



Chemotherapy-induced oral stomatotoxicity

Estomatotoxicidad bucal inducida por quimioterapia

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ABSTRACT

The principal aim of the present study was to determine the type of oral lesions most frequently found in breast cancer patients treated with chemotherapy at the General Hospital in Mexico City and establish under which circumstances these manifestations occur. A file review was undertaken, spanning from 1994 to 1999. Inclusion and exclusion criteria were established. Out of 405 cases under consideration, 327 cases were included in the sample. In these selected cases, stomatotoxicity was present in 129 cases: 89 cases exhibited only a single oral manifestation, 19 cases showed two and 14 cases exhibited more than two (three or more). Relationship between histological lineage was reflected; it was present in the infiltrating ducts, lobular and others ($p < .005$). Treatment schemes with chemotherapy were integrated with 5-fluorouracil, adriamycin, cyclophosphamide and methotrexate ($p < .005$) dosage and stomatotoxicity were related ($p < .005$).

Key words: Stomatotoxicity, mucositis, xerostomy, sialorrhea.

Palabras clave: Estomatotoxicidad, mucositis, xerostomía, sialorrea.

RESUMEN

El objetivo principal de este estudio fue determinar el tipo de lesiones bucales más frecuentes en las pacientes con cáncer de mama tratadas con quimioterapia en el Hospital General de México, y establecer en qué condiciones se presentan dichas manifestaciones. Se realizó una revisión de expedientes entre los años de 1994 y 1999, estableciendo los criterios de inclusión y exclusión. De un total de 405 que fueron considerados, se incluyeron en la muestra 327 expedientes. De ellos, la incidencia de estomatotoxicidad se presentó en 122 casos, 89 de los cuales presentaron una sola manifestación bucal, 19 presentaron dos, y 14 pacientes reportaron más de dos. La relación entre la estirpe histológica del tumor se refleja presentándose en el canalicular infiltrante, lobular y otros ($p < .005$). Los esquemas de tratamiento con quimioterapia fueron integrados con: 5-fluoracilo, adriamicina, ciclofosfamida y metotrexato ($p < .005$). La dosis y estomatotoxicidad se relacionaron con $p < .005$.

INTRODUCTION

Cancer is a chronic-degenerative disease which presently is on the rise due to the increase in life expectancy of the population. In our country, it represents the second cause for mortality. It is characterized by an anarchic growth of cells, which gives rise to the onset of tumors with the potential to disseminate through lymphatic and haematogenic routes. Cancer treatment is multidisciplinary; it can be local, at the affected area, or systemic, by means of chemotherapy.¹

Breast cancer is very frequent in female population. Approximately 6% of all deaths are caused by this disease. Breast cancer is considered a systemic disease; it can be locally treated with surgery and radiotherapy; nevertheless, chemotherapy represents its systemic treatment, which represents an important advance since it favorably impacts in 25 to 50% of the afflicted population.²⁻⁴

Prognosis and treatment protocol mainly depend on two elements: histological lineage and clinical stage.

These two factors must be taken into consideration when establishing a scheme, therapeutic dosage and number of programmed cycles.

DOSAGE

The specialist is the professional who determines, calculates and administers the chemotherapy dosage

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to cancer-afflicted patients. He establishes schemes which refer to selected medication, and cycles which correspond to the number of treatments.

In general terms, it can be established that dosage is based upon weight or body surface of the patient (milligrams/m² surface or milligrams/weight in kilograms). At advanced clinical stages, high dosages and increasing number of cycles are applied, which generally will induce more toxic manifestations.⁵

According to consulted scientific literature, among 40 to 60% of cancer-ridden patients are treated systemically. Of the aforementioned, 40% present oral toxicity, even in cases where the cervico-facial region is not involved in the primary lesion.^{6,7}

Mucositis appears due to a decrease in the renovation rate of the basal epithelium. It becomes thinned down and presents ulcers in the soft tissues, mainly in non-keratinized tissues such as oral and labial mucosae, as well as the lateral and ventral surfaces of the tongue. Severity varies according to the scheme employed, dosage and general state of the mouth before the therapy.

