

Clinical activity of bortezomib in relapsed/refractory MALT lymphomas: results of a phase II study of the International Extranodal Lymphoma Study Group (IELSG)

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Background: The nuclear factor-kappa B activation in mucosa-associated lymphoid tissue (MALT) lymphoma pathogenesis provided the rationale for the evaluation of bortezomib in this malignancy.

Patients and methods: Thirty-two patients with relapsed/refractory MALT lymphoma were enrolled. Thirty-one patients received bortezomib 1.3 mg/m² i.v., on days 1, 4, 8, and 11, for up to six 21-day cycles.

Results: Median age was 63 years (range, 37–82 years). Median number of prior therapies was 2 (range, 1–4). Nine patients had Ann Arbor stage I, 7 patients had stage II, and 16 patients had stage IV. Primary lymphoma localization was the stomach in 14 patients; multiple extranodal sites were present in 10 patients. Among the 29 patients assessable for response, the overall response rate was 48% [95% confidence interval (CI) 29% to 67%], with 9 complete and 5 partial responses. Nine patients experienced stable disease and six had disease progression during therapy. The most relevant adverse events were fatigue, thrombocytopenia, neutropenia, and peripheral neuropathy. After a median follow-up of 24 months, the median duration of response was not reached yet. Five deaths were reported, in two patients due to disease progression.

Conclusion: Bortezomib is active in relapsed MALT lymphomas. Further investigations to identify optimal bortezomib dose, schedule, and combination regimens are needed since the frequent detection of dose-limiting peripheral neuropathy.

Key words: bortezomib, MALT lymphoma, non-Hodgkin’s lymphoma, therapy

introduction

Extranodal marginal zone B-cell lymphoma, also defined as mucosa-associated lymphoid tissue (MALT) lymphoma, represents the third entity in terms of incidence among lymphoid neoplasms in Western countries [1]. MALT lymphoma usually has an indolent course, with a 5-year survival ranging from 80% up to 95%, but with relatively short progression-free survival rates, particularly for patients presenting with advanced stage or unfavorable International Prognostic Index (IPI) [2, 3].

The eradication of *Helicobacter pylori* with antibiotics is considered safe and active as the sole initial treatment in localized gastric MALT lymphoma [2]. Some evidence supports

the antitumor activity of antibiotic therapy directed against *Chlamydomydia psittaci* infection in primary orbital lymphoma and against other microorganisms in other rare locations [4]. However, it is still unknown whether antibiotics will definitively cure the lymphoma.

For the patients who fail to respond to antibiotics and for non-infection-related or disseminated disease, the therapeutic choice includes conventional oncological modalities such as antibody therapy, chemotherapy, radiotherapy, and surgery, alone or in combination [5–11]. Unfortunately, few studies, in most cases with nonrandomized design, addressed the problem. Therefore, optimal therapy for MALT lymphomas remains to be determined and new systemic treatment strategies should be investigated [2].

During the last decade, a number of studies demonstrated clinical efficacy of the proteasome inhibitor bortezomib in multiple myeloma and other hematologic

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malignancies [12–14]. Evidence of significant antitumor activity was reported in different subsets of non-Hodgkin's lymphomas including both indolent and aggressive entities [15–22]. Different molecular mechanisms of action were claimed for bortezomib including cell-cycle deregulation, direct induction of apoptosis, and negative regulation of the nuclear factor-kappa B (NF- κ B) activity [23–25]. The constitutive activation of NF- κ B in MALT lymphomas—which represents the common final molecular pathway of the most frequent genetic lesions associated with the disease [26, 27]—provides a sound rationale for clinical investigations of bortezomib in this clinical setting along with the clinical activity of the drug in several lymphoid neoplasms [13, 14]. The present study, coordinated by the International Extranodal Lymphoma Study Group (IELSG), assessed the antitumor activity of bortezomib, as single agent, in MALT lymphoma patients relapsed or refractory after prior systemic therapy including either chemotherapy or immunotherapy with rituximab.

