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Periodontal status and post-transplantation complications following intensive periodontal treatment in patients underwent allogenic hematopoietic stem cell transplantation conditioned with myeloablative regimen

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Gürgan CA, Özcan M, Karakuş Ö, Zincircioğlu G, Arat M, Soydan E, Topcuoglu P, Gürman G, Bostancı HS. Periodontal status and post-transplantation complications following intensive periodontal treatment in patients underwent allogenic hematopoietic stem cell transplantation conditioned with myeloablative regimen.

Abstract: *Objectives:* Evaluation of the periodontal status is necessary prior to management with high-dose chemotherapy before hematopoietic stem cell therapy (HSCT). During medical therapy, pre-existing periodontal conditions may exacerbate and cause local and systemic complications. When possible, maximal oral health should be achieved prior to engraftment. In this study, we aimed to determine the alterations occurred in the periodontal status of the patients after periodontal treatment and allogenic HSCT and evaluate the effect of intensive periodontal approach on the short-term complications of HSCT. *Methods:* The alterations occurred in the periodontal tissues 3–4 weeks after periodontal treatment and after HSCT periods of 3 months for 29 patients treated with full-mouth periodontal treatment completed in 24 h in addition to eradication of dental foci, and oral hygiene status were evaluated using pocket depth measurements, presence of bleeding on probing and plaque and gingival indices. The incidence and severity of acute graft-versus-host disease (GVHD) and oral mucositis (OM) were recorded. Duration of engraftment period and the episode of febrile neutropenia were also evaluated. *Results:* There were significant improvements in periodontal status after periodontal treatment ($P < 0.001$). There were 14 (48.3%) patients without acute GVHD and 17 (58.6%) patients with no sign of OM. The majority of OM was at grade II level. There was a negative relation that exists between the percentage of BOP (+) sites and presence of OM ($r = -0.518$, $P < 0.05$). *Conclusions:* Together with a significant reduction in gingival inflammation and maintenance of the improvement in periodontal health, remarkable decrease in the incidence and severity of OM were observed.

Key words: hematopoietic stem cell therapy; oral mucositis; periodontal treatment

Introduction

Oral complications requiring dental supportive care are frequent causes of morbidity in hematopoietic stem cell transplantation (HSCT). Managing the dental care of patients before transplantation should be directed towards maintaining oral comfort, while eliminating intraoral problems that could predispose patients to oral infections or haemorrhages. Once patients become neutropenic, oral pathological conditions may be more difficult to diagnose accurately owing to suppression of the cardinal signs of inflammation, be more difficult to treat with conventional therapies and result in treatment-altering conditions that could be life-threatening (1–3).

Oral mucositis (OM) is the most frequent and obvious oral complication seen in HSCT patients (4). Both radiotherapy and chemotherapeutic agents using for the conditioning regimens of transplantation have directly damaged the mucosal progenitor cells, which can lead to loss of mucosal integrity. The degree of severity can range from mild erythema to severe oral mucosal ulcerative breakdown (4, 5). Severe OM can cause intense pain that interferes with eating and significantly affects the patient's quality of life (6, 7). This complication, though rarely fatal, can result in the increased need for antibiotics, narcotic analgesic, hospitalization period and costs (8). OM typically becomes clinically evident shortly after transplantation and peaks 5–7 days post-transplantation and if uncomplicated by trauma or infections, OM usually will resolve spontaneously approximately 15–22 days after transplantation (9).

Evaluation of the periodontal status is necessary prior to management with high-dose chemotherapy and/or HSCT and when the treatment will result in myelosuppression. During conditioning regimen, pre-existing periodontal conditions may exacerbate resulting in local and systemic complications. When possible, maximal oral health should be achieved prior to engraftment. However, brushing and flossing are usually discontinued immediately following the conditioning regimen and re-initiated only after white blood cell counts exceed 2×10^9 L^{-1} mm^{-3}.

