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ORIGINAL ARTICLE

Oral cryotherapy for oral mucositis management in patients receiving allogeneic hematopoietic stem cell transplantation: a prospective randomized study

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Abstract

Purpose To explore the best schedule of oral cryotherapy for the prevention of oral mucositis in recipients of myeloablative hematopoietic stem cell transplantation (HSCT).

Methods A prospective randomized study was conducted to recruit allogeneic HSCT recipients, who were then randomly allocated into four arms to accept the following: oral cryotherapy during the whole course (arm A) or second half of the course (arm B) of cytotoxic agents administration, regular oral cryotherapy twice a day (arm C), or conventional oral care without cryotherapy (arm D). Status of oral mucositis was daily assessed from the first day of conditioning to the 15th day post-HSCT. A myeloablative conditioning regimen was used which was composed of busulfan, cyclophosphamide, and cytarabine.

Results Totally 160 cases were consecutively enrolled in this study, and 145 cases were eligible for oral mucositis assessment. Both arm A and arm B were associated with a lower incidence and short duration of severe mucositis (≥ grade 3), although no statistical difference was found between these two groups ($p = 0.463$, $p = 0.678$). The highest incidence of severe mucositis was observed in arm C. Recovery of mucositis also had a significant diversity among the 4 arms ($F = 4.133$, $p = 0.008$).

Conclusions Risk and outcome of severe oral mucositis could be ameliorated by oral cryotherapy during the administration of cytotoxic agents for allogeneic HSCT patients receiving non-radiation myeloablative conditioning regimen, and a half-course schedule could acquire a comparable efficacy compared with the whole-course schedule.

Keywords Cryotherapy · Oral mucositis · Allogeneic hematopoietic stem cell transplantation

Introduction

Oral mucositis (OM) is defined as an ulcerative and inflammatory disease of the oral mucosa [1, 2]. OM is the most common complication in patients treated with high-dose chemotherapy and/or total body irradiation before hematopoietic stem cell transplantation (HSCT) [3]. Compared with other types of myeloablative conditioning, patients who receive busulfan-cyclophosphamide (BUCY) regimen exhibit a higher incidence of OM [4]. OM is also closely associated with morbidity, treatment compliance, and treatment results, and negatively affects the feeding and quality of life of the patients [3, 5–8].

Cryotherapy, through placing ice cubes in the mouth during chemotherapy administration, causes blood vessel constriction, thereby reducing the penetration of chemotherapy agents into the mucous membrane of the mouth. Cryotherapy has been shown to effectively reduce the incidence and severity

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of oral mucositis in patients receiving high-dose chemotherapy followed by stem cell transplantation [3, 9–13]. In a recent Cochrane review, oral cryotherapy was found to reduce severe OM in adults receiving high-dose melphalan-based chemotherapy before hematopoietic stem cell transplantation [14]. However, some patients complained that a long period of cryotherapy was uncomfortable [10]. It has been reported that cryotherapy during the distribution phase is as effective as cryotherapy of longer duration [11, 15]. Oral cryotherapy is characterized by high safety, few side effects, easy availability, and low cost, which makes its wide application in clinical settings worthwhile [16]. However, it is not clear how this simple method should be applied in HSCT patients receiving different myeloablative conditioning regimes and what timing or duration is optimal [1]. Furthermore, whether cryotherapy could be a part of daily routine nursing practice has received little attention [17]. The aim of the present study was to evaluate the effect of cryotherapy in preventing OM following HSCT with BUCY as a myeloablative conditioning regime and to try to identify the optimal timing and duration.

Patients and methods

Patients and protocol design

This study was conducted in the Bone Marrow Transplantation Unit of the First Affiliated Hospital of Soochow University. Patients with an age ≥ 18 years with confirmed literacy, who were undergoing BUCY regimens as myeloablative conditioning before transplantation, were recruited and randomly assigned to four arms. Patients with clinical evidence of mucositis at enrollment were excluded. Details are shown in Fig. 1.