materials and methods

study design and end points

The primary objective of this nonrandomized phase II study was to assess the overall response rate (ORR) to bortezomib in MALT lymphoma patients. The secondary objective was to assess the toxicity profile of bortezomib in this population. The sample size was based on the primary end point of ORR. The number of patients required was therefore calculated on the assumption that a response rate of at least 40% would be sufficient to consider active experimental therapy. Accordingly, up to 33 patients were required to provide a single-arm study with 80% power at an overall 5% significance level [28].

study sites

The trial was conducted between March 2005 and April 2009 at 10 centers in Italy, Spain, and Switzerland and was carried out according to the principles of the Declaration of Helsinki with its current amendments. All patients gave written informed consent. The protocol and informed-consent forms were approved by the local institutional review boards and ethics committees of each participating institution. This study is registered with ClinicalTrials.gov, number NCT00210327.

patient population and pretreatment evaluation

Patients were eligible if they were >18 years of age and had biopsy-proven extranodal marginal zone B-cell lymphoma of MALT type, arising at any extranodal site, including both localized and advanced stage disease, and diagnosed according to the World Health Organization classification criteria [1], relapsed or refractory after prior systemic therapy including chemotherapy, antibody therapy, or combination of both. Patients who did not achieve an objective response [complete response (CR) or partial response (PR)] to the last prior therapy were defined refractory. All cases had a histological review by expert lymphoma pathologists; in all cases, measurable or evaluable disease, defined according to the National Cancer Institute (NCI) International Workshop criteria, was required [29]. Patients were required to have a performance status (PS) of 0 to 2, according to the criteria of the Eastern Clinical Oncology Group, no prior lymphoma treatment for at least 4 weeks. Patients were not eligible if there was evidence of histological transformation into aggressive lymphoma, central nervous system involvement, previous or concomitant malignancy with the exception of nonmelanoma skin cancer, clinically relevant cardiac disease, and impairment of bone marrow function (neutrophils $<1.0 \times 10^9/l$,

platelets $<30 \times 10^9/l$), unless due to lymphoma involvement. Patients with a positive serological test for the human immunodeficiency virus were also excluded. All patients were clinically staged according to the Ann Arbor criteria and underwent staging procedures including history; physical examination; complete blood counts; chemistry profile; computerized tomography of the chest, abdomen, and pelvis; and bone marrow aspiration/biopsy within the 4 weeks before treatment. Magnetic resonance imaging of the orbit was carried out if clinically required. Endoscopic investigations with multiple mucosal biopsies were carried out in case of gastric lymphoma involvement. The IPI was used to determine the prognostic risk [30].

treatment

All patients were treated with bortezomib (supplied by Johnson & Johnson) at a dose of 1.3 mg/m^2 twice weekly for 2 weeks (days 1, 4, 8, and 11) followed by a 1-week rest period (one cycle); patients were treated for up to a total of six cycles. All cycles were delivered on an outpatient basis. Treatment was discontinued on withdrawal of the patient's consent, disease progression, or the occurrence of unacceptable toxic effects. Growth-stimulating factors were not routinely administered to prevent neutropenia, but patients who experienced grade 3 or 4 neutropenia or developed neutropenic fever between cycles might have received growth factors for subsequent cycles of therapy, at the physician's discretion. No specific recommendation was done for antiviral prophylaxis.

assessment of toxicity

Patients who received at least one dose of bortezomib were included in the analysis of toxicity evaluated and graded according to NCI–Common Toxicity Criteria Toxicity (version 3) [31]. Neuropathic pain and peripheral sensory neuropathy were managed with the use of established dose-modification guidelines [32].

assessment of response

Patients were assessed for response after two and six courses of therapy. Restaging included a repeat of all previously abnormal staging tests. Tumor responses were classified as CR, PR, stable disease (SD), or relapsing/progressive disease according to the NCI standardized response criteria for non-Hodgkin's lymphomas. ORR was defined as the sum of CR and PR rates [29]. For primary gastric localizations, definition of response was based on endoscopic and histological findings after extensive sampling through the gastric mucosa and defined according to the Groupe d'Etude des Lymphomes de l'Adulte (GELA) histological grading system for post-treatment evaluation [33].

