The interaction between oral melphalan and gastric antisecretory drugs: Impact on clinical efficacy and toxicity

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Abstract. The aim of the present study was to clarify whether gastric antisecretory drugs affect the clinical efficacy and toxicity of orally administered melphalan in patients with multiple myeloma. A total of 10 patients receiving bortezomib plus oral melphalan and prednisolone (VMP) therapy between December 2011 and November 2014 were analyzed retrospectively. The patients were divided into a control group (seven patients) and a concomitant group (three patients, who were also administered with gastric antisecretory drugs). The gastric antisecretory drugs included rabeprazole sodium (two patients) and famotidine (one patient). No significant differences between the groups were observed in either the characteristics of the patients or the VMP regimen. The levels of monoclonal protein (M protein) in the control group tended to decrease (with a VMP cycle-dependency), although they were primarily stable in the concomitant group. During the second and third VMP cycles, the levels of M protein were markedly lower in the control group compared with the concomitant group. All the patients in the control group achieved a partial response, whereas those in the concomitant group exhibited stable disease. Hematological toxicity levels were revealed to be comparable between the two groups, whereas gastrointestinal toxicity was more prevalent in the control group. In conclusion, the results of the present study suggested that the clinical efficacy of melphalan may be reduced by the co-administration of gastric antisecretory drugs. This interaction may result in decreased toxicity and clinical efficacy of melphalan.

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Introduction

Multiple myeloma (MM) is a malignant neoplasm characterized by the clonal proliferation of plasma cells in the bone marrow that produce monoclonal protein (M protein) (1,2). Although MM remains an incurable malignancy, the survival rates have improved markedly (2). The first notable improvement came following the introduction of autologous stem cell transplantation (3,4). In addition, the use of drugs with antiangiogenic, antiproliferative and immunomodulatory effects, including thalidomide (5) and lenalidomide (6,7), and proteasome inhibitors, including bortezomib (8,9), were introduced (10). These agents have been combined with melphalan, resulting in high response rates in patients with MM (11-14).

Melphalan is a cytotoxic agent used extensively in the treatment of MM (15,16). For decades, the combination of melphalan with prednisolone provided the standard of care for elderly patients with MM. Previously, a bortezomib plus oral melphalan and prednisolone (VMP) regimen was demonstrated to exert synergistic anticancer effects (17,18), and thus this has become the current standard regimen for patients with MM (11).

The oral bioavailability of melphalan is known to be widely variable (19-21). For example, Sviland *et al* (22) demonstrated that pretreatment of the patients with the histamine 2 (H_2) receptor blocker, cimetidine, reduced the oral bioavailability of mephalan by ~35%. This reduction is thought to stem from the poor absorption of melphalan (19), since its solubility is known to decrease under alkaline pH conditions (23,24). However, this pharmacokinetic interaction has not been conclusively demonstrated to be associated with any reduced clinical efficacy. Furthermore, there is no mention of any drug interactions between oral melphalan and gastric antisecretory drugs in the medical package insert in Japan.

The aim of the present study was to assess whether the clinical efficacy and toxicity of melphalan were influenced by the concomitant use of gastric antisecretory drugs in patients with MM receiving VMP therapy. The clinical significance of the interaction between melphalan and gastric antisecretory drugs was also discussed.

Table I. Characteristics of the patients.

	Control							Concomitant			
Patient no.	1	2	3	4	5	6	7	8	9	10	P-value
Age (years)	79	80	71	74	78	80	63	69	72	70	0.137[a]
Sex	F	M	M	M	F	F	F	M	F	F	1.000[b]
Myeloma type	IgG	IgG	IgG	IgG	BJP	IgG	IgG	IgG	IgG	IgG	1.000[b]
ISS stage	II	III	II	I	II	III	I	III	III	II	0.888[b]
Previous treatment (Number)	Yes (1)	No (0)	No (0)	No (0)	No (0)	No (0)	No (0)	No (0)	No (0)	No (0)	1.000[b]

[a]Mann-whitney U test, [b]Fisher's exact probability test. BJP, Bence Jones protein; IgG, immunoglobulin G; ISS, international staging system.

