Mucositis in head and neck cancer patients undergoing radiochemotherapy*

MUCOSITE EM PACIENTES PORTADORES DE CÂNCER DE CABEÇA E PESCOÇO SUBMETIDOS À RADIOQUIMIOTERAPIA

MUCOSITIS EN PACIENTES PORTADORES DE CÁNCER DE CABEZA Y CUELLO SOMETIDOS A RADIOQUIMIOTERAPIA

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ABSTRACT

The objective of present study was to classify oral mucositis according to the Common Toxicity Criterion (CTC) international parameters in head and neck tumor patients simultaneously treated with radio and chemotherapy, and characterize a patient profile in our area, observing the individuals' habits, tumor characteristics, treatment protocol and acute reaction intensity. Fifty patients undergoing simultaneous 66 to 70 Gy megavoltage radiotherapy and cisplatin/carboplatin chemotherapy were evaluated in this study. Weekly evaluations of the degree of mucositis were perfoemed according to CTC, a four-degree ordinal scale; 36% of all patients and 100% of those with diabetes discontinued treatment due to mucositis, showing that this pathology contributes to the severity of mucositis.

DESCRIPTORS

Head and neck neoplasms
Radiotherapy
Drug therapy
Mucositis
Oncologic nursing

RESUMO

O objetivo do presente trabalho é classificar o grau de mucosite oral de acordo com os parâmetros internacionais do Common Toxicity Criterion (CTC) em pacientes portadores de tumor de cabeça e pescoço submetidos à radioterapia e quimioterapia concomitantes, e caracterizar um perfil dos pacientes em nosso meio, verificando os hábitos dos indivíduos, as características do tumor, o protocolo de tratamento e a intensidade desta reação aguda. Neste estudo foram avaliados 50 pacientes, submetidos à radioterapia em megavoltagem com doses entre 66 a 70 Gy e quimioterapia com cisplatina ou carboplatina concomitante. Semanalmente foi avaliado o grau de mucosite de acordo com o CTC, uma escala ordinal que apresenta 4 graus. Observou-se interrupção do tratamento por mucosite em 36% do total de pacientes e em 100% dos pacientes diabéticos, o que nos permitiu verificar que esta patologia contribui para a gravidade da mucosite

DESCRITORES

Neoplasias de cabeça e pescoço
Radioterapia
Quimioterapia
Mucosite
Enfermagem oncológica

RESUMEN

El trabajo objetivó clasificar el grado de Mucositis ora de acuerdo a parámetros internacionales del CTC en pacientes portadores de tumores de cabeza y cuello sometidos a radioterapia y quimioterapia concomitantes, y caracterizar un perfil de pacientes en nuestro medio, verificando hábitos de los individuos, características del tumor, protocolo de tratamiento e intensidad de esta reacción aguda. Fueron evaluados 50 pacientes sometidos a radioterapia en megavoltaje con dosis entre 66 y 70 G y quimioterapia con cisplatino o carboplatino concomitante. Se evaluó semanalmente el grado de Mucositis según el Common Toxicity Criterio – CTC, una escala ordinal que presenta cuatro grados. Se observó interrupción del tratamiento por Mucositis en 36% del total de pacientes y en 100% de los pacientes diabéticos, lo que nos permite verificar que dicha patología potencia la gravedad de la mucositis.

DESCRIPTORES

Neoplasia de cabeza y cuello
Radioterapia
Quimioterapia
Mucositis
Enfermería oncológica

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INTRODUCTION

Head and neck cancer comprises all carcinomas originating in the muco-squamous epithelium, ranging from the lips, oral and nasal cavities, pharynx to the larynx and middle ear. It is the third most prevalent tumor around the world and represents 7% of the 22.4 million people diagnoses with cancer, excluding non-melanoma skin cancer[1].

With regard to Brazil, in 2010, about 14,120 new cases of mouth cancer occurred. This figure corresponds to the fifth most incident cancer among men and the seventh among women[2].

