Oral management with Polaprezinc solution reduces adverse events in hematopoietic stem cell transplantation patients

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Key words: Oral management, polaprezinc, polyacrylic acid, hematopoietic malignancies, hematopoietic stem cell transplantation

Running title: Oral management in hematopoietic stem cell transplantation

Abstract

The aim of the study was to analyze the effects of gargling and then swallowing of PPAA (polaprezinc in polyacrylic acid solution), in addition to regular oral management, on the patients with hematopoietic neoplasm who were scheduled for hematopoietic stem cell transplantation (HSCT). A total of 120 patients scheduled for HSCT from 2006 to 2016 were recruited. Patient background, oral adverse events, incidence and severity of systemic adverse events (sepsis/septic shock, acute graft-versus-host disease (GVHD) after transplantation), and outcomes (survival/death) were compared between groups treated with and without PPAA. The severities of oral adverse events (oral mucositis, oral pain, and dysgeusia) were significantly lower in patients treated with PPAA. There was no significant difference in the incidence of febrile neutropenia (P=0.622) or sepsis/septic shock (P=0.656) as systemic adverse events. The severity of allograft-induced acute graft-versus-host disease (GVHD) was significantly lower in the PPAA group (P=0.11). There was no significant difference in outcome between the two groups (P=0.286). Within the declared limits of the current study design, it may be concluded that oral management with PPAA reduces adverse events in HSCT. Oral management with concomitant

use of PPAA both decreased oral adverse events and reduced the systemic complication of GVHD.

Introduction

Oral adverse events may develop in response to chemotherapy and radiotherapy given as conditioning regimen before hematopoietic stem cell transplantation (HSCT)[1]. Oral mucositis during this pre-transplant conditioning treatment may cause extensive erosion and hemorrhage accompanied by severe pain in the oral mucosa, and the incidence is high compared with that in remission induction therapy and post-remission therapy[2]. Oral mucositis increases physical and mental distress, and also damages the mucosa as a protective wall against normal flora, which may induce lethal systemic infection[3]. Supportive therapy for primary disease improves the outcome[4-7]. Oral management in malignant neoplastic disease should contribute to improvement of the outcome of the primary disease, rather than improvement of subjective oral symptoms of patients or laboratory data only.

Oral hygiene management, functional oral management (common dental procedure), and some drug therapy are effective for prevention and treatment of oral mucositis and relief of pain[8-10]. Gargling with mouthwash containing azulene sodium sulfonate and rebamipide, use of herbal medicine, and inhalation or ointment application of steroids have been reported as drug therapy

for oral adverse events[11,12]. Allopurinol is used in many hospitals due to its action of inhibiting production of free radicals[11]. Each of these drugs has advantages and disadvantages, but generally the effects are insufficient for oral mucositis [13]. To solve this problem, polaprezinc (catena-(S)-[μ-[N^{α}-(3-Aminopropionyl)histidinato(2-)-N^{1},N^{2},O:N^{τ}]-zinc]: $C_9H_{12}N_4O_3Zn$), a drug used for gastric ulcer treatment that is relatively fast-acting and can be administered for a long time, has been proposed with direct contact of the drug with oral mucosal erosion and ulcer for a prolonged period showing an effect on oral mucositis[14]. Katayama et al. dissolved polaprezinc with sodium polyacrylate (PAA), a food additive, to promote contact of the drug with damaged oral mucosa for a prolonged period, and reported a strong effect[15].

In our hospital, about 25 HSCTs, 10 organ transplants, 10,000 cancer chemotherapy treatments, and 6,000 surgeries under general anesthesia are performed yearly. Supportive therapy for cancer treatment is an important role of dentistry, oral surgery department in a general hospital in addition to hospital dentistry and oral medicine. Our department treats patients with hematopoietic neoplasm scheduled for HSCT with gargling and then swallowing of Polaprezinc in PAA (PPAA), in addition to regular oral management. The aim of this study was to investigate,

the effects of this treatment on the incidence and severity of oral adverse events, sepsis/septic shock, acute graft-versus-host disease (GVHD) after transplantation, and overall outcomes of the primary diseases.

