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Common oral diseases in allogeneic haematopoietic stem cell transplantation (HSCT) recipients pre-HSCT

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Abstract

Objectives: The purpose of this study was to compare the prevalence of common oral diseases between allogeneic haematopoietic stem cell transplantation (HSCT) recipients and healthy controls.

Materials and methods: A total of 143 adult allogeneic HSCT recipients who were treated for haematological malignancies between 2008 and 2016 were included in the study. The HSCT recipients were age and sex matched with healthy controls. A dental examination was performed on the HSCT recipients prior to HSCT. Differences in stimulated saliva flow rate (SSFR), decayed, missing and filled teeth (DMFT) index, number of teeth, number of caries lesions, and measures of current or previous periodontitis (radiological attachment loss >3 mm or probing pocket depth ≥4 mm) between HSCT recipients and controls were examined.

Results: Stimulated saliva flow rate, DMFT index and the number of caries lesions were poorer in the HSCT recipients pre-HSCT compared to controls (all *P*-values <0.05). No statistically significant differences in the measures of current or previous periodontitis were observed.

Conclusions: Stimulated saliva flow rate was low and caries was common in HSCT recipients prior to HSCT. Efficient preventive strategies are important in order to maintain the oral health of these patients.

KEYWORDS

caries, DMFT, haematology, periodontitis, stem cell transplantation

1 | INTRODUCTION

Haematopoietic stem cell transplantation (HSCT) is a treatment used for patients with life-threatening diseases and disorders of the haematopoietic system. HSCT was found to be a curative treatment for some end-stage acute leukaemia patients over 60 years ago. The number of HSCTs increased in recent years, and the milestone of 1 million HSCTs was reached in 2012.[1-3]

Allogeneic HSCT involves an intensive conditioning regimen, that includes high-dose chemotherapy or reduced intensity therapy and, possibly, total body irritation (TBI). The aim of this regimen is the eradication of haematopoietic stem cells and immune system suppression. Haematopoietic multipotent stem cells are collected from a donor, and the cells are infused to re-establish haematopoietic functions.[1,3,4] Subsequent to improvements made in the transplantation procedures in terms of human leucocyte antigen-matching, the control of graft vs host reactions and the control of infectious complications, the number of long-term survivors has been constantly increasing.[5] Nevertheless, allogeneic HSCT remains associated with considerable acute and long-term comorbidities that also affect oral health.[6-8]

Tuomas Waltimo and Matti Mauramo equally contributed to this article.

Several studies investigated the associations of poor oral health with various systemic diseases and cancer development.[9-12] Poor oral health, especially periodontitis, may be associated with certain cancers in different tissues, including those of the mouth, pancreas, colorectum and lungs.[9,11,12] Studies also suggested a relationship between periodontitis and overall cancer mortality.[13,14] The evidence of associations between oral diseases and haematological malignancies is very limited. One study observed that, periodontitis was associated with non-Hodgkin's lymphoma.[15] Another study found an association between periodontitis and haematological cancers in men.[14]

Similar to the studies on the associations between oral diseases and haematological malignancies, descriptive studies focused on the oral health of patients with disorders of the haematopoietic system and/or upcoming HSCT are also scarce. The vast majority of studies on HSCT recipients have focused on post-HSCT symptoms related to GvHD, mucositis and hyposalivation. We have also participated in these studies and showed that HSCT recipients suffer from hyposalivation, especially 6 months after transplantation, and even years post-HSCT.[6,7,16] Hyposalivation is a known risk factor for oral diseases and may predispose patients to caries in particular.[17] In line with this assumption, there is evidence suggesting poor oral health and high dental treatment needs of HSCT recipients pre-HSCT.[18-20] Another very recent study, with a limited number of subjects, observed that patients with newly diagnosed acute leukaemia already have poorer oral health, in terms of caries and periodontitis, prior to any treatments compared with healthy controls.[21]

The current study examined the oral health of allogeneic HSCT recipients pre-HSCT. The hypothesis was that allogeneic HSCT recipients have poorer oral health than healthy controls prior to transplantation.

2 | PATIENTS AND METHODS

The Ethikkommision Nordwest- und Zentralschweiz (EKNZ), Switzerland approved this study (Ref. Nr EKNZ:311-10) which was performed in accordance with the Declaration of Helsinki.

