Photobiomodulation Therapy Prevents Dysgeusia Chemotherapy-Induced in Breast Cancer Women Treated with Doxorubicin Plus Cyclophosphamide: A Triple-Blinded, Randomized, Placebo-Controlled Clinical Trial

Cássia Emanuella Nóbrega, Malta
Federal University of Ceara: Universidade Federal do Ceara
Anna Clara Aragão Matos Carlos
Unichristus: Centro Universitario Christus
Manuele Carine Maciel de Alencar
Cancer Institute of Ceara: Instituto do Cancer do Ceara
Eveline Fernandes Alves e Silva
Cancer Institute of Ceara: Instituto do Cancer do Ceara
Victor Bruno Caitano Nogueira
Cancer Institute of Ceara: Instituto do Cancer do Ceara
Ana Paula Negreiros Nunes Alves
UFC: Universidade Federal do Ceara
Fábio Figueiredo Chaves
Cancer Institute of Ceara: Instituto do Cancer do Ceara
José Fernando Bastos de Moura
Cancer Institute of Ceara: Instituto do Cancer do Ceara
Paulo Goberlânio Barros Silva (paulo_goberlanio@yahoo.com.br)
Federal University of Ceara: Universidade Federal do Ceara https://orcid.org/0000-0002-1513-9027

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Abstract

Purpose

To evaluate the effectiveness of photobiomodulation (PBMT) in preventing dysgeusia in breast cancer patients treated with doxorubicin-cyclophosphamide (AC).

Methods

This is a phase II, randomized, triple-blind, placebo-controlled clinical trial involving 112 breast cancer patients treated with AC. The patients were divided equally into two groups: a test group treated with 2 J red laser and 3 J infrared laser on 21 points that were symmetrically distributed on the tongue on day 0 of four cycles of AC, and an equal placebo group treated with simulated PBMT to blind the patient, evaluator, and statistician. The clinicopathological and sociodemographic data, results of the hematological tests, taste test, and subjective taste analysis, and the QoL, ECOG performance status, body mass index, and other side effects were recorded. The data were analyzed using ANOVA-RM/Bonferroni, Friedman/Dunn, and chi-square/Fisher's exact tests.

Results

PBMT patients showed less objective and subjective taste loss ($p < 0.05$). On the other hand, the placebo group showed a higher ECOG status ($p = 0.037$) and more significant weight loss ($p < 0.001$) after four cycles of AC. The QoL was significantly higherin the PBMT group ($p < 0.05$) at all assessment periods, and PBMT treatment also reduced the incidence of cachexia ($p = 0.020$), anorexia ($p < 0.001$), diarrhea ($p = 0.040$), oral mucositis ($p = 0.020$), and vomiting ($p = 0.008$).

Conclusion

PBMT reduced the taste loss and improved the overall health status and QoL of patients with breast cancer treated with AC.

Trial registration

: Brazilian Clinical Trials Registry (www.ensaiosclinicos.gov.br) approval numberRBR-9qnm34y, registered on 01/05/2021

Introduction

Chemotherapy for breast cancer generally combines antineoplastic drugs, orally or intravenously, that inhibit tumor growth and normal fast-growing cells [1, 2, 3]. Its use in breast cancer can occur after (adjuvant chemotherapy) or before (neoadjuvant chemotherapy) the surgical procedure, during the maintenance phase, or even palliatively in patients with metastatic tumors [2–4].

Although highly effective for most breast tumors, doxorubicin,in combination with cyclophosphamide (AC), has limiting factors such as cardiotoxicity and emergence of multiple drug resistance. Antineoplastic agents used in chemotherapeutic treatment are toxic to normal fast-growing tissues, with the manifestation of side effects during follow-up. The effects predominate in cells with rapid cell division, such as those of the hematopoietic tissue, germ tissue, hair follicle, gastrointestinal lining, and oral cavity [1–3].

Among the various side effects in women treated with AC, the second most frequent non-hematologic complications is taste loss (97.3%) [1, 3, 5]. Taste is essential for recognizing flavors and textures of substances [6]. The disruption of taste tissue homeostasis can be harmful to the taste system [6–7], and chemotherapy can cause direct damage to taste bud cells or indirectly alter brain regions responsible for taste perception [5–8]. Patients with dysgeusia presented with worse overall quality of life (QoL) and reduced food intake and cachexia [6–8].

Photobiomodulation (PBMT) has been used to promote photochemical changes in target tissues without structural loss [9, 10]. These changes occur due to the absorption by the target tissue of the light emitted by PBMT, which occurs at the cellular level, improving metabolism, cell proliferation, and maturation, and decreasing inflammatory mediators. Because it stimulates mitochondrial activity, PBMT acts as an anti-inflammatory, analgesic, and wound-healing agent [10–12].

Considering that there are no treatment/prevention protocols for chemotherapy-induced dysgeusia, and that PBMT is a low-cost therapeutic modality that has enormous benefits in controlling other side effects in the mouth such as oral mucositis, this study aimed to evaluate the influence of PBMT in preventing dysgeusia in breast cancer patients treated with AC.

Materials And Methods

Study design and ethical considerations

This is a phase II, randomized, triple-blind, placebo-controlled clinical trial registered in the Brazilian Clinical Trials Registry (www.ensaiosclinicos.gov.br) following the CONSORT guidelines for clinical trials, with approval protocol number RBR-9qnm34y and ethics approval number 3.286.363 (Instituto do Câncer do Ceará, ICC).

