Oral Changes in Patients Undergoing Chemotherapy for Breast Cancer

Abstract

Background: Breast cancer is one of the most common cancers in India. Most of the patients with breast cancer are treated with chemotherapy which has multiple oral complications. Aims: The objectives of this study were to describe the occurrence of taste disturbances, xerostomia, oral mucositis, and candidal and salivary changes among patients receiving chemotherapy for breast cancer. Methods: Fifty-two women with newly diagnosed breast cancer (without distant metastasis), eligible for adjuvant/neoadjuvant chemotherapy (cyclophosphamide and Adriamycin, 4 cycles × 3 weeks), were included in this study. All the observations were noted before, during (after 6 weeks of starting chemotherapy), and after the completion of chemotherapy (after 12 weeks of starting chemotherapy). Statistical Analysis Used: Variables such as mucositis, salivary flow rate, salivary pH, and candidal carriage rate were compared at baseline, and at 1st and 2nd follow-ups using Wilcoxon signed-rank test (P value corrected for α for pair-wise comparisons). Results: Mean unstimulated whole saliva flow rate reduced from 0.5 ml/min to 0.3 ml/min, and the mean colony-forming units of Candida reduced from 32.3 × 10^3 cells/ml to 13.1 × 10^3 cells/ml at the end of the study period. Xerostomia, taste disturbances, and oral mucosal pigmentation increased from 28.8% to 50%. Conclusions: There was a discernible change in oral mucosal, salivary, and candidal status during the course of the study.

Keywords: Candidiasis, mucositis, oral pigmentation, salivary flow, salivary pH, taste disturbances, unstimulated whole saliva, xerostomia

Introduction

Breast cancer is the most common cancer among women with a wide difference in the range of incidence between countries and regions. The health-care burden on account of breast cancer in developing countries has been steadily rising. The incidence of breast cancer in India is on the rise and is rapidly becoming the most prevalent cancer. It has been reported that 1 in 22 women in India is likely to develop breast cancer, while the figure is definitely more in America with 1 in 8 being diagnosed with breast cancer.

Majority of breast cancer patients in India are treated at locally advanced and metastatic stages. The main reason for this is illiteracy, lack of awareness, and financial constraints. Treatment options available for breast cancer patients include surgery, radiation therapy, chemotherapy, hormone therapy, and biological therapy. Patients considered to have an increased risk of metastatic disease are frequently given chemotherapy in addition to surgery.

This adjuvant chemotherapy is most effective when several cytotoxic agents are administered concurrently. Large tumors necessitate extensive surgery. Neoadjuvant chemotherapy is given in such cases in order to convert patients needing mastectomy into candidates for breast-conserving surgery and to downstream the axillary lymph nodes.

The antineoplastic agents used in the breast cancer treatment regimen include cyclophosphamide, methotrexate, 5-fluorouracil, and epirubicin and are associated with adverse effects such as alopecia, nausea, mucositis, dry mouth, skin changes, dyspnea, edema, and amenorrhea. Some of the cytotoxic effects associated with Adriamycin (doxorubicin)–cyclophosphamide (AC) regimen are myelosuppression and risk of neutropenic sepsis or hemorrhage, nausea and vomiting, mucositis, alopecia, cardiotoxicity, amenorrhea, hematuria, palmar and plantar inflammation, and carcinogenesis. The oral cavity undergoes multiple changes during intensive cancer chemotherapy. AC chemotherapy can cause moderate-to-severe...
oral mucositis. Doxorubicin and cyclophosphamide regimen has been significantly associated with late-onset (10 days after chemotherapy) and low-intensity mucositis. The other oral changes seen are altered taste sensation, xerostomia, and increased prevalence of opportunistic infections such as candidiasis.

Adequate data are not available on various issues relating to breast cancer care in India. Only few studies have documented oral and salivary changes secondary to chemotherapy in breast cancer patients. Hence, this study was conducted to evaluate the oral mucosal abnormalities, microbial changes, salivary alterations, and taste disturbances occurring among patients receiving chemotherapy for breast cancer. The objectives of this study were to describe the occurrence of taste disturbances, xerostomia, mucositis, and pigmentation in patients receiving chemotherapy; to determine the alterations in oral Candida carriage capacity; and also to observe the changes in the salivary flow, pH, and consistency before, during, and after chemotherapy.