Prior to HSCT, all patients underwent an oral examination and during their hospital stay; the patients were instructed to wash the oral cavity with chlorhexidine mouthwash half an hour before and after eating or half an hour before sleeping, for 3 min each time. Dentists were consulted if any oral problems arose, and the use of toothpicks or dental floss was prohibited. Since mucositis symptoms develop between 5 and 14 days following chemotherapy and no subsequent alleviation has been observed in our unit; the stages and grades of oral mucositis were evaluated by a nurse every day from the first day of myeloablative conditioning until the 15th day after HSCT.

Cryotherapy administration

Ice cubes whose corners had been rounded to avoid irritation, with a size (3.2 cm × 3.3 cm × 1 cm) suitable for being easily moved in the mouth, were used. While receiving cryotherapy, the patients were informed of the importance of keeping the oral cavity constantly cool. As the ice cubes melted, patients were advised to spit out the cold liquid and take another ice cube. During cryotherapy, the patients were asked to take as many ice cubes as possible but only one piece at a time, and patients could take a 60–180s break if they felt discomfort.

Transplant procedures

Before transplantation, all the patients received a BUCY regimen (including cytarabine, busulfan, and cyclophosphamide) for myeloablative conditioning for 7 days. Cytarabine (8 g/msq) was used on day 1 to day 2 and was infused for 3 h/day; busulfan (9.6 mg/kg) was used from day 3 to day 5 and was infused for 8 h/day (divided into four infusion periods a day of 2 h each); and cyclophosphamide (3.6 g/msq) was used from day 6 to day 7 and was infused for 3 h/day. Infusion speeds were controlled by infusing pumps (B.Braun Melsungen, Germany).

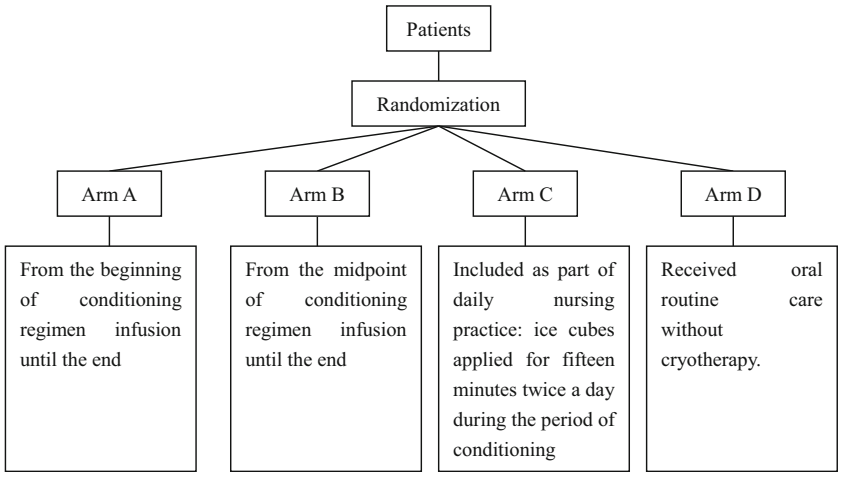

Fig. 1 Patients and design protocol

Evaluations

General data collection form

The data collection form included the following general information about the patient that might influence the development of oral mucositis after conditioning regimen: age, sex, residence, diagnosis, graft type, systemic diseases, oral hygiene habits, oral disease history, dietary habits (fondness of taste), OM history, the frequency of chemotherapy treatment.

Nurse-judged mucositis grading

The nurses utilized the National Cancer Institute Common Toxicity Criteria (NCI-CTC version 2) form to assess oral mucositis [18] according to the following scale: grade 0, none; grade 1, painless ulcers, erythema, and/or mild soreness in the absence of lesions; 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 (or enteral) nutritional support; and grade 4, severe ulceration requiring prophylactic intubation or resulting in documented aspiration pneumonia.

Patient-judged mucositis questionnaire

This questionnaire was developed from a Chinese version of Oral Mucositis Daily Questionnaire (OMDQ), which has 0.959 criterion-related validity compared with the WHO Oral Mucositis Assessment Scale [19]. The form was amended and pretested by the clinical specialists of our center. It contains the grades of symptoms of oral mucositis (such as pain, swallow sense, taste sense), information on the use of ice cubes, and routine oral care.

