Polaprezinc for prevention of oral mucositis in patients receiving chemotherapy followed by hematopoietic stem cell transplantation: a multi-institutional randomized controlled trial

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Polaprezinc for prevention of oral mucositis in patients receiving chemotherapy followed by hematopoietic stem cell transplantation: a multi-institutional randomized controlled trial

Short title: Polaprezinc for prevention of oral mucositis

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Abbreviations

AE	Adverse event
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
HSCT	Hematopoietic stem cell transplantation
KGF-1	Keratinocyte growth factor-1
PBSCT	Peripheral blood stem cell transplantation
PS	Performance status
PZ	Polaprezinc, zinc-L-carnosine
TBI	Total body irradiation

Novelty and Impact

This is the first study to verify the efficacy of polaprezinc (PZ) lozenges for prevention of oral mucositis associated with conditioning chemotherapy in patients undergoing HSCT by a multi-institutional randomized controlled study. We revealed that PZ lozenges were effective for prophylaxis against Grade ≥2 oral mucositis associated with chemotherapy in patients undergoing HSCT without any influence on the HSCT outcome.

Abstract

Oral mucositis is a common and distressing complication in patients receiving high-dose chemotherapy followed by hematopoietic stem cell transplantation (HSCT). We reported previously in a single-center retrospective analysis that zinc-L-carnosine (polaprezinc, PZ) reduced the incidence of oral mucositis associated with HSCT. To verify the accuracy of the prophylactic effect of PZ against oral mucositis, we carried out a multi-institutional prospective randomized controlled study. Patients were randomly allocated to either the prevention group, in which PZ lozenge treatment was started before chemotherapy, or the control group, in which administration of PZ lozenges was initiated immediately after the onset of Grade 2 oral mucositis. Oral mucositis was evaluated daily from the start of chemotherapy to 35 days after transplantation. A total of 91 patients were enrolled, and 88 patients (47 in the control group and 41 in the prevention group) were eligible for data analysis. The incidence of Grade ≥ 2 but not Grade ≥ 3 oral mucositis was significantly reduced in the prevention group compared to the control group (44.7% in control group *vs* 22.0% in the prevention group, $P = 0.025$). There were no significant differences in the incidence rates of other adverse events or the rate of

engraftment (95.6% *vs* 97.2%, *P* = 0.693) between the two groups. These findings suggest that PZ lozenge is effective for prophylaxis against Grade ≥ 2 oral mucositis associated with chemotherapy in patients undergoing HSCT without any influence on the HSCT outcome.

Introduction

Oral mucositis is one of the common complications in patients receiving high dose chemotherapy followed by hematopoietic stem cell transplantation (HSCT).[1-4] Oral mucositis is often accompanied by pain, odynophagia, xerostomia, and dysgeusia, and may lead to subsequent malnutrition and dehydration, which severely impairs patients' quality of life (QOL).[5-7] In severe cases, reduction or discontinuation of chemotherapy is required, which may endanger the success of therapy.[8,9] From the viewpoint of the cost of care associated with hospitalization, medical management, nutritional support, and management of secondary infection, severe oral mucositis has a negative impact on the healthcare economy.[9-11] Therefore, the prevention or amelioration of oral mucositis associated with chemotherapy in patients undergoing HSCT is important.

Several agents, including keratinocyte growth factor-1 (KGF-1),[12-14] which is a recombinant human epidermal growth factor,[15] erythropoietin,[16] misoprostol,[17,18] and amifostine[19,20] have been reported as efficacious for the prevention or treatment of oral mucositis in patients undergoing HSCT. Among them, palifermin, a KGF-1, is the only agent that has been approved by the US Food

and Drug Administration and the European Medicines Agency as a drug for oral mucositis, although the use of palifermin in pediatric patients is open to debate because of the lack of sufficient data on the efficacy and toxicity and long-term follow-up of KGF-1s.[4]

We reported previously that oral ingestion of polaprezinc (PZ), a zinc-L-carnosine, preparation suspended in sodium alginate was highly effective for prevention of oral mucositis associated with radiotherapy in adult patients with head and neck cancer[21,22] as well as in adult[23] and pediatric[24] patients receiving high-dose chemotherapy for HSCT. We found that a newly-developed lozenge preparation containing PZ had efficacy almost comparable to that of the PZ suspension in sodium alginate.[25] However, the effects of PZ for patients receiving high-dose chemotherapy for HSCT have been evaluated only in single-institutional retrospective studies.[23-25] To confirm the preventive effect of PZ against oral mucositis, we have carried out a multi-institutional randomized controlled clinical study evaluating the efficacy of PZ lozenges for prevention of oral mucositis associated with chemotherapy in patients undergoing HSCT.

