The effect of oral management on the severity of oral mucositis during hematopoietic SCT

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The effect of oral management on the severity of oral mucositis during hematopoietic stem cell transplantation (HSCT)

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Abstract

Oral mucositis (OM) is a frequent adverse effect of allogenic or autologous hematopoietic stem cell transplantation (HSCT). It results from direct toxic injury to the mucosal epithelial cells by the immunosuppressive regimen. Here we compared the incidence and severity of OM between a group of 24 patients who received proper oral management during HSCT and a group of 24 who did not. The oral management group received pre-HSCT instruction on oral care and an oral examination in the clean room. Differences in the incidence and severity of OM between the two groups were examined statistically. OM was observed in 14 (58.3%) patients in the oral management group and 22 (91.6%) in the control group. The median of the OM score was 1 for the oral management group (range 0 to 3) and 2 for the control group (range 0 to 3). There was a significant difference in the OM score ($P<0.05$) and in the incidence of OM between the two groups ($P<0.01$). This study shows that oral management may decrease the occurrence of OM. Our results also suggest that it is important to include an oral management provider on the HSCT team.

Key Words: oral mucositis (OM); oral management; hematopoietic stem cell transplantation (HSCT); oral management provider

Introduction

Hematopoietic stem cell transplantation (HSCT) has become an important treatment for myelosuppressed patients with hematological diseases, including acute and chronic leukemias, aplastic anemia, myelodysplastic syndromes, and lymphomas[1,2]. Oral mucositis (OM) is one of the most frequent adverse effects of allogenic or autologous HSCT. It is caused by direct toxic injury to the mucosal epithelial cells. Successful engraftment after HSCT often requires severe myelosuppression, which is accomplished by total body irradiation (TBI), chemotherapy, or a combination of these therapies. These immunosuppressive regimens are toxic to cells and increase the chance of OM.

In one study of HSCT patients, 99% experienced OM, and 67.4% of them had a WHO OM grade of 3 or 4. The OM was treated with strong opiate analgesia for a median of 6 days in 47% of these patients[3]. Mucositis places immunocompromised patients at risk for bacteremia and sepsis. OM also appears to be a significant cost driver in HSCT, as it is associated with an increase in the length of hospital stay and higher inpatient charges[4].

OM results in significant morbidity and impairment of the patients' quality of life. The most common signs and symptoms of OM are erythema, edema, burning sensation, increased sensitivity to hot and spicy foods, white patches on mucous membranes of the cheeks, lips, tongue and palate, and subsequent painful ulcers. The latter make it hard to

swallow, which leads to malnutrition and dehydration, and consequently affect mucosal regeneration[5].

OM lesions usually disappear after recovery without scar formation, unless the OM is worsened by severe infection[6]. Sonis et al. found a relationship between OM and bacteremia, and concluded that poor oral care management could lead to infected oral ulcers and the dissemination of infection[7]. Evidence-based clinical practice guidelines for the care of patients with oral and gastrointestinal mucositis in 2005 newly recommended the use of palifermin for OM associated with HSCT, and cryotherapy for OM associated with high doses of melphalan. To reduce the severity of OM from chemotherapy and/or radiotherapy, oral care includes multidisciplinarily developed and evaluated oral care protocols, and patient and staff education on the use of such protocols[8]. It is also suggested that an experienced oral care provider, that is, a dentist, dental hygienist, or nurse, should be included on the HSCT team. However, although an oral management protocol during HSCT has been recommended, few prospective studies have examined its effectiveness[9,10].

The purpose of this study was to compare the incidence and severity of OM between a group of patients who received proper oral management during HSCT and a group of patients who did not.

Patients and methods

Forty-eight patients suffering from hematologic malignancies who underwent allogeneic or autologous HSCT were enrolled in this study retrospectively (Table 1). The patients were divided into two groups: the oral management group, which consisted of 24 patients who received oral management during HSCT beginning in 2009, and the control group, which consisted of 24 HSCT patients treated in 2007 to 2008, who did not receive oral management. The ethical committee of Tsukuba University Hospital approved this study.

