Xerostomia and chronic oral complications among patients treated with haematopoietic stem cell transplantation

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IN BRIEF

- Patients treated with haematopoietic stem cell transplantation have a high level of xerostomia and a greater severity of several other chronic oral complications.
- The level of xerostomia is associated with the severity of the oral complaints.
- Dental professionals should alleviate these problems as much as possible and prevent secondary complications.

RESEARCH

Objective To assess the severity of xerostomia (subjective dry mouth) in haematopoietic stem cell transplantation (HSCT) patients and to investigate the association of xerostomia with other chronic oral complications. **Design** Cross-sectional study. **Study participants and methods** Participants were 48 patients with a history of HSCT recruited among members of the Dutch Stem Cell Transplantation Contact Group, and a comparison group of 41 age- and sex-matched individuals. Data were collected using the Xerostomia Inventory (XI score) and a seven-item oral health questionnaire. **Results** HSCT patients had a higher XI score than the comparison group, and a greater severity of several oral complaints: painful oral mucosa, altered taste, limited opening of the mouth and problems with tooth brushing. HSCT patients did not report greater pain during cold stimulation of teeth, chipped and cracked teeth or bleeding gums. In HSCT patients, the XI score correlated significantly with the severity of oral mucosal pain, altered taste, limited opening of the mouth, painful teeth following cold stimuli, chipped or cracked teeth, problems with tooth brushing and bleeding gums. In the comparison group, no correlations were observed between XI score and these oral problems. **Conclusion** HSCT patients have more severe xerostomia, which is associated with other oral complaints. Dental professionals should monitor these patients post-transplant for oral complications. Symptoms of dry mouth should be relieved and secondary complications should be prevented.

INTRODUCTION

Nowadays, haematopoietic stem cell transplantation (HSCT) is a widely used potential curative treatment for a number of malignant and non-malignant diseases. HSCT may be autologous, in which patients are transplanted with their own stem cells following conditioning with high-dose chemotherapy with or without total body irradiation (TBI), or allogeneic, in which stem cells are retrieved from a suitable family member or an unrelated donor. Nowadays, peripheral blood is the most frequent source of stem cells, after these have been mobilised from the bone marrow with growth factors.[1]

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An advantage of allogeneic transplantation is that an immunologic response of immunocompetent donor cells against tumour cells is mounted (graft-*versus*-leukemia effect). However, allogeneic transplantation may also be accompanied by graft-*versus*-host disease (GVHD), in which immunologic responses are directed against cells and tissues of the recipient. Until recently, acute GVHD was defined as occuring before 100 days post-transplant, whereas chronic GVHD was defined as occurring after 100 days. This definition appeared to be too stringent, and it is currently preferred to discriminate between acute and chronic GVHD on clinical features rather than on the time of occurrence.[1,2]

Over the last decade, less toxic conditioning regimens have been developed, which made HSCT available to a larger number of patients, including those who were previously considered too old and those with co-morbidities.[3]

Oral complications may develop during the different phases of HSCT.[4] Most transplant centres conduct an oral and dental evaluation before transplant conditioning[5] primarily aimed at preventing infection originating from the oral cavity.[6] The importance of preventing and managing oral complications, such as mucositis, in the immediate post-transplant phase is also well appreciated.[7–9] In contrast, it seems to be less well recognised by physicians and dentists that patients who have undergone HSCT may develop long-term oral and dental complications. These complications have a considerable impact on the quality of life[10] and necessitate a multidisciplinary approach aimed at prevention and management. For example, a dry mouth may affect taste, speaking and swallowing, may cause sleep deprivation, and increase the risk to dental caries[11] and oral mucosal infection. In addition, chronic oral GVHD may compromise salivary gland function[12–14] and may be associated with painful oral mucosal lesions or sclerotic alterations resulting in limited mouth opening.[15] Tooth sensitivity may be a result of GVHD, but may also be associated with its treatment with immunosuppressants. All these complications may result in reduced food intake and hamper oral hygiene measures. Furthermore, there

is recent evidence indicating that chronic oral GVHD significantly increases the risk of developing a second malignancy in the oral cavity.[16]

Little information is available on the prevalence and the severity of late oral complications of HSCT. Therefore, the present study among patients who were treated with autologous and allogeneic HSCT and a comparison group is aimed as a first step to obtain information about the severity of xerostomia and other chronic oral complications that may develop after HSCT.