Patients and methods

Study Design and Patients

Patients with hematological malignancy undergoing HSCT were enrolled between January 2017 and March 2019 and were allocated randomly to either a prevention group (starting PZ lozenges before chemotherapy) or a treatment group as a control (starting PZ lozenges after Grade 2 oral mucositis development). Inclusion criteria were Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, and age of 18–90 y. Patients aged < 18 y and patients who already had oral mucositis before chemotherapy were excluded.

Oral mucositis, xerostomia, taste disturbance, and other adverse events (AEs) were assessed according to the Common Terminology Criteria for Adverse Events (CTCAE version 4) by one to three specified physicians at each hospital who had sufficient ability to conduct appropriate grading of these AEs. The evaluation of AEs was performed in a non-blinded manner. Each patient was assessed daily for oral mucositis from the beginning of chemotherapy until 35 days after transplantation. The maximum Grades of oral mucositis and other

AEs per week were reported.

Randomization

The patients enrolled in this study were randomly assigned to the prevention group or control group according to a random number table in a ratio of 1:1 to receive different treatments.

Endpoints

The primary endpoint of this study was the incidence of Grade $\geq$ 3 oral mucositis. Secondary endpoints were the incidence and severity of oral mucositis, xerostomia, and taste disturbance. The incidence of other non-hematological AEs, the median time of engraftment, and rate of engraftment were also compared between the two groups.

Study Drugs

PZ lozenges were prepared according to our previous report.[25] Briefly, the mixture per tablet, including 18.75 mg polaprezinc (Promac® granules15%, Zeria Pharmaceutical Co. Ltd., Tokyo, Japan), 0.05 g sodium alginate (KIMICA

Algin I-1®, Kimica Co. Ltd., Osaka, Japan), 0.005 g magnesium Stearate (Magnesium Stearate, Mallinckrodt Japan Co. Ltd., Tokyo), 0.0015 g acesulfame potassium (Sunett® Pharma grade Type I, MC Food Specialties Inc., Tokyo), 0.0015 g NL-alpha-aspartyl-L-phenylalanine 1-methyl ester (Aspartame®, Ajinomoto Co., Inc., Tokyo), 0.33 g mannitol (Parteck M100®, Merck Ltd., Tokyo), 0.4 g microcrystalline cellulose (CEOLUS UF-711®, Asahi Kasei chemicals Corp., Tokyo), 0.05 g cornstarch (PC-10®, Asahi Kasei chemicals Corp., Tokyo), 0.01 g fragrance material (dry coat®, Takata Koryo CO.,LTD., Hyogo, Japan), was directly compressed at 15 kN by using a single punch tablet press (TAB ALL N-30E Type®, Okada Seiko Co. Ltd., Tokyo). The content uniformity of the polaprezinc lozenge was tested in 10 separate preparations per lot according to the Japanese Pharmacopoeia 16th edition.[26] For patients, one polaprezinc lozenge was sucked and swallowed 4 times daily.

Statistical Analysis

We expected a 91% incidence of oral mucositis in the control group. Using a chi-squared test adjusted by Yate's method, we calculated that a sample size of 90 patients would be needed to detect a difference of 31% in proportion of the

incidence of oral mucositis between the prevention group and control group with 80% power and a two-sided significance level of 0.05. Data were analyzed with an intention-to-treat approach. The patients' characteristics (Table 1) are described using mean and SD for continuous variables, and frequencies and proportions were used for categorical data. For the analysis of primary endpoints and secondary endpoints of the incidence of an AE, a chi-squared test was conducted. The Mann-Whitney *U*-test was conducted for comparing of time to engraftment. Data were analyzed by using SPSS version 22 (SPSS Inc., Chicago, IL, USA). Two-sided *P*-values of < 0.05 were considered statistically significant.