Adult allogeneic HSCT recipients who were treated in the Department of Hematology, University Hospital Basel, Switzerland, for haematological malignancies between 2008 and 2016, with complete medical and oral health status, were initially included in this prospective cross-sectional study. The study excluded patients whose medical or dental status was not complete or who could not be sex and age matched with a healthy control (Figure 1). The HSCT recipients included in this study may have received anticancer therapies using standard chemotherapy schemas even years before proceeding to HSCT and had received conditioning chemotherapy with or without TBI, as previously described.[6]

The healthy control group was recruited from the Swiss Bone Marrow Donor Registry of The Blood Transfusion Service SRC Basel, Switzerland.[22] The final study groups were formed via blinded matching of the HSCT recipients with controls by age and sex.

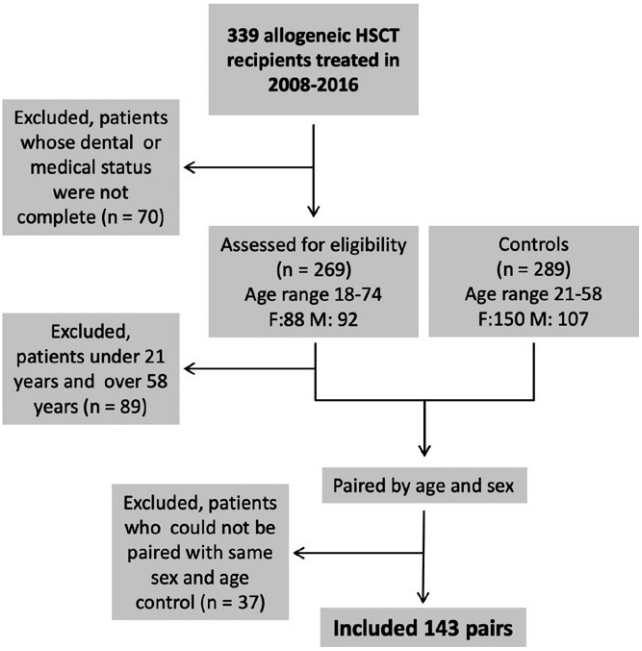

FIGURE 1 Flow diagram showing patient selection for the study

The dental examinations of the patients were carried out by experienced dental practitioners in the Department of Preventive Dentistry and Oral Microbiology, School of Dental Medicine, University of Basel, immediately prior to HSCT (most often a few days prior). A thorough clinical oral examination included a panoramic radiograph and decayed, missing and filled teeth (DMFT) index calculation according to the WHO.[23] Acute oral infections were diagnosed if (a) fistula, (b) symptomatic periapical process, (c) symptomatic deep caries, (d) wound/ulcer or (e) acute periodontal abscess were observed.

Stimulated saliva flow rate (SSFR) was measured at the beginning of the dental examination and before any clinical assessments. SSFR was collected by chewing a neutral paraffin wax. An individually packed, commercially available, neutral piece of paraffin wax (0.9 g/wax; Orion Diagnostica, Espoo, Finland) was chewed for 1 minute while swallowing saliva. Chewing was continued for 5 minutes, and generated saliva was collected. SSFR measurements of ≤0.7 mL/min were defined as hyposalivation and <0.3 mL/min as severe hyposalivation.[17] All relevant medical data, including diagnosis and conditioning-related information, were collected from medical records.

To avoid bacteraemia and to shorten the time needed to perform dental examinations of the severely ill HSCT recipients, ongoing or treated periodontitis was assessed from panoramic radiographs. Periodontitis was determined according to Pepelassi and Diamanti-Kipioti, to be present if radiological attachment loss (RAL), for example, the distance between the cementoenamel junction (CEJ) and the alveolar bone crest was observed to be >3 mm.[24]

The oral health of the healthy control group was similarly examined by the same dental practitioners. Panoramic radiographs were not taken of the healthy control group, but a detailed periodontal

TABLE 1 Descriptives of the study subjects

	Allogeneic HSCT recipients (143)
Age	
Mean; range(y)	44.8 (21-58)
Sex	
Female	73
Male	70
Diagnosis (n; %)	
AML	49 (34.3)
MDS	10 (7.0)
ALL	29 (20.3)
CML	5 (3.5)
CLL	8 (5.6)
PCD	10 (7.0)
MPN	8 (5.6)
MH	3 (2.1)
NHL	18 (12.6)
Other	3 (2.1)
Karnofsky	
Mean; range	92.4 (40-100)
Ablative conditioning (n; %)	
Yes	122 (85.3)
No	21 (19.0)
TBI (n; %)	
Yes	61 (42.7)
No	77 (53.8)
n.app	5 (3.5)

