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Longitudinal Assessment of Hematopoietic Stem Cell Transplantation and Hyposalivation

ABSTRACT

Hyposalivation is a common adverse effect of anti-neoplastic therapy of head and neck cancer, causing impaired quality of life and predisposition to oral infections. However, data on the effects of hematopoietic stem cell transplantation (HSCT) on salivary secretion are scarce. The present study determined stimulated whole-saliva flow rates in HSCT recipients in comparison with a healthy control group. Stimulated whole-saliva flow rates of 228 allogeneic HSCT recipients (134 males, 94 females; mean age, 43 yrs) were examined pre-HSCT and 6, 12, and 24 months post-HSCT. Healthy individuals (n = 144; 69 males, 75 females; mean age, 46 yrs) served as the control group. Stimulated saliva flow rates (mL/min) were measured and analyzed statistically, stratifying for hematological diagnoses and conditioning therapy. Hyposalivation (≤ 0.7 mL/min) was found in 40% ($p < 0.00001$), 53% ($p < 0.00001$), 31% ($p < 0.01$), and 26% (n.s.) of the recipients pre-HSCT, and 6, 12, and 24 months post-HSCT, respectively, whereas 16% of the control individuals had hyposalivation. Severe hyposalivation (≤ 0.3 mL/min) was found in 11%, 18%, 4%, and 4% of the recipients pre-HSCT, and 6, 12, and 24 months post-HSCT, respectively. Additionally, conditioning regimen and sex had an impact on saliva flow. In conclusion, hyposalivation was observed to be a common but generally reversible complication among HSCT recipients.

KEY WORDS: hematopoietic stem cell transplantation, total body irradiation, leukemia, hyposalivation, saliva, conditioning regimen.

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INTRODUCTION

Anti-neoplastic chemotherapy and head and neck radiotherapy can cause considerable acute and long-term adverse effects in the oral cavity (Hong *et al*., 2010). Particularly, irradiation-induced hyposalivation (stimulated saliva flow ≤ 0.7 mL/min) is a common adverse effect of radiotherapy in head and neck malignancies (Sreebny, 2000; Jensen *et al*., 2010; Vissink *et al*., 2010). Since saliva has several protective functions, hyposalivation commonly predisposes to oral diseases including caries, periodontal problems, and yeast infections (Sreebny, 2000; Hong *et al*., 2010; Lalla *et al*., 2010). Additionally, hyposalivation and xerostomia (subjective dry mouth) impair quality of life by causing loss of taste, eating and speaking problems, dysphagia, and impaired sleep quality (Jensen *et al*., 2010).

Hematopoietic stem cell transplantation (HSCT) is widely used as a potentially curative treatment for several malignant and non-malignant hematological diseases (Copelan, 2006). During the past decade, the overall survival rate of HSCT recipients has improved, and the numbers of long-term survivors are increasing (Gratwohl *et al*., 2010). Nevertheless, HSCT remains associated with considerable acute and long-term co-morbidity and mortality (Gratwohl *et al*., 2010). The therapy includes conditioning chemotherapy with or without total body irradiation (TBI) followed by HSCT. The objective of myelo-ablative conditioning is to eradicate malignant cells and induce immunosuppression that permits engraftment (Epstein *et al*., 2009). This conditioning potentially affects salivary glands. Also, management of co-morbidity in patients undergoing HSCT may require a broad repertoire of agents, including opioids, immunosuppressive substances, corticosteroids, and antimicrobials, some of which may contribute to hyposalivation (Sreebny, 2000; Epstein *et al*., 2009). Furthermore, allogeneic HSCT may also be accompanied by graft-*versus*-host disease (GVHD), which can directly compromise salivary gland function (Nagler *et al*., 1996). Despite these factors' potentially affecting salivary gland function, hyposalivation has not been prospectively studied in sufficient numbers of HSCT recipients, and studies focusing on the oral health of this growing group of patients have been urged (Brand *et al*., 2009; Jensen *et al*., 2010). Thus, the present investigation focused on stimulated whole-saliva secretion of patients undergoing allogeneic HSCT.