Toljanic *et al.* (10) have evaluated the outcomes of the previous concept of more conservative approach of keeping teeth in the mouth and the elimination of dental/periodontal foci of infection before cytotoxic regimen in HSCT patients by comparing the frequency of systemic infection caused by dental and/or periodontal origin solely. They concluded that these types of infections were of extremely low incidence and of negligible clinical importance. However, the study published by Elad *et al.* (11) aiming to develop a decision analysis framework that would test the effect of dental and/or periodontal treatment prior to chemotherapy on the survival of the patient suggested that dental treatment prior to chemotherapy was the preferred treatment strategy. According to their case data analysis, 1.8 of every 1000 hemato-oncologic patients or HSCT patients would die compared with the non-treatment group prior to chemotherapy. Moreover, according to the results from the published studies, good oral hygiene could be maintained during and post-HSCT (12), and this maintenance could provide lower incidence and severity of OM (13). Restoration of caries lesions, treatment of periodontal problems and eradication of all intraoral foci (14–17) in addition to professional oral care (18, 19) would result in lower incidence of complications related to HSCT.

Since 2004, intraoral examinations and necessary dental and periodontal treatments were coordinated with the pre-HSCT assessments that formed the part of the routine HSCT protocol in Stem Cell Transplantation Unit at the Faculty of Medicine, Department of Hematology, Ankara University, and included provision of basic dental care to minimize the incidence of oro-dental complications arising during the period of immunosuppression at post-HSCT. As a part of the standard protocol for the eradication of oral foci, all of the scheduled patients for HSCT were first examined by periodontologists. The intraoral care is consisted of extraction of hopeless teeth (i.e. need of endodontic treatment, partially erupted third molars, presence of periapical lesions and advanced periodontal destruction), treatment of caries, non-surgical periodontal treatment completed in 24-h with antimicrobial subgingival irrigation and advices regarding basic preventive oral care. As the dental and periodontal treatments needed long time for healing and recovery, the intraoral consultations and treatments were always initiated as early as possible before HSCT.

The purposes of this study were first, to evaluate the alterations occurred in the periodontal conditions of the patients before and after HSCT and second, to determine the incidence and severity of the short-term complications (i.e. acute graft-versus-host disease (GVHD), presence and severity of OM and number of febrile neutropenia days) of HSCT and the duration of engraftment period in patients who received the intensive periodontal treatment and oral care prior to transplantation.

Study population and methods

Between February 2004 and September 2010, 202 dentate patients who underwent allogeneic HSCT conditioned with a myeloablative regimen were examined before HSCT and received the intensive periodontal treatment and oral care in addition to the necessary dental treatments according to the protocol described below. As part of the treatment protocol of HSCT, all of these patients were invited to the re-evaluation 3 months after HSCT. Among these patients, 29 of them were available for the periodontal re-evaluation. The dropout rate was 85.6% for the follow-up period of 3 months after HSCT. Most of these 202 patients were coming from another city for the treatment and did not want to participate to the re-evaluation after HSCT.

The study group included 17 female and 12 male patients. The mean age of the patients was 32.45 ± 8.44 (19–45 years). The distribution of primary haematologic diseases was as follows: 12 (41.4%) patients with acute myeloblastic leukaemia (AML), 5 (17.2%) acute lymphoblastic leukaemia (ALL) and 12 (41.4%) chronic mylegenous leukaemia (CML). The

sources of hematopoietic stem cells were peripheral blood (n = 14) and bone marrow (n = 15).

Periodontal parameters and evaluation periods

Plaque index (PI), gingival index (GI), pocket depth (PD) and the presence of bleeding on probing [BOP (+)] were recorded at four sites of each tooth before and after (3–4 weeks) periodontal treatment and 3 months after HSCT. The number and percentage of deep pockets (PD ≥ 4 mm) and BOP (+) sites were also calculated. All the periodontal parameters were recorded before dental and periodontal treatments were initiated.

