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ORIGINAL ARTICLE

Evaluation of the risk factors associated with high-dose chemotherapy-induced dysgeusia in patients undergoing autologous hematopoietic stem cell transplantation: possible usefulness of cryotherapy in dysgeusia prevention

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Abstract
Purpose Dysgeusia is one of the sporadic adverse effects induced by chemotherapy, but it remains poorly understood. The aim of this study was to retrospectively identify the risk factors related with dysgeusia in patients undergoing autologous hematopoietic stem cell transplantation (AHSCT).
Methods Forty-eight patients with myeloma or lymphoma undergoing AHSCT were enrolled in this study. Data regarding dysgeusia and symptoms were collected by interviews conducted by medical workers. Patient characteristics and unfavorable effects induced by dysgeusia were obtained from medical records and analyzed. Logistic regression analysis was performed to identify the risk factors related with dysgeusia.
Results Of the 48 patients, 20 (42 %) had dysgeusia after AHSCT. The total period of parenteral nutrition (TPN) administration and period of decreased oral intake in the dysgeusia group were statistically longer than those in the non-dysgeusia group. Multivariate analyses revealed that oral mucositis (odds ratio: 30.3; $p < 0.01$) and the type of chemotherapy prior to AHSCT (odds ratio: 6.56; $p < 0.05$) were independent risk factors, while oral cryotherapy was the independent suppressive factor of dysgeusia (odds ratio: 0.14; $p < 0.05$).
Conclusion Our study showed that dysgeusia after AHSCT led to the decrease in oral intake and extended the TPN administration period. Moreover, MEAM or LEED chemotherapy and oral mucositis were independent risk factors for dysgeusia in patients undergoing AHSCT, while oral cryotherapy was an independent suppressive factor for dysgeusia. Therefore, oral cryotherapy should be implemented into the regimen of supportive care management in patients undergoing AHSCT.

Keywords Dysgeusia · Oral cryotherapy · Autologous hematopoietic stem cell transplantation · Supportive care

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Introduction

Chemotherapy induces various adverse effects, of which dysgeusia is little understood. Dysgeusia is defined as an abnormal sense of taste, an unpleasant alteration of the taste sensation, or a distortion or perversion of the sense of taste [1]. Approximately two out of three cancer patients undergoing chemotherapy experience dysgeusia [2, 3]. Dysgeusia decreases the enjoyment of eating and quality of life (QOL) in cancer patients [4]. Therefore, to improve patients' QOL during chemotherapy, the prevention and treatment of dysgeusia

should be actively addressed. Thus far, oral zinc supplementation or prophylactic administration of amifostine has been reported to prevent dysgeusia [1, 5]. However, success in preventing and treating dysgeusia by these approaches has been poor. Considering this background, currently, resolving dysgeusia in such patients remains challenging until its spontaneous recovery.

At present, autologous hematopoietic stem cell transplantation (AHSCT) is used for the treatment of lymphoma and multiple myeloma, and it can markedly improve treatment outcomes [6, 7]. Prior to the implementation of AHSCT, high-dose chemotherapy is administered to obtain the maximum effects of anticancer drugs. Therefore, more severe adverse effects, i.e., oral mucositis and neutropenia, might occur compared with normal-dose chemotherapy [8]. Besides these, dysgeusia is often observed during AHSCT, but this adverse effect is poorly understood. Options for the treatment of dysgeusia could help improve the QOL and outcome of the entire treatment in patients undergoing AHSCT.

In the present study, to understand dysgeusia and propose an effective intervention in cancer patients with dysgeusia undergoing AHSCT, we retrospectively investigated the clinical effects of dysgeusia and identified clinical risk factors associated with AHSCT-related dysgeusia.

Methods

Study design

We analyzed the case records of patients with lymphoma or myeloma who underwent AHSCT between April 2009 and March 2013 at Tokushima University Hospital. Patients were excluded if they had a history of pre-existing dysgeusia, which left 48 patients who were eligible for this study. These patients were divided to a dysgeusia group, which included patients who had dysgeusia during the treatment, and a control group, in which patients had no dysgeusia during the treatment. Dysgeusia was defined subjectively as a patient's taste disorder revealed by face-to-face interviews performed by medical workers. This study was reviewed and approved by the Ethics Committee of Tokushima University Hospital.

