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Influence of Preventive Protocols on Side Effects of Radiotherapy for Treatment of Head and Neck Cancer

Influencia de los Protocolos de Prevención sobre los Efectos Secundarios de la Radioterapia para el Tratamiento de Cáncer de Cabeza y Cuello

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ABSTRACT: This study evaluated the effect of three preventive protocols and dental treatment on the occurrence of xerostomia, mucositis and candidosis in oncologic patients undergoing radiotherapy for treatment of head and neck cancer. A total of 100 patients were submitted to radiotherapy (RT): thirty-eight did not receive dental treatment prior to RT and oral hygiene instructions were provided in the visits to centers for RT, during and after radiotherapy; sixty-two received endodontic, periodontal, surgical and restorative treatments prior to RT and were instructed to use chlorhexidine gluconate 0.12% oral rinse or sodium fluoride 0.5% oral rinse or 2% sodium iodide (hydrogen peroxide in 10 v/v) during and after RT. Patients underwent dental, periodontal, intra and extra oral examinations immediately before, during and after radiotherapy. Dermatitis, mucositis and xerostomia tended to be almost universal, but the severity of mucositis was significantly lower among patients who received the preventive protocols. The occurrence of candidosis was significantly lower in patients who received preventive dental treatment and chemical protocols. Although preventive dental protocols used in centers for radiotherapy in Brazil are not fully adequate, the results of the present investigation show that they at least minimize the severity of some symptoms, and the lack of a dental protocol is deeply harmful to the patients.

KEY WORDS: radiotherapy, cancer, mucositis, candidosis, dermatitis, xerostomia, prevention.

INTRODUCTION

The head and neck cancer (HNC) represents a serious problem around the world and its treatment frequently involves surgery, radiotherapy (RT), and chemotherapy, even though the use of chemical agents as adjuvants in the treatment for cancer is recent. However, there is enough evidence to show that the radiotherapy in this treatment is compromised due to its several side effects, such asmucositis, xerostomia, radiation caries and osteoradionecrosis, compromising the continuity and intensification of treatment (Duncan *et al.,* 2005).

The prevention and treatment of RT side effects, particularly mucositis, are controversial. In order to reduce the harmful effects of RT, the use of vitamins, hyperbaric oxygen, antibiotics, antiseptics, synthetic prostaglandins, plant extracts, salts and analgesics, alone or in combination, has been described (Duncan *et al.*; Veness *et al.*, 2006; Meca *et al.*, 2009), but these procedures are palliative. In Brazil, three preventive schemes for radiation caries and osteoradionecrosis are followed by most centers for RT: mouth rinses of chlorhexidine gluconate (0.12%), sodium fluoride (0.5%, aqueous solution) and sodium iodide (2%) in hydrogen peroxide (10 v/v). Unfortunately, there are no clinical strong evidences to show that these therapeutic schemes are really effective in a low income population and poor oral hygiene standards.

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Then, this study aimed to evaluate the influence of some preventive protocols and previous dental treatment on the occurrence of xerostomia, candidosis and on occurrence and severity of mucositis in patients undergoing radiotherapy for the treatment of HNC.

MATERIAL AND METHOD

Population. A total of 100 patients (90 males and 10 females) seen at the Megavoltage Radiotherapy Center, Barretos Cancer Hospital, and ABC Radiotherapy Center, Brazil, aged 18-83 years old (mean age 49.87 years old), with histological diagnosis of malignant disease, were included in the study. All patients gave written informed consent to be recruited for this study, which was approved by the Research and Ethics Committee of the School of Dentistry of Aracatuba, Sao Paulo State University - UNESP (Proc. 136/2007). All patients had at least ten teeth after initial dental treatment (IDT) and were able to comply with the preventive clinical protocols. Patients with previous diagnosis of HIV infection, use of antibiotics 3 months before the first visit to the Hospital, uncontrolled significant cardiovascular, pulmonary, renal or hepatic disease were excluded.

