Oral health as a predictive factor for oral mucositis

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OBJECTIVES: Oral mucositis is a complication frequently associated with hematopoietic stem cell transplantation, decreasing a patient's quality of life and increasing the occurrence of opportunistic infections. The purpose of this study was to determine the incidence and severity of oral mucositis and to assess the correlation of this disease with the oral health of an individual at the time of hematopoietic stem cell transplantation.

METHODS: Before transplantation, patients' oral health and inflammatory conditions were determined using the gingival index and the plaque index, which are based on gingival bleeding and the presence of dental plaque, respectively. Additionally, the dental health status was determined using the decayed, missing, and filled teeth index. The monitoring of oral mucositis was based on the World Health Organization grading system and was performed for five periods: from Day 0 to D+5, from D+6 to D+10, from D+11 to D+15, from D+16 to D+20, and from D+21 to D+30.

RESULTS: A total of 97 patients (56% male and 44% female) who underwent hematopoietic stem cell transplantation at the Hospital das Clinicas da Faculdade de Medicina da Universidade de Sao Paulo between January 2008 and July 2009 were prospectively examined. The incidence of ulcerative mucositis was highest from days +6 to +10 and from days +11 to +15 in the patients who underwent autologous and allogeneic hematopoietic stem cell transplantation, respectively.

CONCLUSION: The data, including the dental plaque and periodontal status data, showed that these oral health factors were predictive of the incidence and severity of oral mucositis in a cohort of patients with similar conditioning regimens before hematopoietic stem cell transplantation.

KEYWORDS: Mucositis; Oral Health; Hematopoietic Stem Cell; Transplantation.

■ INTRODUCTION

Oral mucositis (OM) is one of the most significant complications of both autologous and allogeneic hematopoietic stem cell transplantation (HSCT) and is implicated in extended hospitalization, prolonged narcotics use, and the incidence of opportunistic infections (1,2). OM is the result of damage to the epithelial and connective tissues by the toxic effects of the HSCT conditioning regimen (3). The clinical manifestations of OM include signs and symptoms of inflammation, varying from mild erythema, edema, and soreness to severe pain and ulceration that require analgesic

medication (4). Severe OM interferes with daily activities, such as speaking, eating, and swallowing, resulting in dehydration, malnutrition, and opportunistic infections, with a negative impact on the quality of life (5,6) and possibly leading to lower overall survival after HSCT (7).

Comprehensive oral care prior to HSCT is related to briefer OM (8,9). OM negatively affects the transplantation outcome by facilitating opportunistic infections and sepsis, so clinical approaches to reducing OM incidence or severity may increase patient survival and quality of life. The purpose of this study was to determine the incidence and severity of OM and to assess the correlation of this disease with the oral health of an individual at the time of HSCT.

■ PATIENTS AND METHODS

Ninety-seven patients with hematological or solid tumors who underwent HSCT (62 autologous and 35 allogeneic) were enrolled in this prospective study. Patients were all examined in two or more occasions (intraexaminer error) by

the same dentist with expertise and training in OM clinical manifestations and diagnosis. The conditioning regimen comprised high-dose chemotherapy without radiation for all of the participants. Graft-*versus*-host disease (GVHD) prophylaxis in the allogeneic HSCT patients consisted of cyclosporin A plus a short course of methotrexate (MTX) (on days +1, +3, +6, and +11). Supportive care consisted of broad-spectrum antibiotics in addition to antifungal and antiviral prophylaxis, which began at the start of the conditioning regimen. The broad-spectrum antibiotics were changed when the fever was positive. Furthermore, pre-emptive ganciclovir therapy was prescribed when cytomegalovirus (CMV) infection was evident.

