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Low-Level Laser for Prevention of Chemotherapy-Induced Oral Mucositis in Pediatric Patients with Acute Leukemia, HC/UFMG 2012-2013

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Abstract- Oral mucositis (OM) is the non-hematological toxicity with the highest prevalence and morbidity in anticancer treatment. This study evaluated the use of low-level laser for the prevention of chemotherapy-induced OM by comparing 101 cycles with prophylactic irradiation using a gallium aluminum arsenide (GaAlAs) laser diode (λ=660 nm; P=40 mW, dose of 4 J/cm²) and 121 cycles with no irradiation. The conditions associated with oral health, chemotherapy cycles, neutropenia patterns, infectious complications and nutritional status were evaluated. OM occurred in 41.9% of the cycles. The probability of developing OM in the final cycles (7 to 10) was 7.34 times higher than in the initial cycles (1 to 6); 4.19 times higher in febrile neutropenia than in physiological neutropenia; 2.08 times higher when a therapeutic antimicrobial drug was used; and 2.12 times higher when gingivitis was present. After finding similarity between the groups with respect to the variables studied, it was concluded that the application of prophylactic laser did not reduce the frequency of chemotherapy-induced OM but was effective in preventing severe forms of the disease, reducing the occurrence of OM grades III and IV from 22% to 7% with no adverse effects, which justifies its routine use.

I. Introduction

Chemotherapy- or radiation-induced oral mucositis (OM) is an inflammatory reaction resulting from complex interactions among several factors and the main cause of which is the direct and indirect stomatotoxicity of anticancer agents. The condition primarily affects tissues with a high cell turnover rate, such as the oral mucosa, and develops in approximately 40% of patients subjected to chemotherapy (CT) (Epstein & Schubert, 2004; Rubenstein *et al*., 2004).

OM is a common complication with relevant morbidity in which sequelae cause disturbances in the integrity and function of the oral cavity, causing moderate to severe pain; an increased risk of local and systemic infections; functional, nutritional, and sleep disorders; and difficulty in oral hygiene (Maiya *et al*., 2006; Lalla *et al.,* 2008; Mañas *et al.,* 2009). These changes may trigger severe systemic repercussions, such as sepsis and respiratory failure, and require the reduction and/or interruption of the antineoblastic therapy, with implications for the survival of the patient. In addition to their negative effect on the quality of life, the harmful effects of OM increase hospitalization time and treatment costs (Cheng *et al.,* 2012; Carlotto *et al.,* 2013).

Currently, the approach to OM focuses on palliative measures, such as pain management, nutritional support, and the maintenance of good oral hygiene. Low-level laser (LLL) has proven effective as a method for the prophylaxis and/or treatment of OM, producing clinical and functional improvement. LLL accelerates the healing of wounds and has anti-inflammatory, analgesic, and biomodulator effects (Cowen *et al.,* 1997; Bensadoun *et al.,* 1999; Arora *et al.,* 2008; Genot *et al.,*2008; Guatam *et al.,* 2013).

Mastering interventions that prevent this condition is becoming increasingly relevant. This study evaluated the effects of LLL on the prevention of chemotherapy-induced OM in pediatric patients with acute leukemia.

II. Patients and Method

This study was approved by the Ethics and Research Committee of the Federal University of Minas Gerais (Comitê de Ética em Pesquisa da Universidade Federal de Minas Gerais - COEP-UFMG) process no. 01155712600005149. The study was conducted from January 2012 to December 2013, and patients were randomly allocated by doctors of the Teaching Hospital of UFMG (Hospital das Clínicas da UFMG – HC/UFMG). Patients with acute leukemia, from both genders and aged up to 17 years, were included in the study. The CT cycles were divided into two groups: ***group I***: cycles of patients whose oral cavity was prophylactically irradiated with low-intensity laser; ***group II***: cycles of patients not irradiated. Patients with infectious diseases and with other cancers were excluded.

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The sample size (n ≥ 101 cycles/group) was defined considering the 35% prevalence of chemotherapy-induced OM and a decrease of 18% in response to the prophylactic application of LLL, to obtain a statistical power of 80% and a significance level of 5%.

The OM classification recommended by the World Health Organization (WHO) was categorized into three groups: no mucositis (Grade O), mild/moderate mucositis (Grade I and II), and severe mucositis (Grade III and IV).

