The effect of haematopoietic cell transplantation (HCT) on hyposalivation, xerostomia and caries progression

Marjolein Saartje Bulthuis

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Chapter 1

Introduction

Oral side effects are common following cancer therapies (1). One of these therapies, of which the oral side effects are only studied to a limited extent, is haematopoietic (stem) cell transplantation (HCT or HSCT).

Haematopoietic (stem) cell transplantation (HCT or HSCT)

HCT is an established treatment option for myeloid malignancies, lymphoid malignancies, and non-malignant haematological disorders (2, 3). During the past decades, clinical indications for HCT expanded and transplantation procedures improved. The number of yearly HCT continues to rise, resulting in more than 48.000 HCT treatments in Europe during 2019 (3). It is estimated that 1.5 million HCT were performed worldwide by 2019 (4). Slightly more autologous than allogeneic transplantations were reported.

In autologous HCT, stem cells from patients are harvested and stored, followed by a high dose (myeloablative) conditioning regimen, aiming to eradicate the disease (2). Thereafter, stem cells are reinfused to restore the immune system. In allogeneic HCT, stem cells are harvested from a donor. The donor cells play an important role in eradicating the disease by immunologic elimination of malignant stem cells, a phenomenon referred to as graft-versus-tumour effect. Because eradication of the disease does not depend solely on the conditioning regimen in allogeneic HCT recipients, reduced intensity (RIC) or even non-myeloablative (NMA) conditioning regimens might be sufficient to induce immunosuppression. NMA is the least aggressive category of conditioning regimens, while RIC is an intermediate category, which does not fit the definition for myeloablative or NMA (5). RIC and NMA regimens are, because of the reduced toxicity, also available in the older patient population (5).

A disadvantage of introducing stem cells from a donor is the development of graft versus host disease (GvHD): the condition where the donor-derived cells turn against the recipients healthy tissues (2). Chronic GvHD can persist for months to years and may affect multiple organ systems, commonly involving the oral cavity. Both the oral mucosa and the salivary glands might be affected, but these are clinically distinct and independent manifestations of GvHD (6). Preceding and following HCT, a lot of medications are prescribed (7, 8), for example to prevent infections while the immune system is modulated, to relieve symptoms or to prevent or treat GvHD. A brief summary of the main differences between autologous and allogeneic transplantations is listed below.

	Autologous HCT	Allogeneic HCT
stem cell source	recipient's own stem cells	donor stem cells
conditioning regimen	myeloablative	non-myeloablative *or* reduced intensity *or* myeloablative
	in general only chemotherapy	chemotherapy with or without total body irradiation (TBI)
conditioning aims to	eradicate cancer	eradicate cancer and induce immunosuppression that permits engraftment
HCT aims to	improve (disease free) survival	cure the disease and improve survival
main risk	mucositis	graft-versus-host-disease

Saliva and objective mouth dryness (hyposalivation)

Oral side effects are common following cancer treatments comprising chemotherapy and radiotherapy (1). One of these complications is salivary gland hypofunction (9). Following HCT, a decreasing salivary flow rate and compositional changes were reported several days and months post treatment (10). These changes are likely to be caused by the high dose conditioning regimen (11), the high medication intake (12) or the development of cGvHD (13). Even though some recovery in flow rates was seen during the first year post-HCT, flow rates remained lowered compared to healthy controls (7, 14).

Unstimulated whole saliva (UWS), present in the oral cavity in resting conditions, is a viscous fluid mainly produced by the submandibular glands (12). UWS can be easily collected by asking a patient to spit all saliva in a cup for several minutes without making effort to increase salivary flow, whereafter the amount of saliva is weighed and the flow rate is calculated in mL/min (15). The more watery stimulated whole saliva (SWS) is mainly produced by the parotid glands; the production of SWS is initiated by stimuli like chewing, taste and smell. To collect SWS, patients are asked to chew on a piece of (tasteless) chewing gum or paraffin wax for several minutes while saliva is collected. Both types of saliva are essential in maintaining oral health by protecting teeth and oropharyngeal mucosa and maintaining a balanced microbiota (12, 16).

It remains unclear how much saliva is enough to prevent oral problems. Several thresholds are reported in literature to establish a shortage of salivary flow, or hyposalivation. For UWS flow rates, thresholds vary between 0.1 and 0.25 mL/min, while for SWS flow rates, values between 0.1 and 0.7 mL/min are reported (17). As

part of the current thesis, we chose a threshold of 0.2 mL/min for hyposalivation of UWS, because this cut-off point was used before for salivary disfunction in relation to cGvHD (6). For SWS we chose the threshold of 0.7 mL/min.

Subjective mouth dryness (xerostomia)

Objectively measured reduced salivary flow rates might be related to subjective complaints of mouth dryness, or xerostomia (18). The lubricating salivary properties that are particularly attributed to mucins, are essential to moisten the oral mucosa (19). Xerostomia is a bothersome symptom, affecting quality of life negatively (9). The severity of xerostomia can be assessed using a single question or a questionnaire, for example the validated Xerostomia Inventory (20), or a Visual Analogue Scale (21). Furthermore, many questionnaires measuring quality of life after cancer therapy include a question on mouth dryness, like some additional modules of the European Organization for Research and Treatment of Cancer (e.g. EORTC QLQ-OH15) (22).

In healthy individuals, it was suggested that xerostomia occurred when UWS flow rate fell by 40-50% of its normal value (23). The prevalence of xerostomia in HCT recipients was high, even much higher than the prevalence of hyposalivation of UWS (24-26) and SWS (25). This finding suggests that xerostomia may also occur without objective evidence of salivary gland hypofunction. Other factors like oral mucosal moistness (27), which might be associated with mouth breathing (23) or changes in salivary composition (12), contribute to the feeling of mouth dryness as well. Furthermore, perceived stress, that is common in the population of HCT recipients (28), might increase xerostomia without affecting salivary flow significantly (29).

Tooth decay (dental caries)

Dental caries is a biofilm-mediated, diet modulated, multifactorial, non-communicable, dynamic disease resulting in net mineral loss of dental hard tissues (30). It is determined by biological, behavioural, psychosocial, and environmental factors. As a consequence of this process, a caries lesion develops. Caries diagnosis is done by the visual examination of tooth surfaces, eventually in combination with the assessment of dental radiographs. Based on this diagnosis, the dental practitioner might decide to restore the lesion, or to choose for a

preventive or preservative approach (31). Clinical lesion appearance can be classified with the help of the International Caries Detection and Assessment System (ICDAS), resulting in a score that is related to lesion depth and can be used to establish progression over time (32).

The remineralizing, buffering, antibacterial and cleansing salivary functions are essential in the inhibition of caries progression (19). A chronically lowered salivary flow rate was a strong risk indicator in the development dental caries (33). Furthermore, UWS flowrates <0.16mL/min might increase the risk for (root) caries (34). Therefore, HCT recipients might have an increased caries risk. In literature, several cases of allogeneic HCT recipients are shown, who developed cGvHD, and developed extensive dental caries (35). On the other hand, cohort studies could not establish a relation between salivary flow rate and development of caries one year post-HCT (36, 37). It remains unclear whether HCT recipients have an elevated need for dental treatments on the long term.

Obtaining sufficient knowledge on oral side effects from HCT is essential to provide information to HCT recipients. The increasing number of long-term HCT survivors will also visit dental practices, leading to the question whether additional preventive approaches are needed in the care for this population.

Aim of the thesis

The overall aim of this thesis is to describe salivary flow rate, xerostomia and caries progression over time in adult HCT recipients. Furthermore, the following two sub-questions are being addressed:

- Which risk indicators are important in the development of hyposalivation, xerostomia and caries progression?
- To which extent is (change in) salivary flow rate associated with xerostomia and caries progression?

The outline of the thesis

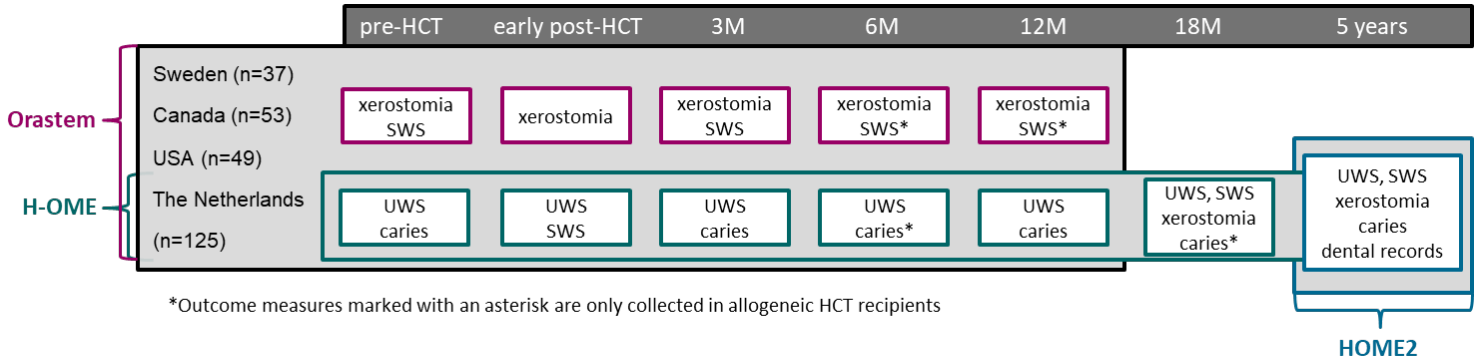
The current evidence on prevalence and severity of xerostomia in HCT recipients is summarised in chapter 3. By means of a systematic review, results of 22 clinical studies that determined xerostomia in HCT recipients over time were combined, risk of bias was assessed and results are graphically shown.

Xerostomia is one of the oral side effects that was measured as part of the Orastem study (figure 1): a prospective, longitudinal, international, observational, multicentre study including autologous and allogeneic HCT recipients. Chapter 4 reports results of the Orastem-study, of which the protocol was published previously (38). Xerostomia was determined in 262 patients pre-HCT, early post-HCT and after 3, 6 and 12 months and SWS was collected several times. The effect of several risk indicators on the severity of xerostomia and SWS flow rate was studied.

The H-OME study (figure 1) is an ancillary study of the Orastem study in which only a subgroup consisting of Dutch patients was included (Netherlands trial register NL5645). Data from 125 patients treated in Amsterdam and Nijmegen were collected pre-HCT, early post-HCT and after 3, 6, 12 and 18 months. Chapter 2 aimed to describe the development of UWS and SWS flow rates and hyposalivation over time. The influence of the conditioning regimen, the type of transplantation, the number of prescribed medications and oral mucosal cGvHD in the development of hyposalivation were explored. Chapter 5 reports on caries progression during the first 18 months post-HCT. The effect of hyposalivation of UWS and SWS in the development of caries lesions was also determined in this chapter.

Survivors of the H-OME study were invited 5 years post-HCT to participate in an additional follow-up study (figure 1). This HOME2 study (Dutch Trial Register NL9825) included 39 dentate HCT survivors, of which some results are reported in chapter 6. UWS and SWS flow rates and xerostomia scores 5 years post-HCT were measured. Furthermore, dental records were retrieved from general dentist to determine the number of performed treatments 5 years before and 5 years after HCT. Based on these data, we explored whether dental treatment need increased post-HCT, and whether this treatment need was influenced by hyposalivation.

The underlying figure shows how the Orastem study, the H-OME study and the HOME2 study are related to each other. Only the subset of outcomes relevant to this thesis is listed here.



*Outcome measures marked with an asterisk are only collected in allogeneic HCT recipients

Abbreviations: UWS, unstimulated whole saliva; SWS, stimulated whole saliva; M, months

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Chapter 2

The effect of conditioning regimen and prescribed medications on hyposalivation in haematopoietic cell transplantation (HCT) patients: an 18-month prospective longitudinal study

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Abstract

Objectives: Haematopoietic cell transplantation (HCT) preceded by a conditioning regimen is an established treatment option for (non)malignant haematologic disorders. We aim to describe the development of hyposalivation over time in HCT recipients, and determine risk indicators.

Materials and methods: A multi-centre prospective longitudinal observational study was conducted. Unstimulated (UWS) and stimulated (SWS) whole saliva was collected before HCT, early post-HCT, and after 3, 6, 12, and 18 months. The effect of type of transplantation (allogeneic vs autologous) and intensity (full vs reduced) of the conditioning regimen on hyposalivation (UWS < 0.2 mL/min; SWS < 0.7 mL/min) was explored.

Results: A total of 125 HCT recipients were included. More than half of the patients had hyposalivation early post-HCT; a quarter still had hyposalivation after 12 months. The conditioning intensity was a risk indicator in the development of hyposalivation of both UWS (OR: 3.9, 95% CI: 1.6–10.6) and SWS (OR: 8.2, 95% CI: 2.9–24.6). After 3 and 12 months, this effect was not statistically significant anymore.

Conclusions: Hyposalivation affects the majority of patients early post-HCT. The conditioning intensity and the type of transplantation were significant risk indicators in the development of hyposalivation. The number of prescribed medications, total body irradiation as part of the conditioning regimen and oral mucosal graft-versus-host disease did not influence hyposalivation significantly.

Clinical relevance: Because of the high prevalence of hyposalivation, HCT recipients will have an increased risk of oral complications. It might be reasonable to plan additional check-ups in the dental practice and consider additional preventive strategies.

Keywords: Haematopoietic cell transplantation, Hyposalivation, Salivary flow rate, Medications

Introduction

Haematopoietic cell transplantation (HCT) is a potentially curative treatment for haematologic cancers and many other non-malignant disorders (1). In HCT, stem cells are either harvested from the patient (autologous HCT) or from a donor (allogeneic HCT). The stem cell infusion is preceded by a conditioning regimen, consisting of chemotherapy with or without total body irradiation (TBI). During the past decades, clinical indications for HCT expanded and transplantation procedures improved, leading to an increased number of long-term survivors (2, 3). Still, HCT is associated with considerable long-term morbidity, and development of oral complications is frequently reported (4, 5).

Some of these oral complications might be related to changes in salivary secretion. Unstimulated whole saliva (UWS), present in the oral cavity in resting conditions, is a viscous fluid mainly produced by the submandibular glands. The more watery stimulated whole saliva (SWS) is mainly produced by the parotid glands; the production of SWS is initiated by stimuli like chewing, taste and smell (6). Both types of saliva are essential in maintaining oral health by protecting teeth and oropharyngeal mucosa and maintaining a balanced microbiota (6, 7). In longitudinal studies, a decline in UWS (8, 9) and in SWS flow rates was reported post-HCT (9-12). SWS flow rates tend to increase again over time (11, 13), while long-term data on UWS flow rates are lacking. Furthermore, salivary flow rates in HCT recipients are lowered compared to healthy controls (11, 12, 14). This decline imposes several risks to the oral cavity, potentially resulting in caries, periodontitis and tooth loss (15).

High-intensity conditioning regimens might result in dysfunction of the major salivary glands (16) and the secretion rate from the minor salivary glands might be reduced as a result of chemotherapy (17). Nevertheless, an association between the intensity of the conditioning regimen and reduction in salivary flow rate could not be established so far. Patients treated with high intensity conditioning demonstrated a tendency towards increasing prevalence of hyposalivation (11), while the intensity of the conditioning regimen was not related to SWS flow rates in regression analyses (12). TBI as part of the conditioning resulted in a delayed recovery of SWS flow rates post-HCT (11).

Polypharmacy is a well-known risk indicator in the development of hyposalivation (6), and might be an explanation for the decline in salivary flow rates in HCT recipients. It was reported that an average of four different medications was used

concomitantly by HCT recipients (12), and that 91% of the allogeneic HCT recipients in that study used medications that were known to reduce salivary flow rate (18). Nevertheless, the number of medications nor the examined pharmaceutical groups were significantly associated with decreased SWS flow rates (12).

Chronic graft-versus-host disease (cGvHD), a complication from allogeneic transplantations, is an immune response of donor-derived cells against recipient tissues (1). cGvHD is associated with histopathological changes in salivary glands, a reduction in salivary flow rate, and changes in the composition of saliva (19). Several studies showed a persistently low salivary flow rate in cGvHD patients with virtually no recovery (14, 20), in contrast to allogeneic patients who did not develop cGvHD and autologous HCT recipients. It was suggested that salivary involvement in cGvHD might be irreversible (21). More recent studies concluded that the effect of cGvHD on SWS flow rate was negligible (12) and that oral mucosal cGvHD was not related to UWS flow rate (22).

We aim to describe the development of hyposalivation of both UWS and SWS over time in HCT recipients, assessing both the period early post-HCT and the long term up to 18 months post treatment. The effect of several risk indicators in the development of hyposalivation will be determined.

Methods

This study is an ancillary study of the Orastem study, a multinational, prospective, observational, longitudinal study on the impact of oral side effects from conditioning therapy before HCT (23). Adult patients (≥ 18 years old) scheduled to receive an autologous or allogeneic HCT at Amsterdam University Medical Center, location AMC or Radboud University Medical Center (Radboudumc) Nijmegen were included. Patients scheduled for allogeneic HCT were eligible for inclusion independent of their diagnosis, while those scheduled for autologous HCT were eligible if diagnosed with multiple myeloma. Patients were excluded if they were not able to understand the provided information, a second HCT was planned in advance or if the time before HCT was too short to consider study participation. This study was registered in the Netherlands trial register (NL5645), approval was obtained by the Medical Research Ethical Committee (NL52117.018.15), and the study was conducted according to GCP guidelines and the World Medical Association Declaration of Helsinki. Before participating, all patients signed informed consent.

Saliva collection

Saliva was collected at the baseline screening preceding the conditioning regimen, and once a week during the first 28 days following HCT while most patients were hospitalised. This resulted in a median of 2 samples (range: 1–4) per patient early post-HCT. All patients underwent saliva collections after 3 and 12 months, and allogeneic HCT recipients had additional saliva collections 6 and 18 months post-HCT.

The protocols for the collection of whole saliva were based on the guidelines for saliva collection of the University of Southern California School of Dentistry (24). Patients were asked to refrain from eating, drinking, toothbrushing and use of chewing gum 1 h before the collection. The collection of UWS started immediately after one swallow. Patients were asked to spit the saliva in a pre-weighed plastic cup for 5 min without making any effort to increase the salivary flow. During the collection of SWS, patients chewed on a piece of neutral chewing gum base. SWS was collected for 2–5 min, and the collection was preceded by swallowing after 1 min of chewing. Directly after collection, samples were weighed and flow rates were estimated by assuming 1 g of saliva equals 1 mL. Hyposalivation of UWS was defined as a flow rate of < 0.2 mL/min, and hyposalivation of SWS as < 0.7 mL/min (25). Patients that had a flow rate below this threshold at least once during the first 28 days post-HCT, were classified as having hyposalivation early post-HCT.

Medication data

Prescribed medications were extracted from the electronic medical record system (EPIC) in both centres. All prescribed medications that the patients were on, in the week preceding the pre-conditioning screening, were extracted. Only when medications during the pre-conditioning screening were not available in EPIC, patient-reported medications were used. Besides, medications were extracted from medical records for all patients that were hospitalised in the Amsterdam UMC, location AMC or the Radboudumc at least 7 days following HCT. Data on prescribed medications were available until resolution of neutropenia or discharge from the hospital. All different systemically administered medications (oral, intravenous, subcutaneous, sublingual, transdermal, rectal, inhalation) were counted; doses were not taken into account. Medications were divided into the following categories:

- Antimicrobials: antibiotics, antifungals, antiviral medications
- Supportive medication: sleep medication, antidepressants, anxiolytics, antacids, antiemetics, analgesics, antihistamines, laxatives, diuretics

- Anticancer and immunosuppressive medication: cytostatics, oncolytics, colony stimulating factors, corticosteroids, other immunosuppressives, protein kinase inhibitors
- Other medication

Oral mucosal cGvHD

Oral mucosal changes related to cGvHD in allogeneic HCT recipients were determined by experienced dentists according to National Institutes of Health (NIH) Oral Mucosal Scale (26). The severity of the three most common manifestations of oral cGvHD was evaluated. Erythema (scored 0–3), lichenoid lesions (scored 0–3), and ulcers (scored 0–6) were added up, resulting in a score between 0 and 12 (27). Patients with an NIH OMS ≥ 2 were assigned as having oral mucosal cGvHD. Oral mucosal changes were evaluated after 3, 6, 12, and 18 months.

Data analysis

The development of hyposalivation of UWS and SWS over time is graphically shown. UWS and SWS flow rates are shown from a subgroup of the present population: only patients from the Radboudumc are included due to higher precision salivary measurements performed in this centre. Salivary flow rates measured during the 4 weeks following HCT were combined, resulting in a mean score early post-HCT. Paired *t*-tests were used to determine changes in flow rates with measurements pre-conditioning. Statistical analyses were performed in R (version 4.1.3) and SPSS (version 27). Line and bar charts were made using GraphPad Prism (version 9.5.0).

Risk indicators

Separate logistic regression models were built to study the influence of the following risk indicators on hyposalivation of UWS and SWS:

1. intensity of the conditioning regimen: a distinction was made between high intensity or myeloablative (MAC) conditioning regimens, and non-myeloablative or reduced intensity or (NMA/RIC) conditioning regimens (28)
2. TBI (yes vs no) as part of the conditioning
3. type of HCT (allogeneic vs autologous)
4. oral mucosal changes related to cGvHD after 3, 6, 12, and 18 months
5. number of prescribed medications during hospitalisation

The influence of the conditioning regimen and type of transplantation (analysis 1, 2 and 3) was determined early post-HCT and after 3 and 12 months. Analysis number four aimed to study the effect of oral mucosal changes related to cGvHD

and simultaneous diagnosis of hyposalivation. In this analysis, one measurement out of four (3, 6, 12, or 18 months) was selected per patient. The first moment a patient developed oral mucosal cGvHD or hyposalivation was selected; the last measurement was used when patients did not develop hyposalivation or oral mucosal cGvHD. The fifth analysis focused on the effect of the number of prescribed medications during the hospitalisation phase, and contemporary hyposalivation. Patients who left the Amsterdam UMC, location AMC or Radboudumc within 7 days after the transplantation, because of transfer to a general hospital or discharge, were not included in this analysis.

Crude models included the above-mentioned risk indicators as only independent variable, while potential confounding factors were added to the adjusted models. The following covariates were considered for inclusion: age, sex, centre of treatment, comorbidities (yes vs no), and pre-conditioning hyposalivation (yes vs no). In fifth analysis, aiming to determine the effect of the number of medications on hyposalivation during hospitalisation, the length of the hospital stay was added as a covariate. The number of covariates in the analysis was restricted based on the extent to which the odds ratio (OR) was affected, resulting in the exclusion of variables with a negligible effect. Results of the analysis are graphically shown as ORs with 95% confidence intervals (95% CI).

Results

In total, 125 patients that were planned for HCT signed informed consent and were included between September 2015 and October 2017. At least one salivary measurement was performed in 107 patients early post-HCT and of these, 86 patients were hospitalised in the Amsterdam UMC, location AMC or Radboudumc for more than 7 days post-HCT. During the study period, 21 HCT recipients (17%) died. The number of patients present at different follow-ups and reasons for loss to follow-up are shown in Fig. 1. The median age of autologous and allogeneic NMA/RIC recipients was 59 years, while allogeneic MAC recipients were younger (median 44.5 years). Baseline characteristics and HCT-related characteristics of the participants are reported in Table 1.

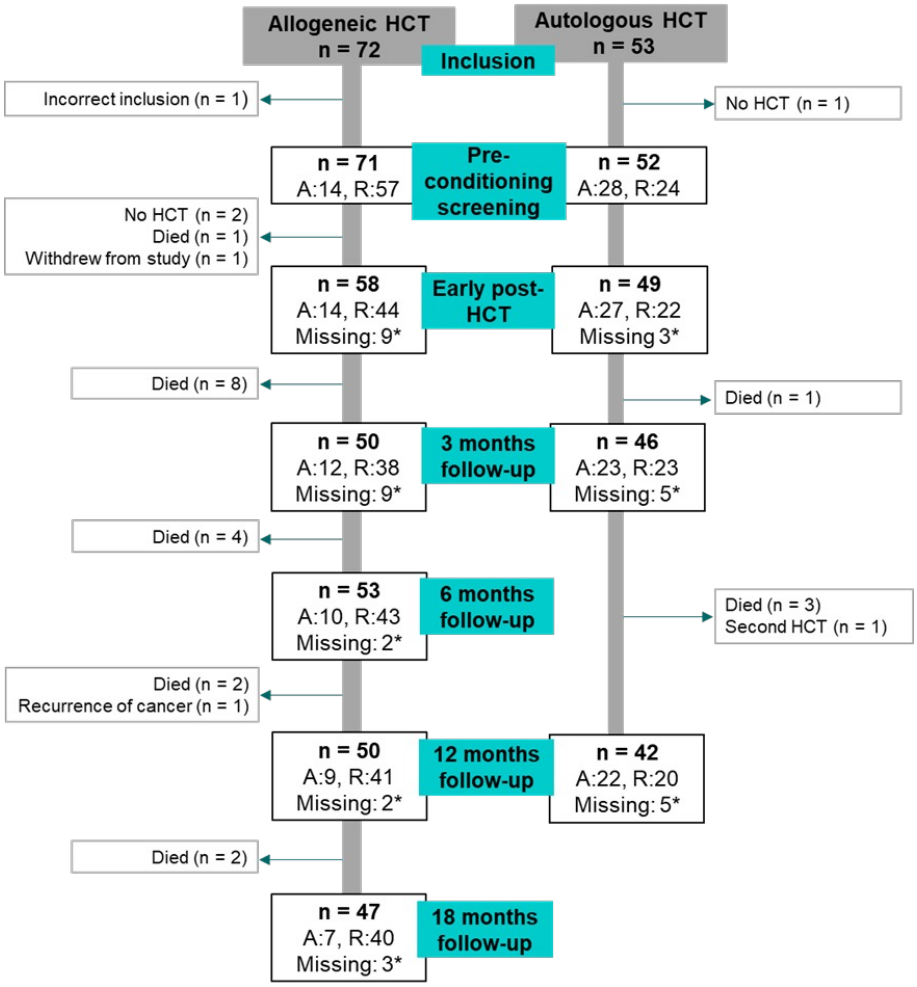


Figure 1. Flowchart of the study

A distinction is made between patients treated at Amsterdam UMC, location AMC (A) and Radboudumc (R). Reasons for exclusion and irreversible loss to follow-up are shown in the grey squares on the left and right side of this diagram. In 12 patients, no saliva was collected early post-HCT because patients were ill/nauseous (n = 5), the hospital stay was too short (n = 6), or unknown reasons (n = 1). Reasons for 26 incidental missed appointments in 23 patients during the long-term follow-up, marked with asterisk in this diagram were the following: unable to come due to hospitalisation, rehabilitation, or illness (n = 4), refused to come or did not come (n = 10), unreachable (n = 3), or other/unknown reasons (n = 9)

Table 1. Baseline characteristics of HCT recipients

	Autologous (52)	**Allogeneic MAC* (14)**	**Allogeneic RIC/NMA* (53)**
Median age in years (range)	59 (33–69)	44.5 (23–55)	59 (19–74)
Gender, n (%) female	24 (46%)	7 (50%)	23 (43%)
Centre			
Amsterdam UMC, location AMC, n	28	3	11
Radboudumc, n	24	11	42
Diagnoses, n			
Acute myeloid leukaemia		8	20
Acute lymphoblastic leukaemia		4	1
Lymphoma		1	7
Chronic lymphocytic leukaemia		1	3
Myelodysplastic syndrome			9
Chronic myeloid leukaemia			2
Myelofibrosis			4
Severe aplastic anaemia			2
Multiple myeloma	52		2
Other			3
Comorbidities (≥1 current medical conditions, other than the diagnoses above), n (%)	25 (48%)	2 (14%)	15 (28%)
Earlier radiation therapy to head and neck region, n (%)	0	0	3 (6%)
Median (range) number of prescribed medications during the week preceding the pre-conditioning screening	6 (0–17)	2 (0–9)	4 (0–15)
Conditioning:			
Myeloablative, n	52	14	
Reduced intensity, n			24
Nonmyeloablative, n			29
Total body irradiation, n		13	32
No total body irradiation, n	52	1	21
Donor:			
Unrelated donor, match		8	36
Unrelated donor, mismatch			3
Sibling donor		6	10

* Four allogeneic HCT recipients who were excluded before the conditioning regimen are not included in this table

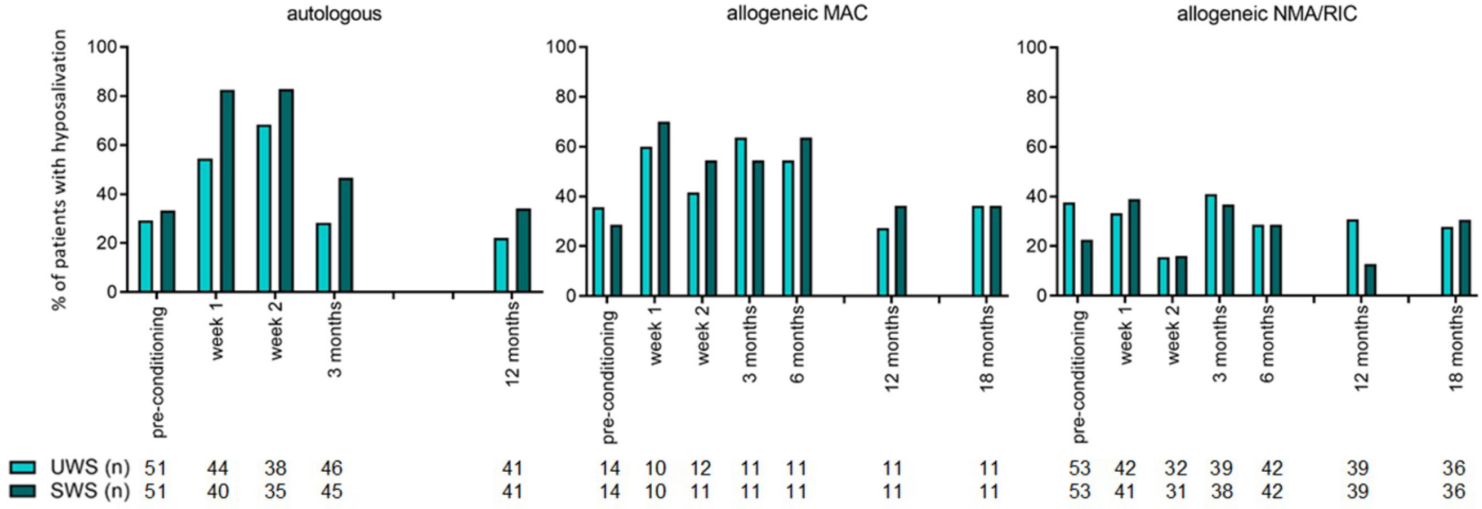


Figure 2. Prevalence of hyposalivation over time

Numbers (n) are the numbers of patients that contributed one or more saliva samples per time point or period. Five SWS samples in two patients are missing due to prothesis, and 2 UWS samples in one patient are missing due to chewing gum use preceding the collection. Furthermore, several patients felt too ill or nauseous, or experienced too much pain in the oral cavity to collect SWS early post-HCT. Abbreviations: UWS, unstimulated whole saliva; SWS, stimulated whole saliva; MAC, myeloablative conditioning; NMA/RIC, non-myeloablative or reduced intensity conditioning

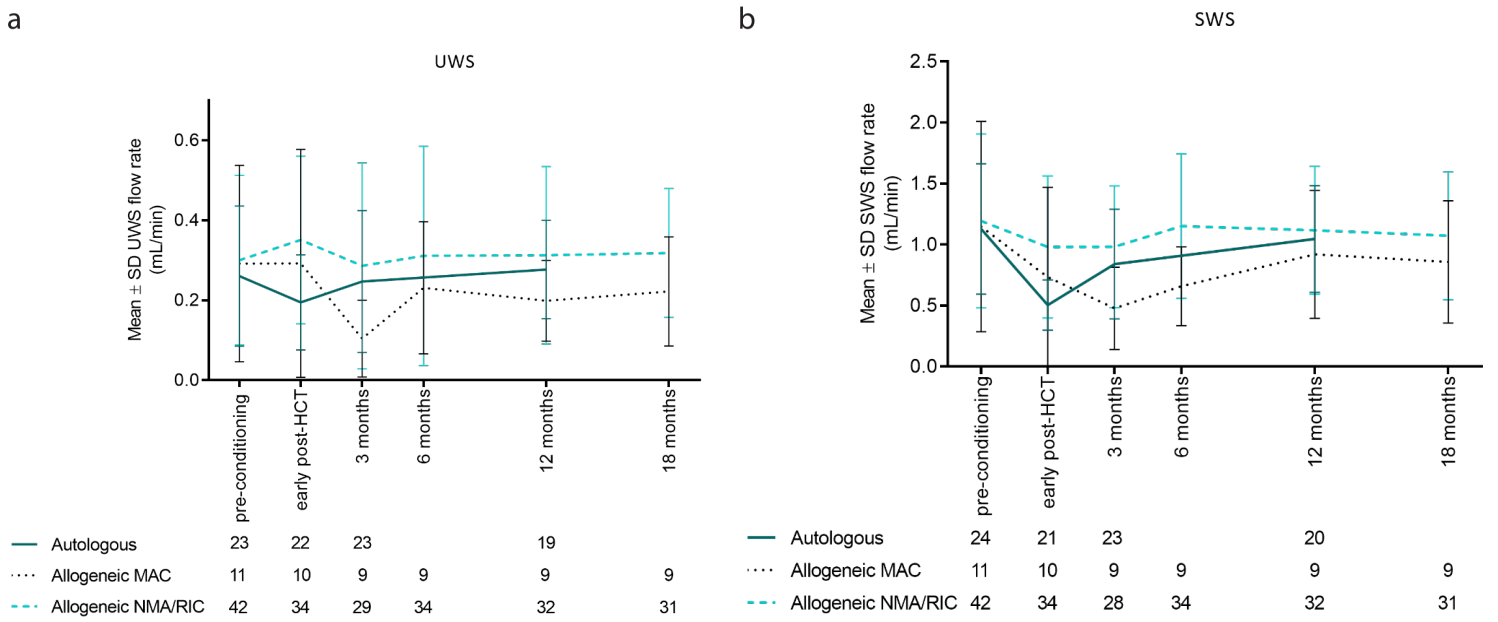


Figure 3. Mean salivary unstimulated whole saliva **(UWS, a)** and salivary stimulated whole saliva **(SWS, b)** flow rates with standard deviations (SD) over time Numbers of patients (n) who contributed saliva sample(s) per time point or period are listed below the graphs. Abbreviations: MAC, myeloablative conditioning; NMA/RIC, non-myeloablative or reduced intensity conditioning

Hyposalivation and salivary flow rate

Saliva samples were collected between 8.30 a.m. and 16.30 p.m. Pre-conditioning, 34% of the patients was diagnosed with hyposalivation of UWS and 29% of SWS. This number increased to 54% and 67% early post-HCT, and diminished to 26% and 25% 12 months post-HCT respectively. The percentage of patients with hyposalivation of UWS and SWS is shown in Fig. 2. The increase in hyposalivation early post-HCT was most pronounced in the autologous HCT recipients; in allogeneic recipients receiving an NMA/RIC conditioning, only limited changes over time were seen.

Salivary flow rates from patients treated at the Radboudumc are shown in Fig. 3a (UWS) and b (SWS). Looking at all patients, SWS flow rates declined the first week after treatment with 0.44 mL/min (95% CI: 0.29–0.58). Flow rates were still reduced 3 months post-HCT (mean decline from baseline: 0.26 mL/min, 95% CI: 0.11–0.41). Twelve months post-HCT, the difference was not statistically significant anymore (mean: 0.11, 95% CI: – 0.03–0.26). The reduction shortly after treatment was most pronounced in the two groups receiving a myeloablative conditioning regimen (autologous and allogeneic MAC). In the autologous subgroup, flow rates started to increase again after the first month. This increase was seen after 3 months for the allogeneic groups.

UWS flow rates seem to follow the same trend over time as SWS, but changes from baseline were less pronounced and did not reach statistical significance. In the allogeneic subgroup receiving NMA/RIC, only limited changes in mean scores were seen. The drop in flow rate for autologous patients was most pronounced early post-HCT, and for allogeneic patients receiving MAC it was most pronounced after 3 months.

Prescribed medications

During the week preceding the pre-conditioning screening, 9 patients (7%) did not use any medication, while 60 patients (49%) used ≥ 5 medications. In total, 59 patients (52%) used anticancer or immunosuppressive medication in this week. Mean numbers of prescribed medications for each category and subgroup in the week preceding the pre-conditioning screening can be found in Fig. 4a.

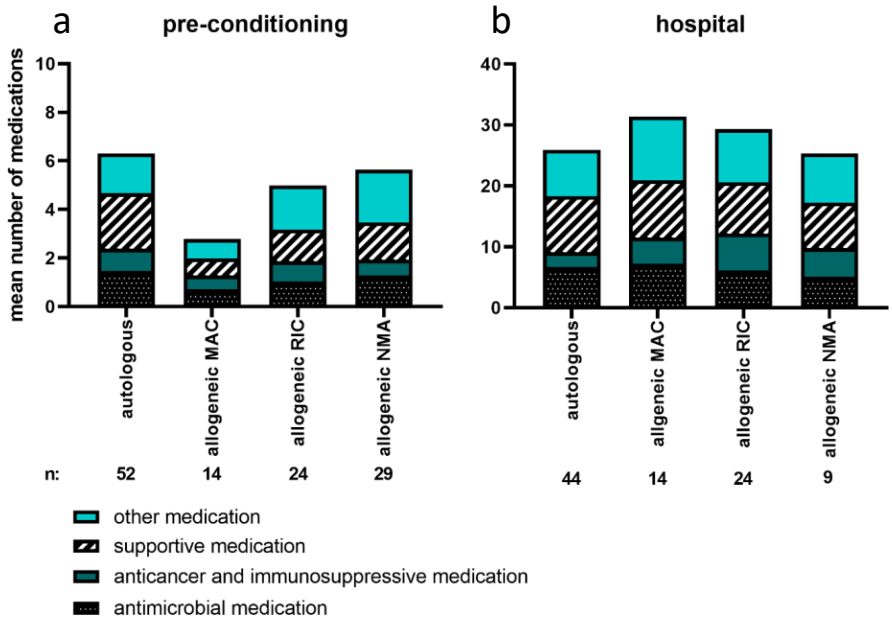


Figure 4. Mean number of prescribed medications during the week preceding the pre-conditioning screening **(a)**, and during the hospitalisation phase **(b)**.
Numbers of patients (n) are listed below the graph. Autologous HCT recipients stayed for median 19 days (range: 15–32) in the hospital, allogeneic myeloablative (MAC) recipients for 24 days (range: 17–33), reduced intensity (RIC) for 24.5 days (range 20–35), and non-myeloablative (NMA) for 16 days (range 14–23)

In total, 27 patients were discharged in the week following HCT. From the remaining patients, medication data was available for a median of 21 days (range: 14–35 days). During this hospital stay, patients used a median of 27 (range: 16–45) different medications. This number of medications includes the conditioning regimen that was administered at the beginning of hospitalisation. Patients used on average 6 different antimicrobial medications (range: 3–15) and 8 different supportive medications (range: 4–16). Mean numbers of prescribed medications for each category and subgroup during hospitalisation are shown in Fig. 4b.