Statistical analysis

The data were recorded and analyzed using the Statistical Program for Social Sciences version 19.0 for Windows (SPSS 19.0). For purposes of analysis, a maximal score of oral mucositis was attributed to each patient. Incidence of oral mucositis was compared among four groups by χ^2 test. The chi-square statistic or Fisher's exact test was applied for categorical variables, and variance analysis and the Kruskal-Wallis test were applied for continuous variables. Multivariate analyses were conducted by logistic regression and linear regression. All p values are two-sided with the type I error rate fixed at 0.05.

Results

Patient characteristics

There were 160 transplant patients enrolled in this study from January 2017 to April 2018. Among these individuals, fifteen patients were excluded due to protocol deviation, including the two patients in arm A who could not endure a long duration of cryotherapy and suffered severe diarrhea; four patients in arm B who had not get cryotherapy accordingly; three patients in arm C and five patients in the arm D because of disease progression; and one patient in arm C quitted because of severe vomiting during myeloablative conditioning. Thus, 145 patients were finally evaluated. Among these individuals, 110 patients were in the experimental groups (38 patients in arm A, 36 patients in arm B and 36 patients in arm C), and 35 patients were in the control group (arm D). Demographic and transplant-related factors were compared among the patients of four arms, and no statistical significance was found (details are shown in Table 1).

Incidence of oral mucositis

According to the nurse-judged mucositis grading, 67.58% of the patients exhibited grade 2–3 mucositis, and no grade 4 mucositis was observed in any group. The mucositis rate was similar between arm A and arm B and between arm C and arm D (Fig. 2). The patients in both arm A and arm B patients presented a lower incidence of mild mucositis compared with those in the arm D over the observation period, while the patients in arm C exhibited more severe mucositis than the control group after chemotherapy (Fig. 2).

The incidence rates of severe oral mucositis (grades 3 and 4) during the observation period were 13.2% in arm A, 19.4% in arm B, 41.7% in arm C, and 39.4% in arm D. There was no significant difference between arm A and arm B ($p = 0.463$). However, compared with arm D, arm A and arm B showed a significant difference ($p = 0.011$, 0.068, respectively); arm C showed no significant difference ($p = 0.848$). In addition, there was a significant difference between arm A and arm C as well as between arm B and arm C ($p = 0.006$ and 0.041, respectively), as shown in Table 2.

Duration and recovery time of severe oral mucositis

The duration of mucositis presented no significant difference in patients with grade 1–2 mucositis (Table 2). The median duration of mucositis of grades 3–4 was 2 days in both arm A (range 1–4) and arm B (range 1–6), which was much shorter than the duration in arm D (7, range 3–20). A significant difference was also found between arm A and arm D and between arm B and arm D ($p = 0.003$, $p = 0.01$). The median duration of mucositis of grades 3–4 was 7 days in arm C,

Table 1 Patient characteristics (*n* (%) except gender in *n*, age in median, and frequency of chemotherapy treatment in mean ± standard)

