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# Effect of leaving chronic oral foci untreated on infectious complications during intensive chemotherapy

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**Background:** Leukaemic patients receiving intensive chemotherapy and patients undergoing autologous stem-cell transplantation (ASCT) are routinely screened for oral foci of infection to reduce infectious complications that could occur during therapy. In this prospective study we assessed the effect of leaving chronic oral foci of infection untreated on the development of infectious complications in intensively treated haematological patients.

**Methods:** We included and prospectively evaluated all intensively treated leukaemic patients and patients undergoing ASCT who were referred to our medical centre between September 2012 and May 2014, and who matched the inclusion/exclusion criteria. Acute oral foci of infection were removed before chemotherapy or ASCT, whereas chronic oral foci were left untreated.

**Results:** In total 28 leukaemic and 35 ASCT patients were included. Acute oral foci of infection were found in 2 leukaemic (7%) and 2 ASCT patients (6%), and chronic oral foci of infection in 24 leukaemic (86%) and 22 ASCT patients (63%). Positive blood cultures with microorganisms potentially originating from the oral cavity occurred in 7 patients during treatment, but were uneventful on development of infectious complications.

**Conclusions:** Our prospective study supports the hypothesis that chronic oral foci of infection can be left untreated as this does not increase infectious complications during intensive chemotherapy.

Patients diagnosed with acute myeloid leukaemia (AML), acute lymphoblastic leukaemia (ALL), multiple myeloma (MM), non-Hodgkin's lymphoma (NHL) or Hodgkin's lymphoma (HL) are usually treated with high-dose chemotherapy upfront or in a salvage setting. High-dose chemotherapy causes severe neutropenia (absolute neutrophil count <500 per  $\mu$ l) for a certain period of time, which puts patients at high risk of infections, sepsis and septic shock (Walsh, 2010). Patients undergoing high-dose chemotherapy are also prone to develop oral side effects such as

oral mucositis, oral dryness, taste changes, and local and systemic infections (Brennan *et al*, 2010). Both neutropenia and oral mucositis significantly increase the risk for infectious complications during chemotherapy in these patients.

Haematologic patients subjected to high-dose chemotherapy are routinely screened for oral foci of infection before starting intensive treatment, as oral foci of infection may cause complications during treatment. Acute exacerbation of oral foci of infection is presumed to result in bacterial translocation from the oral cavity to the blood.

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To minimise the risks of developing oral problems and to reduce the chance of developing neutropenic fever, oral foci of infection, which are anticipated to cause problems during chemotherapy, are routinely eliminated. In our hospital, a team of oral maxillofacial surgeons, hospital dentists and dental hygienists screen the patients for oral foci of infection before the onset of cancer therapy.

It is still unclear which specific oral disorders have to be considered as an oral focus of infection in high-dose chemotherapy patients, which is also the case in head and neck radiotherapy (Schuurhuis *et al*, 2015). Furthermore, the oral side effects of chemotherapy are essentially temporary and reversible, so the risk of developing complications due to oral foci of infection is not higher than in healthy subjects once patients have recovered from chemotherapy (Stokman *et al*, 2008). This is in contrast to head and neck radiotherapy, where the risk of oral foci of infection causing severe morbidity (like osteoradionecrosis) remains high or even increases after completion of radiotherapy (Vissink *et al*, 2003). Thus, the efficacy of dental screening for oral foci of infection in high-dose chemotherapy patients is questionable.

Moreover, leukaemic patients usually have to start chemotherapy shortly after diagnosis. Consequently, if oral foci of infection are found during pre-treatment dental screening, insufficient time is available for effective dental treatment before starting chemotherapy. The decreased healing capacity during the phase of untreated leukaemia is also a factor.

Following intensive chemotherapy, leukaemic patients are expected to experience severe neutropenia for at least 3 weeks, with episodes of neutropenic fever and relatively mild oral mucositis, whereas patients subjected to autologous stem-cell transplantation (ASCT) are expected to experience severe neutropenia for 1–2 weeks, but with a considerably higher chance of severe oral mucositis (Blijlevens *et al*, 2008). Both leukaemic patients and patients treated with high-dose chemotherapy followed by ASCT were included in this study, because the effects of an oral focus of infection and pre-chemotherapy dental treatment might be different due to the difference in duration of neutropenia and severity of oral mucositis between these groups.