Oral mucosal cGvHD

Oral mucosal changes related to cGvHD were seen 28 times in 15 patients (25%). At these 28 occasions, the median NIH OMS was 3 (range 2–8). At the 3 months follow-up visit, oral cGvHD-related mucosal changes were seen in 3 patients, after 6 months in 12 patients, after 12 months in 7 patients, and after 18 months in 6

patients. The majority of patients had no hyposalivation at the visit when mucosal changes were seen (Fig. 5).

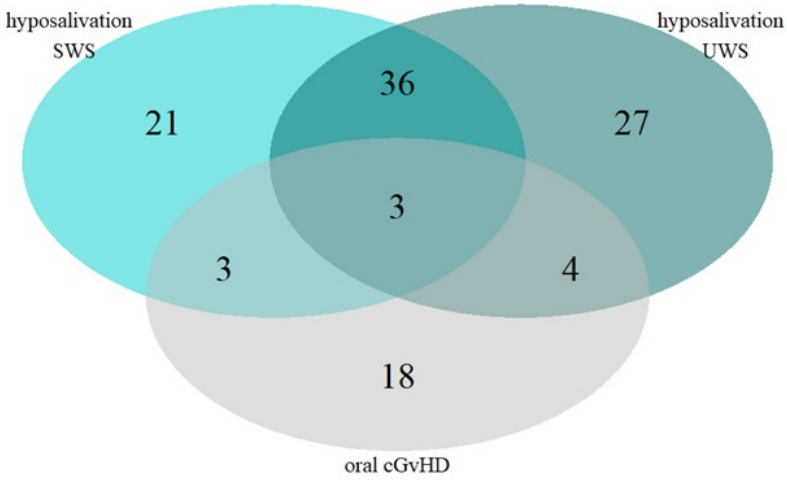


Figure 5. Venn diagram showing the diagnoses of hyposalivation of stimulated whole saliva (SWS), unstimulated whole saliva (UWS), and oral mucosal chronic graft-versus-host disease (cGvHD)
Data of all allogeneic patients seen after 3, 6, 12, and 18 months are combined. Overlap indicates simultaneous diagnoses

Risk indicators

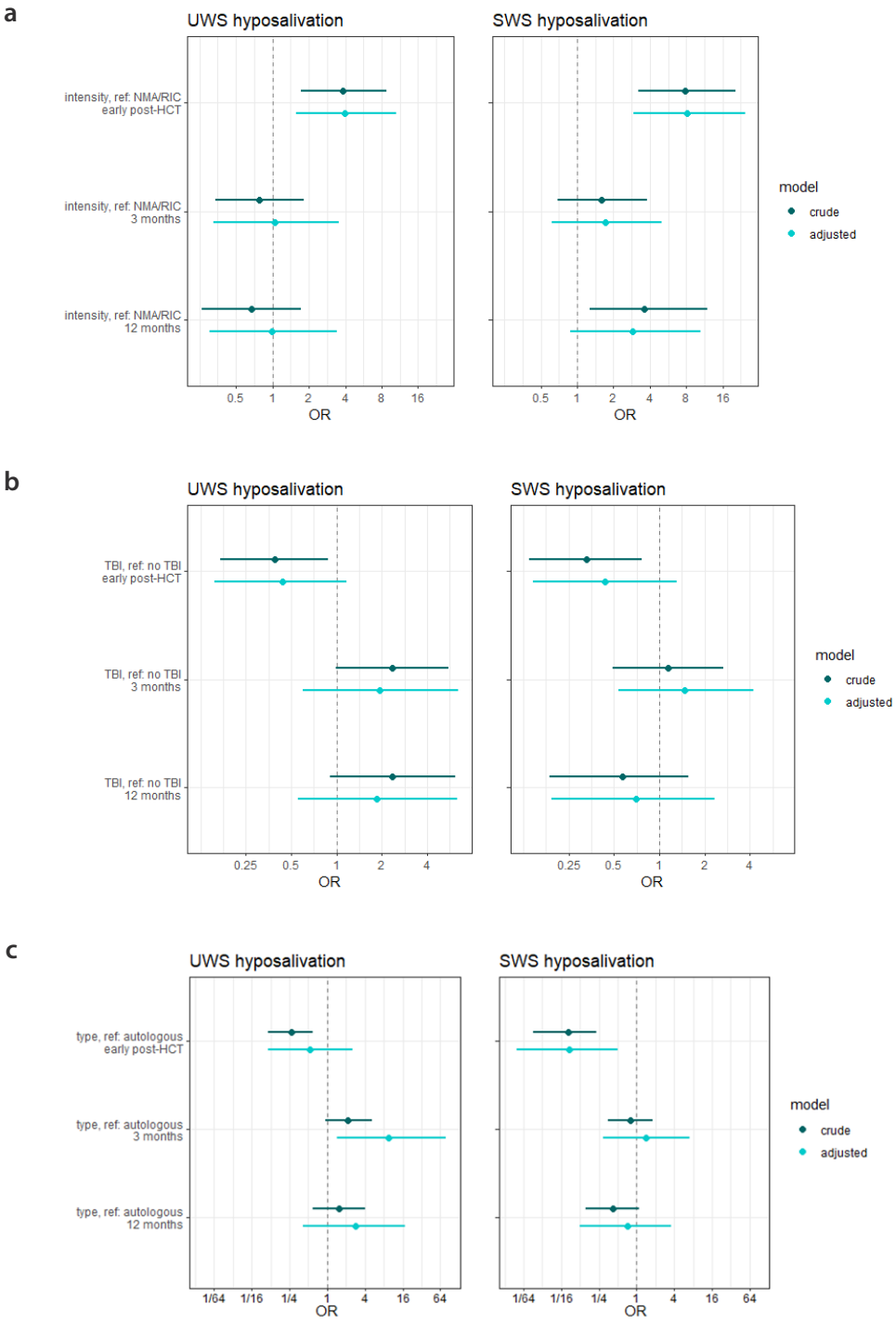
The association between the intensity of the conditioning regimen and hyposalivation is shown in Fig. 6a. Early post-HCT, the intensity was a significant risk indicator in the development of hyposalivation of both UWS and SWS. MAC recipients had, after adjusting, a 3.9 (95% CI: 1.6–10.6) times higher odds of developing hyposalivation of UWS, and an 8.2 (95% CI: 2.9–24.6) times higher odds developing hyposalivation of SWS. After 3 and 12 months, the influence of the intensity of the conditioning regimen on hyposalivation of SWS diminished to non-significant levels. An effect of the intensity on hyposalivation of UWS after 3 and 12 months was lacking.

The association between TBI as part of the conditioning regimen and hyposalivation is shown in Fig. 6b. After adjusting for confounding factors, TBI was not significantly related to hyposalivation of UWS or SWS at any moment. TBI receivers tended to have more hyposalivation of UWS after 3 and 12 months, but this difference did not reach statistical significance.

The association between the type of transplantation and hyposalivation is shown in Fig. 6c. Autologous HCT recipients had more hyposalivation of SWS early post-HCT (OR: 0.08; 95% CI: 0.01–0.5), while allogeneic HCT recipients had more hyposalivation of UWS 3 months post treatment (OR: 9.6; 95% CI: 1.4–77). After 12 months, no significant effect remained.

The association between oral mucosal cGvHD and hyposalivation is shown in Fig. 6d. OR's of below 1, both in the crude and the adjusted models, confirm that oral mucosal changes and hyposalivation do not occur more often simultaneously.

The association between the number of prescribed medications during hospitalisation and hyposalivation early post-HCT is shown in Fig. 6e. No association was found between the number of medications and hyposalivation of SWS. The odds of developing hyposalivation of UWS was 1.1 (95% CI: 1.0–1.2) times higher for every additional medication that was prescribed.


a
UWS hyposalivation
SWS hyposalivation
intensity, ref: NMA/RIC
early post-HCT
intensity, ref: NMA/RIC
3 months
intensity, ref: NMA/RIC
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0.5
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UWS hyposalivation
SWS hyposalivation
TBI, ref: no TBI
early post-HCT
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TBI, ref: no TBI
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SWS hyposalivation
type, ref: autologous
early post-HCT
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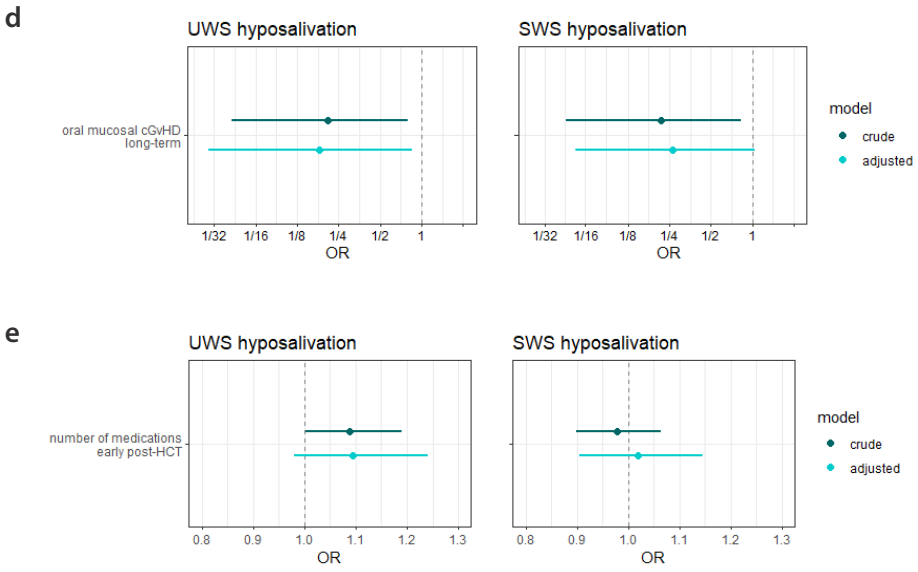

< Figure 6. The relation between several risk indicators and hyposalivation.
Hyposalivation of unstimulated whole saliva (UWS) is shown on the left side, hyposalivation of stimulated whole saliva (SWS) on the right side. Odds ratios (OR) are shown with their 95% confdence interfalls. **a)** Relation between intensity of the conditioning regimen and hyposalivation at diferent moments in time. Myeloablative conditioning regimens are compared to non-myeloablative or reduced intensity (NMA/RIC) conditioning regimens. In the adjusted model, the following variables were added: hyposalivation at baseline (UWS and SWS respectively), total body irradiation, and age. **b)** Relation between total body irradiation (TBI) as part of the conditioning regimen and hyposalivation at diferent moments in time. In the adjusted model, the following variables were added: hyposalivation at baseline (UWS and SWS respectively), the intensity of the conditioning regimen and age. **c)** The relation between the type of transplantation (allogeneic vs autologous) and hyposalivation at diferent moments in time. In the adjusted model, the following variables were added: the intensity of the conditioning regimen, hyposalivation at baseline (UWS and SWS respectively) and age. **d)** Relation between hyposalivation and oral mucosal changes related to chronic graft-versus-host disease (cGvHD) at the same follow-up. In the adjusted model, the following variables were added: hyposalivation at baseline (UWS and SWS respectively), the intensity of the conditioning regimen and age. **e)** The relation between the number of prescribed medications during hospitalisation and hyposalivation early post-HCT. In the adjusted model, the following variables were added: the intensity of the conditioning regimen, hyposalivation at baseline (UWS and SWS respectively), length of hospital stay in days and age

Discussion

The aim of this prospective longitudinal study was to describe the development of hyposalivation over time in HCT recipients, and determine risk indicators. Hyposalivation affected the majority of patients early post-HCT. The intensity of the conditioning regimen was a significant risk indicator in the early post-HCT development of hyposalivation. Autologous HCT recipients had more hyposalivation of SWS early post-HCT, while allogeneic HCT recipients had more hyposalivation of UWS 3 months post treatment. Nor TBI as part of the conditioning regimen, the number of prescribed medications or mucosal oral cGvHD worsened hyposalivation significantly.

The intensity of the conditioning regimen was a significant risk indicator in the development of hyposalivation of both UWS and SWS early post-HCT. This effect was not significant anymore after 3 and 12 months. It was suggested that chemotherapy impaired both acinar and ductal function of salivary gland tissue (29). The finding that MAC-recipients had more hyposalivation than RIC-recipients, confirms the causal relation between the conditioning regimen and salivary dysfunction. Previous studies concluded that patients treated with MAC demonstrated a non-significant tendency for an increasing prevalence of hyposalivation 6 months post-HCT (11), or found no relation between the intensity of the conditioning regimen and hyposalivation (12, 22). None of these studies measured hyposalivation early post-HCT, and might therefore have underestimated the association between intensity and hyposalivation.

No significant relation between TBI and hyposalivation could be established in the current study. Subjects in the current study received a dose between 2 and 9 Gray, which might not have reached the threshold above which salivary gland function will diminish (30). It was reported before that recovery of salivary flow rate was slower after administration of TBI (11). Other studies found no association between salivary hypofunction and TBI (5, 22).

Autologous HCT recipients had a 12 times higher odds (OR: 0.08) of developing hyposalivation of SWS early post-HCT, compared to allogeneic recipients, even after adjusting for confounding factors like the intensity of the conditioning regimen. The autologous HCT recipients included in the current study comprise a homogeneous population: all patients were diagnosed with multiple myeloma and received high dose melphalan as conditioning regimen. Melphalan is one of the chemotherapeutic drugs that is actively secreted by the salivary glands (31), and might therefore be related to an increased reduction in saliva secretion early post-HCT.

In the long term, allogeneic recipients had more hyposalivation of UWS than autologous recipients, a difference that reached significance after 3 months. This increased prevalence of hyposalivation might be explained by histopathological changes in the salivary glands caused by cGvHD (19). Nevertheless, the majority of patients with long-term hyposalivation had no oral mucosal cGvHD simultaneously. This finding is in agreement with literature, and supports the suggestion that salivary gland involvement and oral mucosal cGvHD are common and clinically distinct manifestations of cGvHD (22, 32). Patients with oral mucosal cGvHD even tended to have less hyposalivation. We hypothesize that pain caused by mucosal changes could be related to an increased salivary flow rate, as is seen in other potentially pain inducing conditions or situations of the oral mucosa, like teething (33), and eating spicy foods (34).

HCT recipients used a median of 27 (range: 16–45) different medications during hospitalisation. Because polypharmacy is a well-known risk indicator in the development of hyposalivation (6), it is not surprising that the majority of patients developed hyposalivation early post-HCT. The number of medications had a non-significant effect on hyposalivation of UWS, and the number of medications was not related to hyposalivation of SWS. It is reported in literature that in medication-induced salivary gland hypofunction, UWS flow rate was usually reduced, whereas SWS flow rates were within the normal range (6). A potential effect of the medication might be neglected in the current analysis, because the dose and type of the prescribed medications were not taken into account. Previous publications could also not find an association between the number of medications and decreased SWS (12) or UWS (18) flow rates post-HCT.

A limitation of the current study is the extensive variation in the time of day at which saliva was collected, resulting in a lower precision due to the circadian rhythm (35). Furthermore, the limited number of patients made statistical analysis within the subgroups (e.g. autologous or allogeneic) not meaningful. Nevertheless, clear trends in salivary flow rates over time are seen, that are in agreement with literature. The previous reported lowered UWS flow rates 3 months (8) and lowered SWS flow rates 6 months post allogeneic HCT (11, 13) and recovery after 12 months (11, 13), are in agreement with our results. SWS flow rates decreased shortly after HCT while only limited changes in UWS flow rates were seen at the same time, which is also in agreement with literature (9, 10, 36). One previous publication reported even an increased UWS flow rate in allogeneic HCT recipients early post-HCT (8).

More than half of the HCT recipients was diagnosed with hyposalivation early post-HCT; a quarter still had hyposalivation after 12 months. These numbers are high

compared to the prevalence of hyposalivation in the general population, that was estimated to be 20% (95% CI: 15–25) (37). According to literature, the average UWS flow rate ranges between 0.3 and 0.4 mL/min, and the mean SWS flow rate between 1.5 and 2 mL/min (6). Compared to these values, salivary flow rates in HCT recipients were already low pre-conditioning, and remained lowered after recovery in the long term. Previous publications confirmed that SWS flow rates in HCT recipients remained lowered 6 and 12 months post treatment compared to healthy controls (11, 12).

A sufficient amount of saliva is essential to maintain oral health, and therefore, HCT recipients will have an increased risk for dental caries (38) and complaints of mouth dryness. We recommend treating dentists to be aware of the high prevalence of hyposalivation in HCT recipients, and the increased risk of oral complications. It may be reasonable to plan additional oral check-ups and consider additional preventive strategies.

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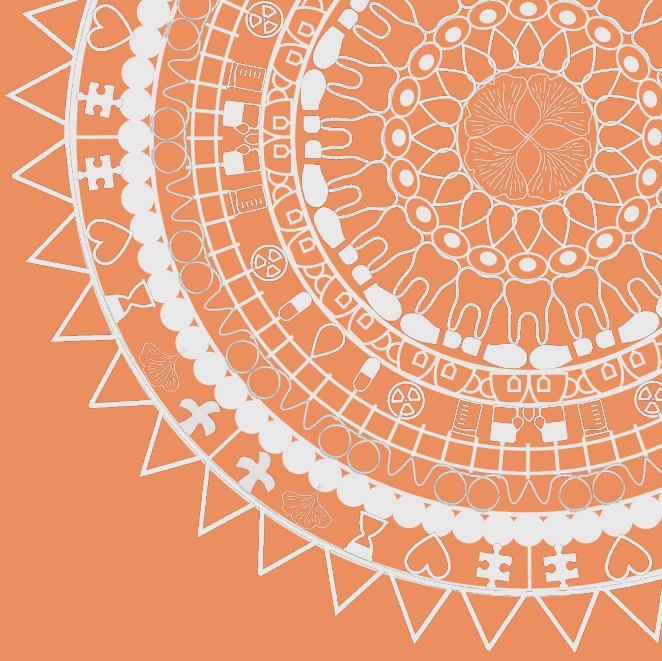

Chapter 3

The effect of haematopoietic stem cell transplantation on patient-reported subjective oral dryness: a systematic review focusing on prevalence, severity and distress

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Abstract

Objective

The aim of the present systematic review is to assess the prevalence and severity of and distress caused by xerostomia over time in adult haematopoietic (stem) cell transplantation (HCT) recipients.

Methods

PubMed, Embase, and the Cochrane Library were searched for papers published between January 2000 and May 2022. Clinical studies were included if patient-reported subjective oral dryness was reported in adult autologous or allogeneic HCT recipients. Risk of bias was assessed according to a quality grading strategy published by the oral care study group of the MASCC/ISOO, resulting in a score between 0 (highest risk of bias) and 10 (lowest risk of bias). Separate analyses focused on autologous HCT recipients, allogeneic HCT recipients receiving a myeloablative conditioning (MAC), and those receiving a reduced intensity conditioning (RIC).

Results

Searches yielded 1792 unique records; 22 studies met the inclusion criteria. The quality scores ranged between 1 and 7, with a median score of 4. The prevalence, severity, and distress of xerostomia increased shortly after HCT. Severity of xerostomia in allogeneic MAC recipients was higher compared to allogeneic RIC recipients 2–5 months post-HCT (mean difference: 18 points on 0–100 scale, 95% CI: 9–27); after 1–2 years, there was no significant difference anymore.

Conclusion

The prevalence of xerostomia in HCT recipients is high in comparison to the general population. The severity of complaints is raised during the first year post-HCT. The intensity of the conditioning plays a key role in the short-term development of xerostomia, while factors affecting the recovery in the long term remain largely unknown.

Introduction

Patient-reported subjective oral dryness, or xerostomia, is a common oral side effect from cancer therapies, especially from radiation therapy in the head and neck region (1). Even though less extensively investigated, the prevalence of xerostomia might also increase after haematopoietic (stem) cell transplantation (HCT) preceded by an intensive conditioning regimen. HCT recipients reported higher levels of xerostomia compared to their partners (2). Jensen et al. conducted a systematic review in 2010 on behalf of the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO). In this review, only three studies assessing xerostomia after HCT could be included. A prevalence of 40% during treatment, and 79% 7 years after treatment was reported (1).

Xerostomia is associated with several symptoms, like discomfort (3) and difficulty with speech and food intake (4). Furthermore, xerostomia influences the quality of life negatively (1); it is rated as one of the most bothersome symptoms (5, 6) and the main long-term oral complaint (7-9) by HCT-recipients. Specific instruments are available to measure the severity of xerostomia, like the Xerostomia Inventory (10). Furthermore, many questionnaires that measure quality of life or symptoms after cancer therapy, include a question about mouth dryness, like some additional modules of the European Organization for Research and Treatment of Cancer (e.g. EORTC QLQ-OH15) (11).

Xerostomia is a patient-reported outcome that is inextricably linked with hyposalivation: an objectively reduced salivary flow rate. Some studies concluded that unstimulated flow rates were related to the subjective feeling of mouth dryness in HCT recipients (12, 13), while other authors could not find a relation between reduced salivary secretion and subjective oral dryness (14). Even though xerostomia is primarily caused by a decrease in the function of the salivary glands (4), other factors like oral mucosal moistness (15), which might be associated with mouth breathing (16) or saliva composition (17), contributes to the feeling of mouth dryness as well. Furthermore, it was suggested that neuropathic mechanisms are involved in the perception of mouth dryness (18). The prevalence of xerostomia in HCT recipients was up to 4.7 times higher than the prevalence of hyposalivation of unstimulated saliva (9, 12, 19) and 2.4 times higher than the prevalence of hyposalivation of stimulated saliva (12).

Salivary flow rates are decreased several days and months after HCT, but appear to improve again over time (20). As a result, it might be expected that xerostomia in HCT recipients is transient in nature. This is in contrast to the prevalence

of xerostomia after radiation therapy in head and neck cancer, that shows an unchanged pattern between 1 month and more than 2 years after treatment (1).

Xerostomia has a multifactorial aetiology and, in this specific population, might be the result of the acute toxicity of the conditioning regimen. Total body irradiation (TBI) as part of the conditioning regimen might have an additional effect compared to chemotherapy alone; it was suggested that TBI caused complaints during or immediately after its administration (21, 22) and that it was related to lack of recovery in the long term (23, 24). Furthermore, the use of (xerogenic) medication (25), perceived stress (26, 27) or the development of chronic graft versus host disease (cGvHD) in allogeneic HCT recipients, might also be related to long-term xerostomia (28).

The prevalence and severity of xerostomia after HCT have not been systematically reviewed since 2010. Furthermore, it remains unclear whether patients that receive higher intensity conditioning regimens are at higher risk of developing xerostomia or whether complaints differ after autologous and allogeneic transplants. Therefore, the aim of the present systematic review is to assess the prevalence and severity of and distress caused by xerostomia over time, in adult HCT recipients, and to determine whether type of transplantation and conditioning regimen influence the severity of xerostomia.

Materials and methods

This systematic review was registered in PROSPERO (CRD42020168364) and followed the guidelines provided in the Transparent Reporting of Systematic Reviews and Meta-analysis (PRISMA) statement (29).

Search strategy

The following databases were searched from January 2000 up to June 2021: the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE via PubMed, and EMBASE via OVID. The search was updated in May 2022. A detailed and broad search strategy was designed with the help of a medical librarian. Because a preliminary search revealed that relevant papers were missed if xerostomia and oral or mouth dryness were used as only outcome terms, a combination of other terms (like: quality of life, side effects, and symptoms) was added to the search strategy (Table S1). In composite scales that assessed multiple systems, the relevant question on xerostomia was used. The reference lists of included studies were

examined to identify additional studies. Duplicate references were identified and removed with the help of EndNote X9 software.

Cohort studies, controlled trials, and cross-sectional studies were considered for inclusion if they reported on xerostomia, defined as patient-reported subjective oral dryness, in a population of adult HCT recipients. Studies were only included if at least 80% of the subjects reached adulthood during HCT and all subjects were ≥ 18 years at the examination. The time since HCT should be clearly specified, comprising the following: studies reporting on xerostomia in the first year post-HCT were only included if the outcome was reported within a range of 1 month. An exception was made when xerostomia was reported at a specific phase of treatment (e.g., discharge from the hospital). No specific time range was required for studies reporting xerostomia > 1 year post-treatment. Prevalence, mean severity, and mean distress scores were the outcomes of interest. Studies were excluded if patients were selected based on complications that developed after HCT, like cGvHD or poor general health. Furthermore, studies were excluded if authors only reported on objective oral dryness, oral dryness based on clinical characteristics as diagnosed by a doctor or dentist, or combined with taste alterations or food intake (e.g. toxicity criteria of the Radiation Therapy Oncology Group (30) or the Common Terminology Criteria for Adverse Events (31)).

Screening and selection

Two review authors (MB and LvG) independently screened titles and abstracts for eligibility. Full-text copies of potentially relevant publications were obtained, even in case of disagreement or doubt. The full-text copies were screened for the words "xerostomia" and "dry." If papers reported on a potentially eligible outcome, full-texts were read to establish whether they met the inclusion criteria.

Data extraction and quality assessment

Data on study design, country, participants (age, diagnosis), treatment (type of HCT, intensity of the conditioning regimen, and TBI), time since HCT, measurement instrument (questionnaire and recall period), and outcome data (prevalence, severity, or distress scores) were extracted from the papers. If one of these variables was missing, the corresponding author was contacted in an attempt to obtain additional data. When outcomes were only graphically shown, data was extracted with a ruler from enlarged graphs, but only when authors were not reached or underlying data was no longer available. If applicable, authors were asked to divide populations of sufficient participants (score 1 or 2 for estimate precision, Table S2) into relevant subgroups.

Quality of the reported outcomes was assessed by two review authors (MB and RT) according to a quality grading strategy published by the oral care study group of the MASCC/ISOO (32). The grading strategy, including adaptations made to fit the current research question, can be found in Table S2. Study characteristics that might have resulted in different forms of bias were numerically scored, which resulted is a score between 0 (highest risk of bias) and 10 (lowest risk of bias). The quality scores were categorized as follows:

- ≤ 3 points: high risk of bias
- 4–6 points: moderate risk of bias
- ≥ 7 points: low risk of bias

Only outcomes with a low or moderate risk of bias were included in the meta-analysis.

Statistical analysis

Results over time are graphically shown for three outcomes separately: prevalence, mean severity, and mean distress. Prevalence was defined as the percentage of patients that experienced xerostomia of all extents, based on questions using a yes/no format or ordinal questionnaires calculating the proportion of patients that report at least "a little," "mild," or "slight" xerostomia. Severity, in some papers also called intensity, referred to the extent to which xerostomia was experienced by patients, measured on ordinal or continuous scales. Distress referred to the degree to which the patient was bothered by the symptom, also measured on an ordinal or continuous scale. In order to be able to combine results from different studies, severity and distress scores were recalculated to a scale from 0 to 100 using the following formula:

$$\text{Rescaled severity/distress scores} = \frac{\text{reported mean score} - \text{lowest response option}}{\textit{range between highest and lowest response option}} * 100$$

In the "Results" section, only rescaled results are reported. The following time periods were chosen to report on xerostomia:

- Baseline: before the conditioning regimen and stem cell infusion
- Week 1: first week after HCT, some papers refer to "neutropenia" or "nadir"
- Week 2–4: continuation of hospitalization phase, including discharge in some studies
- 1–2 months post-HCT: usually the first measurement after discharge
- 2–5 months post-HCT
- 5–8 months post-HCT
- 1–2 years post-HCT: long-term
- > 2 years post-HCT: long-term

Data synthesis

Meta-analyses of rescaled severity scores were performed to facilitate the interpretation of data summarized in graphs. Forest plots were developed with Review Manager software (version 5.3) and summarized as mean differences (MD) and their 95% confidence intervals (95% CI). A fixed-effects model was only used if statistical heterogeneity was judged to be limited; otherwise, a random-effects model was chosen. Meta-analyses were conducted to answer two different research questions:

- To determine changes from baseline, within-study changes were calculated over different time intervals. These within-study changes were aggregated with the help of Review Manager, to summarize the overall change from baseline. Given the demanded experiment vs. control structure, an imaginary control group was entered to Review Manager, with a mean of 0, SD of 0.00001, and *N* of 1,000,000. If SDs from change scores were not reported, the SD was imputed as suggested in the Cochrane Handbook for systematic Reviews of Interventions, chapter 6 (33). In summary, the SD of the change score was imputed based on the known SD from baseline and the follow-up measurement and a correlation coefficient calculated from another study reporting the SD of change scores (if more studies were available, the study with the highest quality was chosen to calculate the correlation coefficient). MDs were calculated between baseline and week 1, 2–5 months, and 1–2 years post-HCT respectively. These time intervals were chosen taking into account the number and the quality of the available studies and the spread over time.
- To determine differences between subgroups, MDs within studies were calculated per time period. These MDs between subgroups within studies were aggregated. MDs were only calculated if at least 3 studies, comparing two subgroups of interest, could be included per time period.

Risk indicators and subgroups

To determine the influence of type of transplantation and conditioning regimen, the following risk indicators were defined:

- Type of transplantation: autologous or allogeneic transplantations
- Intensity of the conditioning regimen: myeloablative (MAC) or non-myeloablative or reduced intensity (RIC)
- For allogeneic transplantations: the development of cGvHD
- Type of the conditioning regimen: chemotherapy or chemotherapy in combination with TBI

For the following subgroups, enough data was available to report data separately: autologous recipients, allogeneic recipients receiving MAC, and those receiving RIC. A narrative approach was used to summarize data on the influence of TBI and cGvHD, because only limited data was available on these risk indicators.

Results

Electronic searches and citation searching retrieved 3923 references. After removing duplicates, conference abstracts, study protocols, and non-English papers, 1792 unique publications remained. Screening of titles and abstracts resulted in discarding of 1429 records. Full-text copies of the remaining 363 publications were obtained, and of these, 295 publications were excluded because no outcome of interest was reported. Full-text reading of the remaining 68 publications resulted in the exclusion of another 42 publications that did not meet the inclusion criteria (Table S3). Study characteristics of the 22 included studies (26 references) are listed in Table1. The flow diagram of this process is presented in Fig. 1 (29).

Authors of 18 studies were contacted in an attempt to obtain additional information. We were unable to reach four authors (23, 43, 52, 55); four authors replied that data was no longer available (37, 47, 48, 50). Four authors provided additional information (19, 36, 38, 41), three authors provided additional data (40, 45, 49) and three authors provided individual patient data (39, 44, 54).

Two randomized clinical trials (48, 50), 13 longitudinal cohort studies and seven cross-sectional studies were included. The majority of the studies was conducted in Europe, while six studies were conducted in the USA, one in Asia, and one in Brazil. The age of the included patients varied considerably between and within the included studies. Several studies reported a mean or median age of below 40 at HCT (6, 41, 53) , while others included patients with a median or mean age of above 60 (43, 49). Patients were diagnosed with a variety of, mostly haematological, diseases, while some studies included patients with solid tumours as well.

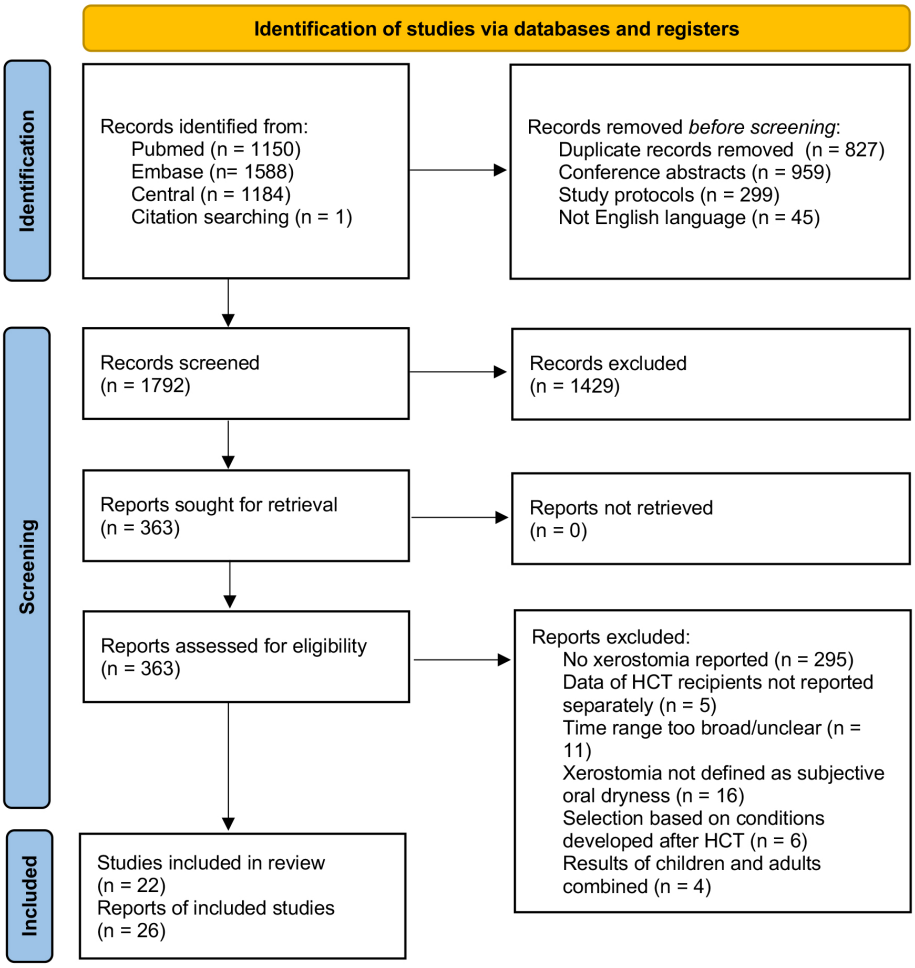

Figure 1. PRISMA flow diagram (29)

Table 1. Characteristics of included studies

	Median age (range) at study	Diagnoses[1]	Treatment	Questionnaire (time frame)	Xerostomia outcome	Time points of xerostomia measurements
Abasaeed 2018 USA (34) Longitudinal	49	AML; MM; MDS; ALL; other	7 autologous 16 allogeneic 20 MAC; 3 RIC 39% TBI	QLQ-H&N35 (last week)	Severity	• Pre-transplant • Day 30 (±5) • Day 80 (±5)
Andersson 2008, 2009, 2011 Sweden (5, 23, 35) Longitudinal	54 (19–70)	Lymphoma; MM; AL; CL; Solid tumours; other	145 autologous 57 allogeneic 167 MAC; 32 RIC 9% TBI	QLQ-HDC-19 (last week)	Prevalence Severity	• Inclusion • Baseline • 1 month post-HCT • 3 months post-HCT[2] • 6 months post-HCT[2] • 12 months post-HCT
Arduino 2022 Italy (19) Cross-sectional	Mean: 54 (SD 11)	AL/MDS; MM; Lymphoma/CLL; other	32 allogeneic 12 MAC; 20 RIC 47% TBI	Asking if xerostomia was present	Prevalence	> 2 years post-HCT 49 months (SD 11) post-HCT
Bennett 2015 USA (36) Longitudinal	Mean: 55 (SD 14)	MM; AML; MS; CLL/ PSS; ALL; NHL; other	18 autologous 14 allogeneic 25 MAC; 7 RIC	PRO-CTCAE (last week)	Severity[2]	Hospital: week 1, 2, 3 and 4 Post-hospital: week 1, 2 3 and 4
Bergkvist 2015 Sweden (37) Cross-sectional	At HCT: 44 (19–61) At study: 49 (21–65)	AL; CL; MPD/ MDS Lymphoma; Myeloma; other	117 allogeneic 69 MAC; 48 RIC 42% TBI	SFID-SCT (last week)	Prevalence	Median 5 (1–11) years post-HCT
Cheon 2021 South Korea (38) Cross-sectional	45 (21–70)	AML; ALL; AA; MS; other	67 allogeneic 17 MAC, 50 RIC No TBI	Is your mouth dry because your saliva has decreased?	Prevalence	> 2 years post-HCT Median 25.7 months
Edman 2001 Sweden (6) Cross-sectional	Mean: 39 (22–62)	CML; AML; other	25 allogeneic 25 MAC[6] 88% TBI	SFID-BMT (last month)	Prevalence	2–4 year post-HCT