All 48 patients received an oral examination prior to transplantation by the same two trained oral health-care professionals. Panoramic radiographs of all the patients were taken. The caries, apical and marginal periodontitis, and impacted third molar were managed according to our previous reports,[11-13] and all the dental management was completed before HSCT. The details of the treatment were as follows. Teeth with dental caries were restored in patients with sufficient time for dental treatment, but observed in those without enough time. Teeth with recently symptomatic apical periodontitis or asymptomatic apical periodontitis and periapical radiolucency of the maximal diameter, i.e., greater than 5 mm, were treated with root canal or dental extraction. In cases of marginal periodontitis, teeth with gingival swelling, pain, and purulent discharge, a

probing depth greater than 8 mm, or severe mobility were removed, while teeth without these signs and symptoms were observed. Tooth brushing instruction and/or scaling was provided. Partially erupted third molars affected by pericoronitis or purulent drainage were extracted, and asymptomatic third molars were not treated.

For the oral management group, oral care instruction for the patients was included in the transplantation conference with the HSCT team before HSCT. These patients received an additional oral examination in the clean room and instructions for tooth brushing and swab use, according to the condition of OM by the dentist and dental hygienist. In both groups, OM was treated with azulene sodium sulfate and a 4% lidocaine mouth rinse. To treat the oral pain, indomethacin intra-oral spray and/or intravenous fentanil were administered during HSCT (Fig 1).

The OM was graded by the nurses of HSCT units using the National Cancer Institute common toxicity criteria (NCI, CTC) Common Terminology Criteria for Adverse Events (CTCAE, ver. 3.0), as follows: Grade 0, none; Grade 1, painless ulcers, erythema, and/or mild soreness without lesion; Grade 2, painful erythema, edema or ulcers, but able to swallow; Grade 3, painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral nutrition support; Grade 4, severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia (Fig. 2).

Differences in the patient characteristics and the incidence and severity of OM between the two groups were determined using the Mann-Whitney U test or Fisher's exact probably test and the chi-square for independence test. A level of $P<0.05$ was considered statistically significant.

Results

The hematologic diagnoses were as follows: 14 patients had malignant lymphoma (ML), 13 had acute myeloid leukemia (AML), 7 had acute lymphoid leukemia (ALL), 4 had myelodysplastic syndrome (MDS), 4 had multiple myeloma (MM), and 6 had others (Table 1). The hematopoietic stem cells were collected from the bone marrow of 20 patients, the peripheral blood of 18, and from umbilical cord blood for 10. The pre-transplant conditioning agents included cyclophosphamide (Cy) and total body irradiation (TBI) for 21 patients, ifosphamide , carboplatin, and etoposide (ICE) for 7, fludarabine (Flu) and others for 6, and others for 14. The dose and schedule of Cy was 60mg/kg (day -3, -2), ICE was consisting from ifosphamide 3,000mg/m^2, carboplatin 400mg/m^2 and etoposide 400mg/m^2 (day-5~-2) and Flu was 25~30mg/m^2 (day -6~-2). TBI was performed for 27 (56.3%) patients, including 16 (66.7%) in the oral management group and 11 (45.8%) in the control group (Table 1).

The 48 patients included 23 males and 25 females, ranging in age from 16 to 66 years with a median of 45 years (Table 2). There were no significant differences in age or gender between the patients in the oral management and control groups. Allogeneic transplantation was performed for 21 patients in the oral management group and 14 in the control group, which represented a significant difference ($P<0.05$). Of the conditioning agents, the ICE and Flu +Mel/TBI regimens were significantly different between the two groups ($P<0.05$). The median number of days with WBC less than 1,000/μl was 19.5 for the oral management group and 11.5 for the control group, which was a significant difference ($P<0.01$).

