Original Research
Immunology

The need for endodontic treatment and systemic characteristics of hematopoietic stem cell transplantation patients

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Abstract: The aim of this study is to investigate the relationship between the epidemiological and clinical profiles of patients before and after hematopoietic stem cell transplantation (HSCT) and the need for endodontic treatment. The subjects included 188 individuals enrolled in the dental care program for transplanted patients of the School of Dentistry, Federal University of Minas Gerais (Faculdade de Odontologia da Universidade Federal de Minas Gerais, FO-UFMG) from March 2011 through March 2016. The patients were subjected to an HSCT conditioning dental regimen based on a thorough clinical and radiographic evaluation. Intraoral periapical and bite-wing X-rays were obtained, and after evaluation, specific dental treatment was planned and performed. The following demographic and clinical data were collected from the patients' medical records: age, gender, transplantation stage, primary disease, transplant type, medication used, complete blood count at the time of visit, and need for endodontic treatment. The Kolmogorov-Smirnov and the chi-square tests were used. Leukemia (31.3%) and multiple myeloma (17.9%) were the most prevalent primary diseases. Most patients were subjected to allogeneic-related transplantation (83.6%). Most patients exhibited platelet counts and hemoglobin concentrations below the reference values in the pre-transplantation stage, while the neutrophil and platelet counts and the hemoglobin levels were within the reference ranges in the post-transplantation stage. The proportions of individuals requiring endodontic treatment were similar between the pre- and post-transplantation groups: 24.3% and 24.7%, respectively. The systemic conditions of the patients referred for dental treatment were compromised.

Keywords: Immunosuppression; Hematopoietic stem cell transplantation; Endodontics.

Introduction

Dental caries and periapical disease are the two most common pathological conditions that affect the mouth; both might be associated with severe systemic complications.[1] Bacterial contamination of the dental pulp might cause its destruction and the consequent development of periapical lesions,[2] which represent a potential site for dissemination

of infection. More than 80% of patients subjected to hematopoietic stem cell transplantation (HSCT) develop at least one episode of infection, and 40% of deaths are due to complications from infection alone or following graft rejection. Approximately 55% of post-transplantation infections are caused by bacteria or viruses, and 15% to 30% are caused by fungi.[3] The occurrence of infection depends on the patient's immune response and degree of immunosuppression.[4]

HSCT is widely performed for the treatment of malignant blood disorders, including acute and chronic leukemia, aplastic anemia, myelodysplastic syndromes, severe combined immunodeficiency, lymphoma and some solid tumors, such as breast cancer. The prevalence of oral complications among autologous and allogeneic HSCT recipients is high, the most common being mucositis, xerostomia, palate disorders, graft versus host disease (GVHD) and infection. Complications are associated with a substantial increase in morbidity, with significant impairment of the patient´s quality of life even many years after transplantation.[5] Complications derived from root canal infections might occur at any stage of the transplantation process and can cause significant problems, such as systemic infection or other disorders, which increase the cost and mortality rate associated with transplantation.[6] While in autologous HSCT transplantation most of these problems become minimized six months after the procedure; patients subjected to allogeneic transplantation might subsequently develop GVHD-related complications.[5]

Prevention of systemic complications demands achieving stabilization or elimination of oral infection before the onset of transplantation or myelosuppressive therapy.[6] Additionally, the possible late consequences of total body irradiation and high-dose chemotherapy in immunosuppressed patients are a cause of much concern.[7]

Global care of patients subjected to HSCT also includes routine dental assessments within a multi-professional context. The aim of the present study was to investigate the relationship between the epidemiological and clinical profiles of patients before and after HSCT and the need for endodontic treatment.

Methodology

Patients

The study population consisted of individuals enrolled in the dental care program for transplanted patients of the School of Dentistry, Federal University of Minas Gerais (Faculdade de Odontologia da Universidade Federal de Minas Gerais, FO-UFMG). These patients were referred by the HSCT service, Clinical Hospital, UFMG (Hospital de Clínicas, HC-UFMG), from March 2011 through March 2016. Patients whose medical records could not be retrieved were excluded from the study. The patients were subjected to an HSCT conditioning dental regimen based on a specific protocol applied at the HSCT Unit, HC-UFMG. The conditioning dental regimen consisted of a thorough clinical and radiographic evaluation of the patient. Intraoral periapical and bite-wing X-rays and panoramic radiographs were obtained. The criteria adopted to determine the need for endodontic treatment were based on clinical and radiographic analyses, along with pulp vitality tests. After further evaluation, specific dental treatment was planned and performed while considering the time available before transplantation and the patient's systemic condition. The patients also received dental care after transplantation to maintain their oral health.

