A phase II study of bortezomib in patients with MALT lymphoma

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ABSTRACT

We have performed a phase II study to evaluate bortezomib in patients with MALT-lymphoma. Sixteen patients entered the trial, 4 had gastric MALT-lymphoma, 7 of the ocular adnexa, one of the colon, and 2 of the parotid, and one patient each the lung and the breast. Bortezomib was given at 1.5 mg/m^2 days 1, 4, 8 and 11; repeated every 21 days. The overall response rate was 80% (13/16); 7 patients achieved complete remission (43%), 6 partial response (37%) and 3 stable disease. After a median follow-up of 23 months (range; 8-26), all patients are alive and 4 have relapsed. Fifteen patients required dose reductions due to either neuropathy (7 patients) or diarrhea (8 patients). Bortezomib appears to be active in patients with MALT-lymphoma. However, an unexpectedly high rate of toxicities was seen, warranting assessment of combination schedules with bortezomib at a lower dose than given in our study (ClinicalTrials.govIdentifier: NCT 00373906).

Key words: bortezomib, MALT lymphoma, chemotherapy.

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Introduction

MALT lymphoma accounts for 7% of all newly diagnosed lymphomas.[1] While predominantly occurring in the stomach, this type of lymphoma may be diagnosed in virtually any organ of the human body. The close association between development of gastric MALT-lymphoma and *Helicobacter pylori* has led to successful attempts to use antibiotic treatment against HP as anti-lymphoma therapy in such patients.[2-4]

In patients with *a priori* disseminated/extragastric disease or refractory to HP-eradication, systemic treatment approaches are being explored due to promising results obtained with phase II studies[5-8] and one controlled trial.[9] In the latter, a significantly superior event free survival at ten years was noted with application of CHOP/CVP chemotherapy as compared to surgery and radiation. In view of the scarce data, however, no standard regimen for systemic therapy of MALT lymphoma has emerged, warranting further studies of novel agents with a potentially favorable toxicity profile.

Bortezomib is the first agent of a novel class of agents targeting the proteasome, which results in the disruption of multiple checkpoints and pathways, ultimately leading to apoptosis.[10,11] Bortezomib has been approved for treatment of multiple myeloma, but has also been tested in various studies of B-cell lymphomas of different histologies.[12] No systematic attempt to test the activity of bortezomib in patients with MALT lymphoma has been reported so far. According to the current notion, MALT lymphoma arises from marginal zone B-cell cells, which are thought to be related to plasma cells.[13] In fact, up to 30% of patients with MALT lymphoma show the feature of plasmacytic differentiation,[14] and up to 40% have a detectable monoclonal immunoglobulin produced by lymphoma cells[15] suggesting a potential relationship between MALT lymphoma and multiple myeloma. Based on this rationale, along with the promising activity of bortezomib in various B-cell lymphomas, we have performed a single institution phase II study in order to assess the clinical activity of bortezomib in patients with MALT lymphoma.

Design and Methods

Patients with histologically verified extranodal marginal zone B-cell lymphoma of the mucosa associated lymphoid tissue (MALT lymphoma) according to the WHO defini-

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Table 1. Patients' characteristics.

Pat. N.	Gender	Age	Localization	Follow-up months	Treatment before bortezomib	Autoimmune disease	Autoimmune antibodies	Cycles	Response	Relapse
01	Male	56	Colon	26	None	None	Neg	8	PR	No
02	Female	48	Stomach, lung, parotid	25	None	None	Neg	8	PR	No
03	Female	56	Ocular adnexa	17	None	None	Neg	8	CR	No
04	Female	64	Ocular adnexa	27	None	None	Neg	8	PR	No
05	Female	64	Stomach	29	HP-eradication	CAT[1]	Thyroglobulin Anti-TPO	8	CR	No
06	Female	33	Ocular adnexa	19	None	None	Neg	8	CR	No
07	Male	72	Stomach	24	HP-eradication	None	ANA/ANF	8	PR	No
08	Female	51	Ocular adnexa, colon	23	Radiation, rituximab	None	ANA/ANF	8	SD	Yes
09	Male	36	Ocular adnexa	26	None	None	ANA/ANF	8	SD	No
10	Female	48	Ocucular anexa	18	None	None	ANA/ANF	4	CR	Yes
11	Male	39	Lung, parotid, stomach, ocular adnexa	23	Surgery, radiation, chemotherapy	None	Neg	8	PR	Yes
12	Female	42	Ocular adnexa, lung, stomach	24	None	None	Neg	8	PR	Yes
13	Female	73	Stomach	13	HP-Eradication	CAT[1]	Thyroglobulin Anti-TPO	8	CR	No
14	Female	75	Parotid	12	None	CREST-syndrome	ANA/ANF	4	CR	No
15	Female	58	Breast	9	None	None	Neg	8	SD	No
16	Female	39	Parotid	11	None	SLE	ANA/ANF	4	CR	No