Previous studies had mixed patient groups and/or a small number of patients (Toljanic *et al*, 1999; Melkos *et al*, 2003) or reported on the need for treatment of postendodontic asymptomatic periapical radiolucencies (Peters *et al*, 1993).

This prospective study tested the hypothesis that chronic oral foci of infection do not have to be eliminated before intensive chemotherapy in leukaemic patients subjected to intensive chemotherapy and MM/NHL/HL patients subjected to high-dose chemotherapy and ASCT. An oral focus of infection was considered chronic if that focus had not exacerbated during the previous 3 months.

## MATERIALS AND METHODS

**Patients.** All patients diagnosed with AML or ALL before remission-induction chemotherapy and patients diagnosed with NHL/HL or MM before high-dose chemotherapy and ASCT, who were referred to the University Medical Center Groningen between September 2012 and May 2014, and who met the inclusion criteria, were included in this study. The medical ethical committee of the University Medical Center of Groningen approved our study protocol (METC 2012/170). Patients with AML were treated with Cytarabine (Ara-C)-based chemotherapy combined with anthracycline. Patients with ALL were treated with intensive chemotherapy according to HOVON-100 and HOVON-71 study protocols (Daenen *et al*, 2012). The NHL/HL patients were treated with BEAM and ASCT (Holmberg and Maloney, 2011; Martin *et al*, 2015) and MM patients with high-dose melphalan ( $100 \text{ mg m}^{-2}$

on days  $-3$  and  $-2$ ) before ASCT (Engelhardt *et al*, 2014). BEAM is a combination of carmustine, etoposide, cytarabine and melphalan.

Patients were included in this study if a pre-chemotherapy/pre-ASCT dental screening was done in the UMCG, if they were fully or partially dentate and were  $>18$  years. Patients were excluded if they were not treated according to the study protocol on the treatment of acute and chronic oral foci.

**Dental screening.** Standard dental screening consisted of the following:

- Intra-oral screening for mucosal and dental pathologies.
- Panoramic radiograph and periapical dental radiographs when indicated, for example, when apical problems were suspected on the panoramic radiograph or other abnormalities were seen.
- Periodontal examination including probing pocket depth measurements, gingival recession, mobility and furcation measurements. Plaque and bleeding scores were assessed as a percentage of the total number of sites with plaque, respectively, bleeding on probing. To quantify periodontal disease, the periodontal inflamed surface area (PISA) was used (Nesse *et al*, 2008).
- Inquiry about oral health maintenance and the number of annual dental visits.

In addition, a baseline throat swab and subgingival samples were taken during the dental screening.

**Elimination of oral foci of infection.** Acute oral pathology and/or teeth causing pain or other symptoms were eliminated pre-chemotherapy, whereas chronic oral foci were not eliminated preceding the chemotherapy based on the study by Toljanic *et al* (1999).

**Data sampling before and during chemotherapy.** On the first day of hospitalisation and before the start of chemotherapy, throat and rectal swabs were collected. Subsequent throat and rectal swabs were taken weekly during hospitalisation (standard care). Haematology nurses daily checked the oral cavity for oral mucositis, according to the WHO mucositis grading scale (Sonis *et al*, 2004).

**Standard care during chemotherapy.** All included patients hospitalised for high-dose chemotherapy were given selective digestive decontamination (SDD) therapy consisting of oral amphotericin B or fluconazole, colistine, and/or trimethoprim/sulfamethoxazole or ciprofloxacin (Silvestri *et al*, 2007; Silvestri *et al*, 2009). During fever (body temperature  $\geq 38.5^\circ\text{C}$ ), irrespective of the neutropenic status of the patient, blood cultures and central line cultures were taken, and after which a piperacilline/tazobactam therapy was started. Radiography of the lungs was performed to exclude pneumonia. Urine cultures were taken. *Clostridium difficile* colitis was excluded. The patients were physically examined by the haematologist or internal medicine physician on a daily basis, and additional blood cultures were taken after 48–72 h of fever.