Personal data and clinical characteristics

Demographic and clinical data were collected from the patients' medical records and included the following: age, gender, transplantation stage, primary disease, transplant type, medication in use, complete blood count at the time of visit, need for endodontic treatment and number of endodontic treatments performed during the conditioning dental regimen. Missing or incomplete data were registered as "Missing/omitted data".

Statistical analysis

In the descriptive analysis, the quantitative variables are expressed as means and standard deviations. The Kolmogorov-Smirnov test was used to investigate whether the data had a normal distribution, and the chi-square test was employed to establish whether there were statistically significant associations between

variables. Statistical significance was defined as a p-value of 0.05 or less.

Ethics issues

The present study complied with the ethics requirements described in Health Ministry Resolution no. 196/96 and was approved by the research ethics committee of UFMG (CAAE: 54829414.7.0000.5149/ ruling:1.569.493; CAAAE: Certificado de Apresentação para Apreciação Ética/Certificate of Presentation for Ethical Appraisal).

Results

Patients' characteristics

A total of 188 individuals enrolled in the Program of Dental Care for Transplanted Patients, FO-UFMG, from March 2011 through March 2016, were included in the study; 60.6% were male, and 39.4% were female. The participants' ages varied from 06 to 69 years old. A total of 103 patients were in the pre-transplantation stage, and 85 were in the post-transplantation stage. Most were allogeneic-related transplants (83.6%), while allogeneic-unrelated transplants corresponded to 9.6% and autologous transplants to 6.8% (Table 1). There was no statistically significant association between gender and donor type (p = 0.57). The median time from diagnosis to transplantation was 12 months.

Table 1. Description of the patients' characteristics.

Variable	Frequency	%
Patients		
Before HSCT	103	54.8
After HSCT	85	45.2
Total	188	100
Gender		
Male	114	60.6
Female	74	39.4
Total	188	100
Transplant type		
Allogeneic related	61	83.6
Allogeneic unrelated	7	9.6
Autologous	5	6.8
Total	73	100
Missing	12	-

HSCT: hematopoietic stem cell transplantation.

Need for endodontic treatment

The frequencies of endodontic treatment were 24.3% and 24.7% before and after HSCT, respectively, corresponding to 23.2% of the targeted sample. No statistically significant difference was observed between the groups (p > 0.05). Most patients required endodontic treatment for more than one tooth.

Systemic disease that led to HSCT

Leukemia corresponded to 31.3% of the cases and was the predominant condition among individuals enrolled in the Program of Dental Care for Transplanted Patients, FO-UFMG, both before and after HSCT. Acute myeloid leukemia (AML) was exhibited by 15.7% of the sample, chronic myeloid leukemia (CML) by 12.4%, acute lymphocytic leukemia (ALL) by 2.7% and chronic lymphocytic leukemia (CLL) by 0.5%. Approximately 15.1% of the patients had bone marrow aplasia, and 17.9% had multiple myeloma (Table 2).

Leukemia was also the main primary disease among transplanted individuals enrolled in the Program of Dental Care for Transplanted Patients, FO-UFMG, 44.1%, with 22.6% cases of AML, 16.7% cases of CML, and 4.8% cases of ALL. Approximately 22.6% of the patients had bone marrow aplasia and 8.3% had myelodysplastic syndromes as the primary disorder.

Table 2. Percentages of systemic diseases exhibited by individuals enrolled in the Program of Dental Care for Transplanted Patients, FO-UFMG.

