Oral Oncol, Eur J Cancer, Vol. 28B, No. 2, pp. 103–107, 1992
Printed In Great Britain

0964–1955/92 $5.00+0.00
Pergamon Press Ltd

# Oral Infection as a Reason for Febrile Episodes in Lymphoma Patients Receiving Cytostatic Drugs

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**56 patients receiving chemotherapy for non-Hodgkin lymphoma or Hodgkin's disease with curative intent were monitored for up to one year after initiation of treatment. During chemotherapy (mean duration 5.2 months), 26 of the patients (46%) suffered from 38 febrile episodes. In only 16 instances was an extraoral cause for the septicaemia found. However, severe dental infection, reflected in an elevated radiological index for the jaws, was found more frequently in patients suffering febrile episodes than in those without ($P = 0.02$). Moderate to severe gingival inflammation was observed during 22 (58%) of episodes. During 71% of the episodes various pathological findings were also recorded in the oral mucosa. No source of infection other than an oral one was found in 42% of the patients. Our results emphasise the importance of oral foci as the possible infection source in patients receiving intensive chemotherapy.**

*Oral Oncol, Eur J Cancer*, Vol. 28B, No. 2, pp. 103–107, 1992.

## INTRODUCTION

THE OUTCOMES of therapy of non-Hodgkin lymphoma and Hodgkin's disease have improved over the past few years. Intensive combination chemotherapy has resulted in response rates of up to 75–90%, depending on stage and histological type of the disease [1]. However, septicaemia remains a major cause of death in such patients [2, 3]. Administration of cytotoxic drugs compromises bone marrow function. There is often concomitant ulceration of the mucous membranes [4–6]. Injured skin or mucosa form ineffective barriers to invasion of the blood by viruses, bacteria and fungi [4, 7]. Cell-mediated immunity is also impaired in patients with lymphoid malignancies, and is further compromised by chemotherapy [2, 8].

Infection has been found to originate in orodental tissue in immunocompromised patients [3, 9–11]. Bergmann found oral foci in 10.5% of cases of septicaemia [3]. In 31.1% of cases an oral focus of infection was probable or possible [3]. Apart from oromucosal ulceration, chronic dental foci of infection can also predispose to septicaemia in immunocompromised patients. It has been shown, for example, that approximately one third of patients require dental treatment before bone marrow transplantation [12]. Careful attention also needs to be paid to the existence of periodontal pockets of infection [5, 13]. Microbes in supragingival plaque are usually aerobic, in the subgingival plaque anaerobic and Gram-negative [11, 13]. Septicaemia in patients receiving cytostatic drugs is often related to Gram-negative bacteria [14, 15]. Granulocytopenia and thrombocytopenia increase the risk of infection. The risk becomes greatest when the white blood cell count (WBC) falls below $1.0 \times 10^9$/l [2, 7, 13, 16, 17].

The aim of the study described here was to determine whether or not there was a relationship between the existence of orodental foci and episodes of fever in patients undergoing cancer treatment. The incidence of pathological findings in oral mucosa and the gingival bleeding index (GBI), a measure of gingival inflammation, were also studied during febrile episodes.

## PATIENTS AND METHODS

*Patients and inclusion criteria*

63 consecutive patients with non-Hodgkin lymphoma and 16 with Hodgkin's disease admitted to the Department of Radiotherapy and Oncology of Helsinki University Central Hospital, Finland, between 1987 and 1989 were enrolled in a 12 month study. The inclusion criteria were a histologically confirmed diagnosis of Hodgkin's disease or non-Hodgkin lymphoma, treatment with combination chemotherapy with curative intent, patient life-expectacy of at least 1 year, no other concomitant disease, and no medication other than that prescribed as cancer chemotherapy. Table 1 shows basic data relating to 56 patients monitored for up to 12 months. 23 patients were excluded for various reasons (Table 2).

The criteria for fever were three oral temperature measurements exceeding 38°C during a 24-hour period, or a single oral temperature measurement of 38.5°C or over [2, 9].

*Informed consent*

During an initial appointment, each patient was informed in detail about the study and asked to sign a consent form

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Received 11 May 1992; accepted 2 June 1992.