Participants and clinical setting: inclusion, exclusion, and withdrawal criteria

Patients aged >18 years, with stage II-IV breast cancer, and free of previous chemotherapy were selected for the first adjuvant, neoadjuvant, or palliative treatment with drug protocols of the combined

doxorubicin (Adrimicin®) and cyclophosphamide (Cytoxan®) (AC). Chemotherapeutic protocols cannot be associated with other drugs.

Patients with a history of radiotherapy to the head and neck, who smoke, with anemia, with untreated diabetes mellitus, with a history of drug use that significantly altered the salivary flow, saliva composition, or taste [6,7], or who are taking centrally acting analgesics or anxiolytics and antidepressants were excluded from the study. Study participants were also excluded if they dropped out of treatment or the study, required a change of chemotherapy protocol that will replace the AC protocol, discontinued chemotherapy for any reason, developed extreme toxicity, or died (Figure 1).

All patients were treated at the chemotherapy outpatient clinic of the Haroldo Juaçaba Hospital/ICC from July-2019 to January-2020.

Study groups and experimental protocol

After signing the informed consent form we performed a baseline clinic evaluation and QoL assessment. So, laser therapy was performed. A therapy EC laser model (DMC®, São Carlos, SP, Brazil) with 100 mW of light output power at a continuous wavelength of 660±10 nm (red) and 808±10 nm (infrared) was used. The device has a tip with an area of 0.09842 cm^2, which was kept in light contact with the treated area during the protocol applications. Patients were treated on the day of chemotherapy infusion and on day 0 (D0) and D+21 (end of one cycle and start of another), from the beginning of the first chemotherapy cycle for four cycles (C1, C2, C3, and C4).

Then, 2 J of red-light per dot, which is used for tissue regeneration during chemotherapy [11], and 3 J of infrared light per dot, which is used for paresthesia [13] (energy density = 20.32 J/cm^2 and 30.48 J/cm^2, respectively) were applied in fourteen points spread symmetrically across the dorsum of the tongue [10,14] (Supplementary File 1).

Outcomes and data analysis

Clinicopathological and sociodemographic data collection and oral health profile

We evaluated the patients' medical records and collected the clinicopathological and sociodemographic data, including age, tumor location, comorbidities, drugs in use, menarche, and menopause, parity, nutritional support, psychological support, and previous surgical and/or radiotherapy treatments. Tumor stage, histological type, and immunohistochemistry profile (hormonal receptors, HER-2 and ki-67) and sociodemographic data were also recorded.

Prior to the first chemotherapy session, the patient's oral cavity was inspected to measure the index of decayed, missing, and filled teeth (DMFT) and the degree of tooth mobility [15]. The collection and evaluation of non-stimulated salivary secretion were performed using the expectoration method at each chemotherapy [16].

Taste acuity evaluation

Taste test

The objective taste test was performed before applying the low-intensity laser on the days of chemotherapy administration. Taste thresholds were performed using 0.01 mol/L, 0.032 mol/L, 0.1 mol/L, 0.32 mol/L, and 1.0 mol/L (0.01–1.0 mol/L) of glucose (sweet), sodium chloride (salty), citric acid (sour), and urea (bitter). A drop for each concentration was placed at the central region of the tongue and swallowed by the patient, starting with the lowest concentration. Then, the individual evaluated the stimulus for 15 s to perceive and identify the flavor. If recognition or identification did not occur, the next concentration was applied. Between the different flavor modalities, the patients rinsed their mouth with distilled water [17].

To calculate the taste loss variation, the −log10 of the concentration of each taste perceived by the patient was calculated, ranging from no taste alteration (−log10(0.01)=2), minimal taste alteration (−log10(0.032)=1.5), moderate taste alteration (−log10(0.1)=1), strong taste alteration (−log10(0.32)=0.5), and severe taste alteration (−log10(1)=0). The sum of taste loss scores adjusted by −log10, which ranges from 0 to 8, was divided by 8 and multiplied by 100 to obtain the Taste Sensitivity Score (TSS, %), according to the formula below:

$$TSS\ (\%) = \frac{[-log10(sweet)]+[-log10(salty)]+[-log10(sour)]+[-log10(bitter)]}{8} \times 100$$

Subjective taste analysis

During the chemotherapy cycles, we questioned the patient about his subjective perception of taste using a Visual Analog Scale (VAS), ranging from 0 to 10, where 0 corresponds to no change and 10 corresponds to a maximum loss of taste. The Common Terminology Criteria for Adverse Events (CTCAE) v3.0 criteria for adverse events classifies the patient's taste as no change (0) to changes in both taste and diet (2) [18]; and the scale of Subjective Total Taste Acuity (STTA) is a total taste acuity scale that classifies the taste as same acuity as before treatment (0) to complete loss of taste acuity (4) [19]. These scales were completed along with VAS at each cycle (every 21 days) of chemotherapy before applying the PBMT/placebo.

QoL analysis, health status and side effects

The Oral Health Impact Profile (OHIP)-14 questionnaire was administered on D0 of each cycle from the beginning of C1. The OHIP-14 is a subjective indicator that measures disability (Disability), discomfort, and handicap (Handicap) attributed to the oral condition through self-assessment and their relationship to the QoL. It consists of 14 questions, a reduced version of the OHIP-49. It is also scored on a Likert-type scale from 1 (never) to 5 (always) [20]. OHIP-14 and incidence of gastrointestinal tract-related side effects

(anorexia, diarrhea, nausea, oral mucositis, and vomiting) were also evaluated were reported at each chemotherapy cycle such as

On C1 and C4 the body mass index (BMI) was calculated and patients were scored in ECOG scale in a range from 0 to 5 [21].

