Prevention of oral mucositis in paediatric patients treated with chemotherapy: a randomised crossover trial comparing two protocols of oral care

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Abstract
This study compared the efficacy of two protocols for oral care using either chlorhexidine or benzydamine as oral rinses to alleviate mucositis in children undergoing chemotherapy. Eligible participants were randomised to receive either protocol for 3 weeks in a two-period crossover design. The occurrence of ulcerative lesions and severity of mucositis were measured at baseline and twice weekly, using the modified Oral Assessment Guide (OAG). Data were continuously analysed by plotting them directly on predefined sequential charts. According to this sequential analysis, the study could be terminated at the 34th within subject comparison, with a statistically significant reduction in ulcerative lesions ($P<0.05$) and severity of mucositis ($P<0.05$) in children on the chlorhexidine protocol. These findings suggest that chlorhexidine together with oral care might be helpful in alleviating mucositis when given prophylactically to children on chemotherapy, but the therapeutic benefit needs to be confirmed in a larger trial

1. Introduction

Oral mucositis is one of the most debilitating complications following chemotherapy, occurring in approximately 52–80% of children with cancer so treated [1, 2 and 3]. Despite this high prevalence, there have been few studies published on reducing the incidence and severity of oral mucositis in children. Oral mucositis remains an unresolved clinical problem for experience oncological teams treating children with chemotherapy.

Oral mucositis normally lasts for 3 weeks, beginning at 3–5 days and peaking at 7–14 days after chemotherapy [4]. The probable mechanisms involve complex biological events mediated by a number of inflammatory cytokines, the direct effect of the chemotherapeutic drug or irradiation on the basal epithelium and connective tissue, and the oral microbial environment [5]. Several therapy- and patient-specific factors, including the chemotherapeutic drug itself, the type of malignancy, age, neutrophil count, and level of oral care, are thought to be important in the aetiology of oral mucositis. To a large extent, the severity of the condition is related to the specific chemotherapeutic agents used: methotrexate, fluorouracil (5-FU), doxorubicin (Adriamycin) and etoposide (VP-16) are particularly stomatotoxic [6 and 7].

Clinically, oral mucositis presents with an initial mucosal erythema, which often progresses to patchy mucositis, and then extensive ulceration and desquamation [8 and 9]. Although it is not a life-threatening complication, its impact in clinical practice is great, and it may have wide-ranging physical and psychosocial implications for patients. The ulcerative lesions are often very painful, requiring treatment with analgesics and supportive nutrition, and the cancer treatment may need to be interrupted or modified. In myelosuppressed individuals, the ulcerative lesions can even predispose to potentially fatal bacteraemia. All these conditions may increase treatment costs, preclude further treatment, jeopardise survival, or irrevocably alter the quality of life of the patient [10 and 11].

Although oral mucositis has been studied for many years, no one strategy or approach has proved to be reliably effective. For nearly all of the existing approaches, the outcomes for children remain unknown. In 1989, a consensus conference on oral complications sponsored by the National Institutes of Health concluded that no currently available drug could effectively prevent or treat oral mucositis [12]. Two recent reviews conducted by the Cochrane Oral Health Group [13] and the Joanna Briggs Institutes [14] identified only that the application of ice chips might possibly prevent bolus fluorouracil-induced mucositis, with few other recommendations for oral mucositis in general. The efficacy of several bioactive factors and immunomodulatory therapy in controlling oral mucositis is now under investigation [15 and 16]. Although these specific therapies may provide new insights into the management of this condition, they are costly, which may limit their widespread application. Given the low cost and simplicity of routine oral care, oral hygiene protocols should be the standard intervention, with specific therapies to be developed in addition [17]. In fact, as the role of oral microflora in the pathogenesis of mucositis becomes increasingly clear, so too does the concept of enhanced oral hygiene in the management of mucositis [5].

