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ORIGINAL ARTICLE

Oral mucositis in acute lymphoblastic leukaemia: analysis of 169 paediatric patients

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Chemotherapy-induced oral mucositis is a frequent therapeutic challenge in cancer patients. The purpose of this retrospective study was to estimate the prevalence and risk factors of oral mucositis in 169 acute lymphoblastic leukaemia (ALL) patients treated according to different chemotherapeutic trials at the Darcy Vargas Children's Hospital from 1994 to 2005. Demographic data, clinical history, chemotherapeutic treatment and patients' follow-up were recorded. The association of oral mucositis with age, gender, leucocyte counts at diagnosis and treatment was assessed by the chi-squared test and multivariate regression analysis. Seventy-seven ALL patients (46%) developed oral mucositis during the treatment. Patient age ($P = 0.33$), gender ($P = 0.08$) and leucocyte counts at diagnosis ($P = 0.34$) showed no correlation with the occurrence of oral mucositis. Multivariate regression analysis showed a significant risk for oral mucositis ($P = 0.009$) for ALL patients treated according to the ALL-BFM-95 protocol. These results strongly suggest the greater stomatotoxic effect of the ALL-BFM-95 trial when compared with Brazilian trials. We concluded that chemotherapy-induced oral mucositis should be systematically analysed prospectively in specialized centres for ALL treatment to establish the degree of toxicity of chemotherapeutic drugs and to improve the quality of life of patients based on more effective therapeutic and prophylactic approaches for prevention of its occurrence.
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Introduction

Acute lymphoblastic leukaemia (ALL) is the most frequent malignancy of childhood. This disease is more prevalent in boys compared with girls (Behrman *et al*, 1996; Pedrosa and Lins, 2002; Farias and Castro, 2004), presenting a peak incidence between 2 and 5 years of age (Swensen *et al*, 1997; Lubin *et al*, 1998; Biondi *et al*, 2000; Hastings, 2002; Laks *et al*, 2003).

The aetiology of most acute leukaemias is uncertain, although their occurrence has been associated with predisposing cytogenetic abnormalities, environmental and viral factors (McKenna, 2000; Hastings, 2002). Currently, evidence suggests that chromosomal alterations and mutations during embryonic development are frequently the initial event of the paediatric leukaemia (Gurney *et al*, 1996; Biondi *et al*, 2000; Felix *et al*, 2000; Greaves, 2002; Deangelo, 2005). In addition, certain syndromes and chromosomal abnormalities including Down syndrome, Fanconi's anemia, Bloom syndrome and ataxia-telangiectasia have also been linked with an increased risk of developing ALL (Behrman *et al*, 1996; Linet *et al*, 1997; Lubin *et al*, 1998; Hastings, 2002).

In general, ALL treatment is relegated to chemotherapy, but in particular subgroups may include radiotherapy and/or stem cell transplantation. Dose intensity is adjusted according to prognostic factors and risk of recurrence. ALL chemotherapeutic protocols include four components: (1) an induction phase aimed at an initial remission induction within 1 month through the use of multiple chemotherapeutic agents; (2) a consolidation phase to eradicate residual leukaemic blasts in patients who are in remission according to morphological criteria; (3) extra-compartment therapy such as central nervous system-directed therapy; and (4) a maintenance phase to further stabilize remission by suppressing re-emergence of a drug-resistant clone through continuing reduction of residual leukaemic cells (Brandalise *et al*, 1993, 2000; Riehm *et al*, 1995, 2002; Laks *et al*, 2003; Scully *et al*, 2006).

One of the most well-known ALL treatment protocols was developed by the Berlin–Frankfurt–Münster (BFM) Group, which led to the achievement of high survival rates (Riehm *et al*, 2002; Laks *et al*, 2003; Scully *et al*, 2006). In the second half of the 1970s, an additional element was introduced by the BFM Group, a re-induction or delayed re-intensification phase (Behrman *et al*, 1996). The Brazilian Childhood Leukaemia Study Group (BCLSG) has also presented protocols for ALL treatment based on previous clinical trials, changing doses and combination of drugs, in order to reduce treatment-related adverse events as well as to improve survival and cure rates (Brandalise *et al*, 2000).