Results

Patient Characteristics

The Consolidated Standards of Reporting Trials (CONSORT) statement is shown in Figure 1. A total of 91 patients were enrolled and randomly allocated to 48 patients in control group and 43 patients in the prevention group. Of these patients, three patients were excluded from this analysis by the following reasons. One patient in the prevention group developed atypical

mycobacteriosis, and could not receive conditioning chemotherapy. Another patient in the prevention group retracted consent before chemotherapy. One patient in the control group suffered from acute respiratory distress syndrome during chemotherapy. Thus, the analysis was conducted using 88 participants, with 47 in the control group and 41 in the prevention group.

In this study, data were analyzed with an intention-to-treat approach. Thus, although seven patients (two patients in the control group and five patients in the prevention group) retracted consent because of unfavorable taste and undesirable texture of the PZ lozenges during the trial, their data until revocation of consent were used for the analysis. Moreover, although two patients in control group incorrectly took PZ lozenges at the start of chemotherapy, they were analyzed as part of the control group.

Patient demographics of the two groups are shown in Table 1. The rates of patients receiving allogeneic-peripheral blood stem cell transplantation (PBSCT) and total body irradiation (TBI) were higher in the prevention group than in control group (allogeneic-PBSCT: 58.5% for prevention group *vs* 34.0% for control group; TBI: 56.1% *vs* 25.5%).

Incidence and Severity of Oral Mucositis and Related Symptoms

As shown in Table 2, pretreatment with PZ lozenges significantly reduced the incidence of Grade ≥ 2 oral mucositis (44.7% in control group *vs* 22.0% in the prevention group, $P = 0.025$), although there was no significant difference in the incidence of Grade ≥ 3 oral mucositis (10.6% *vs* 14.6%, $P = 0.572$). Thus, the present study did not meet the primary endpoint. In addition, the incidence rates of all Grades of anorexia (89.4% vs 92.7%, $P=0.589$), xerostomia (27.7% *vs* 31.7%, $P=0.678$) and taste disturbance (59.6% *vs* 51.2%, $P=0.431$) were not significantly different between the two groups.

The prevalence of the use of opioid analgesics and non-opioid analgesics for the relief of oral pain was not significantly different between the two groups (opioid analgesics: 6.4% in the control group *vs* 12.2% in the prevention group, $P=0.344$; non-opioid analgesics: 12.8% *vs* 12.2%, $P=0.936$).

Rate of Engraftment, Time to Engraftment and Incidence of Other Non-hematological Adverse Events

Seven patients (two patients in the control group and five patients in the prevention group) who retracted consent during the trial were excluded from

analysis of the rate of engraftment and time to engraftment. The rate of engraftment and time to engraftment showed no significant differences between the two groups (Table 3).

Table 4 compares the incidence of all Grades of other non-hematological adverse events. There were no significant differences in the incidence of nausea, vomiting, constipation, diarrhea, peripheral neuropathy, skin disorder, elevation of alanine aminotransferase or serum creatinine, or febrile neutropenia between the two groups. There were no severe AEs associated with PZ lozenges.

Discussion

Our previous retrospective studies indicated that PZ suspension in sodium alginate[22] as well as a PZ lozenge preparation[25] markedly reduced the incidence of moderate-to-severe oral mucositis in patients with hematological cancer who received high-dose chemotherapy. The inhibitory effect of PZ lozenges on the development of Grade ≥ 2 oral mucositis associated with chemotherapy in patients undergoing HSCT was verified by the present multi-institutional randomized controlled trial, although our study failed to meet the primary endpoint (incidence of Grade ≥ 3 mucositis). In the present study, PZ lozenges

were administered immediately after appearance of Grade 2 mucositis in the control group. The incidence rate of Grade ≥ 3 mucositis in this group was 10.6%, which was much lower than those reported by several investigators. Sonis et al.[27] reviewed the incidence of oral mucositis for the Mucositis Study Section of the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society for Oral Oncology (ISOO), in which the incidence rates of Grades 3–4 mucositis exceed 60% in most reports. Blijlevens et al.[28] showed in patients receiving high-dose conditioning chemotherapy before autologous HSCT that Grades 3-4 mucositis appeared in 46% of patients with multiple myeloma and 42% of patients with non-Hodgkin's lymphoma. Moreover, in our previous retrospective studies[22,25] showing the preventive effect of PZ against oral mucositis in patients receiving high-dose chemotherapy for HSCT, Grades 3–4 mucositis occurred in 5 (45.5%) of 11 patients without prophylactic treatment. Therefore, it is highly probable that PZ lozenges are effective in reducing the progression of mucositis symptoms, even when administered after the onset of mild mucositis.