Type of chemotherapy

In the present study, MEAM or LEED chemotherapy was performed prior to the implementation of AHSCT in patients with lymphoma, and high-dose melphalan chemotherapy was performed in patients with myeloma. In the MEAM regimen, ranimustine (300 mg/m^2) was used on day 1; etoposide (200 mg/m^2) and cytarabine (200 mg/m^2), from day 2 to day 5; and melphalan (140 mg/m^2), on day 6 [9]. In the LEED regimen, dexamethasone (40 mg/day) was used from day 1 to day 4; etoposide (300 mg/m^2), from day 1 to day 3; cyclophosphamide (60 mg/kg), from day 1 to day 2; and melphalan (130 mg/m^2), on day 4 [10]. In the high-dose melphalan regimen, melphalan (100 mg/m^2) was used from day 1 to day 2 [11].

Data collection

We collected the following patient data: age; body weight; type of disease; type of chemotherapy prior to the implementation of AHSCT; number of previous regimens; history of diabetes mellitus, neurological disease, or smoking; implementation of oral cryotherapy; and levels of alanine aminotransferase, aspartate aminotransferase, and creatinine clearance. Creatinine clearance was calculated as described by Cockcroft and Gault [12].

Oral cryotherapy entailed sucking of ice chips for 30 min before the administration of melphalan, for 60 min during the infusion of melphalan, and for 30 min after the administration, i.e., for a total of 120 min in each regimen [13]. Adverse events were graded according to the Common Terminology Criteria for Adverse Events v 4.0. We checked medical records to identify any adverse effects above grade 1 after the implementation of AHSCT. The average total calories and protein amount administered per day by total parenteral nutrition (TPN) or oral intake were calculated based on the medical records obtained by medical workers. The changes in serum albumin level and body weight were assessed as nutritional markers during hospitalization. These changes were calculated by subtracting the minimum values after AHSCT from the values before the implementation of AHSCT. The period of TPN administration, period of decrease in oral intake, and hospitalization duration were calculated on the basis of medical records. The period of decrease in oral intake was defined as the period in which the oral intake was less than 50 % compared with that before the implementation of AHSCT [14]. The hospitalization period was defined as the period from the administration of AHSCT to discharge.

Data analysis

The χ^2 test, Fisher's exact probability test, the Mann–Whitney U test, and Student's t test were used to assess differences between the 2 groups. The TPN administration period, period of decrease in oral intake, and hospitalization duration were compared using a Kaplan–Meier plot. In the multivariate logistic regression analysis, the forced entry method was employed using the factors that were significantly different in the univariate analysis. All analyses were performed using Excel (Microsoft). All recorded p values were two-sided, and differences with p values < 0.05 were considered significant.

Results

Patient characteristics

In this study, AHSCT-related dysgeusia occurred in 20 patients (42 %). Table 1 shows the patient characteristics in the two groups. Age; sex; history of diabetes mellitus, neurological disease, or smoking; number of previous regimens before AHSCT; renal function; and liver function did not differ between the two groups. The proportion of lymphoma patients was significantly greater in the dysgeusia group, while the proportion of myeloma patients was significantly greater in the control group. The rate of MEAM or LEED, which was administered in lymphoma patients, was significantly greater in the dysgeusia group, and the rate of high-dose melphalan, which was administered in myeloma patients, was significantly greater in the control group. The implementation rate of oral cryotherapy before melphalan administration was significantly lower in the dysgeusia group than in the control group. The adverse effects other than dysgeusia are shown in Table 2. The rate of oral mucositis was significantly greater in the dysgeusia group than in the control group. The other adverse effects did not differ between the two groups.

Nutritional parameters

The nutritional parameters in both groups are shown in Table 3. The average total energy and total protein administered were lower in the dysgeusia group than in the control group. The oral energy intake and oral protein intake were significantly lower in the dysgeusia group. However, TPN energy and TPN protein were greater—but not significantly—in the dysgeusia group. The changes in serum albumin and body weight after AHSCT did not differ between the two groups. The TPN administration period and oral intake decrease period were significantly longer in the dysgeusia group than in the control group (Fig. 1a, b). The hospitalization period did not differ between the groups (Fig. 1c).