The patients were well instructed by the same oral care professional about dental cleaning and oral hygiene. The specific directives were to clean the oral cavity daily and to rinse with chamomile tea. Oral health was assessed using a transversal evaluation immediately before transplantation and was determined using the gingival index (GI) and the plaque index (PI), which are based on gingival bleeding and the presence of dental plaque, respectively (10,11). The dental health status was determined by the DMFT index, which numerically expresses the prevalence of caries in an individual and is obtained by calculating the number of decayed (D), missing (M), and filled (F) teeth. OM monitoring started on D+1 and continued until D+30 post-transplantation. OM was graded based on the World Health Organization (WHO) grading system (grade 0: no OM; grade 1: pain and erythema; grade 2: ulcerations and can eat solids; grade 3: large ulcers and no solid intake but liquid diet possible; and grade 4: large ulcerations and solid/liquid intake not possible). All of the patients were evaluated daily by the same dentist, and the data were recorded for five periods: from Day 0 to D+5, from D+6 to D+10, from D+11 to D+15, from D+16 to D+20, and from D+21 to D+30. These periods were selected according to the biology of the bone marrow nadir until complete recovery.

Endpoint

The primary endpoint was the incidence of OM at any grade and of any severity in HSCT patients, according to the patients' oral health at the time of transplantation.

Statistical analysis

A linear regression was performed to determine the relationship between oral health (using the plaque, gingival, and DMFT indexes) and the incidence of OM. Additionally, analysis of variance was employed to establish how oral health indexes influence OM. The differences in categorical variables between the groups were evaluated using Fisher's exact test.

Ethics

All of the patients signed an informed consent form that was approved by the Institutional Research and Medical Ethics Committee.

■ RESULTS

Ninety-seven patients (54 males and 43 females) were enrolled in this prospective study. The median age was 41 years old (range: 18 to 65 years). The complete demographic data for both groups are presented in Table 1. Among the patients, OM grade I on the WHO scale was experienced by 47 (48.5%), grade II by 25 (25.8%), grade III by 8 (8.2%), and

Table 1 - Patient characteristics.

	Autologous	Allogeneic (MTX)
Gender (F/M)	31/31	12/23
Median Age (range)	42.5 (19-65)	40 (18-60)
Underlying Diseases		
SAA	0	5
HD	12	0
AML	12	10
CML	0	4
NHL	10	3
MM	25	0
MDS	0	9
Other	0	1
ALL	1	3
Testicular Carcinoma	2	0
Conditioning Regimen		
BEAM	17	0
Flu/Mel	0	1
Bu/Cy	0	5
Bu/Mel	45	29
MTX use	-	35

F: female; M: male; MTX: methotrexate; SAA: severe aplastic anemia; HD: Hodgkin disease; AML: acute myelogenous leukemia; CML: chronic myelogenous leukemia; NHL: non-Hodgkin lymphoma; MM: multiple myeloma; MDS: myelodysplastic syndrome; ALL: acute lymphocytic leukemia; BEAM: conditioning regimen comprising becenum, etoposide, cytarabine, and melphalan; Flu: fludarabine; Mel: melphalan; Bu: busulfan; Cy: cyclophosphamide.

grade IV by 8 (8.2%). Nine (9.3%) patients did not experience any OM. Ulcerative mucositis scores of grades III and IV, according to the WHO assessment scale, revealed a higher incidence from days +6 to +10 in autologous HSCT patients and from days +11 to +15 in allogeneic HSCT patients (Figure 1). An overall evaluation showed a higher incidence of OM, comprising the more severe grades III and IV, with impaired food intake, in allogeneic HSCT patients than in autologous HSCT patients ($p<0.001$).

Oral health index evaluation

According to the PI and GI evaluations, the medians of both indexes were 0.42, and the ranges were from 0.0 to 1.67 for the PI and from 0.0 to 1.90 for the GI. Moreover, the dental DMFT index ranged from 0.0 to 32, with a median of 15.5. The incidence of OM was assessed according to each of the three oral indexes (PI, GI, and DMFT), and the results showed that both the GI ($p = 0.04$) and the PI ($p = 0.01$) positively affected the incidence of OM. Additionally, when the autologous and allogeneic HSCT groups of patients were analyzed separately, the GI and PI were correlated with a higher incidence of OM in each group. In contrast, the dental status measured by the DMFT index did not influence the incidence of OM in either group.

