Oral care in Brazilian bone marrow transplant centers

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Background: *Oral care is a fundamental procedure for the success of the hematopoietic stem cell transplantation, particularly regarding the control of oral infectious diseases. Information about oral care protocols and the inclusion of dental professionals in transplantation medical staff is poorly known.*

Objective: *The aim of this study was to carry out a survey about the protocols of Brazilian dental professionals with regard to oral care of HSCT patients.*

Methods: *A questionnaire was mailed to 36 Brazilian transplant centers with questions about basic oral care protocols, the indication of specific mouthwashes, antibiotic therapy regimens, laser therapy, and treatment of oral mucositis and graft-versus-host disease. All the respondent centers (n = 12) have dentists as members of the HSCT medical staff.*

Results: *The majority indicate non-alcoholic chlorhexidine (n = 9; 75.0%) and sodium bicarbonate (n = 5; 41.7%) as routine mouthwashes. Laser therapy was frequently indicated (n= 9; 75.0%), mainly in the prevention of oral mucositis and in oral pain control. In the post-transplant period, antibiotic therapy was only indicated for invasive dental treatments (n= 8; 66.7%). Several treatments for graft-versus-host disease were mentioned without a trend towards establishing a standard protocol.*

Conclusion: *Basic oral care constitutes regular assessment in the routine treatment of hematopoietic stem cell transplantation patients in Brazilian centers.*

Keywords: *Oral health; Bone marrow transplantation; Mucositis; Graft-versus-host disease*

Introduction

In the last decades, the number of hematopoietic stem cell transplantations (HSCT) has increased significantly around the world.[1] HSCT has shown an important increase since 1990, mainly due to indications for different diseases, use in the older population, and increase in penetrability into the standard target population.[2,3] Annually, it is estimated that 50,000-60,000 HSCT are performed worldwide.[4]

HSCT centers have adopted multidisciplinary teams in order to guarantee the success of treatment and to increase the patient's quality of life during and after transplantation.[5] The dental professional is one of the members of this team, who has the responsibility of preventing oral infections during periods of neutropenia and to reduce oral side effects associated with HSCT.[6] Oral care guidelines are constantly published in order to establish universal protocols for HSCT patients, mainly concerning the prevention and control of oral infectious diseases and oral mucositis.[7,8] However there are some discrepancies in the oral care treatment, especially involving oral mouthwashes, the adoption of antibiotic therapy and alternative therapies for oral mucositis.

In Brazil, bone marrow, peripheral blood stem cells, and umbilical cord transplants have been adopted in private and public hospitals. At present there are 36 active HSCT hospitals accredited by the Brazilian Association for Organ Transplantation (BAOT).[9] In these centers, there are also increasing trends towards extending this therapy to more patients, in particular children with hematological diseases.[10] The number of HSCT over the last three years represents about 7.9 transplants for every one million in the population.[9] In Table 1 there is a brief comparison between the status of HSCT in Brazil, Argentina, South Africa, Australia, and the United States, as well as the data of the European Group for Blood and Marrow Transplantation (EBMT).

Although there is an evident increase in the number of HSCT and presence of well-established HSCT centers, a multi-professional approach is not routine in some Brazilian hospitals. In this context oral care may probably be neglected or restricted to nursing. As oral care trends in Brazilian HSCT patients are not known, it was decided to conduct a survey of the main HSCT centers in this country by means of a questionnaire with open – and closed – ended questions regarding the oral care protocols adopted by these centers.

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The authors declare no competing financial interest

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Table 1 - Number of hematopoietic stem cell transplantation centers in Brazil, in two other developing countries (Argentina and South Africa), in Australia/New Zealand as an example of countries located in other continents, in United States as example of developed country, and in Europe as a whole

Global data (years interval)	Autologous	Allogeneic	Total
Brazil (1999-2009)[9,11]	5,985	5,603	11,588
Australia and New Zealand (1992-2004)[12]	5,520	2,754	8,274
South Africa (1974-2007)[13]	678	571	1,249
Argentina (1991-2008)[14]	964	72	1,036
United States (2000-2009)[15]*	-	-	28,863
EBMT (2008)[16]**	16,028	10,782	26,810

* Registry from the National Marrow Donor Program. [15] Only graphical data about the autologous and allogeneic transplants were available. For annual numerical data, see site [17]
**EBMT - European Group for Blood and Marrow Transplantation. [16] The data were reported by 36 European and 8 affiliated countries, and are restricted to 2008

Obtained data were then compared with those described in the literature.