Controversies and confusions persist on the different measures to be included in protocols of oral care. The Bass method of tooth-brushing and the frequent use of normal saline are generally recommended for individuals undergoing cancer therapy [1 and 18]. Although the use of chlorhexidine in oral mucositis has been widely examined, the results have varied. In fact, the studies on chlorhexidine are difficult to interpret and compare because of differences in the underlying disease, the chosen cancer therapy, the patient's age and the rinse schedules. As chlorhexidine has been shown to reduce oral bacterial and fungal colonisation, some studies support its prophylactic use in patients receiving myelosuppressive therapy [8 and 19]. Benzydamine is a non-steroidal drug with anti-inflammatory, anaesthetic and antimicrobial properties [20]. It has been suggested that it may be more effective when used prophylactically to ‘prevent’ mucositis rather than therapeutically once mucositis is present [21]. Studies on patients receiving irradiation for head-and-neck malignancy have revealed a statistically significant reduction in oral ulceration in patients using benzydamine prophylactically [21 and 22]. No studies have been traced comparing the effects of chlorhexidine and benzydamine rinses in chemotherapy-induced oral mucositis, in particular for patients with childhood cancer. Our aim was therefore to compare the efficacy of two protocols differing in the type of oral rinse, 0.2% w/v chlorhexidine gluconate versus 0.15% w/v benzydamine hydrochloride, in alleviating oral mucositis in children undergoing chemotherapy.

2. Patients and methods

2.1. Setting and sample

The study was conducted in a children's cancer centre in a university-affiliated hospital in Hong Kong after approval from the ethics committee. Children between the ages of 6 and 17 years who had received two consecutive cycles of high-dose or combination chemotherapy for haematological malignancies or solid tumours were enrolled in the study. The children were capable of tooth-brushing and mouth-rinsing as judged by the investigators. The study was conducted in accordance with the pertinent sections of the Declaration of Helsinki; all the children gave their assent to participate and their parents provided written informed consent before enrolling in the study.

2.2. Study design

This was a prospective, randomised, non-blinded, two-period crossover study with continuous sequential analysis. This design was based on the fact that it is extremely difficult to control for all therapy- and patient-specific variables in a single-centre study, and on the practical difficulty of obtaining a sufficient number of participants, given the low incidence of childhood cancer. In addition, the distinguishable colour and taste of chlorhexidine and benzydamine oral rinses meant that blinding was not considered feasible. Eligible participants were randomly assigned to receive either protocol of oral care with chlorhexidine or benzydamine on the initial chemotherapy cycle, and then crossed over at the subsequent cycle (Fig. 1). There would be a period of 1–2 weeks' 'washout' between the two chemotherapy cycles, depending on the treatment protocol. Randomisation was balanced for every four subjects and stratified on the type of chemotherapeutic agent.

Figure 1 here

It is not the usual practice in the institution where the study was conducted to have standard oral care and routine dental examinations before commencing chemotherapy. For the purpose of this study, participants were instructed to maintain strict oral hygiene according to the protocol on the first day of chemotherapy and to continue for the 3 weeks of each study period. The protocol included (a) tooth-brushing using the Bass method and mouth-rinsing with either of the allocated rinses in the early morning and at bedtime; (b) normal saline rinsing within 30 min of meals; (c) normal saline rinsing every 4 h in the first and third week, and every 2 h in the second week after chemotherapy. Participants were instructed to rinse their mouths using a ballooning and sucking motion of the cheeks for 30 s without swallowing. Those who complained of stinging or burning were advised to dilute the oral rinses with an equal volume of normal saline (1:1) [20 and 23]. Special attention was given to maintaining the integrity of the protocol throughout the study, which included pretreatment instruction on oral care, reinforcement practice sessions every week and a cartoon-illustrated reminder. Each participant was given a practice diary; compliance was continuously monitored by assessing the frequency of oral care recorded in the diary, and was counterchecked by determining the amount of rinse used and left in returned bottles. Both the child and parent were also interviewed at each assessment visit about the performance of oral care on the preceding day. The calculation of compliance was based mainly on the diary data, from which the average percentage of oral care performed each day (from 07:00 to 23:00) during the study period was computed as

the sum of the percentage of oral care performed every day divided by 21. The level of oral care considered adequate was set at 80%.

The outcome variables, including the occurrence of ulcerative lesions and severity of oral mucositis, were measured at baseline and twice a week by one of the investigators and an oncology nurse. Both of them had received training on using the chosen scoring system. Ramirez-Amador and colleagues suggest that two time points per week for assessment are sufficient to obtain estimates of oral mucositis and to ensure that oral ulcerative lesions are not missed [9]. A frequency of twice a week also minimises the burden on the participant. More frequent assessment was not otherwise possible as patients were often discharged after chemotherapy and so the analysis would have been complicated by large amounts of missing data.

