Oral mucositis in patients receiving reduced-intensity regimens for allogeneic hematopoietic cell transplantation: comparison with conventional regimen

Kanayo Takahashi[1,2], Yoshihiko Soga[1,3,4], Yumeno Murayama[1,2], Mika Udagawa[1,2], [*]Hitomi Nishimoto[1,2], Yuko Sugiura[1,3], Yoshinobu Maeda[1,5], Mitsune Tanimoto[1,5], Shogo Takashiba[3]

1) Cancer Board for Hematological Malignancy, Okayama University Hospital of Medicine and Dentistry, Okayama, Japan
2) Department of Nursing, Okayama University Hospital of Medicine and Dentistry, Okayama, Japan
3) Department of Pathophysiology - Periodontal Science, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan
4) Dental Section of Perioperative Management Center, Okayama University Hospital of Medicine and Dentistry, Okayama, Japan
5) Department of Hematology, Oncology and Respiratory Medicine, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

*Corresponding author:
Hitomi Nishimoto, RN, CN
Department of Nursing, Okayama University Hospital of Medicine and Dentistry,
2-5-1 Shikata-cho, Okayama 700-8558, Japan
Tel and Fax: 81-86-235-6653
e-mail: me3310@hp.okayama-u.ac.jp

For H. Nishimoto,
Yoshihiko Soga, DDS, Ph.D
Department of Pathophysiology - Periodontal Science, Okayama University
Graduate School of Medicine, Dentistry and Pharmaceutical Sciences,
2-5-1 Shikata-cho, Okayama 700-8525, Japan
Tel: 81-86-235-6677
Fax: 81-86-235-6679
e-mail: y_soga@md.okayama-u.ac.jp

Abstract

Goals of work:

Severe oral mucositis induced by allogeneic hematopoietic cell transplantation (HCT) is associated with intolerable pain and risk of systemic bacteremia infection. Differences between conventional HCT and reduced-intensity regimens for allogeneic HCT (RIST) may influence the occurrence and severity of oral mucositis. Here, we evaluated oral mucositis in patients undergoing RIST and compared the results with those in conventional allogeneic HCT patients to facilitate predictive measures for mucositis.

Patients and methods:

A total of 127 consecutive patients undergoing HCT (conventional: 63; RIST: 64) were included in this study. Severity of oral mucositis during HCT period was evaluated daily. Differences in severity of mucositis among HCT types were analyzed. Use of morphine to control pain due to oral mucositis was evaluated in each HCT method.

Main results:

The severity of oral mucositis was reduced in patients undergoing RIST. Worsening of oral mucositis was delayed in patients receiving RIST. Use of morphine to control pain due to oral mucositis was significantly decreased in patients undergoing RIST compared with those receiving conventional allogeneic HCT.

Conclusions:

The severity of oral mucositis was reduced and the peak day of oral mucositis was delayed in RIST patients compared with those receiving conventional HCT.

Key words

hematopoietic cell transplantation, oral mucositis, reduced-intensity regimens

Introduction

Oral mucositis is one of the most common symptomatic complications associated with chemotherapy, especially hematopoietic stem cell transplantation (HCT) [5,6]. Severe mucositis is associated with not only intolerable pain but also the possible risk of systemic bacteremia infection. Oral mucositis is a significant cause of suffering and morbidity in patients receiving myeloablative chemotherapy [1]. Effective interventions to alleviate this complication without promoting infection are needed [1].

To provide measures for effectively alleviating oral mucositis, it is very important to clarify the clinical time course of oral mucositis during the HCT period. The clinical course of conventional allogeneic HCT is relatively predictable. The severity of clinically evident mucosal damage generally increases and peaks between 6 and 12 days post-HCT with resolution of uncomplicated mucositis occurring over the subsequent 7 to 10 days [2,8].

Reduced-intensity chemotherapy regimens for allogeneic HCT (RIST) have been developed over the past decade to extend HCT therapy to older patients or those with comorbidities. The conditioning regimens typically include a purine analog, such as fludarabine, an alkylating agent, or low-dose total-body irradiation (TBI). The principle underlying reduced-intensity conditioning regimens is to provide tumor killing

by choosing drugs with proven activities against the targeted malignancies while waiting for graft-*versus*-tumor (GVT) effects to occur. Cytotoxic conditioning chemotherapy also serves to suppress the host-versus-graft reactions. The approach to nonmyeloablative conditioning employs an immunosuppressive regimen that is minimally myelosuppressive. Several immunosuppressive drugs are used after HCT for the dual purposes of enhancing engraftment and controlling graft-*versus*-host disease (GVHD) [3]. Thus, these conditioning regimens pre-HCT and immunosuppressive drugs post-HCT may influence the occurrence and severity of oral mucositis.

