

Acute toxicities of chemoradiotherapy treatment in patients with head-neck cancer

Toxicidades agudas do tratamento com quimiorradioterapia em pacientes com câncer de cabeça-pescoço

Toxicidades agudas del tratamiento con quimiorradioterapia en pacientes con cáncer de cabeza y cuello

RESUMO

Objetivo: Identificar e classificar as toxicidades agudas do tratamento concomitante de quimioterapia e radioterapia em pacientes com câncer de cabeça e pescoço. Método: Estudo transversal, quantitativo, descritivo. Foram avaliados 56 pacientes com câncer de cabeça e pescoço em tratamento quimiorradioterápico no Sul do Brasil, entre maio e julho de 2013. Resultados: 89,3% eram homens, com idade entre 46 e 60 anos (57,1%). Sobre as toxicidades da radioterapia, as estruturas mais afetadas foram faringe e esôfago (94,6%), pele (91,1%) e mucosa oral (76,8%), com predomínio dos graus 3, 1 e 2, respectivamente. Em relação à quimioterapia, a mucosite oral grau 1 (50%), alteração grau 1 em sistema nervoso periférico motor (46,4%) e em rede venosa (37,5%), foram os principais achados. Conclusão: Estes sintomas comprometem a adesão ao tratamento e a qualidade de vida, sendo necessário monitorização e avaliação regular dos pacientes, a fim de evitar efeitos secundários graves.

DESCRIPTORES: Neoplasias de Cabeça e Pescoço; Quimiorradioterapia; Testes de Toxicidade Aguda; Avaliação em Enfermagem.

ABSTRACT

Objective: To identify and classify the acute toxicities of the concomitant treatment of chemotherapy and radiotherapy in patients with head and neck cancer. Method: Cross-sectional, quantitative, descriptive study. A total of 56 patients with head and neck cancer undergoing chemoradiation therapy in southern Brazil between May and July 2013 were evaluated. Results: The sample showed that 89.3% were men, aged between 46 and 60 years (57.1%). Regarding radiotherapy toxicities, the most affected structures were pharynx and esophagus (94.6%), skin (91.1%) and oral mucosa (76.8%), with a predominance of grades 3, 1 and 2, respectively. About chemotherapy, grade 1 oral mucositis (50%), grade 1 motor peripheral nervous system alteration (46.4%), grade 1 venous network alteration (37.5%) were the main findings. Conclusion: These symptoms compromise treatment adherence and quality of life, requiring regular monitoring and evaluation of patients, in order to avoid serious side effects.

DESCRIPTORS: Head and Neck Neoplasms; Chemoradiotherapy; Toxicity Tests, Acute; Nursing Assessment.

RESUMEN

Objetivo: Identificar y clasificar las toxicidades agudas del tratamiento concomitante de quimioterapia y radioterapia en pacientes con cáncer de cabeza y cuello. Método: Estudio transversal, cuantitativo, descriptivo. Se evaluaron un total de 56 pacientes con cáncer de cabeza y cuello sometidos a quimiorradioterapia en el sur de Brasil entre mayo y julio de 2013. Se aplicaron cuestionarios para caracterización sociodemográfica y clínica, evaluación de las toxicidades agudas de la radioterapia y la quimioterapia. Resultados: El 89,3% eran hombres, con edades entre 46 y 60 años (57,1%). En cuanto a las toxicidades de la radioterapia, las estructuras más afectadas fueron faringe y esófago (94,6%), piel (91,1%) y mucosa oral (76,8%), con predominio de los grados 3, 1 y 2, respectivamente. Con relación a la quimioterapia, la mucositis oral grado 1 (50%), el sistema nervioso periférico motor grado 1 (46,4%), la alteración de la red venosa grado 1 (37,5%) fueron los principales hallazgos. Conclusión: Estos síntomas comprometen la adherencia al tratamiento y la calidad de vida, requiriendo seguimiento y evaluación periódica de los pacientes para evitar efectos secundarios graves.

DESCRIPTORES: Neoplasias de Cabeza y Cuello; Quimiorradioterapia; Pruebas de Toxicidad Aguda; Evaluación de Enfermería.

