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Effect of Anticancer Drugs on Patients With and Without Initially Reduced Saliva Flow

Jukka H. Meurman, Pekka Laine, Christian Lindqvist, Seppo Pyrhonen and Lasse Teerenhovi

We reported earlier that despite the well-known cytolytic effect of anticancer drugs, mean stimulated salivary flow rates were not significantly affected during a 12-month follow-up of patients undergoing treatment for lymphomas (Laine *et al. Oral Oncol, Eur J Cancer* 1992, 28B, 125–128). Therefore, we set out to investigate in more detail the flow rates and composition of salivas in these patients, but now grouped according to their initial flow rate values, which had been assessed before the start of treatment. 49 patients of the original material (30 men and 19 women, mean age 49.9 years) were divided into hyposalivation and normal flow rate groups, according to their baseline values. Stimulated saliva flow $\geqslant 0.8$ ml/min was regarded as the limit for a normal flow rate. 11 patients were found to have reduced flow at baseline (hyposalivation group), while 38 patients had normal flow rate. Analysis of repeated saliva samples taken during the 12-month follow-up showed that flow rates remained significantly lower in the hyposalivation group compared with those of the other group ($P < 0.001$). Further, the concentrations of total protein, albumin, lysozyme, amylase, IgG, IgA and IgM were, and remained, all significantly higher in patients of the hyposalivation group. Counts for salivary mutans streptococci and yeasts were higher and remained significantly so among patients with hyposalivation than among those with normal flow rate while lactobacilli counts were higher in patients with normal initial flow rate. It should be emphasised that the patients' state of hydration was keenly monitored during the intravenous administration of the cytostatic drugs and, subsequently, the patients' fluid and electrolyte balance was corrected in both groups if necessary. Thus, the saliva values measured before the start of anticancer treatment were found to predict well the patients' salivary characteristics throughout the treatment. Attention should therefore be focused on diagnosing the patients at risk for hyposalivation before anticancer treatment in order to correctly direct the preventive dental care needed.

Keywords: saliva, cytostatic drugs.

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INTRODUCTION

SALIVA IS critical to the maintenance and function of tissues in the mouth [1]. The toxic effects of chemotherapeutic agents used in the treatment of malignancies are known to create severe clinical problems, such as mucositis and ulceration. Cytostatic drugs may also cause changes in salivary gland function, which results in reduced salivary flow rate further complicating the situation in the mouth [2, 3]. The composition of saliva may also change owing to chemotherapy, and whole saliva albumin, for example, has been shown to predict the degree of stomatitis in cancer patients [4].

The saliva of caries-susceptible patients often demonstrates a low buffering capacity and an increase in acidogenic microorganisms, such as mutans streptococci and lactobacilli [5]. It is well established that bacteraemia caused by viridans streptococci, in particular, may lead to severe systemic complications in susceptible patients [6]. Also yeasts can cause fulminating, disseminated and life-threatening disease in immunocompromised patients [7]. Therefore, salivary yeast counts should also be monitored. Yeasts may reflect both altered salivary function and an altered immune response. Salivary diagnostics is of special value to cancer patients, and simple chair-side tests can be used to assess the salivary characteristics most important in this respect.

We investigated recently, in a 1-year follow-up study, the

Correspondence to J.H. Meurman.
J.H. Meurman is at the Faculty of Dentistry, University of Kuopio, PB 1627, SF-70211 Kuopio, Finland; P. Laine and C. Lindqvist are at the Department of Oral and Maxillofacial Surgery, Helsinki University Central Hospital, SF-00130 Helsinki, Finland; and S. Pyrhonen and L. Teerenhovi at the Department of Oncology and Radiotherapy, Helsinki University Central Hospital, SF-00290 Helsinki, Finland.
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salivary flow rate and composition in a group of lymphoma patients who were receiving combination chemotherapy of 6–7 months duration [8]. In contrast to previous reports [3, 9], however, we did not observe stimulated salivary flow rates to be markedly reduced by the cytostatic drug treatment. Therefore, it was thought interesting to analyse the data in more detail, after regrouping the patients so that those who initially had reduced salivary flow rate were compared with those whose saliva flow was regarded normal at the baseline examination, before the start of anticancer treatment.