Methods

The study was approved by the Clinical Research Ethics Committee of our institution.

A questionnaire was prepared, containing both open – and closed – ended questions regarding the following subjects: presence of a dentist as a permanent member of the multidisciplinary team; presence of professionals other than the physicians; existence of previous oral health evaluations as prerequisite for the HSCT; delay of HSCT caused by oral diseases; oral care protocols mainly with regard to the use of mouthwashes, laser therapy, and antibiotic therapy; and protocols for oral graft-versus-host-disease (GVHD). The questions are shown in Table 2. Some of these questions were based on the survey carried out by Guggenheimer et al. of US organ transplant centers.[18] The subjects of the questions was selected considering some dental procedures that are not well explained in the literature, such as antibiotic therapy, mouthwashes, GVHD protocols, and adjuvant or alternative therapies. The questionnaire was mailed to the 36 coordinators of HSCT centers accredited by the BAOT. Replies were tabulated and analyzed as percentages.

Table 2 - Questions mailed to Brazilian hematopoietic stem transplantation (HSCT) centers

Multi-professional team
1. Is there a dentist member in your HSCT center team? Yes / No
2. Apart from the physicians, which professionals are members of the multi-professional team at your center? Nurses / Psychologists / Nutritionists / Physiotherapists / Occupational therapist / Speech therapist

Basic oral care protocols
1. In your center, is evaluation of the mouth before HSCT routine in the transplant procedure? Yes / No
2. Is this a prerequisite for performing HSCT? Yes / No
3. Has there been any situation in which your center was obliged to delay HSCT due to problems in the oral cavity? Yes / No
4. Does your center recommend the use of sodium bicarbonate solution as a mouthwash? Yes / No
5. If yes, for which clinical situation? _____
6. What are other oral care protocols that your center adopts?_____

Specific mouthwashes
1. Does your center recommend any specific mouthwash? Yes /No
2. If yes, what is the type of mouthwash? _____

Laser therapy
1. In your center, is laser therapy indicated for prevention or treatment of oral mucositis? Yes, routinely and integrated with the others multi-professional protocols / Yes, occasionally and without integration with others multi-professional protocols / No

Antibiotic therapy
1. In your center, is antibiotic therapy indicated for oral interventions during the post-transplant period? Yes, only for invasive dental treatment / Yes, for all dental treatment / No

Graft-versus host disease (GVHD)
1. In your center is there a specific protocol for the treatment of oral acute GVHD? Yes / No
2. If yes, what is the protocol or which drugs are used? _____
3. In your center is there a specific protocol for the treatment of oral chronic GVHD? Yes / No
4. If yes, what is the protocol or which drugs are used? _____

Table 3 - Regional distribution of Brazilian hematopoietic stem cell transplantation centers that answered the questionnaire and total number (%) of transplants performed in 2008 in each region

Region	Number of the respondent centers	Number of HSCT in 2008*	
		Autologous	Allogeneic
North	0 (0.0%)	0 (0.0%)	0 (0.0%)
South	3 (25.0%)	99 (12.1%)	107 (17.5%)
Northeast	0 (0.0%)	74 (9.0%)	75 (12.3%)
Southeast	8 (66.7%)	648 (78.9%)	428 (70.2%)
Central	(8.3%)	0 (0.0%)	0 (0.0%)
Total	12 (100.0%)	821 (100.0%)	610 (100.0%)

* Adapted from the Brazilian Transplant Registry [11]

Results

Twelve (33.3%) questionnaires were returned. Table 3 shows the regional distribution of the centers that answered the questionnaire, as well as the number of HSCT in each Brazilian region, according to national registry data. The main HSCT centers are in the Southeast; the State of São Paulo has the highest number of HSCT (21.5 transplants per million inhabitants in 2008).[11] The majority of the centers that answered the questionnaire were located in the southeastern region (Six in the State of São Paulo, and two in the State of Rio de Janeiro). These centers in addition to the other four located in the southern and central regions are responsible for 47.0% of the HSCT performed in Brazil. The questionnaires were answered by dental professionals (n = 7; 58.3%) and by HSCT coordinators (n = 5; 41.7%).