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INTRODUCTION

Head and neck cancer (HNC) is the sixth most common cancer in the world. Squamous cell carcinoma is the most frequent histological type, and affects the upper digestive tract, lip, oral cavity, pharynx (oropharynx, nasopharynx, hypopharynx), maxillary sinuses, nasal cavity and ethmoid sinuses, salivary glands and the thyroid gland.¹ In Brazil, among these tumors, those of the oral cavity, larynx and oropharynx are the most frequent.²

In the conventional treatment of HNC, radiotherapy (RT) is the most used and its indication may vary according to the resectability and anatomical location of the tumor.³ RT can be included in the neoadjuvant or adjuvant clinical protocol alone or in combination with chemotherapy (CT). When used concomitantly, it is associated

with better locoregional disease control when compared with RT alone.⁴

Advances in HNC therapy have resulted in an increase in the overall response rate, overall survival, free from disease progression and unfavorable outcomes.⁵ However, the use of CT-integrated radiation therapy and/or targeted therapies are also related to an increase in acute and late toxicity, despite studies finding these effects acceptable.^{1,6,7}

Acute toxicities occur within three months after the end of cancer treatment, in the modality of combined CT and RT, the most common are mucositis, xeroderma, nausea, dysphagia, dysgeusia and radiodermatitis.⁶⁻⁹ These effects cause discomfort and affect the patient's quality of life.⁶⁻⁹

The monitoring of these patients by the nurse is essential, since he is considered the manager of care, exerting a

positive influence on the conduct and adherence of the treatment, on health education, on the management of adverse events and even on the survival of patients.⁸ Among the duties of the oncology nurse, are the identification of the client's needs according to their biopsychosocial characteristics, associated with their peculiarities, in addition to the planning and execution of actions aimed at preventing and minimizing adverse events and their complications throughout the treatment.^{8,9}

In view of the above, the objective was to identify and classify the acute toxicities of the concomitant treatment of chemotherapy and radiotherapy in patients with head and neck cancer.

METHOD

This is a descriptive, cross-sectional study with a quantitative approach.

ch. Conducted with 56 patients with HNC treated at a High Complexity Center in Oncology in Southern Brazil, which composed a convenience sample. The research was approved by the Research Ethics Committee (CAAE: 07290612.0.0000.0098).

Data collection took place between May and July 2013. Inclusion criteria were: age equal to or greater than 18 years, diagnosis of HNC and concomitant treatment of RT and chemotherapy. Among the exclusion criteria are: previous CT and RT and lack of adherence to treatment.

Patients were invited to participate in the research at the first nursing consultation at the CT or RT outpatient clinic, all who agreed to participate in the research signed the Free and Informed Consent Term (FICT) according to Resolution 466/2012 of the National Health Council. Data collection took place in the second week after the start of treatment, with the application of the following instruments: a sociodemographic and clinical characterization questionnaire prepared by the researchers; guide for the evaluation and classification of the acute toxicities of chemotherapy and radiotherapy, being them respectively, the toxicity graduation criteria elaborated by the National Cancer Institute (INCA - Instituto Nacional do Câncer)⁹ and the Acute Radiation Morbidity Scoring Criteria¹⁰ prepared by the Radiation Therapy Oncology Group (RTOG).

The grading criteria for chemotherapy-related toxicity use a scale from grade zero (no toxicity) to grade four (severe toxicity). The acute toxic effects of CT are grouped by systems, evidenced by signs and symptoms of dermatological, cardiovascular, pulmonary, neurological, gastrointestinal, auditory, ophthalmological, immunological and genitourinary alterations.⁹ The scoring criterion for acute radiation morbidity is¹⁰, graded from zero (no toxicity) to four (severe toxicity), grouped by affected and irradiated anatomical structures

(skin, mucous membrane, pharynx and esophagus, upper abdomen, lower abdomen and genitourinary system). In this study, for RT toxicity, the lower abdomen and genitourinary system were not evaluated, as these areas are not part of the irradiated regions in the RT planning of the HNC.

Data was electronically stored and tabulated in Microsoft Office Excel 365, exported to the Statistical Package for the Social Sciences™ (SPSS for Windows, version 19.0. Variables were analyzed using descriptive statistics.