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; CLL, chronic lymphocytic leukaemia; CML, chronic myeloid leukaemia; MDS, myelodysplastic syndrome; MH, Hodgkin's lymphoma; MPN, myeloproliferative neoplasm; NHL, non-Hodgking's lymphoma; PCD, plasma cell dyscrasia.

examination, including pocket depth measurements, was conducted. Periodontitis was diagnosed to be present if either ≥2 interproximal sites with clinical attachment loss (CAL) ≥3 mm and ≥2 interproximal sites with probing depth (PD) ≥4 mm or ≥1 interproximal site with PD ≥5 mm were observed.[25]

2.1 | Statistics

The means and standard deviation of the oral health parameters, including SSFR, DMFT index, number of teeth, number of caries lesions and the frequency of periodontitis, were calculated and compared between allogeneic HSCT recipients and controls. The Pearson Chi-square, *t* test and Mann-Whitney *U* test were used to determine statistical significance. A *P*-value <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS software, version 23.

3 | RESULTS

3.1 | Study population

A total of 143 of the 339 adult allogeneic HSCT recipients were ultimately included in this study after age- and sex-matching with healthy controls (Figure 1). The mean age of both study groups (HSCT recipients and controls) was 44.8 years (21-58), with 70 male and 73 female subjects per group. Ninety-one (63.6%) of the HSCT recipients had been diagnosed with their haematological malignancy within 1 year, 40 (28.0%) recipients were diagnosed within 1-5 years, and 12 (8.4%) recipients were diagnosed more than 5 years before the pre-HSCT dental check-up. The descriptive statistics and diagnoses of the HSCT recipients are presented in Table 1.

3.2 | Stimulated salivary flow rates

The pre-HSCT SSFRs (n = 120) of the HSCT recipients were significantly lower (mean: 1.1 ± 0.7 mL/min) compared to the SSFRs of the healthy controls (1.4 ± 0.7 mL/min; $P = 0.0015$).

3.3 | Cariological status

The number of caries lesions was significantly higher in HSCT recipients pre-HSCT (mean ± SD: 0.9 ± 1.6) compared to controls (mean ± SD: 0.4 ± 1.0; $P = 0.002$). Similarly, the DMFT index was significantly higher compared with controls ($P = 0.016$). No statistically significant difference in the number of teeth was observed (Table 2).

3.4 | Periodontitis

Periodontitis was present in 53.8% of HSCT recipients and 49.0% of controls. The difference was not statistically significant. The mean RAL of the HSCT recipients was 4.8 mm ± SD: 2.8 mm.

3.5 | Acute infections

Acute symptomatic infections were observed in nine HSCT recipients (6.3%) and none of the controls. One patient had a fistula, two patients had a symptomatic periapical process, four patients had symptomatic caries and two patients had other acute infections.

4 | DISCUSSION

The present study examined the oral health of HSCT recipients pre-HSCT compared with a healthy age- and sex-matched control group. Oral health parameters, including SSFR, DMFT index and number of caries lesions, were statistically significantly poorer in HSCT recipients compared to the controls in the present study.

TABLE 2 Comparisons of DMFT index, number of teeth, number of caries lesions, and presence of periodontitis between HSCT recipients and controls

	Mean (±SD)	Yes (%)	No (%)	*P*-value
Allogeneic HSCT recipients				
DMFT index	16.8 (7.2)			0.016
Number of teeth	26.2 (5.7)			0.222
Number of caries lesion	0.9 (1.6)			0.002
Periodontitis (n; %)		77 (53.8)	66 (46.2)	0.408
Controls				
DMFT index	14.7 (6.5)			
Number of teeth	27.8 (2.5)			
Number of caries lesion	0.4 (1.0)			
Periodontitis (n; %)		70 (49.0)	73 (51.0)	

Previous studies focusing on oral diseases of HSCT recipients pre-HSCT are sparse, and the results are somewhat inconsistent. Similar to our results, a high prevalence of oral diseases was observed in a study by Durey et al (2009), as 93.6% of 94 subjects had some oral disease or a need for dental treatment pre-HSCT and in a study by Elad et al (2003), the prevalence of decayed teeth was 50% and need for scaling and oral hygiene instruction was 47.8% in 46 subjects pre-HSCT.[18,20] However, another study reported no differences in caries parameters of HSCT recipients pre-HSCT compared with a randomly selected registry-based population consisting of a similarly aged group.[26] Busjan et al[21] found that 39 patients with newly diagnosed acute leukaemia already had poorer oral health, including caries and periodontitis, prior to any treatments compared with a healthy control group. These intriguing findings suggest that the preceding therapies do not completely explain the poor oral health of HSCT recipients.