Patients and Methods

Patients

There were 120 patients with hematopoietic neoplasm who were scheduled for HSCT at the Department of Hematology and Medical Oncology of our hospital from January 2006 to August 2016. The PPAA group (n=79) comprised patients who gave consent to use of PPAA after the attending physician requested regular oral management at the oral care unit in our department. The control group (n=41) comprised patients who visited the oral care unit and received only regular oral management without PPAA treatment from before transplantation (Table 1). Oral management included examination of infected lesions in the oral cavity, treatment for these lesions (tooth extraction, treatment of periodontal disease, infected root canal, and dental caries), and oral hygiene instructions from about one month before HSCT. PPAA (1,500 mg polaprezinc

105 dissolved with 250 ml of 0.2% PAA) was dispensed in the hospital. Polaprezinc was provided
106 from Zeria Pharmaceutical (Tokyo, Japan) from 2007 to 2015. Use of PPAA (gargling and
107 then swallowing 5 ml of PPAA, four times per day) was initiated one week before HSCT and the
108 patients were instructed to use this drug daily for 4 weeks. Compliance was checked daily by a
109 nurse.
110
111 Oral and systemic adverse events
112 The following items were investigated: oral adverse events accompanying pretransplant
113 conditioning (oral mucositis, dry mouth, oral pain, oral dysesthesia, dysgeusia); febrile
114 neutropenia (FN); sepsis/septic shock; acute GVHD; and outcome (survival/death). Oral adverse
115 events were evaluated weekly for 4 weeks after HSCT based on the National Cancer Institute
116 Common Terminology Criteria for Adverse Events Version 4.0 (CTCAE Ver. 4.0)[16]
117 (supplemental data 1) and the highest grade was used as the final evaluation. The absence of oral
118 adverse events was judged as Grade 0. The severity of acute GVHD was judged using
119 Glucksberg's classification[17] and factors were investigated in cases with Grade III or severer

acute GVHD, for which treatment is essential, and those with Grade II or milder.

Statistical analysis

Each categorical variable of patient with hematopoietic neoplasm was analyzed using the Chi-squared test between with and without PPAA. Associations of use of PPAA with oral adverse events, complications, and death were analyzed using univariate and multivariable logistic regression analyses with forward selection method (wald) and after adjustment for age and sex were performed in all patients. We also analyzed the association between use of PPAA and GVHD in the allogeneic HSCT (allo-HSCT) recipients using univariate and multivariable logistic regression analyses. All statistical analysis was performed using an assumed type I error rate of 0.05. Statistical analysis was performed using IBM SPSS Statistics 24 for Windows (SPSS Japan Inc., Tokyo, Japan). Factors influencing development of acute GVHD were investigated in 63 allo-HSCT recipients using univariate and multivariable analyses.

Ethics

This study was performed with full consideration of the protection of personal information, and after approval from the Ethics Committee of Dokkyo medical university hospital (approval number: dum 1939).

Results

Patient background

Characteristics, primary disease and treatment of the patient who enrolled in this study were shown in Table 2 and Table 3. For prevention of GVHD, cyclosporine and methotrexate were administered before transplantation from an human leukocyte antigen (HLA) -matched related, and tacrolimus and methotrexate were administered before transplantation from an HLA 1-locus mismatch related, unrelated, and cord blood stem cell transplantation, with reference to the guidelines established by the Japan Society for Hematopoietic Cell Transplantation (volume 4).

Association between oral management using PPAA and adverse events

The severity of oral adverse events was evaluated using CTCAE ver.4 in all patients. The patients

were divided into those who developed low- and high-grade adverse events that did not and did influence food intake or activities of daily living, respectively (Table 4). The frequencies of high-grade oral mucositis (P=0.008), oral pain (P<0.001), and dysgeusia (P=0.004) were significantly lower in the PPAA group (Table 4). The frequencies of high-grade oral mucositis and oral pain in patients who received autologous HSCT (auto-HSCT) (oral mucositis: P=0.001, oral pain: P<0.001) and MAC + unrelated allo-HSCT (oral mucositis: P=0.025, oral pain: P=0.018) were significantly lower in the PPAA group, but there was no significant difference between the groups for those who received reduced-intensity conditioning + allo-HSCT (oral mucositis: P=1, oral pain: P=0.580) (data not shown).

