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Chemotherapy-associated Oral Mucosal Lesions in Patients with Leukaemia or Lymphoma

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In order to determine the incidence rate of oral lesions associated with chemotherapy, as well as its association with clinical and laboratory parameters and potential risk factors, 50 in-patients with non-Hodgkin's lymphoma or leukaemia under chemotherapy were followed from January 1993 to May 1994. Basal and weekly oral examinations were performed. Clinical and laboratory data were registered. Wilcoxon's rank sum test, chi square test, univariate and multivariate logistic regression analyses were used. 36 individuals with leukaemia and 14 with non-Hodgkin's lymphoma were followed for 158 weeks; mean age was 33 years (range 15–85). Oral lesion incidence rate was 45/100 patients-week. Exfoliative cheilitis and infections (herpes and candidosis) were the most common oral complications, followed by haemorrhagic lesions and mucositis. Haemorrhagic lesions correlated with thrombocytopenia (RR = 30.5). Etoposide administration (RR = 8.6), alkylating agents (RR = 15.6), a prior course of chemotherapy (RR = 23.2) and neutropenia (RR = 4.16) were predictors of mucositis. Oral lesions were a common complication in this study, and a possible association of mucositis with several factors is suggested.

Key words: oral complications, mucositis, oral infection, leukaemia, lymphoma, etoposide, alkylating agent

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INTRODUCTION

Oral lesions are a common complication in patients with cancer receiving chemotherapy [1–5]. These events are probably the result of the direct effect of cytotoxic drugs in the rapidly dividing oral epithelium and are manifested by thinning and ulceration of the mucosa. They may be indirectly due to chemotherapy-induced myelosuppression [3] seen as oral bleeding and local infections [3, 6]. These treatment-associated oral complications, particularly mucositis, may produce severe discomfort and pain which interfere with oral feeding, delays or dosage limitations of antineoplastic treatment, and in some patients life-threatening septicaemia [1, 6].

The aim of the present study was to establish the incidence rate of oral lesions in a group of patients with diagnosis of non-Hodgkin's lymphoma or leukaemia receiving chemotherapy at the Instituto Nacional de Cancerologia (INCan) in Mexico City, a national referral centre for adult patients with cancer. We also attempted to determine the association between the incidence rate of oral lesions and clinical and laboratory parameters, as well as the potential risk factors for its development.

MATERIALS AND METHODS

From January 1993 to May 1994, hospitalised, non HIV-infected patients with a diagnosis of non-Hodgkin's lymphoma or acute or chronic leukaemia treated with chemotherapy for the first time or consecutively were included in this study. A baseline oral examination was practiced on every patient before the administration of chemotherapy. Subsequent examinations were performed every week until the patient was discharged, for a maximum of 8 weeks. This examination included a systematic oral examination, a blood cell count, serum albumin and creatinine determinations. Each oral examination was considered an obser-

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vation. Established clinical definitions for oral lesions [7] were followed and the examiner's criteria were standardised.

The assessment of mucositis was qualitative, it was based on the clinical appearance and oral symptoms described in Table 1 [8], without grading it. In order to confirm mucositis, candidal and herpetic infections were excluded. The diagnosis of oral candidosis (angular cheilitis, erythematous and pseudomembranous types) was established when *Candida* hyphae were observed in smears fixed with alcohol and stained with the periodic acid Schiff (PAS) method [9]. The diagnosis of herpetic lesions was confirmed when there were nuclear inclusion bodies in the epithelial cells, observed on smears fixed with alcohol and stained with the Papanicolaou method [10]. The criteria for the diagnosis of oral bacteria infection were based on clinical features [1–3], when candidal or herpetic infections were ruled out. The clinical diagnosis of oral bacterial infection was confirmed by positive haemoculture. Xerostomia was assessed objectively, by rubbing the oral mucosa with a tongue blade, if the tongue blade adhered to the mucosa, xerostomia was considered present.

Patients were instructed to maintain oral hygiene practices or upgrade them if necessary, and to perform a mouthwash with a solution of water and sodium bicarbonate every 4 h. The simplified oral hygiene index [11] was used for scoring the dental plaque at baseline. Two categories of hygiene were considered in the statistical analysis: patients with simplified oral hygiene index score of less than 1.0 comprised the good hygiene category and those who scored $\geqslant 1.0$ were included in the moderate to poor hygiene category.

