Chemotherapy and Radiotherapy induced oral mucosal changes in breast cancer patients – A Cross Sectional Study

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Abstract:

Aim: To assess the oral mucosal changes such as oral mucositis, oromucosal pain, xerostomia, and dysgeusia induced by chemotherapy (CT) and radiotherapy (RT) in patients with breast cancer.**Materials and methods:** The present study was conducted in 60 patients newly diagnosed with grade II and III nonhormonal breast cancer. The patients were divided equally into two groups, namely Group A comprising patients undergoing surgery and chemotherapy, and Group B comprising patients undergoing surgery and radiotherapy. Oral mucosal changes in Group A were assessed at baseline, cycle 2 of CT, and 6 months after CT. Similarly, oral mucosal changes in Group IB, were evaluated at baseline, week 3, and 6 months after RT.**Results:** During CT, oral mucositis and oral mucosal pain were observed in 28 patients (20.33%) and 20 patients (33.3%), respectively. Xerostomia was increased during CT. Dysgeusia was observed in 90% of the patients (n = 27) in Group A. In Group B, no evident alterations of oral mucosal and pain were observed.**Conclusion**: Patients undergoing CT exhibited a higher severity of oral mucositis, xerostomia, oral mucosal pain, and dysgeusia during the treatment than at baseline and 6 months after the treatment. However, patients undergoing RT did not exhibit any postradiation mucosal involvement, possibly because the irradiation field does not include oral mucosa.

Keywords: Breast cancer, chemotherapy, mucositis, radiotherapy, taste alterations, xerostomia

Introduction:

Breast cancer is the most common malignancy among women worldwide, especially in developing Asian countries. Although the breast cancer etiology is unknown, numerous risk factors such as genetic, hormonal, environmental, sociobiological, and physiological factors may influence the development of the disease. [1] Advancements in cancer treatment have remarkably increased the range of therapeutic options available for patients. Multimodal therapy has significantly improved the survival rates in patients with breast cancer over the years. However, the primary treatment modalities include surgery, chemotherapy (CT), radiotherapy (RT), and a combination of RT and CT. Most reported oral adverse effects of CT and RT include oral mucosal changes such as mucositis, oral discomfort, higher susceptibility to infections, and neurotoxicity. The present study attempted to assess the severity of oral mucosal changes in patients with breast cancer for the early diagnosis

of the side effects of CT and RT to reduce morbidity associated with the treatments. [2]

Materials and methods:

The study was conducted in MNJ Institute of Oncology & Regional Cancer Center, Hyderabad. The ethical clearance from the institutional ethical review board (PMVIDS/OMR/003/2011) was obtained and a total of 60 gender - and age-matched patients newly diagnosed with grades II or III nonhormonal breast cancer patients were included. Written consent from each participant was taken and the participants were divided into two equal groups. Group A comprised patients undergoing surgery and CT, with the patients administered adriamycin, 5–fluorouracil, and cyclophosphamide. Group B comprised patients undergoing surgery and RT, with patients receiving a total dose of 50 Gy radiation with a daily dose of 2 Gy for 4 weeks. Patients with history of previous malignancies treated with CT and RT were excluded, and patients diagnosed with Sjogren syndrome ,and patients with active oral mucosal lesions before CT and RT were excluded. The oral mucosal changes in Group A were assessed at baseline, cycle 2 of CT, and 6 months after CT. The oral mucosal changes in Group B were assessed at baseline, week 3, and 6 months after RT. Oral mucositis was assessed based on the World Health Organization (WHO) grading, whereas oromucosal pain was measured using a visual analog scale. Xerostomia was assessed using a subjective evaluation based on a questionnaire proposed by Fox et al. Dysgeusia was evaluated qualitatively using the subjective total taste acuity scale. Statistical analysis was performed using SPSS version 15.0. A P value ≤ 0.05 was considered statistically significant, whereas a P value ≤ 0.01 was considered highly significant.

Results:

The mean age of the patients in Group I and Group II was 43.87 and 46.07, respectively. Mucositis was assessed using WHO grading (Table I).

Table I: Mucositis scoring by WHO

Mucositis scoring	
Grades	
0	No change
1	Soreness/erythema
2	Erythema,ulcers;can eat solids
3	Ulcer;requires liquid diet only
4	Alimenation not possible

Of the 60 patients, 93.3% of patients exhibited grade 0 oral mucositis, whereas only 6.7% exhibited grade I mucositis. After the second CT cycle, 43.3% of patients exhibited grade 0, 93% patients exhibited grade I, and 26.7% patients exhibited grade II mucositis. After 6 months of CT treatment, 90% of patients exhibited grade 0, whereas 20% exhibited grade I mucositis (Table II).