Primary disease	Patient		
	Global	Before HSCT	After HSCT
Leukemia	31.3%	20.8%	44.1%
CML	12.4%	8.9%	16.7%
AML	15.7%	9.9%	22.6%
ALL	2.7%	1.0%	4.8%
CLL	0.5%	1.0%	0.0%
Multiple myeloma	17.9%	27.7%	6.0%
Myelodysplastic syndrome	4.9%	2.0%	8.3%
Bone marrow aplasia	15.1%	8.9%	22.6%
Non-Hodgkin's lymphoma	4.3%	5.0%	3.6%
Hodgkin's lymphoma	4.3%	5.9%	2.4%
Other	22.2%	29.7%	13.1%
Total	100%	100%	100%

HSCT: hematopoietic stem cell transplantation; CML: chronic myeloid leukemia; AML: Acute myeloid leukemia ; ALL: acute lymphocytic leukemia ; CLL: chronic lymphocytic leukemia.

Hematologic analysis before and after HSCT

In most patients (56.5%), the neutrophil count was within the reference range before HSCT. However, the platelet count and hemoglobin concentration were below the reference values in 54.3% and 63% of the sample, respectively. There were no statistically significant relationships between gender ($p > 0.05$) and neutrophil and platelet counts and hemoglobin concentration.

In most individuals in the Program of Dental Care for Transplanted Patients (FO-UFMG), after HSCT, the neutrophil and platelet counts and hemoglobin concentration were within the reference ranges, *i.e.*, 64.4%, 70.4% and 76.1% of the sample, respectively. There were no statistically significant relationships between gender and neutrophil and platelet counts and hemoglobin concentration ($p > 0.05$) (Figure 1).

Prescribed medications and percentages of patients using medication before and after HSCT

Most of the analyzed patients (75.5%) used some medication.

After HSCT, 52.9% of the patients used immunosuppressive agents, and 51.8% of them used antibiotics, with cyclosporine and Bactrim® used as the first choices, respectively.

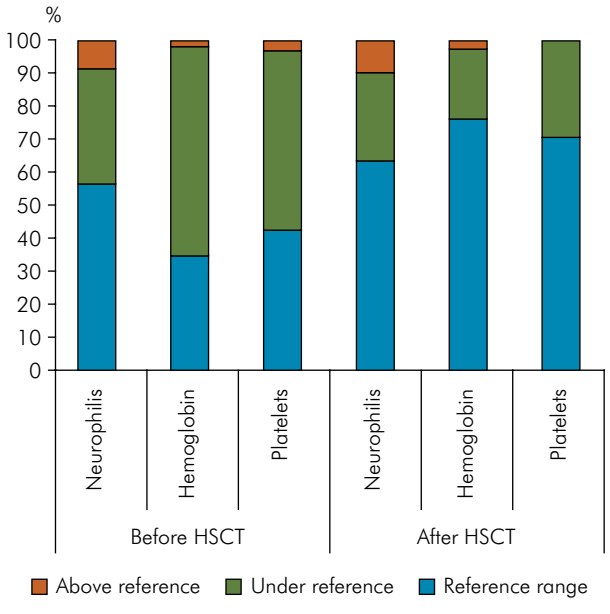

Figure 1. Complete blood results of individuals enrolled in the Program of Dental Care for Transplanted Patients, FO-UFMG.

A total of 23.3% of the patients in the pre-transplantation stage used anticancer drugs, and 13.6% used bisphosphonate. Antihypertensive drugs were continuously used by 20.4% and 25.9% of the patients before and after HSCT, respectively. Steroids were used by 22.3% and 18.8% of the pre- and post-transplantation patients, respectively (Table 3).

Table 3. Percentages of medications used by individuals enrolled in the Program of Dental Care for Transplanted Patients, FO-UFMG.