Multiple logistic regression analysis

To identify the risk factors associated with dysgeusia, univariate and multivariate logistic regression analyses were performed (Table 4). Univariate and multivariate logistic regression analysis revealed that MEAM or LEED chemotherapy (odds ratio, 6.56; 95 % confidence interval (95 % CI), 1.09–

Table 1 Patient characteristics

Factor	Control ($n=28$) Means ± SD or no. of patients (%)	Dysgeusia ($n=20$) Means ± SD or no. of patients (%)	p value
Sex (male/female)	16/12	9/11	0.55[a]
Age, median (range) (year)	56 (42–67)	56 (18–70)	0.37[b]
Type of disease			
Lymphoma (%)	10	14	0.03[a]
Multiple myeloma (%)	18	6	
Type of chemotherapy			
MEAM (%)	9	14	0.03[a]
LEED (%)	1	0	
Mel (%)	18	6	
No. of previous regimens, median (range)	2 (1–5)	2 (1–5)	0.26[b]
History of diabetes mellitus (%)	3 (11)	1 (5)	0.63[c]
History of neurological disease (%)	1 (4)	1 (5)	1.00[c]
History of smoking (%)	9 (32)	9 (45)	0.36[a]
Aspartate aminotransferase (IU/L)	21.4 ± 8.9	24.6 ± 9.6	0.26[d]
Alanine aminotransferase (IU/L)	20.0 ± 9.8	23.8 ± 16.4	0.14[d]
Creatinine clearance (mL/min)	91.5 ± 30.1	99.2 ± 24.5	0.36[d]
Cryotherapy (%)	23 (82)	8 (40)	<0.01[a]

MEAM the chemotherapy included ranimustine, etoposide, cytarabine, and melphalan, *LEED* the chemotherapy included dexamethasone, etoposide, cyclophosphamide, and melphalan, *Mel* the chemotherapy included melphalan

[a] χ^2 test

[b] Mann–Whitney U test

[c] Fisher's exact test

[d] Student's t test

Table 2 Adverse effects in the two groups studied

Factor	Control ($n=28$)	Dysgeusia ($n=20$)	p value
Nausea	19 (68)	11 (55)	0.36[a]
Vomiting	3 (11)	4 (20)	0.43[b]
Diarrhea	22 (79)	14 (70)	0.50[a]
Fatigue	22 (79)	13 (65)	0.30[a]
Febrile neutropenia	22 (79)	18 (90)	0.44[a]
Dry mouth	5 (18)	3 (15)	1.00[b]
Oral candidiasis	1 (4)	2 (10)	0.56[b]
Oral mucositis	1 (4)	11 (55)	<0.01[b]

[a] χ^2 test

[b] Fisher's exact test

39.14) and oral mucositis (odds ratio, 30.3; 95 % CI, 2.46–372.18) were independent risk factors for dysgeusia, while oral cryotherapy (odds ratio, 0.14; 95 % CI, 0.02–0.70) was an independent suppressive factor for dysgeusia.

Discussion

The present study revealed that MEAM or LEED chemotherapy and oral mucositis were independent risk factors for dysgeusia in patients undergoing AHSCT, while oral cryotherapy was an independent suppressive factor for dysgeusia.

In the pretreatment before AHSCT for lymphoma patients, multidrug chemotherapy including melphalan is performed [9, 10], while high-dose melphalan mono-chemotherapy is performed in the pretreatment for myeloma patients [11]. In our study, the number of patients who were administered cryotherapy was 15 (63 %) in the lymphoma group and 16 (67 %) in the myeloma group. Thus, cryotherapy was routinely administered in both groups. Therefore, we speculated that multidrug chemotherapy might increase the risk of dysgeusia compared with melphalan mono-chemotherapy. However, the number of chemotherapy cycles before AHSCT did not differ between the two groups in this study. This indicated that treatment history did not affect the incidence of dysgeusia.

Table 3 Nutrition parameters

	Control	Dysgeusia	p value
Total energy (kcal/day)	1539 ± 367	1249 ± 282	<0.01
Intake energy (kcal/day)	1121 ± 432	685 ± 284	<0.01
TPN energy (kcal/day)	418 ± 326	564 ± 249	0.10
Total protein (g/day)	54 ± 13	43 ± 11	<0.01
Intake protein (g/day)	39 ± 15	24 ± 10	<0.01
TPN protein (g/day)	15 ± 12	20 ± 10	0.20
Change of albumin (g/dL)	−0.62 ± 0.36	−0.54 ± 0.50	0.55
Before AHSCT (g/dL)	3.62 ± 0.34	3.67 ± 0.28	
After AHSCT (g/L)	3.00 ± 0.44	3.12 ± 0.50	
Change of body weight (kg)	−2.98 ± 1.1	−2.87 ± 1.8	0.78
Before AHSCT (kg)	57.5 ± 12.8	61.6 ± 9.6	
After AHSCT (kg)	54.5 ± 12.7	58.7 ± 9.2	

TPN total parenteral nutrition, *AHSCT* autologous hematopoietic stem cell transplantation

All p values were calculated by Student's t test

We found oral mucositis to be an independent risk factor for dysgeusia. A few studies have demonstrated the relationship between oral mucositis and dysgeusia, and oral mucositis by chemotherapy is said to induce the destruction of taste buds [1, 5]. Because the dysfunction of taste buds might be related with dysgeusia, oral mucositis induced by other types of chemotherapy might also be related with the incidence of dysgeusia. Therefore, the prevention of oral mucositis is important to prevent dysgeusia in chemotherapy regimens.

