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ORIGINAL ARTICLE

Determinants of stimulated salivary flow among haematopoietic stem cell transplantation recipients

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Abstract
Objectives The aetiology of hyposalivation in haematopoietic stem cell transplantation (HSCT) recipients is not fully understood. This study examined the effects of treatment-related aetiological factors, particularly medications, on stimulated salivary flow in HSCT recipients.
Subjects and methods Adult HSCT recipients (N = 118, 66 males, 27 autologous and 91 allogeneic transplants) were examined. Stimulated whole salivary flow rates (SWSFR) were measured before HSCT and at 6 and 12 months post-HSCT. Linear regression models were used to analyse the associations of medications and transplant-related factors with salivary flow rates, which were compared to salivary flow rates of generally healthy controls (N = 247).
Results The SWSFR of recipients were lower pre-HSCT (mean ± standard deviation, 0.88 ± 0.56 ml/min; $P < 0.001$), 6 months post-HSCT (0.84 ± 0.61; $P < 0.001$) and 12 months post-HSCT (1.08 ± 0.67; $P = 0.005$) than the SWSFR of controls (1.31 ± 0.65). In addition, hyposalivation (<0.7 ml/min) was more frequent among HSCT recipients pre-HSCT ($P < 0.001$), 6 months post-HSCT ($P < 0.001$) and 12 months post-HSCT ($P = 0.01$) than among controls. The SWSFR was observed to improve over time being significantly higher 12 months post-HSCT compared to pre-HSCT ($P < 0.001$). The observed decrease of salivary flow could not be explained by the examined transplant-related factors and medications.
Conclusions Decreased stimulated salivary flow rates could not be explained by the examined factors alone; these findings indicate that hyposalivation in HSCT recipients exhibits a multifactorial aetiology.
Clinical relevance All HSCT recipients should be considered to be at high risk of hyposalivation and consequent oral diseases, and they should be treated accordingly.

Keywords Saliva · Hyposalivation · Medications · Drugs · Stem cell transplantation · Haematology

Introduction

During the preceding five decades, haematopoietic stem cell transplantation (HSCT) has evolved to become the standard of care for a broad range of disorders and malignancies of the haematopoietic system [1]. This phenomenon can primarily be attributed to the rapid development and improved success rates of HSCT therapy [2]. Although the number of HSCT survivors is increasing, this therapy remains associated with serious and debilitating long-term side effects, such as graft-versus-host disease (GvHD), organ dysfunction and secondary malignancies [3, 4].

There is increasing evidence that HSCT, which includes high-dose chemotherapy either with or without total body irradiation (TBI), can cause acute and long-term side effects in the oral cavity that affect patients' general well-being [5–10].

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Recent studies have particularly focussed on hyposalivation (i.e., reduced salivary flow), which is commonly exhibited by allogeneic HSCT recipients immediately and even decades after HSCT [5–10]. We previously found that the percentages of allogeneic HSCT recipients, who suffer from hyposalivation, as assessed by stimulated whole salivary secretion rates, were 56 % at 6 months post-HSCT, 31 % at 1 year post-HSCT and 26 % at 2 years post-HSCT [8]. Another study reported comparable salivary gland hypofunction and xerostomia findings at 6 to 24 months post-HSCT [9]. Furthermore, we have found that salivary flow rates, tear flow rates and subjective sicca symptoms (e.g. xerostomia, xerophthalmia and dry skin) were significantly affected in extremely long-term survivors of allogeneic HSCT (at a mean duration of 17.5 years after allogeneic HSCT) [10]. Sicca symptoms are also associated with long-lasting impairments in quality of life (QoL) [10].

Hyposalivation post-HSCT may be caused by disease; extremely potent antineoplastic therapies, including HSCT conditioning regimens and comorbidities and their therapies. Standard chemotherapy schemas and conditioning with or without TBI can affect salivary glands [11, 12]. The management of comorbidity in patients may require a wide repertoire of medications, including opioids, immunosuppressive substances, and antimicrobials; certain of these medications may contribute to hyposalivation [13, 14]. Furthermore, allogeneic HSCT may be accompanied by GvHD, which can directly compromise salivary gland function [5]. Hyposalivation is of paramount interest because a dry mouth is subjectively distressing and because saliva has several protective functions in the mouth; moreover, hyposalivation promotes caries, periodontal diseases and oral yeast infections [15, 16]. Therefore, control of hyposalivation has significant impacts with respect to preventing oral and dental morbidities and promoting the general well-being of HSCT recipients.