	Arm A (*n* = 38)	Arm B (*n* = 36)	Arm C (*n* = 36)	Arm D (*n* = 35)	*p* value
Gender (male/female)	26/12	20/16	23/13	18/17	0.44
Age (min-max)	34 (19–62)	35.7 (20–53)	33.9 (19–54)	35.7 (19–54)	0.732
Education					
Primary education or below	0 (0)	3 (8.3)	1 (2.8)	3 (8.6)	0.103
Junior school	10 (26.3)	12 (33.3)	6 (16.7)	3 (8.6)	
High school	10 (26.3)	10 (27.8)	12 (33.3)	12 (34.3)	
College degree or above	18 (47.4)	11 (30.6)	17 (47.2)	17 (48.6)	
Residence					
Urban	24 (63.2)	20 (55.6)	23 (63.9)	28 (80)	0.177
Rural	14 (36.8)	16 (44.4)	13 (36.1)	7 (20)	
Diagnosis					
Leukemia	28 (73.7)	25 (69.4)	27 (75)	27 (77.1)	0.923
Lymphoma	4 (10.5)	2 (5.6)	1 (2.8)	2 (5.7)	
Myelodysplastic syndrome	4 (10.5)	7 (19.4)	5 (13.9)	3 (8.6)	
Aplastic anemia	2 (5.3)	2 (5.6)	3 (8.3)	3 (8.6)	
Frequency of chemotherapy treatment	2.3 ± 2	3.5 ± 3.8	2.4 ± 1	3 ± 3.3	0.688
Graft type					
Matched	10 (26.3)	17 (47.2)	14 (38.9)	9 (25.7)	0.231
Not fully matched	22 (57.9)	15 (41.7)	18 (50)	21 (60)	
Unknown	6 (15.8)	4 (11.1)	4 (11.1)	5 (14.3)	
Systemic disease					
Yes	2 (5.3)	3 (8.3)	0	4 (11.4)	0.213
No	36 (94.7)	33 (91.7)	36 (100)	31 (88.6)	
Regular bush habits					
Once a day (just in the morning)	10 (26.3)	6 (16.7)	6 (16.7)	11 (31.4)	0.352
Twice a day (morning and night)	26 (68.4)	27 (75)	30 (83.3)	23 (65.7)	
Three times a day	2 (5.3)	3 (8.3)	0	1 (2.9)	
OM history					
Yes	21 (55.3)	15 (41.7)	15 (41.7)	20 (57.1)	0.383
No	17 (44.7)	21 (58.3)	21 (58.3)	15 (42.9)	
Oral disease history					
Yes	18 (47.4)	12 (33.3)	13 (36.1)	11 (31.4)	0.488
No	20 (52.6)	24 (66.7)	23 (63.9)	24 (68.6)	
Dietary habits					
Fondness for hot food	16 (42.1)	18 (50)	13 (36.1)	9 (25.7)	0.196
Fondness for cool food	10 (26.3)	7 (19.4)	5 (13.9)	11 (31.4)	0.310
Fondness for sweet food	6 (15.8)	6 (16.7)	5 (13.9)	5 (14.3)	0.987
Fondness for salty food	8 (21.1)	10 (27.8)	3 (8.3)	7 (20)	0.213
Fondness for spicy food	12 (31.6)	11 (30.6)	13 (36.1)	8 (22.9)	0.679

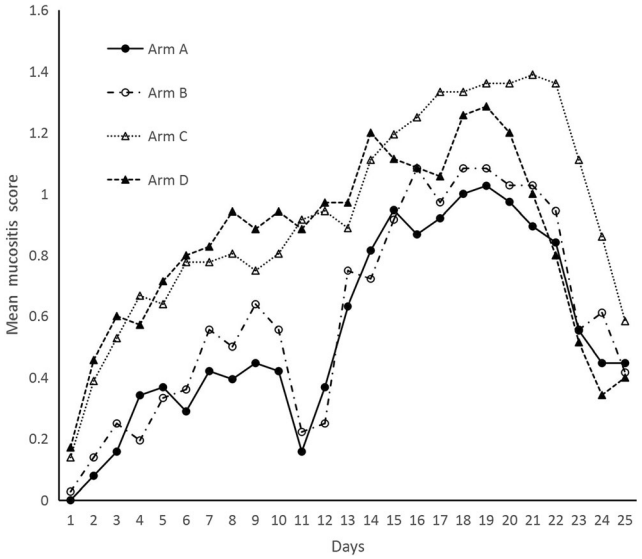

Fig. 2 Incidence of oral mucositis in a different group

although no significant difference was found compared with arm D ($p = 0.072$). However, when arm C was compared with arm A and arm B, significant differences were found ($p = 0.001$, 0.004).

In regard to the time of recovery, the patients in arm A showed an average time of 6. 39± 3.41 days; patients in arm B showed an average time of 6.76 ± 3.17 days; patients in arm C showed an average time of 8.97 ± 4.42 days; and the patients in arm D showed an average time of 9.51 ± 6.96 days. Comparison of the four groups revealed a significant difference ($F = 4.133$, $p = 0.006$), as shown in Table 2.