Almost all chemotherapeutic agents elicit stomatotoxicity to a certain degree. Clinical experiences of some authors reveal the following substances as the most frequent causal agents: anti-metabolites, methotrexate, 5-fluorouracil, doxorubicin, bleomycin, dactinomycin, daunorubicin and cyclophosphamide. If to this we add disrupted renal and hepatic functions, the risk increases as a result of reduced metabolism, which decreases drug secretion. When these circumstances are present, stomatitis cases are more severe and lasting. Histaminic and blood concentrations of cytotoxic agents delay the re-epithelialization process, therefore, as the varied proposed cycles are administered, manifestation probabilities increase.^{8,9}

Breast cancer cases are very frequent in Mexico; therefore, there is a need to administer the aforementioned treatments; most patients seek treatment when the disease is at advanced stages, where stomatological manifestations are already present. These manifestations can be mitigated and sometimes avoided whenever cases are dentally treated before, during and after the chemotherapy treatment.¹⁰⁻¹²

METHODS

A retrospective and descriptive study was undertaken. Clinical files from breast cancer patients from years 1994 through 1999 were reviewed. All files belonged to the Oncology Service of the General

Hospital, Mexico. All studies were conducted in consultation with services pertaining to breast tumors, chemotherapy and maxillofacial prosthesis

EXCLUSION CRITERIA

The following were excluded:

- 1) Patients afflicted with diseases pertaining to the oral cavity exhibiting manifestations before the chemotherapy treatment.
- 2) Patients afflicted with systemic disease and stomatological manifestations such as diabetes mellitus or acquired immunodeficiency syndrome.
- 3) Patients previously subjected to head and neck radiotherapy.

INCLUSION CRITERIA

All files included were of diagnosed breast cancer patients, who had been treated, from the beginning of treatment, at the chemotherapy and maxillofacial services of the General Hospital, Mexico.

The following variables were included:

- 1) Type of lesion through specific search.
- 2) Onset of oral lesions related to the chemotherapy scheme.

Files were examined with the help of a data collection sheet which included: age, gender, histopathological diagnosis, clinical stage, chemotherapy scheme, stomatological group, as well as lesion-specific search.

Results analysis were undertaken according to descriptive statistics methods.

- Student t test for continuous variables.
- χ^2 for non-continuous variables (statistics included).

RESULTS

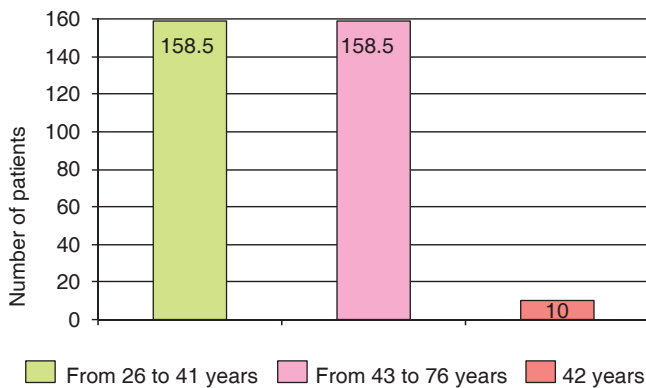
A review of files dating 1994 to 1999 was undertaken. We selected 405 cases of breast cancer patients, out of which only 327 fulfilled the inclusion criteria for the present study.

Breast cancer patients' age ranked from 26 to 76 years, the average was 42 years and the rank 50 years (*Figure 1*).

The histopathological analysis revealed the following: 297 patients presented diagnosis of infiltrating ductal carcinoma, 22 presented diagnosis of lobular carcinoma, and 8 cases were included in the diverse group (papillary, medullar) (*Figure 2*).

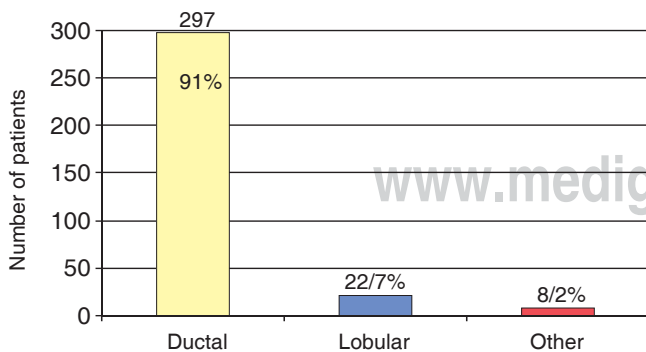
Assessed files revealed that 101 patients were at clinical stage II, 155 patients were at clinical stage III and 71 patients were at clinical stage IV (Figure 3).