STUDY GROUPS & METHODS

The current controlled prospective follow-up study was approved by the Ethics Committee, Basel, Switzerland. Two hundred twenty-eight HSCT recipients (Appendix Table) undergoing transplants in the Department of Hematology, University Hospital Basel, Switzerland, for their hematological malignancies between 2002 and 2009 were included in the study. Dental examinations were conducted by an experienced dentist (TW), and the first examination took place just prior to HSCT. Thus, the patients were already treated for the underlying disease according to standard chemotherapy protocols, as follows: Group for Research on Adult Acute Lymphoblastic Leukemia (GRALL), Berlin-Frankfurt-Münster (BFM), and hyperfractionated chemotherapy (Hyper-CVAD) protocols were used for acute lymphoblastic leukemia. Chemotherapy was administered according to Hemato-Oncology Foundation for Adults in Netherlands/Swiss Group for Clinical Cancer Research (HOVON/SAKK) study for acute myeloblastic leukemia. Chemotherapy schedules used for the treatment of non-Hodgkin's lymphoma included Cyclophosphamide/Doxorubicine/Vincristine/Prednisone (CHOP), Ifosfamid/Cisplatin/Etoposid (ICE), and Hyper-CVAD. Hodgkin's lymphoma was heavily treated before the transplantation, and the procedures used included Adriblastin/Bleomycin/Velbe/Dacarbazin (ABVD), standard and escalated Bleomycin/Etoposid/Adriamycin, Cyclophosphamid/Vincristin/Procarbazin/Prednison (BEACOPP), and radiotherapy. Myelodysplastic syndromes and myeloproliferative neoplasia represented a heterogeneous group of diseases with different therapeutic strategies, ranging from no therapy in myelodysplastic syndromes without leukemic blast cells increase to acute leukemia-like therapy schedules for those with increased leukemic blast cells. Myelo-ablative conditioning regimens administered immediately before transplantation included: Cyclophosphamide + TBI (12 Gy) with or without VP16 or Cyclophosphamide + Busulfan or BEAM. Non-myelo-ablative conditioning included Cyclophosphamide alone and reduced-intensity regimens with Fludarabine + TBI 2 Gy, with or without thymoglobulin.

After HSCT, all patients were included in a prospective oral diseases prevention program, and follow-ups took place at 6, 12, and 24 mos after transplantation, with 109, 99, and 76 individuals, respectively. For the study, the patients were grouped: first, according to primary diagnoses; second, according to dose (Gy) of TBI—*i.e.*, no TBI, low-dose TBI (mean = 1.9), or high-dose TBI (mean = 11.5); and third, according to the preparative regimen (myelo-ablative or no myelo-ablative conditioning). Healthy volunteers (n = 140; 69 males, 75 females; mean age, 46 yrs; age range, 22-61 yrs) with no known medications served as controls. The controls were identified from the Swiss bone marrow donor register, and informed consent was obtained from each individual prior to saliva flow measurements during 2008-2010.

The stimulated whole-saliva flow rate (SWSFR) was measured in the HSCT recipients at each appointment pre-HSCT and 6, 12, and 24 mos post-HSCT. The SWSFR of the control group was measured once. The SWSFR was determined by having the participants chew a piece of commercially available, individually packed, neutral paraffin wax (0.9 g/wax; Orion Diagnostica, Espoo, Finland) for 1 min while swallowing the saliva, followed by a 5-min period of chewing a new piece of wax with all the saliva collected in a graduated (mL) test tube (Sarstedt, Nümbrecht, Germany). SWSFR of ≤ 0.7 mL/min was considered as hyposalivation and ≤ 0.3 mL/min as severe hyposalivation (Sreebny, 2000).

Statistical calculations and graphs were conducted with the publicly available R software (v2.12.1; R Development Core Team, 2010). Statistical significance was tested with two-tailed Fisher's Exact test; p value < 0.05 was considered as statistically significant.

