumitrescu O, O'Connor OA. A phase I study evaluating two dosing schedules of bortezomib (Bor) with rituximab (R), cyclophosphamide (C) and prednisone (P) in patients with relapsed/refractory indolent and mantle cell lymphomas. *Journal of Clinical Oncology*. 2008; 26:8512. Abstract.
- Goy A, Younes A, McLaughlin P, Pro B, Romaguera JE, Hagemester F, Fayad L, Dang NH, Samaniego F, Wang M, Broglio K, Samuels B, Gilles F, Sarris AH, Hart S, Trehu E, Schenkein D, Cabanillas F, Rodriguez AM. Phase II study of proteasome inhibitor bortezomib in relapsed or refractory B-Cell non-Hodgkin's lymphoma. *Journal of Clinical Oncology*. 2005; 23:667–675. [PubMed: 15613697]
- Hainsworth JD, Barton J, Farley C, Schreeder M, Hon J, Greco FA. Weekly treatment with bortezomib for patients with recurrent or refractory multiple myeloma. *Cancer*. 2008; 113:765–771. [PubMed: 18543319]
- Heider U, von Metzler I, Kaiser M, Rosche M, Sterz J, Rotzer S, Rademacher J, Jakob C, Fleissner C, Kuckelkorn U, Kloetzel PM, Sezer O. Synergistic interaction of the histone deacetylase inhibitor SAHA with the proteasome inhibitor bortezomib in mantle cell lymphoma. *European Journal of Haematology*. 2008; 80:133–142. [PubMed: 18005386]
- O'Connor OA, Portlock C, Moskowitz C, Hamlin P, Straus D, Gonen M, Dumitrescu O, Sarasohn D, Butos J, Neylon E, Mac-Gregor Cortelli B, Blumel S, Evens AM, Zelenetz AD, Wright J, Cooper B, Winter J, Vose J. The time to treatment response (ttr) is a major determinant of activity in patients with follicular lymphoma treated with bortezomib. *Clinical Cancer Research*. in press.
- O'Connor OA, Wright J, Moskowitz C, Muzzy J, MacGregor-Cortelli B, Stubblefield M, Straus D, Portlock C, Hamlin P, Choi E, Dumetrescu O, Qin J, Esseltine D, Trehu E, Adams J, Schenkein D, Zelenetz A. Phase II clinical experience with the novel proteasome inhibitor bortezomib in patients with indolent non-Hodgkin's lymphoma and mantle cell lymphoma. *Journal of Clinical Oncology*. 2005; 23:676–684. [PubMed: 15613699]
- Paoluzzi L, Gonen M, Bhagat G, Furman RR, Gardner JR, Scotto L, Gueorguiev VD, Heaney ML, Manova K, O'Connor OA. The BH3-only mimetic ABT-737 synergizes the antineoplastic activity of proteasome inhibitors in lymphoid malignancies. *Blood*. 2008; 112:2906–2916. [PubMed: 18591385]
- Papandreou CN, Daliani DD, Bhagat G, Furman RR, Gardner JR, Scotto L, Gueorguiev VD, Heaney ML, Manova K, O'Connor OA. Phase I trial of the proteasome inhibitor bortezomib in patients with advanced solid tumors with observations in androgen-independent prostate cancer. *Journal of Clinical Oncology*. 2004; 22:2108–2121. [PubMed: 15169797]
- Strauss SJ, Maharaj L, Hoare S, Johnson PW, Radford JA, Vinnecombe S, Millard L, Rohatiner A, Boral A, Trehu E, Schenkein D, Balkwill F, Joel SP, Lister TA. Bortezomib therapy in patients with relapsed or refractory lymphoma: potential correlation of in vitro sensitivity and tumor necrosis factor alpha response with clinical activity. *Journal of Clinical Oncology*. 2006; 24:2105–2112. [PubMed: 16606971]
- Wang M, Han XH, Zhang L, Yang J, Qian JF, Shi YK, Kwak LW, Romaguera J, Yi Q. Bortezomib is synergistic with rituximab and cyclophosphamide in inducing apoptosis of mantle cell lymphoma cells in vitro and in vivo. *Leukemia*. 2008; 22:179–185. [PubMed: 17898787]

Table 1**Patient Demographics**

	Number of Patients	%
Male	16	62%
Female	10	38%
Median Age (years)	65.5	(48,81)
Histology		
Follicular Lymphoma	16	62%
Mantle Cell Lymphoma	10	38%
Median # Prior Therapies		
Alkylator Based		
EPOCH	1	4%
CHOP +/- R	12	46%
MOPP	1	4%
Cyclophosphamide + R	1	4%
HyperCVAD	1	4%
R-ICE	5	19%
Adria, cyclo, taxol	1	4%
R-CBorP	2	8%
CVP +/- R	4	15%
R-PromACE	1	4%
Biological/Experimental		
Rituximab (alone)	12	46%
anti-B1 antibody	1	4%
radioimmunotherapy	6	23%
Peg-IFN, rituximab	1	4%
		0%
Purine analogue-based		
FC +/- R	2	8%
Fludara + Mitoxantrone	1	4%
Fludarabine	2	8%
Radiotherapy	1	4%
ASCT	3	12%

EPOCH, Etoposide, prednisone, vincristine, cyclophosphamide, adriamycin; CHOP, Cyclophosphamide, adriamycin, vincristine, prednisone; R, rituximab; MOPP, Mechlorethamine, vincristine, procarbazine, prednisone; hyperCVAD, Hyperfractionated cyclophosphamide, vincristine, doxorubicin, dexamethasone; R-ICE, Rituximab, ifosfamide, carboplatin, etoposide; Adria, Doxorubicin; cyclo, Cyclophosphamide; R-CBorP, Rituximab, cyclophosphamide, bortezomib, prednisone; CVP, Cyclophosphamide, vincristine, prednisone; R-PromACE, Rituximab, cyclophosphamide, doxorubicin, etoposide, prednisone; Peg-IFN, pegylated interferon; FC, Fludarabine, cyclophosphamide; ASCT, autologous stem cell transplantation

Table 2

Toxicities Occurring in >10% Patients

	grade 1	grade 2	grade 3	grade 4	total	%
Hyperglycaemia	11	7	1		19	73%
Platelets	12	4	2		18	69%
Hemoglobin	9	2	2		13	50%
Leucocytes	4	6	3		13	50%
Hypocalcaemia	9	3			12	46%
Hypoalbuminaemia	9				9	35%
Lymphopenia			9		9	35%
Neutrophils/gran	4	1	2	2	9	35%
Neuropathy-sensory	5	2	1		8	31%
AST	8				8	31%
ALT	8				8	31%
Alkaline phosphatase	6				6	23%
Bilirubin	5				5	19%
Fatigue	2	3			5	19%
Hypernatraemia	5				5	19%
Hyponatraemia	4	1			5	19%
Hypophosphataemia		5			5	19%
Constipation	3	1			4	15%
Creatinine	4				4	15%
Diarrhoea (Patients w/out col)	3	1			4	15%
Dyspnea		4			4	15%
Hyperkalaemia	4				4	15%
Nausea	2	1			3	12%

AST, aspartate transaminase; ALT, alanine transaminase