On the other hand, there were significant differences in several aspects of patients' demographics between the prevention group and the control group,

irrespective of random assignment designed in the present study: 1) TBI was administered to more patients in the prevention group than in the control group (56.1% *vs* 25.5%). 2) The prevalence of allogeneic-PBSCT was higher in the prevention group than in the control group (58.5% *vs* 34.0%). 3) Chemotherapy regimens were different between the two groups.

It has been demonstrated that concurrent TBI is a high risk for developing severe oral mucositis. Sonis et al.[27] reported that Grades 3–4 oral mucositis occurs in 52% of 360 patients receiving busulfan-based regimens without TBI, and 31% of those receiving other conditioning regimens without TBI, but the rate increases to 64% in patients with concurrent TBI. Stiff et al.[29] also indicated that chemotherapy regimens with TBI led to a higher rate of mucositis than chemotherapy alone. They showed by a retrospective analysis of 41 patients that severe mucositis occurs in 30% of patients receiving high-dose chemotherapy alone, but in 65% of patients receiving TBI-based regimens. Haverman et al.[30] reported in a review article that the incidence of oral mucositis in HSCT recipients is enhanced by concurrent TBI and that the risk of mucositis decreases to 30%–50% in patients receiving protocols without TBI.

Allogeneic HSCT puts patients at a high risk for severe oral mucositis.

Vagliano et al.[31] reported in a multicenter study that the occurrence of Grades 3–4 mucositis is significantly higher in patients receiving allogeneic HSCT (177/479 patients, 37.0%) than in those receiving autologous HSCT (155/1077 patients, 14.4%).

In the present study, age was younger in the prevention group than in the control group (48 vs 58 y). It has been shown that the occurrence of severe mucositis (Grades 3–4) is less frequent in elderly patients, in which the rates are 9.2% and 24.4% in patients whose ages are 60–74 y and those of 19-59 y, respectively.[31]

Taken together with all of these data, it seems likely that the prophylactic effect of PZ lozenges observed in the present study (prevention group) was underestimated. In other words, even under such severe conditions PZ lozenges given preventively did significantly reduce the incidence of Grade ≥ 2 oral mucositis as compared with the control group.

Oral acceptability of PZ lozenges was slightly limited, since 4.3% (2/47) patients in the control group and 12.2% (5/41) patients in the prevention group retracted consent for the reason of unfavorable taste and undesirable texture. This finding was unexpected for us. Therefore, up grading of the taste and

texture of the formulation may be required for application to a larger population of patients.

It was also notable that the effect of PZ lozenges was specific for oral mucositis, since the preparation had no influence on the clinical efficacy, such as the rate of engraftment and time to engraftment, or the incidence of other non-hematological adverse events. In addition, no moderate or severe AE related to PZ lozenges was observed. PZ is highly safe and no specific AEs were observed in the present study. Increases in serum triglycerides and alkaline phosphatase; a decrease in serum iron; and gastrointestinal dysfunction such as constipation, stomach discomfort and abdominal distension have been reported after oral administration of PZ, but in rare cases only.[32] A post-marketing surveillance study in 4,879 patients indicated that oral administration of PZ at the usual dose (150mg/day) for gastric ulceration was associated with a very low frequency of such AEs as elevation of serum triglyceride (0.14%) and alkaline phosphatase (0.37%), abdominal distention (0.12%), and constipation (0.25%). In the present study, the lack of obvious AEs associated with PZ may be due to the small dose used (18.75mg×4 time a day).

In their systematic review of randomized clinical trials, Furihata et al.[33]

reported that serum zinc concentration increases after oral administration of PZ (75-300mg/day) in a dose-dependent manner. Of note, this increase is not significant at a dose of 75 mg/day (2.60 μg/dL, P=0.52), but is significant at doses of 150 mg/day (9.07 μg/dL, P<0.001) and 300 mg/day (23.05 μg/dL, P=0.001). In the present study, the dose of PZ was low (18.75mg x 4 time a day). This finding suggests that serum zinc concentration is not significantly increased after treatment with PZ lozenges, albeit that we did not measure zinc levels in the present study.