The Oral Assessment Guide (OAG) designed by Eilers and associates [24], which has been used in different cancer treatments, was used for the purposes of this study. The OAG is applicable in children because of its simplicity and the limited number of items, requiring only 3–4 min to complete. Nevertheless, in order to create a more accurate reflection of the severity of oral mucositis, we made the following minor modifications to the OAG, as detailed in Table 1, with the agreement of oncology researchers and specialists. The item ‘mucous membrane’ was divided into buccal/palatal and labial mucous membranes, as most oral lesions are located in the labial and buccal mucosa. The item ‘teeth/denture’ was deleted, as it does not relate directly to the degree of tissue damage and change. Eight items were assessed and a score of 1 (normal) to 3 (severely affected) was assigned to each. Individual scores were added to produce a mucositis score with a range of 8–24. Interrater reliability for the modified OAG was established using three nurses who completed four oral assessments on children undergoing chemotherapy, with a Kappa coefficient equal to 0.81–0.94. For construct validity, the modified scale was tested prospectively with the same group of children. The pattern of oral mucositis scores followed the clinical condition of the mouth, with increasing scores as the lesions worsened followed by decreasing scores as they healed.

Table 1 here

2.3. Data analysis

Sequential analysis was the chosen method of statistical analysis on outcome variables, in which the presence of any statistical differences in responses was determined after each within-subject comparison. Such analysis is based on the premise that accumulating data can be monitored and analysed continuously, and any decision to stop the trial can be applied immediately. The total number of participants entering the study is therefore not predetermined. The statistical techniques of sequential analysis take into account the effect of increasing the chance of type I error by repeated examination of the accumulating data, so valid interpretations can be made after each within-subject comparison in a crossover trial [25, 26 and 27].

A closed sequential-analysis chart with the boundaries set to give a two-sided significance of 0.05 and a power of 90% for the probability of detecting a critical value of 0.75 was used to compare the effects of chlorhexidine and benzydamine on ulcerative lesions [25] (Fig. 2). With sequential analysis, a preference for chlorhexidine was plotted (by dots) toward the upper boundary if ulcerative lesions

occurred in a participant when using benzydamine, but not chlorhexidine. Conversely, a preference for benzydamine was plotted (by dots) toward the lower boundary if ulcerative lesions occurred when using chlorhexidine, but not benzydamine. If the outcomes for ulcerative lesions were the same, the case would be excluded from plotting on this sequential-analysis chart.

Figure 2 here

Another closed, sequential, t-test analysis chart with the boundaries set to detect a critical difference of 0.6 of a standard deviation with a two-sided significance of 0.05 and a power of 90% was used to examine the differences between chlorhexidine and benzydamine in relation to the severity of oral mucositis [25] (Fig. 3). The area under the curve (AUC) of a severity–time curve, from days 1 to 21, was used to summarise the severity of oral mucositis in individual participants before any sequential analysis. The use of the AUC is considered clinically relevant and statistically valid to the analysis of serial data [28]. With sequential analysis, the sum of the differences in the mean AUC between each within-subject measurement was squared and divided by the square of the sum of the differences in mean AUC, so computing a Z value (Z=(sum d)2/sum d2). The sequential-analysis chart plotted the Z values (by dot) against the number of within-subject comparisons until one of the boundaries was crossed.

Figure 3 here

3. Results

3.1. Study population

Between April 2000 and April 2001, a total of 40 children were enrolled and randomly allocated to receive one of the oral care protocols. 34 participants completed the two protocols for the full period (6 weeks) to enter the sequential analyses, 17 in each protocol. 6 participants were excluded because they were not able to complete the two protocols, either because cancer treatment was withdrawn or they went for a bone marrow transplant (Table 2). As the trial design was crossover rather than parallel, an intention-to-treat analysis after the first oral-care protocol was not considered possible.

Table 2

34 participants were thus included in the sequential analyses; 21 boys and 13 girls, ranging in age from 6 to 16 years (mean 10.3 years (standard deviation (S.D.) 3.3). Their years of schooling ranged from 0 to 11 years (mean 4.5 (S.D. 3)). Before the study, 16 participants (47%) attested to performing oral care in the form of tooth-brushing twice a day. The most common diagnosis was acute lymphoblastic leukaemia (ALL) (56%). The more commonly used chemotherapy regimens included vincristine/doxorubicin (32%), methotrexate (24%) and vincristine/methotrexate (15%). 16 participants (47%) had received chemotherapy previously, with mild to moderate mucositis being reported. Baseline measurements of oral mucosal and myelosuppression status, as well as renal function profiles, were similar and there were no statistically significant differences in these measures before the start of each chemotherapy cycle.