PATIENTS AND METHODS

The study was performed according to the guidelines of the Medical Ethics Committee of the Free University Medical Center, Amsterdam, The Netherlands. All participants were recruited on a voluntary basis at a national meeting of the Dutch Stem Cell Transplantation (SCT) Contact Group, which was attended by approximately 115 individuals (patients and their partners). All study participants received written and oral information.

Forty-eight patients with a history of HSCT were recruited (19 men and 29 women). The mean age of the HSCT patients was 53.0 ± 9.4 years (range 21 to 67 years). Eleven (23%) patients received an autologous HSCT, 33 patients (69%) an allogeneic transplantation, whereas 4 (8%) received autologous HSCT followed by allogeneic HSCT. The mean time since HSCT was 5.5 ± 4.9 years. The diseases for which HSCT was performed are presented in Table 1. At the same meeting, a comparison group was recruited among the partners of HSCT patients (14 men and 27 women). The mean age of the comparison group was 51.5 ± 9.1 years (range 30 to 73 years). The comparison group filled out the questionnaire at the same time as the HSCT patients, but independently from each other.

All study participants completed the Dutch translation of the Xerostomia Inventory.[17–19] This well validated inventory consists of 11 items (see Table 2). Each item is assessed with a five-point Likert scale (never = 1 to very often = 5), resulting in a total XI score ranging between 11 (no xerostomia) and 55 (severe xerostomia). In addition, all study participants completed an oral health questionnaire[20] that explored the severity of seven oral complaints using identical five-point Likert scales.

The data are presented as mean ± standard deviation (SD) and were analysed with SPSS for Windows (version 12.0.1) using the Mann Whitney U test. Potential associations between level of xerostomia and severity of oral complaints were explored

Table 1 Overview of underlying systemic diseases of patients treated with HSCT (n = 48)

Underlying disease	Number of patients
Acute myeloid leukemia	2 (4%)
Acute lymphoblastic leukemia	8 (17%)
Chronic myeloid leukemia	7 (15%)
Chronic lymphoblastic leukemia	2 (4%)
Multiple myeloma	8 (17%)
Hodgkin's lymphoma	1 (2%)
Non-Hodgkin's lymphoma	5 (10%)
Aplastic anaemia	3 (6%)
Other diseases	6 (13%)
Unknown	6 (13%)

Table 2 Items and total score of the Xerostomia Inventory in HSCT patients and in the comparison group (mean score ± SD)

Item	HSCT (n = 48)	Comparison group (n = 41)
I sip liquid to facilitate swallowing	1.79 ± 1.34	1.15 ± 0.42, **p = 0.016**
My mouth feels dry when eating a meal	2.25 ± 1.31	1.27 ± 0.55, **p <0.0005**
I get up at night to drink	2.63 ± 1.58	1.93 ± 1.01, p = 0.062
My mouth feels dry	3.00 ± 1.50	1.73 ± 1.07, **p <0.0005**
I have difficulty in eating dry foods	2.79 ± 1.40	1.37 ± 0.58, **p <0.0005**
I suck sweets or cough lollies to relieve dry mouth	2.42 ± 1.53	1.44 ± 0.67, **p = 0.002**
I have difficulties swallowing certain foods	2.27 ± 1.45	1.22 ± 0.47, **p <0.0005**
The skin of my face feels dry	3.38 ± 1.47	1.71 ± 0.96, **p <0.0005**
My eyes feel dry	3.13 ± 1.61	1.63 ± 0.94, **p <0.0005**
My lips feel dry	3.08 ± 1.51	1.93 ± 1.03, **p <0.0005**
The inside of my nose feels dry	2.46 ± 1.43	1.41 ± 0.83, **p <0.0005**
Total XI score	29.2 ± 12.3	16.8 ± 5.4, **p <0.0005**

Table 3 Severity of oral complaints of patients with HSCT and of the comparison group (mean score ± SD)