The precise mechanisms underlying the preventive effect of PZ against oral mucositis remain to be clarified. Several studies in animal models of stomach cancer and colon cancer showed that PZ inhibits the production of inflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), and matrix metalloproteinase-2 (MMP-2), and induces an anti-inflammatory effect and immune responses *via* inhibition of nuclear factor-*kappa*-light-chain-enhancer of activated B cells (NFκB).[34-37] All of those cytokines and signal molecules are considered to be involved in the pathogenesis of chemotherapy-induced oral mucositis.[38-41] Additionally, PZ inhibits the production of reactive oxygen species and induces insulin-like growth

factor-1 (IGF-1), a polypeptide that plays an important role in gastric epithelial wound repair.[42]

Several limitations of our study warrant mention. First, we were unable to evaluate patient QOL regarding symptoms related to oral mucositis with or without preventive PZ lozenge treatment. Second, oral mucositis and its related symptoms, including xerostomia and taste disturbance, as well as other AEs were not assessed in a blinded fashion.

In conclusion, the efficacy of PZ lozenges for prevention of oral mucositis associated with conditioning chemotherapy in patients undergoing HSCT was verified by a multi-institutional randomized controlled study. The incidence of Grade $\geq$ 2 but not Grade ≥ 3 oral mucositis was significantly reduced by preventive treatment with PZ lozenges. The PZ lozenge preparation had no influence on engraftment. The lozenge preparation was highly safe without any serious side effects. Therefore, PZ lozenge may be useful for prevention of oral mucositis associated with chemotherapy in patients undergoing HSCT.

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Authorship

Conception and design: J.K., Y.I., A.S.

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Final approval of manuscript: All authors.

Disclosure

The authors declare no conflict of interest.

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Data accessibility

Data can be made available upon reasonable request.

Ethics statement

This multi-institutional randomized controlled clinical trial was conducted at four hospitals in Japan and followed the Declaration of Helsinki principles. Ethics committees at each hospital approved the study protocol [approval no. 30–076 (Gifu University Graduate School of Medicine), R16-283 (Hamamatsu University School of Medicine), 396 (Gifu Municipal Hospital), I17030102 (Japanese Red Cross Gifu Hospital)]. All patients gave written informed consent before all study-related procedures. Before commencing, this study was registered at UMIN Clinical Trials Registry as UMIN000025524.

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Figure Legends

Figure 1. CONSORT diagram. Of 91 randomized, 48 and 43 had confirmed eligibility in the control group and the prevention group, respectively. One patient in the prevention group developed mycobacteriosis, and could not receive conditioning chemotherapy. One patient in the prevention group retracted consent before chemotherapy. One patient in control group suffered from acute respiratory distress syndrome during chemotherapy.