Oral mucositis represents a major complication of cytotoxic chemotherapy among ALL children (Sonis, 1998, 2000, 2004; Kostler *et al*, 2001; Naidu *et al*, 2004). The clinical symptoms of mucositis are variable, and generally present as atrophic or erythematous areas, sometimes associated with white desquamative patches in the oral mucosa, which subsequently develop into painful ulcers (Sonis, 2000; Elting *et al*, 2003; Blijlevens, 2005; Scully *et al*, 2006).

Different specialized centres for ALL treatment use different protocols. The purpose of this retrospective study was to estimate the prevalence and risk factors of oral mucositis in ALL paediatric patients treated according to different chemotherapeutic trials.

Patients and methods

All 169 paediatric patients included in this retrospective study were treated according to ALL chemotherapeutic treatment at the Department of Paediatric Oncology of the Darcy Vargas Children's Hospital, São Paulo, from 1994 to 2005. The age of patients ranged from 5 months to 18 years and the following inclusion criteria were used:

1 ALL patients diagnosed and treated exclusively at Darcy Vargas Children's Hospital;
2 The availability of complete medical files containing personal information and clinical history of cancer;
3 ALL patients treated according to (a) BFM Group trials of 1995 and 2002 (ALL-BFM-95 and ALL-BFM-2002) and (b) Brazilian trials of 1993 and 1999 (BCLSG-93 and BCLSG-99).

The Research Ethics Committee of the Darcy Vargas Children's Hospital, São Paulo, Brazil, approved this retrospective study.

Patients' data were collected from their medical records and included sex, age, clinical history (diagnosis, duration of the cancer, leucocyte counts at diagnosis, risk group, simultaneous systemic disease), treatment (ALL treatment trials, chemotherapeutic drugs) and adverse events during follow-up (recurrence, lost to follow-up and death). The occurrence of oral mucositis and other oral diseases were also recorded. The association between oral mucositis and its risk factors including sex, age, leucocyte counts at diagnosis and chemotherapeutic trials was analysed using chi-squared test and multivariate regression analysis with significance at $P = 0.05$.

Results

The distribution of clinical features and outcome of the 169 ALL paediatric patients included in this study are summarized in Tables 1 and 2. A higher frequency of ALL was observed in males (59.2%) compared with females (40.8%) and the leucocyte counts at diagnosis ranged from 100 to 400 000 leucocytes mm^{-3} (Table 1). The age of patients varied from 5 months to 18 years, with the majority of patients (76%) being children under 9 years of age, as shown in Table 1.

Most of the ALL children were treated according to BCLSG-93 and ALL-BFM-95 chemotherapeutic protocols (Table 1) and 90 of them were alive and showed no evidence of cancer (Table 2). Details concerning patients' outcome are provided in Table 2. Sixteen patients died because of ALL and 13 of them were treated according to the ALL-BFM-95 trial. Three patients treated according to the BCLSG-93 protocol died of progressive disease.

Table 1 Distribution of clinical characteristics and chemotherapeutic trials in acute lymphoblastic leukaemia paediatric patients – Darcy Vargas Children's Hospital, São Paulo, Brazil, 1994 to 2005

Characteristic		n	*%*
Sex	Male	100	59.2
	Female	69	40.8
Age	≤ 9 years	128	76.0
	≥10 to ≤18 years	41	24.0
Leucocytes (mm^3)	100–9300	82	48.5
	9400–400 000	82	48.5
	Non-specified	5	3.0
Chemotherapeutic protocols	BCLSG-93	65	38.5
	ALL-BFM-95	74	43.8
	BCLSG-99	26	15.4
	ALL-BFM-02	04	2.3
Total		169	100

n = number of paediatric patients.
BCLSG, Brazilian Childhood Leukaemia Study Group; ALL-BFM, acute lymphoblastic leukaemia–Berlin–Frankfurt–Münster.

