Polaprezinc Prevents Oral Mucositis in Patients Treated with High-dose Chemotherapy Followed by Hematopoietic Stem Cell Transplantation

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Abstract. *We have previously reported that polaprezinc in sodium alginate suspension (P-AG) inhibited the incidence of oral mucositis induced by radiochemotherapy in patients with head and neck cancer. The present study was designed to investigate whether P-AG prevents oral mucositis in all patients (36 patients) with hematological malignancy receiving high-dose chemotherapy and radiotherapy followed by hematopoietic stem cell transplantation (HSCT). P-AG dramatically reduced the incidence of moderate-to-severe oral mucositis as compared to the control group treated with azulene gargle (20% versus 82% for grade≥2, p<0.01; 0% versus 45% for grade≥3, p<0.01). Pain associated with oral mucositis was also significantly (p=0.004) relieved by P-AG, resulting in a reduction in the use of analgesic agents (28% versus 73%, p=0.025). The incidence of xerostomia and taste disturbance tended to be lowered but not significantly by P-AG. On the other hand, P-AG had no influence on the incidence of other adverse events, tumor remission rate or the survival rate. Therefore, P-AG was found to be highly effective in preventing oral mucositis induced not only by radiochemotherapy for head and neck cancer but also by high-dose chemotherapy and radiotherapy followed by HSCT.*

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Oral mucositis is one of the most distress side-effects during cancer therapy, particularly in patients with head-and-neck cancer receiving chemotherapy and/or radiotherapy or those who receive high-dose chemotherapy and radiotherapy followed by hematopoietic stem cell transplantation (HSCT) (1-3). Oral mucositis is painful and requires the use of opioid analgesics (4-6). In severe cases, total parenteral nutrition is needed due to the inability to intake food and drink, which results in the discontinuation of the therapy or reduction in the dose of anticancer drugs (5, 7). Additionally, oral mucositis is associated with blood infections and transplant-related mortality (8).

Although the precise mechanisms of oral mucositis associated with radiotherapy, and chemotherapy, remain to be clarified, oxidative stress, followed by the production of a series of inflammatory cytokines is implicated in the etiology of oral mucositis. Indeed, a positive correlation has been reported to exist between the severity of mucositis and the serum levels of proinflammatory cytokines such as tumor necrosis factor (TNF)α, interleukin (IL)-1 and IL6 (9). The mucosal injury is reported to develop through the following five processes: initiation by production of reactive oxygen species; nuclear factor-κB (NF-κB) activation followed by induction of inflammatory cytokines such as TNFα, IL1β and IL6; TNFα-mediated production of ceramide; and caspase activation that leads to cell apoptosis, ulceration with inflammation, and healing. In addition, oral infection due to myelosuppression by radiotherapy or chemotherapy becomes a secondary cause of oral mucositis (9). Several agents have been tested for prevention of oral mucositis, including antioxidants such as amifostine (10), vitamine E (11), and allopurinol (12); mucosal protectants such as sucralfate (13), benzydamine (14), prostaglandin E1 analog misoprostol (15) and palifermin (16, 17). However, none of them, except for

palifermin, has been confirmed to show any reproducible protective action (18). Palifermin is a keratinocyte growth factor that stimulates cell proliferation, migration, differentiation, survival, and DNA repair (19). This growth factor is approved as an agent that prevents severe oral mucositis induced by high-dose chemotherapy and radiotherapy followed by HSCT.

We recently reported that polaprezinc, a zinc-containing L-carnosine used for the therapy of gastric ulcer, was potentially useful for prevention of oral mucositis and related painful symptoms induced in patients with head and neck cancer receiving chemoradiation therapy (20).

The present retrospective study was designed to investigate whether polaprezinc suspended in sodium alginate solution (P-AG) prevents oral mucositis induced in patients with hematopoietic malignancy receiving high-dose chemotherapy and radiotherapy followed by HSCT.