According to the scheme administered to these patients during treatment, the following was obtained: 201 patients received 5-fluorouracil, cyclophosphamide and doxorubicin (FAC), 84 patients were treated with adriamycin and cyclophosphamide (ACII), 30 patients were treated with cyclophosphamide, methotrexate and 5-fluorouacil (CMF), and only three were treated with 5-fluorouracil plus methrotrexate (5FU + MTX). The following schemes were each used in one case only: Adriamycin (A), 5-fluorouracil (5FU), A + 5FU, platinum and navelvine (OL + NV) (Figure 4).



The number of young patients included in the sample indicates younger population than that reported in the consulted bibliography.

Figure 1. Age of patients.



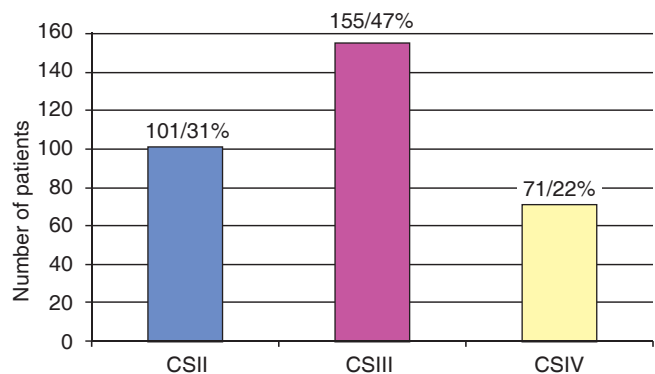
Canalicular histopathological report indicates the fact that due to a therapeutic response to chemotherapy, population will develop stomatotoxicity manifestations.

Figure 2. Histopathological diagnosis.

122 patients out of the 327 files included in this study presented stomatological manifestations. This represents a 37.31% of the studied sample. Out of these 122 patients, 89 exhibited a single oral manifestation during the chemotherapy treatment; 19 exhibited two different manifestations and 14 patients exhibited three or more stomatological manifestations (Figures 5 to 8).

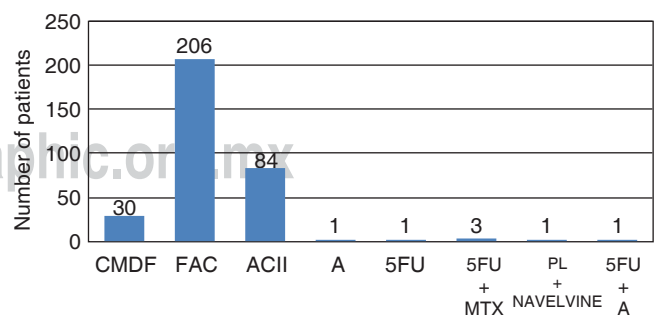
Statistical analysis was developed using the package designed for this purpose. In these analyses, the following variables were included from the data base:

1. Within the scope of the histopathological diagnosis, the following relationships were studied:



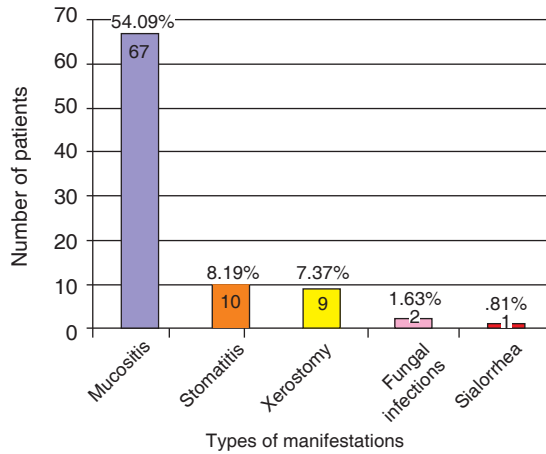
Clinical stages of sample indicate the fact that chemotherapy treatment is necessary in our population, since most cases arrive at advanced stages.