**Oral care and oral problems during chemotherapy.** All patients were advised to continue normal daily oral care (tooth brushing and/or interdental cleaning) as long as possible. In addition, or when brushing was too painful, patients were advised to rinse the oral cavity with saline solution four times per day and not to wear their removable prosthesis, if any, during chemotherapy courses.

ASCT patients were seen by the dental hygienist for oral examination three times per week during their hospital admission. Leukaemic patients were seen by the dental hygienist when oral complaints had developed.

If untreated, chronic oral foci of infection became acute during chemotherapy, or between chemotherapy courses, piperacilline/

tazobactam was given and appropriate dental treatment was rendered.

**Follow-up after treatment.** Patients were followed during the course of their haematologic treatment up until 6 weeks after treatment had ended. Patient charts were reviewed for oral problems during and after treatment. After treatment had ended, patients were seen weekly by the haematologist for check-ups at the outpatient haematology department.

**Microbiological sampling and analysis.** To determine the possible oral origin of microorganisms found in blood cultures, bacteriological samples were taken and compared with the results of blood cultures.

A throat swab of the tonsil area was taken according to the method described by Syed and Loesche (1972). Microbiological analysis of throat swabs was performed according to the standard procedures, and included detection of yeasts, *Staphylococcus aureus* and aerobic Gram-negative rods. Aerobic incubation took place for 48 h at 35 °C.

Periodontal (subgingival) samples were taken from the deepest, bleeding or suppurating pocket in each quadrant of the dentition. Two sterile paper points were inserted to the depth of the pockets, left in place for 10 s and were collected and pooled in 2 ml of reduced transport fluid (Syed and Loesche, 1972). Periodontal samples were processed using culturing technique as described by van Winkelhoff *et al* (1985) and van Steenberg *et al* (1993). Anaerobic cultivation was performed to determine the total periodontal bacterial load and presence and levels of *Aggregatibacter actinomycetemcomitans*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Tannerella forsythia*, *Fusobacterium nucleatum*, *Parvimonas micra* and *Campylobacter rectus*. If Gram-negative aerobic rods or staphylococci were found in positive blood cultures, periodontal samples were also analysed for the presence and levels of these microorganisms.

**Statistical analysis.** All data were recorded using a standardised study form designed for this study. A gap in a sequence of mucositis score values was filled with the same value given before and after a gap. In case of different values before and after a gap, the lowest value was imputed. Data were analysed using descriptive statistics in SPSS Statistics 22 (IBM Corp., Armonk, NY, USA). Testing for significance was done using  $\chi^2$  for binary outcomes (prevalence and presence) and Mann-Whitney tests for continuous outcomes. Values of  $P < 0.05$  were considered significant.

## RESULTS

**Demographics.** In total, 64 patients were included. Statistical analysis was done with 63 patients, as 1 patient with an acute oral focus was not treated according to the inclusion criteria. Demographics of patients before the onset of haematological treatment are shown in Table 1. In the leukaemic group, 28 patients were included, of which 23 were diagnosed with AML, 4 with ALL and 1 with CML blast crisis. In the ASCT group, 35 patients were included, of which 21 were diagnosed with MM, 13 with NHL and 1 with HL. There was no statistically significant difference between the groups regarding male/female ratio and age (Table 1).

During the 6 weeks of follow-up after haematologic treatment, 5 of 28 leukaemic patients died. This was due to refractory disease in 1 patient, recurrence of disease in 2 patients and toxicity of chemotherapy with subsequent complications in 2 patients, with no contribution of oral foci. None of the ASCT patients died before end of follow-up.