The median of the minimum WBC was 0 (range 0-700/μl) for patients in the oral management group, and 0 (range 0-200/μl) for those in the control group. The median number of days in which the patients' temperature was higher than 38 degrees centigrade was 6 (range 0-18) for the oral management group, and 4.5 (range 0-31) for the control group. These differences in fever duration and minimum WBC were not significantly different between the patients in the two groups (Table 2).

OM was observed 14 (58.3%) patients in the oral management group and 22 (91.6%) in the control group (Table 3). The incidence of OM according to CTCAE ver.3.0 is shown in Fig. 3. Grade 0 was observed in 10 patients in the oral management group and 2 in the

control group, which was a significant difference ($P<0.01$). No patient was observed with grade 4 in either group. The median of the worst OM score was 1 for the oral management group (range 0-3), and 2 for the control group (range 0-3), and the difference was significant ($P<0.05$).

The duration of oral pain from OM in the two groups is shown in Table 3. The median number of days of oral pain was 0.5 (range 0 to 21) in the oral management group and 8 (range 0 to 22) in the control group. Although there was no significant difference between the two groups, there was a tendency towards a reduced duration of oral pain in the oral management group ($P<0.1$).

Fentanil administered to patients with oral pain, a sore throat, or other systemic pain. The median total dose of fentanil during HSCT was 1.35 mg (range 0 to 7.7 mg) for the oral management group and 3.95 mg (range 0 to 25 mg) for the control group, which was not significantly different.

The symptom suspecting intestinal mucositis as vomiting, diarrhea and full total parenteral nutrition use was observed in 4 patients in the oral management group and 3 in the control group. Sepsis occurring from OM was observed in 2 patients in the oral management group and 3 in the control group, which was not significantly different (Table 3). All the patients recovered after receiving antibiotics.

Discussion

OM is a prominent adverse effect of the toxicity of the conditioning regimen used for HSCT, and is typically seen within 2 weeks[14]. Moderate to severe mucositis interferes with oral nutrition and quality of life, and frequently leads to secondary infection in HSCT recipients. Therefore, an effective prophylaxis for OM is crucial for improving the treatment outcome of HSCT. Mouth rinsing with water or mouthwash is generally recommended as routine care in patients with OM to reduce the risk of mucositis-associated infection [10]. Although there was no significant difference in the occurrence of sepsis between our two groups of patients, more than 90% of the patients in the control group developed OM. OM of Grade 2 and 3 was observed in about 70% of this group.

Filicko et al. reviewed the special recommendations for patients undergoing HSCT[14]. These include a pre-transplant oral evaluation by a qualified dentist, good routine oral health maintenance during the peri-transplant period, and the maintenance of adequate platelet and neutrophil counts to improve healing. In a recent report, we also suggested the importance of including an experienced oral management provider on the HSCT team[15]. Oral management providers at our hospital include dentists, dental hygienists, and HSCT

unit nurses. In the present study, the oral management group received pre-HSCT oral care instruction, and the control group did not. The instruction on self oral management was provided by a dental hygienist pre-HSCT, and an oral care provider participated in the pre-HSCT conference. During HSCT, the oral examination was performed in the clean room by a dentist and dental hygienist, and additional instruction on oral care was provided at this time. Since an oral care provider began participating in patient care throughout the HSCT, the occurrence rate of OM has decreased from about 90%, to about 60%. The symptoms of intestinal mucositis were in the same incidence of both groups in our study. The oral mucositis decreased clearly in the oral management group. Therefore this improvement was clearly owing to the participation of the oral care provider during HSCT. These findings indicate that an experienced dental provider is a necessary and valuable member of the HSCT team, and that instruction on self care before HSCT, and an oral examination and advice on oral care given to patients in the clean room by the oral care provider are very effective for preventing OM.

