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

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Abstract

Haematopoietic stem cell transplantation (HSCT) preceded by a conditioning regimen is an established treatment option for many haematological diseases. Decreased salivary flow rates after HSCT may increase caries risk. We aim to estimate the extent to which caries lesions develop or progress in adult HSCT recipients and assess its association with salivary flow rates. A multi-centre prospective observational study was conducted in which patients receiving HSCT 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 HSCT and 3, 6, 12, and 18 months post-HSCT. 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 HSCT 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

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not. We conclude that caries progression is a common oral complication in patients after HSCT, and stimulated hyposalivation shortly after treatment is a significant risk indicator for caries progression.

Introduction

Haematopoietic stem cell transplantation (HSCT) is an established treatment option for many malignant and non-malignant blood diseases [Copelan, 2006]. HSCT 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 HSCT) or from a donor (allogeneic HSCT), are infused. The increase in clinical indications for HSCT and improved transplantation procedures have led to an increase in the number of long-term survivors [Niederwieser et al., 2016]. 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 HSCT [Elad et al., 2015]. A high caries prevalence was reported in patients who had undergone allogeneic HSCT 1–14 years previously, in comparison with the general population [Dyer et al., 2018]. HSCT recipients may already be at higher caries risk before the treatment, as patients planned for HSCT were reported to have higher number of decayed, missing, and filled teeth (DMFT), compared with the general population [Mauramo et al., 2019] or with healthy controls [Uutela et al., 2019b, 2020].

Longitudinal studies that confirm the relation between HSCT 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 [Barrach et al., 2015; Boer et al., 2015] or 24 months [Uutela et al., 2019a]. Only one study reported an increase in DMFT score 6 months post-HSCT: 51 new lesions developed in teeth that were previously sound in 36 patients [Ertas et al., 2014]. 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 [Dawes et al., 2015]. Salivary flow rates have been reported to be reduced several days and months after HSCT [van Leeuwen et al., 2019]. 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-HSCT between patients that developed or did not develop new caries lesions could not be established [Heimdahl et al., 1985]. In another study, caries was more prevalent in patients with hyposalivation 6, 12, and 24 months post-treatment, but the difference was not significant [Uutela et al., 2019a].

Taken together, it remains unclear whether HSCT 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 HSCT 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 HSCT [Brennan et al., 2018]. We included adult patients (≥18 years old) scheduled to receive an autologous or allogeneic HSCT at Amsterdam University Medical Center (location Academic Medical Center [AMC]) or Radboud University Medical Center (Radboudumc) Nijmegen. Patients scheduled for allogeneic HSCT were eligible for inclusion independent of their diagnosis, while those scheduled for autologous HSCT were eligible if diagnosed with multiple myeloma. Patients were excluded if they were not able to understand the provided information, a second HSCT was planned in advance, the time before HSCT was too short to consider study participation, or if a transfer to another hospital was planned shortly after HSCT. 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 HSCT (baseline), and 3 and 12 months post-HSCT for all patients. Allogeneic HSCT recipients had additional follow-up examinations after 6 and 18 months.

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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 [Ismail et al., 2007; Ekstrand et al., 2018]. 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 [International Caries Detection and Assessment System [ICDAS] Coordinating Committee, 2005].