Table II. Doses of the chemotherapeutic agents in the VMP regimen.

	Control (n=7)	Concomitant (n=3)	P-value[a]
Bortezomib (mg/m^2)	1.3 (1.0-1.3)	1.3 (1.2-1.3)	0.569
Oral melphalan (mg/m^2)	4.6 (3.4-8.6)	5.5 (5.5-6.1)	0.210
Prednisolone (mg/m^2)	30.0 (12.7-57.5)	37.5 (27.7-38.0)	0.909

Data are shown as the median (range). [a]Mann-whitney U test.

Patients and methods

Ethics statement. The present study was reviewed and approved by the Institutional Review Boards of the Japan Community Health care Organization Kyoto Kuramaguchi Medical Center (Kyoto, Japan; IRB no.: 2015012602). Written patient consent was waived due to the retrospective and observational nature of the study.

Study population and design. A retrospective study was performed at the Japan Community Health care Organization Kyoto Kuramaguchi Medical Center (Kyoto, Japan). A total of 12 patients with MM who received VMP therapy between December 2011 and November 2014 were included. However, two patients from this cohort were excluded from the analysis, due to an inability to measure the level of M protein throughout the first cycle of treatment. The remaining 10 patients were divided into two groups: The concomitant (three patients) and control (seven patients) groups, according to the additional use of gastric antisecretory drugs, or the lack thereof. The VMP regimen consisted of bortezomib (1.3 mg/m^2) administered on days 1, 8, 15 and 22, and oral melphalan (6 mg/m^2) and prednisolone (40 mg/m^2) administered on days 1-4 per one cycle (35 days).

Data collection and definitions. Two parameters were used as measures of clinical efficacy: (i) a reduction in the level of M protein; and (ii) the best response according to the International Myeloma Working Group criteria (25) throughout the course of treatment. The hematological and gastrointestinal (GI) toxicity of melphalan was assessed according to the Common Terminology Criteria for Adverse Events version 4.0 (26), using the highest grade available throughout the duration of the three-cycle treatment for the analysis.

Statistical analysis. The data are expressed as the mean ± standard deviation, or the median (range). Comparisons of the two groups were performed using the unpaired Student's t-test (parametric) or the Mann-Whitney U test (non-parametric). Differences between observed and expected frequencies were evaluated using Fisher's exact probability test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Characteristics of the patients. Table I shows the characteristics of the 10 patients enrolled in the present study. Seven patients were not co-administered gastric antisecretory drugs (control group), and three patients were co-administered gastric antisecretory drugs (two patients were administered rabeprazole sodium, one patient was administered famotidine) in the VMP regimen (concomitant group). Patient no. 1 was changed to the VMP regimen after having received oral melphalan and prednisolone therapy during cycle 1. No significant differences were observed in the characteristics of the patients between the control and concomitant groups.

Table II shows the doses of chemotherapeutic agents in the VMP regimen in the control and concomitant groups. The doses of melphalan were 4.6 and 5.5 mg/m^2 in the control and concomitant groups, respectively; the difference between the two doses was not statistically significant. Furthermore, the doses of other components used in the VMP regimen

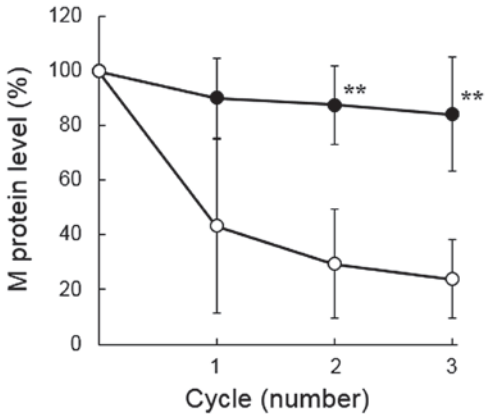

Figure 1. Changes in the level of the M protein in the VMP regimen with or without gastric antisecretory drugs. The level of the M protein prior to the start of the VMP regimen was expressed as 100%. Open and closed circles represent the control (without gastric antisecretory drugs) and concomitant (with gastric antisecretory drugs) groups, respectively. Each symbol represents the mean ± standard deviation. **P<0.01, vs. control (unpaired Student's t test).