The incidence of OM is reported to be 80-99% in patients receiving a myeloablative conditioning regimen[3,16] and the incidence of a toxicity grade of 3 or 4 is reported to be 67.4-98%[3,17]. In the present study, the incidence of OM for the control group agreed with previous reports; however, it was decreased to < 60% in the oral management group. The

incidence of OM of CTCAE grade 3 decreased from 29% to 20.8% after the oral management intervention. The toxicity grades for OM according to the WHO and NCI-CTC criteria are similar; the WHO criteria focus on oral intake and CTCAE focus on the ability to swallow [14]. In our study, the CTCAE were used as follows: Grade 1 was mild, Grade 2 was moderate, Grade 3 was severe, and Grade 4 was life threatening[6]. It is noteworthy that grade 0 OM was observed 41.7% of the patients in the oral management group, but only 8.3% of those in the control group in the present study. However, the number of patients with grade 3 OM did not decrease significantly in the oral management group compared with the control group, suggesting that oral management intervention may decrease not the grade, but the occurrence of OM.

The regimens incurring the most severe OM are reported to be high-dose melphalan, followed by busulphan, cyclophosphamide/TBI, cyclophosphamide/carmustine, and cyclophosphamide/etoposide/carmustine [3]. In the present study, more patients in the oral management group had the fludarabine/melphalan/TBI regimen than in the control group, which could have caused a bias toward a greater occurrence of OM in the oral management group. Moreover patients of the oral management group had more allogeneic transplantations and median number of days of WBC<1,000/ υl significantly. These factors effect to make a severe OM. However, despite these severe conditions, the incidence of OM

clearly decreased in the oral management group. A future trial will be required to confirm the efficacy of oral management in the same regimens to exclude a bias. Concomitant TBI during the conditioning therapy for stem-cell transplantation is also reported to increase the risk of developing OM[18-20]. In our patients, 27 patients (56.3%) received TBI. We did not find any relationship between TBI and the occurrence of OM by univariate analysis.

The panel in 2005 suggested that interdisciplinary systematic oral care protocols geared toward the individual needs of each patient be developed. These protocols include educational approaches involving the patient, the patient's family, and the hospital staff, and quality-improvement processes for evaluating them. A preventive oral care regimen should be part of the routine supportive care in HSCT, along with therapeutic oral care if OM develops. A standardized oral care protocol involving regular, systematic, oral care hygiene with brushing, flossing, bland rinses, and oral moisturizers should be implemented for all patients. An interdisciplinary approach to oral care (for example, by a nurse, physician, dentist, dental hygienist, and others as relevant) will provide the most comprehensive supportive care[8]. Our results support the inclusion of an oral management provider on the HSCT team. In this study, the mechanism by which oral management reduced the OM incidence was not clear. A future trial will be required to confirm the efficacy of this practice and to elucidate the preventive mechanism.

Conclusion

This study shows that oral management may decrease, not the grade, but the occurrence of OM. Our results support the inclusion of an oral management provider on the HSCT team.

Acknowledgements

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Conflict of Interest

The authors indicated no potential conflicts of interest.