For systemic adverse events, there was no significant difference in the incidence of FN (P=0.622) or sepsis/septic shock (P=0.656) between the PPAA and control groups (Table 4). In patients who developed sepsis/septic shock, oral indigenous bacteria were detected in blood culture in 5 patients in the PPAA group and 1 in the control group, with no significant difference between the groups (P=0.600). One patient subsequently died of septic shock in each group. Regarding treatment outcomes, the overall survival rates were 68.4% (54/79) and 58.5% (24/41) in the

PPAA and control groups, respectively, with no significant difference between the groups (P=0.285) (Table 4).

Effect of PPAA on frequency of adverse events

Age, timing and method of transplantation, source of graft, type of chemotherapy as pretransplant conditioning, and irradiation as pretransplant conditioning had an influence on FN, sepsis/septic shock, and treatment outcome in univariate analysis (Table 5). Incidences of oral mucositis (P=0.009), oral pain (P=<0.001), and dysgeusia (P=>0.006) were also significantly lower in the PPAA group in univariate analysis, but PPAA had no influence on systemic adverse events (FN:P=0.622, sepsis or septic shock: P=0.656) or outcome (P=0.286) (Table 5). Use of PPAA remained as a significant factor associated with a lower incidence of oral mucositis, oral pain, and dysgeusia in multivariable analysis and in sex- and age-adjusted multivariable analysis (Table 6).

Influence of oral management using PPAA on acute GVHD in allo-HSCT

In univariate and multivariable analyses, the incidence of severe acute GVHD was significantly

lower in the PPAA group than in the control group (Tables 7, 8). The usage of PPAA was not associated with matching of HLA. We also investigated the factors which influenced the development of chronic GVHD, however no factor was extracted in this experiment (data not shown).

Discussion

Among the patients treated with and without PPAA, the rates of allograft recipients and patients treated with MAC + total body irradiation were significantly higher in the PPAA group. We started to use PPAA in 2008. Therefore, all patients treated before 2008 were included in the control group (no PPAA). From 2008 to 2013, use of PPAA was decided by oral surgeons. Since 2014, all patients have received PPAA. Oral mucositis has been reported to be severer in allo-HSCT than in auto-HSCT recipients[18] and oral surgeons may have made a judgment based on this finding. The reason for the non-use of PPAA in allograft may have been pretreatment with mini and umbilical cord blood transplants. The reasons for the use of PPAA in autograft were recurrence after grafting and transplantation in non-remission in patients planning stronger

intensity pretreatment before grafting and severe mucositis observed in remission therapy and consolidation therapy before grafting. The limitations of this study were that this was not a randomized intervention study but it was a retrospective cohort study and patient selection was biased, suggesting the necessity of sufficient consideration in interpreting the results.

The most important finding in this study was that oral management using PPAA significantly decreased oral adverse events of oral mucositis, oral pain, and dysgeusia in treatment before and after HSCT in patients with hematopoietic neoplasms. Oral mucositis firstly occurs because of free radicals produced by chemotherapy and irradiation, and drug- and irradiation-induced leucopenia then reduces immunity and subsequently causes local infection as secondary oral mucositis [11,13]. Polaprezinc is widely used as an anti-gastric ulcer drug and is a zinc/L-carnosine complex. Zinc is an essential element in vivo that has wound healing, antiulcer, antioxidative, and anti-inflammatory actions, and L-carnosine also has tissue repair, antiulcer, and antioxidative effects[13, 19, 20,21].

It has been reported that Polaprezinc is not absorbed by normal epithelium, but it adheres to and infiltrates ulcer regions, inducing the activation of mesenchymal stem cells, production of insulin-

like growth factor-1 in vascular endothelial cells, and wound healing-promoting effect and anti-ulcer action to protect damaged gastric tissue and skin[21,22]. Regarding antioxidant actions, it has been reported that it removes free radicals in inflammatory regions and antioxidant markers, such as superoxide dismutase-1, superoxide dismutase-2, heme oxygenase-1, peroxiredoxin-1, and peroxiredoxin-V, increased in the Polaprezinc treatment rat model[23]. Several researchers demonstrated that Polaprezinc inhibited production of inflammatory cytokines including tumor necrosis factor-α, interleukin-1β, and interleukin-6[24,25,26,27]. These actions may have contributed to the preventive action of Polaprezinc against oral mucositis.