OM and conditioning regimen

Regardless of the type of high-dose chemotherapy used as a conditioning regimen for HSCT, no difference was noted when comparing high-dose melphalan (Bu/Mel and BEAM) with the other regimen (Bu/Cy and Flu/Mel) ($p = 0.4104$). A conditioning regimen for allogeneic HSCT that included MTX showed a higher incidence of OM compared with a regimen for autologous HSCT that lacked MTX ($p = 0.0004$).
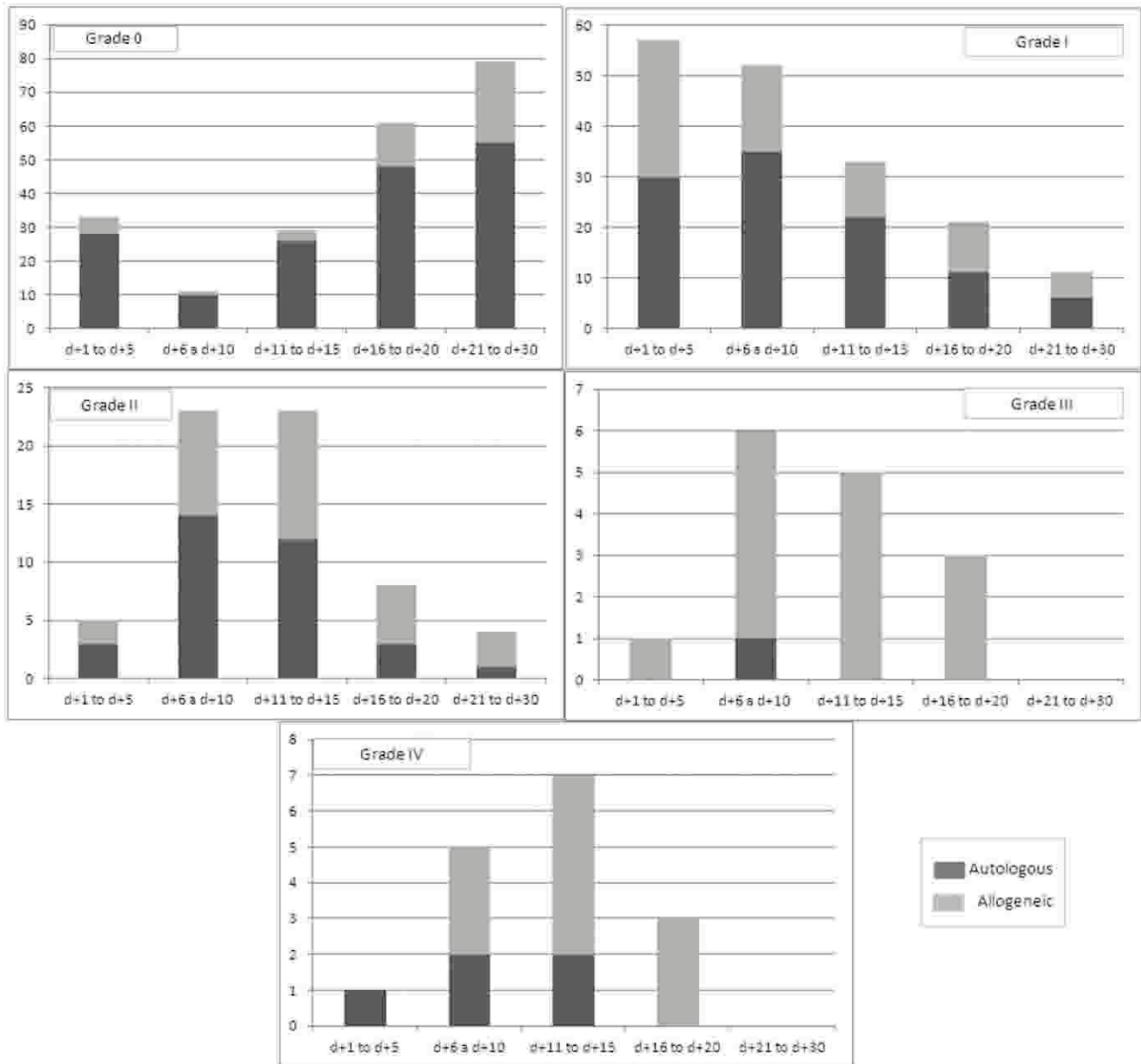
Figure 1 - Global incidence of OM in the patients during the assessment periods (WHO grading scale).