**Methods**

The present study was undertaken to examine the oral effects of chemotherapy for breast cancer among patients attending the Oncology Department of Kasturba Medical College, Manipal. This prospective, observational study of 16-month duration involved, recording oral symptoms and signs in patients with breast cancer before, during, and after chemotherapy. Consecutive women with newly diagnosed breast cancer (without distant metastasis), eligible for adjuvant/neo-adjuvant chemotherapy and willing to participate, were included in the study. Patients with overt distant metastases at the time of diagnosis, previous history of radiation in the head and neck region, and patients with salivary gland disease causing xerostomia were excluded from the study.

The study was approved by the Institutional Ethics Committee (UEC/16/2009). The nature of the study was explained to the patients, and a written informed consent was obtained from each patient willing to participate in the study. All the patients undergoing chemotherapy were advised to rinse their mouth 4 times a day with soda bicarbonate solution during the entire treatment period, as part of their chemotherapy protocol. Oral hygiene instructions were given, and patients were advised to refrain from tobacco chewing and other oral abusive habits. Oral prophylaxis was performed on all the patients before chemotherapy. All patients underwent compulsory regular dental checkup and treatment during chemotherapy as a part of the established protocols in the hospital. Oral hygiene instructions were reinforced at each examination.

A specially designed pro forma was used to record the patient details and disease-related information such as demographic data, presence of comorbid disease, menstrual history, histopathologic type of breast carcinoma, endocrine and human epidermal growth factor receptor 2 (HER2/neu) neu responsiveness; type of chemotherapy and its regimen. Each patient was questioned regarding general health, daily medication intake, current oral symptoms, and history of cold sores, other recurrent intraoral wounds (oral ulceration – at least twice a year), or fungal infection. Patients were asked whether they had any difficulty in swallowing, felt dryness in the mouth when eating a meal, and whether they sipped liquids to aid in swallowing food. Patients answering affirmatively to all these three questions related to oral dryness were considered to have xerostomia. Taste alterations were categorized as ageusia, hypogeusia, dysgeusia, and phantogeusia. Oral examination was carried out, and all findings were recorded in the pro forma. The findings recorded before initiation of chemotherapy were considered baseline values.

Mucositis was defined as “inflammation or ulceration of the oral mucosa occurring during cancer chemotherapy that cannot be characterized clinically or histologically as any other disease,” and was graded according to recommendations by the WHO. The presence of mucosal pigmentation in any part of the oral cavity before, during, and after chemotherapy was noted. The diagnosis of candidiasis was based on the following three working diagnostic criteria: (a) Clinical presence of pseudo-membranous, erythematous lesions, denture stomatitis, and angular cheilitis; (b) Mucosal smear (from tongue scrapings/erythematous lesion) stained using Gram stain showing at least 8–10 yeast cells/oil immersion field; and (c) colony-forming units (CFUs) of Candida >10 × 10^3 units. A positive response to all the three criteria was made a prerequisite to make the diagnosis of candidiasis.