statistical considerations

Statistical analysis was conducted using the STATA 5.0 software package (Stata Statistical Software: Release 5.0; Stata Corporation 1997, College Station, TX). The median follow-up was computed by the reverse Kaplan–Meier method [34]. Response duration and time to treatment failure were defined according to the NCI criteria [29]. Response duration was calculated from the date of achievement of the best response to the date of relapse/progression or last follow-up; progression-free survival was calculated from the date of trial registration to the date of disease progression or death from any cause or last follow-up. Survival probabilities were calculated using the life table method and survival curves were estimated by the method of Kaplan–Meier [35] and reported with 95% Greenwood's confidence intervals (95% CIs); survival differences between patient groups were evaluated using the log-rank test [36]. Binomial exact 95% CIs were calculated for remission rates. Associations in two-way tables were tested for statistical significance using the Fisher's exact test (two tailed). *P*-values of ≤ 0.05 (two-sided test) were considered to indicate statistical significance.

results

patients characteristics

Thirty-two patients with a median age of 63 years (range, 37–82 years) were enrolled. Patient characteristics at the time of study entry are listed in Table 1. The primary site of lymphoma localization was defined as the clinically dominant extranodal component requiring diagnostic investigations and to which treatment is directed at the time of study entry. Stomach was the primary site in 14 patients, 18 patients had a primary non-gastric localization, and in 10 patients multiple extranodal sites were present. No patient had baseline impairment of bone marrow function.

previous treatments

The median time from first diagnosis to study entry was 5 years (range, 0.9–17.6 years). The 14 patients with a primary gastric localization were negative for *H. pylori* infection at the time of study onset. Six of them, with prior evidence of infection, had initial anti-*H. pylori* antibiotic therapy. One more patient, with primary orbit localization had doxycycline therapy to eradicate *Chlamydomphila* infection. All patients received prior systemic therapy with chemotherapy and/or rituximab before entering the study. Median number of prior therapies was 2 (1–4). One patient received only rituximab therapy, 24 additional patients had combination of rituximab plus chemotherapy. Five of these

patients also had prior radiotherapy and three had therapeutic surgery. Among the 31 patients who received chemotherapy, 18 had single alkylating agents (chlorambucil or cyclophosphamide) or the CVP (cyclophosphamide, vincristine, and prednisone) regimen, in 2 cases a fludarabine-based regimen, and 11 patients an anthracycline-containing regimen [CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) or CHOP-like regimens]. In one of these cases prior autologous bone marrow transplantation and in another prior therapy with yttrium 90 ibritumomab tiuxetan were reported. No patient received rituximab within 3 months before enrollment.

treatment

Six patients (19%) completed the treatment program without dose reduction. Thirteen patients (42%) required a dose reduction at least once during treatment program, in 10 patients (32%) due to neuropathic toxicity. Twenty-two patients (71%) had early treatment discontinuation, in most cases due to neuropathic manifestations (nine patients, corresponding to the 29% of the whole cohort) or disease progression (five patients, 16% of the whole cohort). Median number of courses delivered was 4 (range 4–6).

response to bortezomib therapy and outcome

Among the 32 patients enrolled, 3 patients were not evaluated for response. One patient withdrew his consent before treatment start. One patient experienced an ischemic stroke after a single course of therapy. One patient, who received prior chlorambucil therapy, had a diagnosis of acute myeloid leukemia immediately after the completion of the first course of study treatment.