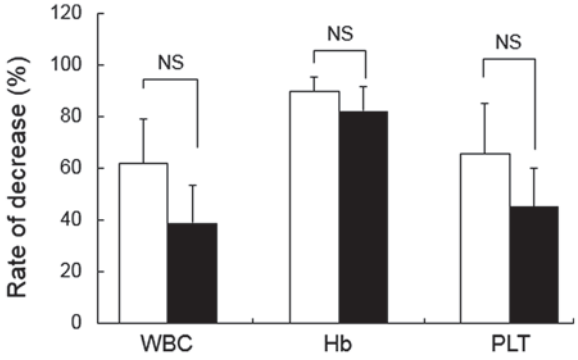

Figure 2. Changes in the WBC count, Hb level and the PLT count in the VMP regimen with or without gastric antisecretory drugs. The WBC count, Hb level or PLT count before the start of the VMP regimen is expressed as 100%. The open and closed columns show the control (without gastric antisecretory drugs) and concomitant (with gastric antisecretory drugs) groups, respectively. Each bar represents the mean ± standard deviation. NS, not significant (unpaired Student's t-test); WBC, white blood cell; Hb, hemoglobin; PLT, platelet.

(bortezomib and prednisolone) revealed no statistically significant differences between the control and concomitant groups.

Clinical efficacy. The levels of M protein over the duration of the treatment period for the two groups are shown in Fig. 1. The levels of M protein in the control group markedly decreased, depending on the number of cycles; however, the levels in the concomitant group remained largely unchanged. The levels of M protein in cycles 2 and 3 were significantly higher in the concomitant group compared with the control group (P<0.01).

The other index of clinical efficacy, i.e. the best response in the three cycles, is summarized in Table III. All the patients in the control group were graded as having a partial response (PR) to the drug therapy, whereas all the patients in the concomitant group were graded as having stable disease (SD). The best response to the VMP regimen was significantly higher for the control group than for the concomitant group.

Table III. Best response obtained in three cycles of the VMP regimen.

	Response		
	PR	SD	P-value[a]
Control (n=7)	7	0	0.008
Concomitant (n=3)	0	3	

PR, partial response; SD, stable disease. The clinical efficacy of the VMP regimen attained its best response in the first three cycles, according to the International Myeloma Working Group criteria. [a]Fisher's exact probability test.

Hematological and GI toxicity. Table IV shows the grade and frequency of selected hematological and GI toxicities. Throughout each treatment cycle, the grade and frequency of leukopenia, anemia and thrombocytopenia were comparable in the two groups. Furthermore, no significant differences were observed in the white blood cell count, hemoglobin level, or the platelet count between the two groups (Fig. 2). Grade 1 GI toxicities were observed in the control group, manifesting as vomiting in one patient, and diarrhea and loss of appetite in two other patients. No GI toxicity was observed in the concomitant group.

Discussion

Limitations to the present study included its retrospective small sample size and a lack of plasma melphalan concentrations. However, the results in the present study are sufficient to call attention to the interaction between melphalan and gastric antisecretory drugs.

In the present study, three of the ten patients received gastric antisecretory drugs in addition to VMP therapy. Of the three patients in the concomitant group, two patients received rabeprazole sodium and one received famotidine. With the exception of the use of gastric antisecretory drugs, the control and the concomitant groups were comparable in terms of the characteristics of the patients (Table I) and the doses of chemotherapeutic agents in the VMP regimen (Table II). However, the decrease in the level of the M protein in treatment cycles 2 and 3 was significantly greater in the control group (Fig. 1), indicating a more favorable clinical response in that cohort. In addition, all the patients in the control group were graded as having a PR to the drug therapy, compared with the SD identified in the concomitant group (Table III). Taken together, these findings suggested that the clinical efficacy of the VMP regimen against MM decreases on co-administration of the gastric antisecretory drugs. As for bortezomib, the pharmacokinetics, efficacy and safety of bortezomib were not affected by co-administration of either the proton-pump inhibitor, omeprazole (27), or the H_2 receptor blocker, lafutidine (28).