Table 1. Basic data of patients with normal vs. low stimulated salivary flow rate measured at the start of the study

	Patients with normal flow rate (≥0.8 ml/min)	Patients with low flow rate (<0.8 ml/min)
Men/women	26/12	4/7
Age (mean with S.D.)	49 (24.7–81)	42.5 (22.5–67.3)
Hodgkin's disease	10	3
Non-Hodgkin lymphoma	28	8

PATIENTS AND METHODS

The patients and their treatment protocol

Details of the study design, data on patients and treatment of their malignancies have been reported earlier [8, 10]. In brief, 79 patients suffering from histologically verified lymphomas were originally included for a 12-month follow-up study, in which their oral health aspects were investigated. The patients received, at prescheduled intervals, combinations of doxorubicin–bleomycin–velbe–dacarbazine (ABVD) or mustine–oncovine–procarbazine–prednisone (MOPP)–ABV hybrid chemotherapy for 6 months for Hodgkin's disease ($n=16$), and combinations of methotrexate–bleomycin–doxorubicin/epiadriamycin – cyclophosphamide – oncovine – dexamethasone (M-BACOD or M-BECOD) for 7 months for non-Hodgkin lymphomas ($n=63$). Of the original 79 patients, 49 completed the 1-year study (13 patients with Hodgkin's disease, 36 with non-Hodgkin lymphomas). The mean age of these patients was 49.9 years (range 22.5–81.7 years), there were 30 men and 19 women, and 16 patients were regular smokers. None of the patients followed-up received radiotherapy, because all such patients were excluded from this report.

In the beginning of the trial, all the patients received twice daily antiseptic mouthwashes containing chlorhexidine, thereafter they rinsed either with sodium fluoride- or amine and stannous fluoride-containing mouthwash solutions according to a prescheduled protocol [11]. It was later observed that the rinsings with chlorhexidine and amine stannous fluoride reduced salivary mutans streptococci counts, while lactobacilli and yeast counts were not affected [12].

The patients were examined and saliva samples were taken before cancer treatment was started, and then 2, 4 and 6 weeks and 2, 4, 6 and 12 months after the start of the treatment. Saliva was collected into ice-chilled tubes by paraffin-wax stimulation, the collection time was 5 min, and saliva secreted during the first 30 s was discarded. Sampling took place always between 1 and 3 p.m., 2 h after a meal, and smoking was not allowed for 1 h before sampling.

Salivary analyses and statistics

Stimulated flow rate was recorded as ml/min, salivary buffering capacity (end pH) determined by using the Dentobuff method (Orion Diagnostica, Espoo, Finland). Lysozyme was assessed with the Quantiplate Lysozyme Test Kit (Kallestad Laboratories Inc., Chaska, Minnesota), amylase by using the Phadebas method (Pharmacia, Uppsala, Sweden), total protein with the Lowry method, albumin with a immunodiffusion method (Albumin Test Kit, Kallestad Laboratories Inc., Austin, Texas), and salivary immunoglobulin concentrations were analysed by using an enzyme immunoassay [13].

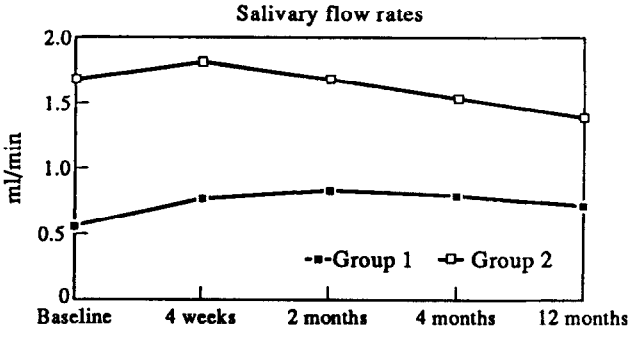

Fig. 1. Mean stimulated salivary flow rates during the study. Group 1 represents patients whose saliva flow before starting chemotherapy was recorded to be below 0.8 ml/min (hyposalivation group), group 2 represents those whose saliva flow was normal (>0.8 ml/min). The patients' anticancer treatments were given in most cases within 6 months after baseline recordings. Difference between groups was and remained statistically highly significant ($P<0.001$).