Table 1. Continued

	Median age (range) at study	Diagnoses[1]	Treatment	Questionnaire (time frame)	Xerostomia outcome	Time points of xerostomia measurements
Eriksson 2022 Sweden (39) Longitudinal	52 (18–65)[3]	AL; MDS; CL; lymphoma, plasma cell disorder; other	195 allogeneic 61 MAC, 134 RIC 29% TBI	SFID-SCT (last week)	Prevalence Severity[3] Distress[3]	• Baseline • 4 months post-HCT • 7 months post-HCT • 13 months post-HCT
Ferreira 2020 Brazil (40) Longitudinal	53 (19–75)	NHL; MM; AML; CML; MS; ALL; Crohn's disease; other	31 autologous 20 allogeneic 51 MAC[6] 10% TBI	QLQ-H&N35 (last week)	Severity[3]	• Before conditioning • During neutropenia
Hayden 2004 Ireland (41) Cross-sectional	At HCT: 36 (14–55) At study: adults	CML	46 allogeneic 46 MAC[3] 29% TBI	QLQ-Leu (last week)	Prevalence Severity	Median 98 months (34–217) post-HCT
Iestra 2002 The Netherlands (42) Longitudinal	Mean (SD) Completers: 44 (11) Dropouts: 40 (11)	Leukaemia; MM; other	60 autologous 58 allogeneic 118 MAC[6] 64% TBI	self-designed questionnaire (>2 days in last 14 days)	Prevalence	• Day 50 (all discharged) • Day 75 • Day 125 • Day 200 • Day 350
Jones 2013 USA (43) Longitudinal	Mean: 62 (SD 7)	MM	66 autologous 66 MAC no TBI	MDASI-MM (past 24 hours)	Prevalence (moderate/severe)[2] Severity	• Before conditioning • 7 days post-HCT
Kirsch 2014 Switzerland (44) Cross-sectional	At HCT: 43 (18–68) At study: 52 (20–76)	AML/CML; ALL/CLL; MS/MPS; HL/NHL; plasma cell disorder; other	361 allogeneic[4] 272 MAC, 86 RIC 58% TBI	PROVIVO (last week)	Prevalence[3] Severity[3] Distress[3]	≥ 1 year post-HCT Median 7.1 year (1–33)
Kolke 2019 USA (45) Longitudinal	Mean: 58 (SD 12)	Lymphoma; MM, Leukaemia; MS; other	33 Autologous 21 allogeneic 40 MAC, 14 RIC[6] 4% TBI	MSAS-SF (last week)	Prevalence[3] Distress[3]	• Prior to hospitalization • Nadir, hospital days 7–13 • Discharge, hospital days 14–24

Table 1. Continued

	Median age (range) at study	Diagnoses[1]	Treatment	Questionnaire (time frame)	Xerostomia outcome	Time points of xerostomia measurements
Larsen 2003, 2004 Sweden (46, 47) Longitudinal	45 (18–65)	breast cancer; CL; AL; MM; other	26 autologous 17 allogeneic 43 MAC 42% TBI	SFID-SCT (moment of answering)	Prevalence Severity[2] Distress[2]	• Admission, day – 11 to – 1 • Day before conditioning • Day of HCT • Start protective care, day 1–6 • Mid protective care • End protective care, day 8–29 • Discharge, day 11–57
Lockhart 2005 USA (48) Longitudinal	Mean (SD) Pilocarpine: 48 (11) Placebo: 46 (10)	breast cancer; lymphoma; MM; AML; other	36 autologous[5] 36 MAC, 11% TBI	VAS (most of the time, asked every day)	Severity (mean and max)[2]	From day 1 of chemotherapy till day 10
Naegele 2018 Germany (49) Longitudinal	61 (43–74)	MM	29 autologous 29 MAC no TBI	PROVIVO (last week)	Prevalence Severity Distress	• Admission, day – 4 to – 3 • Nadir, day 5–8 • Discharge, day 14–21 • 30 days after discharge, day 43–55
Vellenga 2001, van Agthoven 2001 (50, 51) The Netherlands Longitudinal	ABMT: 50 (18–63) PSCT: 51 (18–64)	NHL; HL	118 autologous 118 MAC no TBI	RSCL (last week)	Distress	14 days post-HCT 3 months post-discharge
Warchala 2019 Poland (52) Longitudinal	Mean: 40 (SD 13)	AML; ALL	60 allogeneic	RSCL (last week)	Distress	Discharge (days from HCT not reported)

Table 1. Continued

	Median age (range) at study	Diagnoses[1]	Treatment	Questionnaire (time frame)	Xerostomia outcome	Time points of xerostomia measurements
Watson 2004 United Kingdom (53) Cross-sectional	Age at entry Autologous: 37 (15–52) Allogeneic: 32 (16–49) ≥ 18 at study	AML	74 autologous 97 allogeneic 171 MAC[6] 81% TBI	QLQ-Leu (last month)	Prevalence	≥ 1 year post-HCT Median 14 months (IQR 12–22)
Wood 2013 USA (54) Longitudinal	58	AML; MM; NHL; ALL; MDS; other	10 autologous 22 allogeneic 21 MAC, 11 RIC No TBI	PRO-CTCAE (last week)	Severity[3]	• Baseline (day – 20) • Day 0 • Day 7 • 2–4 weeks (mean, day 14–28)[3] • 1–2 months (mean, day 35–56)[3] • 2–5 months (mean, day 63–100)[3]
Wysocka-Słowik 2021 Poland (55) Longitudinal	Mean: 47 (19–69)	AML	80 allogeneic 54 MAC, 26 RIC	authorial questionnaire	Prevalence Severity	• day – 10 to day – 7 • day + 3 to day + 7 • day + 8 to day + 14

Abbreviations: ABMT, autologous bone marrow transplantation; PSCT, peripheral stem cell transplantation; AA, Aplastic anaemia; AL, Acute leukaemia; ALL, Acute lymphoblastic leukaemia; AML; Acute myeloid leukaemia; CL, Chronic leukaemia; CLL, chronic lymphocytic leukaemia; CML chronic myeloid leukaemia; HL, Hodgkin's lymphoma; MDS, myelodysplastic syndrome; MM, Multiple myeloma; MPS, Myeloproliferative syndrome; MS, Myelodysplastic syndrome; NHL, Non-Hodgkin's lymphoma; PSS, progressive systemic sclerosis; MAC, myeloablative conditioning; RIC, reduced intensity conditioning; TBI, total body irradiation; HCT, haematopoietic cell transplantation; IQR, inter quartile range

[1] Diagnoses are ordered from high prevalence to low prevalence, diagnoses that count for ≤ 5% of the population are included in the category 'other'

[2] Data extracted from graph (Andersson: only subgroups after 3 and 6 months)

[3] Additional data provided by the authors

[4] 15 patients that were < 18 years old at HCT were excluded from the dataset

[5] Only data of 16 patients that received no pilocarpine were included

[6] Doses of the conditioning regimen not reported, the distinction between MAC and RIC was estimated by an haematologist

Quality of reported outcomes

Quality scores of outcomes as reported in the included papers are listed in Table S4. Quality scores ranged between 1 (19) and 7 (23), with a median score of 4. If applicable, subgroups were scored separately because smaller numbers of patients could lead to a lower estimated precision. One study reported outcomes with a low risk of bias (23), the majority was classified to have a moderate risk of bias, and seven were classified to have a high risk of bias (6, 19, 38, 41, 48, 52, 55).

Prevalence of xerostomia

Prevalence of xerostomia over time after HCT is shown in Fig. 2. Prevalence was based on questions using a yes/no format or ordinal questionnaires. The majority of the studies included both autologous and allogeneic HCT recipients. Notwithstanding the heterogeneity between the studies, a clear trend over time is visible. Shortly after treatment, the prevalence of xerostomia increases, affecting the majority of patients during hospitalization. The prevalence starts to decline again after discharge, reaching levels largely comparable to baseline 1–2 years post-HCT. Two studies could not be included in this figure, because results were reported as "> 1 year post-HCT," which overlaps two of the chosen time periods: reported prevalences were 47% (53), and 49% (37). The prevalence of xerostomia in HCT recipients was high compared to the mean prevalence in the general population, as derived from a meta-analysis, including results of 26 epidemiological studies of adult, mostly older, populations (56).

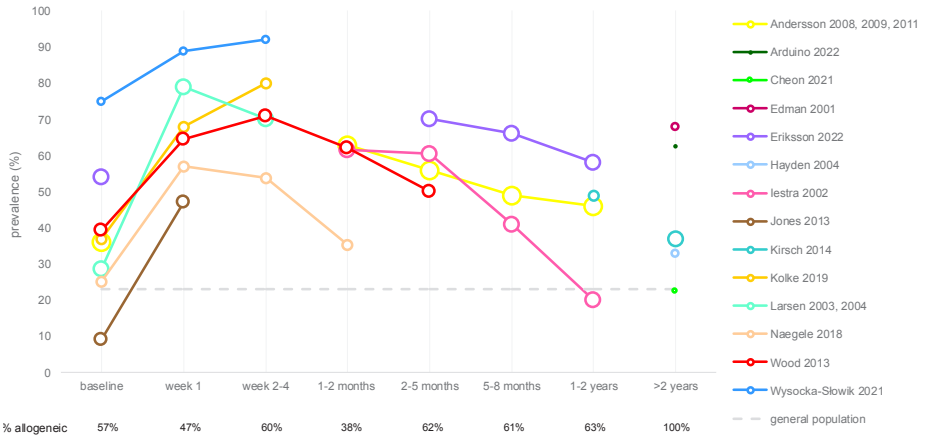

Figure 2. Prevalence of xerostomia over time. Prevalence of xerostomia as reported in 14 studies represented by different colors, including both autologous and allogeneic HCTrecipients. The size of the circles refers to the quality of the reported outcome (the larger the circle, the lower the risk of bias). Proportion of allogeneic HCT recipients per time period is listed below the graph. The gray dotted line represents the prevalence of xerostomia in the general population [56].

Severity of xerostomia

The severity of xerostomia over time after HCT is shown in Fig. 3. The scores were derived from different questionnaires and recalculated to a scale from 0 to 100. The phrasing of the questions and the response options can be found in Table S5a.

Complaints increased shortly after the conditioning regimen: the increase in rescaled severity of xerostomia in the first week post-HCT was on average 28 points (95% CI: 20–37), based on outcomes with a moderate risk of bias as reported in five studies (Figure S1a). Two to 5 months post-HCT, severity of xerostomia was still raised with 13 points compared to baseline (95% CI: 7–18) based on outcomes with a moderate to low risk of bias as reported in four studies (Figure S1b). One to 2 years post-HCT, the severity of xerostomia decreased further, reaching a level close to baseline (MD: 6, 95%CI: 2–10, moderate to low risk of bias, two studies, Figure S1c). No evidence was available to support a further decrease on the very long term.

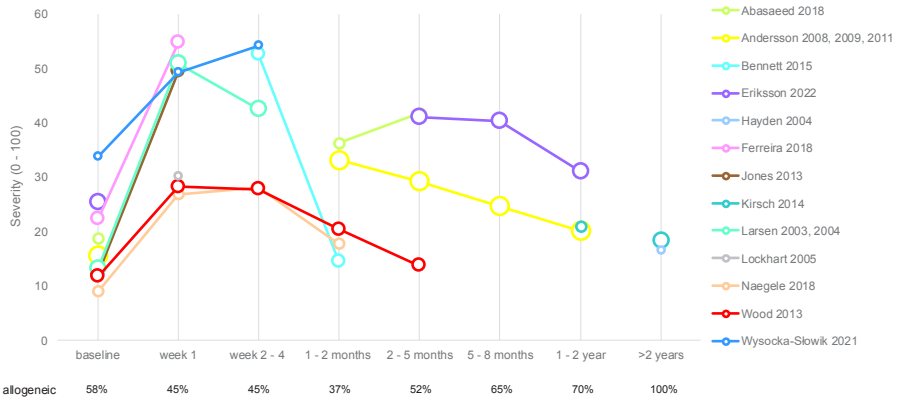

Figure 3. Severity of xerostomia over time. Rescaled severity of xerostomia (0–100) as reported in 13 studies represented by different colors, including both autologous andallogeneic HCT recipients. The size of the circles refers to the quality of the reported outcome (the larger the circle, the lower the riskof bias). Proportion of allogeneic HCT recipients per time period is listed below the graph.

Distress caused by xerostomia

Only seven studies reported distress caused by xerostomia after HCT. Results are shown in Fig. 4. The scores were derived from different questionnaires and recalculated to a scale from 0 to 100. The phrasing of the questions and the response options can be found in Table S5b. The distress caused by xerostomia increased shortly after treatment and decreases in the long term. Results of Warchala et al. (2019) (52) could not be included in this figure because it was unclear if discharge took place within 2–4 weeks post-HCT (52): the rescaled mean distress score was 23 at discharge.

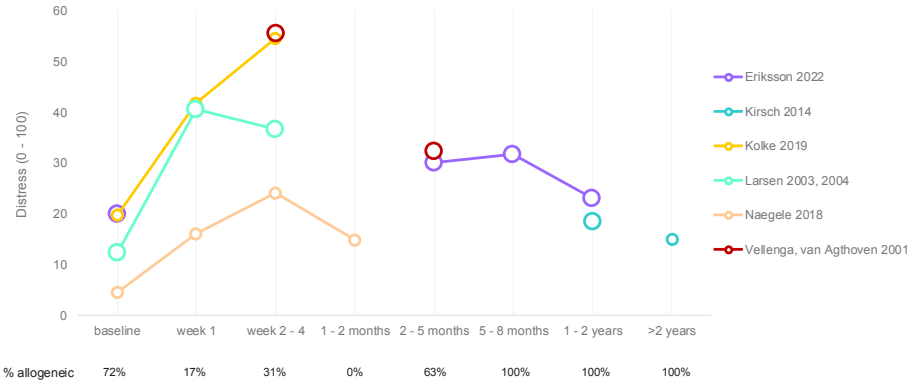

Figure 4. Distress caused by xerostomia over time. Rescaled distress (0–100) caused by xerostomia as reported in 6 studies represented by different colors, including both autologous and allogeneic HCT recipients. The size of the circles refers to the quality of the reported outcome (the larger the circle, the lower the risk of bias). Proportion of allogeneic HCT recipients per time period is listed below the graph.

Risk indicators for the development of xerostomia

Risk indicators were defined to determine the influence of type of transplantation and conditioning regimen on the development of xerostomia. Severity data of autologous recipients, allogeneic recipients receiving MAC, and those receiving RIC could be reported separately. Such a distinction could not be made for prevalence and distress data. Limited data on the other risk indicators, type of conditioning regimen and development of cGvHD, was described. Even though risk indicators are discussed separately below, these factors are not independent.

Type of HCT and intensity of the conditioning regimen

Three studies reported results for autologous and allogeneic recipients separately (23, 53, 54), and two studies divided allogeneic MAC and allogeneic RIC recipients (5, 55). This distinction could be made for two other studies because individual patient data was provided (39, 44). The severity of xerostomia in autologous HCT recipients is shown in Fig. 5a and in allogeneic recipients in Fig. 5b.

In autologous HCT recipients, the severity of xerostomia increased shortly after treatment; the decline started after discharge and resulted 1 year post-HCT in levels similar to baseline. The severity of xerostomia in autologous recipients and allogeneic MAC recipients was comparable during the first week (54) and the first month post-HCT (23, 54). One year post-HCT, allogeneic MAC recipients perceived more severe xerostomia than autologous HCT recipients (23). Furthermore, the prevalence of xerostomia > 1 year post-HCT was 54% in allogeneic MAC recipients,

while it was 39% in autologous recipients (53). Following RIC, only a limited or even no increase in xerostomia was shown in the post-discharge period.

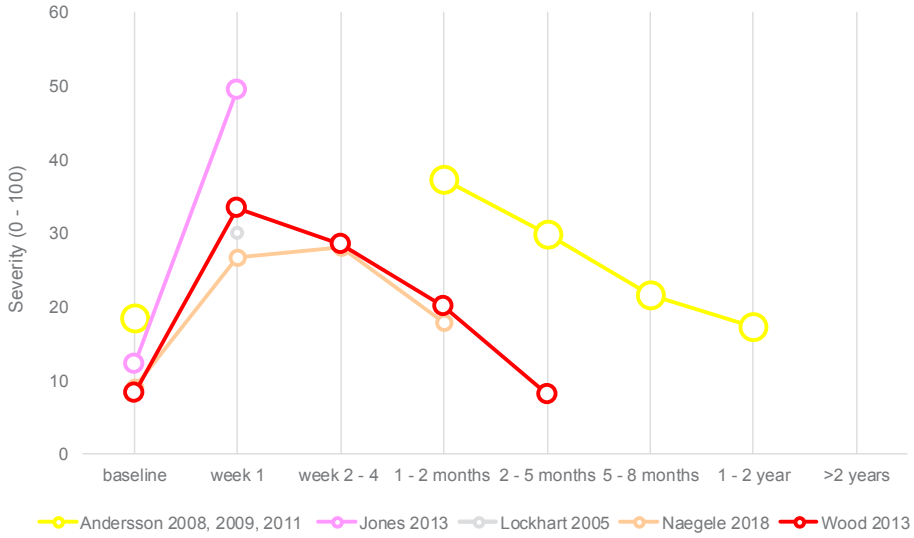

Figure 5a. Severity of xerostomia in autologous HCT recipients. Rescaled severity of xerostomia (0–100) in autologous HCT recipients as reported in 5 studies, represented by different colors. The size of the circles refers to the quality of the reported outcome (the larger the circle, the lower the risk of bias).

Looking at the allogeneic subgroups, it is shown that the heterogeneity between the studies at baseline was substantial. All meta-analysis performed to compare MAC and RIC included three studies reporting outcomes with a moderate risk of bias. There was no difference in the severity scores at baseline, comparing patients planned to receive MAC or RIC (MD: 0, 95% CI: – 13–12, Figure S2a). If the two groups were compared 2–5 months post-HCT, MAC caused more severe xerostomia than RIC: the severity in MAC recipients was 18 points higher (95% CI: 9–27) compared to RIC recipients (Figure S2b). One to 2 years post-HCT, the difference was not significant anymore (MD: 9, 95%CI: – 8–26, Figure S2c).

Development of cGvHD

In cross-sectional studies with a long-term follow-up (> 1 year), the incidence of cGvHD in allogeneic HCT recipients was 45% (37, 44), 48% (41), 54% (38), 59% (19) and 72% (6). In longitudinal studies, the incidence of cGvHD was 39% (5) in the first year after treatment, and 27% 1 year post-HCT (39). None of the included studies determined the relation between cGvHD and xerostomia. Based on the rescaled individual patient data from Kirsch et al. (2014), patients with cGvHD had a higher

prevalence of xerostomia (47%, mean severity: 25) in comparison to those without cGvHD (31%, mean severity: 14) (44).

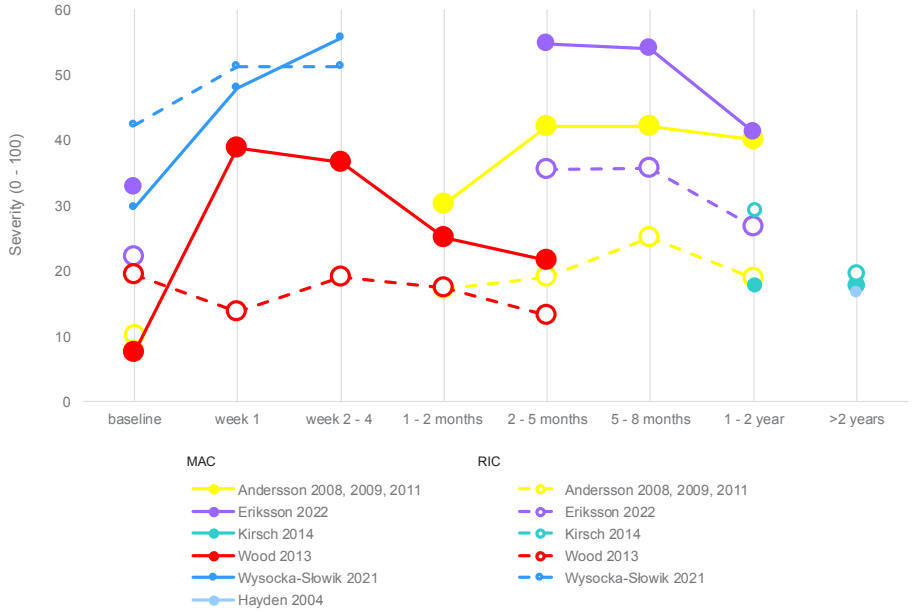

Figure 5b. Severity of xerostomia in allogeneic HCT recipients. Rescaled severity of xerostomia (0–100) in allogeneic HCT recipients as reported in 6 studies, represented by different colors. Patients receiving a myeloablative conditioning regimen (MAC) are represented by solid lines and circles; patients receiving a reduced intensity conditioning regimen (RIC) are represented by dashed lines and empty circles. The size of the circles refers to the quality of the underlying subgroup (the larger the circle, thelower the risk of bias).

Type of conditioning regimen: chemotherapy with or without TBI

Looking at patients included in the subgroups (Fig. 5a, b), 1% of the autologous, 25% of the allogeneic RIC recipients, and 56% of the allogeneic MAC recipients received TBI (proportion of TBI recipients was unclear in one study (55)). Iestra et al. (2002) reported that TBI recipients experienced median 4 (range: 0–4) episodes of xerostomia in the first year post-HCT, while patients treated without TBI experienced median 0 (range: 0–2) episodes (42). Individual patient data from Eriksson et al. (2022) showed that TBI recipients perceived non-significantly more xerostomia during the first year after treatment, in comparison to those that did not receive TBI (39). From Kirsch et al. (2014) individual patient data, it could be calculated that the prevalence of xerostomia between patients that received TBI (38%, mean severity 19) and those that did not receive TBI (37%, mean severity 17) did not differ > 1 year post-HCT (44).

Discussion

From this systematic review, it becomes clear that the prevalence of xerostomia in HCT recipients is high in comparison to the general population (56). This difference already exists at baseline, increases after HCT and remains after recovery in the long term. Based on reported outcomes with a moderate risk of bias, the severity of xerostomia increases shortly after HCT with 28 points on a 0–100 scale (95% CI: 20–37) and declines after discharge from the hospital. We conclude that the severity of xerostomia is still raised 2–5 months post-HCT and reaches scores largely comparable to baseline levels after 1 year. Distress caused by xerostomia follows the same trend over time.

The development of xerostomia is related to the decline in salivary flow rate after HCT (20). Comparing xerostomia with reduction in salivary flow rate, a comparable trend over time is seen. Stimulated flow rate decreases shortly after HCT (24, 40), is still lowered 6 months post-HCT (57, 58), and returns to baseline levels after one year (57, 58). The reduction in salivary flow rate is predominately attributed to the conditioning regimen toxicity, and the high number of medications that the patients use preceding and following the transplantation (9).

The reported prevalence of xerostomia is much higher than the prevalence of hyposalivation (9, 12, 19), thus xerostomia could only partially be explained by a reduction in flow rate. Change in composition (20) and viscosity (59) of saliva, or neuropathic mechanisms (18), might be related to xerostomia as well. Furthermore, we hypothesize that xerostomia might be associated with changes in mucosa due to mucositis or cGvHD. Another risk indicator for the development of xerostomia might be the psychological distress that the patients experience in relation to the disease and the treatment (26, 60).

The intensity of the conditioning regimen is the most objectifiable risk indicator for the development of xerostomia. Severity of xerostomia shows a marked increase in the two subgroups receiving a high intensity conditioning regimen, but not in the subgroup receiving RIC. Higher intensity conditioning is also related to a higher incidence of oral mucositis (61), a higher patient-reported symptom severity (62) and a tendency towards increasing prevalence of hyposalivation (57). We conclude with a moderate risk of bias that severity of xerostomia is higher in allogeneic MAC recipients compared to RIC recipients 2–5 months post-HCT (rescaled MD: 18; 95% CI: 9–27). This difference did not exist at baseline, and is not significant anymore after 1–2 years.

After conducting this systematic review, it remains unclear whether TBI has an additional effect on the development of xerostomia compared to chemotherapy alone. Even though patients who received TBI as part of the conditioning regimen had a higher risk of mouth dryness (63), other publications found no (8) or no significant additional effect of TBI (2). The dose of TBI administered as part of the conditioning regimen might not reach the threshold above which salivary gland function will be diminished (64).

In the autologous subgroup, the severity of xerostomia starts to decline after discharge, reaching baseline levels after 3 or 12 months. The peak in complaints in allogeneic HCT recipients seems to be delayed or prolonged, and baseline levels might not be reached after 1 year. The relatively high post-discharge severity of xerostomia in allogeneic HCT recipients might be related to the development of cGvHD. cGvHD is associated with histopathological changes in salivary glands, a reduction in flow rate, and a change in the composition of saliva (65). None of the included studies determined the relation between cGvHD and xerostomia, but a higher prevalence of xerostomia could be calculated in patients that developed cGvHD in comparison to those without cGvHD (44). This finding is in agreement with the results of several studies that did not meet the inclusion criteria of this review (28, 66-68). Even though a higher prevalence of xerostomia is reported > 1 year post-treatment in allogeneic compared to autologous HCT recipients (53), older studies could not confirm this difference in the long term (69, 70).

The decrease in mouth dryness over time may be affected by loss to follow-up of the patients with the most complaints. Loss to follow-up in the populations is extensive and unavoidable, given that the mortality rate in the first year after treatment is 10% (23), 24% (39) and 25% (42). Relapse (23% (39) and 32% (23) during the first year post-HCT), worsening of physical condition and psychological distress are other reasons for loss to follow-up. The prevalence of xerostomia is lower in study completers in comparison to those that will be lost to follow up in the first year after HCT (42). This difference was clear at any measurement timepoint.

The results of the current review should be interpreted with caution, because the variation between the studies is extensive, and HCT recipients comprise heterogenous populations. The included studies are conducted in different geographic regions and included adult populations of different ages, which might have influenced perceived mouth dryness (56). Furthermore, several questionnaires using different phrasing, different response options and different time frames,

will have provided heterogeneity in the results. For example, studies using a 5- (49, 54) or 10-point scale (43) tend to report lower mean xerostomia scores at baseline than those using a 4-point scale (23, 34, 39, 40, 47, 55). Besides, chosen thresholds to calculate the prevalence of xerostomia influence the results: Jones et al. (43) reported the prevalence of moderate/severe xerostomia, explaining the low prevalence in this study. Because the large heterogeneity between the studies, conclusions about the development of xerostomia over time are only based on within study differences.

Despite the relatively strict inclusion criteria used in the current review, the number of included studies is high in comparison to the previous systematic review conducted in 2010 (1). This high number of included studies can be attributed to the extensive and detailed search strategy. Since xerostomia is reported in most papers as secondary outcome, or as part of a questionnaire assessing symptoms or quality of life, the terms "xerostomia" or "mouth dryness" were not reported in titles and rarely in abstracts. None of the included studies used a questionnaire specifically developed to measure the severity of xerostomia (71). A disadvantage of this approach is that the outcome xerostomia itself is not validated, although it is frequently extracted from validated questionnaires. Even though mean severity or distress scores are not the optimal way of reporting xerostomia, since the underlying data will not be normally distributed, we judged that mean scores are the best outcome to visualize changes over time.

Risk of bias was assessed with the quality grading strategy published by Brennen et al. in 2010 (32), aiming to rate the risk of bias of oral complications from cancer therapies. This strategy was chosen because it matched our research question very well. Another advantage of this approach is that the risk of bias of the xerostomia outcomes was rated instead of the overall study quality, which is more appropriate because the majority of the studies was not designed to report specifically on oral complications. Use of questionnaires that were not validated to measure xerostomia and inclusion of relatively small single-centre populations resulted in reduced quality scores for the xerostomia outcome (median 4, range 1–7). The meta-analysis, conducted to support conclusions drawn from the graphs, includes only studies that reported xerostomia with a moderate to low risk of bias to increase their robustness (72).

Patient-reported subjective mouth dryness or xerostomia is a serious complaint after HCT affecting the majority of the patients. Patient-reported outcome measures are associated with quality of life measures (73) and reflect daily health status

better than clinician reported outcomes (74). Xerostomia is even rated as one of the most bothersome symptoms by patients (5, 6). Complaints in autologous HCT recipients seems to be transient in nature, while severity of xerostomia in allogeneic MAC recipients might remain elevated. The intensity of the conditioning plays a key role in the short-term development of xerostomia, while factors affecting the long-term recovery remain largely unknown. Further longitudinal studies are warranted, focusing on the effect of TBI, medications, and development of cGvHD as potential risk indicators for xerostomia.

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Supplementary files

The following supplementary table and figures can be found online. For the updated meta-analyses, we refer to Chapter 7.

- **Table S3, characteristics of excluded studies**
- **Figure S1, meta-analysis: change in xerostomia (0 – 100) from baseline.**
- **Figure S2, meta-analysis: differences in severity of xerostomia (0 – 100) between allogeneic HCT recipients receiving a myeloablative conditioning (MAC) in comparison to those receiving a reduced intensity conditioning (RIC) at different moments in time**

Table S1a, Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1	MeSH descriptor: [Bone Marrow Transplantation] explode all trees
#2	(((bone marrow or cord blood or cord stem or marrow stem or placental blood or peripheral blood) and (graft* OR transplant*)) or BMT or (stem cell and transplant*) or SCT or HSCT):ti,ab,kw
#3	(Patient Reported Outcome* or PROM):ti,ab,kw
#4	MeSH descriptor: [Xerostomia] explode all trees
#5	(xerostomia or ((dry*or sicca) and (oral or mouth)) or (saliva* and (flow or secret*)) or hyposalivation):ti,ab,kw
#6	MeSH descriptor: [Taste] this term only
#7	MeSH descriptor: [Mouth] explode all trees
#8	MeSH descriptor: [Oral Manifestations] explode all trees
#9	MeSH descriptor: [Saliva] explode all trees
#10	(Oral or taste or tastes or mouth or mouths or saliva* or dentition or questionnaire):ti,ab,kw
#11	MeSH descriptor: [Surveys and Questionnaires] explode all trees
#12	MeSH descriptor: [Quality of Life] explode all trees
#13	(Quality of life or HRQOL or QoL):ti,ab,kw
#14	(MSAS or SFID or QLQ or RSCL or PedsQl or "medical late effects" or "Physical Well Being" or oral complaint* or "oral adverse effects" or "oral side effects" or "oral side effect" or "oral toxicity" or "oral discomfort" or "Symptom scale" or "Symptom Checklist" or "symptom assessment"):ti,ab,kw
#15	#1 or #2
#16	#6 or #7 or #8 or #9 or #10 or #11
#17	#12 OR #13
#18	#16 and #17
#19	#3 or #4 or #5
#20	#18 or #19 or #14
#21	#15 and #20

Table S1b, MEDLINE (Pubmed) search strategy

1: "bone marrow transplantation"[Mesh] OR (("bone marrow"[Tiab] OR cord blood[tiab] OR cord stem[tiab] OR marrow stem[tiab] OR placental blood[tiab] OR peripheral blood[tiab]) AND (graft*[Tiab] OR transplant*[Tiab])) OR BMT[Tiab] OR "stem cell transplantation"[Mesh] OR ("stem cell"[Tiab] AND transplant*[Tiab]) OR SCT[Tiab] OR HSCT[Tiab]
2: "Patient Reported Outcome Measures "[Mesh:noexp] OR PROM[tiab] OR patient reported outcome*[tiab]
3: xerostomia[Mesh:noexp] OR xerostomia[Tiab] OR (dry*[Tiab] OR sicca[Tiab]) AND (oral[Tiab] OR mouth[tiab])
4: saliva*[Tiab] AND (flow[Tiab] or secret*Tiab])) OR hyposalivation[Tiab]
5: "Taste"[Mesh] OR "Mouth"[Mesh] OR "Oral Manifestations"[Mesh] OR "Saliva"[Mesh] OR Oral[tiab] OR Taste[tiab] OR Tastes[tiab] OR Mouth[tiab] OR Mouths[tiab] OR Saliva*[tiab] OR Dentition[tiab]
6: "Dental Health Surveys"[Mesh:noexp] OR "Patient Health Questionnaire"[Mesh] OR "Self Report"[Mesh] OR questionnaire[Tiab] OR "Symptom scale"[Tiab]
7:"Quality of life"[Mesh] OR Quality of life[Tiab] OR HRQOL[Tiab] OR QoL[tiab]
8: (5 OR 6) AND 7
9: MSAS[Tiab] OR SFID[Tiab] OR QLQ[Tiab] OR RSCL[Tiab] OR PedsQl[Tiab]
10: "medical late effects"[Tiab] OR "Physical Well Being"[Tiab] OR oral complaint*[tiab] OR "oral adverse effects"[Tiab] OR "oral side effects"[tiab] OR "oral side effect"[tiab] OR "oral toxicity"[Tiab] OR "oral discomfort"[Tiab] OR "Symptom scale"[Tiab] OR "Symptom Checklist"[Tiab] OR "symptom assessment"[Tiab]
11: 2 OR 3 OR 4 OR 7 OR 8 OR 9 OR 10
12: 1 AND 11

Table S1c, EMBASE (Ovid) search strategy

(exp bone marrow transplantation/ OR ((bone marrow.ti,ab,kw. OR cord blood.ti,ab,kw. OR cord stem.ti,ab,kw. OR marrow stem.ti,ab,kw. OR placental blood.ti,ab,kw. OR peripheral blood.ti,ab,kw.) AND (graft*.ti,ab,kw. OR transplant*.ti,ab,kw.)) OR BMT.ti,ab,kw. OR stem cell transplantation/ or exp allogeneic stem cell transplantation/ or exp autologous stem cell transplantation/ or cord blood stem cell transplantation/ or exp hematopoietic stem cell transplantation/ or nonmyeloablative stem cell transplantation/ or exp peripheral blood stem cell transplantation/ OR (stem cell.ti,ab,kw. AND transplant*.ti,ab,kw.) OR SCT.ti,ab,kw. OR HSCT.ti,ab,kw.)
AND (xerostomia/ OR xerostomia.ti,ab,kw. OR ((dry*.ti,ab,kw. OR sicca.ti,ab,kw.) AND (oral.ti,ab,kw. OR mouth.ti,ab,kw.)) OR (saliv*.ti,ab,kw. AND (flow.ti,ab,kw. or secret*.ti,ab,kw.)) OR hyposalivation. ti,ab,kw. OR MSAS.ti,ab,kw. OR SFID.ti,ab,kw OR medical late effects.ti,ab,kw. OR Physical Well Being. ti,ab,kw. OR oral complaint.ti,ab,kw. OR oral complaints.ti,ab,kw. OR oral adverse effects.ti,ab,kw. OR oral side effects.ti,ab,kw. OR oral side effect.ti,ab,kw.) OR ((Taste/ OR taste discrimination/ OR exp Mouth/ OR mouth tissue/ OR mouth discomfort/ or mouth injury/ or mouth lesion/ OR Saliva/ OR exp salivary gland/ OR exp taste disorder/ OR Oral.ti,ab,kw. OR Taste.ti,ab,kw. OR Tastes.ti,ab,kw. OR Mouth.ti,ab,kw. OR Mouths.ti,ab,kw. OR Saliva*.ti,ab,kw. OR Dentition.ti,ab,kw. OR symptom scales. ti,ab,kw.) AND ("quality of life"/ OR Quality of life.ti,ab,kw. OR HRQOL.ti,ab,kw. OR QoL.ti,ab,kw.))