**Oral foci of infection.** Outcomes of dental screening are presented in Table 1. In the leukaemic group, 24 out of 28

**Table 1. Demographic characteristics of the included patients before haematological treatment**

	Leukaemic group Number of patients (% of group)	ASCT group Number of patients (% of group)
Male/female	16/12	20/15
Age mean (s.d.)	51 (12.4)	51 (10.1)
<b>Last visit to dentist</b>		
Last 6 months	19 (68)	19 (54)
Last year	3 (11)	7 (20)
> 1 years ago	3 (11)	6 (17)
Not reported	3 (11)	3 (9)
<b>Visit to dental hygienist</b>		
At least twice a year	6 (21)	8 (23)
Once a year	3 (11)	5 (14)
Never	18 (64)	21 (60)
Not reported	1 (4)	1 (3)
<b>Oral complaints<sup>a</sup></b>		
No complaints	21 (75)	28 (80)
Not reported	1 (4)	0 (0)
Currently	7 (25)	7 (20)
Last 3 months	10 (36)	9 (26)
<b>Dental status</b>		
Number of teeth	25 (mean); range 10–32	25 (mean); range 9–30
<b>Oral foci of infection total<sup>b</sup></b>		
No oral foci of infection	4 (14)	12 (34)
Acute oral foci of infection	2 (7)	2 (6)
Chronic oral foci of infection	24 (86)	22 (63)
<b>Acute oral foci of infection</b>		
Active pus-producing fistula	1 (4)	1 (3)
Symptomatic periapical granuloma	1 (4)	1 (3)
<b>Chronic oral foci of infection<sup>c</sup></b>		
Periodontal pockets $\geq 6$ mm	13 (46)	11 (31)
Periapical granuloma	10 (36)	10 (29)
Initial endodontic treatment	2 (7)	0 (0)
Furcation involvement	2 (7)	2 (6)
Retained roots	2 (7)	1 (3)
Fully or partially impacted teeth	3 (11)	3 (9)
Caries profunda	2 (7)	1 (3)
Follicular cyst	0 (0)	2 (6)
<b>Periodontal condition</b>		
Healthy periodontium	0 (0)	3 (9)
Periodontal pockets $\geq 4$ mm	27 (96)	32 (91)
Periodontal pockets $\geq 5$ mm	19 (68)	21 (60)
Periodontal pockets $\geq 6$ mm	13 (46)	11 (31)
Periodontal status not reported	1 (4)	0 (0)
PISA score in mm <sup>2</sup> (median, IQR) <sup>d</sup>	533 (199–834)	228 (135–478)
Plaque score (median, IQR) <sup>e,f</sup>	30% (19–50)	25% (20–50)
Bleeding score (median, IQR) <sup>e,g</sup>	45% (20–80)	20% (10–40)
Abbreviations: ASCT = autologous stem-cell transplantation; IQR = interquartile range. Owing to rounding of the percentages, total sums are not always exactly 100%.		
<sup>a</sup> Total sums up to >28 and >35 patients, because some patients had both oral complaints currently and during the last 3 months.		
<sup>b</sup> Total sums up to >28 and >35 patients, because some patients had both acute and chronic oral foci of infection.		
<sup>c</sup> Total sums up to >24 and >22 patients, because some patients had more than one type of chronic oral foci of infection.		
<sup>d</sup> The difference between the groups is significant ( $P = 0.024$ ) using a Mann-Whitney test.		
<sup>e</sup> Plaque and bleeding scores were given as an estimated percentage of the total number of measured sites, after probing periodontal pockets.		
<sup>f</sup> The difference between the groups is not significant ( $P = 0.56$ ) using a Mann-Whitney test.		
<sup>g</sup> The difference between the groups is significant ( $P = 0.005$ ) using a Mann-Whitney test.		

patients (86%) presented with chronic oral foci of infection. Amongst them were 2 patients who had both acute and chronic foci. In the ASCT group, 22 out of 35 patients (63%) presented with chronic oral foci of infection. One patient had both acute and

chronic oral foci. The specific acute and chronic oral foci types are presented in Table 1. Data on visits to the dentist and dental hygienist and data on oral hygiene are also presented in Table 1. The baseline median PISA and bleeding scores were significantly higher in the leukaemic group compared with the ASCT group ( $P = 0.024$  and  $0.005$ , respectively).