Sample Size Calculation

Based on a case-control study, Sánchez-Lara et al. [22] observed that patients with cancer present greater taste distortion than those without cancer (10% vs. 33.3%); thus, 51 patients per study group (chi-square test) were necessary to obtain a sample that represents, with 80% power and 95% confidence, the alternative hypothesis of this study, as estimated using the Fleiss method with continuity correction foreseeing sample loss. Given the possibility of sample loss, 10% was added to the sample, totaling 56 patients per study group.

Randomization and Blinding

The patients were randomly divided into the control group and the test group. Randomization (simple) was performed by a collaborator using the "=randomize()" command of Microsoft Excel (Microsoft Corporation®) by simple randomization in study groups A and B. Then, the randomization numbers were printed on sealed envelopes to identify the group to which the patient belonged. They were opened only by the leading researcher at the time of treatment.

The leading researcher was aided by two collaborators (ACMC and MCMA), who were unaware of the group to which the patient belonged, to perform PBMT protocol and evaluations, thus making the study blind to the evaluators. In addition, the laser protocol was equally applied to both groups; however, the leading researcher simulated the application by turning the device on and off immediately [23], thus blinding the patients. The statistician (PGBS) and the evaluator (ACMC) supporting the work were also unaware of the group to which each patient belonged. Thus, only the principal investigator knew the patients' groups, thus blinding the patient, evaluator, and statistician, making the study triple blind.

Statistical Analysis

Clinical data were expressed as absolute and percentage frequencies and compared using Pearson's chi-square or Fisher's exact test. Data from taste tests and dysgeusia scores were expressed as mean and SD and compared using Mann-Whitney or Friedman/Dunn tests (nonparametric data) (SPSS v20.0, $p<0.05$).

Sample size power

Based on the TSS of breast cancer patients evaluated after four cycles of AC administration treated with PBMT (57.82±21.49%) compared to patients treated with PBMT placebo (43.78±23.16%), the sample of 56 patients per study group used in this study had a power of 91.4% in rejecting the null hypothesis (Student's t-test).

Results

Sociodemographic and clinicopathological characterization of breast cancer patients treated with AC

A total of 56 patients in each group remained until the end of the study. There was no difference in the distribution of these variables between the PBMT and placebo groups (Table 1).

Table 1
Sociodemographic and clinicopathological profile of breast cancer patients treated with Doxorubicin and cyclophosphamide and undergoing PBMT protocol for dysgeusia prevention.

	Group		
	PBMT placebo	**PBMT test**	**p-Value**
Age			
Up to 45 years old	19 (33.9%)	16 (28.6%)	0.541
> 45 years old	37 (66.1%)	40 (71.4%)	
Race			
White	22 (39.3%)	26 (46.4%)	0.445
Brown	34 (60.7%)	30 (53.6%)	
Source			
Metropolitan Area	24 (42.9%)	19 (33.9%)	0.331
Countryside	32 (57.1%)	37 (66.1%)	
Education			
Can read and write	3 (5.4%)	1 (1.8%)	0.627
Elementary School	27 (48.2%)	24 (42.9%)	
High School	13 (23.2%)	14 (25.0%)	
Higher Education	13 (23.2%)	17 (30.4%)	
Nutritional orientation			
No	16 (28.6%)	14 (25.0%)	0.670
Yes	40 (71.4%)	42 (75.0%)	
Before	37 (92.5%)	40 (95.2%)	0.818
During	1 (2.5%)	1 (2.4%)	
After	2 (5.0%)	1 (2.4%)	
Psychological support			
No	13 (23.2%)	18 (32.1%)	0.291
Yes	43 (76.8%)	38 (67.9%)	

*p < 0.05, Fisher's exact test or Pearson's chi-square test (n, %). CT = chemotherapy; HR = hormonal receptor; * TNM staging (Tumor size (T), Nodal involvement (N) and Metastasis (M));

	Group		
Before	41 (97.6%)	38 (97.4%)	0.367
During	1 (2.4%)	0 (0.0%)	
After	0 (0.0%)	1 (2.6%)	
Menarche < 12 years old	25 (46.3%)	20 (38.5%)	0.415
Menopause	34 (60.7%)	30 (53.6%)	0.445
Children	47 (87.0%)	48 (85.7%)	0.840
T			
1	3 (5.6%)	7 (13.0%)	0.035
2	16 (29.6%)	26 (48.1%)*	
3	25 (46.3%)*	12 (22.2%)	
4	10 (18.5%)	9 (16.7%)	
N			
0	11 (19.6%)	20 (36.4%)	0.264
1	27 (48.2%)	20 (36.4%)	
2	15 (26.8%)	12 (21.8%)	
3	3 (5.4%)	3 (5.5%)	
M			
0	41 (82.0%)	42 (85.7%)	0.616
1	9 (18.0%)	7 (14.3%)	
Primary tumor			
Unilateral	54 (96.4%)	55 (98.2%)	0.558
Bilateral	2 (3.6%)	1 (1.8%)	
Phenotype			
Luminal A	7 (12.5%)	6 (10.7%)	0.803
Luminal B	19 (33.9%)	23 (41.1%)	
Hybrid Luminal	11 (19.6%)	12 (21.4%)	

*p < 0.05, Fisher's exact test or Pearson's chi-square test (n, %). CT = chemotherapy; HR = hormonal receptor; * TNM staging (Tumor size (T), Nodal involvement (N) and Metastasis (M));