Apart from the physicians and nursing staff, all the centers have dentists, nutritionists, and psychologists (n = 12; 100.0%) as members of the multidisciplinary team. Nursing assistants (n = 9; 75.0%) and physiotherapists

(n = 10; 83.35) were frequently mentioned. Occupational (n = 7; 58.3%) and Speech (n = 3; 25.0%) therapists were less frequently reported.

Table 4 shows the basic oral protocols mentioned by the centers. All the centers performed dental evaluations before HSCT as a prerequisite for the transplant. Nine (75.0%) centers reported delay in HSCT due to dental problems. Oral hygiene guidance was the most emphasized (n = 5; 41.7%) but recommendations to use ultrasoft toothbrushes and dental floss (n = 3; 25.0%) were also mentioned. Some oral rinses, including antifungal and fluoride solutions were also stated. One center reported prophylactic tooth extraction before HSCT. On the question about the indication of sodium bicarbonate solution, this was recommended by five (41.7%) centers as mouthwash. Justifications for this indication were the maintenance of salivary pH, oral antisepsis mainly against fungal infections, and for the prevention/treatment of oral mucositis.

Table 4 - Basic oral care protocols in hematopoietic stem cell transplantation centers

Basic oral care protocol	Number (%)
Dental evaluation previously to the hematopoietic stem cell transplantation	Yes - 12 (100.0) No - 0 (0)
Oral hygiene instruction	5 (41.7)
Recommendation of:	
Ultrasoft toothbrush	3 (25.0)
Dental floss	3 (25.0)
Prophylactic dental extraction	1 (8.3)
Normal saline mouthwash	1 (8.3)
Antifungal solution	2 (16.7)
Fluoride solution	2 (16.7)
Sodium bicarbonate solution	5 (41.7)
Total of the respondent centers	12 (100.0)

Table 5 shows the types of mouthwashes mentioned by the centers. Specific mouthwashes were indicated by all the centers. The most common mouthwash was non-alcoholic chlorhexidine digluconate (n = 9; 75.0%) as either a commercial or manipulated formula. Benzidamine was indicated in the case of oral mucositis by one center (8.3%). The combination of rifamycin, diphenhydramine hydrochloride with antiseptic rinse and topical anesthetics was mentioned as a mouthwash for cases of dental infections, such as abscesses and gingivitis. Dry mouth mouthwashes were mentioned by only two centers (16.7%). Chamomile and malva tea were briefly mentioned (n = 2; 16.7%) as mouthwashes and beverages indicated for tissue repair.

Table 6 shows the frequency of answers to questions about laser therapy and antibiotic therapy. Laser therapy was not used only by three centers (25%), thus it was routine (n= 6; 50.0%) or sporadic (n = 3; 25.0%) treatment. The recommendation of antibiotic therapy during dental treatment in the post-transplant period was implemented only in invasive procedures by eight centers (66.7%).

Table 5 - Specific mouthwashes in hematopoietic stem cell transplantation centers

Specific mouthwashes	Number (%)
Use of specific mouthwashes	Yes - 12 (100.0) No - 0 (0)
Non-alcoholic digluconate chlorhexidine (0.12%)	9 (75.0)
Digluconate chlorhexidine (0.2%) (Perioxidin®)	1 (8.3)
Rifamycin + diphenhydramine hydrochloride + cetylpyridinium chloride + xylocaine	1 (8.3)
Benzidamine hydrochloride	1 (8.3)
Dry mouth care mouthwash (Biotène®)	2 (16.7)
Chamomile and malva tea	2 (16.7)
Total of the respondent centers	12 (100.0)

Table 6 - Indication of laser therapy and antibiotic therapy in hematopoietic stem cell transplantation centers

Laser therapy and antibiotic therapy	Number (%)
Adoption of routine laser therapy	6 (50.0)
Adoption of non-routine laser therapy	3 (25.0)
Antibiotic therapy for only invasive dental treatment in the post-transplant period	8 (66.7)
Antibiotic therapy for all dental treatment in the post-transplant period	3 (25.0)
Antibiotic therapy dependent upon the immune condition	1 (8.3)
Total of the respondent centers	12 (100.0)

Table 7 - Specific protocols for oral acute and chronic graft-versus host disease in hematopoietic stem cell transplantation centers