Table S2, Quality grading strategy for patient-reported mouth dryness, adapted from Brennan et al. (2010)

Quality measures	Quality points and definitions	Adaptations and additions
Representativeness	2: Multi-institution, consecutive* patients representative of underlying population 1: Single institution, consecutive patients, representative of underlying population 0: Convenience sample	Multi-institution, convenience sample was also classified as 1 * the word 'consecutive' should be reported or consecutive inclusion is likely based on described inclusion- and exclusion criteria, and numbers of excluded patients
Ascertainment bias	2: >4 assessments before/ after HCT 1: 2 – 4 assessments before/ after HCT 0: 1 assessment before/after HCT	Intervals as suggested for patients receiving radiotherapy were used (instead of chemotherapy as suggested by Brennan et al. 2010)
Misclassification bias	1: Prospective (patient or professional) 0: Retrospective (patient recall)	Prospective: time frame of ≤1 week used to recall symptoms Retrospective: time frame of >1 week used to recall symptoms
Examiner bias	1: Blinded 0: Unblinded	Blinded: questionnaire filled out by the patient or interview by blinded examiner Unblinded: interview by unblinded examiner or not reported
Oral complication assessment validity	2: Standard validated scale 1:Well-defined, study-specific scale 0: Not defined	Only studies using a questionnaire validated to measure xerostomia received 2 points
Estimate precision	Sample size sufficient to estimate a prevalence of 20% within 2: ±5% 1: ±10% 0: Greater than 10%	 2: n >246 1: n 61 – 246 0: n < 61

Table S4, quality of included studies

Study	subgroups	Representativeness	Ascertainment bias	Misclassification bias	Examiner bias	Oral complication assessment validity	Estimate precision	Total
Abasaeed 2018		0	1	1	1	1	0	**4**
Andersson 2008, 2009, 2011	total, autologous	1	2	1	1	1	1	**7**
	MAC, RIC	1	2	1	1	1	0	**6**
Arduino 2022		1	0	0	0	0	0	**1**
Bennett 2015		0	2	1	1	1	0	**5**
Bergkvist 2015		1	0	1	1	1	1	**5**
Cheon 2021		0	0	0	1	0	1	**2**
Edman 2001		1	0	0	1	1	0	**3**
Eriksson 2022	Total, RIC	1	1	1	1	1	1	**6**
	MAC	1	1	1	1	1	0	**5**
Hayden 2004		1	0	0	1	1	0	**3**
Ferreira 2018		1	1	1	1	1	0	**5**
Iestra 2002		1	2	0	1	1	1	**6**
Jones 2013		0	1	1	1	1	1	**5**
Kirsch 2014	>2 years total	1	0	1	1	1	2	**6**
	>2 years MAC >2 years RIC	1	0	1	1	1	1	**5**
	1 – 2 years	1	0	1	1	1	0	**4**
Kolke 2019		0	1	1	1	1	0	**4**
Larsen 2003, 2004		1	2	1	1	1	0	**6**
Lockhart 2005		0	0	1	1	1	0	**3**
Naegele 2018		0	1	1	1	1	0	**4**
Vellenga, van Agthoven 2001		1	1	1	1	1	1	**6**
Watson 2004		1	0	0	1	1	1	**4**
Warchala 2019		0	0	1	1	1	0	**3**
Wood 2013		0	2	1	1	1	0	**5**
Wysocka-Słowik 2021	total	0	1	0	1	0	1	**3**
	MAC, RIC	0	1	0	1	0	0	**2**

Table S5, phrasing of the used questionnaires

Table S5a, Questionnaires measuring severity of xerostomia

Questionnaire	Question	Response	Used by
EORTC QLQ-H&N35	During the past week: Have you had a dry mouth?	Not at all; A little; Quite a bit; Very much	Abasaeed 2018 Ferreira 2020
EORTC QLQ-HDC-19[1]	During the past week: Have you had a dry mouth?	4-point response scale ranging from 1 (not at all) to 4 (very much)	Andersson 2008, 2009, 2011
EORTC QLQ-Leu	During the Past MONTH, have you had problems with: mouth dryness?	Not at all; A little; Quite a bit; Very much	Hayden 2004
PRO-CTCAE	In the last 7 days, what was the SEVERITY of your DRY MOUTH at its WORST?	None; Mild; Moderate; Severe; Very severe	Bennet 2015 Wood 2013
PROVIVO			Kirsch 2014 Naegele 2018
SFID-SCT	Have you experienced mouth dryness?	not at all; yes, a little; yes, quite a lot; yes, a lot	Eriksson 2022
		scale ranging from 1 'a little intense' to 3 'very intense'	Larsen 2003, 2004
MDASI-MM	Have you had a dry mouth?	0 – 10 scale ranging from "not present" to "as bad as you can imagine"	Jones 2013
VAS	How does your mouth feel most of the time?	0: not dry at all, 100: dry as a desert	Lockhart 2005
Authorial questionnaire		None; mild; moderate; severe	Wysocka-Słowik 2021

Table S5b, Questionnaires measuring the distress caused by xerostomia

Quesionnaire	Question	Response	Used by
RSCL	Have you, during the past week, been bothered by: dry mouth?	Not at all; A little; Quite a bit; Very much	Vellenga 2001, van Agthoven 2001 Warchala 2019
SIFD-SCT	If you experienced mouth dryness have you been distressed by it?	not at all; yes, a little; yes, quite a lot; yes, a lot	Eriksson 2022
		scale ranging from 0 'no distress till 3 'very distressing	Larsen 2003, 2004
MSAS-SF	Did you have dry mouth? If yes, how much did it distress or bother you?	Not at all; a little bit; somewhat; quite a bit; very much	Kolke 2019
PROVIVO	If dry mouth dryness occurred, how much did it BOTHER or BURDENED you?	None; Mild; Moderate; Severe; Very severe	Kirsch 2014 Naegele 2018

Chapter 4

Subjective Oral Dryness following Haematopoietic Cell Transplantation: A Report from the Orastem Study

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Abstract

Xerostomia, or subjective oral dryness, is a serious complaint after haematopoietic cell transplantation (HCT). Xerostomia is rated as one of the most bothersome symptoms by HCT recipients, negatively affecting quality of life. This substudy of the Orastem study, a prospective longitudinal, international, observational, multicentre study, aimed to describe the prevalence and severity of xerostomia following HCT. Furthermore, the effect of the conditioning regimen, type of transplantation, and oral mucosal changes related to chronic graft-versus-host disease (cGvHD) in the development of xerostomia were studied. All HCT recipients rated xerostomia on a scale of 0 to 10 before the conditioning regimen, several times early post-HCT, and at 3 months post-HCT, and only allogeneic HCT recipients also rated xerostomia at 6 and 12 months post-HCT. In addition, stimulated whole saliva was collected several times. Linear regression models and longitudinal mixed-effects models were created to investigate the influence of risk indicators on xerostomia. A total of 99 autologous and 163 allogeneic HCT recipients were included from 6 study sites in Sweden, Canada, the Netherlands, and the United States. The prevalence of xerostomia was 40% before the conditioning regimen, 87% early post-HCT, and 64% at 3 months post-HCT. Complaints after autologous HCT were transient in nature, while the severity of xerostomia in allogeneic HCT recipients remained elevated at 12 months post-HCT. Compared to autologous HCT recipients, allogeneic HCT recipients experienced 1.0 point more xerostomia (95% confidence interval [CI], .1 to 2.0) early post-HCT and 1.7 points more (95% CI, .4 to 3.0) at 3 months post-HCT. Allogeneic HCT recipients receiving a high-intensity conditioning regimen experienced more xerostomia compared to those receiving a nonmyeloablative or reduced-intensity conditioning regimen. The difference was 2.0 points (95% CI, 1.1 to 2.9) early post-HCT, 1.8 points (95% CI, . 3 to 3.3) after 3 months, and 1.7 points (95% CI, .0 to 3.3) after 12 months. Total body irradiation as part of the conditioning regimen and oral mucosal changes related to cGvHD did not significantly influence the severity of xerostomia. Conditioning regimen intensity was a significant risk indicator in the development of xerostomia, whereas total body irradiation was not. Allogeneic HCT recipients experienced more xerostomia than autologous HCT recipients, a difference that cannot be explained by a reduction in stimulated salivary flow rate or the development of oral mucosal changes related to cGvHD.

Introduction

The oral cavity is a common site of complications of haematopoietic cell transplantation (HCT) and the preceding conditioning regimen. The Orastem observational study was conducted to study the impact of these oral site effects (1). Skallsjö et al. (2) recently reported the first results from the Orastem study. Pre-HCT, xerostomia was the most frequently reported oral symptom; almost 40% of the 272 HCT recipients reported some degree of xerostomia before the conditioning regimen.

Xerostomia is the subjective feeling of oral dryness (3). This self-reported symptom negatively influences quality of life (4) and is associated with oral discomfort (5) and difficulty with speech and food intake (3). HCT recipients rated xerostomia as one of the most bothersome symptoms (6, 7) and the main long-term oral complaint (8-10). Recently, we reported in a systematic review that the prevalence of xerostomia ranged between 49% and 89% early post-HCT (11). Despite the marked long-term recovery, the prevalence of xerostomia remained high at 1 year post-HCT compared to the general population (12). Xerostomia is caused primarily by a decrease in quantitative or qualitative function of the salivary glands (13). In the population of HCT recipients, this decrease might be caused by the acute toxicity of the high-dose conditioning regimen, consisting of chemotherapy with or without total body irradiation (TBI) (11), or by the high number of prescribed medications post-HCT (10). The development of chronic graft-versus-host disease (cGvHD), a complication following allogeneic HCT, also might be related to xerostomia. cGvHD may affect salivary glands and impair salivary flow (14), and also may affect the oral mucosa, characterised by erythema, lichenoid changes and ulceration (15). We hypothesize that oral mucosal changes might interact with the perception of mouth dryness and might result in xerostomia complaints even without a reduction in salivary flow rate.

A widely used method of measuring the quantitative function of the salivary glands is the collection of chewing stimulated whole saliva (SWS). To collect SWS, patients are asked to spit all saliva that accumulates in the mouth while chewing on (tasteless) chewing gum or paraffin wax for several minutes into a cup (16). Even though reduced function is the primary cause of subjective xerostomia complaints, xerostomia also may occur without objective evidence of salivary gland hypofunction, or hyposalivation (17). In HCT recipients, xerostomia was not related to a reduction in SWS flow rate, and the prevalence of xerostomia was 2.4-fold higher than that of hyposalivation of SWS (18). Skallsjo et al. (2) reported a very

weak correlation between SWS flow rate and xerostomia pre-HCT. Here we report longitudinal follow-up data for this population.

The aim of the present study was to determine the prevalence and severity of xerostomia over time in that cohort of HCT recipients. The influence of several risk indicators on xerostomia was assessed, and the relationship between SWS flow rate and xerostomia was explored.

Methods

The current substudy focused on one of the oral side effects, xerostomia and stimulated salivary flow rate, within the Orastem study, a prospective longitudinal, international, observational, multicentre study on the impact of oral side effects from conditioning therapy before HCT (1). In brief, adult (≥18 years) autologous and allogeneic HCT recipients were eligible for inclusion between March 2011 and May 2018. Patients were treated for various malignancies at 6 clinical study sites: Sahlgrenska University Hospital, Gothenburg, Sweden; Karolinska University Hospital Huddinge, Stockholm, Sweden; Atrium Health Carolinas Medical Center, Charlotte, North Carolina; Amsterdam UMC, Amsterdam, The Netherlands; Radboud University Medical Center, Nijmegen, The Netherlands; and BC Cancer, Vancouver, Canada. Combined results of the Swedish centres were reported because of the limited number of included patients in 1 of the centres. Diagnoses eligible for inclusion were reported previously (1), while the inclusion of autologous HCT recipients in the Dutch centres was restricted to the diagnosis of multiple myeloma. Approval from the Ethical Review Board at each study site was obtained, and written informed consent was provided by all patients.

Data on medical diagnosis requiring HCT, type of transplantation, previous radiotherapy to the head and neck region, comorbidities, and current medication use were collected from medical records. Medications used were divided into 36 categories and a category "other" for the remaining medications (Supplementary Table S1). The number of medication categories per patient was counted. Conditioning regimens were divided into 3 intensity categories: myeloablative (MAC), reduced intensity (RIC), and nonmyeloablative (NMA) conditioning regimens. This distinction was made by an haematologist based on the expected duration of cytopenia and requirement for stem cell support (19). Data on smoking habits and alcohol use were obtained by interviewing the patients.

Xerostomia and Salivary Flow Rate

Xerostomia was assessed using a numeric rating scale, ranging from 0 (no dry mouth) to 10 (severe dry mouth). At the preconditioning assessment, participants were asked to answer the following question: "How would you rate your overall feeling of dry mouth?" Early post-HCT, during hospitalization, patients completed a questionnaire 3 times a week. The xerostomia question was phrased slightly differently during this phase, adding a time frame of 24 hours to the wording ("how would you grade your feeling of mouth dryness during the last 24 hours?"). This early post-HCT questionnaire was completed until resolution of neutropenia (ie, absolute granulocyte count $>.5 \times 10^9$) or discharge from the hospital. Allogeneic HCT recipients answered the question on overall mouth dryness (the same question as before conditioning) also after 3, 6, and 12 months, whereas autologous HCT recipients answered the question only at 3 months post-HCT.

SWS was collected at the preconditioning assessment and at 3 months post-HCT. For allogeneic HCT recipients, SWS was also collected at 6 and 12 months post-HCT. Salivary flow was stimulated by chewing on a piece of neutral chewing gum base. SWS was collected for 5 minutes; hyposalivation was defined as a flow rate of <.7 mL/ minute (20).

Oral Mucosal Changes Related to cGvHD

Oral mucosal changes were scored in allogeneic HCT recipients at 3 months, 6 months, and 12 months post-transplantation. The following manifestations of oral mucosal cGvHD were evaluated: erythema, lichenoid changes, and ulcers. Each patient with 1 or more oral manifestations, independent of severity, was classified as having oral mucosal changes related to cGvHD.

Statistics

The overall prevalence of xerostomia was based on scores of 1 and higher. The prevalence was calculated before conditioning, during the first and second weeks post-HCT, and at 3, 6, and 12 months post-HCT. During the first and second weeks post-HCT, the prevalence was calculated based on the highest score for each patient recorded within this time period.

The mean severity of xerostomia, based on the numeric rating scale, was calculated before conditioning and at 3, 6, and 12 months post-HCT. During the early post-HCT phase, the severity of xerostomia was summarized using mean and maximum scores for each patient. Paired *t* tests were used to determine changes in xerostomia at 3 and 12 months compared to preconditioning scores. No statistical tests were

performed to directly assess the increase early post-HCT, because of the slightly different phrasing of the 2 xerostomia questions. Spearman correlation was used to determine the correlation between xerostomia and SWS flow rate, with values reported as Spearman rho (*r*) with *P* value. Several linear regression models were created to investigate the influence of the following risk indicators on xerostomia and SWS flow rate: (1) type of HCT (allogeneic versus autologous); (2) intensity of the conditioning regimen in allogeneic HCT recipients (MAC versus NMA/RIC); (3) TBI (yes versus no) as part of the conditioning regimen in allogeneic HCT recipients; and (4) long-term oral mucosal changes related to cGvHD in allogeneic HCT recipients.

The influence of the type of HCT (analysis 1) was determined early post-HCT and at 3 months post-HCT, whereas the effect of the conditioning regimen (analyses 2 and 3) was also determined at 12 months post-HCT. Longitudinal mixed-effects models were built to study repeated outcome measures: early post-HCT, when xerostomia was measured several times, and in the long term (analysis 4), when xerostomia, SWS flow rate, and oral mucosal cGvHD were recorded several times.

Crude 3- and 12-month models included the aforementioned risk indicators as only independent variables, and time since HCT was added to the longitudinal models. The following confounding factors were added to the adjusted models, whereas some covariates differed by model: age, sex, treatment centre, comorbidities (yes, no), use of (immunosuppressives yes, no), xerostomia score or SWS flow rate preconditioning, and intensity (MAC, NMA/RIC) and/or TBI (yes, no).

Results of the analysis are graphically shown as mean effects with 95% confidence intervals (CIs). Analyses were performed with SAS version 9.4 (SAS Institute). Graphics were created using R version 4.1.3 (R Foundation for Statistical Computing) and Prism version 9.5.0 (GraphPad Software).

Results

A total of 277 patients provided signed informed consent and were included in the Orastem study (2). Of these patients, 262 completed the xerostomia question before HCT, including 163 with planned allogeneic HCT and 99 with planned autologous HCT. Baseline characteristics of this population are reported in Table 1. The majority of autologous HCT recipients were diagnosed with multiple

myeloma, and those receiving allogeneic HCT were mostly diagnosed with acute leukaemia or myelodysplastic syndrome. Before conditioning, females experienced more xerostomia than males, older patients (≥55 years) had more xerostomia compared to younger patients, and xerostomia scores increased when more medication categories were used. Mean preconditioning xerostomia scores as influenced by these and other baseline variables are listed in Supplementary Table S2. Fourteen HCT recipients (4 autologous and 10 allogeneic) died before the 3-month follow-up, whereas another 21 allogeneic HCT recipients died before the 12-month follow-up.

Prevalence of Xerostomia

The prevalence of xerostomia in autologous and allogeneic HCT recipients is shown in Figure 1. Before conditioning, 51% of the autologous HCT recipients experienced xerostomia of some degree, and 13% reported a score >5. These percentages increased to 92% and 46%, respectively, during the first week post-HCT and then declined to 64% and 14%, respectively, at 3 months post-HCT. In allogeneic HCT recipients, 33% experienced xerostomia pre-HCT, and 3% reported a score >5. During the first week post-HCT, these percentages increased to 76% and 28%, respectively. The prevalence of xerostomia decreased in the long term; 48% of the allogeneic HCT recipients still had xerostomia at 12 months post-HCT, and 12% reported a score >5.

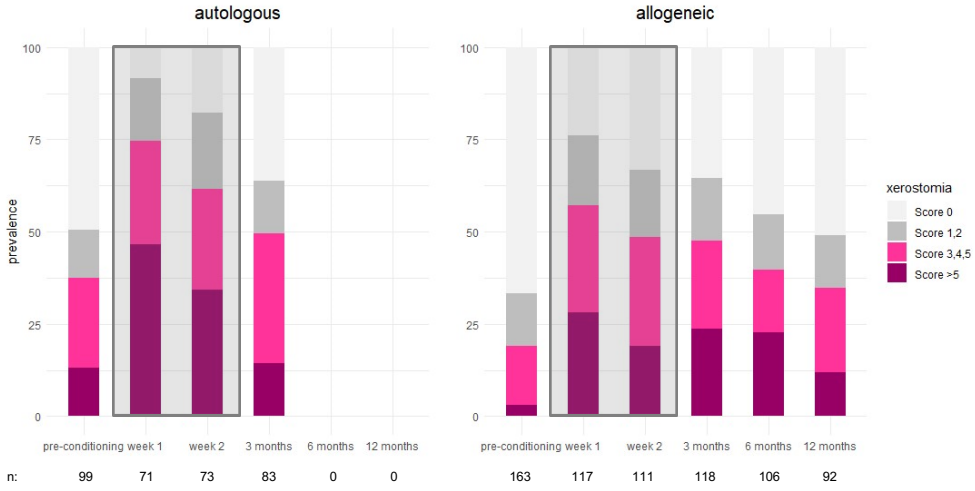


Figure 1. Prevalence of xerostomia in autologous and allogeneic HCT recipients. During the first and second weeks, the highest reported score from each patient was used to calculate the prevalence, as shown in the grey frame. The number of patients who completed the xerostomia question is listed below the graph.

Table 1. Baseline Characteristics

Characteristic	Autologous HCT Recipients (N = 99)	Allogeneic HCT Recipients (N = 163)
Age, yr, median (IQR)	57 (52-63)	56 (42-63)
Female sex, n(%)	43 (43)	65 (40)
Centre, n (%)		
- Gothenburg and Stockholm (Sweden)	19 (19)	18 (11)
- Vancouver (Canada)	22 (22)	31 (19)
- Amsterdam (The Netherlands)	29 (29)	14 (9)
- Nijmegen (The Netherlands)	24 (24)	56 (34)
- Charlotte (USA)	5 (5)	44 (27)
Diagnoses, n (%)		
- AML/ALL/MDS	1 (1)	97 (60)
- Myeloma	75 (76)	3 (2)
- Lymphoma	18 (18)	22 (13)
- Other	5 (5)	41 (25)
Comorbidities*, n (%)	56 (58)	80 (49)
Prior radiation therapy to head and neck region, n (%)	3 (3)	8 (5)
Medication categories, n, median (IQR)	4 (2-6)	3 (2-6)
Use of antineoplastics at baseline, n (%)	8 (8)	33 (21)
Conditioning, n (%)		
- MAC	92 (95)	42 (28)
- RIC	5 (5)	80 (53)
- NMA	0	30 (20)
TBI, n (%)	0	93 (61)
Stem cell source, n (%)		
- Peripheral blood	97(98)	139 (85)
- Bone-marrow	2 (2)	7 (4)
- Cord		6 (4)
- Unknown		11 (7)
Salivary flow rate in mL/5min, median (IQR)**	6 (3.3-8)	5 (3.6-9)

IQR indicates interquartile range; AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia; MDS, myelodysplastic syndrome.

The most frequent comorbidities were hypertension, diabetes mellitus and anaemia. More information on comorbidities was reported previously (2). If an abundant amount of saliva was produced, the collection was occasionally reduced to a minimum of 2 minutes and flowrates were recalculated to mL/5minutes.*

Severity of Xerostomia

Mean xerostomia scores over time are reported in Figure 2. Xerostomia scores in the allogeneic HCT recipients were elevated at 3 months post-HCT compared to before conditioning, an average of 2.3 (95% CI, 1.3 to 3.3) points higher in MAC recipients and 1.7 (95% CI, 1.0 to 2.5) points higher in NMA/RIC recipients. In autologous HCT recipients, xerostomia scores were not significantly different from preconditioning levels at 3 months post-HCT (mean difference, .4; 95% CI, -.2 to 1.0). At 12 months post-HCT, the mean score was still 1.2 points higher (95% CI, -.2 to 2.6) than preconditioning for MAC recipients and .8 point higher (95% CI, .0 to 1.6) than preconditioning for NMA/RIC recipients.

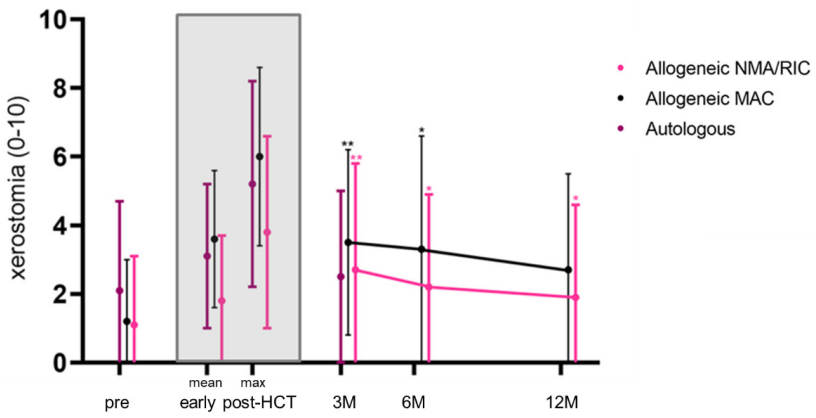


Figure 2. Mean xerostomia scores preconditioning (pre), early post-HCT and 3, 6, and 12 months post-HCT. Mean xerostomia scores and standard deviations are reported separately for allogeneic HCT recipients receiving an MAC conditioning regimen, those receiving an NMA/RIC regimen, and autologous HCT recipients. Early post-HCT, the average of all individual mean and maximum (max) scores is shown in the grey frame. Asterisks indicate whether xerostomia scores are significantly different from preconditioning scores: $^{**}P < .0001$; $^{*}P < .05$.

SWS Flow Rate and Xerostomia

Xerostomia was significantly but weakly correlated to SWS flow rate ($r = -.27$; $P = .0003$) at the 3-month follow-up. The change in xerostomia score after 3 months post-HCT compared to the preconditioning screening was not significantly correlated to the change in SWS flow rate during the same period. More correlation coefficients are reported in Supplementary Table S3.

Oral Mucosal cGvHD, Hyposalivation, and Xerostomia in Allogeneic HCT Recipients

At the 3-month follow-up, 14 allogeneic HCT recipients had oral mucosal erythema, lichenoid changes, or ulcers and were diagnosed as having oral mucosal changes related to cGvHD. Twenty-nine patients were diagnosed with oral mucosal changes at the 6-month follow-up, and 23 were diagnosed at the 12-month follow-up. In total, oral mucosal cGvHD was diagnosed 66 times in 43 patients; 59 of these diagnoses were accompanied by simultaneous measurements of salivary flow rate and xerostomia. The diagnosis of oral mucosal cGvHD was accompanied by the feeling of xerostomia in 71% of the occasions and with a score >5 in 22% (Figure 3).

Hyposalivation of SWS was diagnosed in 43 allogeneic HCT recipients at 3 months post-HCT, in 25 recipients at 6 months post-HCT, and in 18 recipients at 12 months post-HCT. In total, hyposalivation was diagnosed 86 times in 62 patients. Xerostomia was reported at 75% of the visits at which hyposalivation was diagnosed (Figure 3); 44% of these complaints involved a score >5.

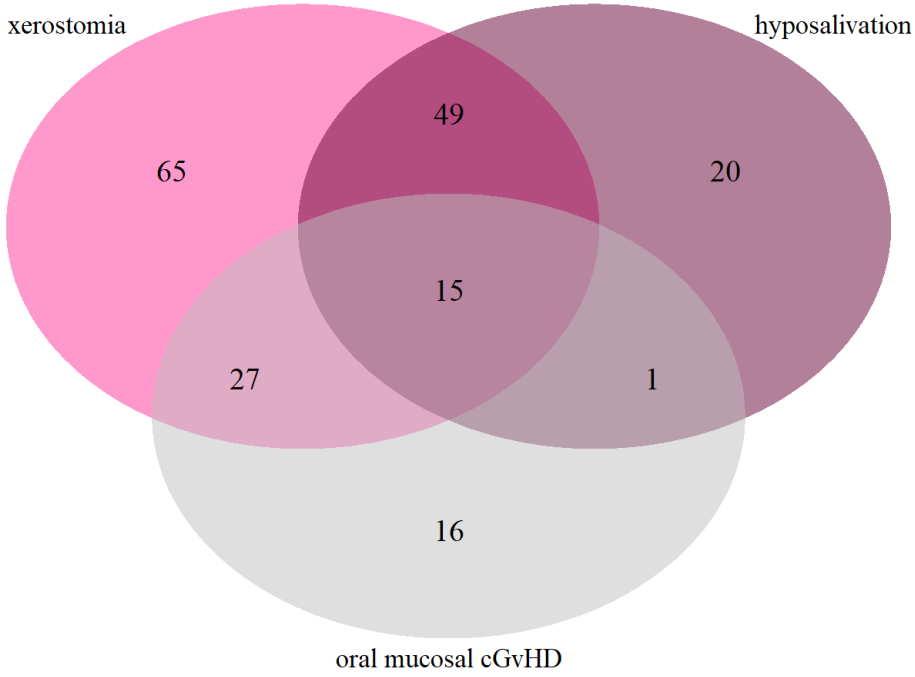


Figure 3. Venn diagram showing xerostomia (score ≥1), hyposalivation (SWS <.7 mL/minute), and oral mucosal changes related to cGvHD. Data from all allogeneic HCT recipients seen after 3, 6, and 12 months are combined. Overlap indicates simultaneous diagnoses.

Risk Indicators

Allogeneic HCT recipients experienced more xerostomia compared to autologous HCT recipients. Based on the crude model, autologous HCT recipients experienced more xerostomia early post-HCT, but adjusting for confounding factors – of which conditioning intensity had the most pronounced influence – reversed the effect. After adjustment, allogeneic HCT recipients experienced 1.0 point more xerostomia (95% CI, .1 to 2.0) early post-HCT and 1.7 points more (95% CI, .4 to 3.0) after 3 months. Type of transplantation was not associated with SWS flow rate at 3 months post-HCT (Figure 4).

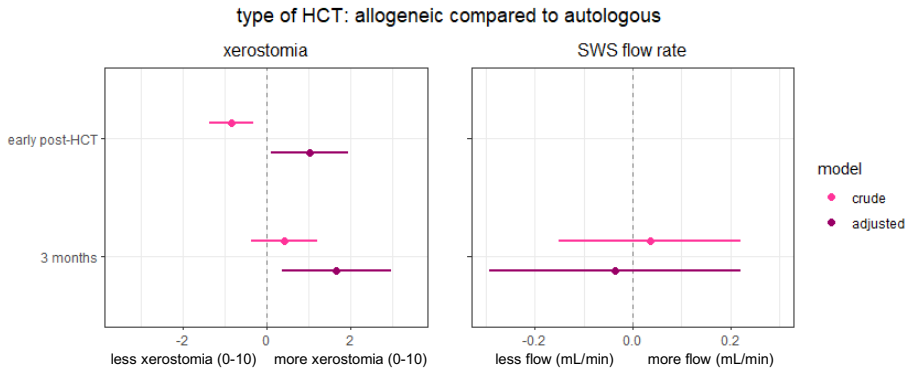
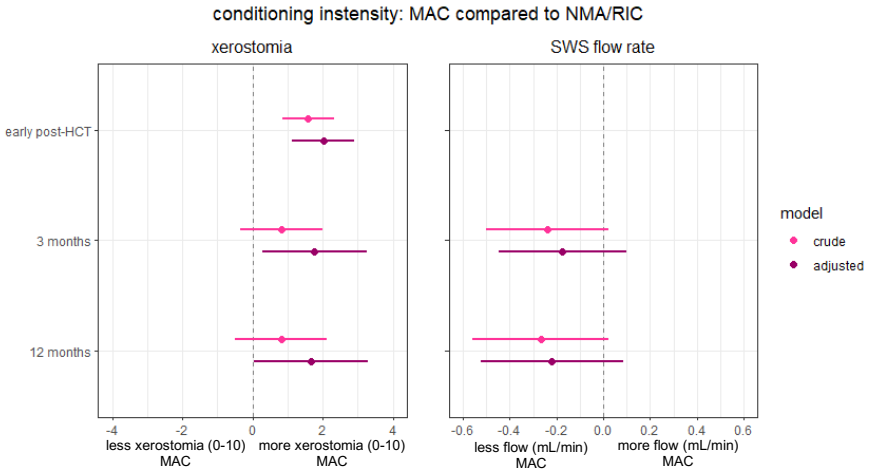


Figure 4. Effect of the type of HCT (allogeneic versus autologous) on xerostomia and SWS in HCT recipients. Mean effects with 95% CIs are reported early post-HCT (longitudinal mixed-effects model) and at 3 months post-HCT (linear regression). The following covariates were added to the adjusted models: time since HCT (only early post-HCT), intensity of the conditioning regimen, total body irradiation (yes versus no), age, sex, treatment centre, comorbidities, and preconditioning xerostomia or SWS flow rate.

Allogeneic HCT recipients receiving MAC experienced more xerostomia compared to those receiving an NMA/RIC regimen. After adjustment, the difference was 2.0 points (95% CI, 1.1 to 2.9) early post-HCT, 1.8 points (95% CI, .3 to 3.3) at 3 months post-HCT, and 1.7 points (95% CI, .0 to 3.3) at 12 months post-HCT. The conditioning intensity was not significantly associated with SWS flow rate at either the 3- or 12- month follow-up (Figure 5a). There was no significant difference in xerostomia or SWS flow rate between allogeneic HCT recipients who received TBI as part of the conditioning regimen and those who received chemotherapy without TBI (Figure 5b).

Combining the 3-, 6-, and 12-month follow-ups in a longitudinal mixed-effects model yielded the following results: allogeneic HCT recipients diagnosed with oral mucosal changes experienced nonsignificantly more xerostomia (difference .4 point; 95% CI, -.4 to 1.2) compared to those with an intact oral mucosa. There was no difference in SWS flow rates between the 2 groups (Figure 6).

5a.



5b.

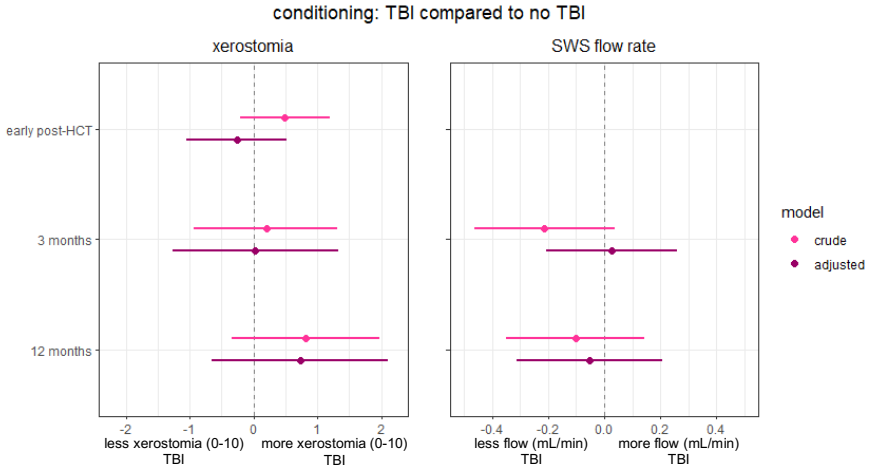


Figure 5. The effect of conditioning intensity (**a**) and TBI (**b**) on xerostomia and SWS in allogeneic HCT recipients. Mean effects with 95% CIs are reported early post-HCT (longitudinal mixed-effects model) and at 3 months and 12 months post-HCT (linear regression). The following covariates were added to the adjusted models: time since HCT (only early post-HCT), age, sex, treatment centre, comorbidities, preconditioning xerostomia or SWS flow rate, and TBI (**a**) or conditioning intensity (**b**).

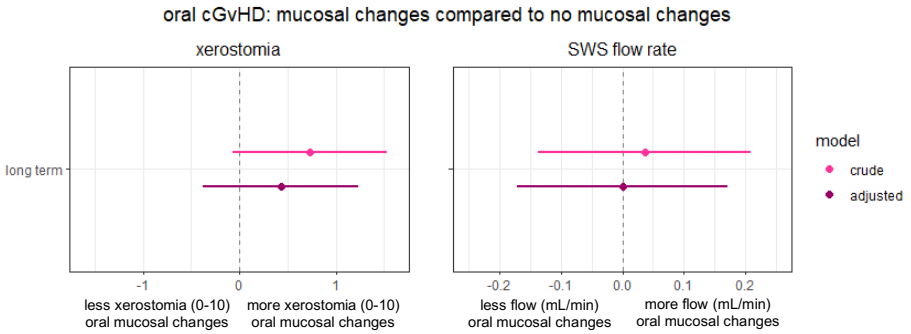


Figure 6. The effect of the oral mucosal changes related to cGvHD on xerostomia and SWS in allogeneic HCT recipients. Results of longitudinal mixed-effects models including 3-, 6-, and 12-month results are reported as mean effects with 95% CIs. The following covariates were added to the adjusted models: time since HCT, intensity of the conditioning regimen, TBI (yes versus no), age, sex, treatment centre, use of immunosuppressives, and preconditioning xerostomia or SWS flow rate.

Discussion

The majority of HCT recipients develop the subjective feeling of xerostomia, which might negatively affect their quality of life (4). The prevalence of xerostomia was already 40% before the start of the conditioning regimen, 88% early post-HCT, and 64% at 3 months post-HCT. In autologous HCT recipients, xerostomia levels comparable to preconditioning levels were reached after 3 months post-HCT, whereas xerostomia levels in allogeneic HCT recipients were still elevated at 12 months post-HCT. The xerostomia development and recovery in the autologous and allogeneic HCT recipients in this longitudinal observational, multicentre cohort were in line with a limited number of previous studies (11).

Allogeneic HCT recipients conditioned with an MAC regimen experienced more xerostomia compared to those receiving an NMA/RIC regimen early post-HCT, at 3 months post-HCT, and even at 12 months post-HCT. The 3-month results confirm the results of the previous meta-analysis, whereas the present study is the first to report a significant difference after 12 months (11). The toxicity of the conditioning regimen induces damage to the salivary glands early post-HCT (21), leading to salivary dysfunction that is likely associated with xerostomia. Inflammatory infiltration in salivary glands was seen up to 3 months post-HCT (21). Our finding that the intensity of the conditioning regimen affected xerostomia even after 12 months suggests that salivary impairment might persist for up to 12 months.

TBI had no additional effect on the development of xerostomia or change in SWS flow rate. Previous publications also reported that TBI did not (9) or did not significantly (22) influence xerostomia or SWS flow rate (9). The dose of TBI administered as part of the conditioning regimen might not reach the threshold above which salivary gland function will be diminished (23). Apart from the conditioning regimen, the high prevalence of xerostomia in HCT recipients also will be related to the high number of medications prescribed pre- and post-HCT. Pre-HCT, the severity of xerostomia tended to increase when more medication categories were used. No data on medication intake was collected post-HCT as part of the current study; nevertheless, as part of an ancillary study of the Orastem study, we previously reported that a subgroup of this population used a median of 27 (range, 16 to 45) different medications during the hospital stay (24). Because polypharmacy is a well-known risk indicator for the development of xerostomia (25, 26), it is not surprising that most patients experienced xerostomia early post-HCT.

Allogeneic HCT recipients experienced more xerostomia compared to autologous HCT recipients. The long-term difference, which is in agreement with literature (27), might be related to the development of salivary gland cGvHD following allogeneic HCT. Previous studies found that allogeneic HCT recipients who developed cGvHD experienced more xerostomia compared to those who did not develop cGvHD (28-31). The most obvious cause of the increase in complaints is the histopathological changes in both major and minor salivary glands caused by cGvHD, affecting salivary gland function (30). Because salivary gland biopsies are not performed regularly to confirm diagnoses of salivary gland cGvHD, and such invasive diagnostic tests were outside the scope of the current study, it is not possible to confirm whether salivary glands were affected by cGvHD in this patient cohort.

Remarkably, allogeneic HCT recipients did not have a lower SWS flow rate at 3 months post-HCT compared to autologous HCT recipients. SWS flow rate is only one aspect of quantitative salivary function; the amount of saliva that is produced under resting conditions and changes in salivary composition, particularly of lubricating mucins, also might result in xerostomia (13). Furthermore, the development of xerostomia might be related to changes in the minor salivary glands, which are often affected in cGvHD (32) but hardly contribute to whole saliva. Based on the weak correlations between SWS flow rate and xerostomia, it can be concluded that a change in SWS is only a small piece of the puzzle of the perception of mouth dryness.

The prevalence of the subjective complaint of xerostomia was higher than the prevalence of an objective reduction in salivary flow, as reported previously (18). This indicates that additional mechanisms might be involved in the aetiology of xerostomia without severely affecting salivary flow. For example, perceived stress, which is common in HCT recipients (33), was associated with xerostomia but did not influence salivary flow significantly (34). It also has been suggested that neuropathic mechanisms might be involved in the perception of mouth dryness (35). Our hypothesis that oral mucosal changes caused by cGvHD might contribute to the perception of xerostomia could not be confirmed in the current population. Oral mucosal changes also were not related to SWS flow rate, confirming that oral mucosal cGvHD and salivary gland involvement are distinct manifestations of cGvHD (36).

Conclusion

Xerostomia is a serious complaint after HCT, affecting the majority of HCT recipients. Complaints after autologous HCT are transient in nature, while the severity of xerostomia in allogeneic HCT recipients remains elevated at 12 months post-transplantation. Conditioning intensity is a significant risk indicator in the development of xerostomia, but TBI is not. Allogeneic HCT recipients experienced more xerostomia than autologous HCT recipients, a difference that cannot be explained by a reduction in SWS flow rate or the development of oral mucosal changes related to cGvHD.