RESULTS

Of the 56 participants evaluated,

there was a predominance of male patients (89.3%); aged between 46 and 60 years (57.1%), with complete elementary education (55.4%). As for the risk factors for HNC, 78.6% were alcoholics at some point in their lives,

57.2% used alcohol for 20 years or more, and 56.8% reported having abandoned this addiction at least 5 years ago. Regarding tobacco consumption, the majority claimed to have used it (87.5%), with 79.6% claiming to have smoked for more than 20 years, and 75% had stopped smoking for one year, and 16.1% continued to smoke even after the oncological diagnosis. Data regarding sociodemographic characterization and consumption of alcohol and

Table 1- Distribution of sociodemographic characteristics and of drinking and smoking habits in patients with head and neck cancer undergoing chemotherapy. Curitiba, PR, Brasil, 2013.

Variables	n	%
Age		
18 to 30 years	1	1,8
30 to 45 years	5	8,9
46 to 60 years	32	57,1
61 to 75 years	17	30,4
Over 76 years old	1	1,8
Gender		
Male	50	89,3
Female	6	10,7
Education		
Illiterate	1	1,8
Incomplete Elementary school	13	23,2
Complete Elementary school	31	55,4
Incomplete High school	1	1,8
Complete High school	7	12,5
Higher education	3	5,4
Drinking habits		
Doesn't drink alcohol	12	21,4
Ex-alcoholic	41	73,2
Alcoholic	3	5,4

tobacco are described in table 1.

The mean radiation dose received was 50.4 Gy, which ranged from 22 to 70 Gy (standard deviation=11.8). Among the comorbidities, systemic arterial hypertension was the most prevalent (84.2%). Other clinical features are shown in Table 2

The details of the grading of acute toxicity according to the anatomical structure can be seen in table 3. Regarding severity, the pharynx and esophagus structures were the most affected, since they presented a higher frequency of toxicity in grade 3 (57.1%) when compared to the other structures, but no study participant developed grade 4. On the skin, 90% had radiodermatitis, with grade 1 being the most prevalent, that is, they had mild erythema, dry scaling and epilation.¹⁰

Regarding the acute toxicities of CT therapy, there was a predominance of oral mucositis (60.7%), constipation (55.4%), changes in the motor peripheral nervous system (PNS) (51.8%), nausea (46.4%) and altered venous network (42.9%). Grade zero portrays the absence of toxicity, it is noteworthy that no participant developed grade 4 related to CT, the distribution of the graduation of these most prevalent toxicities can be seen in table 4.

DISCUSSION

HNC is a generic term defined to describe malignant tumors located mainly in the oral cavity, larynx, pharynx and paranasal sinuses.¹¹ About 40% of HNCs occur in the oral cavity, 15% in the pharynx, 25% in the larynx and the remainder in the remaining sites (salivary glands, thyroid).¹² In this research, the most prevalent tumor locations were the tongue (28.6%), larynx (19.6%) and oropharynx (16.1%).

In Brazil, this set of tumors are among the ten most frequent in the male population over 40 years of age, and, for the female population, in the same age group, among the twenty

Smoking habits		
Non-smoking	7	12,5
Ex-smoker	40	71,4
Smoker	9	16,1
Total	56	100,0

Source: Research Data.

Table 2 - Distribution of oncological patients evaluated according to the clinical characterization relevant to the diagnosis and chemoradiotherapy treatment. Curitiba, PR, Brazil, 2013.

Variables	n	%
Histological diagnosis		
Squamous cell carcinoma	56	100
Clinical staging		
II	3	5,3
III	17	30,4
IV	36	64,3
Tumor location		
Amygdala	4	7,1
Mouth	2	3,6
Esophagus	3	5,4
Hypopharynx	1	1,8
Lower lip	1	1,8
Larynx	11	19,6
Tongue	16	28,6
Oropharynx	9	16,1
Pyriiform sinus	4	7,1
Retromolar trigone	3	5,4
Vallecula	2	3,6
Comorbidities		
Absence of comorbidities	37	66,0
One or more comorbidities	19	34
Radiotherapy Technique		
2D- RT	53	94,6
Intensity Modulated RT (IMRT)	3	5,4
Chemotherapy Protocol		
Cisplatin	4	7,1
Cisplatin+5-Fluorouracil	49	87,5
Carboplatin	3	5,4

Caption: 2D-RT: conventional two-dimensional radiotherapy; Source: Research Data.



most frequent.¹³ In agreement with these data, males prevailed (89.3%); aged between 46 and 60 years (57.1%) and with complete elementary education (55.4%).