Patients and Methods

Study setting and patients. Thirty-six patients (15 years old and older) with hematological malignancy who received high-dose chemotherapy and radiotherapy following HSCT were enrolled. The incidence of oral mucositis and related symptoms was reviewed from medical records of patients who were admitted to the Gifu University Hospital between February 2008 and March 2013. P-AG was used for 25 patients from October 2009. Control group (11 patients) was treated with azulene gargle for prevention of oral mucositis. Azulene oral rinse was prepared by pouring seven drops of 4% liquid solution into 100 ml water. Patients orally rinsed with azulene solution four times a day and continued until one month after transplantation.

This study was carried out in accordance with the guidelines for the care for human study adopted by the Ethics Committee of the Gifu University Graduate School of Medicine, and notified by the Japanese government (approval no. 23-145 of the Institutional Review Board).

Preparation of P-AG. Polaprezinc (Promac granules VR 15%®; Zeria Pharmaceutical Co., Tokyo, Japan) at 0.5 g was suspended in 20 ml of 5% sodium alginate solution to produce P-AG. Four times a day, 5 ml of P-AG suspension was used to orally rinse for 2 min and then swallowed; this continued for one month after transplantation.

Evaluation of oral mucositis and other adverse events. The primary end-point of the present study was the incidence of oral mucositis and the maximal severity of which was assessed over a period of 35 days after the start of chemotherapy. Secondary end-points were the incidence of pain, xerostomia, and taste disturbance and the reduction in the use of analgesics for the relief of oral pain. The incidence of mucositis, pain, xerostomia, and taste disturbance were evaluated and the severity was graded according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) (21). The frequency of use of analgesics, including local anesthetics and opioid analgesics, for the relief of pain associated with oral mucositis was compared between control and P-AG-treated groups. The incidence of other adverse events was also compared between the two groups.

Table I. *Patients' demographics*.

	Control	P-AG	*p*-Value
Number of patients	11	25	
Gender (male/female)	7/4	10/15	0.869[a]
Age, years	49 (15-66)	53 (20-64)	0.709[b]
Labo data			
Total protein (g/dl)	6.6±0.6	6.1±0.7	0.028[c]
Serum albumin (g/dl)	4.0±0.4	3.8±0.6	0.365[c]
AST (U/l)	24±11	23±9	0.829[c]
AlT (U/l)	29±25	30±19	0.934[c]
Serum creatinine (mg/dl)	0.64±0.15	0.66±0.25	0.770[c]
Total bilirubin (mg/dl)	0.8±0.5	0.6±0.3	0.106[c]
White blood cells (n/mm^3)	2472±1458	2753±1703	0.659[b]
Platelet (×10^6/mm^3)	9.4±8.4	9.6±7.9	0.949[c]
Diagnosis			
Acute myeloid leukemia	5	8	0.207[a]
Acute lymphoid leukemia	2	3	
Chronic myeloid leukemia	0	1	
Myelodysplastic syndrome	4	7	
Malignant lymphoma	0	6	
Stem cell source			
Allo-PBSCT	4	1	0.183[a]
UCBT	6	14	
UBMT	2	9	
Conditioning regimen			
Ara-C/CPA/FLU	1	1	<0.001[a]
Ara-C/CPA or FLU or VP16	2	0	
BUS/CPA or FLU or L-PAM	5	3	
CPA	1	0	
Mean (IQR) TBI (Gy)	8.2 (3-12)	6.3 (0-12)	0.446[b]

Values represent the mean±S.D. (range) unless otherwise stated. Allo-PBSCT: Allogeneic peripheral blood stem cell transplantation, UCBT: unrelated cord blood transplantation, UBMT: unrelated bone marrow transplantation, Ara-C: cytarabine, CPA: cyclophosphamide, FLU: fludarabine, VP-16: etoposide, BUS: busulfan, L-PAM: melphalan, TBI: total body irradiation; IQR: interquartile range. [a]Chi-square test, [b]Mann–Whitney *U*-test, [c]*t*-test.