In this study, oral mucositis was evaluated in patients undergoing RIST and the findings were compared with those in conventional allogeneic HCT patients to facilitate effective and predictive measures of the possible risk of systemic bacteremia infection and intolerable pain caused by oral mucositis.

Patients and Methods

Patients

A total of 127 consecutive patients undergoing HCT at Okayama University Hospital of Medicine and Dentistry between 2003 and 2007 (M: 73, F: 54; 43.6±15.2 y) were enrolled in this study. Conventional allogeneic HCT and RIST were administered

to 63 (M: 34, F: 29) and 64 (M: 39, F: 25) patients, respectively. Diseases and HCT protocols are shown in Table 1.

The Ethical Committee of the Department of Nursing, Okayama University Hospital of Medicine and Dentistry, approved this study. Informed consent was obtained from each subject.

Assessment of Oral Mucositis

Severity of oral mucositis in patients undergoing HCT was evaluated every day according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 [9]. The criteria for oral mucositis were as follows:

Grade 1: Erythema of the mucosa

Grade 2: Patchy ulcerations or pseudomembranes

Grade 3: Confluent ulcerations or pseudomembranes; bleeding in response to minor trauma

Grade 4: Tissue necrosis; significant spontaneous bleeding; life-threatening consequences

Grade 5: Death

Assessments were performed as part of daily nursing by nurses under the instruction of dentists and dental hygienists, and the consistency of assessments was

checked during the rounds of dentists and dental hygienists at least once per week.

Assessment of use of morphine to control pain due to oral mucositis

Use of morphine to control pain due to oral mucositis was evaluated for all patients. Differences in the frequency of patients used morphine among HCT types were analyzed.

Statistical analysis:

Differences in the severity of mucositis and use of morphine among HCT types were analyzed by χ^2 test. When the data for χ^2 test analysis included a probability less than 5, Yates' continuity correction was applied. *P*-values were calculated using the statistical software StatFlex (Artech, Osaka, Japan).

Results

Clinical course of oral mucositis in RIST and conventional HCT

The clinical courses of oral mucositis in patients undergoing conventional allogeneic HCT and RIST are shown in Fig. 1(A, B). In conventional HCT, almost all patients suffered from mucosal damage. Severe mucositis (grades 3 and 4) was observed in 22.2% of patients treated using the conventional regimen, while the value in RIST patients was 4.7%. Ulcerative mucositis (> grade 2) was observed in about half of

the patients, while the incidence of ulcerative mucositis (> grade 2) increased slowly and reached only 20% in the patients after RIST. There were no grade 4 lesions in RIST patients.

Clinical courses of oral ulcerative mucositis in RIST and conventional HCT

The clinical courses of oral ulcerative mucositis (> grade 2) in patients receiving RIST and conventional HCT are shown in Fig. 2. Ulcerative mucositis (> grade 2) was detected most frequently 8 days after conventional HCT. However, ulcerative mucositis was detected most frequently in RIST patients on day 11, which was delayed compared with conventional HCT patients.

Maximal severity of mucositis in RIST and conventional HCT

The maximal severities of oral mucositis in patients undergoing conventional allogeneic and RIST are shown in Fig. 3. A significant difference in maximal severity was observed between conventional HCT and RIST ($P<0.05$, χ^2 test), and the severity of oral mucositis was reduced in patients undergoing RIST compared with conventional allogeneic HCT.

Use of morphine to control pain due to oral mucositis

The frequencies of morphine use to control pain due to oral mucositis in patients undergoing conventional HCT and RIST are shown in Fig. 4. Of the patients

receiving conventional HCT, 55.6% required morphine to control pain due to oral mucositis. However, a significantly lower percentage of patients undergoing RIST (12.5%) required morphine to control pain due to oral mucositis.