Dental and intensive periodontal treatment protocol

The consequence of the dental and intensive periodontal treatment protocol was as follows: (i) extraction of the teeth with the need of endodontic treatment, partially erupted third molars with or without symptoms, periapical lesions with or without symptoms and advanced periodontal destruction (i.e. the presence of furcation involvement greater than degree II, loss of two-third of bone support, advanced tooth mobility) under prophylactic antibiotic administration and thrombocyte transfusion when indicated; (ii) full-mouth non-surgical periodontal treatment (i.e. scaling and root planning) with subgingival antimicrobial [chlorhexidine digluconate solution (0.2%)] irrigation completed in 24 h; (iii) restoration of carious lesions that do not need endodontic treatment; (iv) corrections of ill-fitting restorations; (v) oral hygiene instructions (tooth brushing with soft brushes, rinsing with chlorhexidine digluconate (0.2%) and fluoride solution, interdental brushes and/or dental floss) and reinforcement. Artificial saliva solution was also prescribed as required to alleviate dryness. When patients experienced ulceration or profound thrombocytopenia, brushing was discontinued, and intraoral cleaning was performed with sponge brushes or cotton buds moistened in chlorhexidine digluconate solution (0.2%); (vi) control of all scheduled dental treatments and oral hygiene level following dental and periodontal treatments; and (vii) instructions of oral hygiene procedures were also given to the caregivers for the maintenance of oral hygiene level during conditioning regimen and post-HSCT period.

In patients with thrombocytopenia ($<50 \times 10^9$ L^{-1}), the extraction was postponed until the thrombocyte count reach to $>50 \times 10^9$ L^{-1} following transfusion. Patients with granulocyte counts of $<0.5 \times 10^9$ L^{-1} received prophylactic antibiotics (2 g amoxicillin orally 1 h before treatment).

The percentage of patients that received prophylactic antibiotic and thrombocyte transfusion were 10.8 and 17.6, respectively.

Conditioning regimen and HSCT protocol

The patients received homogeneous-type combination therapy to ablate the existing bone marrow that included cyclophosphamide in combination with either busulphan (n = 22, 75.9%) or total body irradiation (n = 7, 24.1%). To minimize the risk of infection following the conditioning regimen, all patients were administered a panel of prophylactic antimicrobial medications including acyclovir, fluconazole, ciprofloxacin, and co-trimoxazole and trimethoprim. When fever developed during neutropenic phase, empirical broad-spectrum antimicrobial agents were administered, on an empirical basis. In all the patients, cyclosporine and short-term methotrexate were used for immunosuppression after the transplantation.

Short-term complications of HSCT

The presence of acute GVHD, non-dental or oro-facial infection and OM, and the severity and duration of OM were recorded from the computer-based transplantation data. Duration of engraftment period for neutrophils is $>0.5 \times 10^9$ mm^{-3} (N05), $>1 \times 10^9$ mm^{-3} (N1) and thrombocytes $>20 \times 10^9$ mm^{-3} (T20), $>50 \times 10^9$ mm^{-3} (T50), and number of febrile neutropenia (i.e. a single-axillar temperature >37.5°C) days were obtained from the computer-based transplantation data of the patients.

Incidence and severity of OM according to World Health Organization (WHO) classification and time elapsed of OM were recorded. The grading of the OM was as follows: Grade 0: none; Grade I: oral soreness ± erythema without ulceration; Grade II: oral erythema, ulcers; patient can swallow solid diet; Grade III: oral ulcers, liquid diet; Grade IV: oral alimentation is not possible. Evaluation of OM was carried out by calibrated and experienced haematologists (ES and MA), and pain was assessed by subjective comments of the patients, and the need of pain killer usage was also recorded.

Initial periodontal evaluations of the patients were carried out by a calibrated single clinician (CAG) before and after periodontal and HSCT. The periodontal treatment of the patients was performed by three clinicians (MO, OK and GZ).

Statistical analysis

To estimate the reliability of the periodontal measurements during the treatment period, 10 randomly selected patients were re-evaluated. The reliability of the continuous variables was expressed as the standard deviation of the differences divided by two. The range of mean error for PD was 0.11–0.16 and indicated stable reliability during the evaluation period. Cohen's kappa (κ) was employed to describe the reliability of discrete GI and BOP values. Based on the duplicate measurements, the κ values of GI and BOP were 0.89 ± 0.04 and 0.91 ± 0.05, respectively.