*Table 1. Characteristics of 79 patients with Hodgkin's disease or non-Hodgkin lymphoma*

| | Completed study ($n=56$) | | Did not complete study ($n=23$) |
|---|---|---|---|
| | Patients with fever | Patients without fever | |
| Mean age (years) | 51.9 | 44.6 | 52.1 |
| Range (years) | 32.3–81.0 | 22.5–69.0 | 19.1–66.3 |
| Sex (M/F) | 14/12 | 19/11 | 8/15 |
| Non-Hodgkin lymphoma ($n$) | 23 | 22 | 18 |
| Hodgkin's disease ($n$) | 3 | 8 | 5 |
| Smokers (%) | 30.8 | 30.0 | 40.0 |

*Table 2. Reasons for drop-out (no. of patients)*

| | |
|---|---|
| Death | 1 |
| Too ill to participate | 3 |
| Lack of motivation | 13 |
| Moved away from Helsinki | 4 |
| Received radiotherapy during febrile episode | 2 |
| Total | 23 |

approved by the Ethical Committee of the Department. The ethical guidelines or the Declaration of Helsinki in its revised form were followed throughout the study [18].

*Cancer chemotherapy*

The patients were receiving for Hodgkin's disease combinations of doxorubicin–bleomycin–vinblastine–dacarbazine (ABVD) or mechlorethamine–vincristine–procarbazine–prednisone/doxorubicin–bleomycin–vinblastine (MOPP/ABV) hybrid chemotherapy. For non-Hodgkin's lymphoma, combinations of methotrexate–bleomycin–doxorubicin or epirubicin–cyclophosphamide–vincristine–dexamethasone (M-BACOD or M-BECOD) was given. MOPP/ABV was given at intervals of 1 month for 6 months, ABVD at intervals of 2 weeks for 6 months, and M-BACOD or M-BECOD for 3-week intervals for 7 months.

*Clinical records and criteria of assessment of severity of oral findings*

The orodental status of patients was recorded in a standard dental surgery at the hospital. Dental and periodontal conditions, and the oral cavity were examined as recommended by the WHO [19, 20]. The decayed, missing, filled tooth-surface index (DMFS) was used in relation to dental records and the gingival bleeding index (GBI) in relation to periodontal records [21]. A GBI of 15% or more was considered to represent moderate to severe gingivitis.

Pathological findings in the oral mucosa were photographed. All intraoral areas exhibiting inflammation or ulceration were considered to indicate infection [9]. Haemorrhage, desquamation, angular cheilitis, acute candidiasis and herpes infection were defined using generally accepted criteria [6, 9]. All clinical examinations were carried out by the same oral surgeon (P.L.). After examination at the start of the study each patient was monitored clinically 2, 4 and 6 weeks, and 2, 4, 6 and 12 months after the onset of the treatment.

Salivary yeast counts were determined by incubating stimulated saliva samples in Oricult-N™ dip-slides (Orion Diagnostica, Espoo, Finland). Counts exceeding 20 colonies per plate were considered high.

A panoramic tomogram (Orthopantomograph OP 3, Palomex/Instrumentarium, Helsinki, Finland) was obtained for each patient during the first appointment. The orthopantomographic index (OPTGI) was used to characterise the severity of dental infection [22, 23]. The index is the arithmetic sum of the number of periapical lesions, vertical bone pockets, radiolucent lesions in furcation areas, and semiretained or embedded teeth with abnormally large pericoronal spaces. An OPTGI of five was taken to represent the limit of risk of severe dental infection [22, 23].

Patients were asked to keep diaries and note in them comments about their oral health.

*Other laboratory test*

Blood samples were taken for culture of aerobic and anaerobic micro-organisms and monitoring of cell counts, in accordance with the treatment protocols of patients, in the Department of Radiotherapy and Oncology. Urine, throat and stool specimens were sent for culture when this was considered necessary by the oncologist. Upper respiratory tract infections and pneumonia were diagnosed on the basis of chest X-rays. Acute gastroenteritis was diagnosed if diarrhoea occurred.

*Statistical methods*

The non-parametric Wilcoxon's signed-rank test was used to compare dental indices in cases with and without febrile episodes. Proportions in subgroups of patients were compared using the $\chi^2$ test with Yates' correction, or the Fisher exact text.