Evaluation of engraftment of HSCT and survival. The time to engraftment, defined as an absolute neutrophil count of 500/mm^3 or more for three consecutive days (22), and the rate of successful engraftment were compared between the P-AG-treated group and the control group. The rates of overall survival and recurrence-free survival at 2 years after HSCT were also compared between the two groups.

Statistical analysis. Data were analyzed using the Statistics Program for Social Science for Windows (SPSS-II, version 11; SPSS, Chicago, IL, USA) and statistically compared between the control and P-AG-treated groups. Parametric data were analyzed by *t*-test or Chi-square test, while non-parametric data were compared by Mann–Whitney *U*-test or Fisher's exact probability test. A *p*-value of less than 0.05 was regarded as statistically significant.

Results

Patients' demographics. As shown in Table I, there were no significant differences in gender, age, clinical data (excluding total protein), type of leukemia and HSCT source between the

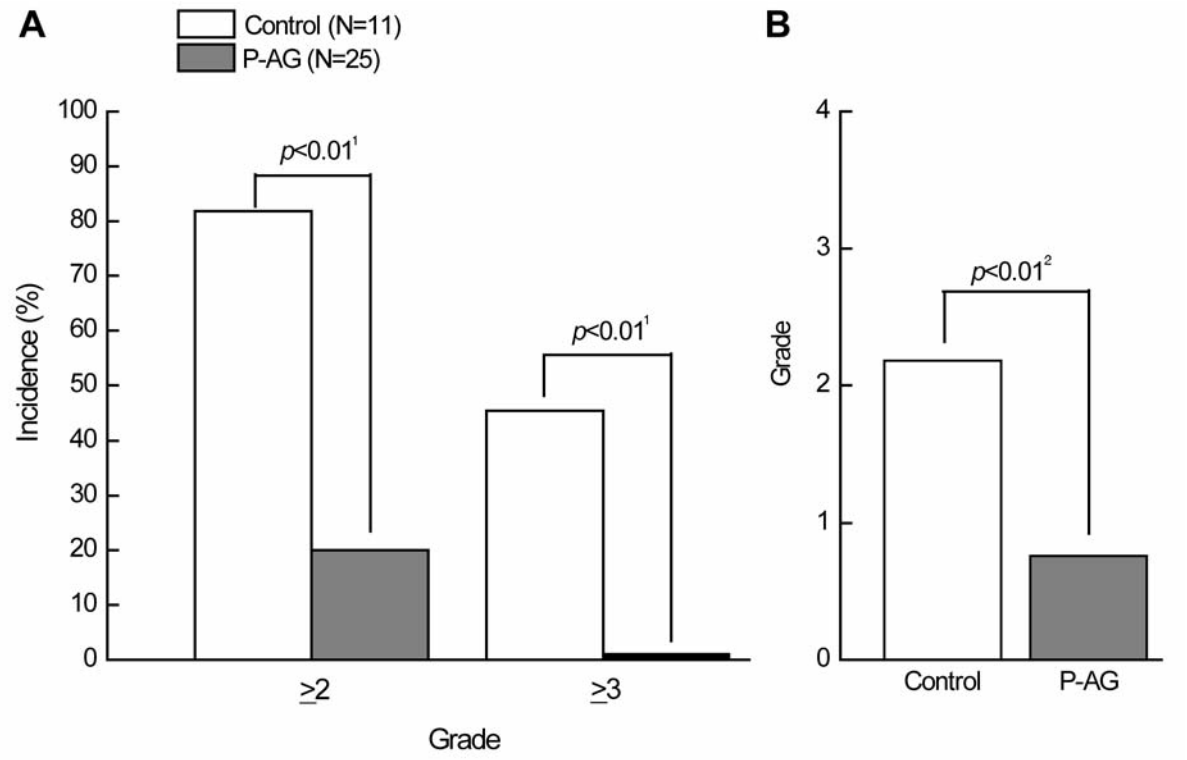

Figure 1. *(A) Comparison of the incidence and (B) the severity of oral mucositis in patients receiving high-dose chemotherapy and radiotherapy followed by HSCT between P-AG and control. 1) Fisher's exact probability test, 2) Mann-Whitney U-test.*

two groups at study entry. The total serum protein was significantly higher in the control group, although the average value was within the normal range. However, chemotherapy regimens were significantly different between the two groups, with cytarabine/fludarabine/cyclophosphamide regimen being predominant in the P-AG-treated group, while cyclophosphamide in combination with cytarabine, fludarabine, etoposide, busulfan or pralidoxime being the major chemotherapy regimen in the control group.