Fourteen (48%; 95% CI 29% to 67%) of the 29 assessable patients had objective responses with nine CRs (31%; 95% CI 15% to 51%) and five PRs (17%; 95% CI 6% to 36%). Responses were observed either in gastric and non-gastric MALT lymphomas (Table 2). In six cases achieving objective response (five CR and one PR), patients were reported as resistant to last prior therapy; in two other refractory patients, a stabilization of disease was reported (Table 3). The median time to best response was 3 months (range, 1–16 months). Whereas in nine patients (31%; 95% CI 15% to 51%) SD was observed, six patients (21%; 95% CI 8% to 40%) experienced a disease progression.

After a median follow-up of 24 months (range, 5–47 months), 4 of the 14 responding patients experienced relapse:

Table 1. Patients' clinical characteristics at study entry

| Features | No. of patients (%) |
|-------------------------------------|---------------------|
| Sex | |
| Males | 17 (53) |
| Females | 15 (47) |
| ECOG PS | |
| 0 | 30 (94) |
| 1 | 2 (6) |
| Ann Arbor stage | |
| I _E | 9 (28) |
| II _E | 7 (22) |
| IV | 16 (50) |
| Serum LDH | |
| Elevated | 3 (9) |
| Serum β ₂ -microglobulin | |
| Elevated | 9 (28) |
| Bone marrow involvement | 3 (9) |
| IPI risk | |
| Low | 17 (53) |
| Low/intermediate | 5 (16) |
| Intermediate/high | 10 (31) |
| High | – |
| Primary site | |
| Stomach | 14 (44) |
| Skin/subcutis | 11 (34) |
| Lung | 4 (13) |
| Genital tract | 1 (3) |
| Pharynx | 1 (3) |
| Orbit | 1 (3) |
| Multiple extranodal sites | 10 (31) |

ECOG, Eastern Clinical Oncology Group; PS, performance status.

Table 2. Best response to bortezomib in 29 assessable patients

| Response | All patients (N = 29), n (%) | Gastric localizations (N = 13), n (%) | Non-gastric localizations (N = 16), n (%) |
|------------------------|---------------------------------|--|--|
| Overall response rate | 14 (48) | 8 (62) | 6 (38) |
| Complete remission | 9 (31) | 6 (46) | 3 (19) |
| Partial remission | 5 (17) | 2 (15) | 3 (19) |
| Stable disease | 9 (31) | 4 (31) | 5 (31) |
| Progression of disease | 6 (21) | 1 (8) | 5 (31) |

Table 3. Information concerning patients responding to study treatment

| Age (years) | Sex | Primary disease site | Ann Arbor stage | Prior therapies | Last response | No. of cycles of bortezomib | Best response to bortezomib |
|-------------|-----|----------------------|-----------------|--|---------------|-----------------------------|-----------------------------|
| 49 | M | Skin | I | R RT | SD | 5 | CR |
| 56 | M | Stomach | I | CLB | PD | 6 | CR |
| 73 | F | Stomach | IV | CLB CLB | CR | 5 | CR |
| 40 | M | Skin | I | R-CLB | CR | 5 | PR |
| 76 | F | Stomach | IV | FN | CR | 3 | PR |
| 62 | F | Lung Skin | IV | R-CVP RT | CR | 4 | PR |
| 65 | F | Skin | I | R-CLB | CR | 5 | CR |
| 46 | F | Stomach | I | Antibiotics CTX R CHOP Surgery | PD | 6 | CR |
| 41 | M | Skin | IV | CHOP R | PR | 6 | CR |
| 43 | M | Stomach | II | Antibiotics R-CLB | SD | 6 | CR |
| 60 | F | Stomach | II | CLB R CLB RT | SD | 4 | PR |
| 77 | M | Stomach | IV | R-CLB | PR | 3 | CR |
| 64 | F | Stomach | I | Antibiotics CHOP R R CLB | SD | 1 | CR |
| 37 | F | Skin | I | R R-CHOP | CR | 6 | PR |

M, male; R, rituximab; SD, stable disease; CR, complete response; RT, radiotherapy; CLB, chlorambucil; PD, progressive disease; F, female; PR, partial response; FN, fludarabine and mitoxantrone; CVP, cyclophosphamide, vincristine, and prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; CTX, cyclophosphamide.

two after a CR and two after a PR. Three of the nine patients in whom an SD was documented after the study treatment experienced a disease progression. No significant difference in the duration of response was seen between the patients achieving a CR and those achieving a PR (58% of CRs and 56% of PRs have not yet relapsed at 4 years). The median response duration was not reached (Figure 1).