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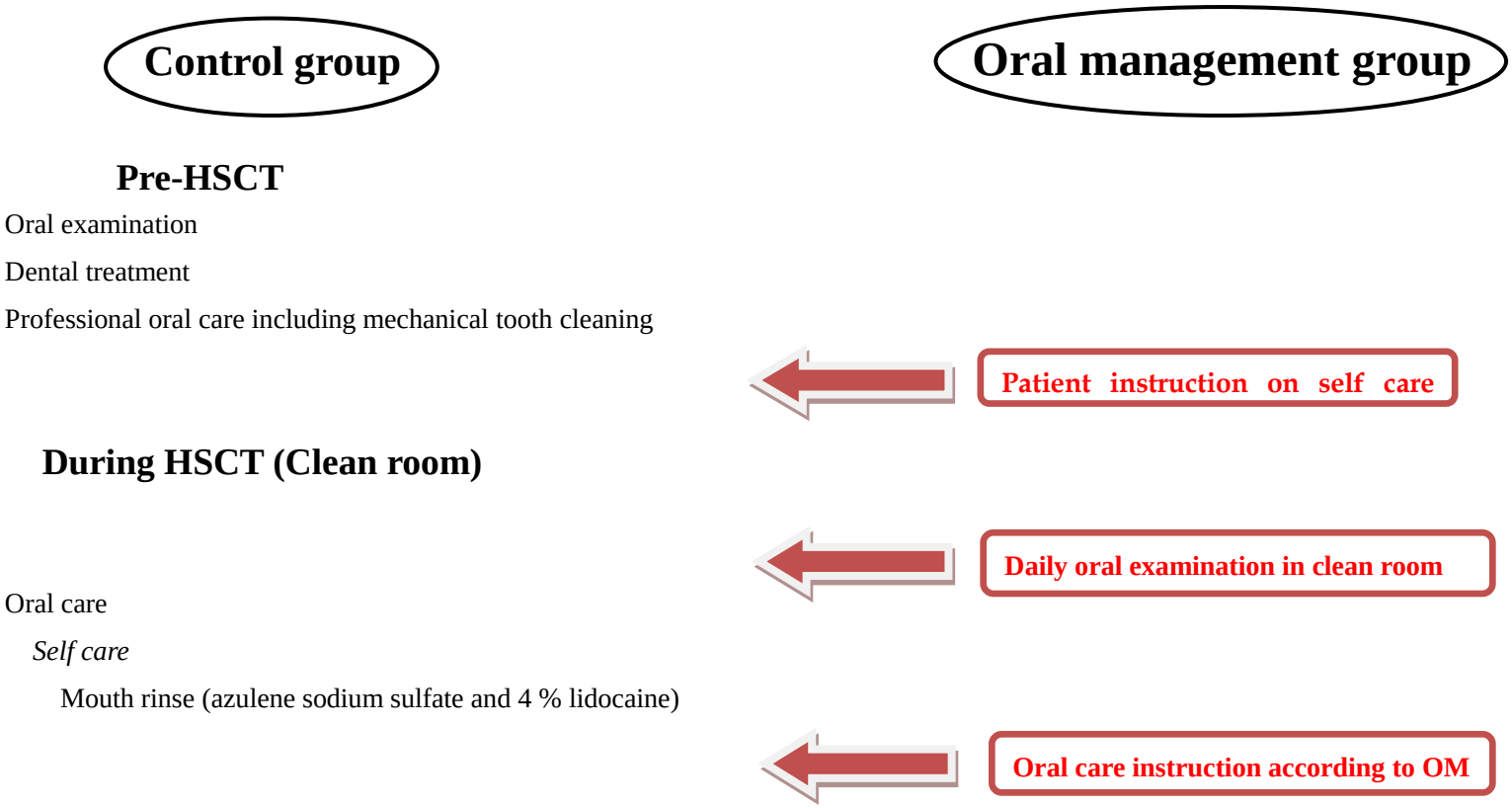
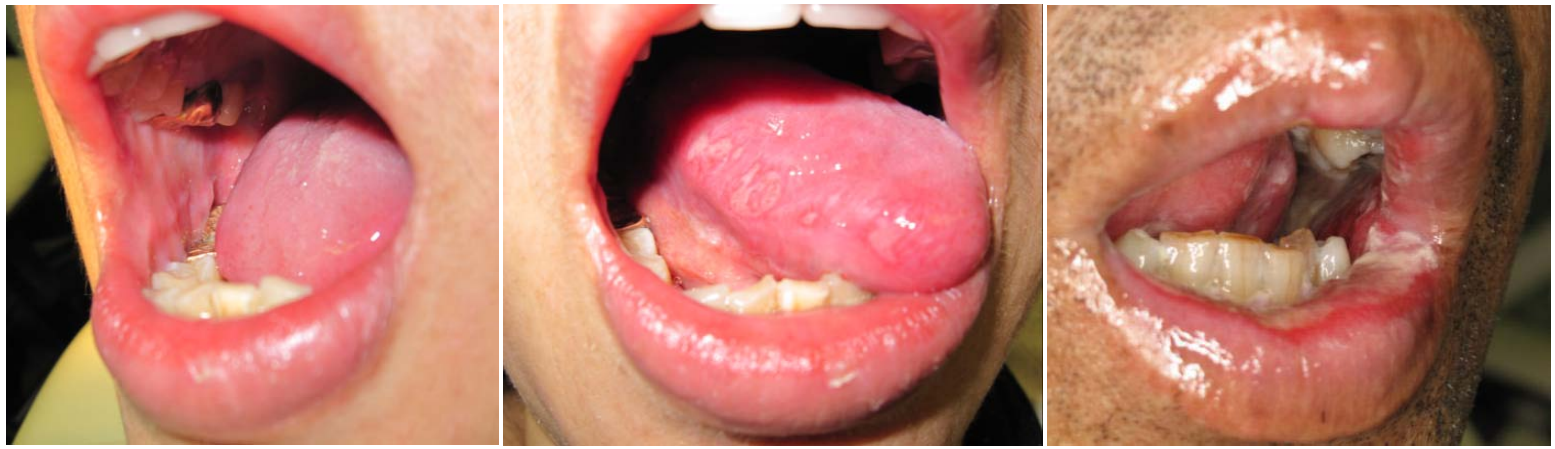