Oral cryotherapy leads to vasoconstriction and decreased blood flow to the oral cavity, which reduces the exposure of anticancer drugs to the buccal mucosa [15]. The implementation of oral cryotherapy before the administration of high-dose melphalan has been found to reduce the incidence of oral mucositis [15–17]. In our study, the incidence of oral mucositis was lower in the patients who had undergone oral cryotherapy before high-dose melphalan administration (13 %) than in those who had not (47 %). Considering this result and oral mucositis as a risk factor for dysgeusia, we hypothesize that oral cryotherapy prevents dysgeusia via the prevention of oral mucositis due to high-dose melphalan. This indicates that oral cryotherapy may prevent dysgeusia in other chemotherapy regimens where evidence for the prevention of oral mucositis by oral cryotherapy is established. Thus far, oral zinc supplementation has been reported to ameliorate dysgeusia in head and neck cancer patients treated with chemotherapy [1, 18, 19]. However, to our knowledge, there have been no reports on dysgeusia prevention by oral zinc supplementation in patients undergoing AHSCT. Therefore, other useful approaches to prevent AHSCT-related dysgeusia have been explored. The present study is the first report describing the potential of oral cryotherapy for supportive therapy in AHSCT-related dysgeusia.

The average total energy intake and total protein intake were lower in the dysgeusia group than in the control group. This may be due to the decrease in oral intake induced by appetite loss associated with dysgeusia. However, oral mucositis might also be associated with the decrease in oral intake. In general, although decreased oral intake due to oral mucositis often recovers within about 2 weeks, the decrease due to dysgeusia might exceed 2 weeks [5]. In our study, the number of patients who had decreased oral intake for over 2 weeks was 7 (25 %) in the control group and 15 (75 %) in the dysgeusia group. Furthermore, the number of patients who had dysgeusia for over 2 weeks was 14 (70 %) in the dysgeusia group. These findings indicate that the oral intake

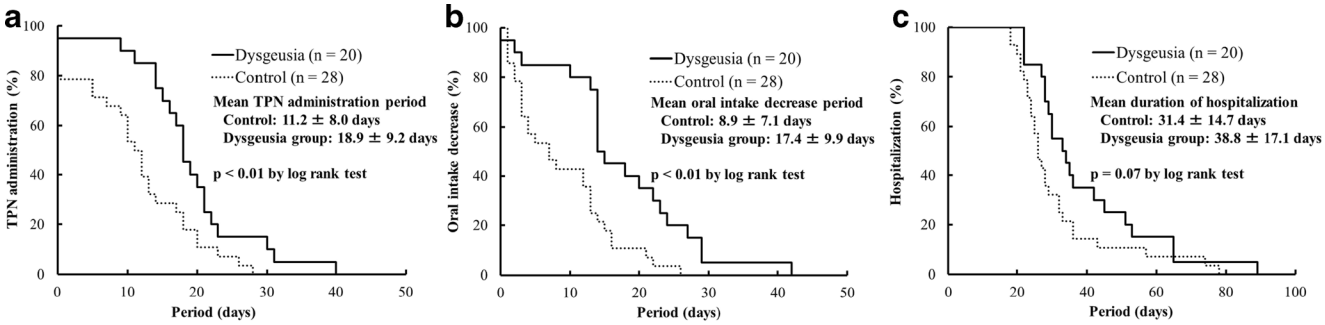

Fig. 1 Kaplan–Meier plots showing the **a** TPN administration period, **b** oral intake decrease period, and **c** hospitalization duration for the dysgeusia and control groups

decrease observed in the dysgeusia group was associated with dysgeusia rather than oral mucositis. On the other hand, serum albumin and body weight as nutrition markers did not differ between the two groups despite the decrease in oral intake in the dysgeusia group. This indicated that serum albumin and body weight might not be adequate to assess nutritional outcomes in our study. Rapid turnover protein, which might reflect the most recent nutritional condition, should be implemented as a nutrition marker [20]. However, we could not obtain these laboratory data because these tests were not routinely performed in the study subjects. A prospective study will be needed to elucidate the relationship between dysgeusia and nutritional condition.