Table 2 Clinical outcome of ALL paediatric patients treated according to different chemotherapeutic protocols – Darcy Vargas Children's Hospital, São Paulo, Brazil, 1994 to 2005

	Chemotherapeutic protocols			
Clinical outcome	*BCLSG-93* (n)	*ALL-BFM-95* (n)	*BCLSG-99* (n)	*ALL-BFM-02* (n)
Leukaemic death	3	13	0	0
Death, UD	2	0	1	0
Alive with ALL	0	28	3	4
Alive, NED	58	32	20	0
Lost to follow-up	2	1	2	0
Total	65	74	26	4

n = number of paediatric patients.
ALL, acute lymphoblastic leukaemia; UD, unrelated to disease; NED, no evidence of disease; BCLSG, Brazilian Childhood Leukaemia Study Group; ALL-BFM, acute lymphoblastic leukaemia–Berlin–Frankfurt–Münster.

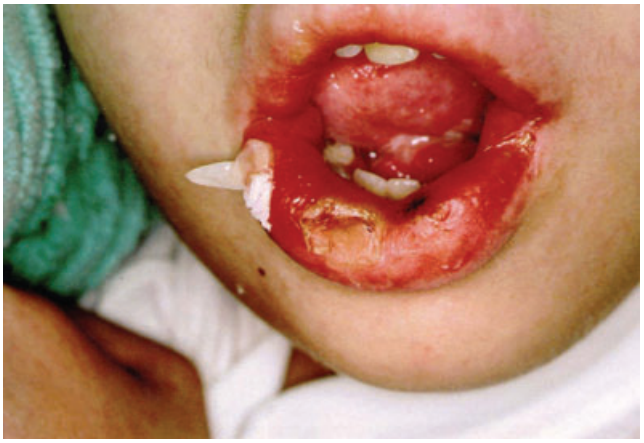

Figure 1 Clinical feature of chemotherapy-induced oral mucositis in a paediatric patient with acute lymphoblastic leukaemia

Seventy-seven ALL patients (46%) developed oral mucositis (Figure 1) during the treatment, as shown in Table 3. Twenty-four of the 77 children (31.1%) presented more than one clinical manifestation of oral mucositis. The occurrence of oral mucositis with regard to sex, age and leucocyte counts at diagnosis is shown in Table 3. Oral mucositis was most frequently detected in females (54%) who were less than 9 years old (48%) and had counts at diagnosis between 9400 and 400 000 leucocytes mm^{-3}. Patient age, gender and leucocyte counts at diagnosis showed no statistical correlation with the occurrence of oral mucositis (Table 3).

The association between oral mucositis and chemotherapeutic protocols can be visualized in Table 4. In multivariate regression analysis, a significant risk for oral mucositis (OR 2.59; 95% CI 1.26–5.33, $P = 0.009$) was observed for ALL patients treated according to the ALL-BFM-95 protocol. The ALL-BFM-02 protocol was excluded from the statistical analysis above.

As a consequence of antineoplastic treatment, some children presented other systemic diseases, such as medication-induced diabetes, medication-induced hepatitis, cardiac disease and venous thrombosis. Infectious diseases also occurred in patients during the chemotherapeutic treatment, as shown in Table 5.

Herpes labialis was the most frequent oral viral infection, detected in 23 ALL patients, 13 of who presented simultaneous oral mucositis. Other oral clinical manifestations including angular cheilitis, actinomycosis and aphthous stomatitis were also observed during the ALL treatment (Table 5).

Table 3 Correlation between oral mucositis, sex, age and leucocyte counts at diagnosis in 169 ALL paediatric patients – Darcy Vargas Children's Hospital, São Paulo, Brazil, 1994 to 2005

		Oral mucositis			
		n	%	*Total*	P
Sex	Male	40	40.0	100	0.08
	Female	37	54.0	69	
Age	≤ 9 years	61	48.0	128	0.33
	≥10–≤18 years	16	39.0	41	
Leucocytes (mm^3)	100–9.300	34	41.0	82	0.34
	9.400–400,000	41	50.0	82	
	Non-specified	04	80.0	05	

n = number of paediatric patients with acute lymphoblastic leukaemia.
P-value obtained by chi-squared test.

Discussion

Mucositis is the most common oral complication among patients receiving ALL chemotherapeutic treatment (Sonis *et al*, 1996, 2004; Epstein and Schubert, 1999; Kostler *et al*, 2001; Barasch and Peterson, 2003; Huber and Terezhalmy, 2005). However, data concerning its occurrence in the paediatric cancer population are scarce. In our series, 46% of ALL children developed oral mucositis during treatment. These results are similar to those found by previous authors (Sonis *et al*, 1996, 2004; Biondi *et al*, 2000; Scully *et al*, 2006), who reported that some degree of oral mucositis occurs in approximately 40% of patients who receive cancer chemotherapy. While our results concerning the percentage of oral mucositis in ALL paediatric patients are similar to others found in the literature, only retrospective studies such as this can estimate the prevalence. A prospective cohort study of children undergoing treatment would provide a more accurate prevalence estimate.