	Group		
HER2	3 (5.4%)	1 (1.8%)	
Triple negative	16 (28.6%)	14 (25.0%)	
HR	37 (66.1%)	41 (73.2%)	0.411
HER2	14 (25.0%)	13 (23.2%)	0.728
Intent CT			
Neoadjuvance	33 (58.9%)	26 (46.4%)	0.389
Adjuvance	20 (35.7%)	25 (44.6%)	
Palliative	3 (5.4%)	5 (8.9%)	
Type of surgery			
Quadrantectomy	24 (58.5%)	24 (47.1%)	0.273
Total mastectomy	17 (41.5%)	27 (52.9%)	
*p < 0.05, Fisher's exact test or Pearson's chi-square test (n, %). CT = chemotherapy; HR = hormonal receptor; * TNM staging (Tumor size (T), Nodal involvement (N) and Metastasis (M));			

Most of the patients treated had tumors at the T2 or T3 stage, with nodal involvement and without distant metastases. Patients treated with placebo had significantly more T3 tumor than those treated with PBMT (p = 0.035). Only three patients had bilateral metasynchronous tumors, and most only had a tumor in one breast. The phenotype of most tumors was luminal B, with most patients positive for hormone receptors and negative for HER2. Neoadjuvant therapy was used in most patients in both the PBMT and placebo groups, and most patients were treated with mastectomy and axillary emptying in both groups. These variables showed no significant differences between the two groups (Table 1).

General health status and weight loss in breast cancer patients treated with AC and given PBMT for prevention of chemotherapy-induced dysgeusia

Only eight patients needed to undergo two more AC cycles, for a total of six cycles of AC, but he patients were evaluated only for the first four cycles to standardize the evaluations. Most patients started chemotherapy treatment with ECOG 0 in C1 and by the end of C4. There was no significant variation in the PBMT group (p = 0.208), while the placebo group showed a significant increase in patients with ECOG > 1 (p = 0.016). At the end of C4, there were significantly more ECOG > 1in the placebo group than in the PBMT group (p = 0.037) (Table 2).

Table 2
General health status at the beginning and end of treatment with Doxorubicin and cyclophosphamide in breast cancer patients undergoing PBMT protocol to prevent chemotherapy-induced dysgeusia.

	Group		
	PBMT placebo	**PBMT test**	**p-Value**
Need for CT postponement	5 (9.1%)	3 (5.8%)	0.514[a]
AC chemotherapy protocol			
AC-4	51 (90.1%)	53 (94.6%)	0.616[a]
AC-6	5 (8.9%)	3 (5.4%)	
ECOG in C1			
0	42 (75.0%)	47 (83.9%)	0.366[a]
1	13 (23.2%)	9 (16.1%)	
2	1 (1.8%)	0 (0.0%)	
3	0 (0.0%)	0 (0.0%)	
ECOG in C4			
0	27 (48.2%)	41 (73.2%)*	0.037[a]
1	22 (39.3%)*	13 (23.2%)	
2	5 (8.9%)*	2 (3.6%)	
3	2 (3.6%)	0 (0.0%)	
BMI (kg/m²)			
C1	28.98 ± 5.36	27.92 ± 4.36	0.425[b]
C4	28.98 ± 5.58	28.86 ± 4.37	0.977[b]
p-Value[c]	0.560	< 0.001[c]	
Percentage change BMI	99.94 ± 8.15	103.60 ± 6.33	0.006[b]
BMI Variation			
> 5% weight loss	11 (19.6%)*	8 (14.3%)	0.020[a]

*p < 0,05, [a] Fisher's exact test or Pearson's chi-square test (n, %); [b]Mann-Whitney test; [c]Wilcoxon test (mean ± SD).
** CT (Chemotherapy); AC (Doxorrucicin and Cyclophosphamide); BMI (Body Mass Index); C1 and C4 (Chemotherapy cycle); ECOG (General Health Scale for Cancer Patients)

	Group		
Between < 5% and > 5% of weight	33 (58.9%)*	22 (39.2%)	
> 5% weight gain	12 (21.4%)	26 (46.4%)*	
BMI in C1			
< 18.5kg/m²	0 (0.0%)	0 (0.0%)	0.837[a]
18.5-25kg/m²	14 (25.0%)	15 (26.8%)	
25-30kg/m²	21 (37.5%)	23 (41.1%)	
> 30kg/m²	21 (37.5%)	18 (32.1%)	
BMI in C4			
< 18.5kg/m²	2 (3.6%)	1 (1.8%)	0.297
18.5-25kg/m²	13 (23.2%)	8 14.3%)	
25-30kg/m²	16 (28.6%)	25 (44.6%)	
> 30kg/m²	25 (44.6%)	22 (39.3%)	

*p < 0,05, [a] Fisher's exact test or Pearson's chi-square test (n, %); [b]Mann-Whitney test; [c]Wilcoxon test (mean ± SD).
** CT (Chemotherapy); AC (Doxorrucicin and Cyclophosphamide); BMI (Body Mass Index); C1 and C4 (Chemotherapy cycle); ECOG (General Health Scale for Cancer Patients)

In C1, the patients' mean BMI started with no statistically significant difference between the two groups (p = 0.425) and remained to have no statistically significant difference at the end of C4 (p = 0.977). However, while the placebo group showed no significant change in BMI throughout the study (p = 0.560), patients in the PBMT group showed a significant (p < 0.001) increase of BMI (p = 0.006). Patients in the placebo group had a higher incidence of weight loss of > 5% or weight maintenance than patients in the PBMT group (p = 0.020). Nonetheless, there was no increase in the incidence of overweight/obesity in both groups (Table 2).