3.2. Carry-over effect

The overall mean AUC for oral mucositis throughout the study was 8.7 (S.D. 4.7) for patients who received chlorhexidine first, and 6.5 (S.D. 5.1) for those who received benzydamine first. There was no statistically significant difference in the patients' mean AUC for oral mucositis according to the order in which the protocols were received ($t=1.31$, $P>0.05$), indicating there was no carry-over effect from the initial oral-care protocol.

3.3. Ulcerative lesions

In this study, 27 and 59% of participants developed ulcerative lesions when receiving the protocols with chlorhexidine and benzydamine, respectively. Most of the ulcerative lesions were located in the buccal mucosa (62%) and labial mucosa (35%). One-third of participants (38%) with haematological malignancies, and more than half of those (55%) with solid tumours, developed ulcerative lesions during chemotherapy (Table 3). Approximately half of all ulcerative lesions occurred in those receiving methotrexate infusions. In Fig. 2, a line is plotted showing the sum of the preferences; it crosses the upper boundary at the 15th preference among the 34 within-subject comparisons, indicating that the use of the chlorhexidine significantly decreased the manifestation of ulcerative lesions compared with benzydamine ($P<0.05$).

Table 3

3.4. Oral mucositis

Oral mucositis appeared around day 3, peaked on day 10 and started to resolve by day 14 after chemotherapy (Fig. 4). The OAG scores for mucositis in patients who used chlorhexidine from days 1 to 21 ranged from 8 to 13 (mean 8.6–9.5; S.D. 0.9–1.5). When using benzydamine patients had higher OAG scores for mucositis (8–18; mean 8.7–10.3, S.D. 0.8–2.2). The AUC for mucositis in patients using chlorhexidine ranged from 0 to 17.5 (mean 6.1, S.D. 4.6). When using benzydamine, patients had a higher range of AUC for mucositis (0–26; mean 8.7, S.D. 6.6). As shown in Fig. 3, a cumulative plot of the AUC was made for each within-subject comparison, and when statistical significance ($P<0.05$) was reached after the 34th comparison this allowed the conclusion that the use of the chlorhexidine significantly reduced the severity of mucositis compared with benzydamine.

Figure 4 here

3.5. Compliance with oral care

Overall, the children using both protocols achieved acceptable compliance (>80%) throughout the 6-week study period. The mean compliance for protocols containing chlorhexidine and benzydamine was 92.6% (S.D. 5.3) and 93.2% (S.D. 5.8), respectively.

4. Discussion

Studies comparing oral rinses are few and those reported have mainly been in adult populations. Our findings indicate a significantly lower incidence and severity of oral mucositis in patients on the protocol with chlorhexidine than with benzydamine. The present data support the findings of earlier, non-randomised studies on chlorhexidine in the prophylaxis of chemotherapy-induced mucositis in children [29 and 30]. However, they contrast with the data of Samaranayake and colleagues, who found no significant difference in irradiation-induced mucositis in patients with head-and-neck

cancer receiving chlorhexidine and benzydamine twice daily [31]. This discrepancy may be due to the small number of patients in Samaranayake's study, which would have reduced the power to detect significant findings. A large, randomised, controlled trial conducted by Dodd and colleagues comparing 222 adult outpatients using either chlorhexidine or water showed that chlorhexidine was not beneficial [32]. In Dodd's study, mucositis was assessed monthly, a method that might be too insensitive to detect mucosal changes and thus a significant proportion of mucositis may have remained undetected in their study. Furthermore, most of their patients were receiving adjuvant chemotherapy for breast and lung cancers, which is not highly stomatotoxic, whereas highly stomatotoxic agents with dose intensification were used in our investigation. High-dose methotrexate is frequently used in the treatment of children with ALL and osteosarcoma. Oral mucositis is a major toxicity associated with methotrexate [6, 7 and 33]. The incidence of ulcerative mucositis was close to 52% for the methotrexate infusions in our study, similar to that found by previous investigators [33]. Nevertheless, it is rather remarkable to find a higher incidence of ulcerative mucositis in a paediatric group with solid tumours than in a group with haematological malignancies. Childers and colleagues also reported similar findings, and suggested that these relate to the use of more dose intensification and combination chemotherapeutic regimens in treating childhood solid tumours in recent years [2].