Eighty-four individuals presented squamous cell carcinoma, five patients harbored acinar cell carcinoma, five patients presented Hodgkin lymphoma, two patients had liposarcoma, two basal cell squamous carcinomas and two patients had malignant undifferentiated neoplasms. RT was carried out by mean of linear accelerator with mean radiation dose received by the patients varied from 4320 to 7020 cGy (mean dose 6233 cGy $\pm$ 954.45 cGy) and the fractioning dose was 180 cGy.

Clinical examinations and preventive protocols. Clinical examinations (soft tissues, dental and periodontal examinations) were performed in the first contact with the patient, before dental treatment (stage 1), before RT (stage 2), 15-22 days after first session of RT (stage 3), immediately after completion of RT (stage 4), and 30 days after RT (stage 5). During these visits, the presence and severity of mucositis were assessed as previously described by Trotti (2000) and Veness et al. Xerostomia was assessed by clinical signs, considering the symptoms described by patients, who received a questionnaire to verify the possibility of mild xerostomia in patients apparently not aware of this condition (Navazesh, 2003).

The patients were divided into two groups:

A) sixty-two patients who received oral hygiene instructions, dental prophylaxis and dental treatment prior to and during radiotherapy. These patients were further separated into three additional groups: 18 used solution of chlorhexidine gluconate oral rinse (0.12%) twice daily (Group I), 23 used sodium fluoride (0.5% in aqueous solution) once daily (Group II), and 21 employed sodium iodide (2%) in hydrogen peroxide (10 vol. v/v; Group III) once daily. The dental treatment consisted of removal of dental elements and trauma, endodontic treatment, scaling and root planning. Diet and nutrition guidelines, as well as hygiene evaluations and guidelines were also provided;

B) thirty-eight patients who did not receive any dental treatment or nutritional and dental guidelines in the prevention of side effects of radiotherapy. This absence of previous dental treatment was consequence of lack of dentists in the centers for radiotherapy or minor importance given to dental treatment by these oncologic patients (Group IV).

During radiotherapy, physical conditions of the patients, such as weight loss, and their complaints, and emotional condition were considered.

Statistical analyses. Statistical analyses were performed using the software Statistical Package for the Social Sciences (SPSS Incs v.13, Chicago, IL, USA). The frequency of detection of the microorganisms was computed for each subject. Significant differences between patients were tested using the Mann-Whitney test, Chi-square test or Fisher's exact test. Any difference of $P<0.05$ was considered statistically significant.

RESULTS AND DISCUSSION

Immediately after RT, mucositis, candidosis and xerostomia were almost universally observed regardless use of preventive protocols and previous dental treatment. Candidosis was present in 33.3 % Group I, 42.1% Group II, 37.5% Group III and in 61.3% Group IV patients and its development was statistically associated with absence of preventive protocols (Chi-square test, P= 0.036) and all preventive scheme presented efficacy in reducing the occurrence of oral

fungal infections 30 d. after conclusion of RT. Pseudomembranous candidosis was the most prevalent oral candidosis.

Occurrence of xerostomia (Chi-square test, P = 0.832) and mucositis (Chi-square test, P = 0.386) was not associated with any preventive protocol. However, patients who received chlorhexidine (Chi-square test, P = 0.031), fluoride (Chi-square test, P = 0.042), and sodium iodide (Chi-square test, P = 0.048) evidenced a significantly mild mucositis than patients who did not receive any preventive protocol. These differences between groups after radiotherapy were exacerbated 30 d. after the conclusion of the treatment and at that moment almost all cases of mucositis level III and IV occurred in patients of Group I. In addition, occurrence of mucositis was associated with the development of xerostomia (Chi-square test, P= 0.026) and most cases of mucositis level III or level IV occurred in patients who received 7020 cGy and harbored complete or partial removable dentures prior radiotherapy (Chi-square test, P=0.038).

In the present study, most patients with HNC are middle aged adult males who were chronic tobacco and alcohol consumers and had advanced tumors. In these patients, dental treatment before RT is necessary to avoid dental extractions and prevent osteoradionecrosis and other traumatic sequelae during and after RT. This is particularly true for patients with low socioeconomic conditions who show poor oral hygiene status (Bonan *et al.*, 2006).