We have previously demonstrated that female sex, TBI and severe chronic GvHD (cGvHD) are associated with an increased prevalence of hyposalivation among allogeneic HSCT recipients [8, 10]. The current study examined the associations of transplant-related factors and medications with stimulated whole salivary flow rates (SWSFR) in autologous and allogeneic HSCT recipients. The hypothesis was that medications can partially explain the reduced SWSFR in these patients.

Subjects and methods

This prospective longitudinal study was approved by the Ethics Committee of Basel (Ethikkommission beider Basel 311/10), Switzerland and was performed in accordance with the Declaration of Helsinki. A total of 118 HSCT recipients with complete medical and dental records who were treated in the Department of Haematology of the University Hospital Basel, Switzerland, for haematological malignancies between 2002 and 2009 were included (Table 1). Patients who received follow-up at other hospitals in Switzerland were excluded from this study.

One experienced dentist (TW) performed dental examinations of patients; the first examination occurred immediately prior to HSCT. At this time, most patients had already been treated for their underlying disease using previously described standard chemotherapy schemas and had received conditioning chemotherapy either with or without TBI [8]. Myeloablative conditioning regimens administered immediately before transplantation included (1) cyclophosphamide + TBI (12 Gy), with or without VP16 (etoposide), and (2) cyclophosphamide + busulfan or BEAM (BCNU (carmustine), etoposide, Ara-C (cytarabine) and melphalan). Non-myeloablative conditioning included cyclophosphamide alone and reduced intensity regimens of fludarabine + TBI (2 Gy), with or without thymoglobulin.

After HSCT, all patients were included in a prospective oral disease prevention programme, and follow-up examinations were performed 6 and 12 months after transplantation in 102 and 95 patients, respectively. The medications prescribed during the examined period were obtained from medical records and grouped according to the pharmacological action [17]. Any medication prescribed during an examined 6-month interval was considered to be used during the interval in question.

A population of healthy volunteers with no self-reported intake of medications served as control subjects (n = 247). These control subjects were recruited from the Swiss bone marrow donor register, and informed consent was obtained from each participant prior to the acquisition of salivary flow measurements, which occurred from 2008 to 2010.

SWSFR were measured in HSCT recipients at each appointment, with appointments occurring pre-HSCT (after conditioning chemotherapy with or without TBI) and 6 and 12 months post-HSCT. SWSFR of control group subjects were measured once. SWSFR were determined as follows. First, a commercially available, individually packed, neutral piece of paraffin wax (0.9 g/wax; Orion Diagnostica, Espoo, Finland) was chewed for 1 min while swallowing saliva. A new piece of wax was then chewed for 5 min; during this time, all generated saliva was collected in a graduated (ml) test tube (Sarstedt, Nümbrecht, Germany) [14]. SWSFR (ml/min) was determined by dividing the volume of the saliva sample by the collection time (in min). An SWSFR of ≤0.7 ml/min was regarded as hyposalivation [14]. Given subjects' stress and anxiety levels, no limitations on eating, drinking, smoking or oral hygiene habits were imposed prior to salivary flow measurements. SWSFR measurements were conducted between 8:00 AM and 4:00 PM.

The mean SWSFR of HSCT recipients were compared to the mean SWSFR of healthy controls. The effects of time and potential influencing factors on the SWSFR of HSCT

Table 1 Demographics, diagnoses and transplantation-related factors of HSCT recipients

	Total (n)	Female (n)	Age (mean)	Autologous (n)	TBI* (n)	Myeloablative conditioning (%)	Identical sibling donor (%)	Matched Unrel. Donor (%)	**cGvHD (n)**
All patients	118	52	49	27	59	56	51	13	60
Acute leukaemia	39	16	46	4	20	74	75	20	22
Acute myeloid leukaemia	23	11	52	3	7	74	70	13	12
Acute lymphoblastic leukaemia	16	5	39	1	13	75	56	31	10
Chronic leukaemia	25	12	53	4	14	52	60	12	14
Chronic myeloid leukaemia	16	6	49	1	10	69	63	19	9
Chronic lymphoblastic leukaemia	9	6	60	3	4	22	56	0	5
Lymphoma	16	5	46	7	7	44	44	6	9
Non-Hodgkin's lymphoma	10	2	52	3	6	40	60	10	6
Hodgkin's lymphoma	6	3	35	4	1	50	17	0	3
Multiple myeloma	42	15	60	10	4	29	29	0	4
Myelodysplastic/Proliferative	15	9	51	2	14	67	47	13	11
Myelodysplastic syndrome	8	5	57	1	6	50	50	25	3
Others	7	4	44	2	7	83	50	0	7
Bone marrow failure	4	4	36	0	1	75	50	25	3