## RESULTS

*Febrile episodes during cancer treatment*

26 of the 56 patients (46%) experienced 38 febrile episodes during chemotherapy (mean duration 5.2 months). Of these 26 patients, 23/45 (51%) had non-Hodgkin lymphoma and 3/11 (27%) Hodgkin's disease. The difference in incidence of febrile episodes between the two groups was statistically significant ($P<0.001$). There was no statistically significant difference between men and women ($P=0.13$). 16 of the 26 patients (62%) experienced only one episode of fever. 8 patients (30%) experienced two episodes and 2 patients (81) three episodes of fever.

During the first 2 months of cancer treatment, there were 22 febrile episodes. The incidence of febrile episodes was highest 4 months after the start of chemotherapy. During the final 6 months follow up only two febrile episodes were recorded, both related to pneumonia diagnosed 1 year after the beginning of cancer treatment (Fig. 1).

Blood was cultured 13 times during the 38 febrile episodes. *Streptococcus pneumoniae* was identified once. All other cultures were negative. One *Staphylococcus aureus* and one herpes simplex virus infection were diagnosed following nasopharyngeal cultures.

A broad-spectrum combination of antibiotic drugs was administered in 27 febrile episodes. In six episodes one antibiotic drug was used (Table 3). A systemic antifungal agent and broad-spectrum antimicrobial drugs were used three times. A topical fungicide was prescribed once. Acyclovir was used against herpes twice. During three febrile periods no antimicrobial medication was given.

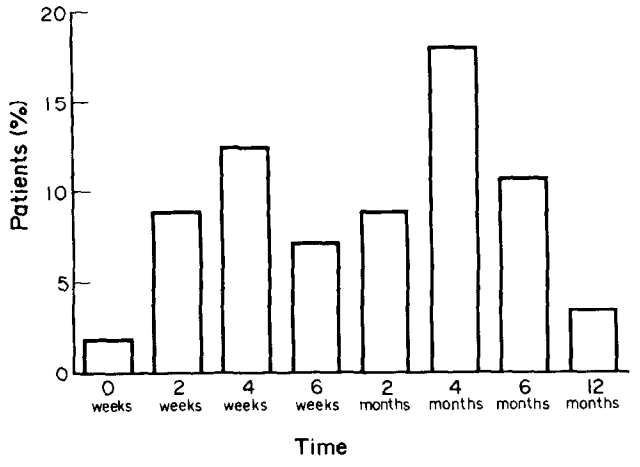


**Fig. 1. Percentages of patients with febrile episodes during the study.**

WBC was below $4.0 \times 10^9$/l in 87% of febrile episodes, and below $1.0 \times 10^9$/l in 11% of febrile episodes. The nadir value of the neutrophil count decreased below the risk level (<500/mm$^3$) in 21% of the febrile episodes. The platelet count fell below $100 \times 10^9$/l only once during the episodes.

*Causes of infection*

A total of 58 foci of infection were identified during the 38 febrile episodes. In 6 episodes (16%), the cause was obviously extraoral (skin infection, upper respiratory tract infection, chemotherapy-related). In 27 febrile episodes (71%), an acute oromucosal lesion was recorded. This finding was the only clinically identifiable cause of infection in 42% of cases. The patients' diaries indicated a higher incidence of labial and oral vesicles than that observed during their visits to the dental surgery. The frequency of the various types of acute oromucosal and other infections is shown in Table 4. No clinically identifiable cause of infection was detected in 13% of febrile episodes.

5 patients died 6–12 months after initiation of chemotherapy. These patients, who all had a non-Hodgkin lymphoma, suffered six febrile episodes. Pneumonia, Candida-superinfection together with infection caused by *Pneumocystis carinii*, and infection in relation to which blood culture results were negative were the causes of death in 3 cases. 2 patients died during aggressive re-induction chemotherapy. The patient in relation to whom blood culture results were negative and no focus of infection was found, had a GBI of 100%, and salivary yeast colonies exceeded 50 per plate.