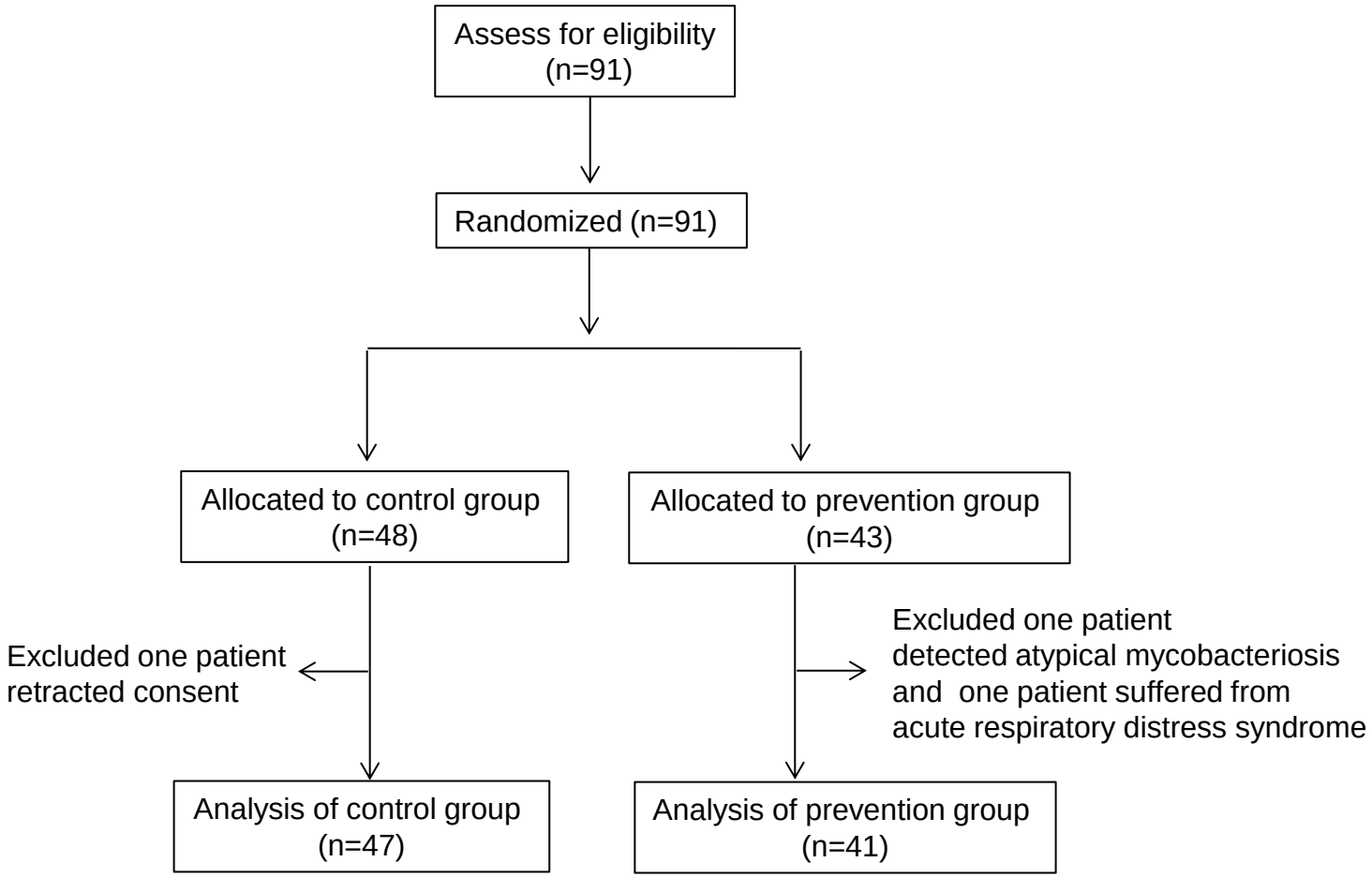
Assess for eligibility
(n=91)
Randomized (n=91)
Allocated to control group
(n=48)
Allocated to prevention group
(n=43)
Excluded one patient
retracted consent
Excluded one patient
detected atypical mycobacteriosis
and one patient suffered from
acute respiratory distress syndrome
Analysis of control group
(n=47)
Analysis of prevention group
(n=41)