The obtained data were analyzed using SPSS for Windows 10.0 Statistical Analysis Program (Microsoft Corp., Chicago, IL, USA). The statistical significance of the differences in parametric among and between the evaluation periods were analyzed using the one-way ANOVA with Bonferroni correction. The relationships between the periodontal parameters and the outcome parameters of HSCT were calculated by the coeffi-

Table 1. **Mean ± standard deviations (min–max values) of the plaque and gingival indices, pocket depth, number and percentage of deep sites (>4 mm) and percentage of bleeding on probing (BOP) (+) for the evaluation periods**

	Before periodontal treatment	*P*-value*	After periodontal treatment	*P*-value†	After HSCT	*P*-value‡
Plaque index	1.92 ± 0.59 (0.92–2.73)	<0.05	0.63 ± 0.45 (0.14–1.46)	N.S.	0.71 ± 0.40 (0.12–1.56)	<0.05
Gingival index	1.18 ± 0.41 (0.44–1.87)	<0.05	0.85 ± 0.40 (0.34–1.15)	N.S.	0.92 ± 0.45 (0.44–1.45)	<0.05
Pocket depth	2.21 ± 0.50 (1.32–3.18)	<0.001	1.56 ± 0.44 (0.96–2.52)	N.S.	1.58 ± 0.5 (0.96–2.76)	<0.001
Number of deep sites	8.77 ± 9.1 (0–31)	<0.05	3.04 ± 5.34 (0–17)	N.S.	2.56 ± 2.39 (0–8)	<0.001
Percentage of deep sites	21.18 ± 19.1 (2–70)	<0.05	11.04 ± 9.34 (0–14)	N.S.	10.04 ± 8.34 (0–12)	<0.001
Percentage of BOP (+) sites	60.91 ± 21.15 (18.96–97.22)	<0.001	18.28 ± 7.14 (5–35.2)	N.S.	19.34 ± 8.48 (12–25)	<0.001

*Difference between before and after periodontal treatment.
†Difference between after periodontal treatment and after hematopoietic stem cell therapy (HSCT).
‡Difference between before periodontal treatment and after HSCT.
N.S., not significant.

cient of Spearman's correlation. *P*-value <0.05 was considered to be statistically significant for all statistical tests.

Results

The mean number of extracted teeth was 2.45 ± 1.25 (range, 0–3), and 87% of the extracted teeth were third molars. The mean number of teeth treated for caries was 5.67 ± 3.56 (range, 2–7). During the dental and periodontal treatments, the tooth extractions were performed under antibiotic prophylaxis in nine patients, and thrombocyte transfusions were performed in six patients before tooth extraction and in seven patients before periodontal treatment.

Significant decreases for PI ($P < 0.01$) and GI ($P < 0.001$) values were observed after periodontal treatment, and the improvement obtained following the periodontal treatment could be maintained even after HSCT period (Table 1).

There were significant ($P < 0.001$) reductions for the mean PD, the percentage values of BOP (+) sites and number and percentage values of deep pockets ($P < 0.05$) between before and after the periodontal treatment (Table 1). However, the observed decreases in the periodontal parameters could not reach to a significant level after HSCT.

Clinical data relating to the proportion of sites showing changes in PD ≥ 2 mm (Fig. 1) and percentage of BOP (+) sites (Fig. 2) over the different time periods revealed that at patient level, the obtained periodontal conditions before HSCT could be maintained following HSCT.

The recorded mean engraftment period for N05 and N1 were 14.43 ± 3.84 (ranges: 3–21 days) and 16.42 ± 2.91 (ranges: 12–21 days), respectively. The same mean values for T20 and T50 were 14.58 ± 4.46 (ranges: 9–24 days) and 18.62 ± 5.5 (ranges: 12–29 days), respectively. The number of febrile neutropenia days was ranged from 1 to 4 days.