Acknowledgments

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Appendix

Table S1, medication categories

1	Analgesics (Non-narcotic)	20	Barbiturates
2	Analgesics (Narcotic)	21	Beta-Blockers
3	Antacids	22	Bronchodilators
4	Antianxiety Drugs	23	Corticosteroids
5	Antiarrhythmics	24	Cough Suppressants
6	Antibiotics	25	Decongestants
7	Anticoagulants and Thrombolytics	26	Diuretics
8	Anticonvulsants	27	Expectorant
9	Antidepressants	28	Hormones
10	Antidiarrheals	29	Hypoglycemics (Oral)
11	Antiemetics	30	Immunosuppressives
12	Antifungals	31	Laxatives
13	Antihistamines	32	Muscle Relaxants
14	Antihypertensives	33	Sex Hormones (Female)
15	Anti-Inflammatories	34	Sex Hormones (Male)
16	Antineoplastics	35	Sleeping Drugs
17	Antipsychotics	36	Vitamins
18	Antipyretics	37	Other
19	Antivirals		

Table S2, The influence of patient characteristics and baseline variables on pre-conditioning xerostomia

		N	Mean baseline xerostomia (SD)
Age	< 55	112	1.2 (2.1)
	55 +	150	1.6 (2.4)
Gender	Male	154	1.2 (2.0)
	Female	108	1.9 (2.5)
Location	Vancouver	53	1.4 (2.3)
	Amsterdam	43	2.6 (2.9)
	Nijmegen	80	1.3 (1.8)
	Charlotte	49	0.9 (2.0)
	Sweden	37	1.3 (2.2)
Earlier radiotherapy to head and neck	No	250	1.5 (2.3)
	Yes	11	1.2 (2.3)
Comorbidities	No other current conditions	123	1.3 (2.1)
	Any condition	136	1.7 (2.4)
Smoke	No	131	1.2 (2.2)
	No, Previous user	115	1.7 (2.3)
	Yes, daily	15	1.7 (2.1)
Alcohol	No	61	1.0 (1.7)
	No, but previous user	85	2.2 (2.5)
	Yes, but not daily	102	1.1 (2.0)
	Yes, daily	11	2.2 (3.1)
Number of medication categories	0	31	0.9 (1.4)
	1 to 4	123	1.2 (2.1)
	5+	98	2.0 (2.6)
Stimulated whole saliva	< 0.7 mL/min	61	2.0 (2.5)
	≥ 0.7 mL/min	189	1.2 (2.0)

Table S3, Correlations between xerostomia scores and stimulated whole saliva (SWS) flow rate on the left side, and correlations between changes in xerostomia scores and changes in SWS flow rates on the right

		Correlation between xerostomia (0 – 10) and SWS flow rate (mL/min)			Correlation between change from the pre-conditioning measurement in xerostomia (0 – 10) and SWS flow rate (mL/min)*		
		Spearman correlation	**p**	**N**	**Spearman correlation**	**p**	**n**
All patients	3 months	-0.27	0.0003	180	-0.12	0.1620	143
Allogeneic patients	3 months	-0.26	0.0068	108	-0.25	0.0399	86
	12 months	-0.32	0.0033	82	-0.39	0.0017	61

* Patients with a xerostomia score of 0 at baseline and an increase in SWS flow rate at the timepoint of interest are excluded from these analyses

Chapter 5

Caries Progression after Haematopoietic Stem Cell Transplantation and the Role of Hyposalivation

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Abstract

Haematopoietic (stem) cell transplantation (HCT) preceded by a conditioning regimen is an established treatment option for many haematological diseases. Decreased salivary flow rates after HCT may increase caries risk. We aim to estimate the extent to which caries lesions develop or progress in adult HCT recipients and assess its association with salivary flow rates. A multi-centre prospective observational study was conducted in which patients receiving HCT were followed up for 18 months. We included 116 patients (median age 56 years, 43% female) from two medical centres in the Netherlands. Unstimulated whole saliva (UWS) and stimulated whole saliva (SWS) were collected, and full caries charts were made before HCT and 3, 6, 12, and 18 months post-HCT. Caries was scored according to the ICDAS criteria by trained dentist-examiners. New dentine lesions or lesion progression into dentine (ICDAS ≥4 or cavitated root lesions) occurred in 32% of patients over 18 months. The median number of affected surfaces was 2 (range: 1–12) per patient with caries progression. The influence of hyposalivation of unstimulated saliva (<0.2 mL/min) and stimulated saliva (<0.7 mL/min) at baseline and after 3 months on caries progression was determined with a negative binomial regression model. Hyposalivation of SWS 3 months after HCT was a significant risk indicator for caries progression (incidence rate ratio: 5.30, 95% CI: 2.09–13.4, $p < 0.001$), while hyposalivation of SWS at baseline and hyposalivation of UWS were not. We conclude that caries progression is a common oral complication in patients after HCT, and stimulated hyposalivation shortly after treatment is a significant risk indicator for caries progression.

Introduction

Haematopoietic (stem) cell transplantation (HCT) is an established treatment option for many malignant and non-malignant blood diseases (1). HCT is preceded by a conditioning regimen, consisting of chemotherapy, total body irradiation, or a combination of both. The conditioning aims to eradicate the disease and modulate the immune system. Thereafter, the stem cells, either harvested at an earlier time from the patient (autologous HCT) or from a donor (allogeneic HCT), are infused. The increase in clinical indications for HCT and improved transplantation procedures have led to an increase in the number of long-term survivors (2). Even though the prevalence of life-threatening complications has decreased over time, less severe side effects are still common.

Tooth decay, or dental caries, is a common finding in survivors of HCT (3). A high caries prevalence was reported in patients who had undergone allogeneic HCT 1–14 years previously, in comparison with the general population (4). HCT recipients may already be at higher caries risk before the treatment, as patients planned for HCT were reported to have higher number of decayed, missing, and filled teeth (DMFT), compared with the general population (5) or with healthy controls (6, 7).

Longitudinal studies that confirm the relation between HCT and development of dental caries are scarce. A number of prospective studies did not notice an increase in DMFT score or new caries lesions after a follow-up of 3 months (8, 9) or 24 months (10). Only one study reported an increase in DMFT score 6 months post-HCT: 51 new lesions developed in teeth that were previously sound in 36 patients (11). However, it must be remembered that DMFT is an insensitive instrument, and caries developing in already restored teeth (either as new primary lesions or as secondary lesions) will not lead to a higher DMFT score. Furthermore, sufficient time is needed for caries lesions to develop, and therefore, a follow-up of 3 or 6 months might be too short to determine caries progression.

Caries risk has been related to reduced salivary flow rates, since a shortage of saliva slows down oral sugar clearance and adversely affects salivary buffering of plaque acid (12). Salivary flow rates have been reported to be reduced several days and months after HCT (13). However, only two studies have investigated the relationship between salivary flow rate and caries in this specific patient group directly, and the evidence is inconclusive. A difference in flow rates of 1 year post-HCT between patients that developed or did not develop new caries lesions could not be established (14). In another study, caries was more prevalent

in patients with hyposalivation 6, 12, and 24 months post-treatment, but the difference was not significant (10).

Taken together, it remains unclear whether HCT recipients are at increased risk of developing caries lesions due to reduced salivary flow rates. Therefore, in this longitudinal multicentre study, we evaluated the caries progression at the surface level in adult patients in a period up to 18 months after HCT and analysed the association with hyposalivation.

Materials and Methods

This study is an ancillary study of the Orastem study, a multinational, prospective, observational, longitudinal study on the impact of oral side effects from conditioning therapy before HCT (15). We included adult patients (≥18 years old) scheduled to receive an autologous or allogeneic HCT at Amsterdam University Medical Center (location Academic Medical Center [AMC]) or Radboud University Medical Center (Radboudumc) Nijmegen. Patients scheduled for allogeneic HCT were eligible for inclusion independent of their diagnosis, while those scheduled for autologous HCT were eligible if diagnosed with multiple myeloma. Patients were excluded if they were not able to understand the provided information, a second HCT was planned in advance, the time before HCT was too short to consider study participation, or if a transfer to another hospital was planned shortly after HCT. Because the present analysis focused on caries progression, the presence of a natural dentition and a completed caries chart at baseline were additional inclusion criteria, only for the current analysis. This study was registered in the Netherlands trial register (NL5645), approval was obtained by the Medical Research Ethical Committee (NL52117.018.15), and the study was conducted according to GCP guidelines and the World Medical Association Declaration of Helsinki. Before participating, all patients signed informed consent.

Dental examinations and saliva collections were carried out before HCT (baseline), and 3 and 12 months post-HCT for all patients. Allogeneic HCT recipients had additional follow-up examinations after 6 and 18 months.

Caries Assessment

Dental examinations were carried out by experienced dentists (AL, JRD, RK, and MCH). All observers were trained in caries detection and the inter-observer agreement between the main observers, using ICDAS scores on clinical photographs, was rated

as good (kappa 0.79 at the level of dentine caries). Examinations were carried out in a fully equipped dental clinic, except for 11 patients treated at the AMC who were visited at home for the 3-month' follow-up. All examinations were carried out with a mouth mirror and periodontal probe, after air drying in the clinical setting, and drying with cotton roles in the at-home examinations. No professional cleaning before examination was performed; where necessary, plaque was removed with a probe during examination. If no recent panoramic radiographs were available, a panoramic radiograph was taken as part of the dental focal infection screening at the first oral examination. Data collection was performed within a setting of a clinical care protocol. Clinical dental parameters at each point in time were used to indicate and monitor preventive treatment. Oral hygiene instruction was provided at baseline and in the follow-up appointments. Other preventive measures were advised on indication and, where needed, invasive treatment was provided or suggested to the patients' dentist.

Caries was assessed clinically according to the ICDAS II, a validated system for measuring dental caries based on visual characteristics (16, 17). ICDAS scores of 2 and higher were recorded for every crown surface; a distinction was made between cavitated and non-cavitated lesions in the recording of root caries. ICDAS score 1 was not recorded. Caries activity was scored for all surfaces.

Higher ICDAS scores are related to higher lesion depth, and scores 4 and higher are assumed to involve dentine. ICDAS 4 refers to an underlying dark shadow from dentine, ICDAS 5 to a distinct cavity with visible dentine, and ICDAS 6 to an extensive distinct cavity with visible dentine (18).

Saliva Collection

The protocols for the collection of whole saliva were based on the guidelines for saliva collection of the University of Southern California School of Dentistry (19). Patients were asked to refrain from eating, drinking and use of chewing gum 1 h before the collection. The collection of unstimulated whole saliva (UWS) started immediately after one swallow. Patients were asked to spit the saliva in a pre-weighed plastic cup for 5 min without making any effort to increase the salivary flow. During the collection of stimulated whole saliva (SWS), patients chewed on a piece of neutral chewing gum base. SWS was collected for 2–5 min, and the collection was preceded by swallowing after 1 min of chewing. Directly after collection, samples were weighed and flow rates were estimated by assuming 1 g of saliva equals 1 mL. Hyposalivation of UWS was defined as a flow rate of <0.2 mL/min, and hyposalivation of SWS as <0.7 mL/min (20-22). The pH was determined using pH-indicator strips (pH-indicator strips 5.5–8.0, Hydrion, New York, NY, USA).

Data Analysis

Caries progression was assessed at surface level, as a difference in ICDAS scores between baseline and the respective follow-ups. Caries progression in a surface was recorded if a new lesion that reached into dentine (ICDAS ≥4 or cavitated root lesions) developed, or if an existing dentine lesion increased in depth (progression from ICDAS 4 to ICDAS 5 or 6, from ICDAS 5 to ICDAS 6, or cavitation of a non-cavitated root lesion at the subsequent follow-up). A patient was classified as showing caries progression, if he or she developed at least one surface with caries progression. A surface in which a restoration was placed during the study, that was not preceded by a caries diagnosis in our study, was not included in the analysis.

For each patient, the number of surfaces with caries progression between baseline and the final follow-up measurement was used as the dependent variable in the main analysis. A negative binomial regression model was built to explore the association between different risk indicators and caries progression. The "baseline model" included hyposalivation and pH of UWS and SWS at baseline as independent variables, in addition to the following patient characteristics at baseline: age, gender, centre (AMC or Radboudumc), and number of dentine lesions. The "3 months' model" included the same variables, except for the following: salivary hyposalivation and pH 3 months post-HCT replaced the same variables at baseline. The length of the follow-up (time at risk) and the number of natural teeth (number of teeth at risk) per patient were added to the models as offset variables. Missing salivary data were substituted with multiple imputations, based on the variables in the negative binomial regression model and several auxiliary variables. The results of 25 imputed datasets, using 20 iterations, were pooled. Results were reported as incidence rate ratios (IRR) and accompanying 95% confidence intervals (95% CI).

In an additional analysis, salivary flow rates of patients with and without caries progression were compared. This analysis included a subgroup of the present population: only patients from the Radboudumc were included due to higher precision salivary measurements performed in this centre. Differences between the 2 groups over time were analysed with a linear mixed-effects model with random intercept. A log transformation was applied to the salivary flow rates to improve model fit, and time was added as a categorical independent variable to the model. Results were reported as re-transformed effects with 95% CI. Statistical analyses were performed in SPSS (version 25) and R (version 3.6.2).

Results

In total, 125 patients that were planned for HCT signed informed consent and were included between September 2015 and October 2017. Of these, 124 received baseline dental screening; however, 8 patients were excluded from this analysis, leaving 116 patients in the present sub-study. The number of patients present at different follow-ups and reasons for loss to follow-up are shown in Figure 1. During the study period, 17 HCT recipients (15%) died, and of these, 8 died before the first follow-up. The baseline appointment took place at a median of 36.5 days (range 3–309 days) before HCT. Baseline characteristics of the participants are reported in Table 1.

Table 1. Baseline characteristics of the included patients

	Allogeneic (67)	**Autologous (49)**
Median age, years (range)	56.0 (19–74)	57.0 (33–69)
Gender, *n* (% female)	29 (43)	21 (43)
Centre		
AMC, n	14	28
Radboudumc, n	53	21
Diagnoses, n		
Acute myeloid leukaemia	28	
Acute lymphoblastic leukaemia	5	
Lymphoma	7	
Chronic lymphocytic leukaemia	3	
Myelodysplastic syndrome	9	
Chronic myeloid leukaemia	3	
Myelofibrosis	5	
Severe aplastic anaemia	2	
Myeloma	2	49
Other	3	
Conditioning, n		
Myeloablative	16	49
Reduced intensity	21	
Nonmyeloablative	26	
Total body irradiation	40	
No total body irradiation	23	49
Not applicable*	4	

* No HCT performed, or withdrawal before HCT.

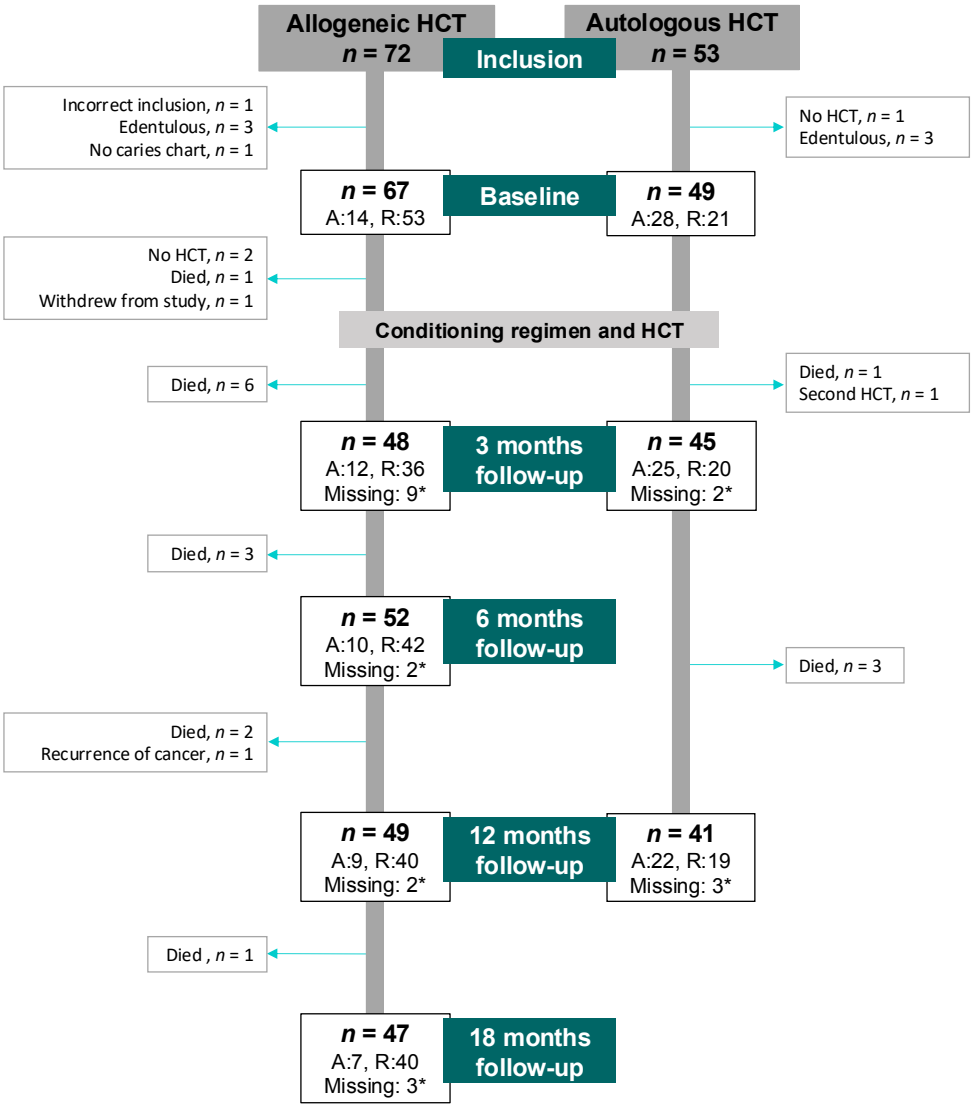

Figure 1. Flow chart of the study. A distinction is made between patients treated at AMC (A) and Radboudumc (R). Reasons for exclusion and irreversible loss to follow-up are shown in the squares on the left and right sides of this diagram. Reasons for 21 incidental missed appointments of 18 patients, marked with * in this diagram, were: unable to come due to hospitalization, rehabilitation or illness (n = 5), refused to come or did not come (n = 7), unreachable (n = 3), or other/unknown reasons (n = 6).

Caries

The prevalence of dentine lesions at baseline is shown in Figure 2, where a distinction is made between cavitated root lesions, and cavitated (ICDAS 5 and 6) and non-cavitated (ICDAS 4) coronal lesions. Dentine caries was prevalent in 53% of the patients at baseline. The mean DMFT score at baseline was 17.1 for the whole population, the average number of teeth present was 24.6, and patients were diagnosed with an average of 1.4 (SD 2.2) lesions.

The cumulative lesion progression over different time periods is shown in Figure 2 as well. After 3 months, 92 patients were seen for follow-up, and 27 new or deeper dentine lesions were observed in 16 patients. Over 18 months, 32% of the patients developed 1 or more surfaces with caries progression. These 33 patients were classified as caries progressive and developed an average of 2.4 (SD 2.3, maximum 12) lesions. A description of patients with and without caries progression is shown in Table 2.

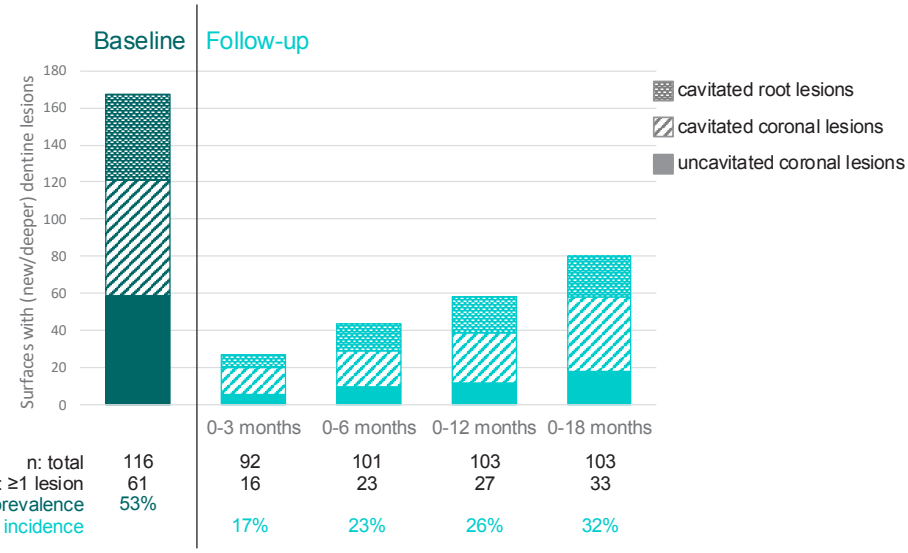

Figure 2. Number of surfaces with dentine lesions at baseline (dark green bar) and cumulative number of surfaces with new or deeper dentine lesions that developed in different time periods (turquoise bars). Numbers (top row, total) shown in the graph represent the numbers of patients that were seen for follow-up in the mentioned time period. Numbers in the second row (≥1 lesion) represent patients with at least 1 dentine lesion at baseline or lesion progression during the follow-up. A distinction is made between cavitated root lesions, cavitated coronal lesions (ICDAS 5 and 6), and non-cavitated coronal lesions (ICDAS 4).

Table 2. Description of patients that developed new or deeper dentine lesions during the complete follow-up (12–18 months), and those without caries progression

	Caries progression (*n* = 33)		**No caries progression (*n* = 70)**	
Surfaces with caries progression, n				
Median (range)	2 (1–12)		0	
Mean (SD)	2.4 (2.3)		0	
Mean length of follow-up in months (range)	14.6 (3–18)		13.5 (3–18)	
Age at HSCT, median (range)	53 (19–69)		56.5 (23–74)	
Gender, % female	36		49	
Centre, % Amsterdam	27		41	
Dental baseline data				
Median number of natural teeth (range)	26 (7–30)		26.5 (6–32)	
Median DMFT,* (range)	19 (4–28)		17 (0–28)	
Median number surfaces with dentine lesions (range)	2 (0–9)		0 (0–4)	
Saliva, collected at	baseline	3 months	baseline	3 months
UWS, % hyposalivation (<0.2 mL/min)	25	46	33	32
Mean pH of UWS (range)	6.2 (5.5–7.0)	6.1 (5.5–7.4)	6.2 (5.8–6.8)	6.3 (5.0–7.6)
SWS, % hyposalivation (<0.7 mL/min)	27	62	26	33
Mean pH of SWS (range)	6.9 (6.0–8.0)	6.6 (6.0–7.6)	7.0 (5.8–8.0)	6.9 (6.0–8.0)

* DMFT: the sum of decayed (diagnosed as ICDAS 4, 5, 6 or cavitated root lesions), missing and filled teeth, excluding wisdom teeth.

The Association of Hyposalivation and Caries Progression

Two separate negative binomial models were built that included salivary parameters at baseline (baseline model) and salivary parameters 3 months post-HCT (3 months model). The association between salivary parameters and caries progression was adjusted for several baseline patient characteristics. Missing salivary data (data of 2 patients at baseline and 3 at the 3 months' follow-up) were substituted with multiple imputations.

The "baseline model" revealed that caries progression was not associated with hyposalivation of UWS (IRR: 1.16, CI: 0.43–3.10), hyposalivation of SWS (IRR: 1.17, CI: 0.41–3.32), pH of UWS (IRR: 0.85, CI: 0.17–4.24), or pH of SWS (IRR: 1.02, CI: 0.38–2.76) at baseline. Results of the "3 months' model" are shown in Table 3. Hyposalivation of SWS 3 months post-HCT was significantly associated with caries progression (IRR: 5.30, CI: 2.09–13.4), while hyposalivation of UWS and pH of both types of saliva were not associated with caries progression. The patient characteristics influenced the outcome as follows: males, younger patients, and patients with dentine lesions at baseline were more likely to develop caries progression.

Table 3. The "3 months model"

Independent variable	IRR	95% CI	p-value
Hyposalivation of UWS, 3 months (<0.2 mL/min)	0.77	0.31–1.93	0.573
Hyposalivation of SWS, 3 months (<0.7 mL/min)	5.30	2.09–13.4	<0.001
pH UWS, 3 months	0.79	0.20–3.11	0.733
pH SWS, 3 months	1.07	0.33–3.46	0.910
Age, years	0.95	0.92–0.98	0.001
Gender (ref. male)	0.21	0.09–0.49	<0.001
Centre (ref. AMC)	1.04	0.42 –2.59	0.930
Number dentine lesions at baseline	1.42	1.18–1.71	<0.001

Associations between different risk indicators and the number of surfaces with caries progression per patient (negative binomial regression). IRR, incidence rate ratio; UWS, unstimulated whole saliva; SWS, stimulated whole saliva.

Differences in Salivary Flow Rates between Patients with and without Caries Progression

Differences in salivary flow rates between patients with and without caries progression were assessed in patients from the Radboudumc. Of the 74 patients that received a baseline screening in this centre, 9 were excluded or lost to follow-up before 3 months, leaving 65 patients in this analysis (24 with and 41 without caries progression). UWS and SWS flow rates over time are shown in Figure 3a, b, respectively. Both UWS and SWS flow rates of patients with caries progression decline after treatment and rise again after 3 months. The difference in UWS flow rates over time was 1.03 (95% CI: 0.73–1.46), which can be interpreted as a non-significant 3% higher UWS flow rate in patients with caries progression, in comparison to those without caries progression. When the SWS flow rates of both groups were compared, patients with caries progression had an SWS flow rate that was 26% lower over time (effect: 0.74; 95% CI: 0.58–0.95, p: 0.016).

Discussion

The aim of our study was to evaluate the caries progression in adult patients in a period up to 18 months after HCT and to analyse the association with hyposalivation. In our population, the mean DMFT score at baseline was 17.1, and the mean number of decayed surfaces was 1.4 (SD: 2.2), which is in line with a Dutch population of comparable age groups (23). Previous publications reported a broad range of DMFT

scores before autologous and allogeneic HCT, varying between 7.0 (11) and 18.9 (10). These broad variations might reflect differences in patient selection and oral health care systems in different countries and emphasize the difficulties when comparing different populations of HCT recipients. It must be taken into account that the baseline screening in the current study was conducted before the HCT and conditioning regimen, but usually, after a period of disease and intensive treatment, which may have influenced caries prevalence and salivary flow rates at baseline.

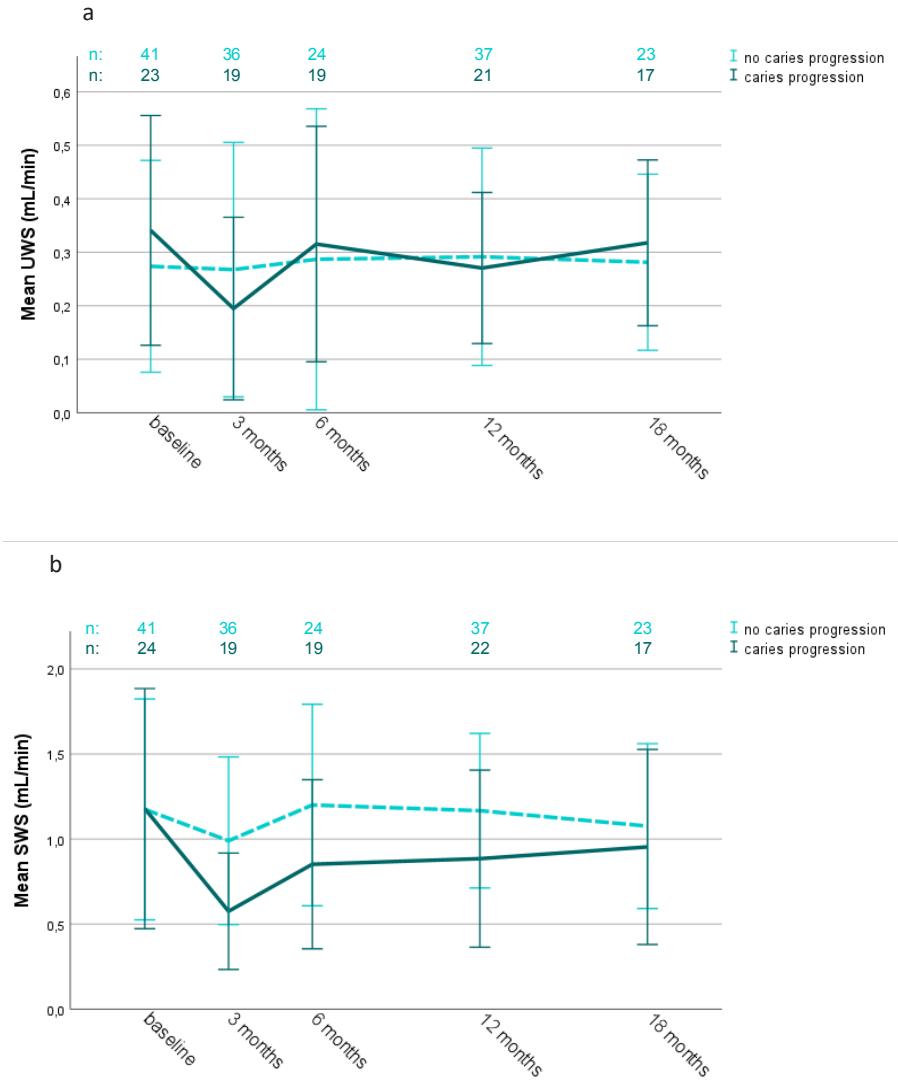

Figure 3. Mean ± 1 SD UWS (a) and SWS (b) flow rates in patients with (solid line) and without (dashed line) caries progression. Two UWS samples of 1 patient were missing due to chewing gum use before the collection and saliva sampling in one autologous patients took place after 6 instead of 3 months.

Several longitudinal studies have reported data on the oral status of HCT recipients. A retrospective study published in 1985 (14), reported that 37% of the patients had an extremely high caries incidence 1-year post-HCT. This high caries incidence has never been confirmed in more recent publications, probably due to the general reduction of caries prevalence during the last decades (24) and the introduction of less intensive conditioning regimens (25). Of the four recent prospective studies that reported caries incidence, only one found a significant increase in DMFT score post-HCT (11). Notwithstanding the close preventive supervision in the current study, caries progression was observed in 17% of the patients 3 months post-HCT, and in 32% during the entire follow-up period. The median number of affected surfaces was 2 (range 1–12) per patient with caries progression. Use of a detailed caries scoring method (ICDAS II) and reporting caries progression at the surface level increased the sensitivity in this study. Unfortunately, it is not possible to compare these numbers to a healthy adult population because longitudinal studies determining caries progression are lacking.

A limitation of the current study is that examiners were calibrated based on photographs instead of real patients. Furthermore, we have to add that not all recorded caries data is included in the current paper. This study focused on lesion progression at the dentine level only, which may have underestimated total lesion progression. ICDAS scores 2 and 3 were also recorded, but proved insufficiently reliable. Professional cleaning is a prerequisite for early lesion detection, and this was not consistently possible in the clinical care setting. Caries activity assessment was used for clinical purposes only and not for analysis, because evidence for the validity of lesion activity scores is limited to children, and even there the validity is limited for smooth surfaces (26, 27).

In the present population, we determined that hyposalivation of SWS 3 months post-HCT was a risk indicator for caries progression. Age, gender, and recent (unrestored) caries experience were added to the model as potential confounding factors. These factors are reported to influence caries risk (28, 29), and are associated with hyposalivation as well (30). These three variables influenced caries progression significantly. Because two academic medical centres participated in this study, differences between the two populations and researchers may have introduced bias. Therefore, the centre where the patient was treated was added as a covariate in the regression analysis, but this variable did not influence the results.

Because development of caries lesions is a multifactorial disease (31), it is assumed that other factors than salivary flow rate will affect caries progression.

Changes in salivary composition post-HCT are reported (13), which might have increased caries risk in the current population. Dental hygiene instructions were provided and an increase in fluoride frequency or concentration was advised on indication. However, HCT recipients might experience difficulties in completing oral hygiene practices during the transplant process due to fatigue and medical complications (32). Furthermore, guidelines on nutrition in cancer patients are mainly based on preventing malnutrition (33) and do not take the prevention of oral diseases into account.

It was expected that subjects with very low UWS flow rates would have a high caries risk due to reduced clearance rates (12). The drop in UWS flow rate at the 3 months' follow-up in patients with caries progression (Fig. 3a) is in agreement with this hypothesis, but a predictive effect of UWS flow rate on caries progression could not be confirmed in the multivariable analysis.

Because UWS flow rates show a circadian rhythm (34), lack of standardisation of collection times may have contributed to reduced precision of this measurement and a non-significant result. The SWS flow rate of patients with caries progression was over time 26% lower in comparison to patients without caries progression. Recently, it was concluded that caries prevalence was consistently but not significantly higher in patients with hyposalivation 6, 12, and 24 months post-HCT (10).

We expect that the drop in salivary flow rates post-HCT will be a direct result of the toxicity of the conditioning regimen (8, 13), or, in case of an allogeneic transplantation, might be the effect of graft versus host disease (GvHD). GvHD is an immune response of donor-derived cells against recipient tissues, which might affect the salivary glands and cause hyposalivation (1). The development of extensive dental caries in patients with GvHD is reported in literature (35). However, in the current population, the number of patients that were diagnosed with GvHD was too small to draw conclusions about its effect on caries progression. As shown in Figure 3b, salivary flow rates rise 3 months after treatment. Still, 25% of the patients were diagnosed with hyposalivation of SWS 12 months post-HCT. An even higher prevalence of 30% hyposalivation was reported in a previous publication (10). It is plausible that patients with prolonged periods of hyposalivation are at even higher risk of developing long-term oral complications such as dental caries. Therefore, studies with a longer follow-up are warranted.

We conclude that caries progression is a common oral complication in patients after HCT. Hyposalivation of SWS after treatment is a significant risk indicator for caries progression; its incidence in patients with hyposalivation 3 months after HCT was 5 times as great as the incidence in those without hyposalivation. This finding will be of special interest in the development of standard care protocols and preventive strategies for this specific patient group. We recommend planning additional oral check-ups after HCT recipients leave hospital. By measuring stimulated salivary flow rate, patients with an increased caries risk can be marked and additional preventive strategies considered. Potentially, this result may be extrapolated to other cancer patients receiving similar chemotherapy protocols.

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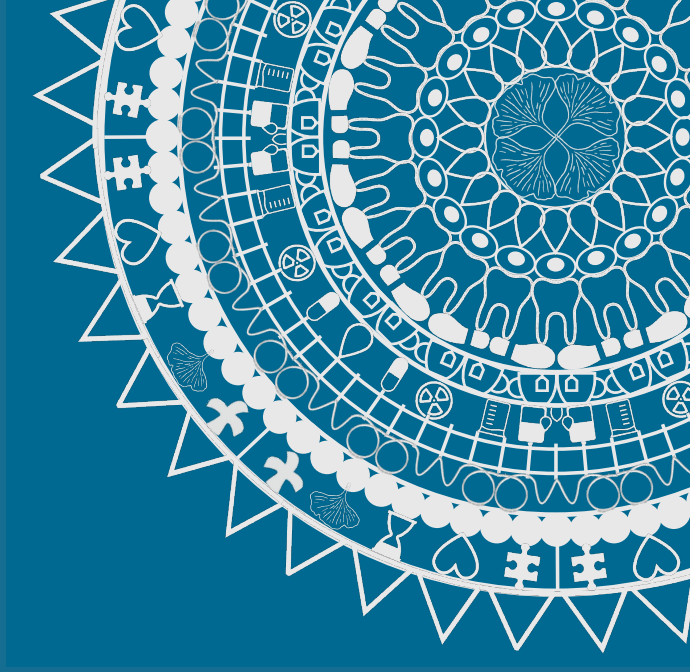

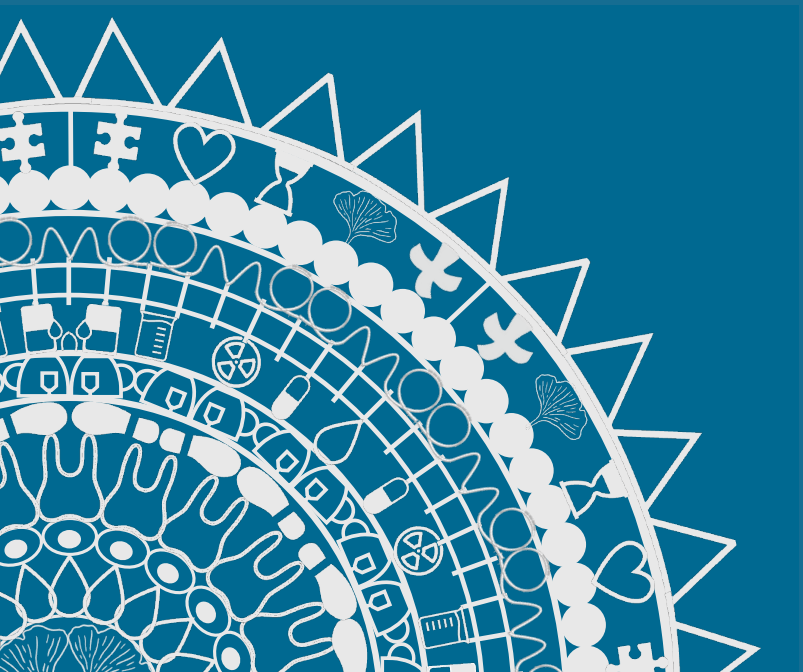

Chapter 6

Salivary flow rate, subjective oral dryness and dental caries 5 years after haematopoietic cell transplantation

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Abstract

Background

The aim of this study was to describe salivary flow rate, subjective oral dryness and dental caries 5 years post haematopoietic cell transplantation (HCT).

Methods

HCT survivors of a previous longitudinal observational cohort study in the Netherlands (the H-OME study) were invited to participate in this additional follow-up after 5 years (the HOME2 study). During the additional follow-up appointment, stimulated (SWS) and unstimulated whole saliva (UWS) was collected, participants rated subjective oral dryness on a 0 – 10 scale, and caries lesions were assessed. Furthermore, dental records, including treatments and radiographs, were requested for the 5 years preceding and the 5 years following transplantation. Paired t-tests were performed to determine changes in UWS and SWS flow rates and subjective oral dryness from pre-HCT, and to compare the number of caries-related dental treatments (restorations, endodontic treatments or extractions) before and after HCT. Hyposalivation of UWS (< 0.2 mL/min) and SWS (< 0.7 mL/min) at 3 and 12 months, was used to explore the predictive potential of hyposalivation on a high dental treatment need (>3 treatments) over the 5 years post-HCT.

Results

Five years post-HCT, 39 HCT survivors were included. The mean UWS flow rate was 0.36 mL/min (SD 0.26) and the mean SWS flow rate 1.02 (SD 0.57); survivors were diagnosed with a median of 0 dentine lesions (range 0 – 12) and 73% reported a subjective oral dryness score ≥1. Survivors underwent a median of 3 (range 0 – 20) dental treatments during the 5 years following transplantation. The mean difference in UWS 5 years post-HCT compared to pre-HCT was 0.03 (95% CI: -0.07 – 10.12), the mean difference for SWS was -0.18 (95% CI: -0.45 – 0.08) and for subjective oral dryness 1.2 (95% CI: 0.2 – 2.1). In the 5 years post-HCT, non-significantly more treatments were performed compared to the 5 years pre-HCT (mean difference: 0.5, 95%CI: -1.2 – 2.2). Seventy eight percent of patients with hyposalivation of SWS at 12 months had a high dental treatment need, compared with 38% with no hyposalivation.

Conclusions

Five years post-HCT, mean UWS and SWS flow rates were not significantly different from pre-HCT levels but subjective oral dryness scores were elevated.