Figure 3. Clinical stage.



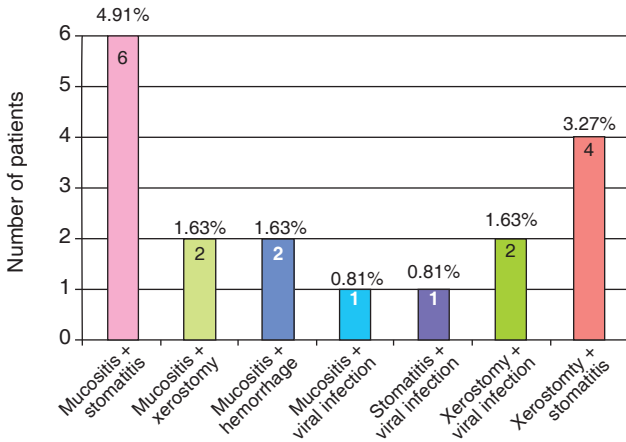
The three most used schemes in breast cancer treatment are reported with direct and indirect stomatotoxicity development, especially on the epithelium.

Figure 4. Chemotherapy schemes.



Stomatitis is present in cases of untreated mucositis. It can also appear as a result of toxicity concentration in cases when the number of cycles is above 6.

Figure 5. Presence of one oral manifestation.



Mucositis is the most frequent manifestation, presenting tendency to be generalized. In the presence of xerostomy, infections develop caused by opportunistic agents.

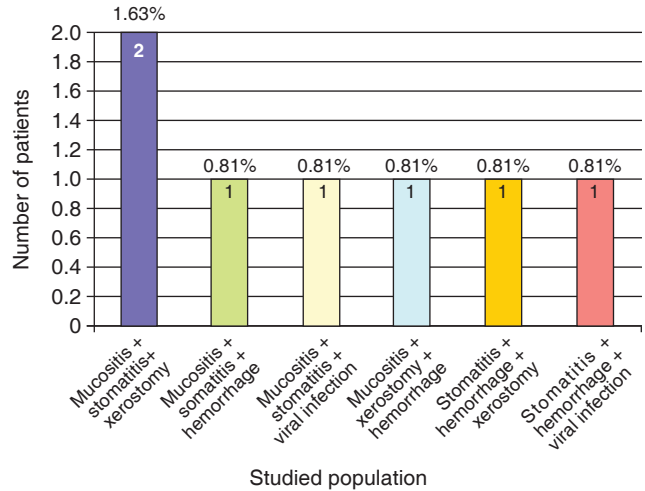
Figure 6. Presence of two oral manifestations.

- a) Infiltrating ductal *versus* lobular.
- b) Infiltrating ductal *versus* others.

In both cases, statistical comparison resulted significant with $p < .005$.

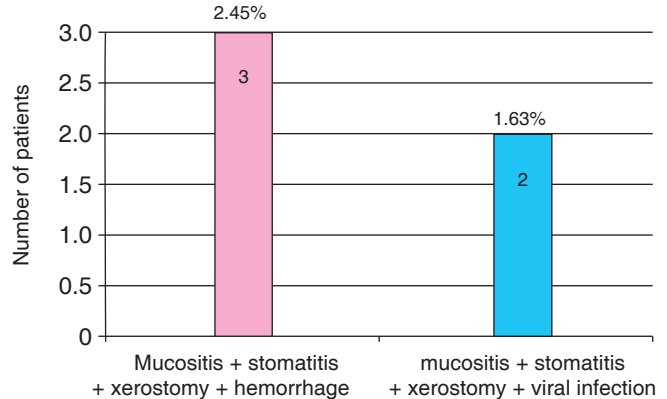
Another studied factor was:

- 2. Different chemotherapy schemes; in this case, the following were compared:



Present in the adriamycin test, frequency of mucositis with xerostomy is the precursor of infections which develop in a greater number of cycles with infections and hemorrhages.

Figure 7. Presence of three oral manifestations.



The most commonly used scheme was fluorouracil, adriamycin and cyclophosphamide (FAC), which induces direct and indirect stomatotoxicity.

Figure 8.

- a) FAC *versus* ACII.
- b) FAV *versus* CMF.