*Oral infection sites and number of febrile episodes*

The mean OPTG score was 4.3 in patients with febrile episodes as compared with 3.2 in cases without febrile episodes. Severe dental infection reflected by an OPTGI of 5 or more was found in 15 out of 26 patients with febrile episodes but in only 7 out of 30 patients without febrile episodes. The

*Table 4. Occurrence of acute oral and other foci of infection during 38 febrile episodes*

| | *n* | % |
|---|---|---|
| Acute gingivitis | 21 | 50.0 |
| Acute oral candidiasis | 11 | 26.2 |
| Oromucosal ulcer | 5 | 11.9 |
| Mucositis | 4 | 9.5 |
| Herpes labialis | 1 | 2.4 |
| Total | 42 | 100.0 |
| Acute skin infection | 7 | 43.7 |
| Fever caused by administration of cytostatic drug | 4 | 25.0 |
| Upper respiratory tract infection | 4 | 25.0 |
| Candida superinfection | 1 | 6.3 |
| Total | 16 | 100.0 |

*Table 3. Antibiotic drugs during fever and occurrence of foci during antibiotic therapy*

| Antibiotic combinations | No. of episodes | No. of foci | | | |
|---|---|---|---|---|---|
| | | Oral | Other | Both | No |
| Cefotaxime /ofloxacin | 4 | 2 | | 2 | |
| /tobramycin | 5 | 2 | 1 | 1 | 1 |
| /ciprofloxacin | 2 | 1 | | | 1 |
| /imipenem | 1 | 1 | | | |
| /trimethoprim–sulphamethoxazole | 1 | 1 | | | |
| /vancomycin | 1 | | 1 | | |
| /ofloxacin /tobramycin | 5 | 3 | | 2 | |
| /metronidazole/tobramycin | 1 | | | 1 | |
| /vancomycin /tobramycin | 1 | 1 | | | |
| Ciprofloxacin/metronidazole | 1 | 1 | | | |
| /phenoxymethylpenicillin | 1 | 1 | | | |
| Netilmicin /carpenicillin | 1 | | | 1 | |
| Trimethoprim–sulphamethoxazole /rifampin | 2 | 2 | | | |
| /clindamycin/tobramycin | 1 | | | 1 | |
| Erythromycin | 3 | 2 | | 1 | |
| Ofloxacin | 1 | 1 | | | |
| Trimethoprim–sulphamethoxazole | 1 | | | 1 | |
| Netilmicin | 1 | | | | 1 |
| Total | 33 | 18 | 2 | 10 | 3 |