Some findings suggest that the frequency and consistency of oral care are more important in reducing oral mucosal damage associated with cancer treatment than the particular agent used [18 and 32]. In the current study, the lack of a control or comparison group with a normal saline and tooth-brushing regimen did not allow us to discern whether the clinical benefits of the protocol were due solely to the chlorhexidine or to the effect of the systematic performance of oral care. Nevertheless, it can be speculated from the data presented here that chlorhexidine may play a part in reducing oral mucosal damage during chemotherapy, possibly through plaque control and a reduction in the oral microflora. Dahllof and colleagues, examining the oral condition of children treated by bone marrow transplantation, found that those patients with no oral plaque who received cancer chemotherapy developed significantly less and a shorter period of mucositis [34]. A study of children with acute leukaemia being treated with chemotherapy showed that chlorhexidine significantly decreased the counts of total aerobes and streptococci [35]. Although benzydamine reportedly has antimicrobial properties [20, 21 and 22], its bland antiseptic effects in suppressing the oral microflora are unclear. In Samaranayake's study, neither chlorhexidine nor benzydamine was found to be effective in controlling the oral carriage of coliforms and Staphylococcus aureus [31]. Quantitative baseline and posttreatment analyses of selected components of the oral microflora are required to validate the efficacy of chlorhexidine and benzydamine in microbial suppression during chemotherapy. In the present study, the 59% prevalence of ulcerative mucositis in children using benzydamine is considerably less than the reported approximately 80% in previous studies [1 and 3], suggesting that benzydamine may have some effects on mucositis. It has been speculated that the anti-inflammatory capacity of benzydamine resulting from its ability to suppress proinflammatory cytokine production may reduce cancer treatment-induced mucosal toxicity [36]. In a recent multicentre study, benzydamine applied 4–8 times daily before and during radiotherapy was effective in the prophylactic treatment of radiation-induced mucositis [37]. In Epstein's study, the frequency of application of

benzydamine was 2–4 times higher than in the present investigation. Therefore, we think that the frequency and duration of benzydamine application might together affect its efficacy. It is likely that children might not receive the maximum benefit from benzydamine by twice-daily rinsing. For this reason, further studies to determine which factors modulate benzydamine's efficacy and the optimal frequency of benzydamine rinses are warranted.

Mouthwash-induced discomfort and variable patient tolerance have been reported in some studies of chlorhexidine and benzydamine rinses [31 and 38]. In this study, the children surprisingly had accepted and tolerated both the oral rinses well, and the level of adherence to the oral care regimen was high. Although some children experienced an initial stinging, dilution with normal saline alleviated this sufficiently to allow the children to continue with the study protocol. In agreement with observations by Lang and co-workers, a 0.2% chlorhexidine rinse is considered acceptable to children [39]. This conclusion is also supported by O'Sullivan and colleagues, who reported 100% compliance in children who had received prophylactic 0.2% chlorhexidine rinses four times a day for the entire duration of the study [35].

In conclusion, chlorhexidine complementing an oral care protocol offers some promise in reducing oral mucositis for children undergoing chemotherapy. However, our findings must be interpreted with caution because the inability to establish a blinded design could influence the reliability and validity of the outcome measures. In addition, the fact that the study was relatively small limits the ability to generalise from the data, so more comprehensive evaluations, including psychosocial outcomes with larger population groups, are required to confirm our findings. As the low incidence of childhood cancer and the wide range in ages pose methodological problems, multi-institutional collaborative research is needed in order to define further the optimal regimen for oral care in children and provide the basis for best practice in relation to oral mucositis.

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Figures and Tables:

Fig. 1. Flow chart of the progress of patients through the trial.