The intensity of total body irradiation and the duration of neutropenia defined as the neutrophil count of less than 500/mm^3 were not significantly different between the two groups.

Effect of P-AG on the incidence and severity of oral mucositis and related symptoms. P-AG markedly reduced the incidence of oral mucositis grade 2 or more ($p<0.01$) and 0% for grade 3 or more ($p<0.01$) compared to the control group (Figure 1A). As shown in Figure 1B, the average grade of oral mucositis was also markedly lowered by P-AG ($p<0.01$).

P-AG significantly reduced the incidence of moderate-to-severe pain (grade 2 or more) associated with oral mucositis ($p=0.004$) (Figure 2A). As a consequence, the use of analgesics such as local anesthetic agents was significantly reduced by P-AG ($p=0.025$), although the use of opioid analgesics was not significantly different between the two groups ($p=0.678$) (Figure 2B). Moreover, the incidence of xerostomia ($p=0.450$) and taste disturbance ($p=0.697$) tended to decrease, although not significantly, by P-AG.

Effect of P-AG on the incidence of other non-hematological adverse events. There were no significant differences in the incidence of other adverse events such as rash, pruritus, erythema, perianal pain, numbness, nausea, vomiting or cough between the control group and P-AG-treated group (Table II). The incidence of malaise was significantly higher in the P-AG group ($p=0.039$).

Comparison of the rates of engraftment of HSCT and survival. The median time to engraftment was not different between P-AG-treated and control groups ($p=0.38$). The rate of successful engraftment tended to be higher, although not significantly, in the P-AG-treated group than in the control group ($p=0.077$). There were no significant differences in the rates of overall survival at two years ($p=0.529$) and recurrence-free survival at two years ($p=0.859$) between the two groups (Table III).