Among the short-term HSCT complications, 15 (51.7%) patients were diagnosed as having acute GVHD, and the presence of infections other than intraoral origin was diagnosed only in 10 (34.5%) patients. There were 12 (41.4%) patients diagnosed as having OM, of whom 4 (33.3%) had grade I, 2 (16.6%) grade II, 5 (51.6%) grade III and 1 (8.3%) grade IV OM. The mean duration of OM was 3.5 ± 2.7 (ranges: 1–9 days). In 12 patients with OM, acute GVHD was diagnosed

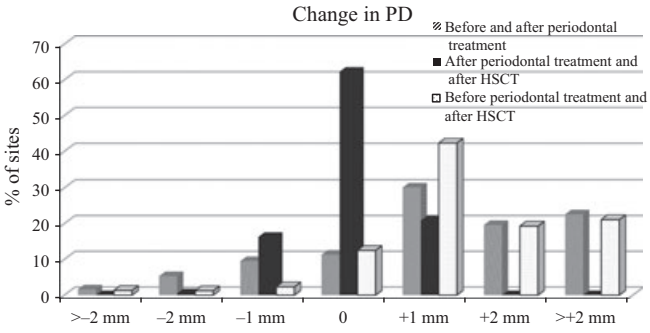

Fig. 1. Distribution of the percentage of sites that showed changes in pocket depth (PD) between before periodontal treatment period up to 3 months after hematopoietic stem cell therapy (HSCT).

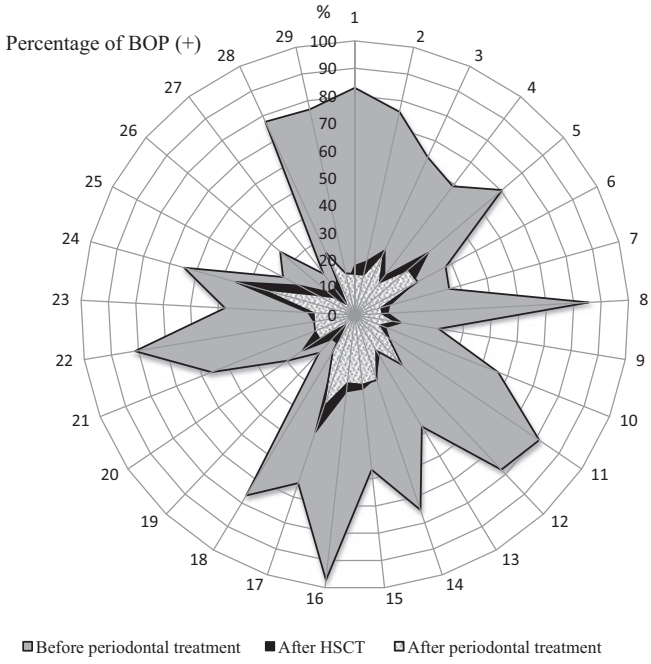

Fig. 2. Percentage of bleeding on probing (BOP) (+) sites before and after periodontal treatment and after hematopoietic stem cell therapy (HSCT) periods at patient level.

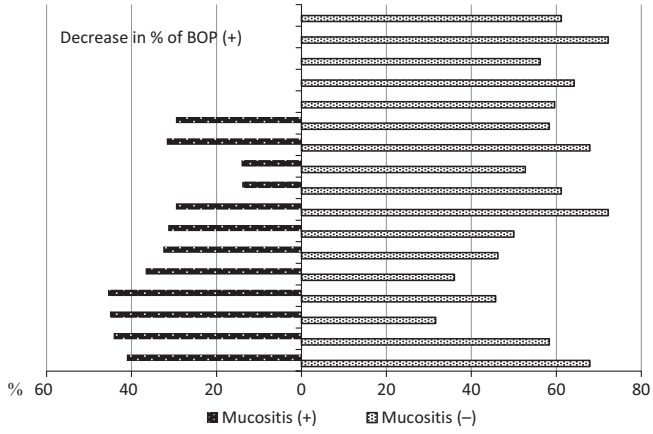

Fig. 3. Percentage of decrease in bleeding on probing (BOP) (+) values for each patient with or without oral mucositis.

only in 6 (50%) of them, and pain killers were administered to five patients with grade II and IV OM.