Sodium alginate and 2% carmellose sodium have also been used as the gargle base materials for polaprezinc[20,28]. However, aggregation and solidification of a green precipitate occurs if the sodium alginate and polaprezinc suspension is left after preparation[28]. Moreover, diarrheal symptoms and a sense of abdominal distension may develop by the carmellose suspension because carmellose sodium is also used as a laxative[28]. The use of sodium alginate and 2% carmellose sodium as base materials needs more consideration regarding adherence to oral mucosa and retention. In the present study, sodium polyacrylate was chosen as the base material

225 due to its high viscosity and safety, and this resulted in superior adherence of polaprezinc to the
226 mucosa and better retention, through which physical protection can be expected and favorable
227 results may have been obtained.
228 In this study, we investigated both the local effects of the professional oral management using
229 PPAA and influences on systemic adverse events and outcome. Unexpectedly, we found no
230 significant effect of this approach on most of the systemic adverse events (sepsis/septic shock and
231 FN) before and after HSCT or on the outcome of patients with hematopoietic neoplasm.
232 However, the severity of acute GVDH after allo-HSCT was reduced. Acute GVHD is a fatal
233 complication of allo-HSCT in which donor T-cells attack genetically several recipient cells. The
234 pathophysiology of acute GVHD can be divided in 3 phases. In Phase 1, pretreatment before
235 grafting induces inflammation in host tissue and damaged cells secrete inflammatory cytokines.
236 On the other hand, microorganism-derived substances, such as endotoxin, flow into the
237 circulation from impaired intestinal mucosa, promoting antigen-presentation and production of
238 inflammatory cytokines in macrophages. In Phase 2, antigen-presentation to donor T cells by
239 antigen-presenting cells, especially, dendritic cells, occurs. Activated T cells become Th1 cells

240 and induce cytotoxic T lymphocytes (CTL). In Phase III, tissue impairment by CTL and

241 cytokines occurs and diagnosed as GVHD[29,30,31]. Thus, gargling and swallowing of PPAA cover

242 and directly protect the ulcer region, acquiring an effect promoting healing of oral mucositis,

243 which may have inhibited the severity of mucositis induced by pretreatment before grafting,

244 release of inflammatory cytokines and the incidence of GVHD by cytokine storm. In addition,

245 Polaprezinc has been reported to exhibit an intestinal mucosa-protecting action. It is presumed

246 that protecting the intestinal mucosa with PPAA reduced the severity of GVHD by suppressing

247 the danger signal derived from exogenous pathogens.

248 Greenberg et al. reported that the incidence of oral infection-induced sepsis was 25% in patients

249 with acute leukemia who started to receive professional oral management prior to chemotherapy,

250 whereas this incidence was 77% in patients who did not receive professional oral management[32].

251 When oral mucosa as a protective wall against the oral bacterial flora is impaired, oral bacteria

252 enters the blood flow and the danger signals from exogenous pathogens will be activated[33]. The

253 danger signals from exogenous pathogens enhance the cytokine storm and endogenous danger

254 signals due to tissue injury caused by donor-derived activated cytotoxic T lymphocytes[33]. Then

255 combination of the exogenous and the endogenous danger signals might aggravate acute

256 GVHD[33] Prevention of oral mucosal damage and promotion of healing by oral management in

257 addition to the protective effect on intestinal mucosa may reduce exogenous danger signals and

258 cytokine storm, and thus reduce the severity of acute GVHD[33]. We also investigated possible

259 organ specificity of reduced severity of acute GVHD, but no organ-specificity was found (data

260 not shown).

261 The results of this study suggest that intense oral management before and after HSCT in patients

262 with hematopoietic neoplasm reduces oral adverse events and can influence systemic

263 complications. Further investigation of the effect of oral management is warranted in studies

264 using endpoints associated with outcomes.

265

266 **Declarations**

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268 **Competing interests:** Polaprezinc was provided from Zeria Pharmaceutical (Tokyo, Japan) from

269 2007 to 2015.

Ethical approval: This study was approved by the Ethics Committee of Dokkyo Medical University Hospital (dmu1939).

Patient Consent: We obtained written informed consents form all patients enrolled in this studay.