Salivary tests included tests for salivary flow and pH. Collection of whole unstimulated saliva was done using spitting technique and was scheduled between 9 am and 11 am to minimize circadian rhythm effects. Patients were instructed not to eat or drink anything 1h before the procedure. Before the collection of saliva, patients were instructed to rinse their mouth with water and sit comfortably in the upright position. Patients were asked to avoid swallowing and to make as few movements as possible during the procedure. Measuring containers were weighed before and after each collection using an electronic scale (Sartorius BA 110S, Sartorius, Germany). The saliva collected in the floor of the mouth was then spit into the preweighed container. Salivary flow rate (ml/min) of the resting whole saliva was estimated by dividing the saliva sample volume (1 g of saliva equals 1 ml) by collection time (3 min). Salivary flow was classified according to Krassse. Salivary pH was assessed using a paper colorimetric test. Buffering capacity was classified according to Wikner and Nedlich. The saliva was allowed to pool in the floor of the mouth for
1 min. Sufficient saliva was drawn from the saliva sample, and one drop was dispensed onto the test strip using a disposable dropper. After a minute, the final pH was read on the reverse side of the strip by comparing the color with a standard chart. The colors had been chosen to indicate low-, intermediate-, or high-buffering capacity (HiMedia Laboratory Pvt. Ltd., Mumbai Laboratory Pvt. Ltd., Mumbai, India). By examining resting saliva in the floor of the mouth, and in the vestibule, a subjective assessment was made as to whether this saliva was (a) clear and watery, (b) bubbly, or (c) white and frothy. It was noticed that, in the latter case, the saliva had a glutinous sticky character.\(^{[27]}\)

For candidal carriage assessment, 0.5 ml of uncentrifuged saliva was spread on Sabouraud dextrose agar (SDA) (HiVeg Agar, Hi Media laboratory Pvt. Ltd., Mumbai, India) plates containing 50 mg of chloramphenicol per ml. Plates were incubated aerobically at 37°C for 24 h.\(^{[28]}\) Candida species developed as cream-colored, convex colonies on SDA. The number of CFUs/ml of saliva was counted.\(^{[29,30]}\) Identification of Candida species was based on the colony morphology and Gram staining.

The treatment protocol was based on the National Comprehensive Cancer Network\(^{[31]}\) clinical practice guidelines. The general workup included history and physical examination, complete blood counts, liver function tests, diagnostic bilateral mammogram and ultrasound as necessary, pathologic review, and determination of hormone receptor status and HER2 status. Bone scan was indicated if symptoms or elevated serum alkaline phosphatase was present. Patients with HER2-positive tumor were treated with preoperative chemotherapy. The systemic adjuvant chemotherapy was decided based on the age of the patient, histology of the tumor, HER2 status, and hormone receptor status.

Adjuvant or neo-adjuvant chemotherapy regimen comprised cyclophosphamide (600 mg/m\(^2\)) and adriamycin (60 mg/m\(^2\)).\(^{[31]}\) Chemotherapy was administered every 3 weeks for a total of four cycles (12 weeks). To prevent and treat chemotherapy-induced nausea, metoclopramide and ondansetron were prescribed.

The patients were followed up after the second cycle of chemotherapy (after 6 weeks of starting chemotherapy) and after the completion of chemotherapy (after 12 weeks of starting chemotherapy). Oral symptoms experienced by the patients from the initiation of chemotherapy till date were recorded and this was followed by oral examination [Figure 1].

Wilcoxon’s signed-rank test was applied for nominal variables (taste disturbances, xerostomia, and oral pigmentation). At baseline, these conditions were not prevalent, hence comparison was made between the 1\(^{st}\) and 2\(^{nd}\) follow-ups. Similarly, variables such as mucositis, salivary flow rate, salivary pH, and candidal carriage rate were compared at baseline, and at 1\(^{st}\) and 2\(^{nd}\) follow-ups using Wilcoxon signed-rank test (\(p\) value corrected for \(\alpha\) for pair-wise comparisons). The level of significance was set at 5%. Statistical analysis was performed using SPSS software version 14 (SPSS Inc., Illinois, USA).

**Results**

A total of 63 women fulfilled the inclusion criteria during the study period. Eleven women were lost to follow-up due to logistical issues and hence were excluded from the study. The study sample thus comprised 52 women. The age range of the women was 27–66 years (mean of 46.7). Comorbid illness in the form of hypertension/diabetes mellitus/asthma/rheumatoid arthritis was reported by 12 patients (23%). Patient details and treatment protocol of the study population have been shown in Table 1.