Table II: Comparison of baseline, 2ND cycle of CT and 6 months' after CT time points with respect to Oro mucositis by Wilcoxon matched pairs test by ranks in Chemotherapy group

Variables	Time points	% of change	Z-value	P-value
Oro mucositis	Baseline vs 2nd cycle	-1149.99	3.4623	0.0005*

	Baseline vs 6 months	-50.00	0.4045	0.6858
	2nd cycle vs 6 months	88.00	3.4078	0.0007*

Additionally, the oromucosal pain increased from mild to moderate in 6.7% of patients before receiving CT and in 33.3% of patients after the second cycle. Oromucosal pain was decreased in 3.3% of the patients after 6 months of CT treatment (Table III).

Table III: Comparison of baseline, 2ND cycle of CTand 6 months' after CT time points with respect to mucosal pain by Wilcoxon matched pairs test by ranks in Chemotherapy group

Variables	Time points	% of change	Z-value	P-value
Mucosal pain	Baeline vs 2nd cycle	-400.00	2.5205	0.0117*
	Baseline vs 6 months	50.00	0.0000	1.0000
	2nd cycle vs 6 months	90.00	2.6656	0.0077*

Dysguesia was more frequently observed during CT treatment than at baseline. Dysgeusia decreased 6 months after completion of CT; however, it was still higher than that at baseline (Table IV).

Table IV: Comparison of baseline, 2ND cycle of CTand 6 months' after CT time points with respect to by Taste disturbances Wilcoxon matched pairs test by ranks in Chemotherapy group

Variables	Time points	% of change	Z-value	P-value
Taste disturbances	Baeline vs 2nd cycle	-587.50	4.2857	0.0000*
	Baseline vs 6 months	25.00	0.0700	0.9442
	2nd cycle vs 6 months	89.09	4.2857	0.0000*

Before CT treatment, 3 patients exhibited moderate xerostomia (score 2), whereas 20% of patients exhibited severe xerostomia (score 3). After cycle 2 of CT treatment, 23.3% of patients exhibited mild xerostomia (score 1), 20% of patients exhibited moderate xerostomia (score 2), and 26.67% of patients exhibited severe xerostomia (score 3). After 6 months of CT, 23% of the patients exhibited moderate xerostomia (score 2) (Table V).

Table V: Comparison of baseline, 2ND cycle of CTand 6 months' after CT time points with respect to dryness by Wilcoxon matched pairs test by ranks in Chemotherapy group.

Variables	Time points	% of change	Z-value	P-value
Dryness	Baeline vs 2nd cycle	-277.78	3.1798	0.0015*
	Baseline vs 6 months	55.56	1.6036	0.1088
	2nd cycle vs 6 months	88.24	3.4078	0.0007*

The difference in oral mucositis, oromucosal pain, dysgeusia, and xerostomia at baseline, week 3 of RT, and 6 months after RT was statistically nonsignificant (Tables VI-IX).

Table VI: Comparison of baseline, 3rd week and 6 months' after RT time points with respect to oro mucositis by Wilcoxon matched pairs test by ranks in Radiotherapy group

Variables	Time points	% of change	Z-value	P-value
Oro mucositis	Baseline vs 3rd week	-66.67	0.0000	1.0000
	Base line vs 6 months	66.67	0.0000	1.0000
	3rd week vs 6 months	80.00	1.8257	0.0679

Table VII: Comparison of baseline, 3rd week and 6 months' after RT time points with respect to mucosal pain by Wilcoxon matched pairs test by ranks in Radiotherapy group.

Variables	Time points	% of change	Z-value	P-value
Mucosal pain	Baseline vs 3rd week	-100.00	0.5345	0.5930
	Base line vs 6 months	100.00	0.0000	1.0000
	3rd week vs 6 months	100.00	0.0000	1.0000

Table VIII: Comparison of baseline, 3rdweek and 6 months' after RT time points with respect to Taste disturbances by Wilcoxon matched pairs test by ranks in Radiotherapy group

Variables	Time points	% of change	Z-value	P-value
Taste disturbances	Baseline vs 3rd week	-63.33	1.8257	0.0679
	Base line vs 6 months	66.67	0.0000	1.0000
	3rd week vs 6 months	66.67	1.8257	1.0000

Table IX: Comparison of baseline, 3rd week and 6 months' after RT time points with respect to dryness by Wilcoxon matched pairs test by ranks in Radiotherapy group

Variables	Time points	% of change	Z-value	P-value
Dryness	Baseline vs 3rd week	-66.67	0.0000	1.0000
	Base line vs 6 months	66.67	0.0000	1.0000
	3rd week vs 6 months	83.33	1.8257	0.0679

Discussion:

