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RAPID COMMUNICATION

The protective effects of lafutidine for bortezomib induced peripheral neuropathy

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Abstract: Peripheral neuropathy (PN) caused by bortezomib is an important complication of multiple myeloma. Subcutaneous injection of bortezomib reduced PN, but 24% of cases were grade 2 PN and 6% of cases were grade 3 PN. PN higher than grade 2 was not resolved by subcutaneous injection. PN higher than grade 3 has serious dose limiting toxicity and is the cause of discontinuing bortezomib treatment. Lafutidine is an H2-blocker with gastroprotective activity and is thought to function by increasing mucosal blood flow via capsaicin sensitive neurons. The same activity of lafutidine is considered to improve glossodynia and taxane induced PN. We hypothesized that lafutidine prevents or improves PN that is caused by bortezomib. In the current study, bortezomib was administered in the usual manner (intravenous administration of bortezomib 1.3 mg/m^2, twice a week for 2 weeks, followed by 1 week without treatment) for up to four cycles to compare our data with other studies. Lafutidine was administered orally at a dose of 10 mg twice daily. In our eight evaluated cases, the total occurrence of PN was four out of eight patients (50%). There were only grade 1 PN (4 out of 8) cases, and no cases higher than grade 2. We conclude that (1) the total occurrence of PN was not improved, (2) there was no PN after the first course, (3) there were only grade 1 cases and there were no cases higher than grade 2, and (4) no cases discontinued bortezomib treatment because of PN. This is the first report showing that lafutidine is useful for the amelioration of bortezomib induced PN.

Keywords: bortezomib induced peripheral neuropathy, lafutidine, capsaicin sensitive neurons, calcitonin gene-related peptide, transient receptor potential 1, multiple myeloma

Introduction

Bortezomib is an important drug for treatment of multiple myeloma (MM).[1–3] However, peripheral neuropathy (PN) is a troublesome adverse event caused by bortezomib.[4,5] PN is the cause of reducing the dose or discontinuing bortezomib treatment.[2,4] Subcutaneous injection of bortezomib reduces PN, however, PN grade 2 (24%) and grade 3 (6%) were still reported.[6] PN higher than grade 3 is not resolved by subcutaneous injection of bortezomib.[6] There are some reviews of bortezomib induced peripheral neuropathy (BIPN).[7,8] The pathogenesis of BIPN is thought to be as follows: (1) mitochondrial and endoplasmic reticulum damage appears to be one of the causes of BIPN; (2) bortezomib activates the mitochondrial based apoptotic pathway;[9] (3) inhibition of nuclear factor kappa B activation, which is the main action of bortezomib,[10] blocks the transcription of nerve growth factor mediated neuronal survival;[11] (4) intramitochondrial calcium concentrations are increased by bortezomib leading to disruption of calcium homeostasis and induction of mitochondrial apoptosis;[12] and (5) proteasome inhibitor induced PN may also affect microtubule associated proteins and cause microtubule stabilization.[13]

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Lafutidine is an H2-receptor antagonist with gastroprotective activity and is thought to function via capsaicin sensitive afferent neurons.[14–17] Capsaicin has gastroprotective activity by increasing mucosal blood flow via capsaicin sensitive afferent neurons.[18,19] The terminals of capsaicin sensitive sensory neurons and their dorsal root ganglia contain transient receptor potential 1 (TRPV1) that is thought to be the receptor for capsaicin.[20] TRPV1, activated by capsaicin, releases calcitonin gene-related peptide (CGRP)[20] which is the major vasodilator released from capsaicin sensitive nerves.[21] Capsaicin and CGRP lose their gastroprotective activity by blockade of the nitric oxide system.[18,21] Moreover, capsaicin is thought to selectively block afferent sensory neurons.[22]

Lafutidine is thought to increase gastric mucosal blood flow by the mechanisms of activation of capsaicin sensitive afferent nerves and nitric oxide.[14] Lafutidine appears to function similarly to capsaicin via the same neurons.[15–17] Lafutidine has been reported to improve glossodynia[20,23] and taxane induced PN.[24] In these reports, it was assumed that the same activity via capsaicin sensitive afferent nerves improves glossodynia and taxane induced PN. We hypothesized that lafutidine prevents or improves PN that is caused by bortezomib. Therefore, we performed a clinical pilot study on bortezomib and lafutidine in patients with MM.