Background

Haematopoietic cell transplantation (HCT) is an established treatment option for haematologic and lymphoid cancers and many other disorders (1). Haematopoietic stem cells, that are either harvested from the patient (autologous HCT) or a donor (allogeneic HCT), are infused after a preparative conditioning regimen. This conditioning regimen aims to eradicate the disease and modulate the immune system, consists of chemotherapy with or without total body irradiation (TBI), and can have a high (myeloablative (MAC)), a reduced (RIC), or even a non-myeloablative intensity (NMA). During the past decades, clinical indications for HCT expanded and transplantation procedures improved, leading to an increased number of long-term survivors (2, 3). Following HCT, development of oral complications and complaints are frequently reported (4, 5).

Cancer treatments are known to induce salivary gland hypofunction (6). In HCT recipients, stimulated whole saliva (SWS) flow rates were already low before HCT, and decreased further shortly post-HCT (7, 8). This decline may be related to the high dose conditioning regimen, and the high number of prescribed medications preceding and following the transplantation (8). SWS flow rates started to increase again 3 or 6 months post-HCT, an increase that lasted until 12 (8) or even 24 months (9). UWS flow rates seem to follow a comparable but less pronounced pattern over time (8, 10). It remains unclear whether further recovery of salivary flow rates might be expected more than 24 months post-HCT. Cross-sectional studies reported that long-term HCT survivors had lower UWS (11, 12) and SWS flow rates compared to controls (11). A reduction in salivary flow rate and impaired recovery in allogeneic HCT recipients might be a result of chronic graft-versus-host disease (cGvHD) (13).

A reduced salivary flow rate might cause the subjective feeling of mouth dryness, or xerostomia (14). An increase in mouth dryness complaints is reported in HCT recipients, simultaneously with a decrease in salivary flow rate. Subjective oral dryness scores increased shortly after treatment, were still raised 2 – 5 months post-HCT, and values largely comparable to baseline were reached after 12 months (15). Nevertheless, complaints remained elevated compared to controls, even on the very long term (11).

Since a shortage of saliva influences oral (sugar) clearance and adversely affects salivary buffering of plaque acid (16), a reduced salivary flow rate might contribute to an increased caries risk (17). In HCT recipients, a reduced SWS flow rate at 3 months post-treatment, resulted in a higher risk of developing dental caries during a period of

18 months (18). After a median follow-up of 4 years, HCT recipients had a higher number of decayed, missing and filled teeth, and worse dental health compared to healthy matched controls (12). We hypothesize that even a short period of hyposalivation might result in initial but irreversible damage to the dental enamel, potentially resulting in caries progression leading to the need for restorative treatment.

We previously conducted a prospective, observational, longitudinal study, recording oral side effects in HCT recipients for 12 to 18 months post-treatment: the H-OME study (8, 18-22). One year post-treatment, 26% of the patients was still diagnosed with hyposalivation of UWS and 25% with hyposalivation of SWS. This raised the questions how dental health would evolve during the following years, and whether further recovery of salivary flow rates could be expected on the longer term. The aim of the present study was to describe UWS and SWS flow rate, subjective oral dryness and dental caries 5 years post-HCT, in the same population. Furthermore, salivary flow rates and subjective oral dryness scores were compared to pre-HCT values. Finally, we explored whether dental treatment need increased as a result of HCT, and whether hyposalivation predicted dental treatment need during a period of 5 years post-HCT, using data from dental records.

Materials and methods

This observational cohort study adds one additional follow-up to the previously closed H-OME study, that focussed on oral side effects pre-HCT, shortly after HCT, and up to 18 months post-HCT. The protocol of the H-OME study is published in the Dutch Trial Register (NL5645) and approval was obtained by the Medical Research Ethical Committee (NL52117.018.15). In short, adult patients (≥18 years old) scheduled to receive an autologous or allogeneic HCT at Amsterdam University Medical Centre (UMC), location AMC, or Radboud university medical center (Radboudumc) Nijmegen were included. Surviving participants from this H-OME study were invited to participate in this additional 5-year follow-up study. Participants that received a second HCT since inclusion in the H-OME study, and those without a remaining natural dentition, were excluded. The current study was registered as HOME2 in the Dutch Trial Register (NL9825). The Local Ethical Committee (registration number 2021–12963) stated that this research was not subjected to the law governing research involving human subjects and no approval from the Local Ethical Committee was necessary. The study was conducted according to GCP guidelines and the World Medical Association Declaration of Helsinki. Before participating, all patients signed a renewed informed consent.

General health and use of medication

Participants were interviewed using questions regarding general health, cancer treatments and comorbidities. Furthermore, patients were asked to bring a list of medications they were using at the time of the 5-year follow-up appointment. When patients forgot this list, they were asked to recall the medications that they were using. Medications were divided into the following categories:

- Antimicrobials: antibiotics, antifungals, antiviral medications
- Supportive medication: sleep medication, antidepressants, anxiolytics, antacids, antiemetics, analgesics, antihistamines, laxatives, diuretics
- Anticancer and immunosuppressive medication: cytostatics, oncolytics, colony stimulating factors, corticosteroids, other immunosuppressives, protein kinase inhibitors
- Other medication

Caries assessment and dental treatments

Dental examinations were carried out by experienced dentists: AL assessed caries lesions from patients treated at the Amsterdam UMC, location AMC, while MB recorded caries lesions from patients treated at the Radboudumc. Caries was assessed clinically according to the ICDAS II (23, 24). ICDAS scores of 2 and higher were recorded for every crown surface; a distinction was made between cavitated and non-cavitated lesions in the recording of root caries.

If patients consented, dental records were requested from dentists treating the patients. Records, including radiographs, were requested for the 5 years preceding, and 5 years following HCT. The number of dental check-ups, tooth extractions, endodontic treatments and restorations (at tooth and surface level) performed during both time periods were extracted. Furthermore, dental records were searched for indications for treatments, and, if not reported, intra-oral radiographs were assessed by experienced dentists (LvG and MB) to determine whether a cariological diagnosis was plausible.

Saliva collection

The protocols for the collection of whole saliva were based on the guidelines for saliva collection of the University of Southern California School of Dentistry (25). Patients were asked to refrain from eating, drinking, toothbrushing and use of chewing gum 1 h before the collection. The collection of UWS started immediately after one swallow. Patients were asked to spit all accumulating saliva in a pre-weighed plastic cup for 5 min without making any effort to increase the salivary

flow. SWS was also collected for 5 min, and the collection was preceded by swallowing after 1 min of chewing. Directly after collection, samples were weighed and flow rates were estimated by assuming 1 g of saliva equals 1 mL. Hyposalivation of UWS was defined as a flow rate of < 0.2 mL/min, and hyposalivation of SWS as < 0.7 mL/min (14, 26, 27).

Current subjective oral dryness

To assess the severity of oral dryness, patients were asked to complete the following question: How would you rate your mouth dryness during the last 24 h? This Likert scale ranged from 0 (no dryness) to 10 (worst possible dryness). The same question was also completed during the previous phases of the H-OME study. Furthermore, patients were asked to complete the EORTC QLQ-OH15 (28). This oral health module comprises a question on mouth dryness on a 4-point Likert scale.

Statistical analysis

UWS and SWS flow rates are reported as mean and standard deviation (SD); median scores and ranges are shown in boxplots. Paired t-tests were performed comparing the 5-year results from a subgroup (only HCT recipients treated at the Radboudumc) with previously reported pre-HCT values (8). Furthermore, unpaired t-test were used to compare differences between subgroups.

Subjective oral dryness scores are reported as mean and SD; median scores and ranges are shown in boxplots. Paired t-test were used to compare subjective oral dryness scores 5 years post-HCT with pre-HCT levels, and unpaired t-tests were used to compare differences between subgroups 5 years post-HCT.

Spearman's correlations, used to determine the correlation between salivary flow rates and subjective oral dryness on the one hand, and the number of used medications and dentine lesions on the other, were reported as Spearman's rho with p-value.

Number of dental treatments (tooth extractions, endodontic treatments and restorations) performed during the 5 years preceding and the 5 years following HCT are reported as median and range. Paired t-test were used to compare the total number of treatments and dental check-ups post-HCT with those pre-HCT.

Hyposalivation of UWS and SWS, measured after 3 and 12 months, was used to predict dental treatment need over the 5 years post-HCT. The number of treatments performed post-HCT was dichotomised based on the median value, resulting in a

group that received 0 – 3 treatments (low dental treatment need), and a group with >3 treatments (high dental treatment need). Results of the crosstabs are presented in bar charts, and sensitivity, specificity, and positive and negative predictive values were calculated.

Statistical analyses were performed with R (version 4.1.3; R Foundation for Statistical Computing, Vienna, Austria) and SPSS (version 29) and graphs were made using R and Excel.

Results

Of the 113 dentate HCT recipients that were included in the H-OME study, 74 were still alive 5 years post-treatment. Of these, 9 were excluded because they received a second HCT. Two patients were not invited (due to health and unknown reason) and 24 patients were not able to come or refused to come due to health (n=4), logistic (n=8), other (n=5) or unknown (n=7) reasons, resulting in the inclusion of 39 (53% of the) survivors. The flow chart, summarizing the number of patients in the H-OME and HOME2 study, is reported in Fig. 1. Baseline characteristics of all 113 dentate HCT recipients and the subgroup of included survivors are listed in Table 1.

Two patients were not registered with a dental healthcare provider; the other 37 patients consented in requesting dental records from their dentist. We received a response from 36 dentists: 26 dental records comprised the complete period of 5 years before and 5 years post-HCT, another 9 records comprised the period partially, and one record did not contain any relevant information.

General health

New medical diagnoses following HCT were reported by 74%. The most frequently self-reported medical conditions were infections (n=9), orthopaedic conditions (n=8) and problems of the skin and eyes (n=5). Furthermore, hypertension, cardiovascular diseases, and neuropathies were each reported by four patients; thyroid abnormalities, another diagnosis of cancer and swallowing problems, by two patients each.

HCT survivors used a median of 3 (range 0 – 15) medications at the time of the 5-year follow-up. The mean number of medications pre-HCT (as reported previously (8)) and 5 years post-HCT, divided into 4 categories, is reported in Fig. 2. Autologous HCT survivors, who were all diagnosed with multiple myeloma (MM),

used a median of 6 medications 5 years post-HCT: 6 out of 15 autologous HCT survivors used medications aiming to treat MM. Of the allogeneic HCT survivors, 2 used medications to suppress cGvHD. HCT survivors that were 54 years or younger at HCT used a median of 1 (range 0 – 12) medications, while older patients used a median of 5 (range 0 – 15) medications. The number of used medications was correlated to the severity of subjective oral dryness (Spearman's rho 0.37, p=0.022), but not to salivary flow rate (Table S1).

Table 1. Pre-HCT characteristics and HCT related information of all included dentate patients and those included in the 5-year follow-up

	All patients (113)	**Survivors (39)**
Median age at HCT in years (range)	56 (19 – 74)	55 (19 – 74)
Gender, n (% female)	51 (45%)	14 (36%)
Centre, n		
AMC	42	10
Radboudumc	71	29
Type of HCT; intensity of conditioning, n		
Autologous	49 (43%)	15 (38%)
Allogeneic MAC	14 (12%)	7 (18%)
RIC	23 (20%)	9 (23%)
NMA	27 (24%)	8 (21%)
Diagnoses, n		
Acute Myeloid Leukaemia	27 (24%)	6 (15%)
Acute Lymphoblastic Leukaemia	5 (4%)	3 (8%)
Lymphoma	7 (6%)	6 (15%)
Chronic Lymphocytic Leukaemia	3	
Myelodysplastic Syndrome	9 (8%)	3 (8%)
Chronic Myeloid Leukaemia	2	1
Myelofibrosis	4	1
Severe Aplastic Anaemia	2	1
Multiple myeloma	51 (45%)	16 (41%)
Other	3	2
Total body irradiation, n	43 (38%)	14 (36%)
No total body irradiation, n	70 (62%)	25 (64%)
Hyposalivation UWS	31%	27%
Hyposalivation SWS	27%	32%
Mean subjective oral dryness score (SD)	1.9 (2.3)	1.5 (1.8)
Median dentine lesions (range)	1 (0 – 10)	0 (0 – 8)
Median DMFT (range)	18 (0 – 28)	17 (2 – 25)

Abbreviations: MAC, myeloablative conditioning; RIC, reduced intensity conditioning; NMA, non-myeloablative conditioning; UWS, unstimulated whole saliva; SWS, stimulated whole saliva; SD, standard deviation; DMFT, decayed missing and filled teeth

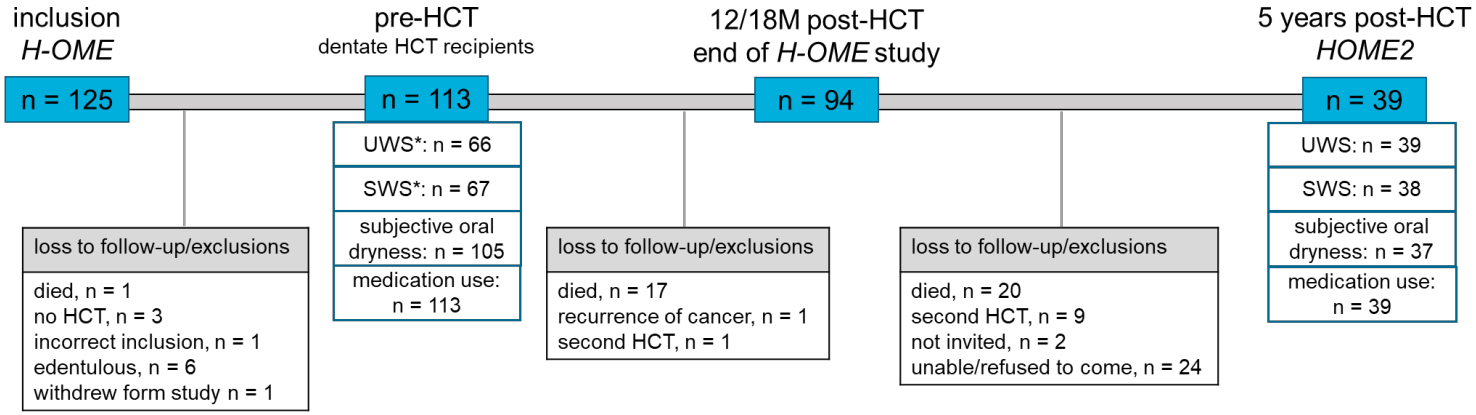

Figure 1. Flow chart combining the number of patients (n) in the previous closed H-OME study and the current HOME2 study. *Pre-HCT, UWS and SWS flow rates were only reported from patients treated at the Radboudumc due to higher precision measurements performed in this centre.
Five years post-HCT, SWS flow rate was missing in one patient due to unknown reasons and subjective oral dryness scores of 2 patients were excluded, because of conflicting answers to the 11-point and 4-point Likert scale that was part of the QLQ-OH15.
Abbreviations: UWS, unstimulated whole saliva; SWS, stimulated whole saliva

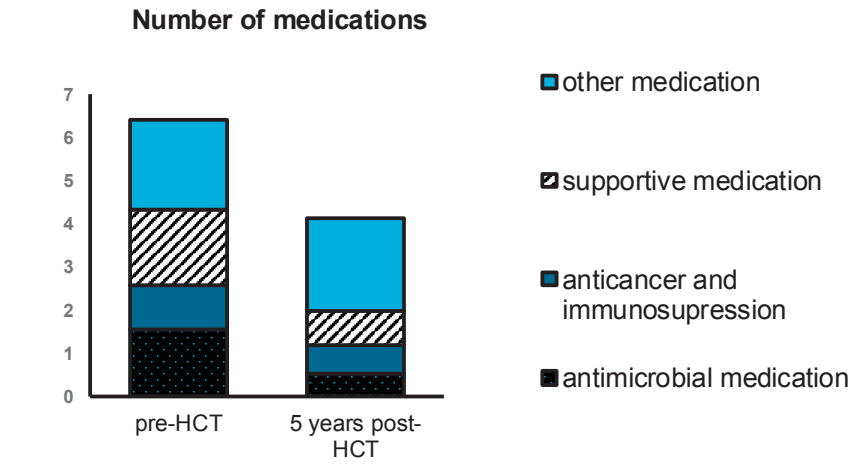

Figure 2. Mean number of medications pre-HCT (during the dental screening) and 5 years post-HCT

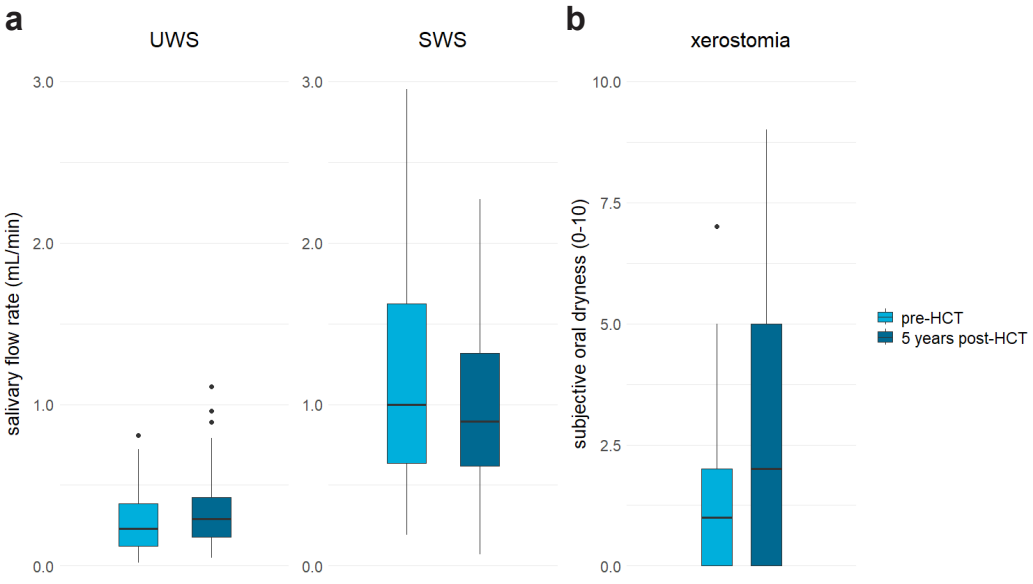

Figure 3. Boxplot of unstimulated (UWS) and stimulated (SWS) whole saliva in mL/min (**a**) and subjective oral dryness (**b**) measured pre-HCT and 5 years post-HCT

Salivary flow rate

Median UWS and SWS flow rates 5 years post-HCT are visualised in Fig. 3a; the mean scores for several subgroups are reported in Table S2. Eleven out of 39 patients (28%) were diagnosed with hyposalivation of UWS and 13/38 patients (34%) were

diagnosed with hyposalivation of SWS. Median pre-HCT salivary flow rates from patients treated at the Radboudumc are also shown in Fig. 3a. Change in salivary flow rate was determined in 27 patients for whom the two measurements were available. The mean UWS flow rate increased with 0.03 mL/min (95%CI:-0.07 – 0.12; p: 0.559) and the mean SWS flow rate decreased (mean difference: -0.18; 95%CI: -0.45 – 0.08; p: 0.167). On average, salivary flow rates did not change significantly, but an increase or decrease was seen in the majority of patients (Fig. 4). Mean change scores in several subgroups are reported in Table S3.

Current subjective oral dryness

Subjective oral dryness scores 5 years post-HCT are shown in Fig. 3b; mean mouth dryness scores for several subgroups are reported in Table S2. Five years post-HCT, 27 out of 37 patients (73%) experienced an oral dryness score ≥1 recently. If oral dryness scores 5 years post-HCT are compared with pre-HCT scores (also shown in Fig. 3b), a mean increase of 1.2 points was reported (95%CI: 0.2 – 2.1; p: 0.019). Mean change scores from baseline in several subgroups are reported in Table S3. An increase in complaints of ≥1 points was seen in the majority of patients (Fig. 4).

Dental caries

When HCT survivors visited our dental clinic 5 years post-HCT, a median of 0 (mean 1.3) dentine lesions (range 0 – 12) was diagnosed. Thirty-eight percent of the 46 detected lesions were non-cavitated coronal lesions (ICDAS 4), 16% were cavitated coronal lesions (ICDAS 5 or 6) and 46% were cavitated root lesions. The number of detected lesions was not correlated to the salivary flow rate 5 years post-HCT (Table S1).

Caries-related dental treatments

During the 5 years before HCT, 123 dental treatments (tooth extractions, endodontic treatments and restorations) were performed in 26 patients. Of these, only 4 treatments (3 extractions and 1 restoration) were performed after the focal infection screening and preceding HCT. Based on data retrieved from dental records and radiographs, it could be established for 11% of the 123 treatments that they were performed due to caries.

During the 5 years following HCT, 170 treatments were performed by the dentist in 35 patients, while an additional 12 treatments were performed in the academical medical centre. Overall, survivors underwent a median of 3 (range 0 – 20) dental treatments. Thirty-three percent of these treatments was performed due to caries, 23% due to other reasons (mostly fracture, trauma and wear) and in 43%, no diagnosis was reported. Based on retrieved radiographs, we established that

another 5% of the treatments, in which no diagnosis was reported, was probably performed due to caries. In the 5 years post-HCT, non-significantly more treatments were performed compared to the 5 years pre-HCT (mean difference: 0.5; 95%CI: -1.2 – 2.2). The number of dental check-ups performed in the general dental practices was comparable pre- and post-HCT (mean difference -0.1; 95%CI: -1.2 – 1.0). In addition to these check-ups, HCT survivors also saw a study dentist several times as part of the H-OME study: these visits were not counted as dental check-ups. Median number of dental treatments (including treatments performed in the academical medical centre) pre- and post-HCT are reported in Table 2.

Table 2. Median number of caries-related dental treatments and check-ups during 5 years before, and 5 years following HCT

	5 years before (n = 26)	**5 years after (n = 35)**
dental check-ups (range)	6 (2 – 9)	5 (0 – 10)
restorations (range)	2 (0 – 19)	3 (0 – 20)
restored surfaces (range)	10 (0 – 80)	7 (0 – 79)
extractions (range)	0 (0 – 4)	0 (0 – 2)
endodontic treatments (range)	0 (0 – 4)	0 (0 – 4)

The predictive potential of hyposalivation in dental treatment need

The number of patients who underwent 0 – 3 treatments (low dental treatment need) and those who underwent >3 dental treatments (high dental treatment need) in the 5 years following HCT is shown in Fig. 5, while a distinction is made between patients with and without hyposalivation. Looking at hyposalivation of UWS (Fig. 5, top row), it is shown that the majority of patients with hyposalivation had a low dental treatment need, and half of the patients with a normal UWS flow rate had a low dental treatment need. The same applies to hyposalivation of SWS at 3 months post-treatment (Fig. 5, bottom left side). Looking at hyposalivation of SWS at 12 months post-treatment (Fig. 5, bottom right side), we see a different picture: the majority (78%) of patients with hyposalivation had a high dental treatment need, while the majority (62%) of patients without hyposalivation had a low dental treatment need. Hyposalivation was considered to be a potential predictor for a high dental treatment need in the current population, and the sensitivity, specificity, and positive and negative predictive values were calculated and reported in Table S4.

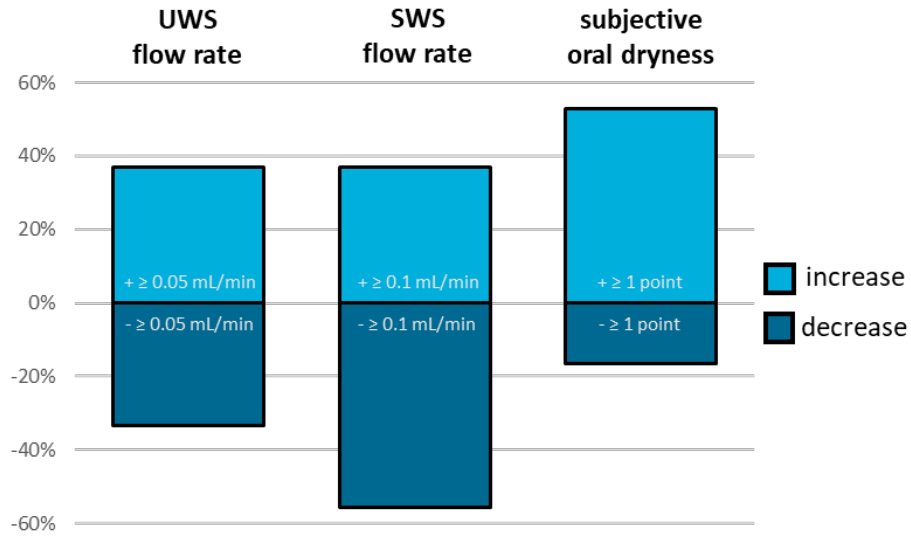

Figure 4. Prevalence of either increase or decrease in UWS flow rate, SWS flow rate and subjective oral dryness score from pre-HCT to 5 years post-HCT

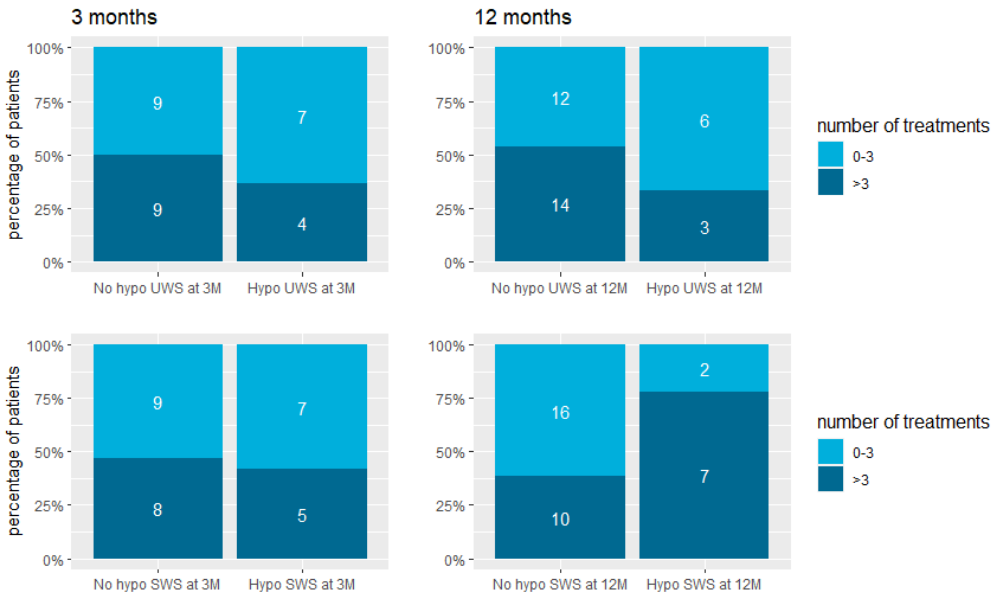

Figure 5. The relation between hyposalivation of unstimulated (UWS) and stimulated whole saliva (SWS), measured 3 and 12 months post-HCT and dental treatment need during 5 years post-HCT. Bar charts represent the number of patients with hyposalivation (hypo) and a high or low dental treatment need

Discussion

The aim of the present study was to describe UWS and SWS flow rates, subjective oral dryness and dental caries 5 years post-HCT. This study added one additional follow-up to the previous closed H-OME study, in which HCT recipients were followed from a pre-HCT measurement to 18 months post-treatment. Data on salivary flow rate (8) and caries progression (18) during the first 18 months were reported previously. The longitudinal follow-up of the same population, made it possible to compare the recently collected 5-year results with the previously published pre-HCT data. Even though the 5-year response rate was quite high, given the high mortality rate and the increased vulnerability in this population, only 39 HCT recipients could be included. This small number of participants limited the possibility of statistical analyses to a mainly descriptive level.

Five years post-HCT, the mean UWS flow rate in 39 survivors was 0.36 mL/min (SD 0.26), and the mean SWS flow rate was 1.02 mL/min (SD 0.57). These results could not be compared to other populations of HCT survivors, as this is the first study assessing oral side effects longitudinally more than 2 years post-HCT. The mean UWS flow rate 5 years post-HCT could be considered as normal, while the mean SWS flow rates remained lowered compared to normal levels (1.5 – 2 mL/min) as reported in literature (29). Mean UWS and SWS flow rates 5 years post-HCT were not significantly different from pre-HCT levels. It should be emphasized that differences between survivors were large, and that an unchanged mean score does not mean that individual patients reach their own pre-HCT value 5 years post-HCT.

Five years post-HCT, 73% of the patients experienced recently a subjective oral dryness score of ≥1. Oral dryness was measured with a non-validated 0 – 10 Likert scale, asking for mouth dryness during the last 24 h, which can be considered as a limitation of the current publication. The prevalence of subjective oral dryness, or xerostomia, cannot be easily compared with other populations of HCT survivors, as several different questions were used to determine its prevalence in literature (15). Based on five cross-sectional studies, in which subjective mouth dryness was assessed with a simple question or a score ≥1 on a 4- or 5-point Likert scale, the prevalence ranged between 22 and 68% (15). In our study, survivors reported to experience a subjective oral dryness score that was 1.2 points higher (0 – 10 scale; 95%CI: 0.2 – 2.1) compared to pre-HCT.

We reported previously that the intensity of the conditioning regimen was a significant risk indicator in the development of hyposalivation and subjective

oral dryness during the first year post-HCT, but its effect tended to diminish over time (8, 15). Five years post-HCT, allogeneic HCT recipients who received a MAC conditioning regimen still had lower salivary flow rates and higher subjective oral dryness scores compared to those with an NMA/RIC regimen, but these differences did not reach statistical significance (Table S2). In addition to these previous studied risk indicators, many other variables might contribute to hyposalivation and oral dryness 5 years post-HCT, like the actual health status, comprising potential recurrence of disease and comorbidities and medication use. Due to the small number of patients that could be included in the current investigation, we can only speculate on potential causes for the development of hyposalivation and subjective oral dryness in HCT recipients. The population was divided in several subgroups, based on some potential causal factors (Table S2), but the differences between these subgroups should be interpreted with caution.

Looking at salivary flow rate, a remarkable difference between subgroups was seen for TBI. Allogeneic patients that received TBI as part of the conditioning had lower UWS and SWS flow rates than those without TBI. However, changes in salivary flow rate from baseline did not reach significance in both groups, indicating that the difference between the subgroups did already exist before the transplantation, and that TBI did not cause a reduction in salivary flow rate. It was reported previously that there was no association between salivary hypofunction and TBI between 6 months and 6 years post-HCT (5), and 2 years post-HCT (30).

Looking at subjective oral dryness, another difference is noticeable. Patients who used 4 or more medications at the 5-years follow-up experienced more subjective oral dryness and demonstrated a significant increase in complaints compared to baseline, while patients who used up to 3 medications experienced half as much complaints and returned to pre-HCT levels after 5 years. The relation between medication intake and subjective oral dryness is in agreement with literature (31).

At the 5 year follow-up, HCT survivors were diagnosed with a median of 0 dentine lesions (range 0 – 12). Because the majority of patients visited the dentist regularly, and this likely resulted in the detection and restoration of caries lesions, this number does not tell us much about caries risk. Therefore, it was not surprising that the number of detected caries lesions was not related to the current salivary flow rate. To gain a better understanding of the progression of caries lesions, we chose to report dental treatment need. It should be emphasised that his approach has it shortcomings. The number of dental treatments might have been underestimated: treatments performed by other dental healthcare providers, emergency dentists

for example, which were not listed in the dental records might have been missed. Furthermore, the number of performed dental treatments might be a result of caries progression, but also of other causes like trauma, fracture and wear, and will be influenced by operator and patient related factors (32). Previously, it was reported that caries was the most common reason for initial restorations and restoration replacement (33). In the current population, the indication for dental treatment remained unclear in 38% post-HCT.

In a previous publication regarding the H-OME population, we concluded that hyposalivation UWS was not related to caries progression, while hyposalivation of SWS 3 months post-HCT was a significant risk indicator (18). A risk indicator does not have to be a useful predictor, as is confirmed in the current study: hyposalivation of SWS 3 months post-HCT did not predict the number of dental treatments during the first 5 years post-HCT. This finding might be caused by the temporary nature of hyposalivation: SWS flow rates in half of the patients with hyposalivation at 3 months, recovered to normal levels after 12 months. On the other hand, 80% of the HCT survivors that was diagnosed with hyposalivation at 12 months, had also hyposalivation of SWS 5 years post-treatment. Those who were diagnosed with hyposalivation of SWS at the 12 months follow-up, were likely to have an increased dental treatment need. Because, in most cases, several years are needed for caries lesions to develop and make restorative treatment necessary (34), it is not surprising that the duration of hyposalivation is an important factor to predict dental treatment need. In the current study, salivary flow rates were only measured at some predetermined times, as a result of which we do not know how salivary flow rates evolved over time. Nevertheless, it seems to be plausible that subjects who were diagnosed with hyposalivation twice, had a prolonged period of insufficient salivary flow.

If hyposalivation of SWS 12 months post-HCT was considered as a predictor for dental treatment need, this test resulted in a low sensitivity and high specificity in the current population. In accordance with this, it was reported previously that a lowered salivary flow rate has a low sensitivity and a high specificity in the prediction of caries prevalence or incidence (17). We want to emphasise that a prolonged period of hyposalivation is only one potential predictor for caries progression or dental treatment need, and that multivariable models are likely needed (35).

Conclusions

Mean unstimulated and stimulated salivary flow rates 5 years after haematopoietic cell transplantation were not significantly different from pre-HCT levels while mean subjective oral dryness scores were increased. Dental treatment need did not increase significantly as a result of HCT. A shortage of UWS and a short-term lowered SWS flow rate did not predict dental treatment need, while a sustained reduction in SWS flow rate might play a role in the prediction of dental treatments.

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Supplementary material

Table S1. Spearman's correlation between salivary flow rate and subjective oral dryness scores, and the number of used medications and dentine lesions 5 years post-HCT

	number of medications	dentine lesions
UWS flowrate (mL/min)	rho: -0.047 p: 0.778	rho: -0.057 p: 0.731
SWS flowrate (mL/min)	rho: -0.186 p: 0.265	rho: -0.163 p: 0.328
subjective oral dryness (0-10)	rho: 0.374 p: 0.022	rho: 0.185 p: 0.273

Table S2. Mean unstimulated (UWS) and stimulated whole saliva (SWS) flow rates and mean subjective oral dryness scores 5 years post-HCT with standard deviations (SD)

	n*	UWS in mL/min		SWS in mL/min		Subjective oral dryness 0-10	
		mean (SD)	p-value	mean (SD)	p-value	Mean (SD)	p-value
Age ≤54 years	17	0.46 (0.29)		1.10 (0.62)		2.4 (2.4)	
Age ≥55 years	22	0.28 (0.22)	0.037	0.96 (0.54)	0.446	3.0 (2.6)	0.467
Autologous	15	0.38 (0.29)		1.08 (0.58)		3.8 (3.1)	
Allogeneic MAC	7	0.27 (0.22)	0.367	0.81 (0.62)	0.345	3.2 (2.1)	0.616
Allogeneic NMA/ RIC	17	0.38 (0.26)	0.321	1.06 (0.56)	0.346	1.7 (1.8)	0.112
Allogeneic TBI	14	0.21 (0.11)		0.67 (0.33)		2.5 (1.9)	
Allogeneic no TBI	10	0.54 (0.26)	0.003	1.44 (0.55)	0.002	1.5 (1.9)	0.208
Male	25	0.36 (0.26)		1.11 (0.58)		2.2 (2.4)	
Female	14	0.36 (0.28)	0.989	0.88 (0.55)	0.236	3.6 (2.7)	0.118
0 – 3 medications	20	0.39 (0.28)		1.11 (0.49)		1.7 (2.0)	
≥4 medications	19	0.33 (0.25)	0.461	0.93 (0.66)	0.366	3.7 (2.6)	0.011

Abbreviations: MAC, myeloablative conditioning; NMA/RIC, non-myeloablative or reduced intensity conditioning; TBI, total body irradiation

*SWS flow rate was missing in one patient, and subjective oral dryness scores were excluded for two patients

Table S3. Mean differences (Δ) with 95% confidence intervals for unstimulated (UWS) and stimulated whole saliva (SWS) flow rates and subjective oral dryness (0-10) 5 years post-HCT compared to pre-HCT. Negative values indicate a decrease in flow rate or complaints, while positive values indicate an increase. Mean differences in subjective oral dryness scores were calculated for HCT survivors treated at the AMC and the Radboudumc, while mean differences in UWS and SWS flow rates were only calculated for patients treated at the Radboudumc.

	Δ UWS in mL/min (95% CI)	**Δ SWS in mL/min (95% CI)**	**Δ subjective oral dryness 0-10 (95% CI)**
All included survivors	0.03 (-0.07 – 0.12) p = 0.559	-0.18 (-0.45 – 0.08) p = 0.167	1.2 (0.2 – 2.1) p = 0.019
Age ≤54 years	0.05 (-0.14 – 0.23)	-0.11 (-0.61 – 0.38)	1.4 (0.1 – 2.7)
Age ≥55 years	0.02 (-0.09 – 0.12)	-0.24 (-0.57 – 0.09)	1.0 (-0.5 – 2.5)
Autologous	-0.02 (-0.17 – 0.13)	-0.30 (-0.83 – 0.22)	1.5 (-0.8 – 3.8)
Allogeneic MAC	0.01 (-0.07 – 0.08)	-0.21 (-0.60 – 0.18)	0.7 (-2.4 – 3.7)
Allogeneic NMA/RIC	0.06 (-0.12 – 0.24)	-0.11 (-0.59 – 0.36)	1.1 (0.2 – 1.9)
Allogeneic TBI	0.02 (-0.04 – 0.09)	-0.11 (-0.41 – 0.18)	0.7 (-0.7 – 2.0)
Allogeneic no TBI	0.07 (-0.23 – 0.36)	-0.18 (-0.93 – 0.58)	1.3 (-0.1 – 2.7)
Male	0.00 (-0.11 – 0.12)	-0.21 (-0.55 – 0.14)	1.0 (-0.1 – 2.2)
Female	0.08 (-0.12 – 0.28)	-0.13 (-0.64 – 0.37)	1.4 (-0.6 – 3.3)
0 – 3 medications	0.02 (-0.14 – 0.17)	-0.25 (-0.68 – 0.19)	0.2 (-1.0 – 1.3)
≥4 medications	0.04 (-0.08 – 0.16)	-0.11 (-0.43 – 0.22)	2.2 (0.7 – 3.7)

Abbreviations: MAC, myeloablative conditioning; NMA/RIC, non-myeloablative or reduced intensity conditioning; TBI, total body irradiation

*SWS flow rate was missing in one patient, and subjective oral dryness scores were excluded for two patients

Table S4. Sensitivity and specificity and positive and negative predictive values accompanying the four different measurements of hyposalivation as reported in figure 5

		Sensitivity	**Specificity**	**Positive predictive value**	**Negative predictive value**
Hyposalivation of UWS	3 months	31%	56%	36%	50%
	12 months	18%	67%	33%	46%
Hyposalivation of SWS	3 months	38%	56%	42%	53%
	12 months	41%	89%	78%	62%

Chapter 7

Additional integrative analyses

In this chapter, some additional analyses are reported, attempting to relate outcomes reported in the previous chapters to each other. First, the xerostomia outcomes reported in chapter 3 and 4 are combined. Secondly, the relation between salivary flow rate (chapter 2) and xerostomia was explored.