Breast cancer is the most commonly diagnosed cancer among women between 40 and 60 years of age.[4] Mortality is higher in patients less than 45 years of age, suggesting that menopause decreases mortality in breast cancer.[23] The mean age of patients in the CT and RT groups in the present study was 43.87 and 46.07 years, respectively. Thus, a majority of the patients were above 40

years of age, and the mucositis severity increased with age. This finding is concurrent with that of McCarthy et al, who concluded that the frequency of mucositis doubled in patients above 50 years of age.[21] The overall frequency of mucositis varied with diagnosis; level of oral health; and the type, dose, and frequency of drug administration. CT-related oral mucosal lesions result from complex underlying cellular and biochemical factors leading to mucosal injury. In a prospective study, McCarthy et al. observed a 22% prevalence of oral mucositis in patients with breast cancer and a 25% prevalence in patients receiving CT for solid malignancies. The studies by Dreizen et al. revealed that the incidence of oral mucositis during CT treatment was 8.4%. This finding is in contrast with that of the present study with a moderately higher frequency of oral mucositis observed during the treatment.[2] The mucositis frequency varied with CT protocols and malignancy. Oral mucositis was a common complication in patients with cancer receiving RT. Vera-Llonch reported that oral mucositis was observed in 29%–66% of patients receiving RT for head and neck cancer. The lesions typically healed in approximately 2–4 weeks after RT.[22]

Oromucosal pain due to oral mucositis was the most frequently reported oral complication of cytotoxic CT treatments, and 40%–70% of patients receiving CT exhibited mucositis. Oral mucositis is painful, adversely affects the ability to eat and speak, and diminishes the quality of life. [3,4] Breach of the mucosal integrity allows pathogens to spread into the surrounding tissue and bloodstream and cause infection with serious consequences, making the "mouth" the most frequent cause for fever in patients with granulocytopenia. Severe mucositis may also prevent the optimal dosing and scheduling of CT. [5,6] In the present study, oral mucosal pain was reported in 20 patients (33.3%) during CT, which was significantly higher than that at baseline and after CT. Jensen et al. reported oromucosal pain in 30% of patients during CT. Mucositis requires palliative care. However, pain associated with mucositis can be managed by topical agents. [7,8] Mucositis pain can be managed with benzydamine hydrochloride, 20% benzocaine, and 2%–4% viscous lidocaine and sucralfate suspension. [1,9]

Taste is a crucial sensation that evaluates the nutritional content of food, supports oral intake, and prevents ingestion of potentially toxic substances. Taste disorders are common in patients with cancer experiencing ageusia, dysgeusia, or hypergeusia. [10,11,12] Dysgeusia is an essential symptom in patients with cancer. Apart from the direct neurotoxic effect on the gustatory cells, dysgeusia is reinforced by other factors such as xerostomia, infections, psychological factors, and the dental treatment considerations of the patient. [13,14] Approximately 2of 3 patients (68%) with cancer receiving CT reported altered sensory perception such as decreased or loss of taste acuity or metallic taste sensation. [1, 15] Altered sensory perception negatively impacts the survival of patients with cancer by causing psychological anxiety and malnutrition. [16] Decreased sensitivity and taste alterations are positively correlated with a decrease in dietary intake and development of food aversion. Many drugs, including cancer chemotherapeutics, are secreted in saliva and directly contact taste receptors. [17,18] Patients may experience metallic or chemical taste on CT delivery, consistent with drug secretion in saliva. [2] In many patients, taste alterations disappear shortly after the end of CT because of the restored cell turnover. In the present study, the majority of the patients (90%) reported dysguesia. [4] This finding is concurrent with that of Yamashita et al., who reported taste disorders (75% to 200%) in most patients with head and neck cancer receiving CT. Taste sensitivity was impaired during RT, and taste thresholds peaked after 3–5 weeks of irradiation therapy. Goldberg et al. reported that RT might cause taste disturbances by destroying taste receptor cells.

Saliva plays a major role in modulating oral cavity health, and disruptions in the quantity and quality of salivary glands excretions may have harmful consequences on oral mucosal health. Saliva protects the oral mucosa and teeth through its lubricating, antimicrobial and acid-neutralization, and solubilization and clearance of food and bacteria. [4,6] Saliva also facilitates taste, mastication, swallowing, and speech. Reduction in the unstimulated whole salivary flow rate and stimulated whole salivary flow rate by CT impairs the watery secretion of acinar salivary cells leading to xerostomia. In the present study, xerostomia was higher during CT treatment than that at baseline and after 6 months of CT. This finding is concurrent with that of Jensen et al. and Meurman et al. [19,20] RT causes xerostomia by damaging

salivary glands. According to Jensen et al., 93% of patients experienced xerostomia during head and neck cancer RT and gradually recovered in 1–2 years post-therapy, depending on the total radiation dosage given to the gland tissue. [14,16] A review of the literature yielded no evidence of oral mucosal complications after RT in patients with breast cancer treated with surgery and RT, possibly because RT complications were anatomically site-specific, and the field of irradiation in breast cancer therapy was far away from the oral cavity. [18]

The present study has certain limitations. The relatively small sample size prevented the generalization of the findings. Further studies with a larger sample and a longer follow-up are required before establishing a proper assessment and management protocol fororomucosal alterations.

Conclusion:

The present study revealed an overall increase in the severity of oral mucositis, oromucosal pain, oral dryness, and taste disturbances in patients undergoing CT compared with baseline and 6 months after CT. However, no postradiation oral mucosal involvement was observed because oral mucosa does not lie in the field of irradiation in breast cancer therapy.

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