PBMT prevents the depreciation of oral health and oral health-related QoL in breast cancer patients treated with AC

Patients in both the placebo group and PBMT group had a high DMFT at the beginning of the study (20.11 ± 9.93 and 20.55 ± 10.07, respectively), with no significant difference between the groups (p = 0.726). There was no significant variation in the dose of AC over time in either group, and there was no significant difference between the PBMT and placebo groups (Table 3).

Table 3
Evaluation of Doxorubicin and Cyclophosphamide dose and oral health status over four chemotherapy sessions in breast cancer patients treated with PBMT protocol to prevent chemotherapy-induced dysgeusia.

	Cycle				
	C1	**C2**	**C3**	**C4**	**p-Value[b]**
Doxorubicin (mg/m²)					
Placebo	62.54 ± 3.62	62.50 ± 3.54	61.99 ± 4.36	61.72 ± 4.46	0.197[b]
Test	62.62 ± 2.74	61.15 ± 9.11	60.63 ± 9.30	60.24 ± 9.45	0.090[b]
p-Value[a]	0.922[a]	0.680[a]	0.735[a]	0.672[a]	
Cyclophosphamide (mg/m²)					
Placebo	628.18 ± 30.57	632.94 ± 68.34	627.82 ± 73.48	625.16 ± 74.41	0.165[b]
Test	622.61 ± 41.95	607.96 ± 96.26	602.70 ± 97.66	598.85 ± 98.94	0.089[b]
p-Value[a]	0.764[a]	0.561[a]	0.605[a]	0.554[a]	
Salivary flow					
Placebo	0.91 ± 0.37	0.93 ± 0.38	0.89 ± 0.34	0.88 ± 0.35	0.892[b]
Test	1.01 ± 0.42	0.98 ± 0.39	0.92 ± 0.38	0.96 ± 0.37	0.078[b]
p-Value[a]	0.164[a]	0.223[a]	0.667[a]	0.063[a]	
Dental Mobility					
Placebo	1.75 ± 1.34	2.02 ± 1.36	2.22 ± 1.30*	2.16 ± 1.61*	0.003[b]
Test	2.05 ± 1.33	2.14 ± 1.31	2.12 ± 1.36	2.06 ± 1.39	0.534[b]
p-Value[a]	0.250[a]	0.655[a]	0.727[a]	0.874[a]	
OHIP-14					
Placebo	9.09 ± 6.30	12.75 ± 7.27*	13.09 ± 7.60*	13.02 ± 7.25*	< 0.001[b]
Test	8.63 ± 6.44	8.54 ± 6.28	7.83 ± 6.26	7.98 ± 6.71	0.877[b]

*p < 0,05 versus C1, [a] Mann-Whitney Test; [b]Friedman/Dunn Test.

	Cycle			
p-Value[a]	0.621[a]	0.001[a]	< 0.001[a]	0.001[a]
*p < 0,05 versus C1, [a] Mann-Whitney Test; [b]Friedman/Dunn Test.				

The mean salivary flow in the placebo group and PBMT groups showed no significant differences at any chemotherapy cycle and no significant variation throughout the study. The tooth mobility scores also showed no significant difference between the groups at any chemotherapy cycle. However, in the placebo group, there was a significant increase at C3 and C4 compared to C1 (p = 0.003), whereas in the PBMT group, there was no significant variation at any cycle (p = 0.534) (Table 3).

Both groups started chemotherapy treatment with equal mean OHIP-14 scores (p = 0.621). From C2 onwards, there was a significant increase in the dissatisfaction scores with oral health-related QoL in the placebo group (p < 0.001), remaining high compared to the PBMT group in C2 (p = 0.001), C3 (p < 0.001), and C4 (p = 0.001). The PBMT group showed no significant variation in OHIP-14 scores over the four cycles of chemotherapy (p = 0.877) (Table 3).

PBMT prevents the reduction of objective taste loss in breast cancer patients treated with AC

The objective evaluation of taste showed significant preservation of taste sensitivity in the PBMT group compared to the placebo group. All flavor sensitivity scores started with no difference between the two groups (p > 0.05). The sweet (p = 0.773), salt (p = 0.611), sour (p = 0.141) and bitter (p = 0.056) sensitivity showed no significant variation in the PBMT group (Supplementary File 2).

The sweet scores in the placebo group, there was a significant reduction at C2 (p < 0.001), with a lower perception of sweet taste than the PBMT group at C2 (p = 0.001), C3 (p = 0.009), and C4 (p < 0.001). Salty taste perception was significantly higher in the PBMT group at C2 (p = 0.010), C3 (p = 0.001), and C4 (p < 0.001). The perception of sour taste was significantly higher in the PBMT group at C2 (p = 0.006), C3 (p = 0.006), and C4 (p = 0.001). And at C3 (p < 0.001) and C4 (p = 0.001), bitter taste sensitivity was significantly higher in the PBMT group than in the placebo group (Supplementary File 2).

TSS of patients started with 54.39 ± 21.77% taste perception in the placebo group and 57.08 ± 21.20% in the PBMT group (p = 0.554). There was no change in the PBMT group throughout the study (p = 0.588), but the placebo group showed a significant reduction starting at C2 (p < 0.001). The objective taste perception scale showed significantly higher values in the PBMT group from C2 to C4 (p < 0.001) (Fig. 2).