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 [Navazeh and Kumar, 2008]. 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 weighted 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 [Sreebny, 1988; Bassim et al., 2015; Proctor and Shaalan, 2021]. 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-HSCT 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 HSCT 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 HSCT 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 HSCT. Baseline characteristics of the participants are reported in Table 1.
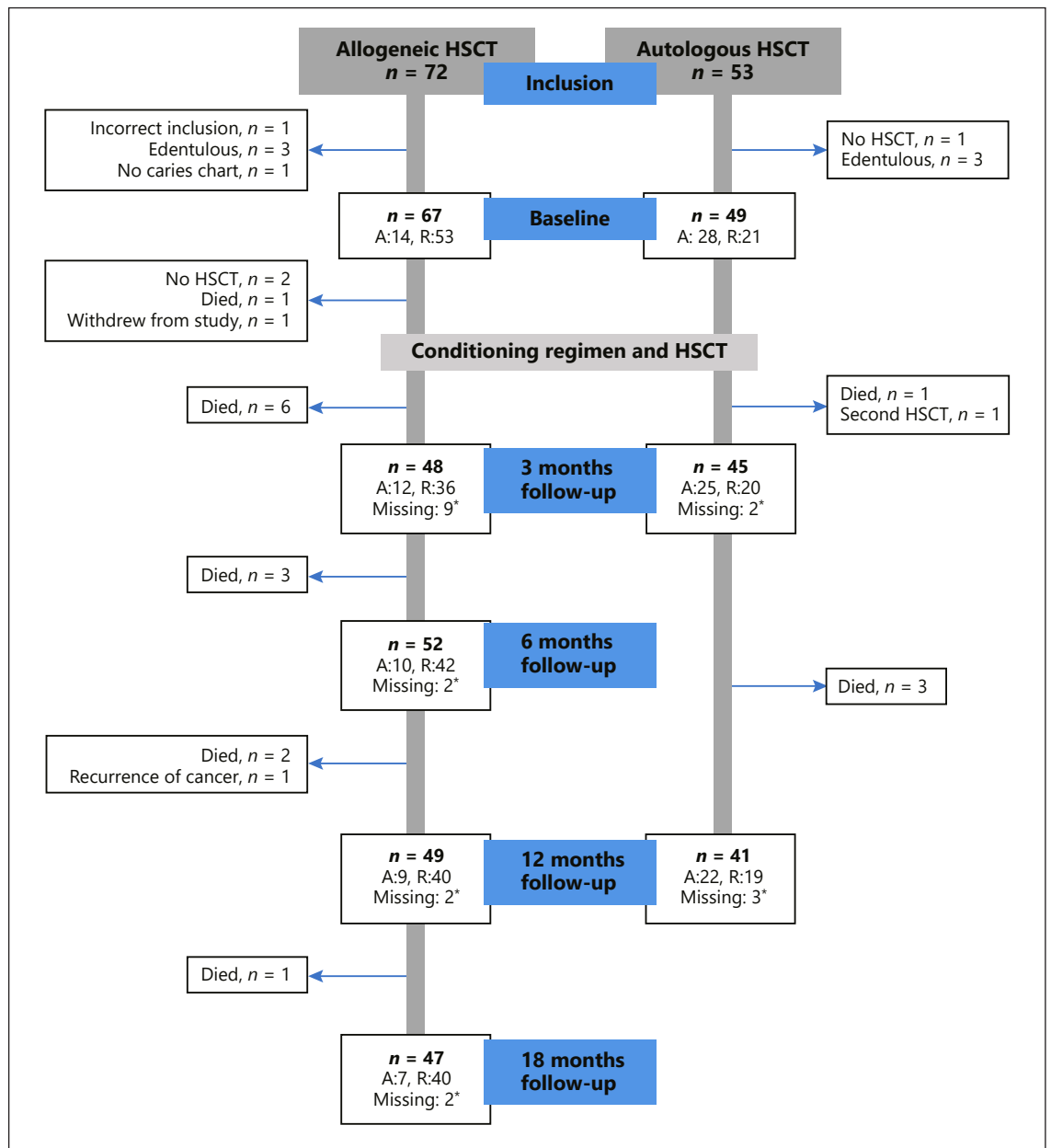
Fig. 1. Flow chart of the study. A distinction is made between patients treated at AMC (A) and Radboudumc (R). Reasons for exclusion and irreversible loss to follow-up are shown in the squares on the left and right sides of this diagram. Reasons for 21 incidental missed appointments of 18 patients, marked 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.

Fig. 2. Number of surfaces with dentine lesions at baseline (blue bar) and cumulative number of surfaces with new or deeper dentine lesions that developed in different time periods (orange/red 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).
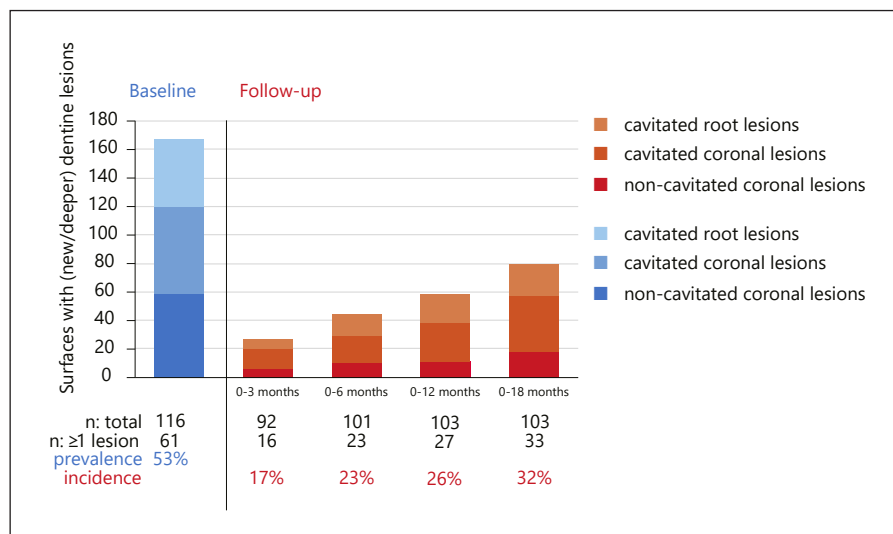
The cumulative lesion progression over different time periods is shown in Figure 2 as well. After 3 months, 92 patients were seen for follow-up, and 27 new or deeper dentine lesions were observed in 16 patients. Over 18 months, 32% of the patients developed 1 or more surfaces with caries progression. 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.