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Table 1. Patients with hematopoietic neoplasms who were enrolled in this study

	Auto-HSCT[b]	Allo-HSCT[c]	Total
PPAA[a] group (n=79)			
From2008 to 2013	18	35	53
After 2014	13	13	26
Control group (n=41)			
Before 2007	9	7	16
From2008 to 2013	17	8	25
Total	57	63	120

a:PPAA:Polaprezinc in Polyacrylic acid solution,

b: Auto-HSCT: Autologous hematopoietic stem cell transplantation

c: Allo-HSCT: Allogeneic hematopoietic stem cell transplantation

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Table 2. Characteristics, primary disease, and treatment of patients who did and did not receive oral management with PPAA[a]

	All patients (n=120)		PPAA[a] With (n=79)		PPAA[a] Without (n=41)		
	n	%	n	%	n	%	*P* value[b]
Demographics							
Sex							
Male	71	59.2	46	58.2	25	61.0	0.771
Female	49	40.8	33	41.8	16	39.0	
Age							
<30	21	17.5	14	17.7	7	17.1	0.334
30-49	48	40.0	35	44.3	13	31.7	
≥50	51	42.5	30	38.0	21	51.2	
Primary disease							
Mature B-cell neoplasms	49	40.8	24	30.4	25	61.0	
Acute myeloid leukemia	38	31.7	31	39.2	7	17.1	
Precursor lymphoid neoplasms	18	15.0	15	19.0	3	7.3	
Hodgkin lymphoma	8	6.7	6	7.6	2	4.9	**0.01**
Myelodysplastic syndromes	4	3.3	1	1.3	3	7.3	
Mature T-cell/NK cell neoplasms	2	1.7	1	1.3	1	2.4	
Chronic myeloid leukemia	1	0.8	1	1.3	0	0.0	
Treatment							
Timing of transplantation							
Remission phase	96	80.0	62	78.5	34	82.9	0.562
Non-remission phase	24	20.0	17	21.5	7	17.1	
Origin of transplant							
Autologous	57	47.5	30	38.0	27	65.9	**0.004**
Allogeneic	63	52.5	49	62.0	14	34.1	
Source of transplant							
Peripheral blood	66	55.0	38	48.1	28	68.3	**0.049**
Bone marrow	41	34.2	33	41.8	8	19.5	
Cord blood	13	10.8	8	10.1	5	12.2	
TBI							
None	62	51.7	33	41.8	29	70.7	
2Gy or 4Gy	13	10.8	10	12.7	3	7.3	**0.011**
12Gr	45	37.5	36	45.6	9	20.0	
Conditioning[c]							
Allo-HSCT							**0.009**
MAC TBI (+)	44	36.7	36	45.6	8	19.5	
TBI (-)	4	3.3	3	3.8	1	2.4	

RIC	15	12.5	10	12.7	5	12.2
Auto-HSCT						
MCVC	32	26.7	20	25.3	12	29.3
Melphalan	17	14.2	5	6.3	12	29.3
M-BEAM	5	4.2	4	5.1	1	2.4
Busulfan, melphalan	3	2.5	1	1.3	2	4.9

a:PPAA: Polaprezinc in Polyacrylic acid solution, b: Chi-squared test,
c: allo-HSCT: allogeneic hematopoietic stem cell transplantation; MAC: myeloablative conditioning; TBI: total body irradiation; RIC: reduced-intensity conditioning; auto-HSCT: Autologous hematopoietic stem cell transplantation; MCVC: ranimustine, carboplatin, etoposide, and cyclophosphamide; M-BEAM: ranimustine, etoposide, cytarabine, melphalan.

Table 3. Number of origin and source of hematopoietic stem cells

Origin	Source		
	Bone marrow	Peripheral blood	Cord blood
Autologous(n=57)	0	57	0
Allogeneic(n=63)			
HLA-matched related	8	8	0
HLA-mismatched related	0	1	0
HLA-matched unrelated	13	0	2
HLA-mismatched unrelated	20	0	11

Table 4. Oral and systemic adverse events and outcomes in patients who did and did not receive oral management with PPAA[a]