The result of correlation analysis showed that the alterations of percentage values of BOP (+) sites reversely related to the presence of OM ($r = -0.518$, $P < 0.05$), and there were no sign of OM in the patients with higher rates of decreases in percentage values of BOP (+) sites (Fig. 3). However, the alterations in periodontal parameters did not influence engraftment period or duration of febrile neutropenia.

Discussion

The improvement in the periodontal status (i.e. PD and percentage values of BOP (+) sites) was noted during the post-periodontal treatment period, and the patients could have also maintained this status during HSCT period (Table 1). These findings are in line with the study reported that patients who have been periodontally treated and maintained their oral health even showed some improvements in their periodontal health during post-HSCT period of 3 months (12). The observed significant reductions in the prevalence of deep pockets was most probably because of the extraction of teeth having advanced periodontal problems and consequently decrease in percentage of BOP (+) sites was also recorded.

A greater proportion of sites showed decrease in PD of ≥1 mm for not only after periodontal treatment but also after HSCT (Fig. 1). Overall, there was statistically significant decrease ($P < 0.001$) in mean PD between the preperiodontal treatment and the post-HSCT periods (Table 1). These observations were also supported by the same amount of significant decrease in percentage values of BOP (+) sites that were stable after HSCT (Fig. 2). Despite the compromised systemic conditions before HSCT, the periodontal health of the patients was relatively good. The majority of the patients exhibited either gingivitis or mild chronic periodontitis as determined by the prevalence of deep pockets and BOP (+) sites. The reasons for this stable status were most probably not only because of the intensive periodontal treatment performed but also the strict oral hygiene protocol implemented as part of the HSCT protocol for the patients that might have influenced the periodontal status. These results also support the findings from the studies indicating the benefits of complete oral care protocol including the periodontal treatment initiated before and maintained during HSCT period (15–17). Some reports showed that even formal oral hygiene instruction and scaling in addition to dental treatments prevented infection (20, 21), yet other reports showed that there was no significant correlation between dental foci and infections, OM, or survival rate in patients with HSCT (14).

Concerning the presence of acute GVHD and non-oral origin infections as post-HSCT complications, our oral care protocol including intensive periodontal treatment resulted in the absence of acute GVHD in almost half of the patients and only 17 (58.6%) patients with no sign of OM. These findings were also compatible with the previous studies (15, 17). OM is a complex biological process involving a series of factors, including cytokine-mediated actions, effects of chemotherapy on the epithelium, generation of reactive oxygen species and bacterial flora of the oral cavity (22). As the patients' oral hygiene is thought to modify the incidence and severity of OM, professional oral health care and treatment are recommended prior to the initiation of conditioning therapy for HSCT (23, 24). In our study, it was difficult to standardize the types of primary haematologic diseases. However, the conditioning regimens were homogeneous-type combination therapy and could affect the time elapsed of OM but not the severity of OM.

For the eradication of dental/oral foci, the most radical approach is the extraction of teeth. In our group, the mean number of extracted and restored teeth were 2.45 ± 1.25 and 5.6 ± 3.56, respectively. The results of the studies dealing with the effect of interventions consisting of dental extraction and/or restorations provided in the prechemotherapy and pre-HSCT time frame did not show any negative bearings on medical outcome (16) in opposite, higher rate of complications in group that had no dental treatment (14). In line with Yamagata *et al.* (25), our treatment approach resulted in less frequent OM. Pre-HSCT dental screening to identify and treat potential oral foci of infection has become standard care in patients scheduled for HSCT therapy (2). The principal aim of screening is to reduce morbidity and mortality, which may arise from oral complications associated with HSCT. Although all potential sources of oral infection should be eliminated by dental and periodontal treatments before the initiation of conditioning, time limitations and the patient's disease status frequently interfere with complete oro-dental treatment. Given this restriction, the removal of potentially preservable diseased teeth may be the only viable treatment option, resulting in oral care that does not best serve the long-term oral needs of the patients, because the removal of multiple teeth may compromise nutrition during and after HSCT therapy. As a further complication of extraction, there is an associated increased risk of infection, bleeding or delayed wound healing that could require postponing the scheduled HSCT. The patients with

