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4 Received: 14 December 2013 Accepted: 31 December 2013 Published: 15 January 2014

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6 **Abstract**

7 Oral mucositis (OM) is the non-hematological toxicity with the highest prevalence and
8 morbidity in anticancer treatment. This study evaluated the use of low-level laser for the
9 prevention of chemotherapy-induced OM by comparing 101 cycles with prophylactic
10 irradiation using a gallium aluminum arsenide (GaAlAs) laser diode ($\lambda=660$ nm; $P=40$ mW,
11 dose of 4 J/cm^2) and 121 cycles with no irradiation. The conditions associated with oral
12 health, chemotherapy cycles, neutropenia patterns, infectious complications and nutritional
13 status were evaluated. OM occurred in 41.9

14

15 **Index terms—**

16 **1 I. Introduction**

17 hemotherapy-or radiation-induced oral mucositis (OM) is an inflammatory reaction resulting from complex
18 interactions among several factors and the main cause of which is the direct and indirect stomatotoxicity of
19 anticancer agents. The condition primarily affects tissues with a high cell turnover rate, such as the oral
20 mucosa, and develops in approximately 40% of patients subjected to chemotherapy (CT) (Epstein & Schubert,
21 2004; Rubenstein et al., 2004).

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

29 Currently, the approach to OM focuses on palliative measures, such as pain management, nutritional support,
30 and the maintenance of good oral hygiene. Low-level laser (LLL) has proven effective as a method for the
31 prophylaxis and/or treatment of OM, producing clinical and functional improvement. LLL accelerates the healing
32 of wounds and has antiinflammatory, analgesic, and biomodulator effects (Cowen et al., 1997; Bensadoun et al.,
33 1999; Arora et al., 2008; Genot et al., 2008; ??uatum et al., 2013).

34 Mastering interventions that prevent this condition is becoming increasingly relevant. This study evaluated
35 the effects of LLL on the prevention of chemotherapy-induced OM in pediatric patients with acute leukemia.
36 The sample size ($n = 101$ cycles/group) was defined considering the 35% prevalence of chemotherapy-induced
37 OM and a decrease of 18% in response to the prophylactic application of LLL, to obtain a statistical power of
38 80% and a significance level of 5%.

39 **2 II. Patients and Method**

40 The OM classification recommended by the World Health Organization (WHO) was categorized into three groups:
41 no mucositis (Grade 0), mild/moderate mucositis (Grade I and II), and severe mucositis (Grade III and IV).

42 Irradiation was performed daily in the whole oral cavity with 4 J/cm^2 red laser energy density (maximum power
43 40 mW ; $\lambda=660$ nm), 10 s per point, in the first three days of each CT cycle, prioritizing the most susceptible
44 intraoral regions. If OM occurred, irradiation was maintained until the complete regression of signs/symptoms.

3 III. RESULTS AND DISCUSSION

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

51 The data were analyzed using SPSS 14.0 for Windows.

52 3 III. Results and Discussion

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

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

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

63 Table 1 shows the distribution of OM severity among the groups, and Table 2 shows independent risk factors
64 associated with the development of the condition. The probability of developing OM in the final cycles (7 to
65 10) was 7.34 times higher than in the initial cycles (1 to 6); 4.19 times higher in febrile neutropenia than in
66 physiological neutropenia; 2.08 times higher when a therapeutic antimicrobial drug was used; and 2.12 times
67 higher when gingivitis was present (Table 2).

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

70 Randomized clinical trials confirmed the potential of LLL in reducing the need for opioid analgesics and
71 parenteral nutrition and also confirmed its remedial action, especially in the last stages of the pathogenesis of
72 OM, but recorded little evidence of prophylactic benefits ??Genot et Volume XIV Issue II Version I Year ()J

73 involving 415 patients, in which LLL was applied at doses higher than 1 J/cm², Bjordal (2011) observed a
74 reduction of 2.72 (95% CI: 1.98-3.74) in the relative risk (RR) of developing OM and a reduction in the severity
75 and duration of the ulcer with therapeutic use. The study by Cruz and colleagues, included in this meta-analysis,
76 concluded that LLL did not show prophylactic benefits regarding OM. However, these authors did not evaluate
77 the effect of the laser on mucositis grading. In a meta-analysis covering 33 studies, other authors (Bensadoun et
78 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
79 doses between 2 and 3 J/cm². This study, whose prophylactic protocol adopted a dose of 4 J/cm², observed a
80 reduction in the severity of the lesions with the use of prophylactic LLL. Severe OM (grade III and IV) occurred
81 in 22% of cycles of patients who did not receive prophylactic LLL and in only 7% of patients who did.

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

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

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

100 It is widely known that inadequate oral hygiene, teeth with carious activity, and chronic and acute infections of
101 the periodontal system are predictors of the incidence and severity of OM (Coracini et al., 2013). The emphasis on
102 oral care results from proven microbial diversity at cancer diagnosis, which favors the pronounced modification of
103 Gram-negative microbiota and worsening of mucositis (Ye et al., 2013). In addition, when the structural integrity
104 is compromised, new glycoconjugate structures become available in the mucosal surface, which, when associated
105 with pseudomembranes, add selective advantages to the oral microbiota, favoring the fixation of opportunistic

106 pathogens and the entry of microorganisms into the submucosa, which may result in systemic spread. (Ducan et
107 al., 2003). Among the studied variables that indicate oral health, only gingivitis was associated with OM risk.

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

114 **4 IV. Conclusion**

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

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

123 **5 V. Conflicts of Interest**

The authors declare no conflict of interest. ¹



Figure 1: C

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Mucositis Severity	Prophylactic Irradiation		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.

Figure 2: Table 1 :

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Figure 3: Table 2 :

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5 V. CONFLICTS OF INTEREST

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