In both cases $p < .005$ (statistically significant).

Finally, the following factors were assessed:

- 3. Stomatological manifestations:

- a) To identify the amount of present manifestations by comparing:

- 1 *versus* 2 (manifestations).
- 1 *versus* 3 (manifestations).

b) To determine the type of manifestations present by comparing:

- Mucositis *versus* sialorrhea.
- Mucositis *versus* xerostomy.
- Mucositis *versus* fungal infections.

Study of these cases revealed values of $p < .005$, indicating statistically significant results.

DISCUSSION

According to consulted literature, the average age of breast cancer patients ranks from 43 to 53 years. In our review we obtained an average of 42 years. This shows a tendency for disease onset in younger women. In our study group, this age range represented 90.82%.^{13,14}

After conducting a histopathological examination of our patients, our review revealed that the most frequent carcinoma was the infiltrative duct carcinoma (91% of cases). Most examined cases (69.12%) were at advanced stages (III and IV). This data was supported by the First National Consensus on Breast Cancer Treatment. This report revealed that in Mexico, 50% of patients were diagnosed at these advanced stages. This fact then renders chemotherapy indispensable in order to increase the life expectancy of patients.^{15,16}

Chemotherapy systemic treatments mainly target cancer cells, preventing their growth and multiplication. Nevertheless, they also act upon rapid-dividing body cells, such as bone marrow cells, digestive tract cells, reproductive system cells, hair follicles, as well as skin cells.¹⁷

Our findings confirm studies reporting chemotherapy schemes, including adriamycin, cyclophosphamide and 5-fluorouracil as the most effective schemes for breast cancer treatment. Due to their moderate cost, these are the most commonly used drugs in third-world countries.^{11,15}

Data found in scientific literature confirm the fact that stomatological manifestations are secondary reactions elicited by chemotherapy. In the present study 100% of all patients received poly-chemotherapy, or at least, some drug reported as associated to stomatological manifestations.¹⁸

Our patients received the following schemes: CMF, FAC, ACII, 5FU, 5FU + MTX, PL + NAVELVINE and 5FU + A)

Our results confirmed those obtained by previous studies, which mention mucositis as a common and potentially serious manifestation caused by chemotherapy.

Out of 122 patients, 91 presented isolated mucositis, or mucositis associated to other manifestations. This represented 54% of our population according to the Oral Mucositis Assessment Scale (OMAS), developed in 1996 by a team of oncology specialized physicians and experts in pain assessment and statistics.

Mucositis can be classified into the following degrees:

- a) Grade 0. No affected sites.
- b) Grade 1. Sore mouth and erythema.
- c) Grade 2. Presence of erythema and ulcers; nevertheless, the patient can ingest solid foods.
- d) Grade 3. Sore and ulcerated mouth; the patient can only achieve liquid diet.
- e) Grade 4. Oral feeding is impossible.^{10,19-26}

In concordance with other authors, we suggest that the chemotherapy drugs which mainly cause mucositis are: 5FU, methotrexate, doxorubicin, bleomycin, dactinomycin, daunomycin, cyclophosphamide, vincristin, cytosine-arabinoside, cisplatin and leucovorin.^{10,23,26,27}

Stomatitis was the manifestation which appeared in second place, since it appeared either by itself or associated with other manifestations in 33 out of the 122 patients (26.95%).

Dreizen and his team indicated that methotrexate (folic acid antagonist) was one of the main causing agents of this manifestation, which is due to a folic acid deficiency that can interfere with epithelial cells production and maturation, thus eliciting atrophy or extinction of lingual papillae as well as ulcer formation, which in turn causes nutritional deficiency in the patient due to the pain these ulcers elicit.^{19,27,36-39}

Other authors have shown that 5FU (furacil metabolic antagonist) is another-stomatitis causing agent, since it produces thymine deficiency, which in turn interferes with nucleic acid synthesis and reflects into a rapid cellular division elicited by a cellular death and growth disequilibrium, provoking then ulceration and epithelial desquamation.^{19,26,28}. Based on the present study, we might also suggest the fact that gingival haemorrhage is another constant manifestation in these patients. It was observed in nine patients, although it was always associated with some other manifestation. Its main cause was vincristin cytosine-arabinside and prednisone. It is

generated by drug-induced thrombocytopenia and by disseminated intravascular coagulation, especially in patients exhibiting platelet levels of 20,000 to 50,000 per mm³.