**Periodontal samples.** The majority of patients in this study had periodontal infection associated with opportunistic oral pathogens. *F. nucleatum*, *Pa. micra*, *Pr. intermedia*, *T. forsythia* and *C. rectus* were isolated in 79%, 71%, 32%, 31% and 24% of patients, respectively. Occasionally, *A. actinomycetemcomitans* (2%) and *P. gingivalis* (5%) were isolated. No significant differences were found between the leukaemic and the ASCT groups regarding the prevalence of periodontal pathogens. In our study cohort, no periodontal pathogens were cultured from any of the blood cultures (Table 2).

**Blood cultures of the leukaemic group.** Blood cultures were indicated because of neutropenic fever in all 28 leukaemic patients (100%). Twenty-five patients (89%) had a total of 57 positive blood cultures. The microorganisms found in the blood cultures are presented in Table 2.

**Blood cultures of the ASCT group.** Blood cultures were indicated because of neutropenic fever in 22 out of 35 ASCT patients (63%), which is significantly lower than in the leukaemic group ( $P = 0.0001$ ). Out of these 22 patients, 11 (50%) had 1 or more positive blood cultures (Table 2), which was significantly lower than in the leukaemic group (89%;  $P = 0.002$ ).

**Table 2. Microorganisms in positive blood cultures and their primary ecological niches, ordered by frequency of occurrence**

Microorganisms cultured from blood	Primary ecological niches <sup>a</sup>	Number of culture-positive subjects	
		Leukemic patients N = 25	ASCT patients N = 11
<i>Staphylococcus epidermidis</i>	S, M	17 (61%)	7 (20%)
<i>Staphylococcus haemolyticus</i>	S	8 (29%)	1 (3%)
<i>Enterococcus faecium</i>	I, S, O, E	7 (25%)	1 (3%)
<i>Streptococcus mitis</i>	M, O, I, V, S	4 (14%)	1 (3%)
<i>Micrococcus luteus</i>	S, E, O, OP	3 (11%)	0
<i>Staphylococcus hominis</i>	S	3 (11%)	0
<i>Bacillus mycoides</i>	E	0	1 (3%)
<i>Burkholderia</i> genus REC A	E, O	1 (4%)	0
<i>Lactobacillus rhamnosus</i>	O	1 (4%)	0
<i>Pantoea gavinae</i>	E	1 (4%)	0
<i>Rothia mucilaginos</i>	OP	1 (4%)	0
<i>Serratia marcescens</i>	S, I	1 (4%)	0
<i>Staphylococcus aureus</i>	S, N, T, P, O	0	1 (3%)
<i>Staphylococcus capitis</i>	S, O	1 (4%)	0
<i>Streptococcus parasanguinis</i>	M, I, V, S, O	1 (4%)	0

Abbreviations: ASCT = autologous stem-cell transplantation; E = environment (plants, animals, soil); I = intestines; M = mucosal tissues; N = nose; O = oral cavity; OP = oropharynx; P = perineum; S = skin; T = throat; V = vagina. More than one microorganism were cultured in some patients and some patients had more than one positive blood culture, so the total sums up to >25 leukaemic and >11 ASCT patients.

<sup>a</sup>The bold letters in this table indicate the microorganisms related to the oral cavity, oropharynx or throat.

**Chronic oral foci of infection related to various clinical parameters.** No significant differences were found between patients with chronic oral foci of infection ( $N = 46$ ) compared with patients without chronic oral foci of infection ( $N = 17$ ) regarding positive blood cultures ( $P = 0.798$ ), duration of neutropenia ( $P = 0.066$ ) or fever ( $P = 0.059$ ), duration of mild ( $P = 0.107$ ) or severe oral mucositis ( $P = 0.398$ ), and prevalence of mild ( $P = 0.273$ ) or severe oral mucositis ( $P = 0.510$ ). Moreover, no significant differences were found when performing a subgroup analysis (leukaemic and ASCT). No differences were found regarding duration of neutropenia and fever, between patients without chronic oral foci of infection at dental screening, patients with untreated chronic oral foci of infection and patients with treated acute oral foci of infection.