When diagnosed early, a better prognosis is observed for the treatment of HNC in patients. The diagnostic time directly influences the staging and regression of the initial tumor, so that the more advanced the stages, the higher the mortality rate.¹⁴ While French and Japanese studies indicated the most advanced stages of the disease as predominant (73.7% and 76.6% of the samples); in an Italian study, 58% were in early stages.^{15,16,17} In the findings of this research, 94.7% had stages III and IV, converging with the results of other studies.

Among the main carcinogenic factors, the use of tobacco and alcohol, combined, increases the chances of developing one of the HNCs by 30 times.¹⁵ A Brazilian case-control study, with patients diagnosed with HNC, inferred that 74.5% of the 2,886 cases analyzed can be attributed to smoking and alcohol consumption. Significant data when considering that tobacco use associated with chemoradiotherapy increases the risk of new tumors.⁵

Continued exposure to tobacco and alcohol proportionately increases the risk of developing HNC. Acetaldehyde, an alcohol metabolite, interferes with DNA synthesis and repair, promoting dysregulation of DNA synthesis and consequent cancerous replication.^{11,18} As for cigarette elements, nitrosamines and genotoxic carcinogenic polycyclic hydrocarbons, in the long term, can also change the molecular profile of individuals and cause mutations. However, not everyone who uses these substances develops HNC, indicating the presence of individual variation in genetic susceptibility.^{3,18} In this survey, 77.3% were alcoholics at some point in their lives and 87.5% were smokers. An important data concerns 16.1% of respondents who remained active smokers during

Table 3 - Distribution of cancer patients undergoing concomitant treatment, according to anatomical structure and grading of radiotherapy toxicities. Curitiba, PR, Brazil, 2013.

Variables	Grade 0		Grade 1		Grade 2		Grade 3	
	n	%	n	%	n	%	n	%
Upper abdomen	15	26,8	6	10,7	33	58,9	2	3,6
Pharynx and Esophagus	3	5,4	9	16,1	12	21,4	32	57,1
Oral mucosa	13	23,2	17	30,4	25	44,6	1	1,8
Skin	5	8,9	28	50	19	33,9	4	7,1

Source: Research Data.

Tabela 4- Distribuição da graduação das toxicidades agudas mais frequentes do tratamento com QT, Curitiba, PR, Brasil, 2013.

Variables	Grade 0		Grade 1		Grade 2		Grade 3	
	n	%	n	%	n	%	n	%
Oral Mucositis	22	39,3	28	50	4	7,2	2	3,6
Constipation	25	44,6	13	23,2	16	28,6	2	3,6
Motor peripheral nervous system	26	46,4	26	46,4	4	7,2	0	0
Nausea	30	53,7	12	21,4	13	23,2	1	1,7
Venous network	32	57,1	21	37,5	3	5,4	0	0

Source: Research Data.

ring the survey period.

Concomitant RT and CT treatment is the standard of choice for locally advanced HNC, particularly when relating cisplatin (CDDP) to RT, as it significantly improves overall survival, progression-free survival, and locoregional control compared to that seen with radiotherapy alone in patients with locally advanced HNC.²⁰ Similarity with data from this research was observed, as 53 patients used CDDP with RT, of these four patients only used CDDP, the others were associated with fluoracyl (5FU).

It is noteworthy that in cases of contraindication to the use of CDDP, carboplatin may be indicated, as occurred in three patients in this study. In a retrospective survey that evaluated 25 patients with HNC who received carboplatin and concomitant RT, showed that complete response was observed in

70% of patients, with a median duration of progression-free survival of 42.7 months, so it may be an option for patients not eligible for CDDP.²¹

In an Indian study that evaluated 109 patients with HNC, 35 underwent concomitant chemotherapy and RT and the most frequent toxicities were: acute mucositis, skin toxicity, xerostomia, weight loss, and trismus. Similar results were observed in this study, thus highlighting the need to guide the importance of maintaining nutritional care and oral hygiene.²⁴

The toxicities caused by chemotherapeutics are related to their nonspecificity by tumor cells and cytotoxic effects on normal cells. These events predominate in cells that are in constant cell division, such as those in hematopoietic tissue, germ tissue, hair follicles, and the gastrointestinal lining. Despite increasing survival, they nega-

tively influence quality of life due to toxicities.^{25,26}

Oral mucositis is a manifestation that appears after CT or RT treatment of HNC, due to myelosuppression, direct cytotoxicity of chemotherapeutic agents, immune suppression or hyperreactivity.²⁰ It is characterized by inflammation and ulceration of the oral mucosa, which becomes swollen, erythematous, and friable, resulting in pain, discomfort, dysphagia, and systemic weakness.^{7,20,21}