The treatments used for this disease involve three modalities: surgery, radiotherapy and chemotherapy, which can be administered exclusively or concomitantly[3].

Head and neck cancer patients who receive radiotherapy can develop reaction of different intensities in the mucosa. The association between radio and chemotherapy increases the incidence, severity and duration of oral mucositis, especially when combinations of different drugs and hyperfractionation schedules are used[4].

Mucositis causes significant pain, chewing and swallowing difficulties and is considered the most debilitating acute reaction during head and neck cancer treatment[3].

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The mechanism through which mucositis occurs is based on the fact that oral mucositis presents high levels of mitotic activity and high cell turnover. Due to the high degree of cell desquamation, there is a continuous need for cell multiplication to recover the oral mucosa. Tissues with high levels of mitotic activity respond rapidly to the radiation, as the most sensitive phases of the cell cycle are G2 and mitosis. Thus, the mucosa is rapidly affected[5]. The same is true for chemotherapeutic drugs. These interfere in the cell proliferation and division process. The fact that the mucous membranes are constantly renewed makes them extremely sensitive to the action of these drugs[5-6].

Among the methods used to assess the mucositis degree in clinical practice, it is important to highlight that adequate mucosa assessment is needed before starting head and neck radiotherapy and chemotherapy, as well as during treatment. A good assessment method needs to consider the patient's report, physical and nutritional status and a detailed oral cavity inspection[5,7].

Among the different mucositis classification scales, an analysis of 400 studies show that 43% use the scale of the National Cancer Common Toxicity Criteria (NCI-CTC), 38% use the World Health Organization (WHO) scale, 10% use specific scales and 5% use scales by collaborating groups, such as the scale the Radiation Therapy Oncology Group (RTOG) and the Eastern Cooperative Oncology Group (ECOG)[5] use.

In this study, we use the scale of the National Cancer Common Toxicity Criteria (NCI-CTC), as a Portuguese version is available which was authorized by the Cancer Therapy Evaluation Program (CTEP), an NCI organ responsible for publishing the table[8].

In view of the importance of mucositis during radiotherapy and chemotherapy for head and neck tumor, this study aims to classify the degree of mucositis according to international CTC 2.0 parameters in patients submitted to concomitant radiotherapy and chemotherapy and to verify whether the individual characteristics of patients, the disease and treatment influence the incidence and severity of the mucositis.

LITERATURE REVIEW

In clinical terms, the installation of mucositis is observed two weeks after the start of radiotherapy. It starts as an inflammatory process of the mucosa, predisposition to opportunistic infection and, depending on its intensity, can evolve to ulceration. Symptoms are pain and difficulties to eat, drink and talk. Consequences include weight loss and worsening of the patient's general condition[9].

Initially, mucositis is characterized by epithelial cell deaths and absence of substitution by new cells. Capillary blood vessels become hyperpermeable, leading to mucosal edema and decreased blood supply. These events determine the appearance of an evolutionary clinical situation with four phases: whitening of the mucosa, erythema, pseudomembrane and ulceration[7].

The most important risk factors determining greater mucosal cell susceptibility to radiotherapy and chemotherapy are: smoking, treatment type, age, chronic illnesses like diabetes[9].

A research accomplished in 1990[10] which involved 41 smokers who received hyperfractionated radiotherapy for head and neck tumor treatment, showed that patients who stopped smoking before the start of treatment presented blander reactions. Patients were divided in four groups: the first included patients who had never smoked, the second patients who had quit smoking before the start of treatment, the third those who quit smoking during treatment, but soon after restarted, and the fourth group with patients who had not quit smoking at any time during treatment. It was observed that the duration of mucositis for patients in groups 1 and 2 was 13 weeks, in comparison with 21 weeks in groups 3 and 4[10].

On the other hand, a research that involved 115 head and neck cancer patients submitted to concomitant radiotherapy and chemotherapy and aimed to observe the influence of cigarettes on tumor response to treatment and survival did not demonstrate any difference between the group of smokers and non-smokers regarding mucositis severity, although patients who smoked during treatment showed a drop in survival rates[11].