Five patients died: two died of disease progression (after the diagnosis of a gastric cancer in one case), one patient died of liver failure, which occurred in the context of hepatitis C virus-related chronic hepatopathy, 5 months after a single cycle of study treatment early interrupted after disease progression with no evidence of toxicity. In one patient, a diagnosis of acute myeloid leukemia was carried out on a bone marrow biopsy whose result was not available at time of treatment start, when the patient had normal blood counts. A fifth patient died of unknown causes 11 months after a single cycle of study treatment interrupted due to ischemic stroke (Table 4).

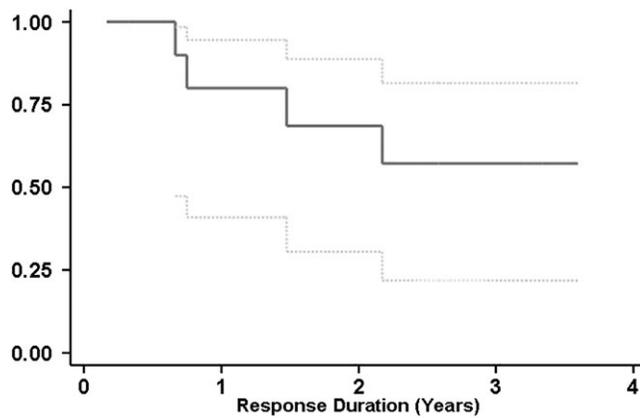
Among the 31 patients who received at least one cycle of study treatment, median progression-free survival was 25 months (range, 1–47 months) (Figure 2).

prognostic factors

Despite the small number of patients, several variables—including sex, age, stage, tumor burden, performance status, lactate dehydrogenase and β 2-microglobulin serum level, IPI, B-symptoms, previous treatment, and bone marrow involvement—were analyzed for their possible association with response, with no significant result. A trend toward an higher probability of response was observed for patients receiving at least three cycles of therapy ($P = 0.08$).

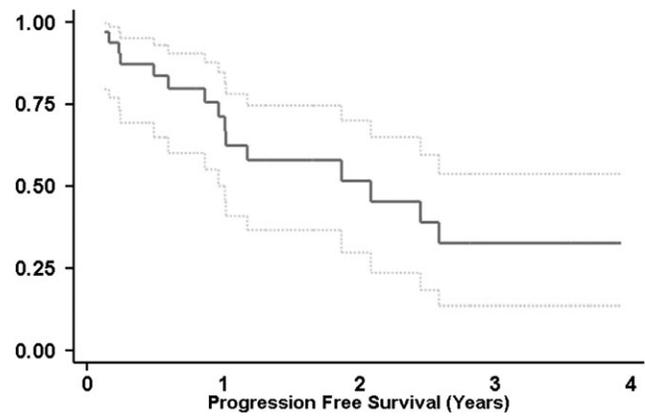
toxicity

The adverse events observed in the 132 courses analyzed for toxicity are reported in Table 5. The majority of these events



| Interval | Entered | Relapsed | Censored | Survival | [95% Conf. Int.] |
|----------|---------|----------|----------|----------|------------------|
| 0 - 1 yr | 14 | 2 | 4 | 0.83 | 0.48 - 0.96 |
| 1 - 2 yr | 8 | 1 | 1 | 0.72 | 0.35 - 0.90 |
| 2 - 3 yr | 6 | 1 | 2 | 0.58 | 0.21 - 0.83 |
| 3 - 4 yr | 3 | 0 | 3 | 0.58 | 0.21 - 0.83 |