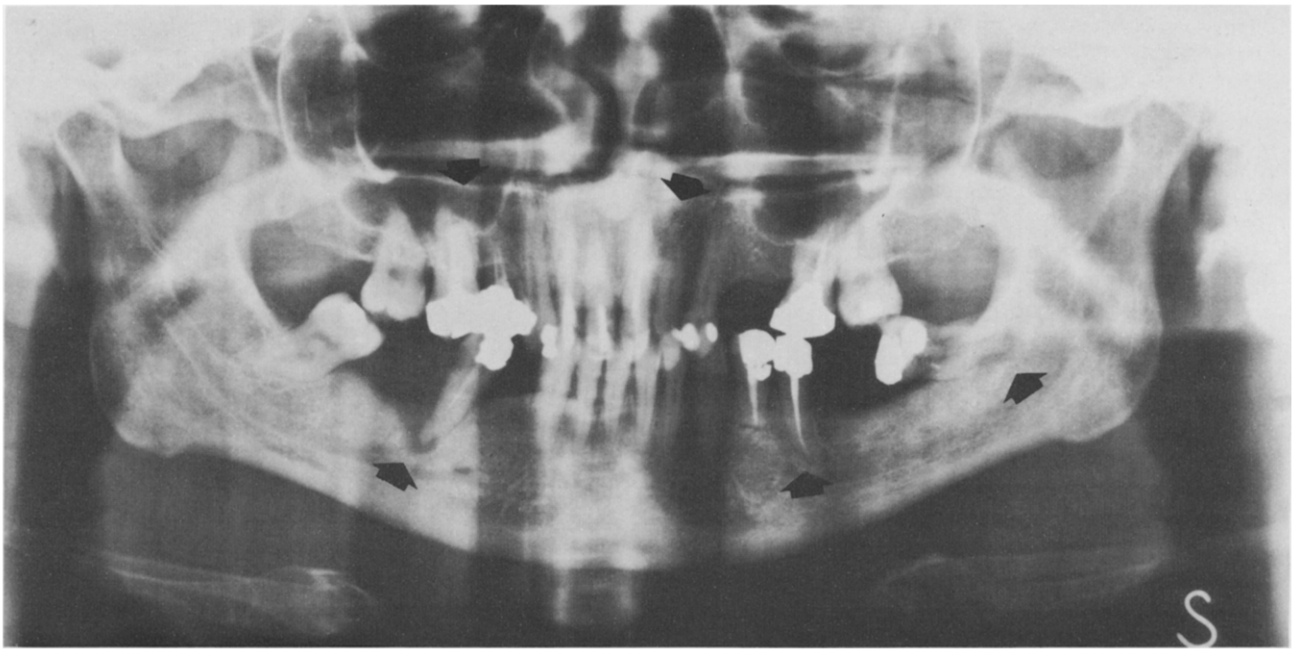

**Fig. 2. A 42-year-old woman with non-Hodgkin lymphoma. Orthopantomogram shows several periapical foci of infection (arrows) and deep periodontal pockets. The OPTGI of the patient was 8. The patient experienced septicaemia 8 weeks after initiation of cancer chemotherapy. The GBI was 100, reflecting her severe gingival bleeding.**

difference is statistically significant ($P=0.02$). More furcation lesions, bone pockets and semiretained teeth were observed in patients with febrile episodes than in those without. There were no statistically significant differences between the two groups in relation to scores for periapical lesions, severe caries lesions or embedded teeth. DMFS scores increased only slightly during the study. An example relating to a patient with severe dental foci of infection is shown in Fig. 2.

*Candida and gingival health*

Oral candidiasis was observed twice. The number of colonies in salivary Candida cultures exceeded 20 colonies per plate during 11 febrile episodes (29%). Moderate to severe gingivitis was found during 22 (58%) of the episodes. A GBI over 5% was found during 81% of periods of fever.

## DISCUSSION

Infection is a major problem in patients undergoing treatment with cytostatic drugs. The predominant cause of death is septicaemia as a result of immunosuppression [2, 3]. During febrile episodes, 40–69% of patients receiving cytostatic treatment were found to have granulocytopenia [1, 24].

In the study reported here, the incidence of leukocytopenia was 87%. A neutrophil count below 500 was observed during 21% of febrile episodes. The micro-organism causing septicaemia and the origin of the septicaemia are often difficult to determine. In our patients, a skin or upper respiratory tract infection was diagnosed during 29% of febrile episodes. However, mild to moderate gingivitis occurred during 58% of febrile episodes and severe gingivitis during 33%. Pathological findings in the oral mucosal membranes were observed during 71% of febrile episodes. Radiological signs of severe dental infection, reflected by an increased OPTGI, were seen significantly more often in cases with febrile episodes than in those without. Higher numbers of vertical periodontal bone pockets, furcation lesions and semiretained teeth were also found in patients with fever. Although the scores for periapical osteitis and severe caries lesions differed less between the groups with and without febrile episodes, such lesions were observed in many patients and could cause systemic infection.

Although no direct microbiological evidence was shown, our results demonstrate the relationship between the orodental tissue infection and fever in lymphoma patients undergoing cytostatic treatment. There is, however, obviously, a risk of infection spreading to the bloodstream from infected mucosal membranes and gingival and intraosseous tissues. The micro-organism causing an acute oral lesion is difficult to determine because the result of culture may reflect microbial colonisation in the oral cavity rather than the organism causing septicaemia. Dental infections are usually chronic, and low-grade, but it has been shown that even chewing and toothbrushing can induce transient bacteraemia, in particular if oral hygiene is poor [25, 26]. We did not culture oral microbial specimens, except for yeasts, because experience in our department shows that results of concomitant blood cultures mostly do not correlate with results of culture of oral microbial specimens. The aim of the study reported here was in any case not to investigate the bacteriology of the febrile episodes but instead to study the possible sites of infection in the oral cavity.

Our findings indicate that careful attention should be paid to the teeth, periodontal tissues and oral mucosal membranes in cancer patients receiving chemotherapy. Panoramic X-rays should be taken to identify chronic foci of infection (especially furcation lesions, bone pockets, semiretained teeth), which should then be dealt with before cancer treatment.

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