**Oral mucosal abnormalities**

None of the patients reported recurrent aphthous ulcers or other mucosal alterations in the past or at baseline. Mucositis as defined by the WHO was assessed. During chemotherapy, 44.2% (\(n = 23\)) of the patients had grade 0 mucositis, 44.3% (\(n = 23\)) of the patients had grade 1–2 mucositis, and 11.5% (\(n = 6\)) of the patients had grade 3 mucositis. Toward the end of chemotherapy, 50% (\(n = 26\)) had grade 0 mucositis, 42.3% (\(n = 22\)) and 7.7% (\(n = 4\)) of the patients had grade 1–2 and grade 3 mucositis, respectively. None of the patients experienced grade 4 mucositis during the study period. Mucositis was seen on bilateral buccal mucosa, tongue, floor of the mouth, labial mucosa, and soft palate. Mucositis was most commonly present on the buccal mucosa and tongue. Oral mucosal pigmentation was seen in 15 individuals (28.8%) during chemotherapy and in 26 individuals (50%) at the end of chemotherapy. This increase in oral mucosal

| Table 1: Descriptive data and treatment protocol of the study population |
|---------------------------------------------------------------|
| **Variables** | **Number(%)** |
| Age range (mean age) | 27-66 years (46.7 years) |
| Comorbid diseases (%) | 12 (23.1) |
| Menstrual history (%) | |
| Premenopausal | 32 (61.5) |
| Postmenopausal | 20 (38.5) |
| Histopathologic type of breast cancer (%) | |
| Infiltrating ductal | 48 (92.3) |
| Lobular | 3 (5.8) |
| Mixed | 1 (1.9) |
| Chemotherapy (%) | |
| Neoadjuvant | 10 (19.2) |
| Adjuvant | 42 (80.8) |
| Surgery (%) | |
| Mastectomy | 36 (69.2) |
| Lumpectomy | 6 (11.5) |
pigmentation was statistically significant ($P < 0.01$). This pigmentation was mostly seen on the tongue.

None of the patients reported of taste disturbances at baseline. During chemotherapy, majority of patients (86.5%) complained of hypogeusia and two (3.9%) patients complained of metallic taste. Thirty-six patients (67.2%) continued to report of taste disturbances after the completion of chemotherapy. This alteration in taste perception as perceived by the study population was statistically significant [Table 2].

**Salivary changes**

Xerostomia was not reported by any patient before the initiation of chemotherapy. This symptom became a prominent feature as the chemotherapy progressed, with 34 patients (65.4%) reporting xerostomia during the first

| Symptom/sign | Baseline (n/%) | 1st follow-up (n/%) | 2nd follow-up (n/%) | $p$ |
|--------------|---------------|---------------------|---------------------|-----|
| Taste disturbances | 0/0 | 45/86.5 | 36/69.2 | $<0.001^*$ |
| Xerostomia | 0/0 | 34/65.4 | 23/44.2 | $<0.001^*$ |
| Pigmentation | 0/0 | 15/28.9 | 26/50 | $<0.001^*$ |
| Salivary consistency | 1/1.9 | 9/17.3 | 2/3.8 | $0.001^*$ |

*Wilcoxon signed-rank test, †Freidman’s test with $p$ value corrected for alpha. Taste disturbances, xerostomia, and pigmentation were statistically compared only between 1st and 2nd follow-ups and not from baseline as their prevalence was zero at baseline. Baseline=Before the commencement of chemotherapy, First follow-up=After 6 weeks of starting chemotherapy, Second follow-up=After 12 weeks of starting chemotherapy*
follow-up and 23 patients (44.2%) at the second follow-up. There was a statistically significant increase in the perception of dry mouth during the study period [Table 2].

There was no significant alteration in the salivary pH during the study period, with mean pH value being 6.19 at baseline and 6.2, both during chemotherapy and at the end of the study period. There was a significant reduction in mean salivary flow rate, from 0.5 ml/min to 0.31 ml/min during chemotherapy and finally to 0.34 ml/min at the end of the study period [Table 3]. Patients reported that the consistency of saliva became progressively more viscous during chemotherapy as compared to the consistency of saliva at baseline. This perceived alteration was statistically significant during the period of treatment [Table 2].