During follow-up, any mucosal change, including number, size, location and date of detection of new oral lesions, was collected and photographed, and clinical and laboratory data were registered. Systemic infection was evaluated by the Haematology and Infectious Diseases Departments [12]. Fever, defined as temperature equal to or greater than 38°C, was recorded if there was at least one episode during the week previous to the observation. The use of antimicrobials was noted if they had been administered within 3 days of the oral examination.

The chemotherapy regimen, dosage, and schedule were registered; initial chemotherapy was defined as the first course of chemotherapy in a previously untreated patient. Consecutive chemotherapy was defined as the ensuing chemotherapy in a patient who had already received it with a minimum of 1 month elapsed after the previous administration of the antineoplastic drug. We considered oral lesions to be the effect of chemotherapy if they occurred during the 3 weeks following its administration.

Table 1. Criteria used to record clinical appearance and symptomatology of mucositis

Clinical appearance	Symptoms
Erythema	None
White patches or pseudomembrane	Minimum discomfort or burning
1 or 2 ulcers <1 cm	Moderate pain but able to eat
More than 2 ulcers <1 cm	Severe pain, unable to eat
1 or 2 ulcers >1 cm	
More than 2 ulcers $\geqslant 1$ cm	

In order to simplify analysis, antineoplastic drugs were classified as alkylating agents (cyclophosphamide, ifosfamide, busulfan and chlorambucil), antibiotics (doxorubicin, daunorubicin, idarubicin and mitoxanthrone) and antimetabolites (6-mercaptopurine, cytosine arabinoside, fludarabine and methotrexate). Etoposide, vincristine, L-asparaginase, prednisone and hydroxyurea were analysed individually.

The frequency of oral lesions was expressed as the incidence rate/100 patients-week. The incidence rate expresses the frequency of oral lesion onsets divided by the sum of the time periods of observation for all individuals studied [13]. The denominator of the incidence rate is often referred to as 'person-time', its dimensionality is time. The formula proposed by Rothman [14], was utilized for the comparison of the incidence rate of oral lesions as rate ratio and 95% confidence interval.

Clinical and laboratory features were compared between those observations with and without a specific oral lesion, considered as cases and controls, respectively. Statistical analysis was performed using Wilcoxon's rank sum test and chi square test. P values equal to or less than 0.05 were considered statistically significant. In order to define independent risk factors for a given oral lesion, a multivariate logistic regression analysis was performed in any case in which two or more variables were found to be associated with the lesion in the univariate analysis. The STATA 3.0 statistical package [15] was used. Continuous variables were dichotomised as follows: haemoglobin <10 and $\geqslant 10$ g/dl, platelets <40 and $\geqslant 40 \times 10^3/mm^3$, leucocytes <1000 and $\geqslant 1000/mm^3$, neutrophils <100 and $\geqslant 100/mm^3$, lymphocytes <500 and $\geqslant 500/mm^3$, albumin <2.5 and $\geqslant 2.5$ g/dl, and creatine <1.5 and $\geqslant 1.5$ mg/dl. The association between potentially predictive variables and the oral lesion was expressed as relative risk (RR) and 95% confidence interval (CI).

RESULTS

25 female and 25 male patients were studied prospectively for a total of 158 weeks. 36 individuals presented with leukaemia, 10 with acute myeloblastic leukaemia, 20 with acute lymphoblastic leukaemia and 6 with chronic leukaemias (3 granulocytic and 3 lymphocytic). All but 6 leukaemia patients were in blast crisis, therefore, they were receiving remission induction chemotherapy. 14 patients had non-Hodgkin's lymphoma, one of whom had a low grade lymphoma, 5 were intermediate grade and 8 were high grade according to the classification of the Working Formulation [16]. 3 patients were receiving chemotherapy as part of their conditioning regimen prior to bone marrow transplant. Global mean age was 33 years with a range of 15 to 85 years. The mean age for leukaemia patients was 30 years, whereas for lymphoma it was 45 years. At basal examination, the simplified oral hygiene index quality was good in 27 (54%) and moderate to poor in 23 (46%) subjects.

The proportion of observations in which the patient used nystatin suspension or chlorhexidine gluconate rinses was 25/158 (16%). Patients were receiving an antifungal agent in 66 (43%), and an antiviral agent in 16 (10%) of 154 observations. Fever was registered in 35/158 (22%) observations; local infection not related to the oral cavity and

systemic infection were recorded in 17 (11%) and 6 (4%) observations, respectively.