Figure 1. Life tables and Kaplan–Meier survival curve with 95% Greenwood confidence interval for response duration from the achievement of best response (nine complete response and five partial response). The median follow-up time for the 14 responding patients was 3 years, 4 of them experienced relapse or progression, median duration of response was not reached.



| Interval | Entered | Relapsed | Censored | Survival | [95% Conf. Int.] |
|----------|---------|----------|----------|----------|------------------|
| 0 - 1 yr | 31 | 10 | 7 | 0.64 | 0.43 - 0.79 |
| 1 - 2 yr | 14 | 2 | 4 | 0.53 | 0.32 - 0.71 |
| 2 - 3 yr | 8 | 3 | 1 | 0.32 | 0.12 - 0.54 |
| 3 - 4 yr | 4 | 0 | 4 | 0.32 | 0.12 - 0.54 |

Figure 2. Life tables and Kaplan–Meier survival curve with 95% Greenwood confidence interval for progression-free survival (PFS). Median PFS was 25 months in the 31 patients who received at least one dose of the study drug.

Table 4. Information concerning the five patients dead during study

| Age (years) | Sex | Primary disease site | Prior therapy | No. of cycles of bortezomib | Response | Time of death | Cause of death |
|-------------|-----|----------------------|---------------|-----------------------------|--------------|--------------------------|------------------------|
| 65 | M | Stomach | R-CLB | 1 | Not assessed | 9 months after study rx | Acute myeloid leukemia |
| 76 | F | Stomach | FN | 3 | PR | 13 months after study rx | Lymphoma |
| 63 | M | Lung | CLB | 1 | Not assessed | 11 months after study rx | Unknown |
| | | | R-CLB | | | | |
| | | | R-CHOP | | | | |
| 81 | F | Orbit | CHOP | 1 | PD | 5 months after study rx | Liver failure |
| | | | RT | | | | |
| 59 | M | Lung | R-CLB | 2 | PD | During rx | Lymphoma |

M, male; R, rituximab; CLB, chlorambucil; rx, therapy; F, female; FN, fludarabine and mitoxantrone; PR, partial response; CHOP, cyclophosphamide, doxorubicin, vincristine, and prednisone; RT, radiotherapy; PD, progressive disease.

were of mild to moderate severity and most of them were reversible. A relevant proportion of patients experienced neurological side-effects (20 patients, 65%; 95% CI 45% to 81%) in terms of peripheral sensory neuropathy, neuropathic pain, and orthostatic hypotension; these manifestations represented main cause of dose reduction and early treatment discontinuation (see above in ‘Treatment’ section). No toxicity-related deaths were observed.

discussion

The relevant pathogenetic role of the constitutive activation of NF- κ B in MALT lymphomas provides the biologic rationale for this phase II study. Indeed, the anti-lymphoma mechanism of action of bortezomib (different from that of either the classical

chemotherapeutic agents or the currently used monoclonal antibodies and leading to a potent inhibition of NF- κ B) strongly supported exploring its clinical activity.

Though bortezomib has been recently shown to be active in untreated patients with MALT lymphomas [37], its toxicity seems to indicate that other approaches may be preferred for frontline treatment in this usually very indolent disease. However, only a very few patients with relapsing/refractory MALT lymphoma have been included in the published clinical trials of bortezomib in indolent lymphomas [38].

The present study is the first one exploring its activity in a pretreated population with a long disease history, with patients often resistant to the last prior systemic therapy, which would represent the most likely setting for its routine clinical use.