The hallmark adverse events of melphalan are known to be hematological and GI toxicities. The present study disclosed no significant difference in the analyses of hematological toxicity between the control and concomitant

Table IV. Hematological and gastrointestinal toxicity.

	Grade	Control (n=7)	Concomitant (n=3)	P-value[a]
Leukopenia	Grade 1/2	5	1	0.500
	Grade 3/4	2	2	
Anemia	Grade 1/2	5	1	0.500
	Grade 3/4	2	2	
Thrombocytopenia	Grade 1/2	3	3	1.000
	Grade 3/4	1	0	
Vomit	Grade 1	1	0	-
Diarrhea	Grade 1	2	0	-
Appetite loss	Grade 1	2	0	-

Evaluation of hematological toxicity adopted a high grade in the first three cycles, according to the Common Terminology Criteria for Adverse Events, version 4.0. [a]Fisher's exact probability test.

groups (Fig. 2 and Table IV), in stark contrast with the clinical efficacy findings reported in the present study. These results are in agreement with previous reports, which cited no significant differences in hematological toxicity among patients receiving oral melphalan following cimetidine pretreatment (22). Therefore, in spite of the decreased bioavailability of melphalan in the concomitant group, the plasma concentrations were likely to have remained within a range in which myelosuppression would be predicted to occur. The observed differences in GI toxicity (Table IV) may be partly explained by the poorer solubility of melphalan tablets with increasing gastric pH.

Taken together, these results suggested that the interaction of the VMP regimen with gastric antisecretory drugs resulted in a marked decrease in the clinical efficacy of melphalan. As such, oral melphalan should not be co-administered with gastric antisecretory drugs, and this drug interaction should prominently feature in the medical package insert.

The mechanism of the interaction between melphalan and gastric antisecretory drugs remains to be fully elucidated. For example, melphalan was reported to be unstable at alkaline pH, and the dissolution of melphalan tablets occurred more slowly at an increased gastric pH (23). Furthermore, Sviland *et al* (22) reported a 35.5% decrease in the oral bioavailability of melphalan in patients pretreated with cimetidine. Therefore, drugs that induce a potent and long-lasting inhibition of gastric acid secretion [a pharmacological hallmark of rabeprazole sodium (29,30) and famotidine] would predispose a patient towards this interaction. Food intake was also reported to decrease the absorption rate of oral melphalan (31,32). It is notable that melphalan was administered before the meal in the present study.

Taken together, the results in the present study suggest that this drug interaction may arise from the poor solubility of the melphalan tablets, brought about by an increase in gastric pH caused by the concomitant use of gastric antisecretory drugs, thereby resulting in a diminished clinical efficacy of melphalan.

In conclusion, the interaction between oral melphalan and gastric antisecretory drugs may result in a marked decrease in its clinical efficacy in the treatment of MM. This drug interaction possibly results from a reduction in the absorption of melphalan caused by an increase in gastric pH. Due to the aforementioned limitations of the current study, further research is necessary to obtain definitive evidence for these conclusions.