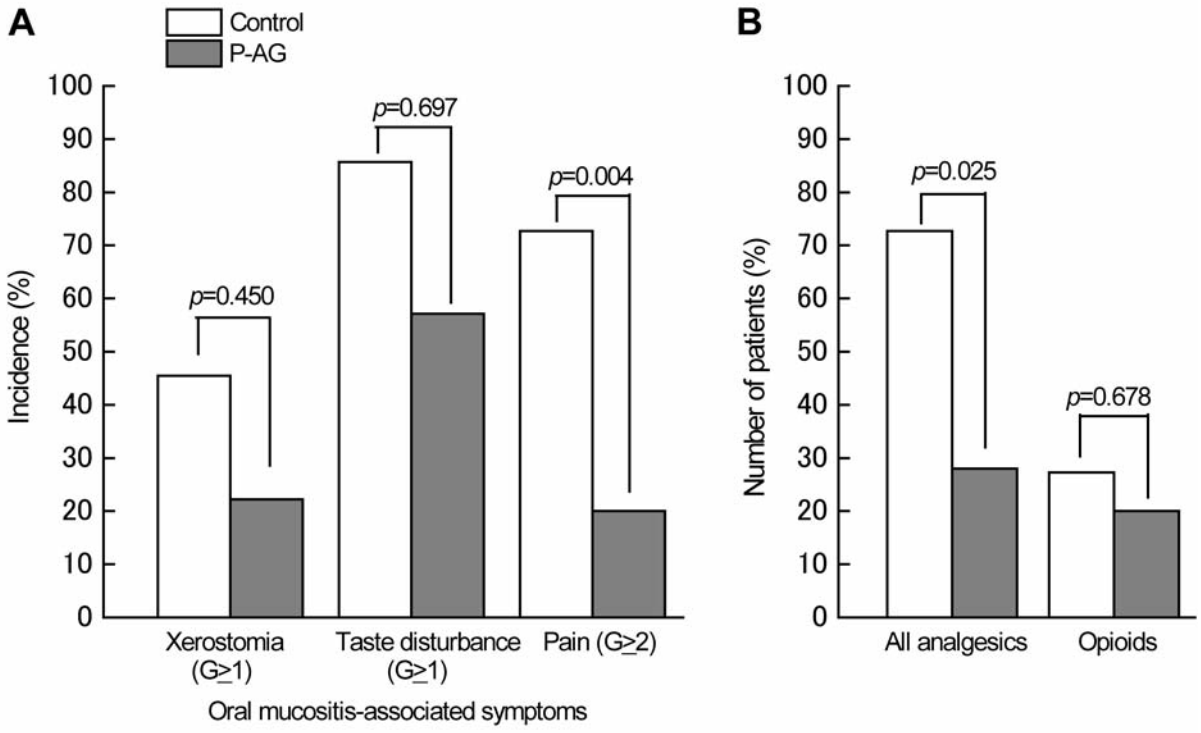

Figure 2. *(A) Comparison of the incidence of oral mucositis-related symptoms such as xerostomia, taste disturbance, and pain. (B) Comparison of the use of anesthetic agents in patients receiving high dose chemotherapy and radiotherapy followed by HSCT between P-AG and control. Data were compared by Fisher's exact probability test.*

Discussion

We report, to our knowledge for the first time, that a zinc-containing anti-ulcer compound polaprezinc can reduce the incidence and severity of oral mucositis associated with high-dose chemotherapy in combination with radiotherapy followed by HSCT. Severe oral mucositis is accompanied by pain, leading to a limitation of oral intake and a disturbance of the quality of life. P-AG significantly lowered the incidence of moderate to severe pain. As a result, the use of analgesic agents was significantly less frequent in patients treated with P-AG.

In the present study, there was a significant difference in the chemotherapy regimens between the two groups, in which a combination of three anticancer drugs such as cytarabine, cyclophosphamide and fludarabine was predominant in the P-AG-treated group, while a combination of two drugs, including cyclophosphamide, cytarabine, fludarabine, etoposide and pralidoxime, was mainly used in the control group. It is unlikely that the intensity of chemotherapy was less potent in the P-AG-treated group than in the control group, since the incidence of non-hematological adverse events, excluding oral mucositis and its related symptoms, was not different between the two groups. Moreover, the clinical outcomes, such as the time-to-engraftment, the rate of engraftment, overall survival and recurrence-free survival, were not significantly different between the P-AG-treated group and the control group. Taken together, it is suggested that P-AG specifically protects oral mucosa from serious injury.

Therapy with P-AG also tended to reduce the incidence of xerostomia and taste disturbance. Therefore, P-AG may have more or less protective effect on the submandibular gland against chemotherapeutic or radiation insults.

At present, we cannot precisely explain the mechanisms underlying the prophylactic effect of P-AG against oral mucositis. Polaprezinc contains zinc. Thus, zinc ion may contribute to the protective action against radiochemotherapy, since zinc sulfate is reported to be effective in reducing the severity of radiation-induced mucositis and oral discomfort in patients with head and neck cancer (23). On the other hand, polaprezinc has been reported to inhibit aspirin-induced lipid peroxidation and TNFα induction in rat gastric mucosa (24), reduce TNFα-induced NF-κB activation and IL8 secretion from gastric epithelial cells (25), reduce ethanol-induced superoxide generation in primary monolayer cultures of rat gastric fundic mucosa by ethanol (26), and induce the antioxidant hemeoxygenase-1 (27).