Irradiation was performed daily in the whole oral cavity with 4 J/cm² red laser energy density (maximum power 40 mW; λ=660 nm), 10 s per point, in the first three days of each CT cycle, prioritizing the most susceptible intraoral regions. If OM occurred, irradiation was maintained until the complete regression of signs/symptoms.

The following variables potentially associated with the risk of OM were selected for study: oral health indicators (carious lesions, tooth exfoliation, tooth eruption, gingivitis, supra-gingival plaque, and/or tartar); nutritional status (unchanged, mild nutritional risk, severe nutritional risk, malnutrition, and obesity); CT cycle phase (induction, reinduction, consolidation, intensification, interphase, and maintenance); neutropenia pattern (physiological neutropenia, febrile neutropenia or neutropenia with no defined focus, and severe neutropenia); and infectious complications (presence of infection, therapeutic use of antimicrobial drugs, and infection group).

The data were analyzed using SPSS 14.0 for *Windows*.

III. Results and Discussion

In total, 233 CT cycles were included. There were 11 losses, five due to absence of dental evaluation and six due to interruption of the CT and/or irradiation cycles. Ultimately, 222 cycles were analyzed: 101 cycles with preventive LLL irradiation and 121 cycles with no irradiation. Laser application was well tolerated, and there were no records of undesirable effects attributable to its use.

The studied variables showed a homologous distribution between the groups. Among these variables, the following showed evidence of risk for OM development: presence of gingivitis (p=0.016), neutropenia (p=0.001), nutritional status (p=0.028) number of the CT cycle (p=0.016), presence of infection (p=0.002), therapeutic use of antimicrobial drug (p=0.002), and infection group (p = 0.013).

The frequency of mucositis was similar between the groups (p=0.851): 42.6% (43/101) in irradiated cycles with prophylactic LLL and 41.3% (50/121) in cycles with no irradiation.

Table 1 shows the distribution of OM severity among the groups, and Table 2 shows independent risk factors associated with the development of the condition.

Table 1 : Severity of chemotherapy-induced oral mucositis in pediatric patients with acute leukemia, according to group (irradiated with prophylactic LLL and not irradiated), HC/UFMG, 2012-2013

Mucositis Severity	Prophylactic Irradiation With LLL		No Prophylactic Irradiation		P
	n	%	n	%	
Grade 1 or 2	40	93.0	39	78.0	0.043
Grade 3 or 4	3	7.0	11	22.0	
Total	43	100	50	100	

Note: The significance probability refers to the Chi-square test. n=number of chemotherapy cycles.

Table 2 : Factors associated with the development of chemotherapy-induced oral mucositis in pediatric patients with acute leukemia, HC/UFMG, 2012-2013

Variable	Coefficient	Wald's χ^2	p	OR (odds ratio)
Intercept	-2.007	32.359	< 0.001	
Cycle number	1.994	15.337	< 0.001	7.34
Neutropenia	1.432	11.005	0.001	4.19
Indication for antibiotics	0.734	3.471	0.062	2.08
Gingivitis	0.749	4.107	0.043	2.12

The probability of developing OM in the final cycles (7 to 10) was 7.34 times higher than in the initial cycles (1 to 6); 4.19 times higher in febrile neutropenia than in physiological neutropenia; 2.08 times higher when a therapeutic antimicrobial drug was used; and 2.12 times higher when gingivitis was present (Table 2).

The use of LLL at the beginning of each chemotherapy cycle did not reduce the risk of occurrence of OM but did reduce the severity of the condition.

Randomized clinical trials confirmed the potential of LLL in reducing the need for opioid analgesics and parenteral nutrition and also confirmed its remedial action, especially in the last stages of the pathogenesis of OM, but recorded little evidence of prophylactic benefits (Genot *et al.,* 2005; Cruz *et al.,* 2007; Abramoff *et al.,* 2008; Cauwels *et al.,* 2011; Arbabi-Kalati *et al.,* 2013; Guatam *et al.,* 2013).

