Bortezomib in combination with dexamethasone for patients with relapsed Hodgkin's lymphoma: results of a prematurely closed phase II study (NCT00148018)

We conducted a two-stage phase II study to investigate the activity of bortezomib and dexamethasone in patients with relapsed Hodgkin's lymphoma. The study was prematurely closed after the first stage with twelve enrolled patients because no response was observed. A meta-analysis of all four available studies evaluating bortezomib in this population showed no activity of bortezomib (combined response rate: 0.03; 95%-CI: 0.01 to 0.12).

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Hodgkin/Reed-Sternberg cells are known to be resistant to apoptosis due to over-expression of nuclear factor-κB (NF-κB).[1] The proteasome inhibitor bortezomib is known to inhibit the activation of NF-κB.[2] Its activity has been shown in HL-derived cell lines.[3] We therefore evaluated the anti-tumor activity of bortezomib in combination with dexamethasone in patients with relapsed Hodgkin's lymphoma.

Ethical approval was sought in every participating institution before initiation of this phase II study. All participants gave written informed consent before entering the study. Patients must have had progressive, histologically proven Hodgkin's lymphoma after at least one chemo- or radiotherapy. All patients were treated with 1.3 mg/m^3 bortezomib intravenously and 20 mg dexamethasone orally on days 1, 4, 8, and 11 of a three-weekly cycle for up to eight cycles. A detailed schedule and dose modification scheme based on the package insert was employed if patients experienced toxicities. Patients were staged and restaged according to standard criteria before study treatment.[4,5] Toxicities were assessed at each study visit according to National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0. After every other cycle patients were clinically restaged and an interim staging with computed tomography of initially involved sites was performed after four cycles. Final treatment evaluation was performed 29 days after the last treatment cycle. Response to treatment was assessed and defined according to standard criteria.[4,5]

This study was a two-stage phase II study. The primary outcome was overall response rate (ORR; partial or complete responses). Sample size was calculated according to Simon's optimal design. With type I error set at 0.1 to conclude the activity of an uninteresting regimen (ORR <5%) and type II error set at 0.1 implying the rejection of an active regimen (ORR >20%) it was necessary to recruit twelve patients in the first stage of the study. If one or more responses had been observed 25 additional patients would have been recruited. Secondary endpoints of the study were toxicity, event-free survival, duration of response, and treatment administration procedures. In order to facilitate interpretation of our study results, we performed a systematic review and meta-analysis of all prospective phase II studies of bortezomib reporting response data for at least one patient with Hodgkin's lymphoma. We combined data on overall response using binomial regression analysis.

Between January 2005 and February 2006 a total of twelve patients were enrolled in the first stage of the study as specified in the protocol (Table 1). The median concentration of circulating proteasome was higher in study patients (n=8) compared to controls (431 ng/ml versus 210 ng/ml; p<0.001). All twelve patients were assessable for treatment administration and response. Eleven patients were assessable for toxicity.

Overall, 28 cycles were administered with a median of two cycles per patient (range: 2-8) (Table 1). The median received total dose was 10.4 mg/m^2 (range: 8.3 -36.8 mg/m^2) resulting in a median standardized received dose of 0.25 (range: 0.20-0.88). Three patients had at least one treatment delay, two had at least one dose modification, and three patients had both, treatment delay and dose modification, all because of toxicities. Two patients with

Table 1. Characteristics of patients and summary of results.