Protocol	Number (%)
Specific protocol for acute oral GVHD	Yes - 4 (33.3)) No - 8 (66.7)
Propionate clobetasol	2 (16.7)
Corticoids	1 (8.3)
Prednisolone plus cyclosporine	1 (8.3)
Proservation	1 (8.3)
Specific protocol for chronic GVHD	Yes - 9 (75.0) No - 3 (25.0)
Clobetasol gel (0.05%)	3 (25.0)
Clobetasol propionate rinse (0.02%)	1 (8.3)
Cyclosporine plus prednisolone	1 (8.3)
Tacrolimus plus prednisolone	1 (8.3)
Beclamethasone rinse followed by topical nistatin	1 (8.3)
Laser therapy and topical tacrolimus	2 (16.7)
Laser therapy in the case of pain	1 (8.3)
Total of the respondent centers	12 (100.0)

The results of GVHD protocols are summarized in Table 7. For acute GVHD (aGVHD), some centers (n = 4; 33.3%) mentioned specific protocols, which were variable. On the other hand, the majority of the centers (n = 9; 75.0%) showed specific protocols for chronic GVHD (cGVHD), which were also variable and involved rinses and application of corticosteroid gels, in particular clobetasol, and laser therapy.

Discussion

At present HSCT is considered one of the most promising therapies for malignant hematological diseases, with an increase in the survival rate in the countries with a significant number of HSCT cases.[4] In Brazil, there has been a rapid increase in the number of these transplants and at present transplants exceed South Africa, Argentina, and Australia/New Zealand in absolute numbers (Table 1). In this scenario, it was seen that the multidisciplinary team in Brazilian HSCT centers seems to be consolidated, with a permanent multi-professional approach. The questionnaire adopted in this study was sufficient for this analysis though it was adapted from an international reference[18] focused on transplant centers in general. It was useful for this study since it contains global questions regarding oral care for the majority of transplantation situations.

This survey reveals that the dental professional makes a regular assessment of the oral cavity and consistently practices oral hygiene techniques. This was a surprise considering the barriers to the implementation of oral care for cancer patients and in transplant centers that exist worldwide, such as gaps in knowledge, inconsistent or absent oral care assessment, diverse oral care regimens and practices, and lack of interdisciplinary collaboration.[19]

Despite the fact that the Brazilian dentist is integrated into the HSCT medical team, some barriers were indirectly detected in this survey. Although the respondent centers represent only 33.3% of the Brazilian bone marrow transplantation centers, they are responsible for 47.0% of HSCT performed in Brazil and constitute a representative sample of the health systems in the main Brazilian regions. Diverse oral care regimens and practice were mentioned by the centers. This diversity has also previously been reported by US HSCT centers.[20,21] Some agreement was found as regards the adoption of oral care regimens, such as dental evaluation before HSCT, oral hygiene guidance and monitoring during transplants. These are considered "good clinical practices"[6] and fundamental for successful HSCT, particularly considering that these actions provide an efficient control of oral infections.[22,23] However, other oral therapies that were very frequently mentioned in this survey have been questioned, such as the indication of sodium bicarbonate solution for HSCT patients. Bicarbonate of soda solution has been used as an antiseptic mouthwash and/or in the prevention and treatment of oral mucositis. It is considered a potent cleaning agent, enhancing the removal of oral debris,[24] but it may lead to irritation of the oral mucosa when used for long periods or in incorrect concentrations. Due to this potential toxicity, and based on some clinical trials that have shown no efficacy of the salt solutions in the treatment of oral mucositis,[24-26] the indication of this rinse for critical patients has not been encouraged. It is believed that the large scale adoption of this saline solution in Brazil is due to its low cost and easy manipulation.

Among the specific mouthwashes, non-alcoholic chlorhexidine solution was the most frequently mentioned. This highlights the permanent oral care management in infection control by the majority of the centers. In addition to its indication as an oral antiseptic, chlorhexidine has also been used in the treatment of oral mucositis, but without proven success.[25,26] By means of the questionnaire it was not possible to detect the objective reasons (whether it was because of the desirable action against oral mucositis or as a broad spectrum mouthwash against oral infections) for the use of chlorhexidine by dentists. A more comprehensive study must be conducted to elucidate the dental professional's judgment on the indication of chlorhexidine.