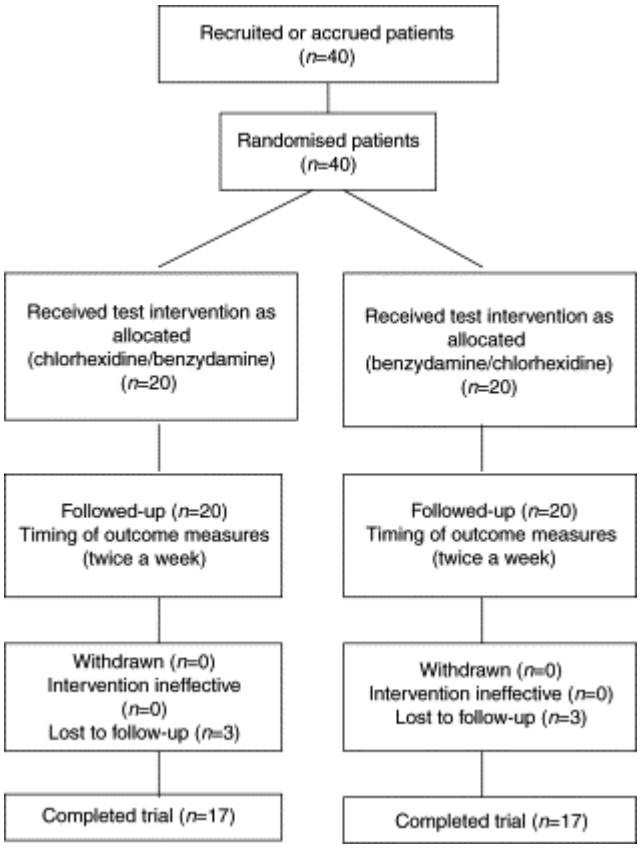

Table 1. Oral assessment guide (OAG)

	Score		
Item	1	2	3
Voice	Normal	Deeper or raspy	Difficulty talking or painful
Swallow	Normal swallow	Some pain on swallowing	Unable to swallow
Lips	Smooth and painful and moist	Dry or cracked	Ulcerated bleeding
Tongue	Pink and moist and papillae present	Coated or loss of papillae with a shiny appearance with or without redness	Blistered or cracked
Saliva	Watery	Thick or ropy	Absent
Mucous membrane (buccal mucosa, palate)	Pink and moist	Reddened or coated (increased whiteness) without ulceration	Ulceration with or without bleeding
Mucous membrane (labial mucosa)	Pink and moist	Reddened or coated (increased whiteness) without ulceration	Ulceration with or without bleeding
Gingiva	Pink and stippled and firm	Oedematous with or without redness	Spontaneous bleeding or bleeding with pressure

Fig. 2. Sequential-analysis chart for within-subject comparisons on ulcerative lesion manifestation. L, lower boundary; M, middle boundary; U, upper boundary.

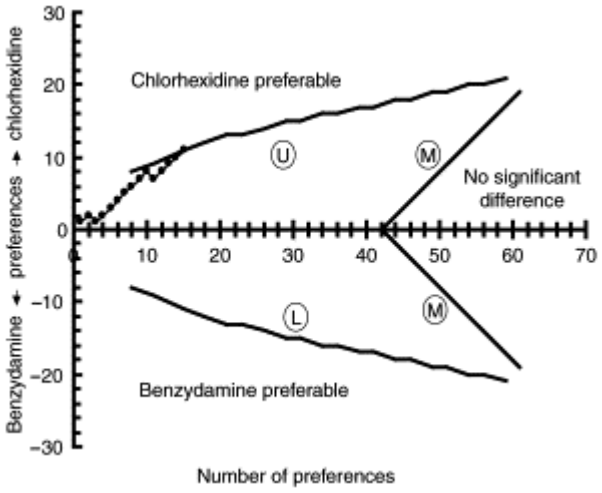

Fig. 3. Sequential *t*-test analysis chart for within-subject comparison on AUC values for oral mucositis. AUC, area under the curve; M, middle boundary; U, upper boundary