Specifically concerning radiotherapy, some factors can influence mucositis severity, including total dose, treated volume, fractioning and treatment time[12]. One study[13] confirms high incidence levels of mucositis in patients who receive radiotherapy, with 97% for patients receiving radiotherapy in a conventional fractioning schedule, 100% for patients with altered fractioning (accelerated or hyperfractionated fractioning) and 89% for patients receiving conventional fractioning radiotherapy and chemotherapy at the same time. This same study highlights that accelerated radiotherapy schedules can influence mucositis severity: 53% of patients with degree 3 and 4 mucositis were submitted to radiotherapy with fractioning alterations, in comparison with 34% of patients who received conventional fractioning and 43 % for patients treated with conventional fractioning radiotherapy and chemotherapy at the same time[13]. The incidence of degree 3 and 4 mucositis corresponded to 47% of patients treated with accelerated or hyperfractioning. In patients who received 70Gy with a daily fraction of 200 cGy for 7 weeks, the incidence level amounted to 25%[12-13].

As for age, young patients concomitantly submitted to radiotherapy and chemotherapy are more prone to mucositis development due to the high mitotic activity of the epithelial cells. On the other hand, elderly would be less prone to mucositis due to their low mitotic activity. With regard to elderly patients submitted to chemotherapy, however, the physiological decline of the kidney function can contribute to the development of mucositis at more advanced ages if no dose adjustment is made according to the capacity of the patient's kidney function. When the kidney function decreases, excretion time for the drug increases, so that it remains in the body longer and, hence, can cause more damage. The relation between the cell replication rate and the severity of damage the ionizing radiation causes suggests that, the higher the age, the lesser the severity of the reactions[14]. Another study[15] suggested that oral mucosa cell reparation is impaired with aging, contributing to the development of more severe mucositis.

With regard to diabetes, as this disease entails systemic repercussions, it can influence mucositis severity. Research shows that type I and II diabetes patients are at greater risk of developing gingivitis and periodontal disease due to the impaired healing and metalloproteinase enzymes' rapid degradation of the collagen[16].

METHOD

An observational cohort study was developed between January and December 2006 at a teaching hospital in São Paulo City. Approval from the hospital's Institutional Review Board was obtained under process 0365/05.

Out of 175 head and neck cancer patients forwarded to the Radiotherapy Sector, 50 complied with the inclusion criteria. Twenty-one of these were submitted to surgery, followed by radiotherapy and adjuvant chemotherapy, while 29 only received concomitant radiotherapy and chemotherapy.

The inclusion criteria in this study were: Patients over 18 years of age, diagnosed with head and neck cancer with histological evidence, in the following primary sites: oral cavity, oropharynx, hypopharynx, larynx and maxillary sinus, submitted to concomitant radiotherapy and chemotherapy, who signed the informed consent term.

The following exclusion criteria were adopted: Patients with enhanced trismus, making tge adequate inspection of the oral cavity and oropharynx impossible; patients submitted to another chemotherapy protocol, patients previously submitted to radiotherapy and/or chemotherapy and patients who did not conclude the initially proposed treatment.

Patients were submitted to radiotherapy with opposing parallel cervicofacial fields, with the total dose ranging between 66 and 70 Gy, in fractions of 2gy/day em aparelho de megavoltagem. They received chemotherapy withReceberam quimioterapia com cisplatina na dose 30 mg/m2 of cisplatin per week or weekly carboplatin, calculated according to the plasma concentration curve.

The nurse interviewed the patients on the treatment planning day. On this occasion, the first mucosa assessment took place, repeated every week during the entire treatment. The radiotherapist assessed the degree of mucositis, followed by the nurse.

For the interview, a form was prepared with general information, a history with individual aspects for each patient, disease and treatment characteristics.