RESULTS

Stimulated Whole-saliva Flow Rates

Hyposalivation (≤ 0.7 mL/min) was common among HSCT recipients (Fig. A, Table 1). Forty percent, 53%, 31%, and 26% of the patients suffered from hyposalivation (median SWSFR: 0.9, 0.6, 0.8, and 0.8 mL/min) pre-HSCT and 6, 12, and 24 mos post-HSCT, respectively. Compared with the control group (hyposalivation, 16%; median SWSFR, 1.3 mL/min), the differences were statistically significant at pre-HSCT ($p < 0.00001$) and 6 ($p < 0.00001$) and 12 ($p < 0.01$) mos post-HSCT, but not at 24 mos post-HSCT. Pre-HSCT, females demonstrated a higher prevalence of hyposalivation than males ($p < 0.01$). Thereafter, saliva flow in both sexes showed similar trends of higher prevalence of hyposalivation 6 mos post-HSCT and a gradual recovery up to 24 mos post-HSCT. However, among females, hyposalivation remained slightly more common and recovery was slower and less complete than in males (Figs. B, C). Age had no influence on hyposalivation (data not shown).

Severe hyposalivation was common, particularly 6 mos post-HSCT. SWSFR of ≤ 0.3 mL/min was found in 11%, 18%, 4%, and 4% of recipients pre-HSCT and 6, 12, and 24 mos after HSCT, respectively (Fig., Table 1). In the control group, only 2 (1%) out of 144 healthy individuals had a SWSFR of ≤ 0.3 mL/min. Severe hyposalivation (≤ 0.3 mL/min) seems to predict persistent hyposalivation (≤ 0.7 mL/min). Of those with severe hyposalivation 6 mos post-HSCT, 70% (n = 9) and 67% (n = 8) still suffered from hyposalivation 12 and 24 mos post-HSCT, respectively. These patients differed significantly from those with SWSFR of > 0.3 mL/min at 6 mos post-HSCT, among whom only 23% ($p < 0.01$) at 12 mos post-HSCT and 13% ($p < 0.001$) at 24 mos post-HSCT had hyposalivation.

Ninety-two patients (40%) died during the study period, most of them within 6 mos post-HSCT. Hyposalivation at pre-HSCT was significantly more common among the deceased patients (hyposalivation, 48%) compared with the survivors after the study period (hyposalivation, 34%; $p < 0.05$).

The Influence of Diagnoses on Saliva Flow Rates

The prevalence of hyposalivation did not differ significantly among leukemia diagnoses (data not shown; see diagnoses in Appendix Table). Because of a large variety of diagnoses and thus a small number of individuals within a diagnosis, the patients were also subdivided into broader diagnostic groups