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-HSCT (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-HSCT 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:

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		
Myeloablative	16	49
Reduced intensity	21	
Nonmyeloablative	26	
Total body irradiation	40	
No total body irradiation	23	49
Not applicable*	4	

* No HSCT performed, or withdrawal before HSCT.

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.

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.

males, younger patients, and patients with dentine lesions at baseline were more likely to develop caries progression.

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 HSCT and to analyse the association with hyposalivation. In our population, the mean DMFT score at baseline
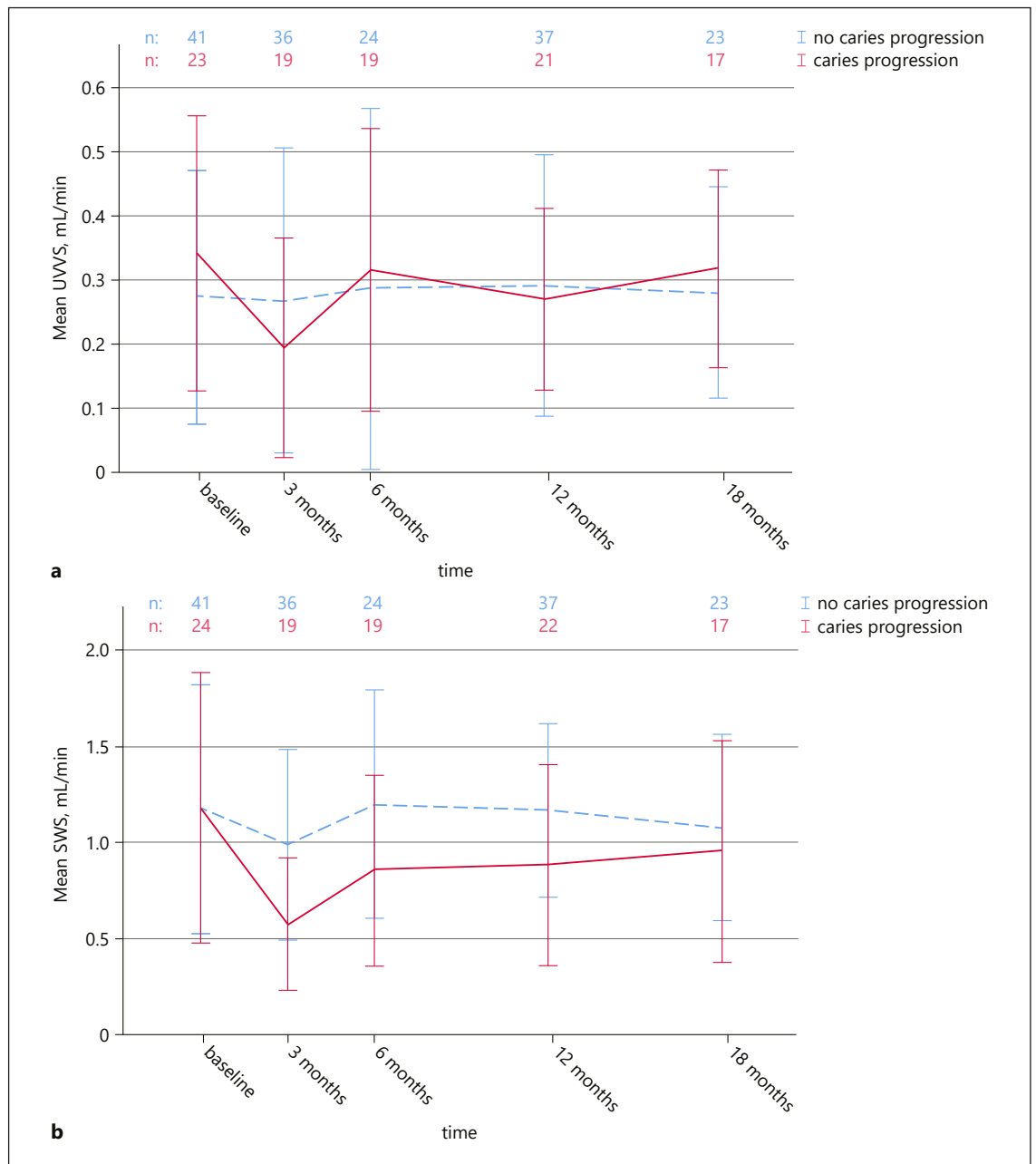
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Fig. 3. Mean ± 1 SD UWS (**a**) and SWS (**b**) flow rates in patients with (solid line) and without (dashed line) caries progression. Two UWS samples of 1 patient were missing due to chewing gum use before the collection and saliva sampling in one autologous patients took place after 6 instead of 3 months.