Question 1: Are the xerostomia results as reported in the Orastem study in accordance with the results from the systematic review?

The prevalence and severity of xerostomia in HCT recipients was described in chapter 3 and 4. While chapter 3 summarized results from systematically retrieved publications, chapter 4 reported results of a longitudinal, observational multinational cohort study (the Orastem study). Now this thesis is almost finalised, the question was raised whether results of these two chapters were in accordance with each other.

Xerostomia scores from the Orastem study were recalculated to a 0-100 scale and were added to the previously reported forest plots as developed with Review Manager software (version 5.3). The adapted meta-analyses, summarising change form baseline early post-HCT, 2 – 5 months post-HCT and 1 – 2 years post-HCT, are shown in Fig. 1 (a–c). Change in xerostomia scores early post-HCT was not determined in the Orastem population, because of different phrasing of the xerostomia questions. However, a similar question was answered at both moments by the H-OME participants, enabling us to add these results (change between baseline and the measurement closest to day 10) to the meta-analysis. Forest plots summarising the differences between myeloablative (MAC) and reduced intensity (RIC) conditioning regimens are also shown in Fig. 1 (d–f).

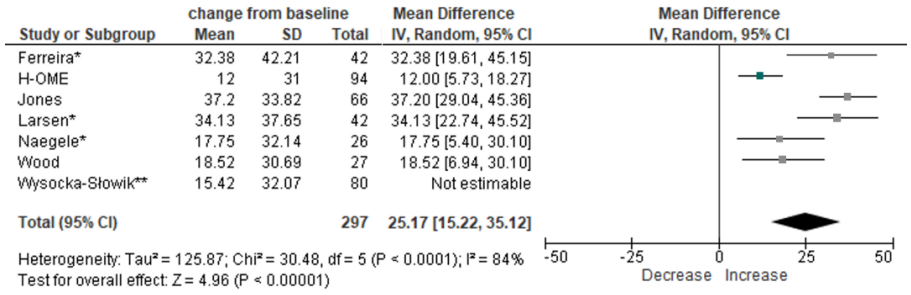

Figure 1a. Change in severity of xerostomia between baseline and early post-HCT; results from the H-OME study were added to the forest plots as reported in chapter 3

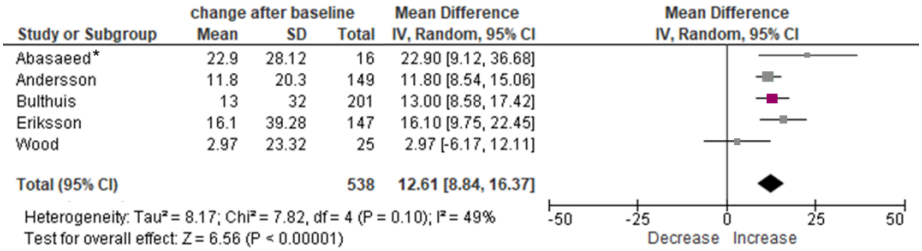

Figure 1b. Change in severity of xerostomia between baseline and 2 – 5 months post-HCT, results from the Orastem study (Bulthuis) were added to the forest plots as reported in chapter 3

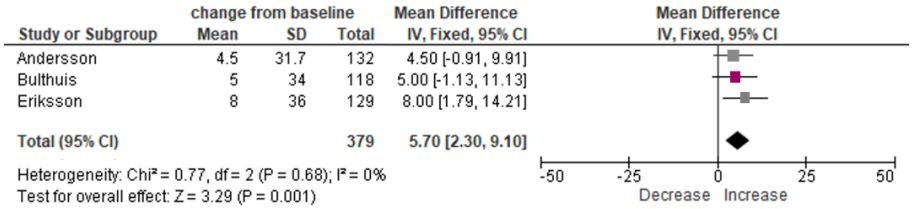

Figure 1c. Change in severity of xerostomia between baseline and week 1 – 2 years post-HCT; results from the Orastem study (Bulthuis) were added to the forest plots as reported in chapter 3

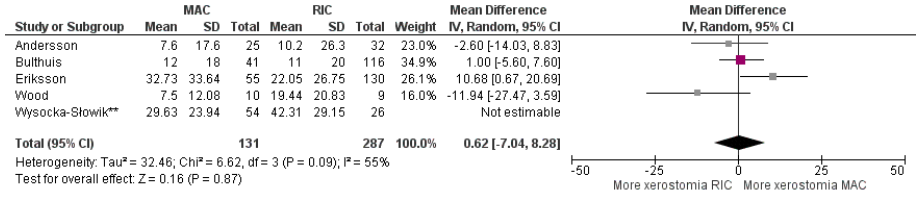

Figure 1d. Difference between MAC and RIC pre-HCT. Results from the Orastem study (Bulthuis) were added to the forest plots as reported in chapter 3

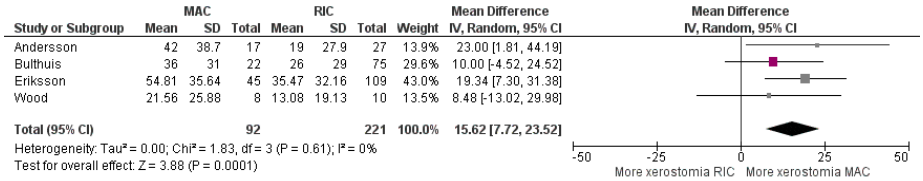

Figure 1e. Difference between MAC and RIC 2 – 5 months post-HCT. Results from the Orastem study (Bulthuis) were added to the forest plots as reported in chapter 3

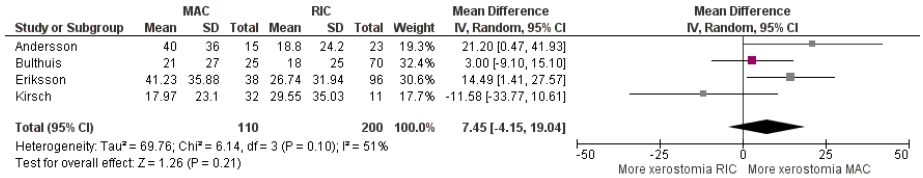

Figure 1f. Difference between MAC and RIC 1 – 2 years post-HCT. Results from the Orastem study (Bulthuis) were added to the forest plots as reported in chapter 3

SD's for change score were imputed with the help of a correlation coefficient as suggested in the Cochrane Handbook for systematic Reviews of Interventions, chapter 6 (1) Results reported by Wysocka-Słowik received no weight in the meta-analysis because the quality rating resulted in 3 points, which was categorized as a high risk of bias*

Xerostomia scores derived from the Orastem study and the H-OME study, were in line with the systematically retrieved results. Results of the analyses did not change significantly by adding the additional data. Results of the adapted meta-analyses were added to table 3 as reported in the summary (chapter 9).

Question 2: to what extent are salivary flow rates and xerostomia scores correlated?

Relations between stimulated whole saliva (SWS) and xerostomia scores were determined in chapter 4. The low correlations between SWS flow rate and xerostomia raised the question to what extent unstimulated whole saliva (UWS) flow rates correlated with xerostomia scores. UWS flow rates were not collected as part of the Orastem study, but they were collected by a subgroups of patients treated in the Netherlands (H-OME and HOME2). To answer the following two sub questions, only data from patients treated at the Radboudumc were used. Statistical analyses were performed using SPSS (version 29) and R (version 4.1.3; R Foundation for Statistical Computing, Vienna, Austria).

a. Is the severity of xerostomia related to UWS and SWS flow rates at each timepoint?

Pearson correlation was used to answer this question, based on patients treated at the Radboudumc. Early post-HCT, one timepoint (closest to day 10) was selected for each patient. Pearson correlations between xerostomia scores (0-10) and UWS and SWS flow rates are reported in table 1.

Table 1. Pearson correlations (r) between xerostomia scores (0-10) and UWS and SWS flow rates in mL/min (H-OME and HOME2 study)

	pre-HCT (n=75)	day 10 (n=61)	3 months (n=59)	12 months (n=56)	5 years (n=27)
UWS	r: -0.37; p: 0.001	r: -0.44; p <0.001	r: -0.40; p: 0.002	r: -0.43; p: 0.001	-0.34; p: 0.079
SWS	r: -0.18; p: 0.127	r: -0.26; p: 0.066	r: -0.36; p: 0.006	r: -0.32: p: 0.016	-0.47; p: 0.013

Xerostomia scores were weakly to moderately correlated to UWS and SWS flow rates at different moments in time. The relation between UWS flow rate and xerostomia tended to be stronger than the relation between SWS flow rate and xerostomia. The correlation between SWS flow rate and xerostomia tended to increase over time.

b. Is the severity of xerostomia related to UWS and SWS flow rates within subjects over time?

Pearson correlations were calculated for each patient treated in Nijmegen with at least 4 simultaneous measurements of xerostomia and UWS or SWS. Early post-HCT, one timepoint (closest to day 10) was selected for each patient. The mean standard error was added to patients with a correlation of 0. Thereafter, meta-analyses were developed, summarizing the Pearson correlations calculated for each patient using a random effects model. Forest plots are shown in Fig. 2a. A meta-analysis of 59 Pearson correlation coefficients resulted in a mean correlation between UWS and xerostomia of -0.40 (95% CI: -0.54 – -0.26; I^2: 62%) and between SWS and xerostomia of -0.29 (95%CI: -0.46 – -0.12; I^2: 72%; n=53). Changes in xerostomia scores were weakly related to changes in SWS flow rates, and moderately to changes in UWS flow rates.

c. Can the development of xerostomia be explained by UWS flow rates reaching a threshold of 0.1 mL/min or 0.2 mL/min?

In total, 420 simultaneous measurements of xerostomia and UWS and SWS flow rate were available, as collected from 79 patients. Crosstabs were made to study the relation between xerostomia (score ≥1) and hyposalivation of UWS, using the following thresholds: <0.1 mL/min and <0.2 mL/min. Results are presented in bar charts (Fig. 2b). In 76% of the occasions when UWS flow rate was lower than 0.2 mL/min, the patient experienced xerostomia of some degree. If the threshold was lowered to 0.1 mL/min, this percentage increased to 90%. On the other hand, flow rates within the normal range did not result in the absence of complaints: xerostomia was experienced at more than half of the occasions when UWS flow rates fell within normal levels. We conclude that hyposalivation of UWS is likely to result in xerostomia, while normal UWS flow rates are not associated with the absence of xerostomia complaints

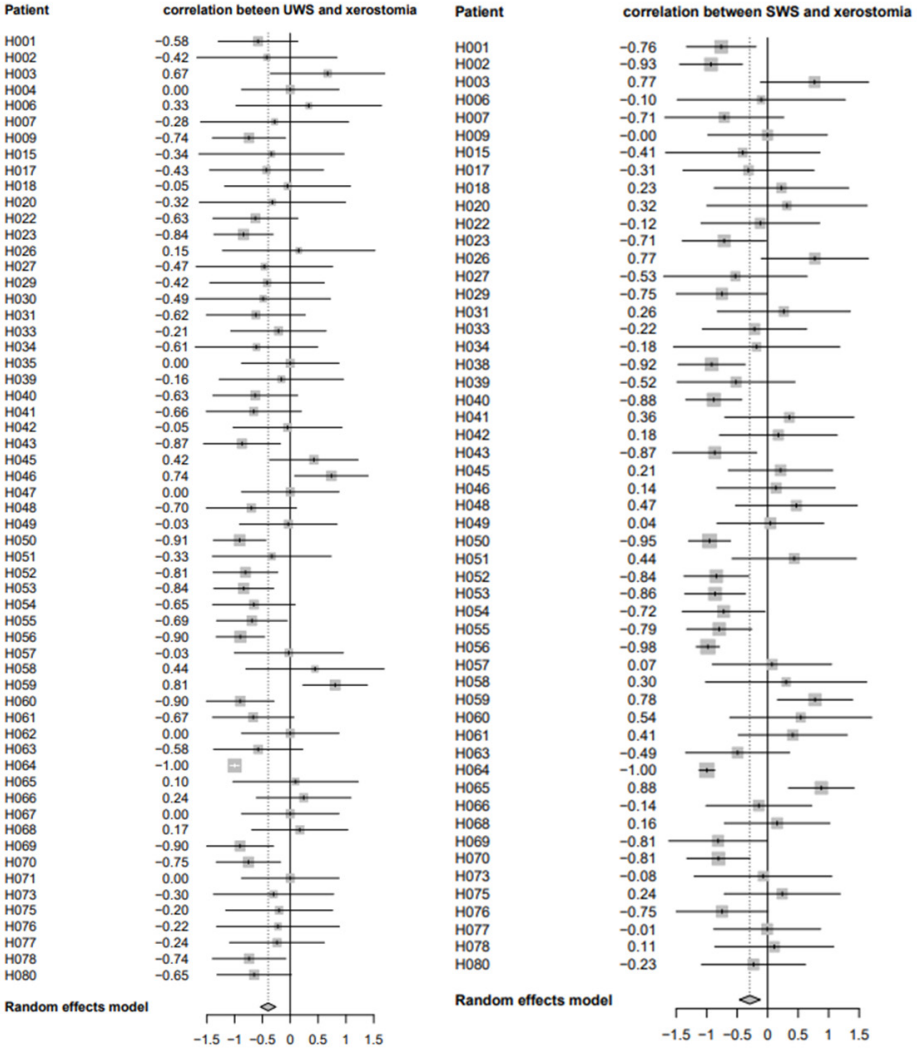

Figure 2a. Meta-analyses of Pearson correlations between xerostomia scores (0-10) and UWS (left) and SWS (right) flow rates.

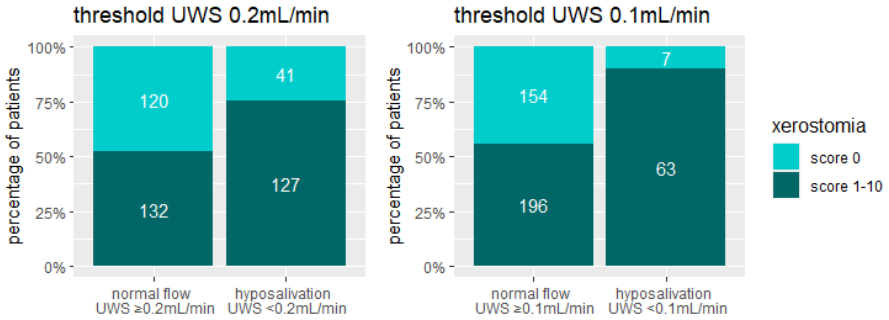

Figure 2b. Relation between the simultaneous presence of hyposalivation of UWS and a xerostomia score ≥1 (results of H-OME en HOME2 combined).

d. Is a decline in UWS flow rate of >50% a useful predictor for development of xerostomia in the population of HCT recipients?

To calculate the predictive potential of a decline in UWS flow rate of >50%, every timepoint with a xerostomia score of 0 was selected and compared with the next timepoint. Results are presented in Fig. 2c. The figure revealed that a decline in UWS flow rate of >50% could not predict the development of xerostomia in the current population of HCT recipients.

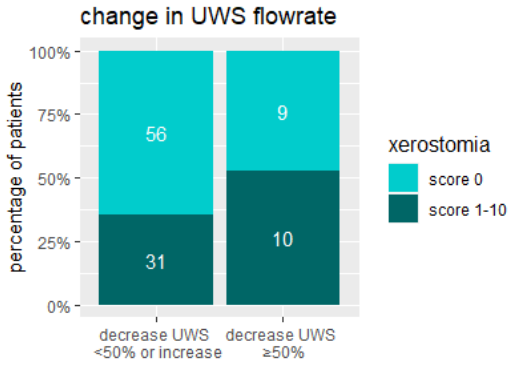

Figure 2c. Relation between a decrease of >50% in UWS flow rate and the presence of a xerostomia score ≥1 at the second timepoint (results of H-OME en HOME2 combined).

1. Higgins J, Li T, Deeks J. Handbook for Systematic Reviews of Interventions version 6.3 Cochrane2022. Available from: www.training.cochrane.org/handbook.

Chapter 8

General discussion

The overall aim of this thesis was to describe salivary flow rate, xerostomia and caries progression over time in adult haematopoietic cell transplantation (HCT) recipients. All chapters of this thesis focussed on one or more of these oral side effects before HCT, shortly after HCT and on the long term up to 5 years post-HCT. Results of a longitudinal, observational, multinational cohort study, the Orastem study, were reported in chapter 4. Chapters 2, 5 and 6 reported results of a subgroup of this population, including patients treated in the Netherlands: the H-OME and HOME2 study. Results of a systematic review were reported in chapter 3. Finally, chapter 7 reported some additional analyses attempting to relate oral side effects, as reported in the previous chapters, to each other.

Salivary flow rate

HCT influenced salivary flow rate significantly; this relation is the common thread in this thesis. Mean stimulated whole saliva (SWS) flow rates decreased shortly after HCT, were still reduced 3 months post-treatment, and returned to pre-HCT levels after 1 year (chapter 2). No further recovery was seen between 1 and 5 years post-HCT (chapter 6); mean SWS flow rates remained reduced compared to the average of 1.5 to 2.0 mL/min (1). Mean unstimulated whole saliva (UWS) flow rates followed the same trend over time, even though differences from baseline did not reach statistical significance (chapters 2 and 6). UWS flow rates reached values comparable to normal levels (0.3 – 0.4 mL/min(1)) 5 years post-HCT.

An important limitation of the current thesis was the suboptimal collection of saliva in the H-OME study. The time of day when saliva was collected was not standardised due to logistic reasons. Salivary flow rate is known to fluctuate strongly during the day (2), resulting in a reduced precision of flow rates in the H-OME population. Furthermore, we decided not to report salivary flow rates from a subgroup, due to the use of a scale with insufficient resolution, which resulted in less power. Finally, we have to mention that in some cases, collection time of SWS was reduced from 5 minutes to a minimum of 2 minutes if an abundant amount of saliva was produced. Because the duration of SWS collection influences flow rates (3), this might also have influenced the precision of our results.

Xerostomia

The prevalence and severity of xerostomia in HCT recipients was reported in chapters 3 and 4. Overall, the results derived from the Orastem study supported the systematically retrieved results. Xerostomia increased shortly after treatment and the severity was raised 2-5 months post-HCT. Even though complaints decreased over time until 1 year post-HCT, baseline levels were not reached. Complaints even tended to increase between 1 year and 5 years post-HCT. Xerostomia complaints in HCT recipients were high compared to the general population (4) before treatment and at all follow-ups. It was reported previously that the prevalence of xerostomia was lower in study completers compared to those who dropped out during a longitudinal study (5); in the H-OME and HOME2 study, there was no difference in the severity of xerostomia between these two groups (data not shown).

In the systematic review (chapter 3), we summarized papers reporting data on xerostomia in relation to time post-HCT. In total, 22 papers could be included; a number that was very high compared to a previous review (6). An extensive search strategy was used in our review, enabling the additional inclusion of papers reporting xerostomia as secondary outcome. This approach revealed a large amount of 'hidden' data, with a unique added value to the existing literature. We suggest that this approach might also be used to determine xerostomia in different populations of cancer survivors.

In chapter 3, xerostomia scores derived from different questionnaires were rescaled to a 0-100 scale and shown graphically. A recent systematic review discussed the diversity and variability in the reporting of xerostomia in clinical research (7) and stated that inconsistencies hindered the comparison and synthesis of robust evidence in systematic reviews and meta-analyses. It remained unclear to which extend xerostomia was influenced by different phrasing, response options, and time frames used in the questionnaires. Data collected as part of the Orastem and the HOME2 study, gave us the possibility to speculate on this question. Based on the strong correlations between two xerostomia questions that were answered at the same session (see frame below), we conclude that the chosen questionnaire was of limited influence on the xerostomia outcomes.

A limitation of the Orastem study was the use of two different xerostomia questionnaires. The XerostomiaVAS asked for overall mouth dryness, while a time frame of 24 hours was added to the QolXerGrade. Pre-HCT, only the XerostomiaVAS was completed, early post-HCT only the QolXerGrade, and on the long term,

both questionnaires were completed by allogeneic patients, while autologous HCT recipients only completed the QolXerGrade. The alternated use of these two xerostomia questions made the analyses in chapter 4 unnecessarily complicated, and led to our decision not to use parts of the xerostomia data. In contrast to the Orastem study, participants of the H-OME and HOME2 study answered the QolXerGrade at all visits; this data is reported in chapters 6 and 7. Is was concluded that xerostomia was the most frequent oral problem reported pre-HCT (8), that the vast majority developed xerostomia early post-HCT (chapter 4), and that complaints were still common 5 years post-HCT (chapter 6). Because xerostomia is known to influence quality of life negatively (9), we suggest that future research might focus on symptoms related to xerostomia and use validated questionnaires.

Orastem participants answered two xerostomia questions on a 0-10 scale (Xerostomia VAS and QolXergrade) 3, 6 and 12 months post-HCT. Both questionnaires were completed simultaneously 410 times, resulting in a Pearson correlation coefficient of 0.92. The added time frame of 24 hours (QolXerGrade) resulted in a mean score that was 0.19 points or 8% lower. As part of the HOME2 study, the QolXerGrade could be compared with the xerostomia question as included in the OH-15 questionnaire, asking for mouth dryness during the last week on a 4-point scale. Comparing the two xerostomia questions 5 years post-HCT in 37 patients resulted in a Pearson Correlation of 0.89.

Relation between salivary flow rate and xerostomia

It is reported that xerostomia is primarily caused by a marked decrease in the function of the salivary glands (10) but also that xerostomia may not reflect actual salivary gland capabilities or performance (11). Results of the Orastem study revealed a very weak correlation between SWS flow rate and xerostomia scores pre-HCT (8); post-HCT, correlations as reported in chapter 4 were also weak. Heterogeneity between populations might have influenced these results; in the Orastem population, pronounced differences in mean xerostomia scores between centres already existed at baseline (chapter 4). It was reported previously that the geographic location was a source of heterogeneity when xerostomia in different populations was compared (4). Additional data collected as part of the H-OME and HOME2 study, gave us the possibility to explore the relation between salivary flow rate (UWS and SWS) and xerostomia in a more homogenous population (chapter 7).

Additional integrative analyses, as reported in chapter 7 revealed that xerostomia scores and UWS and SWS flow rates, determined simultaneously in patients treated at the Radboudumc, were weakly to moderately correlated at different moments in time. The relation between UWS flow rate and xerostomia tended to be stronger than the relation between SWS flow rate and xerostomia. Exploring the relation between changes in flow rates and xerostomia within subjects over time, resulted in a weak correlation for SWS (r: -0.29; 95%CI: -0.46 – -0.12) and a moderate correlation for UWS (r: -0.40; 95% CI: -0.54 – -0.26). Because the viscous UWS is essential to moisten and lubricate the oral mucosa (12), it is obvious that a lack of UWS might lead to complaints. Correlations between salivary flow rate and xerostomia are influenced by the following: a 'normal' salivary flow rate might increase or decrease over time, while a 'normal' xerostomia score (score of 0), can only remain stable or increase over time. In addition, salivary flow rates might only correlate to xerostomia scores if flow rates reach values below a certain threshold.

In chapter 7, the influence of hyposalivation of UWS on the development of xerostomia was also studied. In 76% of the occasions when UWS flow rate was lower than 0.2 mL/min, the patient experienced xerostomia of some degree. If the threshold was lowered to 0.1 mL/min, this percentage increased to 90%. On the other hand, flow rates within the normal range did not result in the absence of complaints: xerostomia was experienced at more than half of the occasions when UWS flow rates fell within normal levels. Furthermore, we conclude that a decline in UWS of >50% could not predict xerostomia in the population of HCT recipients. This analysis was inspired by a study by Dawes et al., suggesting that xerostomia occurred in healthy individuals when UWS flow rate fell by 40-50% of its normal value (13). In the population of HCT recipients, the pre-conditioning salivary flow rates did not represent normal values, as they were already reduced (chapter 2), potentially due to intensive (chemotherapeutic) treatment preceding HCT. Salivary flow rates are not determined commonly as part of regular dental care in healthy individuals, thus 'normal' values are in general unknown. Only in Sweden, dental students are taught to measure salivary flow rates of their patients to provide baseline values (14); a valuable approach that could also be introduced in other countries.

Comparing xerostomia with a reduction in salivary flow rate in HCT recipients revealed a comparable trend over time, with two exceptions. Firstly, early post-HCT, the severity of xerostomia increased in allogeneic HCT recipients, while UWS flow rates did not decrease. Secondly, mean salivary flow rates remained stable between 1 and 5 years post-HCT, while xerostomia complaints increased during

the same period. We suggest that, in HCT recipients, additional mechanisms might be involved in the aetiology of xerostomia without severely affecting salivary flow rate. For example, perceived stress, that is common in HCT recipients (15), is related to the development of xerostomia while salivary flow rates were not influenced significantly (16). The influence of chronic graft-versus-host disease (cGvHD) and medication intake on xerostomia and salivary flow rate will be discussed in the following section.

Risk indicators

Several risk indicators in the development of hyposalivation and xerostomia were studied in this thesis. Most risk indicators had a comparable effect on hyposalivation and xerostomia. The most pronounced risk indicator was the intensity of the conditioning regimen: patients that received a high intensity regimen had more hyposalivation and perceived more xerostomia compared to those receiving a reduced or non-myeloablative regimen (chapters 2 to 4). This finding confirms the suggestion that changes in salivary flow rate in HCT recipients are a direct result of toxicity of the conditioning regimen (17). Total body irradiation (TBI) as part of the conditioning did not influence hyposalivation or xerostomia. We suggested that the dose between 2 and 9 Gray that HCT recipients received, did not reach the threshold above which salivary gland function would diminish (18). TBI recipients tended to experience more xerostomia and had lower salivary flow rates compared to those receiving chemotherapy alone 5 years post-HCT, but this difference already existed at baseline (chapter 6).

Allogeneic HCT recipients experienced more xerostomia than autologous HCT recipients during the first year post-treatment (chapter 4). On the other hand, autologous HCT recipients were more often diagnosed with hyposalivation of SWS and had lower UWS and SWS flow rates early post-HCT (chapter 2). Allogeneic HCT recipients differ from the autologous, since they are at risk of developing cGvHD, which might affect the salivary glands and oral mucosa (19). Oral GvHD is, per definition, classified under chronic GvHD, and includes xerostomia as a distinctive feature (20). Salivary cGvHD is associated with a reduction in salivary flow rate and changes in the composition of saliva (21), and with an impaired recovery (22). Furthermore, cGvHD might lead to fibrosis and atrophy of the minor salivary glands, which is indicative of long-term damage (23). Because salivary gland biopsies were not performed in the current study, we could not confirm whether salivary cGvHD could explain reduced flow rates in allogeneic patients. It was previously

reported that salivary and oral mucosal cGvHD were not correlated (23), which is in agreement with the results of chapter 2. Patients diagnosed with oral mucosal changes related to cGvHD even tended to have less hyposalivation of UWS and SWS. We hypothesised that pain caused by mucosal changes could be related to increased salivary flow rates, as is seen in other potentially pain inducing situations of the oral mucosa, like teething (24), and eating spicy foods (25). We hypothesised that oral mucosal changes might contribute to the perception of xerostomia, even without changes in salivary flow rate, but could not confirm this hypothesis in chapter 4. We suggest that an additional study is warranted to explore the relation between oral mucosal changes, ideally using the National Institutes of Health Oral Mucosal Scale (19), recorded by calibrated examiners.

The number of used medications during hospitalisation was not related to the development of hyposalivation (chapter 2) or mean xerostomia scores (not reported results from H-OME study). The influence of medication use might have been missed because the dosage, type of medication and concurrent use were not taken into account. Five years post-HCT, medication use had a pronounced effect on xerostomia, while only a limited effect on salivary flow rate was noticed (chapter 6). Reviews on the effect of medications on salivary disfunction (14, 26, 27) included mostly studies reporting xerostomia as an adverse effect with no objective measurements of salivary flow rates or composition. It remains to be clarified whether changes in composition of saliva can affect xerostomia (14). Nevertheless, we hypothesise that some medications could influence the concentration of proteins secreted by salivary glands, thereby influencing xerostomia complaints. In HCT recipients, changes in salivary proteins were determined several days and months post-treatment: no change was seen in total protein concentration (28). We suggest that the difference in medication use between allogeneic and autologous HCT recipients, in particular the use of immunosuppressives, might be an explanation for the differences in xerostomia and salivary flow rate between the two groups.

Caries lesions and dental treatment need

Caries progression was observed in 32% of the HCT recipients within 18 months post-treatment; the median number of affected surfaces was 2 (range 1–12) per patient with caries progression (chapter 5). It was not possible to compare these numbers to a healthy adult population, because longitudinal studies determining caries progression are lacking. A limitation in the recording of caries was that

calibration was done based on photographs instead of real patients. Even though good quality photographs alone may be used for training and calibration (29), we suggest that differences between examiners might have affected caries progression in the different centres.

During the 5 years following HCT, survivors were treated with a mean of 4.7 (range 0 – 20) dental restorations, of which at least 39% (mean 1.9; range 0 – 19) was due to dental caries (chapter 6). Data from a practice based-research network in the Netherlands reported a mean of 0.8 restorations made due to caries in participants aged ≥26 within a timeframe of 2.5 years; 49% of the total number of restorations was made due to caries (30). In the 5 years post-HCT, HOME2 participants underwent non-significantly more dental restorations compared to the 5 years pre-HCT. Overall, we cannot conclude that HCT recipients have an increased dental treatment need. This non-significant result might be related to the extensive heterogeneity between the subjects, and the relative limited number of patients whose dental records were available before and after HCT (n=26). Because the indication for dental treatments remained unknown in a substantial part of the cases, we could not determine the effect of HCT on treatments due to caries.

Hyposalivation of SWS 3 months post-treatment was a risk indicator for caries progression during the first 18 months post-treatment (chapter 5). Furthermore, hyposalivation of SWS at 12 months has the largest potential to be a clinical applicable predictor for dental treatment need (chapter 6). Previous publications reported that in an elderly hospitalised population (31), in asthmatics (32), and in long-term cyclic antidepressant drugs users (33), decreased SWS flow rates were related to higher caries scores. On the other hand, it was reported that UWS reflected general oral health better than SWS (34, 35). We could not find any relation between hyposalivation of UWS and caries progression or dental treatment need. However, our results do not deny the importance of UWS in the prevention of caries: the non-significant effect of UWS in the current population might be due to a lack of precision, as is explained earlier. Hyposalivation of UWS and SWS cannot be separated, because these two are significantly correlated (35). However, results of the current thesis suggest that SWS has an important function in the prevention of dental caries.

Dentist perspective

Because the number of long-term HCT survivors increases (36), they are likely to visit general dental practices. Dentists should be aware of an increased risk of dental problems in HCT recipients, especially during the first year post-HCT. We recommend dentists to ask HCT survivors every dental check-up whether they experience any complaints. For the treatment of xerostomia or hyposalivation, we refer to the Dutch clinical practice guideline "Xerostomia and hyposalivation related to medication and polypharmacy" (www.hetkimo.nl).

Based on the results of this thesis, we suggest an additional caries preventive approach in HCT recipients. We advise dentists to emphasize the importance of proper dental hygiene and give additional preventive instructions before the start of the conditioning regimen. It should be kept in mind that HCT recipients might experience difficulties in completing oral hygiene practices during the transplant process (37). We propose to consider an increase in fluoride concentration (38), in line with the previous mentioned KIMO guideline. The use of toothpaste containing 5000 ppm fluoride once a day, from the start of the conditioning regimen up to 3 months post-HCT, might be a suitable preventive approach. In those patients with a high past caries experience, the use of additional fluoride might be prolonged to 12 months post-HCT. Twelve months post-HCT, we advise dentists to measure SWS flow rates. Measurement of SWS flow rate is easy to perform and can be performed in the general dental practice. If SWS flow rates remain reduced (<0.7mL/min), we encourage to continue the use of a high fluoride concentration. Otherwise, performing normal dental hygiene might be sufficient. The measurement of SWS flow rate might be repeated yearly as part of the regular dental check-up in those patients with an increased caries progression.

Patients perspective

For HCT-recipients, it is important to realise that oral complaints are common following HCT. Several long-term side effects are reported by the Dutch patient organisation for blood cancers (www.hematon.nl), like problems of thyroid or eyes, and psychosocial problems. Based on the results of this thesis, xerostomia should definitely be on the list of long-term side effects. For those patients who develop xerostomia or hyposalivation, it is wise to stick to advice given by the dentist, as reported above, to prevent development of dental caries. We have to emphasize that this research focussed at population level, thus, it is impossible to predict oral symptoms or complications in individual patients.

Conclusions

- Mean UWS and SWS flow rates declined post-HCT, this decline was temporary in nature and baseline levels were reached after 1 year. Nevertheless, mean SWS flow rates remained reduced compared to normal levels
- The mean severity of xerostomia increased post-HCT; even though xerostomia decreased during the first year post-HCT, complaints remained elevated in the majority of patients
- Dental treatment need increased not significantly as a result of HCT
- The severity of xerostomia was weakly correlated to SWS flow rates and moderately to UWS flow rates
- Hyposalivation of UWS was likely to result in xerostomia, while normal UWS flow rates did not result in the absence of xerostomia complaints
- Hyposalivation of SWS 3 months post-HCT was a risk indicator for caries progression, and hyposalivation of SWS at 12 months has the largest potential to be a clinical applicable predictor for dental treatment need. Hyposalivation of UWS did not result in an increased caries risk or dental treatment need.

Generalisability of the results

The longitudinal study design of the H-OME and HOME2 study, where whole saliva and xerostomia scores were repeatedly collected simultaneously, gave us a unique insight in the relation between these two variables. Previous publications reported conflicting results on the relation between salivary flow rates and xerostomia (11). We concluded that changes in UWS flow rate were moderately related to xerostomia within subjects, while changes in SWS flow rate resulted in a weak correlation. These results might be generalizable to other populations with reduced salivary flow rates, like cancer survivor that received chemotherapy or radiotherapy, and long-term medication users.

This longitudinal study design, where a (temporary) decline in salivary flow rate was induced by HCT and the accompanying conditioning regimen, gave us a unique possibility to study the relation between hyposalivation and caries progression. A systematic review concluded previously that a chronically low salivary flow rate was the strongest indicator of an increased caries prevalence or incidence (39); only half of the underlying studies did actually find a significant relation, and most studies comprised a cross-sectional design. Our study adds important information to the existing evidence on the relation between salivary flow and caries progression.

We suggest that our results might also be valuable to other populations with reduced salivary flow rates, like cancer survivor that received chemotherapy or radiotherapy, and long-term medication users. We encourage dentists to consider the measurement of SWS flow rate in patients suspected of hyposalivation, due to a medical condition, medication use or xerostomia complaints. Hyposalivation of SWS increases the risk for caries progression and dental treatment need, and justifies the need for additional prevention.

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Chapter 9

Summaries

Summary

Haematopoietic cell transplantation (HCT) preceded by a conditioning regimen is an established treatment option for many (non)malignant haematologic disorders. Stem cells are harvested from the patient in autologous HCT, and from a donor in allogeneic HCT. The preparative conditioning regimen consists of chemotherapy with or without total body irradiation (TBI). This intensive treatment is associated with considerable long-term morbidity, and development of oral side effects is frequently reported. In this thesis, the influence of HCT on several oral side effects was studied.

It was reported before that HCT was associated with a reduction in salivary flow rate. However, the duration and severity of this reduction remained unclear. Salivary flow rate can be easily determined by collecting whole saliva, of which two types are distinguished: unstimulated saliva (UWS) is present in the mouth under resting conditions, while chewing stimulated saliva (SWS) has a higher flowrate and differs in composition. Hyposalivation is defined as a shortage of saliva: we used a threshold of 0.2 mL/min for UWS and 0.7 mL/min for SWS. A shortage of saliva might lead to subjective complaints of mouth dryness, or xerostomia. Furthermore, a lack of saliva leads to a reduced protection of the oral cavity, which might result in tooth decay or dental caries. Dental caries might result in the need for restorative treatment.

In **chapter 2**, the development of hyposalivation over time in HCT recipients was described, and risk indicators were determined. Data used for this chapter were derived from the H-OME study: a multi-centre prospective longitudinal observational study, including 125 HCT recipients treated in two Dutch centres. UWS and SWS was collected before HCT, early post-HCT, and after 3, 6, 12 and 18 months. Results are summarised in table 1 and 2. We conclude that more than half of the patients had hyposalivation early post-HCT and a quarter still had hyposalivation after 12 months. The conditioning intensity was a risk indicator in the development of hyposalivation of both UWS and SWS. After 3 and 12 months, this effect was not significant anymore. The number of prescribed medications, TBI as part of the conditioning regimen and oral mucosal graft-versus-host disease did not influence hyposalivation significantly.

Hyposalivation might lead to xerostomia, this outcome is central to **chapter 3**. This chapter reported the results of a systematic review, focussing on the prevalence and severity of, and distress caused by xerostomia over time in HCT recipients.