	All patients (n=129)		PPAA[a] With (n=79)		PPAA[a] Without (n=41)		*P* value[b]
	n	%	n	%	n	%	
Oral adverse events							
Oral mucositis							
0, 1, 2	93	77.5	67	84.8	26	63.4	**0.008**
3, 4	27	22.5	12	15.2	15	36.6	
Dry mouth							
0,1	113	94.2	74	93.7	39	95.1	1.000
2,3	7	5.8	5	6.3	2	4.9	
Oral pain							
0,1	68	56.7	58	73.4	10	24.4	**<0.001**
2,3	52	43.3	21	26.6	31	75.6	
Oral dysesthesia							
0,1	120	100.0	79	100	41	100	N/A
2,3	0	0.0	N/A	N/A	N/A	N/A	
Dysgeusia							
0	94	78.3	68	86.1	26	63.4	**0.004**
1,2	26	21.7	11	13.9	11	36.6	
Systemic adverse events							
Febrile neutropenia							
0	49	40.8	31	39.2	18	43.9	0.622
3,4	71	59.2	48	60.8	23	56.1	
Sepsis or septic shock							
No	103	85.8	67	84.8	36	87.8	0.665
Yes	17	14.2	12	15.2	5	12.2	
Outcome							
Survival	78	65.0	54	68.4	24	58.5	0.285
Death[c]	42	35.0	25	31.6	17	41.5	

a: Polaprezinc in Polyacrylic acid solution, b: Chi-squared test or Fisher's exact test, c: Details of death were from present illness (n=21), treatment-related death (n=21), and other disease (n=2).

Table 5. Associations of use of PPAA[a] with oral adverse events, complications, and death in univariate logistic regression analysis

		Oral mucositis (Grade3,4)	Dry mouth (Grade2,3)	Oral pain (Grade2,3)	Dysgeusia (Grade1,2)	Febrile neutropenia (Grade3,4)	Sepsis or septic shock	Death
Sex	Male vs Female	0.83	0.92	1.19	1.40	0.65	0.98	1.19
		(0.35-1.96)	(0.20-4.28)	(0.57-2.49)	(0.57-3.46)	(0.61-1.37)	(0.35-2.79)	(0.55-2.57)
		0.665	0.911	0.644	0.467	0.257	0.975	0.654
Age	30-49 yr. vs <30 yr.	0.40	1.33	0.37	0.95	0.76	1.36	**0.23**
		(0.12-1.30)	(0.13-13.62)	(0.13-1.06)	(0.28-3.19)	(0.26-2.24)	(0.25-7.35)	**(0.08-0.68)**
		0.129	0.808	0.065	0.936	0.622	0.723	**0.008**
	≥50 yr. vs <30 yr.	0.620	1.25	0.43	0.78	0.61	2.04	**0.28**
		(0.20-1.88)	(0.12-12.7)	(0.15-1.22	(0.23-2.64)	(0.21-1.76)	(0.40-10.34)	**(0.10-0.81)**
		0.393	0.851	0.113	0.690	0.359	0.391	**0.019**
Timing of transplantation	Remission vs Non-remission phase	0.64	N/A	1.09	1.49	1.29	0.54	**0.19**
		(0.23-1.75)		(0.44-2.70)	(0.46-4.81)	(0.52-3.18)	(0.17-1.73)	**(0.07-0.48)**
		0.384		0.854	0.508	0.578	0.300	**0.001**
Transplantation method	Allogeneic vs Autologous	1.42	0.66	1.10	0.48	1.46	2.45	**4.85**
		(0.60-3.39)	(0.14-3.10)	(0.53-2.27)	(0.20-1.18)	(0.70-3.03)	(0.80-7.44)	**(2.09-11.27)**
		0.426	0.601	0.796	0.109	0.312	0.115	**<0.001**
Source of transplant	Cord blood vs Peripheral blood	2.22	N/A	1.32	0.26	3.13	**7.22**	**6.00**
		(0.58-8.52)		(0.40-4.37)	(0.03-2.16)	(0.79-12.44)	**(1.89-27.67)**	**(1.64-21.94)**
		0.224		0.651	0.213	0.104	**0.004**	**0.007**
	Bone marrow vs Peripheral blood	2.07	1.22	1.47	0.88	1.82	0.91	1.54
		(0.81-5.26)	(0.26-5.77)	(0.67-3.22)	(0.35-2.23)	(0.81-4.06)	(0.25-3.33)	(0.67-3.55)
		0.127	0.799	0.341	0.785	0.147	0.888	0.312
Conditioning with chemotherapy[b]	MCVC vs RIC	0.92	0.93	0.90	1.82	0.44	0.39	**0.02**
		(0.20-4.33)	(0.08-11.18)	(0.26-3.16)	(0.42-7.90)	(0.12-1.58)	(0.08-1.85)	**(0.002-0.16)**
		0.909	0.957	0.869	0.425	0.210	0.238	**<0.001**
	MAC vs RIC	1.49	0.61	1.27	0.68	0.83	0.55	0.42
		(0.36-6.12)	(0.05-7.22)	(0.39-4.13)	(0.15-3.05)	(0.25-2.83)	(0.14-2.17)	(0.13-1.43)
		0.584	0.694	0.692	0.618	0.770	0.394	0.165
	Other vs RIC	1.00	1.22	1.39	1.26	0.89	0.12	0.28
		(0.20-4.96)	(0.10-14.69)	(0.38-5.07)	(0.27-6.03)	(0.23-3.43)	(0.01-1.15)	(0.07-1.08)
		1.000	0.877	0.623	0.770	0.864	0.065	0.065
TBI[c]	2Gy or 4Gy vs None	1.56	1.21	0.62	0.52	1.32	1.23	**7.42**
		(0.36-6.70)	(0.12-11.79)	(0.17-2.22)	(0.10-2.62)	(0.39-4.48)	(0.23-6.58)	**(2.04-27.04)**
		0.550	0.871	0.458	0.430	0.659	0.811	**0.002**