■ **DISCUSSION**

HSCT can lead to acute complications in the oral mucosa and salivary glands (1,12). Recently, we showed that comprehensive oral care is directly related to the incidence of OM (9). In this study, our results showed that dental plaque, a known causative factor in oral inflammation, was a determinant of the incidence of OM.

OM is a major debilitating complication of stem cell transplantation that causes distressing symptoms in patients and has economic and clinical implications (1). Although OM is a widely studied condition, the current prospective study identifies oral health at the time of transplantation to be an important predictive factor for OM incidence. Ruescher and colleagues (2) reported an increase in alpha hemolytic bacteremia in OM after autologous stem cell transplantation.

The researchers also considered the economic and clinical importance of OM. An increase in cost and longer hospitalization were also demonstrated to be associated with OM by Sonis et al. (1). Dental plaque and periodontal disease are two factors contributing to bacteremia after transplantation, thereby increasing hospitalization. Dentists must address these issues to reduce complications after HSCT.

It is well established that OM incidence is higher in allogeneic, rather than autologous, HSCT, possibly as a consequence of MTX administration in allogeneic HSCT. Clinicians should provide more attention to these allogeneic HSCT patients due to the patients' higher incidence of OM (13,14). Ohbayashi et al. (13) reported an 80.5% incidence of OM in a group using MTX, compared with 19.5% in a group that did not use this drug (13). In another study, Wardley et al. (15) reported the highest OM incidence for melphalan

200 (3.6), followed by busulfan (2.6), cyclophosphamide/TBI (2.3), and cyclophosphamide-carmustine and CVB (1.4). In the current study, the patients underwent high-dose chemotherapy without total body irradiation as a preparative regimen. The objective was to analyze similar conditioning regimens, with most patients using high-dose melphalan followed by BEAM. Our results show that there was no association between the preparative regimens and that the incidence of OM was similar between the groups ($p = 0.4104$).

However, a higher OM incidence was noted when comparing the regimens that included MTX. In addition, the allogeneic HSCT group exhibited a longer healing time than the autologous HSCT group ($p<0.001$). The data presented here show that OM is not only caused by the conditioning regimen but also by other factors, such as oral health status. OM in the patients enrolled in this study was evaluated using the WHO grading scale.

Melkos and colleagues (16) reported that patients with no dental care before HSCT showed a higher incidence of complications, indicating the importance of a dental evaluation and appropriate intervention before HSCT. In a complementary study, the incidence of OM was compared between patients who did and did not receive oral care before HSCT. The results showed no differences in OM incidence, although the healing time was reduced in the patients who received oral care (9). In the present study, the PI and GI were positively correlated with OM incidence. This finding is consistent with the assumption that oral care prior to HSCT can decrease OM severity and incidence by reducing dental plaque and gingival inflammation. Recently, our group reported that reducing dental plaque and gingival inflammation by oral care was positively correlated with OM (9), corroborating the idea that oral inflammation is predictive of OM incidence and healing time.

Cancer treatment is becoming increasingly more effective but is associated with both short-term and long-term side effects. Oral side effects continue to cause complications despite the variety of agents used to prevent these effects. One of the side effects is oral mucositis, a very debilitating condition. Thus, protocols for preventing and treating OM in patients with a reduced salivary flow and/or dental caries are necessary. These patients require prophylactic care to avoid life-threatening systemic infections that begin in the mouth (17). We agree with other authors that good oral health directly influences patients' quality of life (9), so a standardized oral care protocol with regular and systematic oral hygiene, comprising brushing and flossing, must be part of the multidisciplinary approach to treating HSCT patients (18).

In conclusion, the data, including the dental plaque and periodontal status data, showed that these oral health factors were predictive of OM incidence and severity in a cohort of patients with similar conditioning regimens before HSCT.

■ ACKNOWLEDGMENTS

■ AUTHOR CONTRIBUTIONS

Coracin FL was the investigator and manuscript author. Santos PS was the co-investigator and performed the clinical review of the manuscript. Nunes FD was the project principal investigator, contributed to the study design and performed the technical review of the manuscript. Gallottini MH contributed to the clinical and technical review of manuscript. Saboya R, Musqueira PT and Barban A participated in patient recruitment and clinical review. Chamone DA and Dulley FL performed the technical review of the manuscript.

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