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 [Vermaire and Schuller, 2019]. Previous publications reported a broad range of DMFT scores before autologous and allogeneic HSCT, varying between 7.0 [Ertas et al., 2014] and 18.9 [Uutela et al., 2019a]. 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 HSCT recipients. It must

be taken into account that the baseline screening in the current study was conducted before the HSCT 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.

Several longitudinal studies have reported data on the oral status of HSCT recipients. A retrospective study published in 1985 [Heimdahl et al., 1985] reported that 37% of the patients had an extremely high caries incidence 1-year post-HSCT. 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 [Brown et al., 2002] and the introduction of less intensive conditioning regimens [Bacigalupo et al., 2009]. Of the four recent prospective studies that reported caries incidence, only one found a significant increase in DMFT score post-HSCT [Ertas et al., 2014]. Notwithstanding the close preventive supervision in the current study, caries progression was observed in 17% of the patients 3 months post-HSCT, 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 [Guedes et al., 2014; Drancourt et al., 2019].

In the present population, we determined that hyposalivation of SWS 3 months post-HSCT 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 [Powell, 1998; Splieth et al., 2003] and are associated with hyposalivation as well

[Heintze et al., 1983]. 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 [Pitts et al., 2017], it is assumed that other factors than salivary flow rate will affect caries progression. Changes in salivary composition post-HSCT are reported [van Leeuwen et al., 2019], 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, HSCT recipients might experience difficulties in completing oral hygiene practices during the transplant process due to fatigue and medical complications [Wilson-Dewhurst et al., 2020]. Furthermore, guidelines on nutrition in cancer patients are mainly based on preventing malnutrition [Muscaritoli et al., 2021] 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 [Dawes et al., 2015]. The drop in the 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 [Dawes, 1972], lack of standardization 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-HSCT [Uutela et al., 2019a].

We expect that the drop in salivary flow rates post-HSCT will be a direct result of the toxicity of the conditioning regimen [Boer et al., 2015; van Leeuwen et al., 2019], 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 [Copelan, 2006]. The development of extensive dental caries in patients with GvHD is reported in the literature [Castellarin et al., 2012]. However, in the current population, the number of patients that

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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-HSCT. An even higher prevalence of 30% hyposalivation was reported in a previous publication [Uutela et al., 2019a]. 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 HSCT. Hyposalivation of SWS after treatment is a significant risk indicator for caries progression; its incidence in patients with hyposalivation 3 months after HSCT 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 HSCT 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.

Statement of Ethics

Ethical approval was obtained (NL52117.018.15) and the study was conducted according to GCP guidelines and the World Medical Association Declaration of Helsinki. Before participating, written informed consent was obtained from all patients.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Author Contributions

Judith E. Raber-Durlacher, Michael T. Brennan, Inger von Bültzingslöwen, Nicole M.A. Blijlevens, and Marie-Charlotte D.N.J.M. Huysmans contributed to the conception and design of the Orastem study, while Judith E. Raber-Durlacher, Nicole M.A. Blijlevens, and Frederik R. Rozema concepted the Dutch sub-study (H-OME). Marjolein S. Bulthuis, Lucky L.A. van Gennip, Renske Z. Thomas, Stephanie J.M. van Leeuwen, and Marie-Charlotte D.N.J.M. Huysmans designed the current ancillary study. Alexa M.G.A. Laheij, Judith E. Raber-Durlacher, and Marie-Charlotte D.N.J.M. Huysmans collected the clinical data. Marjolein S. Bulthuis and Ewald M. Bronkhorst performed the statistical analysis. Marjolein S. Bulthuis drafted the paper and the manuscript was critically reviewed by all authors.

Data Availability Statement

The data that support the findings of this study are available under request from the first author.

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