The mean CFUs of *Candida* decreased from $32.3 \times 10^3$ CFU/ml at baseline to $22 \times 10^4$ CFU/ml during the study and to $13.1 \times 10^3$ CFU/ml at the end of the study. However, this decrease in CFU of *Candida* was not statistically significant [Table 3]. At baseline, none of the patients had oral candidiasis. However, six patients had growth on SDA medium. At the first follow-up, only one patient presented with CFU of *Candida* without clinical evidence of candidiasis, and at the second follow-up, none of the patients had neither infection nor CFU of *Candida*.

**Discussion**

The prevalence of oral mucosal lesions increased during chemotherapy. The prevalence of oral mucositis in our study was 55.7% during the first follow-up and 50% at the second follow-up. This increased prevalence rate in our study may be due to a smaller sample size. Mucositis usually occurred 1 week after the administration of chemotherapeutic drugs. We found that grade 1–2 mucositis was seen in 44.1% of patients at the first follow-up and in 42.3% of patients at the second follow-up. This is marginally higher than those reported by other studies – 18%–34.5%.[10,32‑35] However, the chemotherapeutic regimens used in these studies were different from our study. The severity of mucositis is variable. It has been attributed to multiple factors such as genetic factors, age of the patient, type of cancer, treatment regimen, and level of oral hygiene compliance.[36,37] None of the patients developed severe (WHO grade 4) oral mucositis. This could be explained by compulsory oral care for the patients. Patients subjected to meticulous dental care during treatment show a significant reduction in the frequency of oral complications associated with chemotherapy.[38‑40] Previous research has showed that additional oral care was important and had positive attenuation effect on the development of oral mucositis.[41]

There was a statistically significant increase in pigmentation of the oral mucosa at the end of the study period. This finding is in accordance with the results of the studies reported by other investigators.[42]

Increase in pigmentation could be attributed to the postinflammatory pigmentation or the effect of the chemotherapeutic drugs or their metabolites. Adjuvant drugs for comorbid conditions were not found to be associated with pigmentation.

A large proportion of the patients in the study reported of taste disturbances after chemotherapy was initiated. Chemotherapeutic drugs are said to be evident in saliva for many days following the treatment, depending on the type of drug, its dosage, and its metabolism.[43] All these drugs, their metabolites, as well as other medications such as antiemetics can lead to taste disturbances.[106] Among other medications, we found only amloidipine to be significantly associated with taste alteration. The drastic increase in subjective complaints of taste disturbance during chemotherapy was likely to be associated with salivary concentrations of AC directly acting on the taste receptor cells, thereby resulting in distorted taste perception. The reduced salivary flow,[44,45] with alteration in salivary consistency, could have also contributed to altered taste

| Variable                             | Mean±SD | p            |
|--------------------------------------|---------|--------------|
|                                      | Baseline (A) | 1st follow-up (B) | 2nd follow-up (C) |
| Mucositis                            | 0.00±0.00 | 0.46±1.1 | 0.51±1.1 | 0.004 (A vs. B) | 0.001 (A vs. C) | 0.654 (B vs. C) | <0.001 (A vs. B) | <0.001 (A vs. C) | 0.2 (B vs. C) | <0.78 (A vs. B) | <0.8 (A vs. C) | 1 (B vs. C) | <0.7 (A vs. B) | <0.3 (A vs. C) | 0.1 (B vs. C) |
| Salivary flow rate (mL/min)          | 0.5±0.3 | 0.3±0.3 | 0.3±0.3 | 0.654 (B vs. C) | <0.001 (A vs. B) | <0.001 (A vs. C) | 0.2 (B vs. C) | <0.78 (A vs. B) | <0.8 (A vs. C) | 1 (B vs. C) | <0.7 (A vs. B) | <0.3 (A vs. C) | 0.1 (B vs. C) |
| Salivary pH                           | 6.2±0.4 | 6.2±0.3 | 6.2±0.4 | 0.654 (B vs. C) | <0.001 (A vs. B) | <0.001 (A vs. C) | 0.2 (B vs. C) | <0.78 (A vs. B) | <0.8 (A vs. C) | 1 (B vs. C) | <0.7 (A vs. B) | <0.3 (A vs. C) | 0.1 (B vs. C) |
| Candidal carriage rate (10^3 cells/mL) | 32.3±79.7 | 22.0±62.7 | 13.1±48.2 | 0.654 (B vs. C) | <0.001 (A vs. B) | <0.001 (A vs. C) | 0.2 (B vs. C) | <0.78 (A vs. B) | <0.8 (A vs. C) | 1 (B vs. C) | <0.7 (A vs. B) | <0.3 (A vs. C) | 0.1 (B vs. C) |