Patients and methods

Fourteen cases of MM treated with bortezomib and dexamethasone therapy (BD) from November 2010 to January 2012 were included in this pilot study. Table 1 shows the patient characteristics. Five newly diagnosed patients received intravenous high dose dexamethasone therapy[25] before BD. Nine patients were refractory or relapsed cases. Four patients had a vertebral compression fracture, two patients had a rib fracture, and two patients had plasmacytoma of the bones at the beginning of BD. Bortezomib was administered in the usual manner (intravenous administration of bortezomib 1.3 mg/m^2, twice a week for 2 weeks, followed by 1 week without treatment) for up to four cycles. Dexamethasone was administered using a modified method, by infusing intravenously at a dose of 33 mg/patient simultaneously with bortezomib. PN was evaluated at the beginning of every course, from the first course to the end of the fourth course. At this time, lafutidine was administered orally at a dose of 10 mg twice a day throughout the study period with written informed consent under the permission of the Institutional Review Board (of Sakai City Hospital). After four courses, bortezomib was continued, but not administered in the usual manner. Intravenous administration, twice a week, for a period of 2 weeks, was too difficult to continue for elderly patients because of the frequency of therapy, general fatigue

Table 1 Patient characteristics and results (n = 14)

Case no	Age/sex	Type of MM	States at the start of BD	Previous therapy	PN (grade)	Results
1	68/M	IgG κ	Vertebral compression fracture	MP/DMVM	0	Completed 4 courses without skipping
2	51/M	IgA κ	Vertebral compression fracture	HDD	1	Finished 4 courses with long-term skipping
3	77/M	IgG κ	Nothing particular	RT/BIS/DEXA	0	Completed 4 courses without skipping
4	60/F	λ BJP	Anemia	VAD/MP	0	Completed 4 courses without skipping
5	66/M	κ BJP	Diabetic nephropathy	HDD	–	Dropped out within 2 courses because of disqualification
6	75/F	IgG κ	Vertebral compression fracture	DMVM/IFN/MP	1	Finished 4 courses with skipping
7	59/F	IgG λ	Nothing particular	HDD	1	Completed 4 courses without skipping
8	80/F	IgA κ	Vertebral compression fracture	DMVM	–	Dropped out within 2 courses because of general fatigue and diarrhea
9	61/F	IgG κ	Rib fracture	HDD	1	Completed 4 courses without skipping but with reduced dose
10	64/F	IgD λ	Diabetic nephropathy	HDD	–	Dropped out for leukemic change after 2 courses
11	63/M	IgG κ	Rib fracture	DMVM	–	Dropped out within 2 courses because of general fatigue
12	73/F	IgA κ	Nothing particular	DMVM	–	Dropped out within 2 courses because of general fatigue
13	75/F	IgA κ	Plasmacytoma of bone	MP	0	Completed 4 courses without skipping
14	78/M	IgG κ	Plasmacytoma of bone	DMVM/MP	–	Dropped out within 2 courses because of general fatigue and diarrhea

Abbreviations: BD, bortezomib/dexamethasone; BIS, bisphosphonate; BJP, Bence-Jones protein; DEXA, dexamethasone; DMVM, dexamethasone/melphalan/vincristine/ranimustine; F, female; HDD, high dose dexamethasone; IFN, interferon; Ig, immunoglobulin; M, male; MM, multiple myeloma; MP, melphalan/prednisolone; PN, peripheral neuropathy; RT, radiation therapy; VAD, vincristine/doxorubicin/dexamethasone.

and/or diarrhea. Moreover, Richardson et al reported a dose modification guideline of bortezomib,[5] and we adopted intravenous administration of bortezomib once a week or less after four courses.