**Microorganisms found in blood culture possibly related to oral cavity.** In our study cohort, no periodontal pathogens were initially cultured from any of the positive blood cultures (Table 2). After specific culturing for Gram-negative aerobic rods and staphylococci, which was done if these microorganisms were found in positive blood cultures, one match was found between positive blood cultures and periodontal samples for *S. haemolyticus*. Microorganisms potentially originating from the oral cavity, oropharynx and/or throat were found in the blood cultures of seven patients; five leukaemic and two ASCT patients (indicated by bold letters in Table 2). These microorganisms were not periodontal pathogens and were not found in any of the throat swabs.

Table 3 shows that no possible contributing factors were found that differed significantly for the seven patients with positive blood cultures with microorganisms possibly related to the oral cavity, compared with the patients with positive blood cultures with microorganisms unrelated to the oral cavity ( $n = 29$ ). Furthermore, four of these seven patients had oral complications during chemotherapy unrelated to oral foci of infection (oral mucositis,  $N = 4$ ; herpes simplex virus,  $N = 1$ ; and pulpitis,  $N = 1$ ).

**Neutropenia, fever and oral mucositis.** A significantly higher prevalence of severe oral mucositis ( $P = 0.014$ ) was found amongst leukaemic patients (57%) compared with ASCT patients (26%). No oral mucositis was observed in 47% of the ASCT patients, which was significantly higher than in leukaemic patients (11%;  $P = 0.002$ ). No significant differences were found between leukaemic patients and ASCT patients regarding the duration ( $P = 0.890$ ) of severe oral mucositis. A median of 5 days was seen in both groups. There was no relation between the severity of mucositis and chronic oral foci of infection at baseline ( $P = 0.269$ ).

No significant differences were found between patients with positive blood cultures compared with patients with negative blood cultures regarding the duration ( $P = 0.648$ ) or prevalence of severe oral mucositis ( $P = 0.717$ ). However, patients with positive blood cultures had a significantly longer duration of mild oral mucositis than patients with negative blood cultures ( $P = 0.039$ ). Prevalence of mild oral mucositis was not significantly different between patients with positive or negative blood cultures ( $P = 0.700$ ).

**Periodontal health and positive blood cultures.** No significant differences were found between patients with positive blood cultures compared with patients with negative blood cultures regarding periodontal inflamed surface area as measured with PISA at baseline ( $P = 0.379$ ). In line with this observation, patients with positive blood cultures did not have significantly higher plaque and bleeding scores at baseline compared with patients with negative blood cultures ( $P = 0.338$  and  $P = 0.990$ , respectively).

**Oral complications during haematologic treatment.** During haematologic treatment, oral complications other than oral mucositis were seen ( $N = 15$ ; 24%; nine leukaemic and six ASCT patients). The prevalence of exacerbation of chronic oral foci during haematologic treatment was 4% in this study. One AML

**Table 3.** Comparison between patients with positive blood cultures with microorganisms possibly related to the oral cavity and patients with positive blood cultures with microorganisms unrelated to the oral cavity