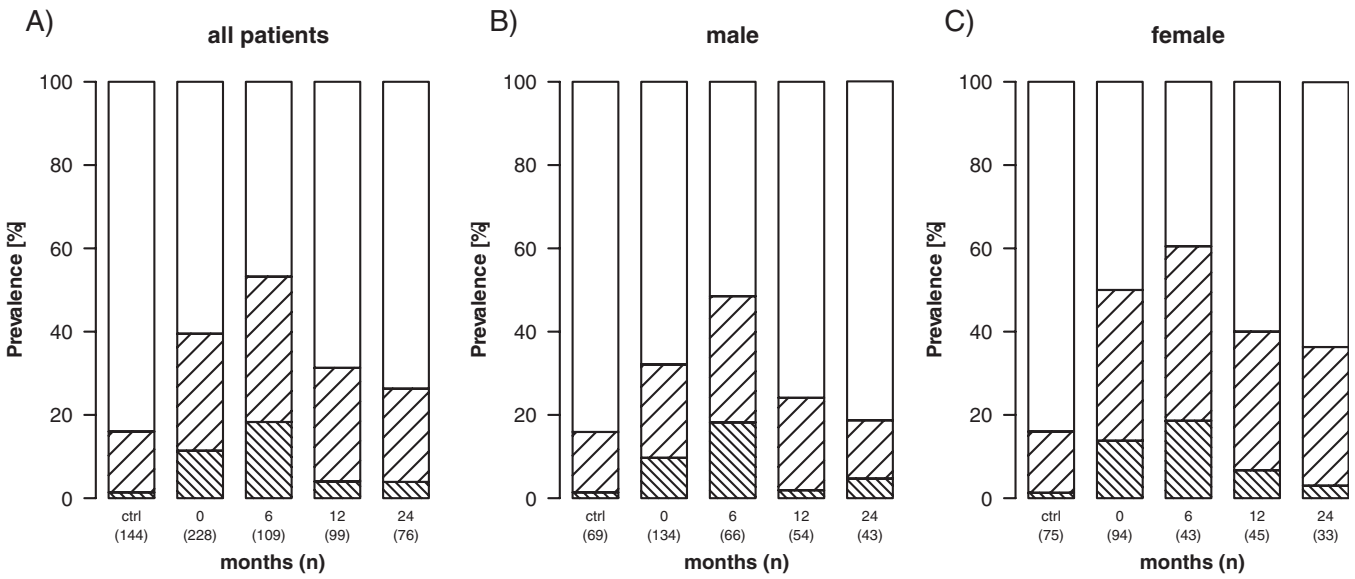

Figure. Prevalence of hyposalivation (stimulated whole saliva) in the control (ctrl) group (n = 144) and HSCT recipients (n = 229), and according to gender, 0 (pre-HSCT) and 6, 12, and 24 mos post-HSCT. White corresponds to prevalence of normal stimulated whole-saliva flow rate (SWSFR) defined as > 0.7 mL/min, light striping corresponds to hyposalivation (0.3 mL/min ≤ SWSFR ≤ 0.7 mL/min), and dense striping to severe hyposalivation (SFR ≤ 0.3 mL/min).

(Table 1). Pre-HSCT, hyposalivation (≤ 0.7 mL/min) was common in all groups, varying from 35% (median SWSFR 1.0 mL/min) in chronic leukemia to 50% (median SWSFR 0.7 mL/min) in lymphoma. In all groups, hyposalivation was most frequently encountered 6 mos post-HSCT (Table 1). During the observation period of 12 to 24 mos, recovery of saliva flow rates was moderate in the patients with acute leukemia and lymphoma, while the patients with plasma cell disorders recovered completely. However, those with chronic leukemia and myelodysplastic/proliferative syndromes showed no, or only a limited, recovery of salivary hypofunction (Table 1).

The Influence of Conditioning Therapy on Saliva Flow Rates

Patients with TBI showed an increased prevalence of hyposalivation at pre-HSCT and 6 mos post-HSCT, but not 12 or 24 mos following transplant (Table 1). Surprisingly, pre-HSCT hyposalivation was more common among the patients who received low-dose TBI (53%, $p < 0.05$) as part of their conditioning, but not among those treated with high-dose TBI (hyposalivation, 38%), in comparison with 'no TBI' patients (hyposalivation, 34%). In all TBI groups, hyposalivation was most common at 6 mos post-HSCT: 36% of the individuals without TBI, 57% with low-dose TBI, and 64% with high-dose TBI suffered from hyposalivation. However, at 6 mos post-HSCT, only the difference between high-dose and no TBI was statistically significant ($p < 0.05$). Recovery of the saliva flow rate was slower after TBI. Thus, 36% and 37% of the patients who had received either low-dose TBI or high-dose TBI and 18% of the no-TBI group suffered from hyposalivation 12 mos post-HSCT. However, in this regard, the differences between the groups at 12 and 24 mos post-HSCT were statistically non-significant (Table 1).

Patients treated with myelo-ablative conditioning demonstrated a tendency (n.s.) toward increasing prevalence of hyposalivation, particularly 6 mos post-HSCT (Table 1).

DISCUSSION

This study showed hyposalivation to be common among HSCT recipients. Pre-HSCT, the recipients already had an increased prevalence of hyposalivation compared with those in the control group, showing that the disease together with chemotherapy can induce hyposalivation. However, 6 mos after the conditioning and HSCT, hyposalivation was observed to be most prevalent, since over half (53%) of the individuals had a stimulated whole-saliva flow rate of ≤ 0.7 mL/min. Thereafter, a gradual recovery of the salivary hypofunction was observed, but one-third (31%) and one-fourth (26%) of the individuals still suffered from hyposalivation 12 and 24 mos post-HSCT, respectively. Additionally, persistent severe hyposalivation (≤ 0.3 mL/min) was found in some patients over the entire observation period of 2 yrs. Female sex and TBI increased the prevalence of hyposalivation. Furthermore, hyposalivation at pre-HSCT was associated with poorer survival of the recipients.