The criterion adopted to assess the degree of mucositis was the Common Toxicity Criterion – CTC, which is a four-degree ordinal scale: Grade 0-no change; Grade 1-erythema of the mucosa; Grade 2-patchy pseudomembranous reaction (patches generally = 1.5 cm in diameter and non-contiguous); Grade 3-confluent pseudomembranous reaction (contiguous patches generally > 1.5 in diameter); Grade 4-necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion[8]. According to the evolution of the oral mucositis during treatment, therapeutic measures were taken, depending on the presented degree.

The parameters for individual clinical characteristics of the disease, of the mucositis (global incidence of different grades, incidence per anatomic region, grades according to weeks of treatment) and main complaints reported by the patients were submitted to descriptive analysis.

The parameters for the reaction of the mucosa according to individual clinical characteristics were submitted to inferential analysis. For the inferential analysis, the patients were grouped as follows: patients whose treatment was not suspended because of the mucositis (grades 0, 1 and 2*) and patients whose treatment was suspended because of the mucositis (grades 2** and 3). The treatment suspension criterion adopted for grade 2 patients was reported dysphagia and odynophagia, compromising nutrition and the presence of non-confluent but patchy pseudomembranous reaction.

The statistical tests used were: Fisher's exact test (P) and chi-square (x2).

For all tests, the rejection level of the null hypothesis was set at 0.05 or 5% ($p < 0.05$), marking significant ratios with an asterisk and non-significant ones with (NS).

RESULTS

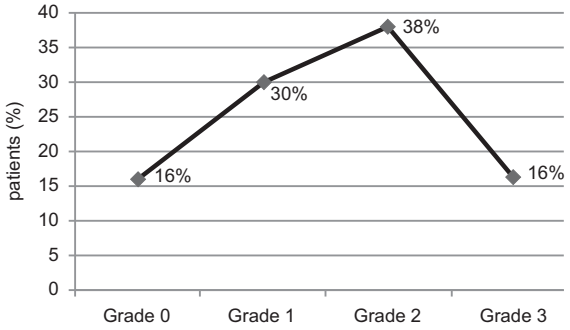
In this study, 45 (90%) patients were male and 5 (10%) female. The mean age was 58 years, 39 (78%) patients were white and 11 (22%) black. Fourty (80%) patients indicated they had quit smoking before the start of treatment, while 8 (16%) admitted they had not quit smoking and only 2 (4%) affirmed they had never smoked. Only 15 (30%) patients were hypertensive and 3 (6%) diabetic.

As for the primary site, 10 patients suffered from oral cavity cancer, 32 oropharyngeal, 4 hypopharyngeal, 3 laryngeal and 1 maxillary sinus cancer.

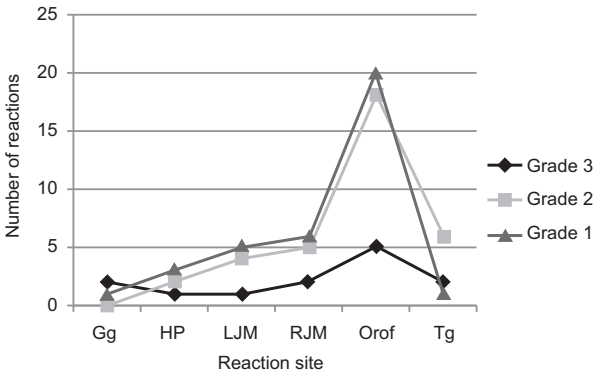
A predominance of grade 1 and 2 mucositis was observed (68%) (Picture 1), with higher incidence levels in the oropharyngeal region (51%) (Picture 2), between the third and sixth week of treatment (Picture 3).

Of all patients, 86% had their treatment interrupted at some time, in 36% of treatment due to mucositis. The mean interruption time was 5.9 days.