Oral complaint	HSCT (n = 48)	Comparison group (n = 41)
Painful oral mucosa	1.98 ± 1.19	1.33 ± 0.73, **p = 0.005**
Altered taste	2.54 ± 1.41	1.29 ± 0.56, **p <0.0005**
Limited opening of the mouth	1.89 ± 1.30	1.02 ± 0.16, **p <0.0005**
Painful teeth during cold stimuli	2.80 ± 1.27	2.46 ± 0.82, p = 0.176
Chipped or cracked teeth	2.09 ± 1.48	1.53 ± 0.72, p = 0.270
Problems with tooth brushing	1.80 ± 1.13	1.15 ± 0.43, **p = 0.002**
Bleeding gums	2.14 ± 1.15	1.94 ± 0.79, p = 0.683

with Spearman's rank order correlation coefficients; p values <0.05 were considered statistically significant.

RESULTS

The HSCT patients and the comparison group did not differ significantly with regard to gender and age. Study participants with a history of HSCT had a much higher level of xerostomia than the comparison group (29.2 *versus* 16.8, Table 2). Significant differences were observed for each item of the Xerostomia Inventory, with the exception of 'I get up at night to drink' for which a near-significant difference was observed (p = 0.062).

HSCT patients also reported greater severity of several oral problems (for example, painful oral mucosa, altered taste, limited opening of mouth and problems with tooth brushing) (Table 3). HSCT patients did not differ from the comparison group with regard to the severity of tooth sensitivity during cold stimuli, chipped and cracked teeth or self-reported gum bleeding. When the patients were compared according to the indication for HSCT (Table 1), no significant differences in level of xerostomia and severity of oral problems were observed (data not shown).

In HSCT patients, the XI score correlated significantly with the severity of painful oral mucosa, altered taste, limited opening of the mouth, painful teeth during cold stimuli, chipped or cracked teeth, problems with tooth brushing and bleeding gums (Table 4). In the comparison group, however, no significant correlations were observed between XI score and the severity of oral problems.

The severity of xerostomia and oral complaints in patients with HSCT was not significantly associated with TBI given before HSCT or the type of stem cell transplantation (Table 5). However, those patients that received TBI showed a near significant difference for more severe altered taste than HSCT recipients in which TBI has not been part of the conditioning regimen (p = 0.051).

The majority of the patients (86%) that received an allogeneic transplantation reported having active GVHD or a history of GVHD affecting the oral cavity as well as other organs. When the HSCT patients were compared according to GVHD, the patients with a history of GVHD had significantly more problems opening their mouths than allogeneic patients without GVHD and patients receiving an autologous HSCT (Table 6). A history of GVHD was also associated with a near significant increase in oral mucosal pain (p = 0.078).

Table 4 Non-parametric correlations between severity of xerostomia and oral complaints in HSCT patients (Spearman's rank order coefficient, n = 42–48)

	Xerostomia
Painful oral mucosa	0.689, **p <0.0005**
Altered taste	0.582, **p <0.0005**
Limited mouth opening	0.456, **p = 0.001**
Painful teeth following cold stimuli	0.444, **p = 0.003**
Chipped or cracked teeth	0.407, **p = 0.006**
Problems with tooth brushing	0.463, **p = 0.002**
Bleeding gums	0.349, **p = 0.020**

Table 5 Severity of xerostomia and oral complaints in patients treated with HSCT, classified according to whether or not they received total body irradiation (TBI) before HSCT (mean score ± SD)

	TBI (n = 33)	No TBI (n = 13)
Xerostomia (XI score)	31.2 ± 12.9	25.0 ± 10.4, p = 0.172
Painful oral mucosa	2.12 ± 1.27	1.77 ± 1.01, p = 0.462
Altered taste	2.88 ± 1.47	1.92 ± 0.95, p = 0.051
Limited opening of the mouth	2.10 ± 1.42	1.54 ± 0.97, p = 0.257
Painful teeth following cold stimuli	2.73 ± 1.26	3.08 ± 1.31, p = 0.483
Chipped or cracked teeth	2.17 ± 1.55	1.53 ± 0.72, p = 0.967
Problems with tooth brushing	1.83 ± 1.15	1.67 ± 1.15, p = 0.650
Bleeding gums	2.13 ± 1.17	2.17 ± 1.79, p = 0.957