PBMT for prevention of chemotherapy-induced dysgeusia prevents the reduction of subjective taste loss in breast cancer patients treated with AC

Subjective taste assessment showed similar onset between the two groups at C1 for both VAS (p = 0.313), CTCAE scale (p = 1.000), and STTA (p = 1.000). There was a significant increase in VAS

dissatisfaction scores with taste ($p < 0.001$) in both groups. However, while the PBMT group showed an increase from C3, the placebo group showed an increase from C2. VAS scores were also significantly higher in the placebo group than in the PBMT group at C2 ($p < 0.001$), C3 ($p < 0.001$), and C4 ($p < 0.001$) (Fig. 2).

In both groups, CTCAE scores started at 0.00 ± 0.00 in both groups and increased significantly in the placebo group from C2 ($p < 0.001$) and in the PBMT group from C3 ($p < 0.001$). At C2 ($p < 0.001$), C3 ($p < 0.001$), and C4 ($p < 0.001$), the CTCAE dysgeusia scores were significantly higher in the placebo group than in the PBMT group. Taste STTA scores started at 0.00 ± 0.00 in both groups and increased significantly in the placebo group from C2 ($p < 0.001$) and in the PBMT group from C3 ($p < 0.001$). From C2 ($p < 0.001$), C3 ($p < 0.001$), and C4 ($p < 0.001$), the STTA taste loss scores were significantly higher in the placebo group than in the PBMT group (Fig. 2).

PBMT for prevention of dysgeusia secondarily reduces the incidence and severity of chemotherapy-related side effects in breast cancer patients treated with AC

The PBMT-treated group showed a 0.43-fold (95CI = 0.35–0.53) reduction in the incidence of anorexia over the four cycles of chemotherapy ($p < 0.001$), and the incidence of diarrhea was 0.63-fold (95% CI = 0.41–0.97) lower in the PBMT group than in the chemotherapy protocol ($p = 0.040$). PBMT treatment did not significantly influence the incidence of nausea ($p = 0.070$); however, in the PBMT group, the incidence of oral mucositis was reduced 0.57 (95% CI = 0.36–0.92) times ($p = 0.020$), and the incidence of vomiting demonstrated a 0.75 (95% CI = 0.61–0.93) times reduction ($p = 0.008$). Overall, the PBMT group showed a 0.89-fold (95% CI = 0.85–0.93) reduction in the incidence of side effects related to the gastrointestinal tract ($p < 0.001$) (Fig. 3).

Discussion

We showed that PBMT prevents dysgeusia during chemotherapy with AC. AC constitutes the first-line pharmacological treatment [4, 23, 24], but it is strongly related to side effects such dysgeusia [25]. Any disturbance in the ability to differentiate the perception of taste can modify salt and sugar intake, increase the risk of malnutrition, and affect the QoL [25, 26].

In a systematic review by Bressan et al. [27], it was observed that among the side effects caused by antineoplastic therapies, oral mucositis, nausea, vomiting, diarrhea, and dysgeusia were the most reported side effects associated with nutritional changes. Changes in taste due to chemotherapy may contribute to the high prevalence of malnutrition in cancer patients, and it is estimated that 50–70% of cancer patients suffer from taste disorders [5, 25].

The nutritional follow-up that most patients in this study underwent justifies the low weight loss in the placebo group, because most oncologic patients suffer from weight loss, causing a general worsening of their health status due to cachexia [27, 28], which leads to intolerance to therapy and a higher risk of other side effects [10, 29, 30]. Dysgeusia is a critical adverse effect in this process, interfering with the

nutritional status [5, 8]. In this study, PBMT lead to a significant increase in BMI, which may be associated with the low incidence of dysgeusia during treatment [30, 31].

Taste is essential in generating satisfaction during food intake, and the reduction in gustatory function in breast cancer patients begins soon after the first cycle of chemotherapy [5]. The perception of salty taste has beenthe most affected [30]. This is a common side effect of systemic cancer therapy and negatively impacts the QoL of patients [32]. However, PBMT maintained taste quality and prevented loss of all taste scores.

Oppositely to PBMT, the placebo group showed an increase in the degree of tooth mobility. Dysentery is linked to side effects such as nausea and vomiting cravings [8, 29, 31, 33]. The reduction of these side effects in the present study may have contributed to better oral hygiene and dental health status [34].

As previously described [29], gustatory function decreased throughout chemotherapy treatment regardless of the affected tastes, and the longer the treatment time, the higher the incidence of dysgeusia [35], directly affecting nutritional status [29]. The placebo group showed increasing objective (taste scores) and subjective (CTCAE, STTA, and VAS scores) alterations throughout the treatment for all the analyzed flavors from the second chemotherapy cycle, while in the PBMT group, these alterations were significantly controlled with a consequent reduction in the incidence of cachexia maintaining weight that is an important factor that contributes to general health status during cancer treatment.

In our study, besides controlling weight loss, general health status (ECOG) and anorexia, the proposed preventive PBMT protocol significantly controlled the increased incidence of nausea, vomiting, diarrhea, and oral mucositis [35–38]. The PBMT used in the present study as a preventive measure for dysgeusia played an essential role in preventing these various complications, which has already been described in literature [39–41].

Taste loss due to chemotherapy is strongly associated with inflammation and cytokines [42]. Because PBMT exhibits anti-inflammatory and antioxidant capacity [35, 36, 38, 43], we consider the mechanisms involved in preventing taste loss during chemotherapy with AC observed in this study to be locally inflammatory in nature [8].