Oral lesions were found in 71 (45%) of the 158 observations, corresponding to 38 patients (76%). Exfoliative cheilitis was found in 33 patients (66%), haemorrhagic lesions in 20 individuals (41%), herpetic lesions in 14 subjects (28%), mucositis and xerostomia in 12 patients each (24% respectively), candidosis in 11 individuals (22%) and bacterial alterations in 2 patients (4%). Overall 38 subjects (76%) presented one or more than one oral lesion. The overall incidence rate of oral lesions was 45/100 patient-week; 45.5/100 patient-week in leukaemic patients, and 43/100 patient-week in patients with non-Hodgkin's lymphoma. No significant difference was observed in relation to the overall incidence rate of oral lesions by gender (RR = 1.0; CI = 0.5–2.1), nor by age (RR = 1.32; CI = 0.7–2.6). The incidence rate by type of oral lesion and week of follow-up is presented in Table 2. Mucositis was the only lesion in which having received a prior course of chemotherapy constituted a significant risk (rate ratio = 20.7, CI = 2.7–159). Oral hygiene did not correlate with the presence of mucositis (RR = 1.1; CI = 0.2–6.6).

Figure 1 shows the relationship between the incidence rate of mucositis and the absolute neutrophil count by week during the administration of chemotherapy. As can be seen, the neutrophil count dropped abruptly between the first and second week of follow-up, associated with an increase in the incidence of mucositis.

In our cases, mucositis presented predominantly with erythema and pseudomembrane (Table 3). Most of the cases were asymptomatic, and only when ulceration was present was there moderate to severe pain. Chemotherapy was administered mostly in combination using etoposide, alkylating and antimetabolite agents.

Clinically candidosis presented as an erythematous lesion in 6 of 11 cases, followed by angular cheilitis (3/11) and finally the pseudomembranous variety (2/11). Gingiva and palate were the most common sites. Most lesions were detected on the third week (range 1–7), with a median duration of two (range 1–3).

Intra-oral herpetic infection, mainly involving keratinised epithelium (hard palate, gingiva and dorsal tongue) was observed in 10 of the 14 patients (71%) with herpetic infection. The median week of detection was the third, with median duration of 2 weeks. Only one patient with herpetic lesions on the lip was receiving an antiviral drug.

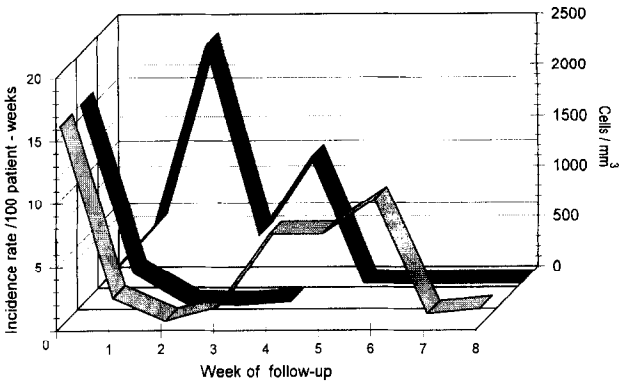

Fig. 1. Relationship between the incidence rate of mucositis and the absolute neutrophil count by week during chemotherapy.

The results of the univariate statistical analysis of different features potentially predictive of oral complications are shown in Table 4. In this analysis, bacterial oral lesions were excluded because of the small number of cases (two). For exfoliative cheilitis and xerostomia none of the variables demonstrated statistical significance. The presence of candidosis increased in patients with low levels of albumin (RR = 4.1, CI = 1.9–8.7).

The results of the multivariate statistical analysis predicting the development of mucositis are shown in Table 5. In the multivariate analysis, leucocytes were not considered as a variable due to their colinearity with neutrophils and because the majority of patients with leukaemia were in blast crisis. Haemorrhagic lesions were strongly associated with low platelet count (RR = 30.6; CI = 3.5–266.9). A marginal relationship was noted between the appearance of herpetic lesions and low levels of neutrophils, (RR = 3.04; CI = 0.91–10.2), or fever (RR = 2.93; CI = 0.88–9.8).