Discussion

The results of this study can be summarized as follows. 1) Severity of oral mucositis was reduced in patients undergoing RIST compared with those receiving conventional allogeneic HCT. 2) The worsening of oral mucositis was delayed in patients receiving RIST compared with those receiving conventional HCT. 3) Use of morphine to control pain due to oral mucositis was significantly decreased in patients undergoing RIST compared with those receiving conventional allogeneic HCT.

The severity of clinically evident mucosal damage generally increases and peaks between 6 and 12 days post-HCT with resolution of uncomplicated mucositis occurring over the subsequent 7 to 10 days [2,8], consistent with our findings in conventional HCT patients. On the other hand, there was a characteristic tendency toward a delay in the increase of mucosal damage in RIST patients compared with patients receiving conventional HCT. Furthermore, the frequency of ulcerative lesions was low compared with the conventional HCT patients throughout the HCT period as

shown in Fig. 2. In both conventional HCT and RIST, postgrafting immunosuppression mainly by methotrexate (MTX) is used for the dual purposes of enhancing engraftment and controlling GVHD [3]. We usually administer MTX on days 3, 7, and 10 after both HCT regimens. An intensive conditioning regimen for HCT resulted in severe mucositis about 10 days after conventional HCT and may have made the side effects of MTX unclear. However, in patients undergoing RIST, oral mucositis due to the conditioning regimen was mild and the delayed peak severity of oral mucositis was associated with MTX rather than the conditioning regimen.

Severe mucositis is associated with a risk of systemic infection related to bacteremia. Our previous studies showed that not only that normal oral flora but also opportunistic bacteria appear on the oral mucosa [7]. It was also reported that the appearance of multidrug-resistant opportunistic bacteria may be involved in fatal sepsis [4]. The reduced-intensity conditioning regimen for HCT leads to a reduction in the degree of oral mucositis, which may explain the reduced risk of infection in cases treated in this way.

Severe oral mucositis is also associated with intolerable pain, which is often controlled with by administration of morphine. Recent trends in cancer pain control recommend the appropriate use of narcotics to minimize pain. Our hospital also has this

policy, and the use of narcotics in cancer treatment has increased during the examination period (2003–2007). Despite this trend, the use of morphine was significantly lower in RIST patients compared to those receiving conventional HCT. As RIST leads to a decrease in use of narcotics, the major side effects of morphine, such as ileus, could be avoided.

From the perspective of medical staff providing oral care during HCT, including nurses, dentists, and dental hygienists, oral care for oral mucositis should be given priority in conventional allogeneic HCT patients rather than RIST patients. On the other hand, it should be understood that there is a tendency for the peak of oral mucositis to be delayed in RIST patients, and attention should be paid to the most severe period although it may be relatively mild compared with conventional HCT.

In conclusion, we compared oral mucositis in patients undergoing RIST to that in those receiving conventional allogeneic HCT. Severity of oral mucositis was reduced and the peak day of oral mucositis was delayed in RIST patients compared with that in conventional HCT patients.

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Table

Table 1. Diseases of patients

Diseases	Conventional HCT	RIST	Total
Acute myelogenous leukemia	18	15	33
Myelodysplastic syndromes	6	9	15
Malignant lymphoma	17	24	41
Acute lymphoblastic leukemia	16	5	21
Aplastic anemia	2	2	4
Acute myelomonocytic leukemia	2	1	3
Chronic myelogenous leukemia	2		2
Acute myelofibrosis		1	1
Multiple myeloma		1	1
Paroxysmal nocturnal hemoglobinuria		1	1
Chronic active Epstein-Barr virus infection		1	1
Solid tumor		4	4
Total	63	64	127