Table II. *Incidence of other non-hematological adverse events.*

	n (%)		
	Control	P-AG	*p*-Value
Rash	2 (18%)	4 (16%)	0.746
Pruritus	4 (36%)	3 (12%)	0.213
Erythema	3 (27%)	8 (32%)	0.913
Perianal pain	2 (18%)	3 (12%)	0.976
Numbness	3 (27%)	4 (16%)	0.741
Malaise	7 (63%)	24 (96%)	0.039
Nausea	9 (81%)	19 (76%)	0.784
Vomiting	4 (36%)	7 (28%)	0.913
Cough	1 (9%)	2 (8%)	0.585

P-AG: Polaprezinc suspended in sodium alginate solution. Data were compared by Chi-square test.

Table III. *Effects of P-AG on engraftment and survival in patients treated with high-dose chemotherapy and hematopoietic stem cell transplantation.*

	Control	P-AG	*p*-Value
Time to engraftment (days)[a]	19.5 (14.5-22.0)	20.5 (17.5-24.0)	0.380
Rate of engraftment	72.7% (8/11)	96.0% (24/25)	0.077
Survival at 2 years			
Overall	36.4% (4/11)	57.1% (8/14)	0.529
Recurrence-free	45% (5/11)	50% (7/14)	0.859

P-AG: Polaprezinc suspended in sodium alginate solution, [a]Median and lower and upper quartiles. Statistical analysis was carried out by chi-square test.

The activation of NF-κB by oxidative stress followed by excessive production of inflammatory cytokines, including TNFα, IL1 and IL6, is considered to be involved in the pathogenesis of chemotherapy- and radiotherapy-induced oral mucositis (9). Therefore, the antioxidative as well as the inhibitory effects of polaprezinc on the production of inflammatory cytokines may contribute to the prophylactic action of this compound against oral mucositis.

Palifermin is currently an approved agent for prophylaxis against severe oral mucositis induced by high-dose chemotherapy and radiotherapy followed by HSCT but not by radiochemotherapy for head and neck cancer. Several randomized control trails have demonstrated the effect of palifermin for prevention of oral mucositis in patients receiving high-dose chemotherapy and radiotherapy followed by HSCT (17, 28, 29). Spielberger *et al*. reported that palifermin reduced the incidence of grade 4 oral mucositis (20% versus 62%), patient-reported soreness of mouth and throat, the use of opioid analgesics (212 mg *versus* 535 mg), and the incidence of use of total parenteral nutrition (31% *versus* 55%) (17).

In addition, palifermin is reported to confer weak but significant protection against severe oral mucositis induced by radiochemotherapy in patients with head and neck cancer (16, 30). However, palifermin failed to significantly suppress the maximum severity of oral mucositis or patient reported outcomes in patients with multiple myeloma receiving high-dose melphalan before auto-stem cell transplantation (31). Brizel *et al*. also reported no significant effect of palifermin on the incidence of oral mucositis induced by radiochemotherapy for head and neck cancer (32).

We previously reported that P-AG markedly reduced the incidence of grade 3 and 4 oral mucositis induced by radiochemotherapy in patients with head and neck cancer. P-AG was shown to be effective for prevention of oral mucositis not only in patients with hematopoietic malignancy receiving high-dose chemotherapy/radiotherapy but also in those with head and neck cancer who undertook radiochemotherapy.

Several limitations exist to the present study. Firstly, this was a retrospective study, in which chemotherapeutic regimens followed by HSCT differed between the two groups. Secondly, the study was carried out in a small population at a medium size university hospital. Therefore, a randomized control study on a larger scale is required to demonstrate the prophylactic effect of P-AG against oral mucositis induced by high-dose chemotherapy with radiotherapy followed by HSCT.

In conclusion, P-AG was found to be effective in reducing the incidence of severe painful oral mucositis induced in patients with hematopoietic malignancy who received high-dose chemotherapy and radiotherapy followed by HSCT. P-AG is safe and inexpensive. Therefore, the compound may become a highly cost-effective agent that is useful for prevention of oral mucositis during cancer therapy.

Conflicts of Interest

The Authors declare that no conflict of interest, with any company and other organization, exists pertaining to this article mentioned regarding the content, conclusion and significance of the research, as well as the opinions therein.

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