The most significant limitation of the proposed protocol was the application time. Despite being extremely practical because it is a single application and can be performed on the day of the chemotherapy session, avoiding additional patient displacement (increased costs, discomfort, and dropout frequency), [5, 8] the application lasts 15–20 min, which tires the medical professional and the patient [38, 43]. And, although this was a single-center study with a single chemotherapy protocol used, this is the first triple-blind randomized clinical trial that highlights the promising function of PBMT in preventing trans-chemotherapy taste loss.

Conclusion

PBMT is effective in preventing chemotherapy-induced dysgeusia and weight loss. PBMT reduced the incidence of gastrointestinal-related side effects and contributed to the maintenance of the general health status of breast cancer patients treated with AC.

Declarations

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Funding

Not applicable

Conflicts of interest

No conflicts of interest

Ethics approval

This study was approved by the Ethics Committee of the Haroldo Juaçaba Hospital (HHJ) (Instituto do Câncer do Ceará - ICC) under protocol number 3.286.363. All ethical aspects expressed in Resolution No. 466 of 2012 of the National Health Council/Ministry of Health, which brings the guidelines and regulatory standards for research with human beings and in accordance with the National Research Ethics Committee (CONEP) standard, were respected.

Consent to participate

Informed consent was obtained from all individual participants included in the study

Consent for publication

The authors affirm that human research participants provided informed consent for publication

Availability of Data

Not applicable

Authors' Contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Cássia Emanuella Nóbrega Malta, Anna Clara Aragão Matos Carlos and Paulo Goberlânio de Barros Silva. The first draft of the manuscript was written by Cássia Emanuella

Nóbrega Malta and Paulo Goberlânio de Barros Silva and all authors Manuele Carine Maciel de Alencar, Eveline Fernandes Alves e Silva,Victor Bruno Caitano Nogueira, Ana Paula Negreiros Nunes Alves, Fábio Figueiredo Chaves and José Fernando Bastos de Moura included patients, performed systemic analysis and commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figures

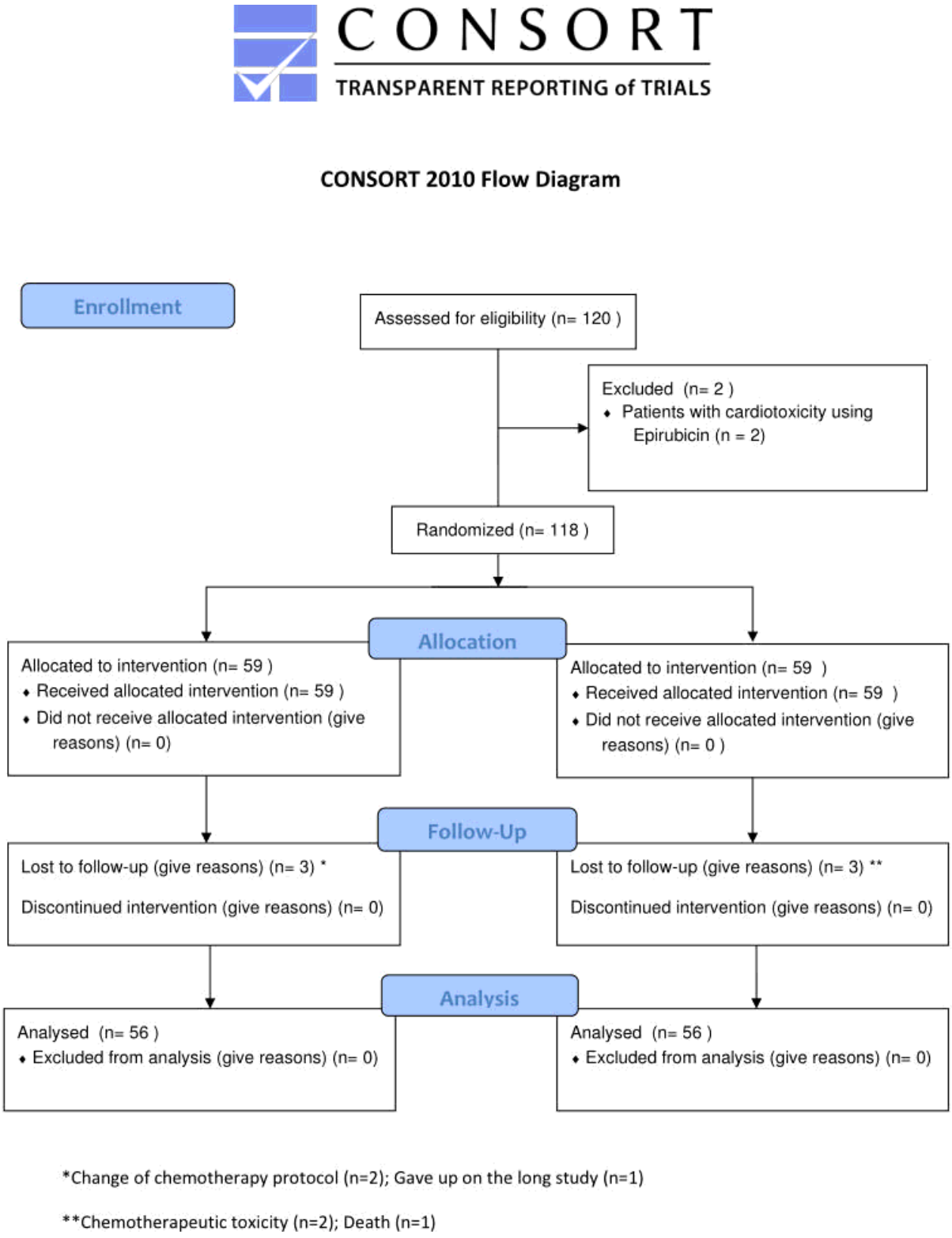

Figure 1

CONSORT flowchart with inclusion, exclusion, and analysis criteria for breast cancer patients treated with Doxorubicin and cyclophosphamide and undergoing a randomized, triple-blind placebo-controlled clinical trial.