Medication	Patients (%)		
	Global	Before HSCT	After HSCT
In use	75.5	75.7	75.3
Immunosuppressant	23.9	0.0	52.9
Tacrolimus	5.3	0.0	11.8
Cyclosporine	18.6	0.0	41.2
Steroids	20.7	22.3	18.8
Opioid analgesics	4.8	6.8	2.4
Antibiotics	41.0	32	51.8
Bactrim®	36.8	27.2	48.2
Penicillin	4.8	3.9	5.9
Clindamycin	0.5	0.0	1.2
Cephalosporin	0.5	1.0	0.0
Tetracycline	0.5	1.0	0.0
Norfloxacin	2.0	1.0	3.5
Antifungal	1.0	1.9	0.0
Acyclovir	1.0	1.9	0.0
Antihypertensives	22.9	20.4	25.9
Nifedipine/Amlodipine	8.5	1.9	16.5
Atenolol/Propranolol/Metoprolol	5.3	5.8	4.7
Losartan	6.4	7.8	4.7
Captopril/Enalapril	6.4	5.8	7.1
Antineoplastic	13.8	23.3	2.4
Cyclophosphamide	7.0	11.7	1.2
Hydroxyurea	2.0	2.9	1.2
Dasatinib/Sprycel®	2.0	3.9	0.0
Imatinib	1.5	2.9	0.0
Other	1.5	3.9	0.0
Bisphosphonate	9.6	13.6	4.7
Diuretics	4.8	6.8	2.4
Hydrochlorothiazide	2.0	3.9	0.0
Furosemide	1.5	2.9	0.0
Spironolactone	1.5	1.0	2.4
Antacid	35.7	22.3	51.8
Hormone supplements	5.3	1.0	10.6
Vitamin complex	3.7	4.9	2.4
Anticoagulant	9.6	16.5	1.2
Antidepressant	7.0	7.8	5.9

HSCT: hematopoietic stem cell transplantation.

Discussion

Apical periodontitis is an inflammatory disease that affects the tissues surrounding the apical portion of the dental root and is primarily caused by microorganisms infecting the root canal. It represents a potential site for dissemination of infection.[2] Root canal infections among autologous and allogeneic HSCT recipients can be associated with a substantial increase in morbidity, with significant impairment of the patient´s quality of life.[5] This study evaluated the need for endodontic treatment in patients before and after HSCT by analyzing their systemic data and correlating these data with the risk of persistent endodontic infections among HSCT recipients.

Autologous HSCT is used for the treatment of malignant conditions, such as multiple myeloma and Hodgkin's and non-Hodgkin's lymphoma. Allogeneic transplantation is often the first-choice treatment for several malignant blood diseases, such as AML, CML, ALL, CLL and severe aplastic anemia. In the present study, almost all of the participants with the above-mentioned conditions were subjected to allogeneic HSCT (83.6%). In addition, a retrospective cohort study conducted in Brazil found that most (72%) among 731 patients subjected to HSCT for the treatment of AML received allogeneic transplants.[8] However, these findings disagree with other reports in the literature. One study performed in Spain found that among 228 patients subjected to HSCT, 55.7% received autologous transplants and 44.3% received allogeneic transplants.[9] Another study analyzed data from 1516 transplant centers in 75 countries and demonstrated that the largest proportion of patients received autologous transplants (58%).[10] The mortality rate is lower for autologous compared to allogeneic transplantation, with the 5-year mortality associated with allogeneic transplantation varying from 24% to 34%.[11,12]

Interestingly, most of the patients analyzed in the present study were male. This finding disagrees with findings corresponding to individuals infected with human immunodeficiency virus (HIV) and subjected to highly active antiretroviral therapy (HAART) and patients with aplastic anemia, most of whom are female (57.2% and 56.5%, respectively).[13,14] The median time from diagnosis to transplantation was rather long, approximately 12 months. In one retrospective study conducted in Porto Alegre, Rio Grande do Sul (RS), Brazil, in 2013,[15] the time to transplantation was less than 12 months for the majority (62.9%) of patients (n = 278) subjected to allogeneic HSCT.

Leukemia was the main reason for the analyzed population to be included in the study groups, i.e., before or after HSCT. In other studies, leukemia was also the main primary malignant disease that led to transplantation.[9,10,15,16] The fact that only 6% of the 84 patients subjected to transplantation had multiple myeloma is noteworthy. The reason for such a low prevalence of this condition is that the odds of a cure are very low, and patients exhibit poor survival rates.[17,18] In contrast, another study reported a larger proportion of patients with multiple myeloma (20.15%) among 137 individuals subjected to HSCT.[19]

As a rule, patients subjected to HSCT exhibit pancytopenia before and immediately after transplantation and remain in a state of neutropenia for approximately 6 to 12 months after the procedure. Root canal infections might have serious consequences during this neutropenic period and can eventually compromise graft success.[20] The high risk of bacterial infection after HSCT is due to severe neutropenia and the damage to the body barriers caused by the conditioning regime.[21] In our study, only 56.5% of the patients in the pre-transplantation stage exhibited neutrophil counts within the reference range; this proportion was lower compared to the transplanted patients (63.4%). In addition, most of the patients in the pre-transplantation stage had platelet counts and hemoglobin concentrations below the reference values.