Other specific mouthwashes were infrequently mentioned, such as benzidamine and rifamycin added to Benadryl®, and natural agents (chamomile and malva tea). The indications of benzidamine mouthwashes in the oral cavity, particularly for HSCT patients, have been seriously discussed. An evidence-based study demonstrated no efficacy of this anti-inflammatory drug in the treatment of oral mucositis.[26] Rifamycin with Benadryl® solution is similar to that described by Dodd et al.[24] as a "magic solution". This mouthwash was indicated in the present survey only for oral infections and not for oral mucositis. This latter indication seems to be ineffective according to the literature.[24,26] Chamomile and Malva tea have antimicrobial, anti-oxidant, anti-inflammatory, and analgesic effects[27,28] that have been applied for oral mucosa repair. The efficacy of these plants on healing in HSCT patients is controversial, particularly in relation to chamomile, which has been more extensively studied.[25] Although these rinses were rarely mentioned, they signal a trend to empirical indication of mouthwashes for HSCT patients.

Prophylactic antibiotic therapy for dental treatment in HSCT patients has been discussed in the literature.[29,30] Some of these reports established a protocol for antibiotic administration based on the neutrophil counts in the myeloablative period before HSCT. Morimoto et al.[29] recommend oral cephalosporin administration for HSCT patients with low neutrophil counts (1000/mm^3 or less) when tooth extraction or scaling is necessary before the transplant. In a situation in which the neutrophil count is very low (100-150/mm^3), the same authors indicate intravenous antibiotic therapy for invasive dental treatment. In the post-transplant period, there are no reports that describe the antibiotic protocol during dental treatment. In the present survey the majority of the centers recommend prophylactic antibiotics only for invasive dental treatment, which is in agreement with the general rules established for HSCT patients as regards to infection control in the post-transplant period.[23,31] Prophylactic antibiotics for all dental procedures should be carefully reconsidered when the patient has venous access devices or presents late complications, such as GVHD and disorders in the liver, lung, muscles, and endocrine system.[31]

Another finding in this survey was a trend towards the indication of laser therapy for oral mucositis. Although there are few evidence-based studies confirming the efficacy of laser therapy in oral mucositis control, HSCT guidelines to dental professionals recommend the indication of laser in HSCT centers with adequate equipment and qualified professionals.[7,8] Studies have demonstrated some clinical evidence of low energy laser in the reduction of the incidence[32] and severity[33,34] of oral mucositis in HSCT patients. In the present survey, 50.0% of the centers used laser therapy routinely in oral care and 25.0% sporadically when pain control in the oral cavity is necessary, which may indicate that there is a consensus in Brazilian centers as regards the adoption of laser as an adjuvant therapy. Further investigations must be conducted to identify the parameters used for laser as well as the level of efficacy and cost/benefits of this therapy in HSCT centers.

Treatment protocols for oral cGVHD were adopted in the majority of Brazilian centers. These protocols were quite variable but mainly involved corticoids and laser therapy. Clobetasol gel was the most indicated, probably due to its high potency, improved absorption, and the fact that it needs to be applied only twice a day.[35] One center mentioned beclamethasone rinse and topical nistatin, which indicates concern about the risk of oral candidiasis inherent to topical corticoid therapies.[35] Laser therapy was the second most frequently mentioned modality for oral cGVHD treatment. A clinical report observed pain reduction and the efficacy of CO_2 laser as symptomatic treatment for oral cGVHD in four patients.[36] Low-energy laser therapy with a diode laser was also reported as a suitable adjunct to immunosuppressive therapy of cGVHD.[37] Because there were only two single clinical reports describing the advantages of laser therapy for cGVHD in five patients, further studies must be conducted to confirm this efficacy.

The low frequency of protocols for oral aGVHD may be due to the fact that this morbidity is self-limiting,[35] with oral symptoms partially reduced by systemic therapy. Additionally, the frequency of oral aGVHD is lower than that of oral cGVHD and frequently confounded with oral mucositis.[35]

In conclusion, this survey indicates the trends in oral management of HSCT patients in Brazilian transplant centers. All the treatment modalities mentioned in the questionnaires were found in the literature; some of them are controversial, others considered standard protocols. Great heterogeneity was detected in the opinions as regards the treatment of oral mucositis and GVHD, as well as a trend towards the adoption of alternative therapies, such as laser therapy. Apart from this, it seems that the dental professional is an active member of the multi-professional team in HSCT centers and that the basic oral care constitutes a regular part of the routine treatment of HSCT patients. A comprehensive study is necessary to detect details of the protocols, particularly in regards to the frequency of application and doses in the majority of the treatments.

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