Table 5. Worse toxicity per patient (*n*)^a

| Toxicity | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|-------------------------------|---------|---------|---------|---------|
| Fatigue | 2 | 3 | 3 | 1 |
| Neuropathic pain | 2 | 4 | 3 | – |
| Peripheral sensory neuropathy | 2 | 8 | 4 | – |
| Cutaneous rash | 3 | 3 | 1 | – |
| Neutropenia | 1 | 2 | 4 | – |
| Thrombocytopenia | 3 | 3 | 4 | – |
| Anemia | – | – | 1 | – |
| Nausea | 2 | 4 | – | – |
| Orthostatic hypotension | – | – | 1 | – |
| Vomiting | 1 | 2 | – | – |
| Infection ^b | 2 | 3 | 1 | – |
| Diarrhea | 3 | 1 | – | – |
| Constipation | 1 | – | 2 | – |
| Fever | 2 | 2 | – | – |
| Headaches | 3 | – | – | – |
| Conjunctivitis | 3 | – | – | – |
| Transaminase | – | 1 | 1 | – |
| Phlebitis | – | 1 | – | – |
| Ischemic stroke | – | – | 1 | – |
| Hypercalcemia | – | 1 | – | – |

^aObserved in 132 cycles of therapy analyzed in 31 patients.

^bOne case of herpes simplex virus 1 infection Grade 1, one case of gastroenteritis Grade 1, two cases of herpes zoster virus (HZV) infection Grade 2, one case of HZV infection Grade 3, and one case of urinary tract infection Grade 2.

The rate and duration of objective responses observed in our study confirm that bortezomib is an active agent in MALT lymphoma. The ORR (48%; 95% CI 29% to 67%) seems lower than the one recently reported in a smaller phase II study by Troch et al. [37] from Austria (81%, 95% CI 54–96%). This difference is very likely due to the different patient selection since our study enrolled pretreated patients all with at least a line of previous systemic chemotherapy and/or rituximab, while in the Austrian trial, 15 of the 16 enrolled patients were chemotherapy naive. The higher dose planned in this study probably has a minor role since most patients had an early dose reduction due to the high rate of neurotoxic adverse events observed.

In our study, response to bortezomib was observed in MALT lymphoma with different primary anatomic sites, with all stages according to Ann Arbor and with different IPI risk. More interestingly, 60% of the patients who were refractory to the last previous systemic therapy had an objective response to bortezomib. Responses also occurred in patients who required dose reductions or who early discontinued the treatment, receiving a lower number of doses than planned, mostly due to the occurrence of adverse events.

The findings of the present study, together with the extremely high remission rate described in untreated patients in the study by Troch et al. [37], confirm that the inhibition of the proteasome might play a role in the disease control of MALT lymphomas through the inhibition of the NF- κ B pathway, as predicted by its peculiar pathogenetic molecular lesions [26, 27] and, perhaps also, by interfering with other intracellular signaling pathways [39].

However, the relevant proportion of patients who experienced toxic events, mainly neuropathic manifestation (64%; 95% CI 45% to 80%) with a negative impact on quality of life, represents a matter of serious concern in a population of patients with an indolent lymphoma.

Whereas no clear explanation of the high proportion of peripheral neuropathy—described also by other studies and not clearly associated with previous treatments [37]—can be recognized, a solution can be possibly achieved with the adoption of a weekly schedule, suggested to be less toxic [40].

The potential reduction of the antitumor activity related to a weekly schedule [41] may be counterbalanced by the combination with other active antitumor agents with different toxicity profiles. In this perspective, a number of reports support the safety of bortezomib combined with different agents, including conventional chemotherapeutic drugs [20, 21, 42] and, obviously, monoclonal antibodies [40]. Preclinical data offer interesting perspectives with respect to the combination of bortezomib with different biologic agents [43, 44]. However, only a very few MALT lymphoma patients have been treated in the studies exploring these combinations [40, 42].

In conclusions, a relevant clinical activity of bortezomib was confirmed in a homogeneous series of pretreated MALT lymphoma patients with relevant representation of adverse prognostic factors. The frequent peripheral neuropathy may, however, reduce the number of patients in whom it can represent a clinically reasonable therapeutic tool. Our findings support the development of novel proteasome inhibitors as well as the exploration of less toxic bortezomib schedules. Further investigations are required in order to identify optimal dose, schedule, and combination regimen.

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disclosure

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