* Total body irradiation

recipients were analysed using a linear-mixed effects model. SWSFR were the dependent variable. The independent variables were age, sex, time, history of cGvHD, graft type (autologous or allogeneic), stem cell source (bone marrow or peripheral blood), regimen intensity (myeloablative versus reduced), HLA matching (related, unrelated, fully matched or mismatched), diagnosis, medication group and number of drugs. Medication groups with <10 subjects (i.e. groups for medications that were rarely prescribed) were excluded from the analyses of this study. $P < 0.05$ was considered to be statistically significant. A professional biostatistician performed statistical analyses using R software, version 2.15.1.

Results

HSCT recipients ($n = 118$—66 males, 52 females; mean age—49.3 years; age range—22–74 years) and 247 controls (106 males, 141 females; mean age—43 years, age range—22–74 years) were included in the study. Among the HSCT recipients, 27 subjects received autologous HSCT and 91 subjects received allogeneic HSCT. In total, 50 % ($n = 59$) of HSCT recipients received TBI and 56 % ($n = 66$) of HSCT recipients received a myeloablative conditioning regimen (Table 1).

The SWSFR of HSCT recipients were significantly lower pre-HSCT ($n = 118$; mean SWSFR ± standard deviation (SD) (ml/min), 0.88 ± 0.56; $P < 0.001$), 6 months post-HSCT ($n = 102$; SWSFR, 0.84 ± 0.61; $P < 0.001$) and 12 months post-HSCT ($n = 95$; SWSFR, 1.08 ± 0.67; $P = 0.0052$) than the SWSFR of healthy controls ($n = 247$; SWSFR, 1.31 ± 0.65). Hyposalivation (SWSFR < 0.7 ml/min) was significantly more frequent among HSCT recipients pre-HSCT (hyposalivation, 42.3 %; $P < 0.001$), 6 months post-HSCT (hyposalivation, 51.0 %; $P < 0.001$) and 12 months post-HSCT (hyposalivation, 29.2 %; $P = 0.01$) than among healthy controls (hyposalivation, 16 %).

The regression analysis revealed that female gender has significantly lower levels of SWSFRs compared to male gender ($P = 0.005$). In addition, SWSFRs tend to improve over time and the flow rates were significantly higher 12 months post-HSCT compared to pre-HSCT ($P = 0.0005$) (Table 2). However, none of the examined transplant-related factors, which included cGvHD, graft type (autologous or allogeneic), myeloablative full intensity versus reduced intensity conditioning, stem cell source (bone marrow or peripheral blood), HLA matching and diagnosis were associated with altered salivary flow in HSCT recipients (Table 2; data on stem cell source, HLA matching and diagnosis not shown).

An average of four (SD, 1.7; range, 0–8) different medications were used concomitantly by HSCT recipients. In descending order, the medications most commonly used by HSCT recipients were antivirals; antifungals; antacids; antineoplastics and immunosuppressants; antibacterials; corticosteroids; cardiovascular drugs, which were limited to antihypertensives for the study population; antiemetics; anxiolytics and antidepressants. Neither the number of medications used by a recipient nor the examined pharmaceutical groups were significantly associated with decreased SWSFR. (Tables 2 and 3).

Table 2 Multiple regression analysis of the relationships of age, gender, time, graft type, regimen, cGVHD and number of medications with stimulated salivary flow

	GMR*	95 % CI	*P* value
Model 1			
Age	1.00	0.99 to 1.01	
Gender (female)	0.74	0.59 to 0.91	*0.005*
Time (6-months post-HSCT)	0.92	0.82 to 1.04	0.19
Time (12-months post-HSCT)	1.27	1.11 to 1.44	*0.0005*
Model 2; graft type			
Model 1 + Autologous graft	1.02	0.78 to 1.33	0.88
Model 3; full intensity regimen			
Model 1 + Full intensity regimen	0.84	0.61 to 1.16	0.28
Model 3; chronic graft-versus-host disease			
Model 1 + cGVHD	1.07	0.92 to 1.24	0.40
Model 4; number of medications			
Model 1 + Medications (<2 vs. >4)	0.92	0.75 to 1.13	0.42
Model 1 + Medications (2–4 vs. >4)	0.93	0.82 to 1.07	0.31