At the beginning of every course, PN was evaluated by the Short Form McGill Pain Questionnaire,[27] the Patient Neurotoxicity Questionnaire,[28] the visual analog scale, and the National Cancer Institute's Common Terminology Criteria for Adverse Events version 3. Statistical analyses were performed with Fisher's exact test using JMP version 10.0 (SAS Institute Inc., Cary, NC, USA).

Results

All 14 cases received the first course of bortezomib. PN was not observed after the first course. Six cases dropped out before the third course, not because of PN, but because of progression of the disease, disqualification, general fatigue, or diarrhea. No cases discontinued bortezomib therapy because of PN. Six patients completed four courses of bortezomib without missing any treatment. Among these patients, two of the six patients (33%) developed PN grade 1. The other four patients did not develop PN. Including those patients who missed treatment with or without a reduction in dose, eight patients finished four courses of bortezomib. We evaluated these eight cases. PN developed in four of the eight patients (50%). However, all PN cases were grade 1 and there were no severe cases. PN higher than grade 2 was not observed in this study (Table 1).

Discussion

In our pilot study, PN was not observed after the first course. However, in a Japanese Phase I/II study, at least 14.71% of patients had PN after the first course.[26] In another Japanese report, at least 20% of patients had PN after the first course.[29] Therefore, lafutidine may prevent PN, at least until the end of the first course.

In our study, six of 14 cases (43%) dropped out of bortezomib treatment before the third cycle. However, in the Study of Uncontrolled Myeloma Management (SUMMIT) trial,[1] 54 of 202 cases (27%) discontinued treatment early because of progressive disease and 45 of 202 cases (22%) did so because of adverse events. Therefore, 99 of 202 cases (49%) dropped out of treatment early in the SUMMIT trial. The high dropout rate seems to be common to bortezomib treatment.

PN was evaluated until the end of the fourth course because the onset of PN in a previous Japanese trial was 47%, with a median time of 79 days (almost four courses).[26] In another Japanese report, PN was observed within two courses,[29] and a median time of five courses,[30] and three courses[31] have been reported. Because our study had no control group, it was important to compare the occurrence of PN with something else. Therefore, PN after four courses was evaluated under similar conditions to compare our results with previous studies. We thought that it was necessary to complete four courses to compare our results with those from other studies.

The effects of lafutidine on PN were observed in eight patients who finished four courses with or without missing treatment. The occurrence of PN in this study was compared with that in other reports as follows and is summarized in Table 2. The total occurrence of PN in this study was 50%. It was 47% in a Japanese Phase I/II study,[26] ≥40% in a study from Kyushu University,[29] and ≥87% in a study from the Niigata Cancer Center.[30] The total occurrence of PN was not improved in our study. However, in our study, all the cases were grade 1 and there were no severe cases.

PN higher than grade 3 was not observed in the current study. The percentage of PN higher than grade 3 was 3% in the Japanese Phase I/II study, 13% in the study from Kyushu University, 6.7% in the study from Niigata Cancer

Table 2 Comparison of the current study with previous reports

Reports	Number (%)				
	Total occurrence of PN	Grade 1	Grade 2	Higher than grade 2	Higher than grade 3
This trial (n = 8)	4 (50)	4 (50)	0	0	0
Japanese Phase I/II study[26] (n = 34)	16 (47)	–	–	–	1 (3)
Kyushu University Hospital[29] (n = 15)	≥6 (≥40)	–	–	–	2 (13)
Niigata Cancer Center[30] (n = 60)	≥52 (≥87)	–	–	–	4 (6.7)
Six institutes in Kyoto and Osaka[31] (n = 88)	51 (58)				22 (25)
For reference					
VISTA[3] (n = 340)	159 (47)	(15)	(19)	–	45 (13)
APEX[5] (n = 331)	124 (37)	(10)	(18)	–	30 (9)
Moreau et al[6] (n = 74)	33 (44)	–	21 (28)	30 (40.1)*	9 (12.1)

Note: *$P = 0.0242$.