Mutans streptococci, lactobacilli and yeast counts were studied by using the Dentocult-SM, Dentocult-LB, and Oricult-N dip-slides, respectively (Orion Diagnostica, Espoo, Finland). The validity of these methods has been analysed and found to be good [14–16].

Based on the initial flow rate values, digotomised into two groups, those having flow rates below 0.8 ml/min and those with 0.8 ml/min or more, the data on salivary characteristics and composition were analysed accordingly, with respect to time. The significance between means was determined using the rank-sum test, and analysis of variance was used for continuous data. All P values given are based on two-tailed tests of significance.

RESULTS

11 patients were found to have low stimulated salivary flow rates at the start of the trial (group 1), while normal flow rates were recorded in 38 patients (group 2). Characteristics of the patients in these two groups are given in Table 1.

Throughout the 12-month follow-up, the salivary flow rates remained significantly lower in the patients with initially recorded hyposalivation, compared with those whose baseline saliva flow was normal (mean flow rates 0.7 ± 0.4 ml/min vs. 1.6 ± 0.7 ml/min, respectively, $P<0.001$). Mean salivary flow rate values with respect to the 12-month follow-up are shown in Fig. 1.

Table 2. Salivary composition in the patients with (group 1) or without (group 2) initial hyposalivation during the study

	Baseline	During 4 months of active cytostatic drug treatment	12-month follow-up	Significance between groups
Lysozyme (mg/l)				
Group 1	46.7±79.1	15.1±10.8	45.5±61.8	
Group 2	13.5±15.3	16.4±14.5	31.7±37.8	NS
Amylase (U/ml)				
Group 1	493.6±457.6	591.9±740.2	560.8±497.7	
Group 2	379.4±267.1	360.7±263.3	380.6±278.3	NS
Total protein (mg/ml)				
Group 1	2.6±1.9	2.2±1.3	2.3±1.2	
Group 2	1.5±0.4	1.6±0.6	2.0±1.9	$P=0.01$
Albumin (μg/ml)				
Group 1	229.2±433.2	204.7±447.3	307.3±495.0	
Group 2	69.0±72.6	66.4±71.9	94.0±71.0	$P=0.02$
IgG (mg/l)				
Group 1	37.0±39.9	35.7±79.1	49.2±63.0	
Group 2	17.9±19.1	12.3±13.2	22.0±32.6	$P=0.01$
IgM (mg/l)				
Group 1	11.7±11.9	6.9±7.7	10.1±8.4	
Group 2	4.8±5.2	4.1±4.9	5.3±5.2	$P=0.2$
IgA (mg/l)				
Group 1	134.3±131.1	68.2±58.3	124.8±76.9	
Group 2	52.7±27.4	48.9±38.7	66.1±43.3	$P<0.001$

The same trend as with flow rates was observed with the buffering capacity of saliva: those with initially low buffering capacities showed low values throughout, while the patients whose salivary buffering was higher usually had high values, irrespective of the cytostatic drug treatment. For example, mean end pH values, as scored with the Dentobuff method at baseline, were 4.2±0.8 in the hyposalivation group and 5.1±1.2 in the group with normal saliva flow. The mean 12-month follow-up values were 4.3±0.8 in group 1 and 5.1±1.2 in group 2, respectively. The differences between the groups were statistically significant throughout the study also in this respect ($P<0.001$).

In both groups, salivary lysozyme concentrations were reduced during the cytostatic drug administration periods. However, the values had returned to the baseline levels by the 12-month follow-up examination. The patients with initial low salivary flow rate had consistently higher lysozyme concentrations throughout the study than those with normal saliva flow (Table 2). The same was observed in amylase, albumin, total protein and the immunoglobulin concentrations. The results are given in Table 2. Differences between the groups were statistically significant in all these parameters, except in lysozyme, where the difference was not statistically significant.