* Geometric mean ratio (GMR) of stimulated saliva flow rates

Discussion

This study examined the associations of medications and transplant-related factors with SWSFR in HSCT recipients. Low SWSFR with a tendency towards improvement over time was observed in HSCT recipients during the 12-month study period. This result is consistent with the findings of our previous study [8]. However, in contrast to our hypothesis, none of the studied transplantation-related factors or medications explained the decreased SWSFR among HSCT recipients.

Consistent with our observations, several prior studies have demonstrated that reduced salivary flow is common and persistent among HSCT recipients [6, 8–11]. Nonetheless, the aetiological factors of hyposalivation have received little research attention. In their seminal study, Imanguli et al. [7] analysed factors that could potentially contribute to salivary gland dysfunction in HSCT recipients with cGVHD. In line with the results of the current study, these researchers found no associations of demographics and transplantation-related factors including age, intensity and type of the conditioning regimen, type of donor, severity of oral mucosal cGVHD or time after diagnosis of cGVHD with salivary gland dysfunction. Additionally, a recent study determined that in HSCT recipients, xerostomia was not associated with time, GVHD or stem cell source [9].

Sicca symptoms including xerostomia and dry eyes are very common in cGVHD patients. It has been show that salivary gland involvement is a clinically distinct manifestation of cGVHD [5, 7, 18]. In many of the studies focusing on GVHD and sicca symptoms, only subjects with the condition have been included without comparison to HSCT recipients without GVHD. However, in the current study, we examined all HSCT recipients with or without cGVHD and the effect of cGVHD on salivary flow rate was negligible. In our previous study, apart from severe cGVHD that was associated with xerostomia ($P = 0.03$), a history of GVHD or the presence of GVHD at present did not correlate with sicca symptoms nor with hyposalivation among very long-term HSCT survivors [10]. Thus, our results suggest that hyposalivation is independent and a common phenomenon after HSCT regardless of GVHD.

Table 3 Medications and stimulated whole saliva flow rates (SWSFR; ml/min) before HSCT and at 6 and 12 months post-HSCT

	Pre-HSCT			6 months post-HSCT			12 months post-HSCT		
	n (M)	SWSFR*	SD	*n* (M)	SWSFR*	SD	*n* (M)	SWSFR*	SD
Antacids	104 (58)	0.9	0.6	89 (50)	0.8	0.6	67 (35)	1.1	0.7
Antibacterials	100 (54)	0.9	0.6	86 (48)	0.9	0.6	60 (30)	1.1	0.7
Antidepressants	16 (8)	0.8	0.6	11 (6)	0.6	0.4	na	na	na
Antiemetics	18 (11)	0.8	0.5	10 (3)	0.7	0.4	na	na	na
Antihypertensives	22 (12)	0.8	0.6	23 (12)	0.9	0.8	20 (12)	1.3	0.9
Antifungals	106 (58)	0.9	0.6	92 (52)	0.9	0.6	54 (27)	1.1	0.7
Antivirals	107 (57)	0.9	0.6	89 (49)	0.8	0.6	66 (32)	1.1	0.7
Anxiolytics	17 (7)	0.9	0.4	na	na	na	na	na	na
Corticosteroids	58 (32)	0.9	0.5	63 (34)	0.8	0.6	45 (27)	1.3	0.7
Antineoplastics and immunosuppressants	103 (59)	0.9	0.6	44 (25)	0.8	0.5	40 (20)	1.1	0.6
Other drugs	27 (14)	0.9	0.4	30 (16)	0.9	0.8	28 (15)	1.0	0.6

All *P* values > 0.05 (for users versus non-users of a medication)

na not applicable; less than 10 users of the pharmaceutical in question

* mean

In contrast to prior reports, the present study examined not only allogeneic HSCT recipients but also autologous HSCT recipients. Autologous and allogeneic HSCT recipients suffered from equally reduced SWSFR. This novel finding suggests that salivary flow reduction cannot be caused solely by the immunological disadvantages of allogeneic transplantation, such as GvHD. Instead, similarities between the diseases treated by autologous and allogeneic HSCT, including the medications used in both types of cases, may play significant roles in the aetiology of hyposalivation.