In this study, the toxicity that affects the oral mucosa was the most reported by patients on chemotherapy, with 50% presenting grade I (presence of erythema and pain); and in relation to RT, it was considered the third toxicity that most bothered the patients, but the most frequent degree was 2 (presence of erythema and ulcers, but the patient eats normally). Similarly, it occurred in a study carried out in the southeastern region of Brazil, in which the authors described mucositis as the most prevalent complication in the combined treatment with CT and RT.²⁷

Constipation was found in 31 patients, grade 2 being the most prevalent, with 28.6%. It is noteworthy that CDDP, carboplatin and 5FU are chemotherapeutic agents that induce gastrointestinal symptoms such as nausea, vomiting and diarrhea.^{5,21} It is inferred from this result that patients are using opioids to relieve cancer pain, thus causing constipation. Another reason that can be inferred would be the decrease in food intake as a result of mucositis and nausea.

When approaching the RT modality, 53 patients underwent conventional RT (2D-RT) and three received intensity-modulated radiotherapy (IMRT). IMRT has been used since 1995, represents a major therapeutic advance for patients who underwent this technique, confer the ability to create treatment fields with varying intensity of radioactive beams through the use of inverse planning and the iterative optimization

of algorithms.²² In addition, lower doses of radiation are delivered to normal tissues, while maintaining or increasing the dose in the target areas, being the most appropriate option compared to 2D-RT and three-dimensional conformal radiotherapy, for this reason it causes less toxicities.²² However, in Brazil, in the context of the Unified Health System (SUS), this high-cost procedure has not yet been incorporated into the list of treatments available for this type of tumor in early and locally advanced stages²³, it should be noted that the present research had a philanthropic hospital as its scenario, where 95% of the consultations are aimed at SUS users.

Although concomitant CT and RT have adequate clinical results, it is observed that patients are affected by toxicities, especially radiodermatitis and dysphagia.²⁸ Radiodermatitis is defined as a set of skin lesions caused by excessive exposure to ionizing radiation, which leads to skin dehydration and can lead to complications such as ulceration or local infection.⁶ It is estimated that 80 to 90% of patients treated with RT develop some form of skin reaction.²⁹

In this study, 91% of the patients had some type of radiodermatitis, the most prevalent being grade I. As for prevention and treatment, there are recommendations on the use of essential fatty acids (EFA), hydrocolloid plates, products based on Aloe vera and *Calendula officinalis*. In addition, the use of light technology such as photobiomodulation has good effects on healing, pain reduction and inflammation reduction.²⁹

Pharyngeal and esophageal toxicity correspond to dysphagia or severe odynophagia with dehydration, requiring the use of a nasogastric or enteral tube for feeding, and in more severe cases parenteral nutrition.²⁸ It was found in 94.6% of patients in this study, dysphagia is a common sequela in HNC during and after chemoradiotherapy. 70% have dysphagia 12 months after the end

of treatment, causing swallowing problems and a negative impact on quality of life.³⁰

It is noteworthy that these adverse events can be prevented or minimized through personalized self-care guidelines for patients and caregivers, according to their biopsychosocial peculiarities, on specific aspects of their therapy, combined with adequate nutritional support, implementation of clinical protocols for early interventions, based on scientific evidence.^{8,12}

CONCLUSION

The pharynx and esophagus, skin and oral mucosa structures were the most affected by ionizing radiation. In relation to chemotherapy, oral mucositis, alteration in motor PNS evidenced by the sensation of subjective weakness, constipation and nausea, were the most frequent symptoms. Therefore, the most prominent acute toxicities, resulting from the concomitant treatment, were dysphagia, oral mucositis and radiodermatitis; with variable levels, but no participant developed the most severe level.

The presence of toxicities resulting from the concomitant treatment can influence the adherence to therapy and the quality of life of patients with HNC. These patients must be monitored and evaluated periodically in order to prevent and reduce the degree of severity of adverse events, avoiding complications and possible interruptions of treatment, providing an improvement in the health-related quality of life of these individuals.

The results of this investigation can contribute to the clinical practice of nurses in oncology, providing a basis for an evidence-based activity, helping in the planning and management of care for this clientele. However, further research on the subject should be encouraged.

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