			Baseline				Results	
Patient ID	*Age [years]*	*Sex*	*No. of prior therapies*	*Duration of last response [months]*	*Number of bortezomib cycles received*	*Toxicities**	*Reason for early treatment termination*	*Best response*
1	21	Female	2	5	2	Infection °II (2 x)	PD	PD
2	25	Male	2	2	4	Infection °II, II, neuropathic pain°	PD	PD
3	51	Female	9	n/a	2	None	PD	PD
4	44	Male	2	7	3	Neutropenia °IV, thrombocytopenia (1 x°II, 1 x °III)	Toxicity	SD
5	28	Male	3	0	8	Herpes zoster °III	PD	PD
6	20	Male	2	9	4	None	PD	PD
7	50	Male	3	4	2	Thrombocytopenia ° IV, loss of appetite °IV, epistaxis °III, cough °III, sleep disturbance °III	PD	PD
8	50	Male	4	3	5	Lymphopenia °III, thrombocytopenia °II	PD	PD
9	26	Male	3	0	2	Paralytic ileus °IV,diarrhea °III, sleep disturbance °III	Toxicity	SD
10	32	Male	4	16	2	Abdominal pain °II	PD	PD
11	55	Male	7	0	2	Thrombocytopenia °IV	PD	PD
12	59	Female	n/a	5	2	n/a	PD	PD

*n/a, not available; PD, progressive disease; SD, stable disease; * Only toxicities ≥°II which required some form of dose modification/delay or early treatment termination are reported.*

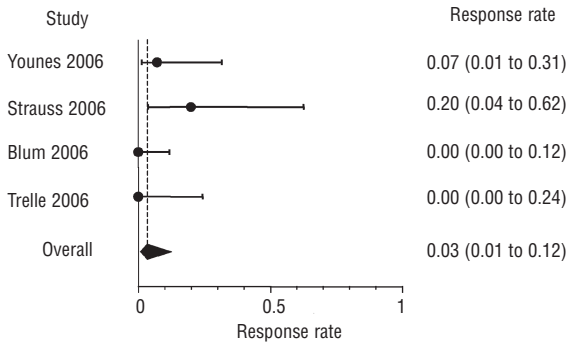

Figure 1. Meta-analysis of phase II studies of bortezomib in Hodgkin's lymphoma.

stable disease, prematurely discontinued study treatment due to toxicities after two and three cycles, respectively. All of the other ten patients had progressive disease (overall response rate: 0.0; 95%-CI: 0.0 to 0.24). Nine of these prematurely discontinued study treatment after a median of two cycles (range: 2-5 cycles) and only one received all eight cycles (Table 1). Since no response was observed in the first twelve patients the study was stopped after the first stage. Eight patients experienced at least one toxicity greater than grade I requiring some dose modifications, treatment delays, or discontinuation (Table 1). We identified three other studies reporting response data for patients with Hodgkin's lymphoma.[6-8] Patients in all of these studies received the same dose of bortezomib within the same schedule as our study but without dexamethasone. Overall, results of all four studies agree in showing that bortezomib has no or only limited single-agent activity and this was confirmed by meta-analysis (Figure 1).

Laboratory studies with Hodgkin's lymphoma derived cell cultures showed that bortezomib potentiates the activity of chemotherapy.[9] Animal studies further indicate that the combination of an anti-CD30 antibody with bortezomib might be more promising than single-agent bortezomib.[10] Further studies of bortezomib in Hodgkin's lymphoma might therefore only be justified with combinations of bortezomib. However, the use of bortezomib combined with dexamethasone is not encouraged in patients with relapsed Hodgkin's lymphoma.

Sven Trelle,° Orhan Sezer,# Ralph Naumann,@ Mathias Rummel,^ Ulrich Keller,§ Andreas Engert,* Peter Borchmann**

**Department I of Internal Medicine, University of Cologne, Germany; °Department of Social and Preventive Medicine, University of Berne, Switzerland; #Department of Internal Medicine II, Charité Campus Mitte Berlin, Germany; @Department of Internal Medicine I, Technical University Dresden, Germany; ^Department of Internal Medicine II, University of Frankfurt, Germany; §Department of Internal Medicine III, Technical University Munich, Germany*

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Key words: bortezomib, Hodgkin's disease, lymphoma, phase II clinical trial, recurrence.

Correspondence: Peter Borchmann, Klinik I für Innere Medizin, Klinikum der Universität zu Köln, 50924 Köln, Germany.
Phone: international +41.221.478-5933.
E-mail: peter.borchmann@uni-koeln.de

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