Fig 1. Method of oral management for the oral management and control groups



Grade 1 Grade 2 Grade 3

Fig 2. OM according to NCI, CTCAE ver.3.0

Grade 0, none; Grade 1, painless ulcers, erythema, and/or mild soreness without lesion; Grade 2, painful erythema, edema or ulcers, but able to swallow; Grade 3, painful erythema, edema, or ulcers preventing swallowing or requiring hydration or parenteral nutrition support; Grade 4, severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia.

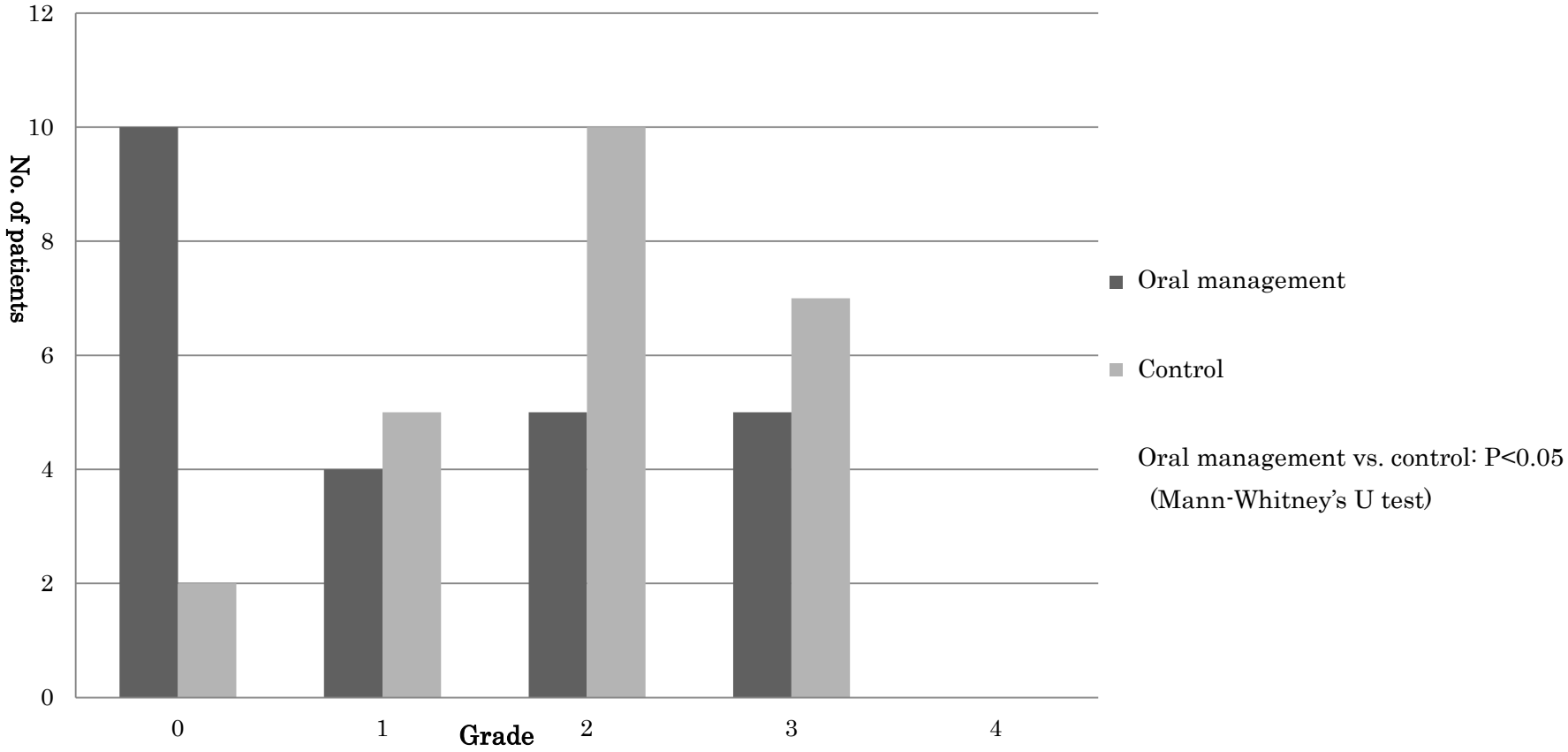


Fig 3. Worst oral mucositis grade according to CTCAE ver. 3.0

Table 1. Oncologic diagnoses and treatment

Disease	No. of patients		
	Oral management group (n=24)	Control group (n=24)	Total
ML	4	10	14
AML	9	4	13
ALL	2	5	7
MDS	4	0	4
MM	2	2	4
AA	2	1	3
Others	1	2	3

Type of transplantation	No. of patients		
	Oral management group (n=24)	Control group (n=24)	Total
BMT	9	11	20
PBSCT	7	11	18
UCBT	8	2	10

Pre-transplant conditioning agents	No. of patients		
	Oral management group (n=24)	Control group (n=24)	Total
Cy/TBI	10	11	21
ICE	1	6	7
Flu+others	4	2	6
Flu+Mel/TBI	5	0	5
Cy+others	2	2	4
Mel	2	2	4
Others	0	1	1
Total body irradiation	16	11	27 (56.3%)