Manifestation of oral mucositis

According to patient-judge mucositis questionnaire, 63.45% patients had taste change; 18.62% patients had a limitation of mouth opening; 49.66% patients had a limitation of swallowing; 33.79% patients had a limitation of speaking, and 60% patients had a limitation of sleeping. Compared with four groups, the incidence of taste change had a significant difference ($p = 0.015$), as shown in Table 3.

Multivariate analysis

In multivariate logistic regression analysis, arm A was a dependent affect factor with the incidence of severe oral mucositis (OR = 0.022, 0.080–0.821), and there was no statistical significance between arm A and arm B ($p = 0.530$).

The correlation between the time of recovery and certain variables was analyzed through multiple linear regression (Table 4). The analysis showed that the time of recovery was significantly associated with patient's education level ($p = 0.048$), oral mucositis history ($p = 0.041$), and dietary habits (fondness for hot food) ($p = 0.032$). No significant correlation was found between the time of recovery and other variables, including sex, age, diagnosis, graft types, the frequency of chemotherapy treatment, and underlying disease.

Discussion

This study explored the role of cryotherapy in the prevention of oral mucositis in patients receiving a BUCY regimen (containing cytarabine, busulfan, and cyclophosphamide) as their myeloablative conditioning regimen. All these chemotherapeutic agents have a short plasma half-life, produce active metabolites, and have negative effects on the oral mucosa [4, 20]. We found that cryotherapy with a certain timing and duration (arm A and arm B) could significantly decrease the incidence of severe oral mucositis and reduce the recovery time of oral mucositis. However, it is not desirable to use cryotherapy as daily oral care (arm C).

The mechanisms by which oral cryotherapy alleviates oral mucositis are thought to be related to local vasoconstriction, causing decreased blood flow to the oral mucosa, thus

Table 2 Effect of cryotherapy on oral mucositis

Score of oral mucositis	Arm A ($n = 38$)	Arm B ($n = 36$)	Arm C ($n = 36$)	Arm D ($n = 35$)	p value
Grade 0	5	3	1	4	
Grade 1	9	10	5	10	
Grade 2	19	16	15	8	
Grade 3	5	7	15	13	
Grade 4	0	0	0	0	
Incidence grade 1–2 (%)	28 (73.7)	26 (72.2)	20 (55.6)	18 (51.4)	0.109
Incidence grade 3–4 (%)	5 (13.2)	7 (19.4)	15 (41.7)	13 (39.4)	0.012
Mucositis duration					
1–2 median (range)	10 (2–23)	11 (5–20)	11 (1–22)	12 (2–24)	0.946
3–4 median (range)	2 (1–4)	2 (1–6)	7 (1–18)	7 (3–20)	0.001
Time of recovery (Mean ± standard)	6.39 ± 3.41	6.76 ± 3.17	8.97 ± 4.42	9.51 ± 6.96	0.006

Table 3 Manifestation of oral mucositis

Patient-judged manifestation of oral mucositis	Arm A ($n = 38$)	Arm B ($n = 36$)	Arm C ($n = 36$)	Arm D ($n = 35$)	p value
Taste change (%)	65.79	41.67	72.22	74.29	0.015
Limitation of mouth opening (%)	13.16	19.44	27.78	14.29	0.363
Limitation of swallowing (%)	55.26	44.44	63.89	54.29	0.431
Limitation of speaking (%)	39.47	22.22	41.67	31.43	0.285
Limitation of sleeping (%)	68.42	50	52.78	68.58	0.214

reducing the distribution of the drugs among the cells located in the mucous membranes and decreasing the risk of oral mucositis development [2, 21]. Although cryotherapy is generally regarded as a safe and well-tolerated method, it can sometimes be painful and constitute a negative stimulus to mucosa if excessively applied [2, 22]. Pharmacologic studies have shown that the concentration of drugs delivered to a patient is higher during the distribution phase than during the elimination phase and therefore plays a more crucial role in causing oral mucositis [13, 18]. We hypothesized that shorter administration of cryotherapy, only during the drug distribution phase, might be effective and easily tolerated. However, in clinical practice, nurses could not always apply cryotherapy at the correct time, and they complained that these interventions require much time in routine care. Therefore, the present study was designed to assess the efficacy of cryotherapy in stem cell transplantation following the administration of a highly toxic myeloablative regimen and to compare the effect of a short or long period of application of cryotherapy as well as whether cryotherapy could be included as a part of daily oral care. Our study showed a significant reduction in the incidence and/or severity of oral mucositis by nurse assessment, according to a lower incidence of score 3–4 oral mucositis as well as a shorter duration of grade 3–4 mucositis noted in arm B. We also found that cryotherapy could not be used casually, as it could increase the incidence or duration of OM, as noted in arm C.