Variables	Patients with microorganisms related to the oral cavity (total N = 7)	Patients with microorganisms unrelated to the oral cavity (total N = 29)	P-value
Baseline presence of acute oral foci of infection	0	3	0.374 <sup>a</sup>
Baseline presence of chronic oral foci of infection	6	21	0.466 <sup>a</sup>
Baseline presence of periodontal pockets $\geq 6$ mm	2	12	0.533 <sup>a</sup>
Baseline presence of periapical granuloma	5	11	0.109 <sup>a</sup>
Baseline presence of caries profunda	1	2	0.526 <sup>a</sup>
Baseline presence of impacted teeth	2	4	0.346 <sup>a</sup>
Smoking, yes/no	1/6	7 <sup>b</sup> /21	0.546 <sup>a</sup>
	<b>Median (IQR)</b>	<b>Median (IQR)</b>	<b>P-value</b>
Duration of neutropenia in days	11 (7–41)	23 (8–46)	0.531
Duration of fever in days	9 (4–24)	9 (4.5–15)	0.969
Duration of severe oral mucositis in days in 17 patients with severe oral mucositis	3.5 (1.25–8), N = 4	5 (2.5–9.5), N = 13	0.477
PISA score in mm <sup>2</sup>	419.5 (94.5–1025) <sup>c</sup>	412 (142–650.75) <sup>b</sup>	1.0
Plaque scores in %	25 (10–57.5) <sup>c</sup>	30 (20–50) <sup>b</sup>	0.494
Bleeding scores in %	30 (7.5–76.25) <sup>c</sup>	30 (20–50) <sup>b</sup>	0.612
Age in years	49 (28–62)	50 (44–60)	0.969

Abbreviations: IQR = interquartile range; PISA = periodontal inflamed surface area.  
<sup>a</sup>Results  $\chi^2$  tests. All other variables were tested using Mann–Whitney tests.  
<sup>b</sup>Because of missing value, N = 28.  
<sup>c</sup>Because of missing value, N = 6.

patient with an acute exacerbation of an asymptomatic periapical granuloma present at baseline and one ASCT patient with an acute exacerbation of pre-existent gingivitis, which were both uneventful. Oral complications not related to chronic oral foci of infection observed were oral pain ( $N=3$ ), oral herpes simplex infection ( $N=5$ ), peri-oral herpes simplex ( $N=3$ ), mandibular swelling ( $N=1$ ) and oral candidiasis ( $N=1$ ). No significant differences were found between patients with oral complications ( $N=15$ ) and patients without oral complications ( $N=48$ ) regarding presence of acute ( $P=0.954$ ) or chronic oral foci of infection ( $P=0.197$ ), periodontal disease (pockets  $\geq 6$  mm;  $P=0.437$ ), PISA score ( $P=0.474$ ), smoking ( $P=0.102$ ), plaque scores ( $P=0.941$ ), bleeding scores ( $P=0.456$ ), age ( $P=0.127$ ), positive blood cultures ( $P=0.453$ ), or a significantly different duration of neutropenia ( $P=0.398$ ), fever ( $P=0.278$ ) or severe oral mucositis ( $P=0.214$ ).

## DISCUSSION

The results of this prospective study show that leaving chronic oral foci of infection untreated before intensive chemotherapy and ASCT (and during neutropenia with or without oral mucositis) does not increase the morbidity of the cancer treatment, in particular regarding infectious complications such as bacterial sepsis, nor does it increase mortality.

A significantly longer median duration of neutropenia, significantly more positive blood cultures and significantly more severe oral mucositis were found in leukaemic patients compared with ASCT patients. This might explain why more leukaemic patients (18%) had positive blood cultures with microorganisms possibly related to the oral cavity than ASCT patients (6%). However, positive blood cultures were not associated with a specific microorganism present in the oral cavity and the

gastrointestinal tract as assessed with cultures from periodontal samples, throat and rectal swabs.

**Comparison with previous studies.** Neutropenic fever was seen in all leukaemic patients, which corresponds with literature reporting neutropenic fever seen in 85–97% of neutropenic episodes (Hamalainen *et al*, 2008; De Rosa *et al*, 2013). In our study, neutropenic fever was seen less frequently in ASCT patients (63%), which was expected based on previous studies (39–84%) (Blanes *et al*, 2013; Musso *et al*, 2015; Zhang *et al*, 2015). Positive blood cultures were found in 89% of leukaemic and 50% of ASCT patients in our study, which is high compared with data from the literature (Hamalainen *et al*, 2008; McCann *et al*, 2009; Eleutherakis-Papaikovou *et al*, 2010; De Rosa *et al*, 2013). However, comparing our data with that from previous studies is difficult due to varying patient groups and inconsistencies in reporting.