Our results demonstrate that ALL was most frequent in males (59.2%) under 9 years of age, with the majority of cases (65%) occurring in children between the ages of 2 and 5 years, as described by previous studies (Gurney *et al*, 1996; Linet *et al*, 1997; Felix *et al*, 2000; Hastings, 2002; Pedrosa and Lins, 2002; Oliveira *et al*, 2004).

This study showed a higher frequency of oral mucositis (48%) in children aged ≤ 9 years compared with patients between 10 and 18 years of age (39%). Despite no significant differences, these results agree with other studies (Pico *et al*, 1998; Scully *et al*, 2006) that have observed that this stomatologic complication most frequently affects children under 12 years of age.

The higher incidence of oral mucositis observed in younger patients, when compared with elderly patients, can be attributed to the higher mitotic rate of their basal cells, causing the loss of the ability of the tissue to renew itself with consequent atrophy, thinning and ulceration of the mucosal epithelium (Pico *et al*, 1998; Scully *et al*, 2006).

A higher frequency of chemotherapy-induced oral mucositis (54%) was noted in females, despite the majority of our population being composed of males. However, gender was not correlated with incidence of oral mucositis. Our data are not concordant with those of the study of Vokurka *et al* (2006), who suggested that females appear to be more susceptible to this post-chemotherapy complication and that gender may play an important role as an independent risk factor and as a predictor for oral mucositis in high-dose chemotherapy settings. In addition, our findings are consistent with

Table 4 Multivariate logistic regression for risk of occurrence of oral mucositis in 169 ALL paediatric patients – Darcy Vargas Children's Hospital, São Paulo, Brazil, 1994 to 2005

							95% CI OR	
Variable		*Mucositis (%)*	*B*	*seB*	P	*OR*	*Inf.*	*Sup.*
Sex	Male (0)	40.0						
	Female (1)	54.0	0.44	0.34	0.206	1.55	0.79	3.03
Age	≤ 9 years (0)	48.0						
	≥10 to ≤18 years (1)	39.0	−0.16	0.41	0.697	0.85	0.38	1.90
Leucocytes	100–9300 (0)	45.3						
	9400–400 000 (1)	54.7	0.19	0.33	0.560	1.22	0.63	2.34
Protocols	BCLSG-93 (0)	30.8						
	ALL-BFM-95 (1)	56.8	0.95	0.37	0.009	2.59	1.26	5.33
	BCLSG-99 (1)	46.2	0.63	0.49	0.206	1.87	0.71	4.91

n = number of paediatric patients.
BCLSG, Brazilian Childhood Leukaemia Study Group; ALL-BFM, acute lymphoblastic leukaemia–Berlin–Frankfurt–Münster; se, standard error; OR, odds ratio; 95% CI, confidence interval 95%.
P-value obtained by multivariate logistic regression analysis.

Barasch and Peterson (2003), who suggested that it remains unclear as to how the combined risk factors of age and gender affect the incidence and severity of oral mucositis in chemotherapy-treated patients.

Oral mucositis was most frequent among paediatric patients who had high leucocyte counts at diagnosis (9400 to 400 000 leucocytes mm^{-3}). High white blood cell counts generally reflect a higher risk of relapse, worsening in prognosis and use of more aggressive therapies, as previously observed in treatment protocols developed by the BFM Group and BCLSG (Brandalise *et al*, 1993, 2000; Riehm *et al*, 1995, 2002).

Multivariable regression analysis showed a significant risk for oral mucositis (OR = 2.59, $P = 0.009$) for ALL patients treated according to the ALL-BFM-95 protocol. In this regimen, higher number and doses of chemotherapeutic agents are employed during the induction phase, aimed at eradicating the leukaemic blast count to less than 5% in the marrow, restoration of normal haematopoiesis and remission of clinical symptomatology (Riehm *et al*, 1995, 2002). The higher frequency of oral mucositis observed in patients treated according to the ALL-BFM-95 protocol may reflect a higher systemic toxicity employed in this regimen. In addition, the intervals between drug administration seem to be more important than total dosage (Scully *et al*, 2006), as the risk of developing oral mucositis increases with the number of chemotherapeutic cycles (Kostler *et al*, 2001; Naidu *et al*, 2004).