In our study, the number of patients with a history of diabetes mellitus or neurological diseases was not significantly different. The rate of dry mouth or oral candidiasis induced by chemotherapy also did not differ between the two groups. Neurological toxicity effects of the chemotherapy were not observed in either group. Moreover, five patients in the dysgeusia group and three in the control group routinely used anticholinergic drugs or antihistamine drugs, which induce a decrease in saliva secretion. Therefore, we speculated that these factors were not associated with the incidence of dysgeusia in our study. However, olfactory disorder, which is associated with dysgeusia, and oral care by dentists and dental hygienists, which is associated with the decrease in the incidence of oral mucositis, were not assessed in our study [5, 21]. In future studies, the association between these factors and dysgeusia will need to be investigated.

In this study, we defined dysgeusia subjectively on the basis of face-to-face interviews. According to this screening, 20 patients (42 %) were diagnosed with dysgeusia in our

Table 4 Univariate and multivariate logistic regression analysis for dysgeusia

Factors	Univariate analysis			Multivariate analysis		
	Odds ratio	95 % CI	*p* value	Odds ratio	95 % CI	*p* value
Male sex	0.87	0.27–2.77	0.81	–	–	–
Age	1.02	0.96–1.08	0.54	–	–	–
Chemotherapy of MEAM or LEED	4.20	1.23–14.37	0.02	6.56	1.09–39.14	0.039
No. of previous regimens	1.38	0.78–2.43	0.26	–	–	–
History of smoking	1.72	0.52–5.65	0.37	–	–	–
Aspartate aminotransferase	0.99	0.93–1.06	0.79	–	–	–
Alanine aminotransferase	1.00	0.97–1.05	0.73	–	–	–
Creatinine clearance	0.98	0.96–1.01	0.21	–	–	–
Cryotherapy	0.14	0.039–0.54	<0.01	0.14	0.02–0.70	0.035
Nausea	0.58	0.18–1.89	0.37	–	–	–
Vomiting	2.08	0.41–10.56	0.38	–	–	–
Diarrhea	0.63	0.17–2.37	0.50	–	–	–
Fatigue	0.51	0.14–1.83	0.30	–	–	–
Febrile neutropenia	2.45	0.44–13.67	0.31	–	–	–
Oral mucositis	33.0	3.72–292.4	<0.01	30.3	2.46–372.18	<0.01

MEAM the chemotherapy included ranimustine, etoposide, cytarabine, and melphalan, *LEED* the chemotherapy included dexamethasone, etoposide, cyclophosphamide, and melphalan

study. This value is consistent with those of previous studies, and our definition is adequate for the assessment of dysgeusia. However, face-to-face interviews could not adequately assess the nature of dysgeusia. Moreover, interview bias may occur if a respondent seeks to satisfy the interviewer with responses [22]. In previous studies, dysgeusia was measured by validated scale analysis using the filter paper disk method or a scoring method using a 16-item questionnaire [4, 22, 23]. To enhance and corroborate the reliability of our data, analyses using these validated assessment protocols are needed.

Because our present study was an early-phase study, it had certain limitations, as described above. To analyze the possibility that cryotherapy suppresses AHSCT-related dysgeusia, as shown in our study, prospective studies assessing dysgeusia using the validated protocols in a larger number of patients undergoing melphalan mono-chemotherapy are warranted. On the basis of findings from a larger prospective study, supportive care for AHSCT-related dysgeusia can be proposed and implemented.

Conclusion

The present study showed that dysgeusia after AHSCT led to a decrease in oral intake and extended the TPN administration period. Moreover, MEAM or LEED chemotherapy and oral mucositis were independent risk factors for dysgeusia in patients undergoing AHSCT, while oral cryotherapy was an independent suppressive factor for dysgeusia. Although further prospective analyses with more patients are needed to confirm whether cryotherapy suppresses AHSCT-related dysgeusia, the incorporation of oral cryotherapy into the supportive care regimen in high-dose chemotherapy prior to AHSCT might help improve patients' QOL.

Compliance with ethical standards This study was reviewed and approved by the Ethics Committee of Tokushima University Hospital.

Conflict of interest The authors declare that they have no conflicts of interest.

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