Instead of systemic complications of chronic oral foci, local complications, such as interchemotherapy acute conversions of previously diagnosed chronic dental disease, were assessed by Toljanic *et al* (1999). An incidence rate of 4% was reported, which is comparable to our data. However, both haematologic and solid malignant neoplasms were included in Toljanic's study, which hampers comparison, and, more importantly, no information was provided on blood cultures.

Bacteraemia was predominately caused by Gram-positive bacteria in our study. In line with our results, previous studies described a shift in time from the predominance of Gram-negative bacteria to the predominance of Gram-positive bacteria (Horasan *et al*, 2011). *S. epidermidis* was most often found in our positive blood cultures (Table 2). This microorganism is a common cause of bacteraemia and is associated with central venous catheters, which were used in all of our patients (David *et al*, 2005). In accordance with the studies by Sonis *et al* (2001) and McCann *et al* (2009), we found that patients with oral mucositis had a

significantly longer duration of neutropenia and fever than patients without oral mucositis. The first prospective study with oral mucositis as the main objective showed severe oral mucositis in 46% of MM patients and 42% of NHL patients (Blijlevens *et al*, 2008). The lower percentage of severe oral mucositis among ASCT patients in our study (26%) might be due to the fact that MM patients receiving high-dose melphalan ( $n = 21$ ) were given ice cubes in the mouth (cryotherapy) during chemotherapy infusion, as advised by the guidelines of MASCC/ISOO (Lalla *et al*, 2014) and in other reviews (Worthington *et al*, 2011; Wang *et al*, 2015).

Microorganisms potentially originating from the oral cavity, oropharynx and throat were found in the blood cultures of just seven patients (Table 2). We expected the number of oral microorganisms found in blood cultures to be higher, as even tooth brushing, a seemingly harmless daily activity, can cause bacteraemia with oral microorganisms (Lockhart *et al*, 2008). Especially in immunocompromised patients, as in our study, bacteraemia is expected to occur more often and to last longer, increasing the chances of detecting the causative microorganism by blood culturing. The patients in our study with oral mucositis hardly brushed, but frequently rinsed the oral cavity, which could explain the lower frequency of bacteraemia, together with the use of SDD.

**Implications.** The outcomes of our study indicate that chronic oral foci of infection without acute signs or symptoms can be left untreated in patients receiving ASCT and/or intensive chemotherapy. This allows for a less aggressive approach with no removal of chronic oral foci of infection before starting chemotherapy. Such an approach is likely to be beneficial for haematologic patients, as removal of teeth may compromise nutrition, and malnutrition is associated with lower quality of life (Jager-Wittenaar *et al*, 2011). Tooth extraction also leads to a risk for infection, bleeding or delayed wound healing, which may require postponing oncologic treatment (Yamagata *et al*, 2006), or otherwise increase bacteraemia with a higher chance of septic complications. For survivors, treatment of diseased teeth can be postponed until oncologic treatment is completed. Moreover, pre-chemotherapy dental workup will be less time consuming when only acute oral foci of infection, seen in <10% of our patients, have to be treated instead of all the chronic oral foci seen in over 70% of our patients.

**Suggestions for additional research.** Future prospective studies with larger patient groups are needed, to see if leaving chronic oral foci untreated may lead to a significantly longer duration of fever and neutropenia, as our results showed a strong trend when comparing duration of neutropenia ( $P = 0.066$ ) and fever ( $P = 0.059$ ) in patients with and without chronic oral foci of infection. Future study methods should enable comparison between studies, as sample size calculation showed that over 4000 patients will be needed to find a significant difference between patients with and without chronic oral foci of infection, regarding positive blood cultures (respectively, 73% and 69% of those patients had positive blood cultures in our study). The cost-effectiveness of this less aggressive approach should be studied, and the improvement in quality of life may be confirmed in future studies.

In conclusion, our prospective study supports the hypothesis that chronic oral foci, if they had not exacerbated during the previous 3 months, do not have to be eliminated before intensive chemotherapy, as they do not increase infectious complications in these patients.

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## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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