A=Baseline - before the commencement of chemotherapy, B=First follow-up - after 6 weeks of starting chemotherapy, C=Second follow-up - after 12 weeks of starting chemotherapy, SD=Standard deviation.
sensation.\[46\] We did find xerostomia to be associated with taste alterations in the study population. Taste alterations and mucosal ulcers have been reported in breast cancer patients undergoing chemotherapy with cyclophosphamide, epirubicin or methotrexate, and 5-fluorouracil. The prevalence of taste disturbances reported in our study was similar to those reported by other investigators.\[47\]

There was a statistically significant increase in the perception of dry mouth during the study period. Other investigators\[48\] have reported that changes in chemical composition or physical characteristics of saliva, such as viscosity, may also influence the generation of the sensory signal perceived as dryness. Thus, alteration in viscosity could have also been a reason for xerostomia. It has been observed that individuals with taste disturbances complained of subjective oral dryness, although most had normal whole unstimulated saliva.\[49\]

Spitting technique was used to collect saliva, as it was considered that the patients would accept the noninvasive technique more readily. There was a significant decrease in salivary flow in our study. This finding is in accordance with the results reported by many other investigators.\[50-52\] The ductal and acinar cells of the salivary glands are adversely affected by the chemotherapeutic agents leading to low salivary flow.\[53\] Our study showed that, despite the decrease in salivary flow during chemotherapy, candidal counts in the saliva decreased. This result is in contrast to other reports.\[51,54\] However, this reduction in candidal counts was not significant. It has also been observed that none of the patients had any clinical evidence of candidiasis. The ideal pH required for fungal growth is 4–5\[55\] whereas the mean pH of saliva in the present study was 6.2, which could have inhibited candidal overgrowth. The patients in the study adhered to a strict sodium bicarbonate oral rinse regimen. Sodium bicarbonate has an immediate effect in reducing the acidity of oral fluids; it dilutes accumulating mucus and discourages colonization by yeast and aciduric bacteria.\[56\] The physical action of the rinse as well as its role in maintaining the pH of the oral cavity could have also contributed to reduction of the candidal load in the oral cavity.

As some of the oral changes were subjectively assessed, there is a possibility of recall bias. The confounding effects of comorbid diseases and their treatments on the development of candidiasis and salivary changes cannot be completely ruled out. Logistic and time issues did not allow a larger sample size and a more vigorous study design (inclusion criteria) to avoid the confounding bias.

Conclusion

In the recent years, patient-reported outcomes are considered increasingly important and are gaining widespread acceptance in health sciences research. This study sought to evaluate the effects of adjuvant chemotherapy on oral health of breast cancer patients and found some changes which could contribute to patient discomfort. There was a discernible change in oral mucosal, salivary, and candidal status during the course of the study. Majority of the patients had only mild mucositis. There was a subjective increase in xerostomia, taste alteration, mucosal pigmentation, and viscosity of saliva coupled with a significant reduction in salivary flow rate during the period of chemotherapy. Suitable changes in treatment regimens may help in mitigating these effects of chemotherapy. Hong et al.\[57\] in a review stated that “Oncologists who understand the types and causes of taste and olfactory abnormalities may be better prepared to discuss and empathize with these negative side effects. Physician recognition that these side effects may indirectly or directly affect patient recovery is important, and sharing of the causation of these abnormalities and possible mediation strategies should enhance the physician–patient relationship.” There is a need for future chemotherapeutic strategies to place prime importance on patient comfort when treating malignancies.

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Conflicts of interest

There are no conflicts of interest.

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