PubMed, Embase, and the Cochrane Library were searched for papers published between January 2000 and May 2022. Clinical studies were included if xerostomia was reported in adult autologous or allogeneic HCT recipients. Risk of bias was assessed according to a quality grading strategy published by the oral care study group of the MASCC/ISOO, resulting in a score between 0 (highest risk of bias) and 10 (lowest risk of bias). Searches yielded 1792 unique records; 22 studies met the inclusion criteria. The quality scores ranged between 1 and 7, with a median score of 4. The prevalence of xerostomia was high in comparison to the general population. The prevalence, severity and distress of xerostomia increased shortly after HCT and the severity of complaints was raised during the first year post-HCT. Patients receiving a high intensity conditioning experienced 18 points more xerostomia (0-100 scale, 95% CI: 9 – 27) 2 – 5 months post-HCT, compared to those receiving a reduced intensity conditioning; after 1 – 2 years, there was no significant difference anymore.

Chapter 4 also reported on xerostomia, while in this chapter, results of the Orastem study were described. The Orastem study is a prospective, longitudinal, international, observational, multicentre study including 99 autologous and 163 allogeneic HCT recipients. HCT recipients rated xerostomia on a 0-10 scale before the conditioning regimen, several times early post-HCT, and after 3 months, while only allogeneic HCT recipients also answered the question after 6 and 12 months. Furthermore, SWS was collected several times. Linear regression models and longitudinal mixed effects models were created to investigate the influence of risk indicators on xerostomia. Results are reported in table 3. Complaints after autologous HCT were transient in nature, while the severity of xerostomia in allogeneic HCT recipients remained elevated 12 months post-treatment. Allogeneic HCT recipients receiving a high intensity conditioning experienced more xerostomia compared to those receiving a reduced intensity conditioning. TBI and oral mucosal changes related to chronic graft-versus-host disease did not influence the severity of xerostomia significantly.

Hyposalivation might also lead to caries progression; this association was central to **chapter 5**. Caries progression was determined in 116 dentate H-OME participants. Full caries charts, according to the ICDAS criteria, were made before HCT and 3, 6, 12 and 18 months post-HCT by trained dentist-examiners. New dentine lesions or lesion progression into dentine (ICDAS ≥4 or cavitated root lesions) occurred in 32% of patients over 18 months. The median number of affected surfaces was 2 (range: 1 – 12) per patient with caries progression. The influence of hyposalivation of UWS and SWS at baseline and after 3 months on caries progression was determined

with a negative binomial regression model. The effect of hyposalivation on caries progression is summarized in table 1 and 2 (bottom rows).

All previous mentioned outcomes (hyposalivation, xerostomia and dental caries) 5 years post-HCT were reported in **chapter 6**. This HOME2 study added one additional follow-up to the H-OME study. All dentate HCT survivors were invited, resulting in the inclusion of 39 participants. Once more, UWS and SWS was collected, participants rated the severity of xerostomia on a 0-10 scale, and caries lesions were assessed. Furthermore, dental records were requested for the 5 years preceding and 5 years following HCT. UWS en SWS flow rates and xerostomia scores are summarised in tables 1, 2 and 3 (rightmost columns). Survivors underwent a median of 3 (range 0 – 20) dental treatments (tooth extractions, endodontic treatments and restorations) during 5 years following transplantation; 39% of these treatments was due to caries. In the 5 years following transplantation, non-significantly more treatments were performed compared the five years preceding transplantation (mean difference 0.5, 95%CI -1.2 – 2.2). The effect of hyposalivation on dental treatment need is summarized in table 1 and 2 (bottom rows).

Some additional analyses were added to this thesis, in an attempt to relate outcomes reported in the previous chapters, to each other. These additional analyses are described in **chapter 7.** First, we added the xerostomia results of the Orastem study (chapter 4) to the meta-analyses as reported in chapter 3. Overall, the results derived from the Orastem study supported the systematically retrieved results. Results of this adapted meta-analyses were reported in table 3. Secondly, xerostomia scores were related to salivary flow rates in a subgroup of patients form the H-OME and HOME2 study. We conclude that the severity of xerostomia was weakly correlated to SWS flow rates and moderately to UWS flow rates, and that hyposalivation of UWS was likely to result in xerostomia, while normal UWS flow rates did not result in the absence of xerostomia complaints.

Summary of conclusions: UWS and SWS flow rates declined post-HCT, this decline was temporary in nature and baseline levels were reached after 1 year. Nevertheless, SWS flow rates remained reduced compared to normal levels. The severity of xerostomia increased post-HCT; even though xerostomia decreased during the first year post-HCT, complaints remained elevated in the majority of patients. A high intensity conditioning regimen increased the risk for hyposalivation and xerostomia. Hyposalivation of SWS 3 months post-HCT was a risk indicator for caries progression and hyposalivation of SWS at 12 months might be a clinical applicable predictor for dental treatment need.

Table 1. Unstimulated whole saliva (UWS)

	pre-HCT	early post-HCT	3 months post-HCT	1 year post-HCT	5 years post-HCT
Flow rate (mL/min)	Auto: 0.26 (SD 0.18) Allo MAC: 0.29 (SD 0.25) Allo NMA/RIC: 0.3 (SD 0.21) *Ch.2*	Auto: 0.19 (SD 0.12) Allo MAC: 0.29 (SD 0.29) Allo NMA/RIC: 0.35 (SD 0.21) *Ch.2*	Auto: 0.25 (SD 0.18) Allo MAC: 0.10 (SD 0.09) Allo NMA/RIC: 0.29 (SD 0.26) *Ch.2*	Auto: 0.28 (SD 0.12) Allo MAC: 0.20 (SD 0.10) Allo NMA/RIC: .31(SD 0.22) *Ch.2*	Flow rate: 0.36 mL/min (SD 0.26) 28% hyposalivation *Ch.6*
Changes from baseline		No significant changes *Ch.2*	No significant changes *Ch.2*	No significant changes *Ch.2*	No significant changes *Ch.6*
Risk indicators for hyposalivation		MAC > NMA/RIC *Ch.2*	allogeneic > autologous *Ch.2*	No significant risk indicators *Ch.2*	
Effect of hyposalivation on caries	hyposalivation: not associated with caries progression in 18 months *Ch.5*		hyposalivation: not associated with caries progression in 18 months no predictor for dental treatment need in 5 years *Ch.5, 6*	hyposalivation: no predictor for dental treatment need in 5 years *Ch.6*	

Table 2. Stimulated whole saliva (SWS)

	pre-HCT	early post-HCT	3 months post-HCT	1-2 years post-HCT	5 years post-HCT
Flow rate (mL/min)	Auto: 1.13 (SD 0.54) Allo MAC: 1.14 (SD 0.86) Allo NMA/RIC: 1.19 (SD 0.71) *Ch.2*	Auto: 0.50 (SD 0.21) Allo MAC: 0.73 (SD 0.73) Allo NMA/RIC: 0.98 (SD 0.58) *Ch.2*	Auto: 0.84 (SD 0.45) Allo MAC: 0.48 (SD 0.34) Allo NMA/RIC: 0.98 (SD 0.50) *Ch.2*	Auto: 1.0 (SD 0.44) Allo MAC: 0.92 (SD 0.52) Allo NMA/RIC: 1.1(SD 0.52) *Ch.2*	Flow rate: 1.0 mL/min (SD 0.57) 24% hyposalivation *Ch.6*
Changes from baseline		decline 0.44 mL/min (95% CI: 0.29 – 0.58) *Ch.2*	decline 0.26 mL/min (95% CI: 0.11 – 0.41) *Ch.2*	No significant changes *Ch.2*	No significance changes *Ch.6*
Risk indicators for hyposalivation		autologous > allogeneic MAC > NMA/RIC Ch.2	No significant risk indicators Ch.2, 4	No significant risk indicators Ch.2, 4	
Effect of hyposalivation on caries	hyposalivation: not associated with caries progression in 18 months *Ch.5*		hyposalivation: - more caries progression in 18 months (IRR: 5.3, 95% CI: 2.1–13.4) - no predictor for dental treatment need in 5 years *Ch.5, 6*	hyposalivation: might be a clinical applicable predictor for dental treatment need in 5 years *Ch.6*	

Table 3. xerostomia (scale 0-10)

	Pre-HCT			early post-HCT	2-5 months post-HCT	1-2 years post-HCT	5 years post-HCT
Values		severity	prev.	severity	severity	severity	Severity: 2.8
	Auto:	1.1 (SD 1.9)	51%	Auto: 3.1 (SD 2.1)	Auto: 2.5 (SD 2.5)	Auto: 1.7 (SD 2.4)	(range: 0 – 9)
	Allo MAC:	1.2 (SD 1.9)	39%	Allo MAC: 3.6 (SD 2.0)	Allo MAC: 3.5 (SD 2.7)	Allo MAC: 2.7 (SD 2.8)	Prevalence: 73%
	Allo NMA/RIC:	1.1 (SD 2.0)	31%	Allo NMA/RIC: 1.8 (SD 1.9)	Allo NMA/RIC: 2.7 (SD 3.1)	Allo NMA/RIC: 1.9 (SD 2.7)	*Ch.6*
	Ch.4			*Ch.4*	*Ch.4*	*Ch.4*	
Changes from baseline				Increase: 2.5 (95% CI: 1.5 – 3.5) *Ch.7*	Increase: 1.3 (95%CI: 0.9 – 1.6) *Ch.7*	Increase 0.6 (95% CI: 0.2 – 0.9) *Ch.7*	Increase 1.2 (95% CI: 0.2 – 2.1) *Ch. 6*
Risk indicators				allogeneic > autologous MAC > NMA/RIC *Ch.4, 7*	allogeneic > autologous MAC > NMA/RIC *Ch.4, 7*	MAC > NMA/RIC *Ch.7*	more medications > more xerostomia *Ch.6*

Abbreviations:
Ch, chapter; CI, confidence interval; allo, allogeneic; auto, autologous; HCT, haematopoietic cell transplantation; IRR, incidence rate ratio; MAC, myeloablative conditioning; NMA/RIC, non-myeloablative or reduced intensity conditioning; prev, prevalence, SD, standard deviation

Nederlandse samenvatting

Hematopoëtische cel transplantatie (HCT) is een veel gebruikte behandeling voor (kwaadaardige) bloedziektes zoals leukemie. De stamcellen die gebruikt worden voor deze behandeling zijn afkomstig van de patiënt zelf (autologe transplantatie) of van een donor (allogene transplantatie). Voordat de bloedcellen worden toegediend aan de patiënt, wordt een voorbereidende behandeling uitgevoerd met chemotherapie, soms in combinatie met totale lichaamsbestraling. Het doel van deze conditionering is om de kwaadaardige of afwijkende bloedcellen te doden, en het afweersysteem te onderdrukken. HCT is een zware behandeling, die flink wat bijwerkingen kan veroorzaken. Eén van de plekken waar bijwerkingen kunnen ontstaan is de mondholte; dit proefschrift gaat over deze bijwerkingen.

Het was al bekend dat HCT verandering in het speeksel kan veroorzaken, maar de ernst van deze bijwerking bleef tot nu toe onduidelijk. De veranderingen in het speeksel kunnen veroorzaakt worden door schade aan de speekselklieren als gevolg van de zware conditionering of het hoge aantal medicijnen rond de transplantatie. Daarnaast kan het ontstaan van een omgekeerde afstotingsreactie (Graft-versus-Host-ziekte) een rol spelen bij speekselveranderingen na allogene transplantatie.

Speeksel kan eenvoudig worden verzameld door een patiënt te vragen om al het speeksel, dat zich in de mond verzamelt gedurende enkele minuten, uit te spugen in een bekertje. Door het gewicht van het speeksel te delen door de verzameltijd, kan de speekselvloed worden berekend in mL/min. We onderscheiden twee typen speeksel: ongestimuleerd speeksel, dat altijd aanwezig is in de mond, en gestimuleerd speeksel, dat ontstaat tijdens kauwen of als reactie op een (zure) smaak. Een tekort aan speeksel wordt ook wel hyposalivatie genoemd. Als afkappunt voor hyposalivatie van ongestimuleerd speeksel hanteren we 0,2 mL/min, en voor gestimuleerd speeksel 0,7 mL/min. Hyposalivatie kan leiden tot het gevoel van monddroogte, wat ook wel xerostomie wordt genoemd. Ook zal hyposalivatie leiden tot minder bescherming van de mondholte, waardoor tandbederf (cariës) kan ontstaan. Het cariësproces leidt tot cariëslaesies of caviteiten ('gaatjes' in de volksmond), die in een gevorderd stadium behandeling door middel van restauraties (vullingen) noodzakelijk zullen maken.

Hoofdstuk 2 van dit proefschrift gaat over veranderingen in speekselvloed als gevolg van HCT. In dit hoofdstuk worden de resultaten van de H-OME studie beschreven: een prospectieve, longitudinale, observationele studie, waarin 125 HCT ontvangers behandeld in het Amsterdam UMC en het Radboudumc zijn

geïncludeerd. Ongestimuleerd en gestimuleerd speeksel werden verzameld vóór HCT, meerdere malen kort na HCT, en na 3, 6, 12 en 18 maanden. De gemiddelde speekselvloed daalde kort na transplantatie, was verlaagd 3 maanden daarna, en bereikte het beginniveau na 12 maanden. Voor de transplantatie had 34% van de patiënten hyposalivatie van ongestimuleerd en 29% van gestimuleerd speeksel. Deze percentages stegen tot respectievelijk 54% en 67% kort na HCT, en daalden weer tot 26% en 25% op 12 maanden. Een hoge intensiteit van de conditionering bleek het risico op hyposalivatie van ongestimuleerd speeksel kort na HCT met een factor 4 (95% betrouwbaarheidsinterval (95% BI): 2 – 11) te verhogen, voor gestimuleerd speeksel was dit een factor 8 (95% BI: 3 – 25). Dit effect was niet meer significant na 3 en 12 maanden. Totale lichaamsbestraling als onderdeel van de conditionering, het aantal gebruikte medicijnen, en het ontstaan van een omgekeerde afstotingsreactie van het mondslijmvlies hadden geen invloed op het ontstaan van hyposalivatie.

Hyposalivatie kan leiden tot xerostomie, de bijwerking die centraal staat in **hoofdstuk 3**. In dit hoofdstuk worden de resultaten van een systematisch literatuuronderzoek gerapporteerd. Verschillende medisch wetenschappelijke zoeksystemen werden gebruikt (PubMed, Embase, en Cochrane Library) om alle studies (gepubliceerd tussen 2000 en 2022) te achterhalen die iets rapporteerden over xerostomie na HCT. Wij waren hierbij zowel geïnteresseerd in de prevalentie en ernst van xerostomie, als in de last die de xerostomie veroorzaakte. De zoekstrategie leverde 1792 unieke onderzoeken op, waarvan 22 aan de inclusiecriteria voldeden. De kwaliteit van de studies werd beoordeeld op een schaal van 0-10, waarbij 10 de hoogst mogelijke kwaliteit zou zijn. Dit resulteerde bij de 22 studies in een mediane waarde van 4; de scores liepen uiteen van 1 tot 7. De prevalentie, ernst en de last die xerostomie veroorzaakte steeg kort na transplantatie en bleef verhoogd gedurende het eerste jaar. Patiënten die een zware conditionering kregen ervaarden 18 punten meer xerostomie (op een 0-100 schaal, 95% BI: 9 – 27) 2 tot 5 maanden na HCT, in vergelijking met mensen die een lagere dosering van de conditionering hadden kregen. Na 1 tot 2 jaar was dit effect niet meer significant.

Ook **hoofdstuk 4** gaat over xerostomie. In dit hoofdstuk worden de resultaten beschreven van de Orastem studie, een prospectieve, longitudinale, internationale, observationele studie. Naast de Nederlandse patiëntengroep die in hoofdstuk 3 beschreven wordt, maken ook patiënten uit Zweden, Amerika en Canada deel uit van dit onderzoek. In totaal werden 163 allogene en 99 autologe HCT-ontvangers geïncludeerd. De patiënten beoordeelden de droogte van hun mond op een 0-10 schaal voor de transplantatie, meerdere malen kort na de transplantatie, en na

3, 6 en 12 maanden. Ook gestimuleerd speeksel werd meerdere malen verzameld. De prevalentie van xerostomie was 40% voor de transplantatie, 87% kort na de transplantatie en 64% na 3 maanden. Klachten na autologe transplantaties waren van voorbijgaande aard, terwijl de klachten in allogene patiënten verhoogd bleven na 12 maanden. Allogene HCT-ontvangers die een zware conditionering ondergingen, ervaarden meer xerostomie dan de mensen met een lichtere conditionering. Totale lichaamsbestraling als onderdeel van de conditionering en het ontstaan van een omgekeerde afstotingsreactie van het mondslijmvlies hadden geen invloed op het ontstaan van xerostomie.

Hyposalivatie kan ook leiden tot het ontstaan van cariës, de relatie die centraal staat in **hoofdstuk 5.** Het ontstaan van cariës werd beoordeeld bij 116 patiënten van de H-OME studie (dezelfde populatie als in hoofdstuk 2). Caries werd beoordeeld vóór de transplantatie, en na 3, 6, 12 en 18 maanden. Nieuwe of diepere laesies in het dentine (tandbeen) werden gezien in 32% van de patiënten gedurende 18 maanden. Bij de patiënten met cariësprogressie waren gemiddeld 2 vlakken aangedaan (maximum 12). Hyposalivatie van gestimuleerd speeksel na 3 maanden resulteerde in een 5 keer hoger risico (95% BI: 2 – 12) op het ontstaan van cariës. Dit was niet het geval bij hyposalivatie vóór HCT of hyposalivatie van ongestimuleerd speeksel.

Alle eerder genoemde uitkomsten (hyposalivatie, xerostomie en cariës) zoals aanwezig 5 jaar na HCT worden beschreven in **hoofdstuk 6**. Deze HOME2 studie voegde een extra meetmoment toe aan de H-OME studie. Alle deelnemers (met eigen tanden en/of kiezen) van de eerdere studie die nog in leven waren na 5 jaar, werden opnieuw uitgenodigd, wat resulteerde in de inclusie van 39 deelnemers. Nogmaals werd gestimuleerd en ongestimuleerd speeksel verzameld, werden deelnemers gevraagd om xerostomie te scoren op een 0-10 schaal en werden cariëslaesies beoordeeld. Ook werden tandheelkundige dossiers opgevraagd, van de periode 5 jaar vóór, en 5 jaar na de transplantatie, om het aantal restauraties, wortelkanaalbehandelingen en extracties ('trekken', in de volksmond) van tanden en kiezen te bepalen. Van de deelnemers ervaarde 73% enige mate van xerostomie, 33% had hyposalivatie van gestimuleerd speeksel en 28% van ongestimuleerd speeksel 5 jaar na de transplantatie. De deelnemers ondergingen gemiddeld 3 (spreiding 0 – 20) behandelingen aan tanden en kiezen in de 5 jaar na HCT, zeker 39% van deze behandelingen was het gevolg van cariës. Het aantal behandelingen na HCT was niet significant hoger (verschil 0,5; 95% BI: -1,2 – 2,2) in vergelijking met de 5 jaar voor HCT. Hyposalivatie van gestimuleerd speeksel na 12 maanden zou een bruikbare voorspeller kunnen zijn voor het aantal behandelingen van tanden en kiezen in 5 jaar.

Enkele extra analyses werden toegevoegd aan dit proefschrift, in een poging om de eerder gerapporteerde uitkomsten aan elkaar te relateren. De toegevoegde analyses zijn gerapporteerd in **hoofdstuk 7**. Hierin zijn de gegevens over xerostomie van de Orastem studie (hoofdstuk 4) toegevoegd aan de meta-analyses (hoofdstuk 3). Resultaten van de Orastem studie bleken de systematisch verkregen resultaten te ondersteunen. Daarnaast werd onderzocht in hoeverre speekselvloed en xerostomie gerelateerd zijn. We concluderen dat xerostomie zwak gerelateerd is aan de gestimuleerde speekselvloed, en matig aan ongestimuleerde speekselvloed. Hyposalivatie van ongestimuleerd speeksel gaat meestal samen met xerostomie, maar een normale ongestimuleerde speekselvloed blijkt geen relatie te hebben met de afwezigheid van xerostomie.

Samenvatting van de conclusies

Ongestimuleerde en gestimuleerde speekselvloed daalden kort na HCT, deze daling bleek tijdelijk te zijn en beginwaarden werden bereikt na 1 jaar. Toch bleef de gestimuleerde speekselvloed verlaagd in vergelijking met normale waarden. De ernst van xerostomie nam toe na HCT; hoewel de klachten gedurende het eerste jaar weer afnamen, bleven er xerostomieklachten bestaan in de meerderheid van de patiënten. Een hogere dosering van de conditionering vergrootte het risico op hyposalivatie en xerostomie. Hyposalivatie van gestimuleerd speeksel na 3 maanden vergrootte het risico op het ontstaan van cariëslaesies, en hyposalivatie van gestimuleerd speeksel na 12 maanden zou een bruikbare voorspeller kunnen zijn voor het aantal behandelingen aan tanden en kiezen in 5 jaar.

Appendices

Data management plan

Portfolio

Curriculum Vitae

List of publications and affiliations

Dankwoord

Data management plan

Ethics and privacy

Chapters 2 and 4 to 7 of this thesis are based on the results of medical-scientific research with human participants and were conducted in accordance with the ICH-GCP guidelines (Good Clinical Practice). For the international multicentre Orastem study, approval from the Ethical Review Boards at each study site was obtained (1) as described in chapter 4. Dutch participants of the Orastem study were also part of the H-OME study described in chapter 2 and 5. For these participants, treated at Amsterdam University Medical Center (UMC), location AMC, or Radboud university medical center (Radboudumc) Nijmegen, approval was obtained by the Medical Research Ethical Committee (NL52117.018.15). The Local Ethical Committee stated that the HOME2 study, reported in chapter 6, was not subjected to the law governing research involving human subjects and no approval from the Local Ethical Committee was necessary (registration number 2021-12963). Informed consent was obtained from all Orastem participants (including the H-OME participants), while a renewed informed consent was signed by all participants included in the additional 5 years follow-up (HOME2). The H-OME and HOME2 study were registered in the Dutch Trial Register (NL5645; NL9825). For the H-OME study, funding was received from the Dutch Cancer Society (ACTA 2014-7468).

Data collection and storage

For the H-OME and HOME 2 study (chapter 2, and 5 – 7), all paper data (including salivary flow rates, questionnaires, caries charts etc.) were bundled per patient in a folder. Folders from patients treated at the Radboudumc were stored in the department Archive (Dentistry building of Radboudumc, room M362.04.422A). Each folder was coded with a unique individual subject code to warrant the privacy of the participants. The list with codes of all participants is stored at the Radboudumc department server (H:\UMCFS012\THKdata$\ALG PCT\Orastem) and secured with a password. Medication data was extracted from (electronic) health records (EPIC). Dental records received from the HOME2 participants treated at the Radboudumc were stored in their individual records in Dentium (dental patient administration system, Netpoint). Dental records were pseudonymized, printed, and added to their individual folders. Pseudonymized data collected for the H-OME and HOME2 study was entered into Castor EDC. Data used in chapter 5 (first publication) were exported from Castor EDC to Excel, organized in Excel, and subsequently analysed in SPSS (version 25). Data used in later publications (chapter 2 and 6) were organized in SPSS and analysed in R (R Foundation for Statistical Computing,

Vienna, Austria). SPSS files and R syntaxes are stored at the H-drive ((\\UMCFS012\THKdata$\ALG PCT\Orastem).

Pseudonymized data collected for the Orastem study (chapter 4) were entered in an online program called MedView which was developed by The Institutes of Odontology, Goteborg University, and Department of Computing Science, Chalmers University of Technology (2). Study data was loaded into a secure database at the University of Gothenburg, Sweden, and all analyses were done by statisticians at the Wake Forest University School of Medicine, USA.

The systematic review, as reported in chapter 3 was registered in PROSPERO (CRD42020168364) and followed the guidelines provided in the Transparent Reporting of Systematic Reviews and Meta-analysis (PRISMA) statement (3). Authors of several included studies were contacted in an attempt to obtain additional information. As a result, four authors provided additional information, three authors provided additional data, and three authors provided individual patient data. As suggested by one of the authors, both parties signed an agreement on the sharing of pseudonymized personal data. All correspondence with the authors, received data and the signed agreement are stored at the H-drive.

Availability of data

All studies are published open access. The data will be archived for 15 years after termination of the study. Research data collected as part of the Orastem study could not be shared publicly because of ethical and legal restrictions on sharing our data set according to Swedish law. Study data contain sensitive patient information that can be connected to individual patients. It may be possible to identify and connect personal information from the data set, even though data is de-identified. Furthermore, data of the H-OME and HOME2 study could not be made publicly available because participants did not give permission to share individual data.

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PhD portfolio of M.S. Bulthuis

Department:	Dentistry
PhD period:	01/03/2019 – 29/02/2024
PhD Supervisor(s):	Prof. Dr. M.C.D.N.J.M. Huysmans, Prof. Dr. N.M.A Blijlevens
PhD Co-supervisor(s):	Dr. R.Z. Thomas, Dr. S.J.M. van Leeuwen

Training activities	Hours
Courses	
• RIHS - Introduction course for PhD candidates (2019)	15.00
• Biostatistics for PhD students at the department of dentistry (2020)	28.00
• RU - Scientific Writing for PhD candidates (2021)	84.00
• Radboudumc - Scientific integrity (2021)	20.00
• RU - Projectmanagement for PhD candidates (2021)	52.00
• RU - Presentation Skills (2023)	42.00
Seminars	
• Seminars and workshop Nathaniel Treister (2023)	8.00
• Dentistry research seminars (3x oral presentation) (2019-2024)	50.00
Conferences	
• RIHS - PhD retreat, Den Bosch (oral presentation) (2019)	24.00
• The summer webinar on saliva (2020)	2.00
• 68th ORCA congress, online (oral presentation) (2021)	20.00
• Dutch Dental Science days (oral presentation) (2022)	24.00
• Per-IADR Oral health research congress Marseille (oral presentation) (2022)	32.00
• Dutch Dental Science days (oral presentation) (2023)	16.00
• Saliva symposium, Egmond aan Zee (oral presentation) (2023)	24.00
• Dutch Dental Science days (oral presentation) (2024)	24.00
• MASSC Lille (oral presentation) (2024)	32.00

Other	
• Radboudumc - eBROK course (2020)	42.00
• InScience film festival, research: do you suffer from dry mouth? (2023)	28.00
• Reviewing a scientific article for Scientific Reports (2023)	4.00
• Herregistratie eBrok (2023)	5.00
• Journal club (2020, 2023-2024)	14.00
• Editing the Wikipedia page on saliva and xerostomia (2024)	8.00
• Reviewing a scientific article for Supportive Care in Cancer (2024)	4.00
• Reviewing a scientific article for BMC Oral Health (2024)	4.00
Teaching activities	
Lecturing	
• Werkgroepen 'pathologie in de mond', bachelor tandheelkunde (2023)	8.00
• Kennisclip on saliva (2023)	20.00
Supervision of internships / other	
• Supervision master thesis: Rick de Vos (2020-2021)	56.00
• Supervision master thesis: Rozemarijn Nass (2021-2022)	28.00
• Supervision master thesis: Jean-Luc Meijers (2023-2024)	12.00
Total	**730.00**

Curriculum Vitae

Foto: Joost Hoving/NTVT

Marjolein Saartje Bulthuis werd geboren op 18 november 1986 in Leiderdorp. In 2005 haalde ze haar gymnasiumdiploma aan het Pascal College te Zaandam, waarna ze begon met de studie tandheelkunde aan het Academisch Centrum Tandheelkunde Amsterdam (ACTA). De wetenschappelijke bachelor stage deed ze bij de afdeling orale biochemie, naar het effect van lolly's op tanderosie. Sindsdien was het haar droom om echt wetenschappelijk onderzoek te mogen doen.

In 2012 haalde ze haar tandartsdiploma, waarna ze enkele jaren als docent verbonden was aan ACTA en de Hogeschool Utrecht. In 2016 startte ze met de opleiding Evidence based Practice in Healthcare aan de Universiteit van Amsterdam; deze opleiding rondde ze in 2019 af. Sinds 2018 werkt ze met veel plezier bij de Jeugdtandverzorging in Zoetermeer. In 2019 kreeg ze de mogelijkheid om een promotieonderzoek te starten bij de afdeling tandheelkunde van het RadboudUMC. Hoewel Nijmegen niet om de hoek lag, greep ze deze kans graag aan. In 5 jaar schreef ze het proefschrift getiteld "The effect of haematopoietic cell transplantation (HCT) on hyposalivation, xerostomia and caries progression" dat hier voor u ligt.

Tijdens het promotietraject had ze plannen om naar Nijmegen te verhuizen, maar het vele thuiswerken tijdens de Covid-periode bracht hier verandering in. Haar toekomst lijkt toch in het westen van het land te liggen, waar ze dit najaar zal gaan samenwonen met haar vriend Nicky.

List of publications

Related to this thesis

Bulthuis MS[1], van Gennip LLA[1], Thomas RZ[1], Bronkhorst EM[1], Laheij AMGA[2,3], Raber-Durlacher JE[2,3], Rozema FR[2,3], Brennan MT[4,5], von Bültzingslöwen I[6], Blijlevens NMA[7], Huysmans MCDNJM[1], van Leeuwen SJM[1]. *The effect of conditioning regimen and prescribed medications on hyposalivation in haematopoietic cell transplantation (HCT) patients: an 18-month prospective longitudinal study* Clin Oral Investig. 2023 Dec;27(12):7369-7381. doi: 10.1007/s00784-023-05327-1.

Bulthuis MS[1], van Gennip LLA[1], Bronkhorst EM[1], Blijlevens NMA[1], Huysmans MCDNJM[1], van Leeuwen SJM[1], Thomas RZ[1]. *The effect of hematopoietic stem cell transplantation on patient-reported subjective oral dryness: a systematic review focusing on prevalence, severity and distress* Support Care Cancer. 2023 Jul 8;31(8):449. doi: 10.1007/s00520-023-07921-1.PMID: 37421511

Bulthuis MS[1], van Leeuwen SJM[1], Thomas RZ[1], van Gennip LLA[1], Whiteside HM[8], Isom S[8], Kline DM[8], Laheij AMGA[2,3], Raber-Durlacher JE[2,3], Hasséus B[9], Johansson JE[10], Hovan AJ[11], Brennan MT[4,5], von Bültzingslöwen I[6], Huysmans MCDNJM[1], Blijlevens NMA[7]. *Subjective Oral Dryness following Hematopoietic Cell Transplantation: A Report from the Orastem Study* Transplant Cell Ther. 2024 Apr;30(4):446.e1-446.e11. doi: 10.1016/j.jtct.2024.01.067.

Bulthuis MS[1], van Gennip LLA[1], Thomas RZ[1], Bronkhorst EM[1], Laheij AMGA[2,3], Raber-Durlacher JE[2,3], Rozema FR[2,3], Brennan MT[4,5], von Bültzingslöwen I[6], Blijlevens NMA[7], van Leeuwen SJM[1], Huysmans MCDNJM[1]. *Caries Progression after Haematopoietic Stem Cell Transplantation and the Role of Hyposalivation* Caries Res. 2022;56(3):187-196. doi: 10.1159/000525599

Bulthuis MS[1], van Gennip LLA[1], Thomas RZ[1], van Leeuwen SJM[1], Bronkhorst EM[1], Laheij AMGA[2,3], Raber-Durlacher JE[2,3], Blijlevens NMA[7], Huysmans MCDNJM[1]. *Salivary flow rate, subjective oral dryness and dental caries 5 years after haematopoietic cell transplantation* BMC Oral Health 2024 Sep 10;24(1):1058. doi: 10.1186/s12903-024-04804-7.

Other publications

van Gennip LLA, **Bulthuis MS**, Blijlevens NMA, Huysmans MCDNJM, van Leeuwen SJM, Thomas RZ. *Caries, periodontitis and tooth loss after haematopoietic stem cell transplantation: A systematic review* Oral Dis. 2023 Oct;29(7):2578-2591. doi: 10.1111/odi.14358.

Bulthuis MS, Jager DHJ, Brand HS. *Relationship among perceived stress, xerostomia, and salivary flow rate in patients visiting a saliva clinic* Clin Oral Investig. 2018 Dec;22(9):3121-3127. doi: 10.1007/s00784-018-2393-2.

Brand HS, Gambon DL, Paap A, **Bulthuis MS**, Veerman EC, Amerongen AV. *The erosive potential of lollipops* Int Dent J. 2009 Dec;59(6):358-62.PMID: 20162948

List of (co)author affiliations of all papers related to this thesis

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[11] Oral Oncology and Dentistry, British Columbia Cancer, Vancouver, British Columbia, Canada

Dankwoord

Vijf jaar geleden begon ik aan deze uitdaging: als PhD student mocht ik parttime onderzoek doen naar het effect van hematopoëtische stamceltransplantaties op de mondgezondheid. Ik kijk met heel veel plezier terug op deze jaren, die voor mij voorbij zijn gevlogen! Jaren lang ging mijn wekker vroeg op donderdagochtend, waarna ik om 6.39 uur in de trein stapte en mij laptop open klapte. En, hoewel ik geen ochtendmens ben, kon ik vaak niet wachten om aan de slag te gaan. In dit dankwoord mag ik jullie allemaal bedanken, die ervoor gezorgd hebben dat dit zulke mooie jaren zijn geweest. Ik zou het dolgraag nog eens over doen. Terugkijkend was het niet zwaar, maar gewoon leuk. Behalve de laatste maand, toen was het pittig en leuk.

Allereerst wil ik mijn promotieteam bedanken. Dank dat jullie het mogelijk hebben gemaakt dat ik promotieonderzoek mocht doen. Het was voor mij een lang gekoesterde wens: echt een cadeautje! Marie-Charlotte: zonder jou had ik nooit zo'n mooi boekje kunnen maken. Jouw betrokkenheid en heldere sturing waren onmisbaar in het proces. Ik blijf onder de indruk hoe jij, terwijl ik in een projectoverleg soms chaotisch van onderwerp kan wisselen, altijd precies weet waar ik het over heb, en hoe je mij het afgelopen jaar de ruimte hebt gegeven om eigenwijs te zijn. Nicole, jouw hematologische kennis was onmisbaar voor dit onderzoek. Als beginnend PhD student en eenvoudige tandarts vond ik onze overleggen eerst best spannend. In de loop der jaren kreeg ik steeds meer lol in onze overleggen en inmiddels kan ik de manier waarop je ons uitdaagt, en jouw humor, erg waarderen. Stephanie, jouw betrokkenheid en kennis van de Orastem studie waren erg belangrijk in mijn project. Het was hartstikke fijn dat ik je alles kon vragen, dat hulp altijd dichtbij was, en dat ik met jou als copromotor ook echt kon samenwerken. Je gaf me veel mooie herinneringen: samen (met de trein!) naar de IADR in Marseille, en samen naar het laatste concert van Nick en Simon. Renske, jouw gezelligheid, vrolijke lach en eerlijke feedback hebben extra kleur gegeven aan mijn boekje. Dan wil ik hier ook Ewald noemen: hoewel je geen deel uitmaakte van mijn promotieteam, heb je een onmisbare bijdrage geleverd aan alle hoofdstukken. Ik heb ontzettend veel van jou geleerd: jij hielp me de weg terug te vinden als ik verdwaald was in de statistiek, en redde me van verdrinking in de error's van R en het pierenbad. Dankjewel voor de gezelligheid, jouw humor, en het voorkomen dat de kaft van mijn boekje roze zou worden.

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wij met z'n tweeën tegelijkertijd aan hetzelfde project werkten. Je bent een grote steun geweest, en jouw epidemiologische kennis voegde echt wat toe. Ik vond het erg leuk dat we samen het H-OME2 onderzoek hebben opgezet en de patiënten hebben onderzocht, maar dat we ook veel saaie klusjes samen konden doen, zoals data invoeren en controleren. En als afsluiting samen naar Lille voor de MASCC, een hele mooie herinnering! Sylvia, ook jij was onmisbaar bij het opzetten en uitvoeren van de HOME2 studie. Jij bent altijd punctueel, hebt aan een half woord genoeg, en hebt ervoor gezorgd dat veel van onze patiënten 5 jaar na de transplantatie opnieuw wilden deelnemen aan ons onderzoek.

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Gwendolyn en Thushiga, dankjewel dat wij al zo lang vriendinnen zijn! Ik geniet er altijd van om weer lekker te theeleuten en bij te kletsen, en vind het mooi om te weten dat afstand hierbij niet belangrijk is. Onze wandelingen het afgelopen jaar, van Amsterdam richting Westerbork, waren perfect om mijn hoofd leeg te maken, alles te kunnen delen, een beetje sportief te zijn en lekker te eten!

Papa en mama, dank dat jullie mij altijd steunen. Dank dat jullie altijd voor mij klaar staan om alle mogelijke klusjes uit te voeren, en dat ik altijd welkom ben om gezellig te komen eten. Elianne, mijn lieve kleine zus, wat is het bijzonder dat jij soms ook mijn grote voorbeeld kunt zijn! Dat jij in het verre Nijmegen woonde om een PhD te doen, heeft gemaakt dat ik ook bij het Radboud durfde te solliciteren. Het was erg gezellig dat ik, tijdens mijn eerste jaren in Nijmegen, elke week bij jou kon logeren. Terugdenkend was de Covid-lockdown ook een hele gezellige tijd: jij kwam bij mij inwonen, en dagelijks werkten wij tegelijkertijd aan ons proefschrift. Zo konden we elkaar motiveren om door te werken, maar ook pauzes te nemen. En dan moet ik natuurlijk de Nijmeegse vierdaagse noemen: waarvoor we samen hebben getraind en die we samen hebben gelopen. Het was geweldig, het was afzien, en ik had het absoluut niet willen missen! Ik doe dit graag nog eens over, maar dan met wat minder complicaties… Natuurlijk wil ik ook mijn vriend Nicky bedanken. Dankjewel dat je er de afgelopen tijd altijd geduldig voor mij bent geweest. Ik vind het fijn dat je mij de tijd hebt gegund om het altijd druk te hebben. Ik kijk uit naar het nieuwe project was voor ons ligt, om samen een toekomst op te bouwen in de buurt van Leiden!

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Ik heb genoten van de jaren dat in Nijmegen promotieonderzoek mocht doen. Dankjulliewel!

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