No previous studies have focussed on medications as a cause of hyposalivation in HSCT recipients, although most medications, particularly in the context of polypharmacy, are well-known causes of hyposalivation [13, 14]. A wide range of medications is commonly utilized during the course of HSCT. Standard chemotherapy schemas initially aimed against the underlying disease are followed by high-dose conditioning regimens with highly potent cytotoxic agents [2]. Co-morbidities after grafting, such as GvHD and infections, are routinely managed with a broad repertoire of medications, including immunosuppressive substances, corticosteroids, antimicrobials and opioids [19–21]. Anxiety and discomfort related to patients' treatments and diseases often require the use of antidepressants and anxiolytics. Nearly, all of these medications have potential adverse effects that include decreased salivary secretion and xerostomia [22]. Nonetheless, the current study failed to demonstrate any associations between reduced SWSFR and medications.

Several factors could contribute to this somewhat unexpected result. First, baseline SWSFR levels were not measured in healthy states prior to the initiation of antineoplastic treatments. Thus, even prior to HSCT, the SWSFR of transplantation recipients was already likely to be lower than the SWSFR of healthy controls. The therapeutic regimen that preceded the first salivary flow measurements may have substantially affected SWSFR and thereby concealed the xerogenic effects of subsequent medications. Additionally, it is challenging to unambiguously assess medications, particularly in the examined population, which generally consisted of subjects who used several concomitant medications. Medication use was determined from medical records, but these data cannot guarantee that patients continuously used all of their prescribed medications. In addition, there is limited understanding of the long-term effects of salivary gland dysfunction caused by polypharmacy. Cytotoxic agents could be expected to cause long-lasting damage to the secretory cells of salivary glands, whereas diuretics may produce more transient effects. However, in contrast to our expectations, the SWSFR of HSCT recipients who used less than two medications and HSCT recipients who used more than four different medications were equally low.

In this study, a well-established and reliable paraffin gum-based method was used to measure SWSFR [14, 23]. Relative to other sialometric approaches such as gland-derived suction-based techniques or imaging techniques like sialography, the collection of stimulated whole saliva conserves time, is uninvasive, inexpensive and easy to repeat with high retest reliability. In this way, a good overall picture of the function of all the major salivary glands can be achieved in an easy numeric form (ml/min), without causing excess stress to severely ill patients. Stimulated saliva is particularly important during eating; in fact, discomfort related to hyposalivation may contribute to the malnutrition that is commonly observed among HSCT recipients. However, in addition to stimulated saliva, studies have demonstrated that also low levels of unstimulated saliva are common among HSCT recipients correlating with poor QoL [7, 10]. Relative to stimulated saliva, unstimulated saliva is likely to be a better metric for assessing xerostomia because salivary secretion is unstimulated during most of the day. This limitation of the present study warrants further investigation to compare the rationales for using stimulated versus unstimulated salivary flow measurements to evaluate healthy subjects and medically compromised patients. Additionally, xerostomia was not assessed in this study but warrabts further studies.

SWSFR measurements were one component of the relatively comprehensive medical evaluations performed prior to transplantation and at 6 and 12 months post-HSCT; such evaluations typically involve anxiety and fear regarding treatments and diseases. The stressful nature of the salivary measurement setting may have significantly contributed to the observations of reduced stimulated salivary flow among HSCT recipients. In fact, the partial recovery of stimulated salivary flow observed at 12 months post-HSCT may be caused by a reduction in stress. Stimulated and unstimulated salivary flow rates are easy and inexpensive to measure; thus, HSCT recipients could assess these rates in a stress-free manner at home. Using this approach, measurements could be obtained at short time intervals to allow for analyses of the effects of short-term medication use on salivary flow rates.

In conclusion, autologous and allogeneic HSCT recipients suffered from low stimulated whole saliva secretion and hyposalivation during the 12-month study period. Demographics, transplantation-related factors and medications were not associated with low SWSFR. These results indicate that hyposalivation among these subjects is a multi-causal phenomenon that involves several concurrent aetiological factors. At present, all HSCT recipients should be considered to be at high risk of hyposalivation and consequent oral diseases, and they should be treated accordingly.