	12Gy vs None	2.35	0.67	1.32	0.62	1.49	1.24	**4.85**
		(0.93-5.93)	(0.12-3.85)	(0.61-2.87)	(0.24-1.61)	(0.68-3.29)	(0.42-3.72)	**(2.02-11.63)**
		0.071	0.658	0.476	0.328	0.320	0.697	**<0.001**
PPAA[a]	With vs Without	**0.31**	1.32	**0.12**	**0.28**	1.21	1.29	0.65
		(0.13-0.75)	(0.24-7.11)	**(0.05-0.28)**	**(0.11-0.69)**	(0.56-2.60)	(0.42-3.95)	(0.30-1.43)
		0.009	0.748	**<0.001**	**0.006**	0.622	0.656	0.286

The upper row presents odds ratio, and the middle row is 95% confidence interval, and the lower row is *P* value.

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a: PPAA: Polaprezinc in Polyacrylic acid solution,

b: RIC: reduced-intensity conditioning; MCVC: ranimustine, carboplatin, etoposide, and cyclophosphamide; MAC: myeloablative conditioning; Other: M-BEAM (ranimustine, etoposide, cytarabine, melphalan), melphalan, and busulfan-melphalan,

c: TBI: total body irradiation.

Table 6. Oral adverse event-related factors in multivariable logistic regression analysis

		Oral mucositis (Grade3,4)	Oral pain (Grade2,3)	Dysgeusia (Grade1,2)
Using forward selection method (wald)				
TBI[a]	2Gy or 4Gy vs None	2.62	1.14	
		(0.53-12.89)	(0.25-5.27)	
		0.236	0.867	
	12Gy vs None	**4.45**	**3.34**	
		(1.48-13.41)	**(1.22-9.16)**	
		0.008	**0.019**	
PPAA[b]	With vs Without	**0.18**	**0.08**	**0.28**
		(0.06-0.52)	**(0.03-0.21)**	**(0.11-0.69)**
		0.001	**<0.001**	**0.006**
Using forward selection method (wald) adjusted for sex and age				
TBI[a]	2Gy or 4Gy vs None	2.18	1.07	
		(0.43-11.07)	(0.22-5.22)	
		0.314	0.935	
	12Gy vs None	**5.73**	**3.84**	
		(1.60-20.53)	**(1.23-12.00)**	
		0.007	**0.020**	
PPAA[b]	With vs Without	**0.18**	**0.08**	**0.28**
		(0.06-0.52)	**(0.03-0.21)**	**(0.11-0.70)**
		0.002	**<0.001**	**0.006**

The upper row presents odds ratio, and the middle row is 95% confidence interval, and the lower row is *P* value.

a: TBI: total body irradiation, b: PPAA: Polaprezinc in Polyacrylic acid solution.