One third (36.4%) of the HSCT recipients in our study were diagnosed with their haematological malignancies over 1 year before the pre-HSCT dental check-up. Therefore, the likelihood that the preceding anticancer therapies also affected oral health is high among these recipients. HSCT recipients commonly receive intensive conditioning chemotherapy, with or without TBI, prior to HSCT.[4] Chemotherapy and the conditioning elicit oral morbidity, particularly hyposalivation.[6-8,17,27] The present study is also consistent with, and further confirms, our previous results, in which SSFR was lower pre-HSCT compared to a control group.[6,7,16] Saliva protects against oral diseases, and the hyposalivation observed in this study may markedly contribute to oral comorbidities.[17]

We did not have information on the dental treatment history of the HSCT recipients prior to our examination. Therefore, the patients may have had dental care, more than usual, between their initial diagnosis and HSCT. This treatment could explain the difference in DMFT index. However, and contrary to this assumption, the number of caries was higher in the HSCT recipients compared to the controls. One limitation of this study is that information on preceding dental treatments was not available. Further studies are needed, particularly to investigate whether hyposalivation is already more common in patients with haematological disorders at the time of diagnosis.

Poor oral health, especially periodontitis and tooth loss, was linked to several systemic diseases, cancers and increased mortality.[9-12,15] However, there is little evidence suggesting poor oral health as a risk factor for haematological malignancies.[14,15] The influence of periodontitis and other oral infections on treatment outcomes and oral and systemic morbidity in haematological malignancies was suggested already decades ago.[28-32] However, some studies of particular chronic oral infections found not association with severe systemic complications post-HSCT.[33,34] Therefore, the effects of periodontitis and poor oral health on treatment outcomes and oral comorbidity post-HSCT are not clear and warrant further study. However, periodontal diseases are, at least, common in HSCT recipients.[18,19,35] Our results on periodontitis are consistent with previous studies, as in the current study, a high prevalence of periodontitis, in terms of RAL >3 mm, was observed in 53.8% of these HSCT recipients.[18,19,35] Periodontitis was slightly more prevalent in HSCT recipients compared with the controls, but the result was not statistically significant. Owing to different measurement methods for the presence of periodontitis between HSCT recipients and controls, comparison must be treated with caution. Our examinations could not include all of the necessary oral parameters to assess periodontal and gingival diseases and oral hygiene due to the often poor health conditions, immunosuppression and time limitations. Periodontitis in HSCT recipients was determined via measuring radiological attachment loss from panoramic radiographs, and periodontitis in the controls was determined via measuring clinical attachment loss and probing pocket depth. According to the recommendation by Pepelassi and Diamanti-Kipioti, the bone level in panoramic radiographs was considered to be normal if the distance between CEJ and AC was up to 3 mm. Therefore, alveolar bone was considered lost, indicating periodontitis, if the CEJ-AC distance was >3 mm.[24] This RAL-based method was used for HSCT recipients, as in our previous study, to avoid bacteraemia and to keep the dental visits short, because these visits occurred just prior to transplantation.[26] This method may cause inaccuracies in the diagnosis of periodontitis, and it is possible

that early signs of periodontal disease and gingivitis were not noticed.[24,36] Furthermore, information on the activity of periodontal disease or past treatment of periodontitis could not be obtained with this method. This limitation should be considered a weakness of the methodology, but this method was chosen to avoid harming the HSCT recipients.

The HSCT recipients were compared with a healthy control group that was recruited from the Swiss Bone Marrow Donor Registry. Bone marrow donors are often relatives of HSCT recipients, and the controls were age- and sex-matched with the recipients to enhance the comparability even further. In the limits of this study, oral health habits or lifestyle-related confounders were not available and could not be adjusted for in this study. However, the prevalence of smoking was somewhat lower among HSCT recipients compared with the controls (36% vs 41%). Due to the narrow age distribution (26-58 years) and female prevalence in the controls, the oldest HSCT recipients were excluded from the study (Figure 1). Younger subjects generally have fewer medications and other illnesses, and this removes some of the most relevant confounders and makes the study groups highly comparable. Further studies, with longitudinal follow-up, on the associations of biochemical, social and behavioural factors with oral health in HSCT recipients are warranted.

In conclusion, oral examinations pre-HSCT showed a high prevalence of oral disorders in HSCT recipients. These findings support the recommendations for an early dental check-up prior to HSCT to eliminate acute infection foci, prepare HSCT recipients, and, if possible, investigate the effects of oral disorders on post-HSCT complications.[29,37]

CONFLICT OF INTEREST

The authors state no conflict of interest.

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