DISCUSSION

Our study confirms earlier work [2–5, 17], which has reported that oral changes are a frequent finding in leukaemic and lymphoma patients in chemotherapy. Exfoliative cheilitis, a term that describes the non-specific chronic exfo-

Table 2. Oral lesion incidence rate by week of follow-up*

Oral lesions	Week of follow-up 1	2	3	4	5	6	7	8	Overall†
Exfoliative cheilitis	17.5	27.3	11.5	31.6	20	57.1	33.3	25	23.2
Haemorrhagic	15.8	15.6	16	11	9.1	12.5	20	0	14.3
Herpetic lesions	2.4	18.4	13.6	11.7	0	12.5	0	0	9.9
Mucositis	4.6	18.9	3.8	10	0	0	0	0	7.8
Xerostomia	4.6	5.1	7.7	10.5	9.1	12.5	20	25	7.7
Candidosis	9.5	8.1	11.5	0	0	0	20	0	7.3
Bacterial infections	2.4	2.6	0	0	0	0	0	0	1.3
All oral lesions‡	41.8	56.4	40.7	42.8	27.3	62.5	40	25	44.9

* Incidence rate/100 patient-weeks.

† Overall incidence rate/100 patient-weeks by lesion.

‡ All oral lesions included mucositis, haemorrhagic lesions, exfoliative cheilitis, xerostomia, bacterial, viral and fungal infections.

Table 3. Clinical features of mucositis

P	Sex	Age	Clinical appearance	Symptoms	Site	Detection*	Duration†	Nt/μl
1	M	28	White patches and pseudomembrane	None	Hard palate	2	1	ND
2	M	28	⩾2 ulcers <1 cm	Moderate pain	Floor of mouth, buccal sulcus	2	1	5.4
3	F	72	Erythema	Minimum discomfort	Gingiva	1	2	72.8
4	M	85	White patches and pseudomembrane	None	ND	4	1	33.6
5	M	60	Multiple ulcers >1 cm	Severe pain	Buccal mucosa, ventral tongue, anterior tonsil	2	1	7.7
6	M	21	Erythema	None	Labial mucosa	2	1	5.0
7	F	27	Erythema	None	Buccal mucosa, gingiva, floor of mouth	3	3	0
8	M	20	White patches and pseudomembrane	Severe pain	Ventral and lateral tongue, gingiva, hard palate	2	2	49.3
9	M	27	Erythema	None	Ventral tongue	2	1	43.6
10	F	53	Erythema	None	Labial mucosa	2	1	25.2
11	M	32	White patches and pseudomembrane	None	Lateral borders of the tongue	1	2	561
12	F	17	White patches and pseudomembrane	None	Lateral borders of the tongue	4	1	ND

P, patient; Nt = neutrophil counts at time of detection; ND, no data.
*Week of detection.
†Duration in weeks.

liation of the superficial layers of epithelium at the vermillion border of the lips [18], was the oral condition most often observed.

Infections were a common type of oral complication in patients undergoing chemotherapy as other authors have reported [2, 3]. Similar to what has been reported elsewhere [17], herpetic lesions (28%) were most frequent, followed by oral candidosis, in contrast to what others have observed [2, 3, 19]. The lower frequency of candidosis, as in other series [17], may be associated with the fact that the majority of the patients were receiving an antifungal agent, while only a few cases were undergoing antiviral treatment. Most reports [3, 20, 21] describe only the pseudomembranous type of oral candidosis; in our study, the predominant variety was the erythematous.

Like others [22], we found that the most frequent site of herpetic infection was the hard palate. It has been reported that herpetic lesions are associated with low neutrophil counts and fever [23]; in the present study this association did not prove to be significant, probably due to the small number of cases. Drug-induced thrombocytopenia, possibly related to antimetabolite agents [24], seemed to be the most important contributing factor for haemorrhagic oral lesions in our patients, as has been reported elsewhere [17, 20, 25].

Although the oral mucosa is particularly susceptible to the toxic effect of chemotherapeutic agents as a result of its relatively high renewal rate (between 4 and 14 days) [26, 27], the frequency of mucositis varies. In patients receiving chemotherapy for solid tumours, cases of mild mucositis have been reported in 21% of the patients [28]. In contrast, up to 90% of bone marrow transplant recipients present ulcerative mucositis [21, 29–31] because they are exposed to more aggressive chemotherapy regimens. Similarly, mucositis is frequently (65%) seen in paediatric oncologic patients [20, 31, 32]. In our study, mucositis was a common oral complication, occurring in 12 (24%) of our patients. It is noteworthy that having received a prior course of chemotherapy was a significant risk factor for mucositis; therefore, prophylactic measures should be applied with particular care in these patients.