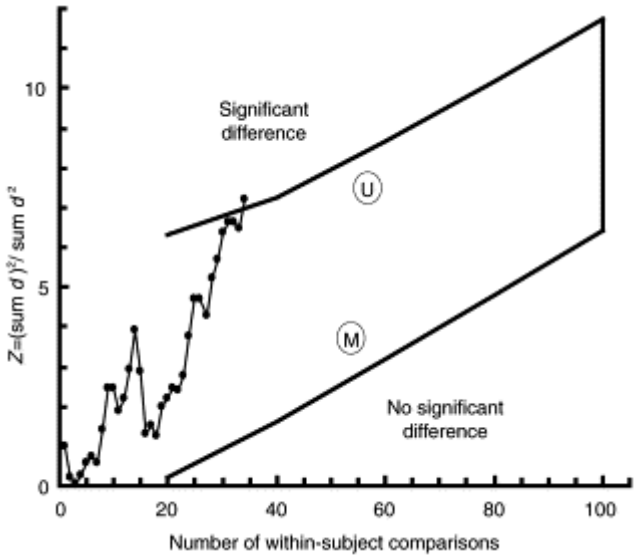

Table 2. Demographic and clinical characteristics of participants

Subject no.	Gender/age (years)	Diagnosis	Chemotherapy regimen	Protocol order
1	M/16	Osteosarcoma	MTX	CHD/BZD
2	M/7	ALL	VCR/MTX	BZD/CHD
3	F/12	Hepatocellular carcinoma	Cisplatin/5-FU	CHD/BZD
4[a]	M/11	ALL	VCR/MTX	BZD/CHD
5	M/9	ALL	VCR/MTX	BZD/CHD
6	F/6	AML	Ara-C/ADR/VP-16	BZD/CHD
7	M/14	ALL	VCR/MTX	CHD/BZD
8	F/7	ALL	VCR/ADR	CHD/BZD
9	F/11	AML	Ara-C/ADR/VP-16	BZD/CHD
10	F/12	Osteosarcoma	MTX	BZD/CHD
11	M/8	ALL	VCR/MTX	CHD/BZD
12[a]	M/8	ALL	VCR/MTX	CHD/BZD
13	M/15	AML	Ara-C/ADR/VP-16	CHD/BZD
14	F/7	Anaplastic large-cell lymphoma	VCR/CPM/VP-16/Ara-C/MTX	BZD/CHD
15[a]	M/13	Burkitt's lymphoma	MTX	BZD/CHD
16	M/13	Osteosarcoma	MTX	CHD/BZD
17	F/12	Osteosarcoma	MTX	BZD/CHD
18	M/11	AML	Ara-C/ADR/VP-16	CHD/BZD
19	F/13	ALL	VCR/MTX	CHD/BZD
20	F/16	Rhabdomyosarcoma	VCR/Actinomycin-D/CPM	BZD/CHD
21	F/9	Rhabdomyosarcoma	VCR/Actinomycin-D/CPM	CHD/BZD
22	M/11	ALL	VCR/ADR	CHD/BZD
23	F/10	Ewing's sarcoma	VCR/Ifosfamide/ADR/VP-16	BZD/CHD
24	F/8	AML	Ara-C/ADR/VP-16	BZD/CHD
25	M/16	Osteosarcoma	Cisplatin/ADR	BZD/CHD
26	M/7	ALL	VCR/ADR	CHD/BZD
27	M/5	ALL	VCR/ADR	CHD/BZD
28	M/16	ALL	VCR/ADR	BZD/CHD
29	M/13	Osteosarcoma	MTX	BZD/CHD
30	M/9	ALL	VCR/ADR	BZD/CHD
31	M/12	ALL	MTX	CHD/BZD
32	F/16	ALL	MTX	CHD/BZD
33	F/6	ALL	VCR/ADR	CHD/BZD
34	M/7	ALL	VCR/ADR	CHD/BZD
35	M/6	ALL	VCR/ADR	BZD/CHD
36	M/6	ALL	VCR/ADR	BZD/CHD
37[a]	M/12	Osteosarcoma	MTX	BZD/CHD
38[a]	F/14	CML	Ara-C/ADR/VP-16	CHD/BZD
39	M/12	ALL	VCR/ADR	CHD/BZD
40	M/9	ALL	MTX	BZD/CHD

ADR, doxorubicin; ALL, acute lymphoblastic leukaemia; AML, acute myeloblastic leukaemia; BZD, benzydamine; CHD, chlorhexidine; CML, chronic myeloblastic leukaemia; CPM, cyclophosphamide; DNR, daunorubicin; MTX, methotrexate; VCR, vincristine; VP-16, etoposide; M, male; F, female.

[a] Case excluded from sequential analysis.

Table 3. Malignancies and frequency of chemotherapy infusions affected with oral ulcers

	AML (n=5)	ALL (n=19)	Osteosarcoma (n=6)	Rhabdomyosarcoma (n=1)	Ewing's sarcoma (n=1)	Lymphoma (n=1)	Hepatocellular carcinoma (n=1)
No. of chemotherapy infusions	10	38	12	2	2	2	2
Frequency of chemotherapy infusions (%) affected with oral ulcers							
Chlorhexidine	2 (20)	4 (11)	2 (17)	0 (0)	1(50)	0(0)	0(0)