HSCT is a common treatment for hematological diseases such as leukemia (Copelan, 2006). However, this intensive therapy can cause considerable co-morbidity, and the therapies of co-morbidity may again require a broad repertoire of therapeutic agents (Dykewicz, 2001; Maertens *et al*., 2007; Jancel and Penzak, 2009). Malnutrition is common and often related to oral graft-*versus*-host disease (GVHD) (Imanguli *et al*., 2008; Hull *et al*., 2011). Furthermore, acute or chronic GVHD can cause oral mucositis,

Table 1. Saliva Flow Rates of Hematopoietic Stem Cell Transplantation Recipients

Study Groups/Variable	Pre-HSCT	6 mos Post-HSCT	12 mos Post-HSCT	24 mos Post-HSCT	Controls
All patients					
Median stimulated whole SFR (mL/min), (n)	0.9 (229)	0.6 (109)	0.8 (99)	0.8 (76)	1.3 (144)
Stimulated whole SFR range (mL/min)	0.0 - 3.1	0.1 - 2.4	0.2 - 2.4	0.2 - 2.1	0.2 - 3.6
Hyposalivation (≤ 0.7 mL/min) %, (n)	39% (90)	53% (58)	31% (31)	26% (20)	16% (23)
Hyposalivation (≤ 0.3 mL/min) %, (n)	11% (26)	18% (20)	4% (4)	4% (3)	1% (2)
Acute leukemia (AL)					
Median stimulated whole SFR (mL/min), (n)	0.9 (113)	0.5 (48)	0.8 (39)	0.8 (31)	
Stimulated whole SFR range (mL/min)	0.0 - 2.8	0.1 - 2.1	0.2 - 2.4	0.2 - 2.1	
Hyposalivation (≤ 0.7 mL/min) %, (n)	41% (46)	56% (27)	36% (14)	26% (8)	
Hyposalivation (≤ 0.3 mL/min) %, (n)	15% (16)	21% (10)	5% (2)	6% (2)	
Chronic leukemia (CL)					
Median stimulated whole SFR (mL/min), (n)	1.0 (31)	0.9 (16)	0.9 (20)	0.6 (14)	
Stimulated whole SFR range (mL/min)	0.2 - 3.1	0.3 - 2.4	0.2 - 2.4	0.3 - 1.4	
Hyposalivation (≤ 0.7 mL/min) %, (n)	35% (11)	38% (6)	25% (5)	36% (5)	
Hyposalivation (≤ 0.3 mL/min) %, (n)	10% (3)	6% (1)	5% (1)	0% (0)	
Lymphoma (LYMPH)					
Median stimulated whole SFR (mL/min), (n)	0.7 (26)	0.6 (19)	1.2 (15)	1.2 (12)	
Stimulated whole SFR range (mL/min)	0.2 - 1.8	0.2 - 1.8	0.5 - 2.0	0.4 - 1.9	
Hyposalivation (≤ 0.7 mL/min) %, (n)	50% (13)	63% (12)	20% (3)	17% (2)	
Hyposalivation (≤ 0.3 mL/min) %, (n)	8% (2)	26% (5)	0% (0)	0% (0)	
Plasma cell disorders (PC)					
Median stimulated whole SFR (mL/min), (n)	1.0 (11)	0.8 (6)	0.7 (4)	1.3 (5)	
Stimulated whole SFR range (mL/min)	0.2 - 2.1	0.2 - 1.2	0.4 - 1.0	1.3 - 1.3	
Hyposalivation (≤ 0.7 mL/min) %, (n)	36% (4)	50% (3)	25% (1)	0% (0)	
Hyposalivation (≤ 0.3 mL/min) %, (n)	9% (1)	17% (1)	0% (0)	0% (0)	
Myelodysplastic/Proliferative (MDP)					