Table 4. Univariate analysis of the potential variables associated with development of oral lesions

Variable	Relative risk (95% CI)			
	Mucositis	Haemorrhagic lesions	Herpetic lesions	All oral lesions
Fever	NS	NS	2.1 (1.39–3.12)	1.5 (1.01–2.28)
Consecutive chemotherapy	3.1 (2.27–4.18)	NS	NS	NS
Etoposide	7.3 (2.34–22.78)	NS	NS	NS
Alkylating agents	9.1 (2.8–8.30)	NS	NS	NS
Antimetabolites	NS	3 (1.12–8.0)	NS	NS
Cyclosporine	5.5 (1.8–16.9)	NS	NS	NS
< 40 platelets × 10^3/mm^3	NS	33.1 (4.2–261)	NS	1.5 (1.1–2.07)
< 1000 leucocytes/mm^3	2.3 (1.91–2.8)	NS	1.7 (1.26–2.42)	1.5 (1.06–2.06)
< 100 neutrophils/mm^3	2.8 (2.04–3.9)	3.4 (1.06–10.9)	2.1 (1.36–3.23)	1.8 (1.15–2.71)
< 500 lymphocytes/mm^3	2.0 (1.23–3.11)	NS	NS	NS

NS, non significant.

Table 5. Multivariate analysis of the variables associated with development of mucositis

Variable	Relative risk (95% CI)	*P* value
Consecutive chemotherapy	23.2 (2.26–237.8)	0.008
Etoposide	8.6 (2.37–31.4)	0.001
Alkylating agents	15.6 (3.38–72)	0.001
< 100 neutrophils/mm^3	4.2 (1.04–16.7)	0.04

In our study as well as others [28, 30], the non-keratinised mucosa was the predominant site for mucositis, probably as a result of its faster turnover rate [26, 27] compared with the keratinised mucosa, and lack of a cornified layer. Nevertheless, this pattern contrasts with that described by others who consider that both keratinised and non-keratinised mucosa are equally affected by mucositis [2].

A longitudinal study of oral ulcerative mucositis (UM) in bone marrow transplant recipients [30] found that most patients experienced onset of UM at a median day 11–12 after the conditioning regimen. Similar results were found in the present study, in which the most frequent week of detection for mucositis was the second (7/12). In our study, the precise day of onset and resolution could not be specified because we carried out oral examinations on a weekly basis, but it is unlikely that cases of mucositis occurred and healed during this interval. However, we suggest that follow-up of this patient population should be done at least twice a week, to ensure lesions are not missed. In contrast to other reports [21, 33], the association of mucositis and poor quality of oral hygiene was not observed.

Some authors consider mucositis not to be directly related to a specific chemotherapy agent [34], whereas others have mentioned the possible relationship of mucositis with specific cytotoxic drugs [24, 30, 35–39]. In the present study, the multivariate analysis showed that both etoposide and alkylating agents were independent predictors of mucositis development. Mucositis appears to be the major toxic effect of etoposide-containing regimens in paediatric and adult bone marrow recipients [31, 40], either administered as a single agent [40–42], combined with others [30, 41–44], or with total body irradiation (TBI) [45]. Similarly, mucositis was likely to develop in patients given an alkylating agent alone [46], in combination or with total body irradiation [29–31, 42, 43].

Caution must be taken when interpreting our findings, because several factors could have influenced the development and severity of mucositis, such as doses, schedule, combination of drugs, patient status and probably individual capacity to tolerate chemotherapy [34, 42]. Further studies are required in order to assess the impact of these elements which could influence its development.

We also found, as have others [20, 21, 30], that mucositis was directly related to severe neutropenia. The pathogenesis of mucositis seems to be related to the cytotoxic effect of chemotherapy agents which may act in parallel on cells with a high turnover such as bone marrow cells and basal cells of the oral mucosa. In addition, neutropenia is, in itself, a risk factor for mucositis, independent of its cause.

There is limited and controversial information regarding salivary gland dysfunction in patients receiving conventional chemotherapy [47, 48]. In our patients, xerostomia was a frequent finding, with no significantly associated risk factor. Nonetheless, several organic or functional changes affecting the salivary system may be involved in the development of xerostomia, such as stress and use of anti-emetic drugs [47, 49]. It has been reported that the presence of this condition predisposes to the development of exfoliative cheilitis [49] and candidosis; however, these associations were not observed in our results.

In conclusion, oral lesions are a frequent complication of patients receiving chemotherapy. Exfoliative cheilitis and infections (herpes and candidosis) are the most common, followed by haemorrhagic lesions and mucositis. Larger studies are required to fully evaluate the stomatotoxic effect of all chemotherapy agents, single or combined, in order to facilitate the establishment of prophylactic measures that could prevent or reduce chemotherapy-associated oral complications.

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