Table 7. Characteristics, HLA[a] matching, and severity of acute GVHD[b] in allogeneic hematopoietic stem cell transplantation recipients who did and did not receive oral management with PPAA[c]

	All patients (n=63)		PPAA[c] With (n=49)		PPAA[c] Without (n=14)		*P* value[d]
	n	%	n	%	n	%	
Sex							
Male	35	55.6	26	53.1	9	64.3	0.456
Female	28	44.4	23	46.9	5	35.7	
Age							
<30	17	270	12	24.5	5	35.7	0.625
30-49	29	46	24	49.0	5	35.7	
≥50	17	27	13	26.5	4	28.6	
Primary disease							
Mature B-cell neoplasms	3	4.8	1	2.0	2	14.3	
Acute myeloid leukemia	35	55.6	30	61.2	5	35.7	
Precursor lymphoid neoplasms	18	28.6	15	30.6	3	21.4	**0.027**
Myelodysplastic syndromes	4	6.3	1	2.0	3	21.4	
Mature T-cell/NK cell neoplasms	2	3.2	1	2.0	1	7.1	
Chronic myeloid leukemia	1	1.6	1	2.0	0	0.0	
HLA[a] matching							
Full match	31	49.2	26	53.1	5	35.7	0.252
Mismatch	32	50.8	23	46.9	9	64.3	
Acute GVHD[b]							
0, I, II	55	87.3	46	93.9	9	64.3	**0.01**
III, IV	8	12.7	3	6.1	5	35.7	

a: HLA: human leukocyte antigen, b: GVHD: graft-versus-host disease, c: PPAA: polaprezinc dissolved with sodium polyacrylate ,d: Chi-squared test or Fisher's exact test.

Table 8. Association between use of PPAA[a] and GVHD[b]

		Severe acute GVHD[b] (GradeⅢ, Ⅳ)	
		Univariate analysis	Multivariable analysis[c]
Sex	Male vs Female	2.69 (0.50-14.51) 0.250	2.57 (0.41-16.24) 0.316
Age	30-49 yr. vs <30 yr.	0.87 (0.13-5.78) 0.881	1.03 (0.13-8.53) 0.976
	≥50 yr. vs <30 yr.	1.61 (0.23-11.09) 0.630	2.16 (0.24-19.45) 0.493
HLA[d] matching	Mismatch vs Full match	0.96 (0.22-4.25) 0.962	0.55 (0.10-3.16) 0.504
PPAA[a]	With vs Without	**0.12** **(0.02-0.58)** **0.009**	**0.11** **(0.02-0.61)** **0.011**

The upper row presents odds ratio, and the middle row is 95% confidence interval, and the lower row is *P* value.

a: PPAA:Polaprezinc in Polyacrylic acid solution, b:GVHD: graft-versus-host disease, c: Sex, age, HLA-compatibility, and PPAA was used as input in the multivariable logistic regression analysis model, d:HLA: human leukocyte antigen.

Supplemental data 1. Oral adverse events from CTCAE ver4

MedDRA v12.0 Code	CTCAE v4.0 SOC	CTCAE v4.0 Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	CTCAE v4.0 AE Term Definition
10013781	Gastrointestinal disorders	Dry mouth	Symptomatic (e.g., dry or thick saliva) without significant dietary alteration; unstimulated saliva flow >0.2 ml/min	Moderate symptoms; oral intake alterations (e.g., copious water, other lubricants, diet limited to purees and/or soft, moist foods); unstimulated saliva 0.1 to 0.2 ml/min	Inability to adequately aliment orally; tube feeding or TPN indicated; unstimulated saliva <0.1 ml/min	-	-	A disorder characterized by reduced salivary flow in the oral cavity.
10028130	Gastrointestinal disorders	Mucositis oral	Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; not interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death	A disorder characterized by inflammation of the oral mucosal.
10054520	Gastrointestinal disorders	Oral dysesthesia	Mild discomfort; not interfering with oral intake	Moderate pain; interfering with oral intake	Disabling pain; tube feeding or TPN indicated	-	-	A disorder characterized by a burning or tingling sensation on the lips, tongue or entire mouth.
10031009	Gastrointestinal disorders	Oral pain	Mild pain	Moderate pain; limiting instrumental ADL	Severe pain; limiting self care ADL	-	-	A disorder characterized by a sensation of marked discomfort in the mouth, tongue or lips.
10013911	Nervous system disorders	Dysgeusia	Altered taste but no change in diet	Altered taste with change in diet (e.g., oral supplements); noxious or unpleasant taste; loss of taste	-	-	-	A disorder characterized by abnormal sensual experience with the taste of foodstuffs; it can be related to a decrease in the sense of smell.

Common Terminology Criteria for Adverse Events (CT-CAE) v.4.0. http://ctep.cancer.gov/protocolDevelopment/electronic_ap-plications/ctc.htm#ctc_40