Median stimulated whole SFR (mL/min), (n)	1.0 (38)	0.5 (15)	0.8 (17)	0.7 (14)	
Stimulated whole SFR range (mL/min)	0.2 - 2.8	0.2 - 1.3	0.2 - 1.5	0.3 - 1.4	
Hyposalivation (≤ 0.7 mL/min) %, (n)	37% (14)	60% (9)	35% (6)	36% (5)	
Hyposalivation (≤ 0.3 mL/min) %, (n)	8% (3)	20% (3)	6% (1)	7% (1)	
No TBI					
Median stimulated whole SFR (mL/min), (n)	1.0 (68)	0.8 (28)	0.9 (28)	0.7 (18)	
Stimulated whole SFR range (mL/min)	0.1 - 3.1	0.3 - 1.8	0.4 - 2.1	0.2 - 1.6	
Hyposalivation (≤ 0.7 mL/min) %, (n)	34% (23)	36% (10)	18% (5)	28% (5)	
Hyposalivation (≤ 0.3 mL/min) %, (n)	9% (5)	7% (2)	0% (0)	6% (1)	
Low-dose TBI					
Median stimulated whole SFR (mL/min), (n)	0.7 (49)	0.6 (23)	0.7 (25)	0.9 (19)	
Stimulated whole SFR range (mL/min)	0.2 - 2.8	0.2 - 2.4	0.4 - 2.4	0.3 - 1.9	
Hyposalivation (≤ 0.7 mL/min) %, (n)	53% (26)	57% (13)	36% (9)	26% (5)	
Hyposalivation (≤ 0.3 mL/min) %, (n)	12% (6)	17% (4)	0% (0)	5% (1)	
High-dose TBI					
Median stimulated whole SFR (mL/min), (n)	0.9 (91)	0.5 (47)	0.8 (35)	0.8 (31)	
Stimulated whole SFR range (mL/min)	0.0 - 2.8	0.1 - 2.1	0.2 - 2.4	0.3 - 2.1	
Hyposalivation (≤ 0.7 mL/min) %, (n)	38% (35)	64% (30)	37% (13)	26% (8)	
Hyposalivation (≤ 0.3 mL/min) %, (n)	13% (12)	23% (11)	9% (3)	3% (1)	
Non-myelo-ablative treatment					
Median stimulated whole SFR (mL/min), (n)	0.8 (52)	0.76 (28)	0.8 (25)	1.2 (19)	
Stimulated whole SFR range (mL/min)	0.2 - 2.8	0.2 - 2.4	0.4 - 2.0	0.4 - 1.9	
Hyposalivation (≤ 0.7 mL/min) %, (n)	40% (21)	43% (12)	28% (7)	11% (2)	
Hyposalivation (≤ 0.3 mL/min) %, (n)	10% (5)	7% (2)	0% (0)	0% (0)	
Myelo-ablative treatment					
Median stimulated whole SFR (mL/min), (n)	0.9 (176)	0.5 (81)	0.8 (74)	0.8 (57)	
Stimulated whole SFR range (mL/min)	0.0 - 3.1	0.1 - 2.1	0.2 - 2.4	0.2 - 2.1	
Hyposalivation (≤ 0.7 mL/min) %, (n)	39% (69)	57% (46)	32% (24)	32% (18)	
Hyposalivation (≤ 0.3 mL/min) %, (n)	12% (21)	22% (18)	5% (4)	5% (3)	

frequently associated with dry mouth, oral discomfort, and weight loss (Mohty *et al*., 2002; Lew and Smith, 2007). Since chemotherapy, head and neck irradiation, polypharmacy, and malnutrition are all well-known individual causes of hyposalivation, it was not surprising to observe a high prevalence of hyposalivation in HSCT recipients (Sreebny, 2000; Soini *et al*., 2006; Moore and Guggenheimer, 2008; Jensen *et al*., 2010). Despite its relevance, few studies on this oral complication of HSCT exist.