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Compliance with ethical standards

Conflict of interest All authors (MM, LR, AMR, AR, TW) declare that he/she has no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee (Ethics Committee of Basel (Ethikkommission beider Basel 311/10), Switzerland) and with the 1964 Helsinki declaration and its later amendments.

Informed consent In this prospective, register-based study, no informed consent was obtained from the individuals.

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References

1. Gratwohl A, Baldomero H, Aljurf M, et al. (2010) Hematopoietic stem cell transplantation: a global perspective. JAMA 303: 1617–1624
2. Appelbaum FR (2007) Hematopoietic-cell transplantation at 50. N Engl J Med 357:1472–1475
3. Bhatia S, Francisco L, Carter A, et al. (2007) Late mortality after allogeneic hematopoietic cell transplantation and functional status of long-term survivors: report from the bone marrow transplant survivor study. Blood 110:3784–3792
4. Mohty B, Mohty M (2011) Long-term complications and side effects after allogeneic hematopoietic stem cell transplantation: an update. Blood Cancer J 1:e16
5. Nagler R, Marmary Y, Krausz Y, Chisin R, Markitziu A, Nagler A (1996) Major salivary gland dysfunction in human acute and chronic graft-versus-host disease (GVHD). Bone Marrow Transplant 17: 219–242
6. Brand HS, Bots CP, Raber-Durlacher JE (2009) Xerostomia and chronic oral complications among patients treated with haematopoietic stem cell transplantation. Br Dent J 207:E17 discussion 428-429
7. Imanguli MM, Atkinson JC, Mitchell SA, et al. (2010) Salivary gland involvement in chronic graft-versus-host disease: prevalence, clinical significance, and recommendations for evaluation. Biol Blood Marrow Transplant 16:1362–1369
8. Laaksonen M, Ramseier AM, Rovo A, et al. (2011) Longitudinal assessment of hematopoietic stem cell transplantation and hyposalivation. J Dent Res 90:1177–1182
9. Hull KM, Kerridge I, Schifter M (2012) Long-term oral complications of allogeneic haematopoietic SCT. Bone Marrow Transplant 47:265–270
10. Daikeler T, Mauramo M, Rovó A, et al. (2013) Sicca symptoms and its impact on quality of life (QoL) among very long-term survivors after hematopoietic stem cell transplantation (HSCT) in comparison with their respective sibling donors. Bone Marrow Transplant 48: 988–993
11. Jones LR, Toth BB, Keene HJ (1992) Effects of total body irradiation on salivary gland function and caries-associated oral microflora in bone marrow transplant patients. Oral Surg Oral Med Oral Pathol 73:670–676
12. Jensen SB, Pedersen AM, Vissink A, et al. (2010) A systematic review of salivary gland hypofunction and xerostomia induced by cancer therapies: prevalence, severity and impact on quality of life. Support Care Cancer 18:1039–1060
13. Sreebny LM (2000) Saliva in health and disease: an appraisal and update. Int Dent J 50:140–161
14. Sreebny LM, Vissink A (2010) Dry mouth: the malevolent symptom: A clinical guide. Wiley-Bleckwell, Iowa, USA
15. Hong CH, Napeñas JJ, Hodgson BD, et al. (2010) A systematic review of dental disease in patients undergoing cancer therapy. Support Care Cancer 18:1007–1021
16. Lalla RV, Latortue MC, Hong CH, et al. (2010) A systematic review of oral fungal infections in patients receiving cancer therapy. Support Care Cancer 18:985–992
17. SC Sweetman (ed), The Complete Drug Reference 33th edition, Martindale, 2002 London, UK
18. Noce CW, Gomes A, Copello A, et al. (2011) Oral involvement of chronic graft-versus-host disease in hematopoietic stem cell transplant recipients. Gen Dent 59:458–462
19. Dykewicz CA (2001) Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis 33:139–144
20. Jancel T, Penzak SR (2009) Antiviral therapy in patients with hematologic malignancies, transplantation, and aplastic anemia. Semin Hematol 46:230–247
21. Maertens J, Frère P, Lass-Flörl C, Heinz W, Cornely OA (2007) Primary antifungal prophylaxis in leukaemia patients. Eur J Cancer Suppl 5:43–48
22. Drug Facts and Comparisons (2012) Walters Kluwer, St. US, Louis
23. Navazesh M, Christensen CM (1982) A comparison of whole mouth resting and stimulated salivary measurement procedures. J Dent Res 10:1158–1162