Table 5 Simultaneous occurrence of oral mucositis and others diseases in ALL paediatric patients – Darcy Vargas Children's Hospital, São Paulo, Brazil, 1994 to 2005

	Oral mucositis	
Simultaneous disease	n	*%*
Systemic diseases		
Sickle cell anaemia	1	1.3
Bronchitis	2	2.6
Cardiac disease	4	5.2
Diabetes (medication)	3	3.9
Hepatitis	4	5.2
Herpes Zoster	3	3.9
Pneumonia	5	6.5
Down syndrome	6	7.8
Sinusitis	5	6.5
Venous thrombosis	2	2.6
Varicella	8	10.4
Oral diseases		
Actinomycosis	1	1.3
Aphthous stomatitis	6	7.8
Herpes labialis	13	16.9
Coated tongue	0	0
Angular cheilitis	9	11.7
Total	77	100

n = number of ALL paediatric patients.

According to BCLSG-93 (Brandalise *et al*, 1993, 2000), BCLSG-99 (Brandalise *et al*, 2000), ALL-BFM 95 and ALL-BFM 02 protocols, drugs such as methotrexate (MTX), danorrubicin, vepesid, cyclophosphamide, 6-mercaptopurine and 6-thioguanine exhibit pronounced stomatotoxic effects. MTX is one of the most effective agents currently used for treating childhood ALL. It blocks malignant cell proliferation by acting as a folic acid antagonist (Brandalise *et al*, 2000; Scully *et al*, 2006). However, because of its direct stomatotoxic effect, oral mucositis represents one of many clinical side effects of MTX toxicity.

As a consequence of immunosuppressive therapy for ALL treatment, many clinical complications observed in our sample (Table 5) are generally expected (Brandalise *et al*, 1993, 2000; Riehm *et al*, 1995, 2002), including diabetes related to asparaginase therapy, cardiac disease, medication-induced hepatitis and infectious diseases with systemic manifestation. As part of the ulcerative/microbiological phase, myelosuppression and inflammation lead to the breakdown of the mucosa, thereby compromising the ability of the patient to resist entry of pathogens, which renders them susceptible to infection from a number of sources, including viral, fungal and bacterial infections. Patients with mucositis have a greater relative risk of septicaemia (Sonis *et al*, 1996, 2004; Pico *et al*, 1998; Epstein and Schubert, 1999;

Sonis, 2000). In addition to its impact on patients' treatment course, on quality of life, morbidity and mortality, mucositis also has a significant economic cost (Pico *et al*, 1998; Epstein and Schubert, 1999; Elting *et al*, 2003; Oliveira *et al*, 2004; Blijlevens, 2005; Lalla and Peterson, 2005).

Despite the fact that cure rates in childhood ALL range from 70% to 80% (Pui, 1995; Swensen *et al*, 1997; Pui and Evans, 1998; Greaves, 2002; Pui *et al*, 2002; Oliveira *et al*, 2004), in our series, 13 patients treated by the ALL-BFM 95 protocol and three treated according to BCLSG-93 died of ALL during the last 11 years. As the majority of our patients are in follow-up or had finished at least 5 years of treatment, cure rates could not be established. Only 29 (50%) of 58 patients treated according to the BCLSG-93 protocol who are alive and without treatment can be considered cured.

In conclusion, chemotherapy-induced oral mucositis should be systematically analysed prospectively in specialized centres for ALL treatment in order to establish the degree of toxicity of chemotherapeutic drugs and to improve the quality of life of patients based on more effective therapeutic and prophylactic approaches for prevention of its occurrence.

Author contributions

SLC Figliolia: collected all data, DT Oliveira: designed study, MC Pereira: drafted paper, JRP Lauris: statistical analysis, AR Maurício: clinical orientation, DT Oliveira: clinical orientation, ML Mello de Andrea: clinical supervisor.

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