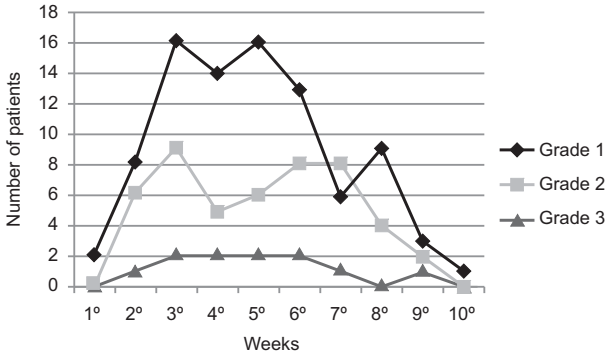
The main complaints the patients reported after the start of treatment were loss of taste (41%) and xerostomia (29%) (Picture 4).



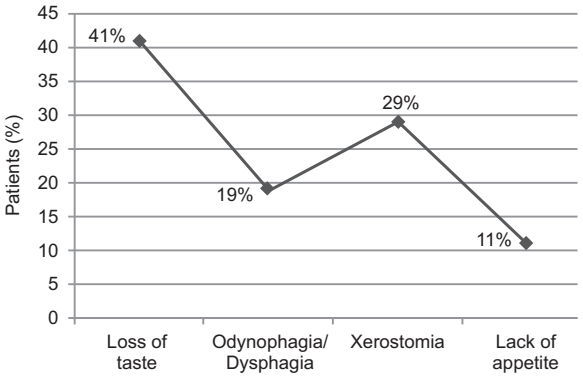
Picture 1 – Incidence of different grades of mucositis



Picture 2 – Incidence of mucositis according to topography



Picture 3 – Grade of mucositis according to treatment weeks



Picture 4 – Main patient complaints

The analysis of patients' individual clinical characteristics, disease and treatment characteristics showed that diabetes significantly increases mucositis severity (Table 1).

Table 1- Interrupted (IT) and non-interrupted (NIT) treatment due to mucositis classified according to CTC 2.0 - São Paulo – 2005/2006

	NIT Grade 0.1 and 2* N (%)	IT Grade 2** e 3 N (%)	Total N (%)	P
Age range				
Up to 60years	21 (67.7)	10 (32.2)	31 (100)	0.96 (NS)
More than 60 years	13 (68.4)	6 (31.5)	19 (100)	
Gender				
Female	3 (60)	2 (40)	5 (100)	0.60 (NS)
Male	31 (68.9)	14 (31.1)	45 (100)	
Race				
Black	7 (63.6)	4 (36.3)	11 (100)	0.49 (NS)
White	27 (69.2)	12 (30.8)	39 (100)	
Hypertension				
Yes	10 (66.7)	5 (33.3)	15 (100)	0.57 (NS)
No	24 (68.6)	11 (31.4)	35 (100%)	
Diabetes				
Yes	0	3 (100)	3 (100)	0.02*
No	34 (72.3)	13 (27.7)	47 (100)	
Smoking				
Smoker	7 (77.8)	2 (22.2)	9 (100)	0.44 (NS)
Former smoker	25 (64.1)	14 (35.9)	39 (100)	
Non smoker	2 (100)	0	2 (100)	
Staging				
II	4 (100)	0	4 (100)	0.37 (NS)
III	6 (60)	4 (40)	10 (100)	
IVA	19 (63.3)	11 (36.7)	30 (100)	
IVB	5 (83.3)	1 (16.7)	6 (100)	
Surgery				
Yes	19 (73.1)	7 (26.9)	26 (100)	0.54 (NS)
No	15 (62.5)	9 (37.5)	24 (100)	

Grade 2* non-interrupted treatment (NIT);
Grade 2 ** interrupted treatment (IT)

DISCUSSION

Mucositis is quite a common complication in head and neck cancer patients treated with chemotherapy and radiotherapy. It is associated with discomfort and intake and swallowing difficulty, and its consequences can range from treatment interruption to nasogastric probe use and hospitalization[9].