[1]*chronic autoimmune thyroiditis.*

tion,[2] without signs of transformation to diffuse large B-cell lymphoma as evidenced by mapping biopsies, were eligible for enrolment in this prospective phase II study.

Diagnosis of MALT lymphoma was carried out on biopsy samples evaluated by two reference hematopathologists (AC, LM) according to the recent WHO classification.[13] Immunological phenotyping on paraffin sections was done for demonstration of light-chain restriction and the phenotype $CD20^{+}CD5^{-}CD10^{-}$ cyclinD1-$CD23^{-}$, which is consistent with MALT lymphoma. Both patients with newly diagnosed MALT lymphoma or relapsing/progressing after prior therapy were eligible. In terms of prior chemotherapy or radiation, an interval of at least eight weeks between completion of therapy and initiation of treatment with bortezomib was required. In case of gastric lymphoma, patients with disease dissemination beyond the stomach were immediately eligible, while patients undergoing HP-eradication as initial therapy had to be refractory to antibiotic treatment for at least 12 months for inclusion. Only patients aged older than 18 years with a WHO performance status ≥2 were eligible, and adequate renal (serum creatinine <1.5 mg/dL), liver (total bilirubin <2.0 mg/dL and transaminase level <two times the upper limits of normal) and bone marrow (leukocyte count >3500 /mm^3, platelet count >100,000 /mm^3) functions were also prerequisites. Patients with severe concomitant diseases including another malignancy within the last five years, active infections, psychiatric disorders or peripheral neuropathies were not eligible. In female patients of childbearing age, a pregnancy had to be excluded before inclusion in the trial, and patients were required to use adequate contraception during the whole duration of treatment.

All patients gave written informed consent according to institutional guidelines, and the trial was approved by the local Ethical Committee. In addition, the trial had been registered at *www.clinicaltrials.gov* before the start of the study (*ClinicalTrials.govIdentifier:NCT 00373906*).

All patients underwent extensive staging according to our standard protocol[16] before initiation of therapy. Staging was performed according to the Ann Arbor staging system as modified by Mushoff and Radaskiewicz[16] for gastric lymphoma.

Bortezomib was given by intravenous bolus injection at a dose of 1.5 mg/m^2 on days 1, 4, 8 and 11, repeated every 21 days. Routine pre-medication consisted of an intravenous 5HT3 anatgonist given immediately before application of chemotherapy and hydration with 500 mL NaCl i.v after injection of bortezomib.

In case of toxicities exceeding WHO grade 3 (both for hematologic and non-hematologic toxicities except neuropathy), the further application of bortezomib was delayed either until the side effects had resolved to WHO grade 1 or better (for non-hematologic toxic-

ities), and until a hemoglobin value of >7.5 g/dL, an ANC of >0.75×10⁹/L and a platelet count of >50×10⁹/L had been reached. For the following cycle, the dose of bortezomib had to be reduced to 1.3 mg/m² (if the patient had been receiving 1.5 mg/m²), 1.0 mg/m² (if the patient had been given 1.3 mg/m²) and finally 0.7 mg/m² (if the preceding cycle had been at a dose of 1.0 mg/m²). Dose reductions below 0.7 mg/m² were not allowed as per protocol, and patients had to be excluded from the study. In terms of neuropathy, no actions regarding bortezomib dose were taken in case of grade 1 toxicity, while the drug was reduced one dose-level in case of neuropathy grade 2, by 2 dose levels in case of grade 3 toxicity and discontinued for grade 4 toxicity.