References

1. Raab MS, Podar K, Breitkreutz I, Richardson PG and Anderson KC: Multiple myeloma. Lancet 374: 324-339, 2009.
2. Palumbo A and Anderson K: Multiple myeloma. N Engl J Med 364: 1046-1060, 2011.
3. Harousseau JL and Moreau P: Autologous hematopoietic stem-cell transplantation for multiple myeloma. N Engl J Med 360: 2645-2654, 2009.
4. Shimazaki C: Autologous stem cell transplantation for multiple myeloma: History and future. Int J Myeloma 3: 55-66, 2013.
5. Rajkumar SV, Blood E, Vesole D, Fonseca R and Greipp PR: Eastern Cooperative Oncology Group: Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: A clinical trial coordinated by the Eastern cooperative oncology group. J Clin Oncol 24: 431-436, 2006.
6. Zonder JA, Crowley J, Hussein MA, Bolejack V, Moore DF Sr, Whittenberger BF, Abidi MH, Durie BG and Barlogie B: Lenalidomide and high-dose dexamethasone compared with dexamethasone as initial therapy for multiple myeloma: A randomized southwest oncology group trial (S0232). Blood 116: 5838-5841, 2010.
7. Dimopoulos MA, Chen C, Spencer A, Niesvizky R, Attal M, Stadtmauer EA, Petrucci MT, Yu Z, Olesnyckyj M, Zeldis JB, *et al*: Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia 23: 2147-2152, 2009.
8. Harousseau JL, Attal M, Avet-Loiseau H, Marit G, Caillot D, Mohty M, Lenain P, Hulin C, Facon T, Casassus P, *et al*: Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: Results of the IFM 2005-01 phase III trial. J Clin Oncol 28: 4621-4629, 2010.
9. Richardson PG, Sonneveld P, Schuster M, Irwin D, Stadtmauer E, Facon T, Harousseau JL, Ben-Yehuda D, Lonial S, Goldschmidt H, *et al*: Extended follow-up of a phase 3 trial in relapsed multiple myeloma: Final time-to-event results of the APEX trial. Blood 110: 3557-3560, 2007.
10. Ria R, Reale A and Vacca A: Novel agents and new therapeutic approaches for treatment of multiple myeloma. World J Methodol 4: 73-90, 2014.
11. Harousseau JL, Palumbo A, Richardson PG, Schlag R, Dimopoulos MA, Shpilberg O, Kropff M, Kentos A, Cavo M, Golenkov A, *et al*: Superior outcomes associated with complete response in newly diagnosed multiple myeloma patients treated with nonintensive therapy: Analysis of the phase 3 VISTA study of bortezomib plus melphalan-prednisone versus melphalan-prednisone. Blood 116: 3743-3750, 2010.