Xerostomia is one of the major side effects of RT for HNC and the degree of destruction of glandular tissue depends largely on the dose of radiation administered and the salivary tissues are extremely sensitive to radiation in doses greater than 3000 Gy, which is sufficient to change salivary function permanently, although a partial recovery of the gland is likely to occur after 6-12 months (Cassolato& Turnbull, 2003). In the present investigation, xerostomia was the most prominent side effect of RT in the early stages of the RT and influenced the development of mucositis, probably due to reduction of the protective activities of saliva and

Table I. Oral conditions of the experimental groups at different moments. 1Group I, N= 18; Group II, N= 23; Group III, N= 21; Group IV, N= 38. Total = 100. 2Group I, N= 15; Group II, N= 19; Group III, N= 16; Group IV, N= 31.Total = 81. 3Group I, N= 12; Group II, N= 14; Group III, N= 13; Group IV, N= 21. Total= 60.

Side effect	Occurrence of side effects of radiotherapy N (%)		
	Before RT[1]	After RT[2]	30 d. after RT[3]
Mucositis			
Group I	0 (0.0)	12 (80.0)	6 (50.0)
Group II	0 (0.0)	14 (73.68)	8 (57.14)
Group III	0 (0.0)	13 (81.25)	8 (61.54)
Group IV	0 (0.0)	26 (83.87)	20 (95.24)
Dermatitis			
Group I	0 (0.0)	12 (80.0)	8 (66.67)
Group II	0 (0.0)	14 (73.68)	10 (71.43)
Group III	0 (0.0)	13 (81.25)	9 (69.23)
Group IV	1 (2.63)	26 (83.87)	17 (80.85)
Candidosis			
Group I	0 (0.0)	5 (33.33)	1 (8.33)
Group II	0 (0.0)	8 (42.11)	2 (14.28)
Group III	0 (0.0)	6 (37.50)	1 (7.33)
Group IV	1 (2.63)	19 (61.29)	12 (45.45)
Xerostomia			
Group I	2 (11.11)	13 (86.67)	9 (75.0)
Group II	4 (17.39)	16 (84.21)	9 (64.29)
Group III	2 (9.52)	14 (87.50)	8 (61.54)
Group IV	5 (13.16)	26 (83.87)	15 (71.43)

improvement of microbial colonization, especially fungi. It is well established the role of xerostomia in the development of candidosis and radiation caries (Guggenheimer & Moore, 2003). Immediately after RT, mucositis, candidosis and xerostomia were almost universally observed regardless use of preventive protocols and previous dental treatment.

The risk of mucositis has been a major concern for patients who receive RT for head and neck cancer (Jham et al., 2007), and the high susceptibility to mucositis is related to quantitative and qualitative changes in saliva, oral microbiota and immunological status (Leung *et al.,* 2001). Then, preventive measures before, during and after radiotherapy are necessary and should include instructions regarding diet, oral hygiene and application of chemical compounds to prevent microbial accumulation on oral surfaces.

Radiotherapy increases Candida carriage during the period immediately after RT and several factors may contribute for oral colonization by these microbial species, such as xerostomia induced by radiation, smoking, alcohol abuse and presence of prostheses (Mizugai *et al.*, 2007), and these fungi may exacerbate the inflammatory reactions in the oral mucosa, even in patients without clinical signs of candidosis.

Patients wearing complete or partial removable dentures were instructed not to use these prosthetic devices during and after radiotherapy, but this recommendation was not followed in the early stages of therapy, what, may have exacerbated the mucositis, particularly in Group IV, where hygiene standards of the prostheses were particularly unsatisfactory. However, the results presented here are related to a short period of time, immediately before, during and after RT, and these effects may represent the acute phase of mucositis, dermatitis and xerostomia, which can change in extended period of clinical evaluation.

Since the presence of oral microorganisms is thought to adversely affect the course of mucositis, antimicrobial therapy has been studied as an approach to intervention. The results of Tables I and II confirm data from Mecca *et al*. (2009), showing that the severity of mucositis may be mitigated by non-invasive or high cost procedures, such as use of oral rinses containing chlorhexidine, sodium fluoride or sodium iodide. Of these compounds, only chlorhexidine presents a significant antimicrobial activity on oral microorganisms (Saadeh, 2005), although some results from our laboratory show that the sodium iodide in hydrogen peroxide also has moderate inhibitory activity.