Bortezomib (Velcade®) was provided free of charge by Janssen Cilag Pharma, Vienna, Austria

Complete blood counts were evaluated immediately at the start of each cycle and on day 8. In case of a persisting nadir of the white blood cells ≤3.0×10⁹/L (or neutrophiles ≤1.0×10⁹/L) and/or the platelets ≤100×10⁹/L, the next treatment cycle was delayed by one week until normal values had been achieved. Restaging was performed after 4 cycles, and treatment was continued in the absence of progressive disease for a maximum of 8 cycles. Assessment of response was performed according to standard guidelines[17] and according to the GELA-criteria as outlined by Copie-Bergmann and co-workers[18] in cases of lymphoma restricted to the stomach, and the time to relapse and failure free interval were calculated from the first time of documented remission, follow-up time from first application of bortezomib.

Primary endpoint of the study was the objective response rate, i.e. rate of partial remissions (PR) and complete remissions (CR), while tolerance of chemotherapy in this cohort of patients was the secondary endpoint. Based on the hypothesis of an expected response rate between 40-60%, the planned number of patients for inclusion in the study was 16 according to the Simon rule.[19]

Results and Discussion

Sixteen consecutive patients were included in the study (12 female/4 patients male). Fourteen patients had newly diagnosed or untreated MALT lymphoma, while 2 patients presented with systemic relapse from lung lymphoma following surgery, radiation and chemotherapy in one patient and from orbital lymphoma following radiation and rituximab in the other case. Detailed patient characteristics are shown in Table 1. In the 14 patients with untreated lymphoma, 3 had been refractory to HP-eradication administered for localized gastric MALT lymphoma. Out of the remaining 11 patients, 2 presented with gastric plus extragastric MALT-lymphoma, and 9 had extragastric disease. Four patients had an underlying autoimmune condition, i.e. autoimmune thyroiditis in 2 patients and CREST-syndrome and SLE in one case each. An additional 4 patients had elevated anti-nuclear antibody titres without clinical signs of overt autoimmune disease. A monoclonal immunoglobulin of similar isotpye as the lymphoma cell surface Ig was detected in the blood of 5/16 patients (31%).

The median number of cycles given to our patients was 8 (range; 4-8), with 3 patients discontinuing treatment (one in CR and the other in PR) after 4 courses due to personal reasons. Toxicities were mainly non-hematologic, while no cases of hematotoxicity exceeding WHO grade 2 were reported in our cohort of patients (Table 2). All patients except one, however, required dose reductions from 1.5 mg/m² to 1.3 mg/m², and 9 of these 15 patients required further dose reduc-

Table 2. Side effects.

Pat. N.	1.5 mg/m²	1.3 mg/m²	1.0 mg/m²	Toxicity leading to dose reduction	Toxicities encountered
01	Cycle 1-4	Cycle 5	Cycle 6-8	Polyneuropathy	PNP II, exanthem
02	Cycle 1-4	Cycle 5	Cycle 6-8	Polyneuropathy	PNP II
03	Cycle 1-2	Cycle 3-6	Cycle 7-8	Polyneuropathy	PNP II, nausea, emesis II
04	Cycle 1-5	Cycle 6-8		Polyneuropathy	PNP II, diarrhea II, nausea
05	Cycle 1-2	Cycle 3-4	Cycle 5-8	Diarrhea	PNP II, diarrhea II, nausea, emesis II
06	Cycle 1-2	Cycle 3-6	Cycle 7-8	Diarrhea	PNP II, diarrhea III, nausea, emesis III, arthralgia
07	Cycle 1-4	Cycle 5-6	Cycle 7-8	Diarrhea	PNP I, diarrhea I, nausea
08	Cycle 1-3	Cycle 4	Cycle 5-8	Polyneuropathy	PNP II, arthralgia
09	Cycle 1-4	Cycle 5-8	–	Polyneuropathy	PNP II, exanthem
10	Cycle 1-4	–	–	–	–
11	Cycle 1-4	Cycle 5-6	Cycle 7-8	Polyneuropathy	PNP II
12	Cycle 1-2	Cycle 3-8		Diarrhea	Diarrhea III, nausea, exanthem
13	Cycle 1	Cycle 2	Cycle 3-8	Diarrhea	PNP I diarrhea I,
14	Cycle 1	Cycle 2-3		Diarrhea	Diarrhea I
15	Cycle 1-6	Cycle 7-8		Diarrhea	PNP I, diarrhea III
16	Cycle 1	Cycle 2-4		Fever	Fever IVw