Figures

Fig. 1

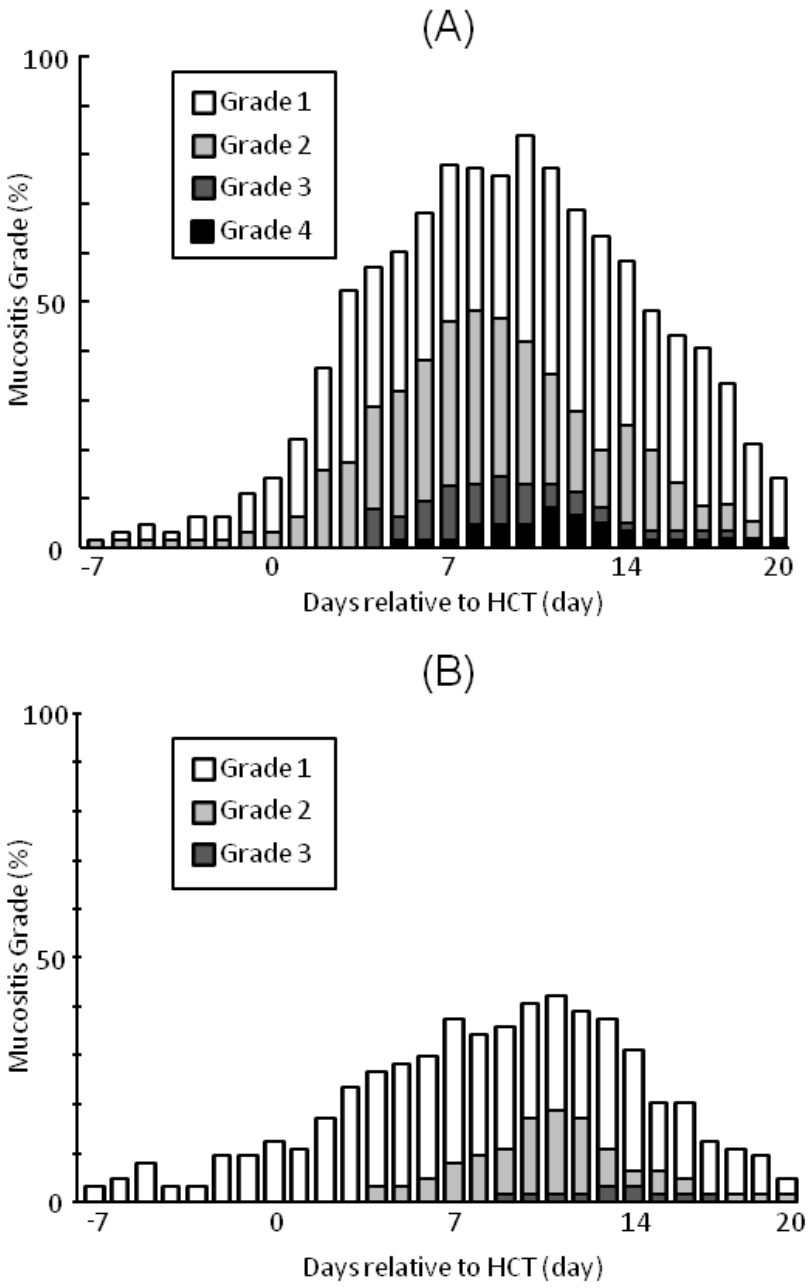

Fig. 2

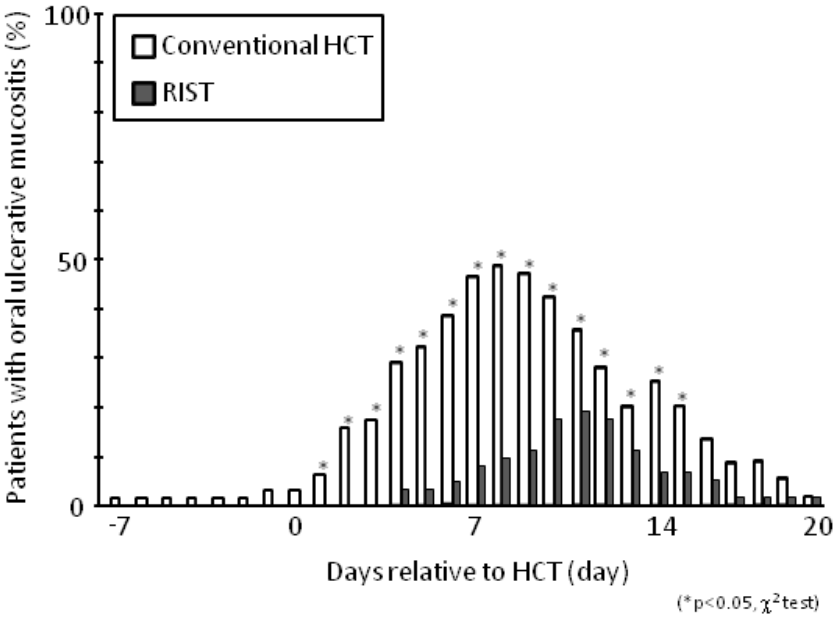
Patients with oral ulcerative mucositis (%)
100
50
0
Conventional HCT
RIST
-7
0
7
14
20
Days relative to HCT (day)
(*p<0.05, χ²test)