no sign of OM were the ones who showed more decrease in their percentage values of BOP (+) sites (Fig. 3). Kashiwazaki *et al.* (18) retrospectively studied 140 adult patients who had received allogeneic HSCT, with or without professional oral health care and reported that the incidence of OM was 66.7% (52/78) in the patients who had received professional oral health care, compared to 93.5% (58/62) in their control group.

The recorded mean engraftment period for N05 and N1 were 14.43 ± 3.84 (ranges: 3–21 days) and 16.42 ± 2.91 (ranges: 12–21 days), respectively. The same mean values for T20 and T50 were 14.58 ± 4.46 (ranges: 9–24 days) and 18.62 ± 5.5 (ranges: 12–29 days), respectively. The number of febrile neutropenia days was ranged from 1 to 4 days, which is compatible with the study by Kashiwazaki *et al.* (18) who have confirmed that the incidence of febrile neutropenia and the maximal level of CRP were significantly lower in the professionally applied oral health care group than in not professionally treated group. The biofilm protects the adhering bacteria against environmental attacks. Antibiotics or oral rinses are unable to penetrate the plaque to reach the linking film bacteria. However, oral rinses and other detergents may be effective in preventing oral disease when used in addition to the mechanical removal of plaque. Mechanical removal of dental plaque, that is, tooth brushing, is indispensable to decreasing the biofilm and essential in oral care protocol.

Patients' daily oral hygiene regimens should be evaluated carefully and modified based on their medical conditions, gingival health, manual dexterity and motivational levels. Patients must be made aware of the possible severe consequences of oral neglect on their proposed medical therapies and future quality of life. Santos *et al.* (19) studied the effects of oral care prior to HSCT on the severity of OM and observed that although there were no differences in the incidence or severity of OM among the groups, the patients that received oral care prior to HSCT presented a shorter time elapsed ($P < 0.001$) compared with the one did not received it. The study evaluating oral hygiene of patients without any intervention showed a higher percentage of OM in patients with high plaque and gingival indices (77.4%) against those who had little or no visible plaque (65.7%) (13). Likewise, patients who brushed their teeth three times/day have presented OM in only 26.7% of cases, against those who did not brush, or brushed only once a day (65.9% vs. 68.4%) ($P < 0.05$) (13). According to our findings, incidence of OM was 41.4% (12 patients), which is compatible with the results of the above-mentioned studies. In another retrospective investigation, 64% of patients with chronic periodontal disease had positive blood cultures associated with clinical signs of septicaemia during the initial 100 days after HSCT (26). Although the majority of our patients exhibited mild chronic periodontitis, still the 25% of the deep pockets and 33% of the BOP (+) sites were available after HSCT. The existence of OM could have influenced on these unchanged values causing difficulties in brushing.

Initially, we aimed to evaluate all the patients underwent allogenic HSCT conditioned with myeloablative regimen and received the dental and periodontal treatment protocol. However, the dropout rate was very high that was the major limitation of the study. In addition to this, the lack of a control group without treatment was another limitation.

Within these above-mentioned limits, the our findings suggest that together with the reduction in the gingival inflammation following intensive non-surgical periodontal treatment and maintenance of this obtained improvement, the risk for periodontal infection decreased. Therefore, the remarkable decreases in both incidence and time elapsed of OM might be the consequences of this improvement in patients who underwent allogeneic HSCT conditioned with a myeloablative regimen.

Conflict of interest

The authors declare that they have no conflict of interest.

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