Results on the salivary microbial counts are summarised in Fig. 2. Counts for mutans streptococci were significantly reduced after start of chemotherapy. At baseline, all patients in group 1 had mutans streptococci in their saliva, while 2 weeks after initiation of therapy 30.2% of the salivary cultivations of the patients were negative in this respect. At the 6-month follow-up of the initially hyposalivated patients, when practically all the group 1 patients had received their anticancer treatment, no growth was observed in 18.2%, while high

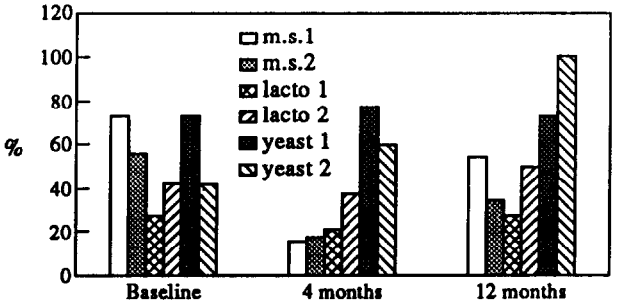

Fig. 2. Per cent distribution of salivary mutans streptococci (m.s.), lactobacilli (lacto) and yeast counts (yeast) in group 1 and group 2 patients before starting chemotherapy (baseline), 4 months after initiation of treatment, and 6 months after its termination (12 months follow-up).

counts ($>10^6$ CFU/ml) were observed in 54.4%, respectively. In patients of group 2, 97.4% had mutans streptococci in their saliva at baseline, which percentage was reduced to 68.3% 2 weeks after initiation of therapy. At 6-month follow-up, 71.1% had mutans streptococci in their saliva, 26.3% of those were highly infected ($>10^6$ CFU/ml). By end of the study, 54.4% of group 1 and 34.2% of group 2 patients had high salivary mutans counts.

High lactobacilli counts ($>10^6$ CFU/ml) were observed in 27.3% of group 1, and 42.1% of group 2 patients before starting chemotherapy. After 2-week treatment, the respective percentages were 20.8 and 37.3%. At 6-month follow-up, 30% of the initially hyposalivated patients were heavily infected with latobacilli, 42.1% of those with normal flow rate had high counts. At 1-year follow-up, high latobacilli counts

were found in 27.3% of group 1, and in 50% of group 2 patients, respectively.

At baseline, salivary yeasts were detected in 42.1% of initially hyposalivated patients, and in 72.7% among those with normal flow rate. At the 6-month follow-up, positive yeast counts were seen in all group 1 patients, and in 60.5% of group 2 patients, respectively. By the end of the study, yeast counts were positive in 72.7% of group 1, and in 100% of group 2 patients, respectively.

DISCUSSION

The patients of this study gave their saliva samples always during their stay in the hospital, either as outpatients in the polyclinic where the cytostatics were being administered, or during their stay at the ward. The cytostatic drugs were often given by intravenous infusions and, as said, the patient's fluid and electrolyte balance was followed-up and corrected if necessary. The saliva sampling had to be taken when the patient's lymphoma treatment allowed him/her to leave the ward and come to the dentist's office. Thus, the time for sampling could not be selected on the basis of whether the patient was receiving intravenous infusion or not. This aspect puts further emphasis on the present results because it can be anticipated that those patients who indeed had reduced saliva flow during the measurements might have been even more hyposalivated if they had not been receiving the infusions. Since we were not able to control the effect of the patient's fluid and electrolyte balance on their salivary secretion in the present study, for obvious reasons, we have now started a study to investigate this effect in another patient material. It has been suggested that the degree of hydration is indeed the most important factor affecting saliva flow. For example, Holmes [17] reported that if body water content was reduced by 8%, salivary secretion decreased pratically to zero, and Shannon [18] has stated that hyperhydration causes increased saliva flow.