Oral mucositis is an important, painful complication of myeloablative conditioning that requires intervention. Mucositis related to direct stomatoxicity usually develops within 3 to 7 days after chemotherapy and improves within approximately 2 to 3 weeks, in parallel with neutrophil recovery [20, 23]. Previous studies showed that the severity and duration of oral mucositis in patients undergoing myeloablative conditioning with high-dose melphalan regimes exceeded those associated with busulfan, and cryotherapy could prevent severe oral mucositis under melphalan treatment [4, 22, 24]. Our study showed that the median recovery duration for oral mucositis under BUCY myeloablative conditioning was less than 10 days. A shortened duration of cryotherapy could significantly reduce the duration of recovery from oral mucositis (the median recovery time for oral mucositis in arm B patients was 2 days).

OM has been complained by patients as the most debilitating complication of HSCT, while they reported it could affect their oral functions [25]. In our study, we found 63.45% patients had taste change, which was the most common manifestation patients reported. Cryotherapy might be a good intervention to alleviate taste change [26]. As we found, patients received certain timing and duration cryotherapy (arm A and arm B) reported less incidence of taste change than patients with no cryotherapy (arm D).

The factors associated with the duration of recovery from oral mucositis were of less concern. For nurses, it is important to have knowledge of effective intervention measures and provide patients with good advice when they suffer from OM. In our research, we found that patients with a lower educational level exhibited a longer recovery time from OM (OR = − .728, − .082~1.538). The reason for this finding is probably that patients with poorer education often do not understand the importance of oral hygiene well or pay little attention to oral hygiene while undergoing hematopoietic stem cell transplantation. We also found that patients with a history of OM usually performed oral care carefully and maintained better oral hygiene conditions when they suffered OM during HSCT. Chinese people are fond of hot food due to the belief that consuming hot food is a healthful dietary habit and keeps their body healthy. However, when patients have oral mucositis, hot food stimulates the local mucosa and worsens their lesions. Accordingly, we found that patients who prefer hot food exhibited a longer recovery time from oral mucositis (OR = 1.368, − 2.964~0.227).

Conclusion

In conclusion, we found that cryotherapy during the administration of cytotoxic agents for allogeneic HSCT patients receiving non-radiation myeloablative conditioning regimen could decrease the incidence and duration of severe oral mucositis and a half-course schedule could acquire a comparable efficacy compared with the whole-course schedule. However, cryotherapy should not be applied as a part of daily routine care because this could damage the oral mucosa. During mucositis, patients with poor education or who are fond of hot food may suffer a long duration of recovery. Nurses should

Table 4 Multiple linear regression analysis of oral mucositis recovery duration

Variable	OR	95% CI		*p* value
Education	− 0.728	− 0.082	1.538	0.048
History of OM	− 1.492	− 3.054	0.070	0.041
Dietary habits				
Fondness for hot food	1.368	− 2.964	0.227	0.032
Fondness for cool food	1.08	− 0.874	3.035	0.276
Fondness for spicy food	− 0.278	− 2.174	1.619	0.773
Fondness for sweet food	− 1.019	− 3.321	1.283	0.383
Fondness for salty food	− 0.966	− 3.017	1.085	0.353
Diagnosis	0.643	− 0.172	1.459	0.121
Frequency of chemotherapy treatment	0.089	− 0.205	0.382	0.551
Graft type	− 0.317	− 1.198	0.563	0.477
Systemic disease	− 0.128	− 1.925	1.668	0.888

convey more concern and advise these patients to maintain their oral hygiene during the period of HSCT.

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Compliance with ethical standards All participants provided informed consent, and the study was approved by the ethical institution of the First Affiliated Hospital of Soochow University (no. 2017021).

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

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