In line with the current study, Hull *et al*. (2011) observed that salivary gland hypofunction is the most common oral complication of HSCT 6 to 24 mos post-HSCT, with 34% of the recipients demonstrating some degree of hypofunction. In the present study, the progress of salivary secretion was also examined, and a general trend of improving saliva flow rates after HSCT was observed. However, 2 yrs post-HSCT, 26% of all recipients still suffered from hyposalivation and 4% from severe hyposalivation, but their mean saliva flow rate had nevertheless returned almost to normal and did not differ from the control levels. Similar results of transient hyposalivation as well as xerostomia have also been obtained in other studies of HSCT recipients (Jones *et al*., 1992; Chaushu *et al*., 1995; Buchali *et al*., 2000; Majhail *et al*., 2007). HSCT recipients conditioned only with lymph node irradiation and chemotherapy, or chemotherapy alone, have displayed a faster and more complete recovery of saliva flow 2 to 5 mos after engrafting compared with those conditioned with TBI (Chaushu *et al*., 1995; Dahllöf *et al*., 1997). These observations are consistent with those of the present study, suggesting that the conditioning regimen may have a crucial role in predisposing to hyposalivation post-HSCT. In the current study, TBI was observed to increase the prevalence of hyposalivation up to 6 mos post-HSCT. Thereafter, the hyposalivation rates did not differ according to TBI. Also, myelo-ablative conditioning was associated with a slightly increased prevalence of hyposalivation.

Besides the conditioning regimen, the degree of hyposalivation has been suggested to depend on individual patient characteristics, such as age and sex (Mira *et al*., 1981; Vissink *et al*., 2003). In agreement with this suggestion, females in the current study were observed to encounter hyposalivation significantly more often pre-HSCT, and their recovery was slower and less complete than that in males. In terms of age, the study population was relatively homogenic, most of the subjects being 40 to 50 yrs of age, and no association of age with hyposalivation was observed.

Because of the large variety of leukemia diagnoses, and thus relatively few individuals *per* diagnosis, no differences in the prevalence of hyposalivation could be demonstrated among the diagnoses. Similar to the current study, a study by Brand *et al*. (2009) on a small number of HSCT recipients (n = 48) also observed no associations between the diagnosis and subjective feeling of dry mouth (xerostomia). Although, the primary diagnoses were not associated with the saliva flow rates, for the broader diagnose groups an association was found. The individuals with chronic leukemia and myelodysplastic/proliferative syndromes showed no, or only a limited, recovery of salivary hypofunction. This persistent hyposalivation can partly be explained by the higher proportion of females in these diagnostic groups. However, the main reasons may still be the differences in the medications used for co-morbidity, or they may be due to GVHD. However, within the limits of the present study, the influence of these factors could not be analyzed, but this important topic remains for further investigations.

In the present study, only stimulated whole saliva was collected. The collection method was found to be simple and fast enough to suit medically compromised patients as well. However, unstimulated whole saliva, which may have a greater impact on the overall feeling of oral dryness (xerostomia), was not measured. Stimulated saliva is present in the mouth for up to 2 hrs of the day and is primarily associated with alimentary functions (Sreebny, 2000). Thus, decreased secretion of stimulated whole saliva has a great impact on oral functions, *i.e*., bolus formation, chewing, and swallowing. Additionally, stimulated saliva has protective functions enhancing oral clearance, buffering harmful oral acids, and aiding the remineralization of teeth. In this regard, transient reduction of stimulated saliva secretion can also significantly impair the quality of life by causing taste loss and eating and speaking problems, and can increase the risk of caries, erosion, and mucosal infections. These important oral complications of HSCT therapies require more research on oral and dental infections and the composition of saliva. Furthermore, patient-reported outcomes, particularly xerostomia, as well as altered taste, painful mucosa, and sensitive teeth need further assessment.

In conclusion, hyposalivation was observed to be a common but generally reversible complication within 24 mos after HSCT. Thus, the measurement of stimulated whole-saliva flow rates, individual analysis of the risk of oral diseases, and proper preventive measurement should be considered as essentials in the supportive care of HSCT recipients.

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