Other factors claimed to affect saliva flow in general are the patient's age and gender. Women usually have lower flow rates than men probably due to hormonal differences but also due to the smaller size of their glands [19, 20]. This difference between genders has also been observed in our patients [8]. More women than men were classified as having initially reduced flow rates. The effect of patient's age on saliva flow is a controversial issue. Histological studies have shown age-related changes in salivary gland structure [21], and the flow from submandibular gland has been shown to decrease with age [22]. However, a recent comprehensive study by Närhi *et al.* [23] on over 75-year-old subjects clearly showed that age as such does not affect saliva flow. The reason which causes reduced saliva flow in the elderly is their medication, in particular cardiovascular medicines and diuretics [22]. In the present study the patients having low flow rates were younger on average than those with normal saliva flow, which further supports the view that decreased saliva flow is not correlated with increasing age of a patient.

Modern, intensive chemotherapy is often intended to be curative. Therefore, many patients return to normal life after the treatment. This aspect emphasises the need for counselling the patients in maintaining satisfactory oral health during the treatment, so that any detrimental side-effects on the teeth, for example, could be avoided. In this, saliva diagnosis is of primary importance [24]. But, above all, because dental infections can be life-threatening during anticancer treatment, the patients' need for preventive dental care cannot be underestimated [10, 25–27]. One clinical problem in saliva diagnosis is that the range of normality is so broad. It is particularly difficult to determine whether a patient has an abnormally low flow rate [28]. We chose the threshold of 0.8 ml/min based on the current practice in our clinic and dental schools in Finland, where this value for stimulated salivary flow rate has been successfully used since early 1970s to reflect reduced saliva flow in adults. It should be pointed out, however, that patients can be categorised as having dry mouth only on the basis of their subjective symptoms. The threshold value we used is practical in clinical decision making; in assessing the patients' need for preventive dental therapy. In case of our lymphoma patients who during their cytostatic drug treatment suffered from a variety of oral lesions during their treatment [29], it was not possible to assess what was the effect of dry mouth on subject symptoms, such as burning or smarting pain in the mouth. It is known from other contexts that dry mouth alone may cause many such symptoms [30, 31].

Low saliva flow is accompanied with increased concentrations of all salivary constituents. Therefore, it was not unexpected to observe that salivary total protein, albumin, and immunoglobulin concentrations were significantly higher in group 1 patients with hyposalivation. The finding that lysozyme and amylase were also higher but not significantly among those with reduced saliva flow, might have been due to the small size of group 1 with subsequently large individual variations of these constituents. Lysozyme may also derive from the inflammatory cells entering the oral cavity, and amylase, which was found to be fairly stable during the cytostatic drug treatment of our patients [8], may reflect functional capacity of the salivary gland [32]. We have recently discussed the role and function of the salivary constituents we measured, and we will therefore not repeat it here [8].

Mutans streptococci and latobacilli were monitored in order to assess the patients' risk for caries during their treatment. It has been previously shown that oral streptococci are particularly sensitive to cytostatic drugs which may be secreted into saliva in concentrations exceeding the *in vitro* established MIC values of the drugs [33]. In the present study, we noted that starting the cytostatic drug treatment significantly reduced salivary counts of mutans streptococci, in particular, but after treatment high counts were again encountered. The counts of all salivary micro-organisms monitored were significantly higher in patients with initially reduced flow rate in comparison to those with normal saliva flow. This finding again emphasises the need for focusing dental preventive therapy in particular to those patients with reduced saliva flow.

Yeasts were also encountered more often in patients with reduced saliva flow, which was not unexpected either. The prevalence of yeasts in saliva in "normal" individuals has been stated to be 37% [34]. However, in medically compromised patients the occurrence of salivary yeasts may be much higher. In particular, in patients with malignant diseases yeasts are known to be able to cause fulminating and life-threatening diseases [7, 35]. In the present study, yeasts were detected in all group 1 patients by the end of the follow-up, which finding should further alert the clinician with respect to hyposalivation.

To sum up, we have shown in this study that the patient's baseline salivary secretion rate predicted well his/her saliva

flow throughout the approximately 6-month treatment phase with cytostatic drugs, and the subsequent 6-month follow-up. Patients who had reduced saliva flow before the start of anticancer therapy remained hyposalivated all the time. They also had significantly higher concentrations of all salivary constitutents analysed, and higher salivary microbial counts, than patients whose saliva flow was categorised as normal at the start of therapy.

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