HSCT induces a state of immunosuppression, made even worse by various medications, as shown in the present study. Approximately 20.74% of the patients used steroids, which have strong effects on the distribution and function of neutrophils, monocytes and lymphocytes. In cancer patients, steroids seldom are the only class of immunosuppressive drugs prescribed; therefore, it is difficult to assess their impact on the immune system. The risk of infection is associated with the dose and duration of treatment, the degree of neutropenia and the use of immunosuppressive agents (https://www.nccn.org/professional/physician_gls/PDF/infections.pdf).

Prophylactic antibiotic therapy is commonly indicated after HSCT. In our study, 51.8% of the transplanted patients used antibiotics. The NCCN (National Comprehensive Cancer Network) guidelines classify cancer patients as at low, medium or high risk for infection based on factors such as primary disease, duration of neutropenia, first exposure to chemotherapy, degree of disease activity and intensity of immunosuppressive therapy. Antimicrobial prophylaxis should be considered for individuals at medium or high risk of infection. Fluoroquinolones (Bactrim®) are the antibiotics indicated to patients with chemotherapy-induced neutropenia and significantly reduce the incidence of infection with Gram-negative bacteria. Antibiotic prophylaxis against pneumococcal infection is indicated for patients with low immunoglobulin (Ig)G levels and chronic GVHD. Antibiotic prophylaxis must also be prescribed to patients vaccinated against pneumococcal disease and should last at least one year following HSCT.[22]

HSCT makes patients more susceptible to infection, as the oral cavity is a relevant source of pathogens likely to cause systemic disorders in this population.[5] It is believed that infections of oral origin occur in approximately 80% of cases.[11] Pulpal and periradicular diseases usually result from direct or indirect involvement of microorganisms present in the oral cavity.[23,24,25] Changes might occur in the oral microbiota before and after chemotherapy.[26] One cohort study found significant increases of oral colonization by opportunistic pathogens, such as *Enterococcus faecalis* and *Candida* spp., among individuals subjected to allogeneic transplantation.[27] Medically relevant microorganisms, such as *Pseudomonas aeruginosa*, *Staphylococcus aureus, Escherichia coli, Streptococcus sanguinis* and *Prevotella intermedia*[28,29,30,31] have been detected in infected root canal systems, which highlights the need for endodontic treatment, especially in the case of immunosuppressed patients, such as the patients analyzed in the present study.

Analyses of the need for endodontic treatment of a given population are difficult to find in the international literature;[13,14] the same applies to cases of patients subjected to or to being subjected to HSCT. In the present study, 23.2% of the patients required endodontic intervention. This rate seems quite high when compared to those found for Brazil as a whole within the context of the Health Ministry "SB Brasil" (Oral Health, Saúde Bucal – SB) program, which were 6.2% and 4.3% for the age ranges 15 to 19 and 35 to 44 years old, respectively. Rates varying from 1.8% to 13% were published for adolescents in Lithuania and Manhattan (USA), respectively.[32,33] The rates found in the present study are also somewhat higher than those obtained for individuals with sickle cell anemia (10.2%)[14] and HIV-seropositivity under HAART (14%),[13] which is fully consistent with the severe degree of immunosuppression exhibited by patients subjected to HSCT. Although HSCT is crucial for the improvement and survival of patients, infection after transplantation is a relevant cause of morbidity and mortality. Countless factors determine the success or failure of this type of systemic intervention.

Conclusion

The systemic conditions of the patients referred for dental treatment were compromised, especially in the pre-transplantation stage, and were associated with a high prevalence of the need for endodontic treatment. In the last instance, these findings show that when untreated, root canal infections will unequivocally compromise attempts at ensuring global health for this population of patients, along with HSCT itself. Finally, the present study incisively seeks to bring the need for consistent interdisciplinary analysis into debate in the various fields of knowledge to attain increasingly more satisfactory and substantial results in the attempt at ensuring global health to patients requiring stem cell transplantation.

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