Table II. Occurrence and severity of mucositis associated with radiotherapy for treatment of head and neck cancer. Data obtained immediately after RT and 30d after RT. 1Group I, N= 15; Group II, N= 19; Group III, N= 16; Group IV, N= 31.Total = 81. 2Group I, N= 12; Group II, N= 14; Group III, N= 13; Group IV, N= 21. Total= 60.

Severity of mucositis	**Groups**			
	Group I	**Group II**	**Group III**	**Group IV**
Immediately After RT[1]				
Absence of Mucositis	3 (20.0)	5 (26.3)	3 (18.8)	5 (16.1)
Level I	5 (33.3)	3 (15.8)	1 (6.3)	3 (9.7)
Level II	2 (13.3)	3 (15.8)	3 (18.8)	3 (9.7)
Level III	4 (26.7)	6 (31.6)	6 (37.5)	12 (38.7)
Level IV	1 (20.0)	2 (10.5)	3 (18.8)	8 (25.8)
Total	12 (80.0)	14 (73.7)	13 (81.3)	26 (83.9)
30 days after RT[2]				
Absence of Mucositis	6 (50.0)	5 (35.7)	5 (38.5)	1 (4.8)
Level I	3 (25.0)	3 (21.4)	2 (15.4)	3 (14.3)
Level II	2 (16.7)	2 (14.3)	3 (23.1)	3 (14.3)
Level III	1 (8.3)	3 (21.4)	2 (15.4)	10 (47.6)
Level IV	0 (0.0)	1 (7.1)	1 (7.7)	4 (19.1)
Total	6 (50.0)	9 (64.3)	8 (61.5)	20 (95.2)

Many patients with head and neck cancer have poor oral hygiene behaviors and the adhesion of the patients to the preventive protocols in addition to follow-up visits (Chambers *et al.,* 2006), seems to be as important as chlorhexidine or other solutions for the prevention of side effects of radiotherapy. In this study, patients were invited to return monthly to dental office and this regimen probably interfered with the patients' compliance and, as a consequence, with clinical and microbiological outcomes of the preventive protocols.

Although preventive dental protocols used in centers for radiotherapy in Brazil are not fully adequate, since they do not modify or avoid cellular damage associated with RT, the results of the present investigation show that they minimize the severity of some symptoms, and the lack of a preventive dental protocol is deeply harmful to the patients.

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RESUMEN: Este estudio evaluó el efecto de tres protocolos de prevención y tratamiento dental en la aparición de xerostomía, mucositis y candidosis en pacientes oncológicos sometidos a radioterapia para el tratamiento de cáncer de cabeza y cuello. Un total de 100 pacientes fueron sometidos a radioterapia: treinta y ocho no recibieron tratamiento dental y instrucciones de higiene oral antes de la radioterapia y se presentaron en las visitas a los centros de radioterapia, durante y después de la radioterapia; sesenta y dos tratamiento dental y instrucciones de higiene oral antes de la radioterapia, y se instruyó a utilizar clorhexidina al 0,12% o el enjuague bucal con fluoruro de sodio al 0,5% el enjuague bucal o 2% de yoduro de sodio (peróxido de hidrógeno en 10 v/v) durante y después de la radioterapia. Los pacientes fueron sometidos dental, periodontal, intra y extra exámenes orales inmediatamente antes de la radioterapia, durante y después de la radioterapia. Dermatitis, mucositis y la xerostomía tendido a ser casi universal, pero la gravedad de la mucositis fue significativamente menor entre los pacientes que recibieron los protocolos de prevención. La aparición de candidiasis fue significativamente menor en pacientes que recibieron tratamiento dental preventivo y protocolos químicos. Aunque los protocolos de prevención dental utilizando en los centros de radioterapia en Brasil no son suficientes, los resultados de la investigación muestran que actualmente, al menos, minimizar la gravedad de algunos síntomas, y de la falta de un protocolo dental es profundamente perjudicial para los pacientes.

PALABRAS CLAVE: radioterapia, cáncer, mucositis, candidiasis, dermatitis, xerostomía, prevención.

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