12. Kapoor P, Rajkumar SV, Dispenzieri A, Gertz MA, Lacy MQ, Dingli D, Mikhael JR, Roy V, Kyle RA, Greipp PR, *et al*: Melphalan and prednisone versus melphalan, prednisone and thalidomide for elderly and/or transplant ineligible patients with multiple myeloma: A meta-analysis. Leukemia 25: 689-696, 2011.
13. Palumbo A, Hajek R, Delforge M, Kropff M, Petrucci MT, Catalano J, Gisslinger H, Wiktor-Jędrzejczak W, Zodelava M, Weisel K, *et al*: Continuous lenalidomide treatment for newly diagnosed multiple myeloma. N Engl J Med 366: 1759-1769, 2012.
14. Palumbo A, Bringhen S, Rossi D, Cavalli M, Larocca A, Ria R, Offidani M, Patriarca F, Nozzoli C, Guglielmelli T, *et al*: Bortezomib-melphalan-prednisone-thalidomide followed by maintenance with bortezomib-thalidomide compared with bortezomib-melphalan-prednisone for initial treatment of multiple myeloma: A randomized controlled trial. J Clin Oncol 28: 5101-5109, 2010.
15. Alexanian R, Haut A, Khan AU, Lane M, McKelvey EM, Migliore PJ, Stuckey WJ Jr and Wilson HE: Treatment for multiple myeloma. Combination chemotherapy with different melphalan dose regimens. JAMA 208: 1680-1685, 1969.
16. Combination chemotherapy versus melphalan plus prednisone as treatment for multiple myeloma: An overview of 6,633 patients from 27 randomized trials. Myeloma Trialists' Collaborative Group. J Clin Oncol 16: 3832-3842, 1998.
17. Ma MH, Yang HH, Parker K, Manyak S, Friedman JM, Altamirano C, Wu ZQ, Borad MJ, Frantzen M, Roussos E, *et al*: The proteasome inhibitor PS-341 markedly enhances sensitivity of multiple myeloma tumor cells to chemotherapeutic agents. Clin Cancer Res 9: 1136-1144, 2003.
18. Mitsiades N, Mitsiades CS, Richardson PG, Poulaki V, Tai YT, Chauhan D, Fanourakis G, Gu X, Bailey C, Joseph M, *et al*: The proteasome inhibitor PS-341 potentiates sensitivity of multiple myeloma cells to conventional chemotherapeutic agents: Therapeutic applications. Blood 101: 2377-2380, 2003.
19. Woodhouse KW, Hamilton P, Lennard A and Rawlins MD: The pharmacokinetics of melphalan in patients with multiple myeloma: An intravenous/oral study using a conventional dose regimen. Eur J Clin Pharmacol 24: 283-285, 1983.
20. Bosanquet AG and Gilby ED: Pharmacokinetics of oral and intravenous melphalan during routine treatment of multiple myeloma. Eur J Cancer Clin Oncol 18: 355-362, 1982.
21. Ehrsson H, Eksborg S, Osterborg A, Mellstedt H and Lindfors A: Oral melphalan pharmacokinetics-relation to dose in patients with multiple myeloma. Med Oncol Tumor Pharmacother 6: 151-154, 1989.
22. Sviland L, Robinson A, Proctor SJ and Bateman DN: Interaction of cimetidine with oral melphalan. A pharmacokinetic study. Cancer Chemother Pharmacol 20: 173-175, 1987.
23. Alberts DS, Chang SY, Chen HS, Evans TL and Moon TE: Oral melphalan kinetics. Clin Pharmacol Ther 26: 737-745, 1979.
24. Tabibi SE and Cradock JC: Stability of melphalan in infusion fluids. Am J Hosp Pharm 41: 1380-1382, 1984.
25. Durie BG, Harousseau JL, Miguel JS, Bladé J, Barlogie B, Anderson K, Gertz M, Dimopoulos M, Westin J, Sonneveld P, *et al*: International Myeloma Working Group: International uniform response criteria for multiple myeloma. Leukemia 20: 1467-1473, 2006.
26. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0, U.S. Department of Health and Human Sciences, National Institutes of Health, National Cancer Institute. Published May 28, 2009 (v4.03: June 14, 2010).
27. Quinn DI, Nemunaitis J, Fuloria J, Britten CD, Gabrail N, Yee L, Acharya M, Chan K, Cohen N and Dudov A: Effect of the cytochrome P450 2C19 inhibitor omeprazole on the pharmacokinetics and safety profile of bortezomib in patients with advanced solid tumours, non-Hodgkin's lymphoma or multiple myeloma. Clin Pharmacokinet 48: 199-209, 2009.
28. Tsukaguchi M, Shibano M, Matsuura A and Mukai S: The protective effects of lafutidine for bortezomib induced peripheral neuropathy. J Blood Med 4: 81-85, 2013.
29. Dammann HG, Burkhardt F and Wolf N: The effects of oral rabeprazole on endocrine and gastric secretory function in healthy volunteers. Aliment Pharmacol Ther 13: 1195-1203, 1999.
30. Adachi K, Katsube T, Kawamura A, Takashima T, Yuki M, Amano K, Ishihara S, Fukuda R, Watanabe M and Kinoshita Y: CYP2C19 genotype status and intragastric pH during dosing with lansoprazole or rabeprazole. Aliment Pharmacol Ther 14: 1259-1266, 2000.
31. Bosanquet AG and Gilby ED: Comparison of the fed and fasting states on the absorption of melphalan in multiple myeloma. Cancer Chemother Pharmacol 12: 183-186, 1984.
32. Reece PA, Kotasek D, Morris RG, Dale BM and Sage RE: The effect of food on oral melphalan absorption. Cancer Chemother Pharmacol 16: 194-197, 1986.