TABLE 1. Patient demographics

	Control group (N = 47)	Prevention group (N = 41)
Sex (male/female), N (%)	24 (51.1)/23 (48.9)	24 (58.5)/17 (41.5)
Age (median, range)	58 (29–72)	48 (18–67)
Lab data		
Serum albumin (g/dL)	4.0 ± 0.5	4.0 ± 0.4
Lactate dehydrogenase (U/L)	310.6 ± 708.9	211.8 ± 125.1
Aspartate transaminase (U/L)	21.2 ± 13.8	21.1 ± 8.4
Alanine aminotransferase (U/L)	18.4 ± 10.6	19.3 ± 9.6
Serum creatinine (mg/dL)	0.68 ± 0.22	0.70 ± 0.25
White blood cells (n/mm^3)	4424 ± 4597	3183 ± 1454
Hemoglobin (g/dL)	10.2 ± 1.5	10.2 ± 1.9
Platelets (×10^6/mm^3)	20.8 ± 12.1	23.3 ± 38.3
Diagnosis, N (%)		
Acute myeloid leukemia	2 (4.3)	7 (17.1)
Acute lymphoid leukemia	1 (2.1)	1 (2.4)
Chronic myelogenous leukemia	2 (4.3)	2 (4.9)
B-lymphoblastic leukemia	3 (6.4)	2 (4.9)
Malignant lymphoma	17 (36.2)	17 (41.5)
Multiple Myeloma	14 (29.8)	3 (7.3)
Myelodysplastic syndromes	6 (12.8)	5 (12.2)
Others	3 (6.4)	4 (9.8)
Conditioning regimen, N (%)		
Ara-C/CPA ± Flu or ETP/MCNU	2 (4.3)	12 (29.3)
Ara-C/MCNU/L-PAM ± ETP	9 (19.1)	11 (26.8)
CPA	5 (10.6)	6 (14.6)
CPA/L-PAM ± ETP or Flu	8 (17.0)	2 (4.9)
CPA/BU ± ATG	1 (2.1)	1 (2.4)
Flu ± BU ± L-PAM	5 (10.6)	2 (4.9)
L-PAM/MCNU	1 (2.1)	0
L-PAM or BU	16 (34.0)	7 (17.1)
Stem cell source, n (%)		
Autologous-PBSCT	31 (66.0)	17 (41.5)
Allogeneic-PBSCT	16 (34.0)	24 (58.5)
TBI (Gy), n (%)	12 (25.5)	23 (56.1)

Abbreviations: Ara-C: cytarabine; MCNU: ranimustine L-PAM: melphalan; ETP: etoposide; CPA: cyclophosphamide; Flu: fludarabin; BU: busulfan; ATG: thymoglobulin; PBSCT: peripheral blood stem cell transplantation, TBI: total body irradiation

TABLE 2. The incidence of oral mucositis, anorexia, xerostomia, and taste loss

	Control group (N = 47)		Prevention group (N = 41)		*P* value
	n	%	n	%	
Oral mucositis, n (%)					
Grade 0	18	38.3	21	51.2	
Grade ≥1	29	61.7	20	48.8	0.224
Grade ≥2	21	44.7	9	22.0	0.025*
Grade ≥3	5	10.6	6	14.6	0.572
Anorexia, n (%)					
Grade 0	5	10.6	3	7.3	
Grade ≥1	42	89.4	38	92.7	0.589
Grade ≥2	40	85.1	31	75.6	0.260
Grade ≥3	29	61.7	23	56.1	0.594
Xerostomia, n (%)					
Grade 0	34	72.3	28	68.3	
Grade ≥1	13	27.7	13	31.7	0.678
Grade ≥2	1	2.1	2	4.9	0.478
Grade ≥3	0		0		
Taste disturbance, n (%)					
Grade 0	19	40.4	20	48.8	
Grade ≥1	28	59.6	21	51.2	0.431
Grade ≥2	4	8.5	3	7.3	0.836
Grade ≥3	0		0		

Statistical analysis was carried out by the Chi-squared test.

TABLE 3. Time to engraftment and rate of engraftment

	Control group (N = 45)	Prevention group (N = 36)	*P* value
Time to engraftment, d [a]	15.6 ± 5.9	14.9 ± 5.0	0.474 [b]
Rate of engraftment, %	95.6	97.2	0.693 [c]

[a] Median and lower and upper quartiles. Statistical analysis was carried out by [b] Mann-Whitney U-test and [c] Chi-square test.

TABLE 4. The incidence of other adverse events

	Control group (N= 47)		Prevention group (N= 41)		*P*-value
	N	%	N	%	
Nausea	34	72.3	31	75.6	0.728
Vomiting	11	23.4	8	19.5	0.658
Constipation	8	17	11	26.8	0.245
Diarrhea	37	78.7	34	82.9	0.618
Peripheral neuropathy	22	46.8	11	26.8	0.053
Skin disorder	9	19.1	10	24.4	0.551
Alanine aminotransferase increased	23	48.9	20	48.8	0.988
Serum creatinine increased	3	6.4	1	2.4	0.376
Febrile neutropenia	35	74.5	31	75.6	0.902
White blood cell decreased	44	93.6	40	97.6	0.376
Anemia	44	93.6	40	97.6	0.376
Platelet count decreased	44	93.6	40	97.6	0.376

Statistical analysis was carried out by the Chi-squared test.