These drugs alter blood cell maturation and synthesis causing leukopenia, thrombocytopenia and anemia, depriving the immune system of protection. Myelosuppression can precipitate spontaneous periodontal bleeding and exacerbate chronic periodontal disease, as well as pulp problems.^{19,29,30}

Xerostomia was another commonly found manifestation in our patients. It was found in 27 out of the 122 patients (22.05%). This proportion was concurrent with data previously found in scientific literature.

Xerostomia appears as a mucositis aggregated or secondary effect. From the second day onwards, there is qualitative and quantitative reduction of salivary flow. Acini atrophy, cell necrosis, degeneration and salivary gland fibrosis are also present. All these factors elicit decrease²⁹ of salivary flow and its pH, as well as saliva's buffering capacity. All the aforementioned factors accelerate periodontal deterioration and enhance the onset of dental caries.

This decrease of salivary proteins, minerals and enzymes directly affects tooth remineralization. Other affected functions are the patient's diction, mastication and deglutition.^{14,30-35}

There are reports indicating that cyclophosphamide, doxorubicin and vincristin are causing agents for viral infections. Our study seems to concur with this assertion: 8 patients (7.32% of the sample) presented viral infections during treatment, in all cases associated to other manifestations.

According to William Carl and his group²⁸ this manifestation takes place because drugs interfere with the growth and maturation of oral mucosa cells, by reducing the tissue that functions as a barrier for this type of infections. Dreizen and his team¹⁹ supported this same theory. They further suggested that, in addition to viral infections, fungal infections might occur. Nevertheless, in the present study, only two patients were found to exhibit fungal infection; this represented a minimal percentage (1.63%). These infections were caused by oral flora and saliva alterations, and were mainly triggered by the use of prednisone, vincristin, doxorubicin and methotrexate.^{10,21,22}

Some studies mention the presence of sialorrhea as another frequent manifestation. Nevertheless, in the present study we only found this condition in one patient (0.81%). Authors report that sialorrhea has its onset before xerostomia, which then would explain

that it is common to report the latter and not suitably assess the presence of sialorrhea in these patients.²⁹

The present study on stomatotoxicity manifestations induced by chemotherapy-treated breast cancer clearly establishes the need to formalize simultaneous treatment between the oncologist and a specialized stomatologist.

Appropriate oral care is critical during chemotherapy treatments. Manifestations will thus be prevented or reduced, and the patient will be able to eat properly and, thus, not delay her chemotherapy treatment. Prevention of stomatological manifestations reported in the present study shows the importance of conducting a meticulous oral examination in patients who are chemotherapy candidates.

CONCLUSIONS

1. Chemotherapy-induced stomatological manifestations in breast cancer patients mainly appear when schemes based on 5FU, adriamycin and cyclophosphatase are used.
2. The most frequent stomatological manifestations in patients included in this study were: mucositis, stomatitis, xerostomia and viral and fungal infections.
3. Based on the results obtained in the present study, it can be suggested that all patients treated with chemotherapy must receive dental treatment before, during and after chemotherapy treatment. A radiographic study of the patient must be obtained so as to devise a treatment plan which must include preventive measures, within the scope of the programmed conventional treatments. Special attention must be given to population with the same characteristics as the one studied in this sample, since they are normally afflicted by periodontal problems. Special care must be given to plaque control as well as topical fluoride application.

PROPOSAL

Elimination of dental and periodontal disease (caries, dental plaque and dental calculi) is of paramount importance. Poor fillings must also be redressed before the patient initiates her chemotherapy treatment.

Due to the aforementioned reasons, it is paramount to emit early diagnosis and devise appropriate treatment for fungal and viral infections in order to avoid generalized infections in the patient.

We will additionally require a comprehensive study for this chemotherapy-treated population, as well as for others. This study will enable us to know alterations

that might appear in the saliva's enzymatic quality, as well as alterations appearing on the enamel structure, which can affect the quality of life of a population which every day presents increasing survival rates to breast cancer.

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