ML, malignant lymphoma; AML, acute myeloid leukemia; ALL, acute lymphoid leukemia; MDS, myelodysplastic syndrome; MM, multiple myeloma; AA, aplastic anemia; BMT, bone marrow transplantation; PBSCT, peripheral blood stem cell transplantation; UCBT, umbilical cord blood transplantation

Cy, cyclophosphamide; TBI, total body irradiation; ICE, ifosphamide, carboplatin, etoposide; Flu, fludarabine; Mel, melphalan

Table 2. Patient characteristics

Characteristic	Oral management (n=24)	Control (n=24)	P
Median age, years (range)	48 (20-63)	41.5 (16-66)	n.s.
Gender (male/female)	10/14	13/11	n.s.
Type of transplant (allogeneic/autologous)	21/3	14/10	<0.05
Median number of days of WBC<1,000/μl (range)	19.5 (1-61)	11.5 (4-79)	<0.01
Median of minimum WBC, /μl (range)	0 (0-700)	0 (0-200)	n.s.
Median number of febrile days (>38ºC) (range)	6 (0-18)	4.5 (0-31)	n.s.

n.s., not significant

Table 3. Characteristics of oral mucositis in the oral management and control groups

Characteristics	Oral management (n=24)	Control (n=24)	P
Median of worst oral mucositis score (CTCAE ver 3.0)	1 (0-3)	2 (0-3)	<0.05
Oral mucositis (OM)	14 (58.3%)	22 (91.6%)	<0.01
Median number of days with oral pain	0.5 (0-21)	8 (0-22)	n.s.
Median total dose of fentanyl (mg)	1.35 (0-7.7)	3.95 (0-25)	n.s.
Sepsis from oral mucositis	2	3	n.s.

n.s., not significant