In this research, the predominance of grade 1 (30%) and 2 (38%) mucositis was observed, with the oropharynx as the main site. This is due to the fact that most patients in the sample presented oropharyngeal and oral cavity tumors. In literature, we found a study of head and neck cancer patients submitted to different treatment types: concomitant radiotherapy and chemotherapy, convential or hyperfractionated radiotherapy, or chemotherapy only. The presented results were very close to those found in this study, in which 83% of patients presented some grade of mucositis; the moderate grade predominated in 35%[17]. In another study of head and neck cancer patients submitted to different treatment modes, however, 91% of patients developed some grade of mucositis, but grade 3 (60%) predominated[18].

Higher mucositis incidence levels were found between the third and sixth weeks of treatment, with a predominance of grade 1 and 2 reactions. Another study shows higher incidence levels of mucositis between the third and seventh week of treatment, with a predominance of grade 3, when patients were treated with concomitant radiotherapy and chemotherapy, but with altered fractionation; which could justify the higher incidence level of grade 3[18]. Another factor is that, in the present study, some patients' treatment was interrupted when they suffered from grade 2 mucositis, which did not permit the evolution of toxicity. In literature, we found studies that affirm that, after one or two weeks of radiotherapy, oral erythema can be verified. After the second week, with about 20 Gy, edema can be verified; the erythema is no longer that visible due to the pressure exerted on the capillary vessels; this is provoked by the accumulation of extravascular liquid. After 3 weeks, with about 30Gy, vascular permeability is enhanced, contributing to increase the edema[19-20]. Based on these studies, it is perceived that the signs become more evident as from the third week, without ignoring individual variations in responses.

As for individual clinical factors, our results showed that age was not an important factor for mucositis severity. Some authors mention that that the chance of mucositis decreases with age. This is supposedly due to the low rate of cell replication in elderly patients, as cells with high mitotic activity are more sensitive to radiotherapy and chemotherapy. It should be highlighted that the mean age of the study participants was lower (57.52 years) in comparison with the literature (61.3 and 60.7 years)[9,17].

Regarding smoking, this factor showed no statistical significance, probably due to the low incidence level of smokers in our sample. The results showed that (16%) admitted smoking during treatment, and only two had their treatment interrupted because of the mucositis. Research is found in the literature with diverging results; while some did not observe influence from smoking on mucositis, others affirmed that smoking exerted influence when the irradiated volume was smaller[10-11]. It should be taken into account that, in these studies, patients were submitted to different treatments.

Concerning diabetes, although a small number of patients in our sample (6%) presented the disease, 100% had their treatment interrupted due to the severity of the mucositis, as evidenced by the statistical significance. In literature, we found a research that observed that oral cavity and oropharyngeal cancer patients who were diabetics and submitted to radiotherapy with altered fractioning were at greater risk of developing grade 3 and 4 mucositis[17]. Furthermore, studies were observed in which the authors affirm that, as a systemic disease, diabetes can influence mucositis severity, and that this pathology should be taken into account in patients receiving head and neck irradiation[21].

According to the literature, type 1 and 2 diabetes patients are at greater risk of developing gingivitis and peri-

odontal disease. This is due to impaired healing after rapid collagen degradation by metalloproteinase enzymes. In addition, the inflammatory process is accelerated, which hampers healing, enhances monocyte response, induces high levels of glycosylated proteins, increases the advanced glycation end products (AGEs) in tissues and decreases the chemotaxis of neutrophils[16,21-22]. Thus, based on the above information and the present study results, we believe that diabetic patients submitted to radiotherapy and chemotherapy, treatments that induce inflammation, can present predisposition to the development of more severe mucositis, due to factors sensitizing the oral mucosa.

CONCLUSION

When analyzed on the whole, the present study data show that head and neck cancer patients submitted to concomitant radiotherapy and chemotherapy predominantly present grade 1 and 2 mucositis between the third and sixth week of treatment. Among individual patient, disease and treatment characteristics, only diabetes enhanced the development of severe mucositis. Therefore, we believe that diabetic patients can benefits from more frequent monitoring during treatment, including specific orientation and care, such as glucose and medication control. It is important for nurses to heed these parameters, considering that, in view of their presence at the radiotherapy and chemotherapy sectors, they can collaborate to enhance treatment and improve patients' quality of life.

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