tions to 1.0 mg/m^2. Only 3/15 patients required a reduction before the third course of therapy, while 4 patients had the first reduction at cycle 3, five at cycle 5, and one patient each at cycle 4, 6 and 7, respectively. Dose reductions as per protocol were either due to diarrhea, emesis and neuropathy or a combination thereof in 14 patients, while recurring fever without signs of infection was the reason in one additional patient, who suffered from an underlying SLE. Interestingly, the rheumatologic complaints of this patient improved dramatically for the time of therapy. Thirteen patients (80%) developed neuropathy (5 cases of grade 1, 8 grade 2), and 8 patients (50%) had diarrhea (grade 1 in 3, grade 2 in 2 and grade 3 in a total of 3 patients). Slight arthralgias were seen in 2 patients, while 6 (38%) complained of mild nausea, and 4 had WHO grade rated emesis; grade 1 in one patient, grade 2 in 2 and grade 3 in one patient. Three patients (19%) had a transient bortezomib-related exanthema.

In total, 13/16 patients (80%) showed an objective response, while 3 patients had stable disease. Seven patients were rated as CR (43%), while 6 had a PR (37%). Three patients had been rated as PR in the initial restaging and showed a delayed CR after 8 courses. After a median follow-up of 23 months (range; 9-29), all patients are alive. Four have relapsed/progressed, with the time to relapse and next treatment being 6-22 months, respectively. The remaining 12 patients continue to be in ongoing remission/stable disease (Table 1), with the median PFS being 22 months.

Our data demonstrate that bortezomib is active in patients with MALT lymphoma, with the overall response rate being a promising 80% (13/16 patients). Seven patients were rated as CR (43%), while 6 had a PR (37%). A recent paper by Goy and co-workers[12] has applied the same dose and schedule in patients with various types of B-cell lymphomas. In their study, the overall response rate of patients with mantle cell lymphoma was 41% (with 50% of responding patients each reaching CR and PR), while it was lower at 19% for the mixed population of other B-cell lymphomas, including diffuse large B-cell lymphoma and various types of indolent lymphomas. In spite of the highly pre-treated patient population in this series, dose reductions were only required in 18% of patients. Our schedule had thus been chosen in analogy to allow for indirect comparison with other types of lymphoma, and because the dose and schedule had been tolerated without substantial side effects.

The rate of toxicity, however, was much higher than expected in our cohort of patients, as all patients except one required at least one dose reduction. The main reasons for dose reduction were neuropathy and diarrhea, which necessitated at least one dose reduction in 15/16 patients (Table 2). We cannot offer a definite explanation for this finding and the difference to other reports with less substantial toxicity. One of the major differences is the median number of cycles administered, which was 8 in our pilot study, the minimum number of cycles administered being 4. In contrast, the study by Goy and co-workers[20] reported a median number of 2 cycles per patient, which was in part due to rapid progression especially in the patients with DLBCL. In fact, the required dose reductions occurred before cycle 3 in only 3 of the 15 patients, while reductions were performed at or after the third course in the remaining 12 cases (Table 1). In view of the relatively indolent nature of MALT lymphoma with the respective long durations of treatment and survival, the issue of both acute and delayed toxicity is indeed a substantial one. As has already been discussed with other chemotherapeutic regimens in MALT lymphoma,[21,22] regimens with low toxicity should preferentially be applied, and promising results have been obtained with fludarabine-based[22] therapies or cladribine,[5] with response rates at prolonged follow-up reaching 100% in selected subgroups of patients. Especially with cladribine, a 100% CR rate was seen in gastric lymphoma, while extragastric localizations had a much less favorable course.[5,7] While the number of patients is small in our study, the results again suggest a favorable response rate for patients with gastric lymphoma.

Given the favorable overall response rate, we think that bortezomib warrants further investigation in patients with MALT lymphoma. The relatively high toxicity nevertheless suggests that further trials should be performed at lower doses and in combination with other potentially active agents.

Authorship and Disclosures

Study design: MT, MR; patient management: MT, CJ, AP, MF, WH, CZ, MR; evaluation of histologies: LM, AC; assessment and analysis of data: MT, CJ, AP, LM, MR; manuscript writing: MT, MR.

The authors reported no potential conflicts of interest.

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