Two recent meta-analyses showed evidence of the effect of LLL. When analyzing 11 randomized studies involving 415 patients, in which LLL was applied at doses higher than 1 J/cm², Bjordal (2011) observed a reduction of 2.72 (95% CI: 1.98-3.74) in the relative risk (RR) of developing OM and a reduction in the severity and duration of the ulcer with therapeutic use. The study by Cruz and colleagues, included in this meta-analysis, concluded that LLL did not show prophylactic benefits regarding OM. However, these authors did not evaluate the effect of the laser on mucositis grading.

In a meta-analysis covering 33 studies, other authors (Bensadoun *et al.,* 2012) found a decrease of 2.45 (95% CI: 1.85-3.18) in the RR of developing OM when LLL was applied in doses between 2 and 3 J/cm². This study, whose prophylactic protocol adopted a dose of 4 J/cm², observed a reduction in the severity of the lesions with the use of prophylactic LLL. Severe OM (grade III and IV) occurred in 22% of cycles of patients who did not receive prophylactic LLL and in only 7% of patients who did.

The identification of OM risk factors is often not an easy task. The complex interaction among several factors that define the pathogenesis and intensity of OM results in wide individual variation, in which patients of the same age treated with identical CT protocols and similar oral hygiene patterns progress with different clinical presentations (Who *et al.,* 1993; Cheng *et al.,* 2011). The screening of patients prophylactically subjected to LLL, performed randomly by physicians of the service, could have selected patients with a higher risk of OM occurrence. However, the data analysis did not show differences between the groups, which allowed for assessment of the risk of OM occurrence and its severity.

The risk of OM occurrence may vary between cycles, and the anxiety level and previous history of mucositis are risk factors associated with a higher probability of occurrence (Cheng *et al.,* 2011). Our results showed a tendency of association between the occurrence of mucositis and the cumulative effect of CT, with an increased risk of mucositis in cycles subsequent to the sixth.

The literature describes OM as an important signal of severity and, at the same time, a consequence of the immune status and cytotoxic response of the individual. Souza et al. (2008) showed that the presence of a mucositis grade higher than two (WHO) is predictive of severity in cancer patients with febrile neutropenia. The oral microbiota of neutropenic patients is different from the oral microbiota of healthy people. The ulcerations found in neutropenic patients are clinically visible when the first evidence of neutropenia appears, and they represent a four times higher risk factor for sepsis (Sonis, 1998). Our results show neutropenia as a significant independent risk factor for the development of mucositis.

It is widely known that inadequate oral hygiene, teeth with carious activity, and chronic and acute infections of the periodontal system are predictors of the incidence and severity of OM (Coracin *et al.,* 2013). The emphasis on oral care results from proven microbial diversity at cancer diagnosis, which favors the pronounced modification of Gram-negative microbiota and worsening of mucositis

(Ye *et al.,* 2013). In addition, when the structural integrity is compromised, new glycoconjugate structures become available in the mucosal surface, which, when associated with pseudomembranes, add selective advantages to the oral microbiota, favoring the fixation of opportunistic pathogens and the entry of microorganisms into the submucosa, which may result in systemic spread. (Ducan *et al.,* 2003). Among the studied variables that indicate oral health, only gingivitis was associated with OM risk.

Nutritional status is believed to be among the main factors that modulate the stomatotoxicity of antiblastic therapy. Children undergoing chemotherapy may have reduced food intake due to poor appetite or stomatotoxic involvement, which puts them at risk of malnutrition and intolerance to treatment, and also due to increased local and systemic infections, which expand the already extensive factors that negatively affect the quality of life of cancer patients (Andrassy *et al.,* 1998; Lobato-Mendizábal *et al.,* 1989; Hafiz *et al.,* 2008). In this study, nutritional status did not influence the development of OM.

IV. Conclusion

There was a higher risk of mucositis under the following conditions: from the 6th CT cycle on; in the presence of fever, the therapeutic use of an antimicrobial drug, or severe neutropenia; and in the presence of gingivitis. The similarity between groups reinforces the data presented regarding the beneficial effects of LLL in reducing OM severity. OM grades III and IV decreased from 22% in cycles not irradiated to 7% in prophylactically irradiated cycles.

The adjustment of the laser therapy protocol remains a challenge, especially regarding the daily doses, the frequency of radiation, and the identification of independent risk factors, which could signal adjustments in irradiation flows.

V. Conflicts of Interest

The authors declare no conflict of interest.

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