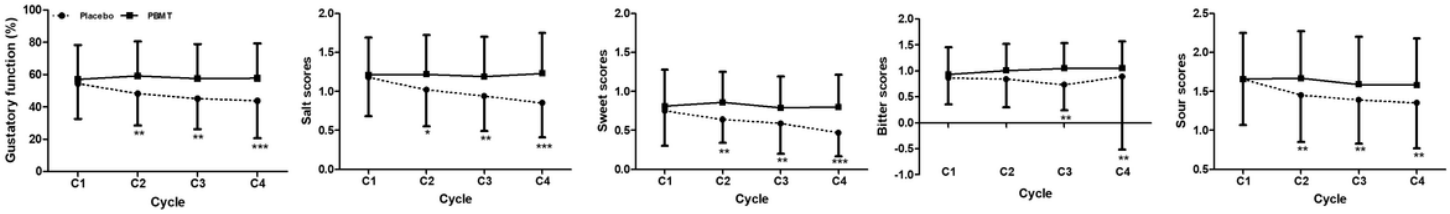

Figure 2

Objective and subjetive analysis of taste function over four administrations of Doxorubicin and cyclophosphamide in breast cancer patients undergoing PBMT protocol for dysgeusia prevention.

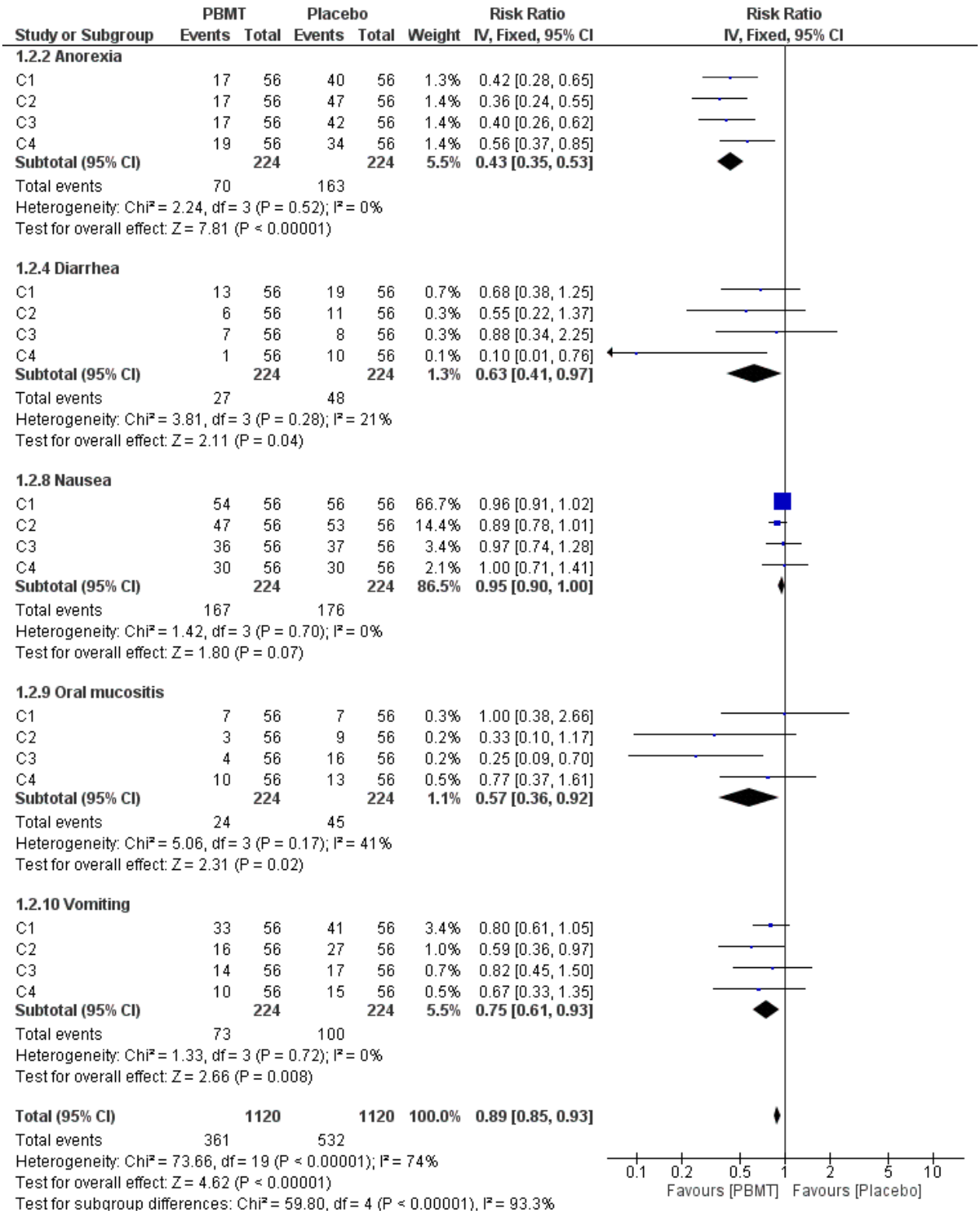

Figure 3

Valuation of incidence of chemotherapy-associated side effects over four sessions of AC administration

Supplementary Files

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