Abbreviations: PN, peripheral neuropathy; VISTA, Velcade as Initial Standard Therapy in multiple myeloma Assessment with melphalan and prednisone; APEX, Assessment of Proteasome inhibition for Extending remissions.

Center, and 25% in the study from six institutes in Kyoto and Osaka.[31]

Subcutaneous injection of bortezomib reduced BIPN, however, it was still reported that there were cases of BIPN grade 2 or worse (24%) and grade 3 or worse (6%).[6] PN higher than grade 3 was not resolved by subcutaneous injection of bortezomib.[6] PN higher than grade 3 is thought to have serious dose limiting toxicity and is the cause of discontinuing bortezomib treatment.

Some studies have reported that discontinuation of bortezomib treatment was required because of BIPN.[4,5,29] With regard to discontinuing treatment, in the Phase III Assessment of Proteasome inhibition for Extending remissions (APEX) study, it was reported that 31 of 331 patients (9%) had to discontinue bortezomib treatment because of BIPN, and 14 of 331 (4%) patients who discontinued treatment because of PN higher than grade 2 did so within the first three cycles.[5] When comparing the discontinuation of bortezomib therapy because of BIPN within the first three cycles, which was a similar short-term observation between studies, in our study, the rate of discontinuation of bortezomib was 0% and in the Phase III APEX trial it was 4%.

Moreau et al reported that PN higher than grade 2 occurred in 30 of 74 patients (40.1%) in the group receiving intravenous bortezomib at a cumulative dose of 20.8 mg/m^2, which is consistent with four complete treatment cycles.[6] The cohort in our study was too small for statistical analysis, but between the study by Moreau et al and ours, a significant statistical difference ($P = 0.0242$) was suspected. Moreover, in a study from Kyushu University,[29] two out of ten patients required discontinuation of bortezomib treatment because of BIPN within two courses. Our results suggested that PN higher than grade 3 was prevented by lafutidine treatment, and no patients discontinued treatment because of PN. We concluded that PN was mild in all patients, with no severe cases.

We speculate that lafutidine protected the progress of severe PN. The reason why lafutidine prevents severe PN is unknown. Lafutidine increases gastric mucosal blood flow by the mechanisms of capsaicin sensitive afferent nerves and nitric oxide.[14] Capsaicin has been reported to increase local blood flow[18,19] and to selectively block afferent sensory neurons via capsaicin sensitive afferent neurons.[22] Lafutidine appears to function in a similar manner to capsaicin via the same neurons.[15–17] There are some reports that lafutidine improves glossodynia[20,23] and taxane induced PN.[24] In these reports, it was assumed that lafutidine works in a similar manner to capsaicin via capsaicin sensitive afferent neurons and lafutidine increases local blood flow. We believe that the same activity of lafutidine via capsaicin sensitive afferent neurons protected against the progress of severe PN in our patients.

In the above mentioned reports,[20,23,24] lafutidine was administered after developing PN and it improved PN, whereas in our study, it was administered before PN and was thought to protect against the progression of severe PN. The discrepancy between these previous studies and our study appears to depend on the timing of administration of lafutidine. In either case, whether lafutidine was administered before or after developing PN, lafutidine was effective for PN. There were no adverse events of lafutidine treatment in the current study. We conclude that lafutidine is a useful drug for treating BIPN and speculate activity via capsaicin sensitive neurons leads to improvement or reduction of neurotoxicity. However, this result is only from a pilot study. Further studies are required to determine the effects of lafutidine on PN.

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Disclosure

The authors declare no conflicts of interest in this work.

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