Table 6 Severity of xerostomia and oral complaints in patients treated with HSCT, classified according to whether or not they suffered from graft-versus-host disease (GVHD) after stem cell transplantation (mean score ± SD)

	History of GVHD (n = 32)	No history of GVHD (n = 15)
Xerostomia (XI score)	31.2 ± 12.8	25.1 ± 11.0, p = 0.112
Painful oral mucosa	2.22 ± 1.26	1.53 ± 0.92, p = 0.078
Altered taste	2.81 ± 1.47	2.07 ± 1.16, p = 0.110
Limited opening of the mouth	2.23 ± 1.45	1.27 ± 0.59, **p = 0.025**
Painful teeth following cold stimuli	2.90 ± 1.26	2.57 ± 1.34, p = 0.455
Chipped or cracked teeth	2.17 ± 1.47	2.00 ± 1.57, p = 0.587
Problems with tooth brushing	1.83 ± 1.23	1.64 ± 0.93, p = 0.918
Bleeding gums	2.10 ± 1.11	2.14 ± 1.29, p = 0.957

DISCUSSION

The present study indicates that HSCT patients have significantly higher levels of xerostomia as well as several other oral complaints including painful oral mucosal surfaces, altered taste, limited opening of the mouth and difficulties with tooth brushing, than the comparison group. In addition, the sensation of dry mouth correlated significantly with other self-reported oral problems.

It should be emphasised that this cross-sectional study has several limitations. Relatively small numbers of study participants were included and indications for

HSCT, cancer therapies and conditioning before transplantation, transplant type, as well as the time post-transplant varied considerably. Furthermore, we did not have information about whether the underlying disease was in complete remission. It is thus possible that oral complications were not only induced by the cancer treatment, but the underlying disease may also have contributed. For example, oral manifestations of multiple myeloma have been reported which included toothache, mucosal ulceration and gingival bleeding.[21] However, in our study the oral problems of the patients with multiple myeloma were not different from the other HSCT recipients.

HSCT conditioning regimens as well as chronic GVHD may affect salivary functioning. Recent research has suggested that chronic dry mouth is not a trivial condition. It does not only affect oral health, but its impact extends beyond the oral cavity, affecting the quality of day-to-day life.[10] In a Swedish study in which autologous as well as allogeneic HSCT recipients were followed longitudinally, xerostomia was rated as one of the most distressing symptoms at discharge as well as one year post-transplant.[22] The present study also indicated that dry mouth represents a significant late complication in these patients, and in our study dry mouth is also reported to be a frequent complaint in patients without GVHD.

Xerostomia has been found to be indicative for hyposalivation (objective salivary gland dysfunction) in long-term paediatric HSCT patients.[23] Insufficient salivary production is associated with numerous compromised oral defence mechanisms.[24] It contributes to a greater risk for secondary oral complications (for example dental caries, periodontal and mucosal infection), which may further negatively affect quality of life. In addition, HSCT patients in our study reported difficulties with performing oral hygiene, which may further contribute to the risk to develop oral sequelae.

Sclerotic changes resulting in a limited opening of the mouth may develop in patients with chronic GVDH following allogeneic transplantation[25,26] (Table 5). It has been suggested that inflammation and scarring of the masticatory muscles and the oral mucosa may restrict the oral opening to such an extent that it limits the patient's ability to perform oral hygiene procedures adequately.[4,14] However, in our study patients with GVHD did not report more problems with tooth brushing than HSCT patients without GVHD (Table 6), although there was a near-significant difference towards more severe oral mucosal pain in patients with GVHD after an allogeneic transplantation (Table 6). This observation corroborates studies reporting that GVHD may be associated with higher mucosal sensitivity and painful oral lesions.[4,15]

CONCLUSION

The present study indicates that HSCT patients have higher levels of xerostomia and more severe oral complications than a comparison group. It is recommended that dental professionals become more involved in providing supportive care to these patients and cooperate with the medical and nursing caregivers. HSCT patients should be monitored post-transplant for oral complications and actively asked if they experience any oral problems. In patients with salivary dysfunction, symptoms should be relieved and secondary complications should be prevented. Further longitudinal studies stratified for different types of HSCT, aimed at assessing the prevalence and the severity of subjective as well as objective long-term oral complications in HSCT patients, are warranted.

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