Fig. 3

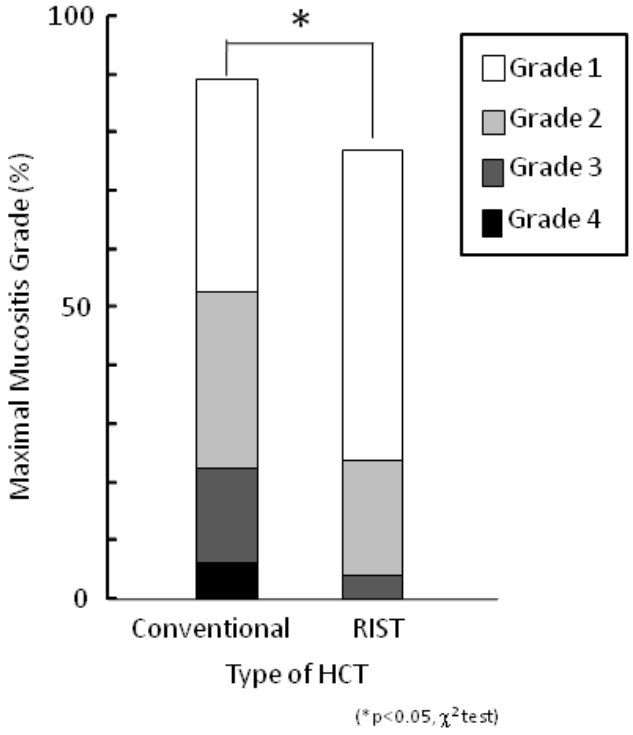
100
50
0
*
Grade 1
Grade 2
Grade 3
Grade 4
Maximal Mucositis Grade (%)
Conventional
RIST
Type of HCT
(*p<0.05, χ²test)

Fig. 4

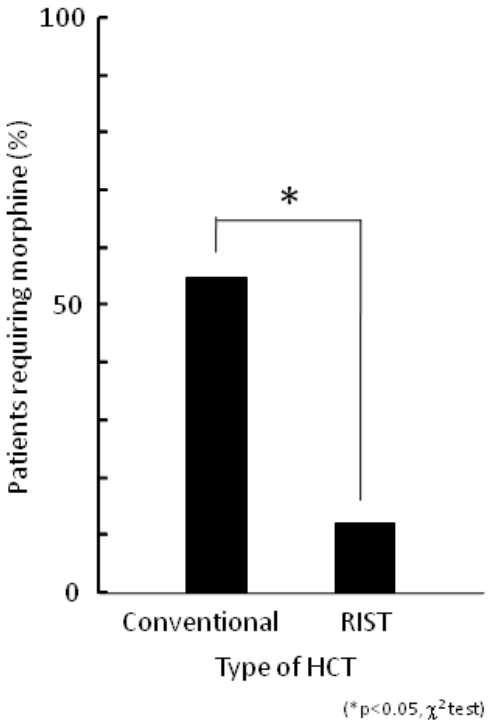
100
50
0
Patients requiring morphine (%)
*
Conventional
RIST
Type of HCT
(*p<0.05, χ2 test)

Figure legends

Fig. 1 Clinical course of oral mucositis in conventional HCT and RIST

(A) Conventional HCT. (B) RIST. The severity of oral mucositis in patients undergoing HCT was evaluated every day according to the NCI-CTCAE version 3.0. Definitions of each grade are described in the “Patients and Methods” section.

Fig. 2 Clinical courses of oral ulcerative mucositis in conventional HCT and RIST

Frequencies of patients with oral ulcerative mucositis (NCI-CTCAE criteria grade>2) during the HCT period. Differences between conventional HCT and RIST on each day were analyzed by χ^2 test.

Fig. 3 Maximal severity of mucositis in conventional HCT and RIST

Maximal severities of oral mucositis in patients undergoing conventional allogeneic and RIST. Grades were examined by NCI-CTCAE version 3.0. Definitions of each grade are described in the “Patients and Methods” section.

Fig. 4 Use of morphine to control pain due to oral mucositis in conventional HCT and RIST

Frequencies of patients requiring morphine in each HCT regimen.