



Use of Guarana for Hot Flashes after Breast Cancer: Randomized, Double-Blind, Placebo-Controlled Phase II Trial

Abna Faustina de Sousa Vieira, Vitor Augusto Queiroz Mauad*, Daniel Cubero, Patrícia Xavier Santi and Auro del Giglio

Faculdade de Medicina da Fundacao ABC (School of Medicine of the ABC Foundation), AV Lauro Gomes, 2000, Santo Andre, SP, Brazil – 09060-870; vitormauad.medabc@gmail.com

Abstract

Background: Hot flashes are common in menopausal women and significantly affect the quality of life of many patients diagnosed with breast cancer for which hormone replacement therapy is not indicated. In a previous uncontrolled study, guarana (*Paullinia cupana*) showed significant decreases in the amount and intensity of hot flashes in this group of women. **Hypothesis/Purpose:** The main objective was to reduce the intensity and frequency of hot flashes with the use of PC-18, compared with placebo in women who survived breast cancer without current evidence of disease. **Study Design:** The present study consists of a double-blind, randomized, placebo-controlled, uni-institutional, two-arm phase II clinical trial. **Methods:** The experimental group received the purified dry extract of *Paullinia cupana* (PC-18) at a dose of 37.5 g twice daily, while the other group received placebo, also twice daily. **Results:** The study included 40 patients who had completed surgical, chemotherapeutic and/or radiotherapeutic treatment for more than 3 months and who were on adjuvant hormone therapy at the time of inclusion, 20 in each arm. Both groups showed significant reductions in the number and intensity of hot flashes, with no significant difference between the arms. There was a higher intensity and frequency of hot flashes in patients receiving tamoxifen compared with those who received aromatase inhibitors. The toxicities observed were not very significant. **Conclusion:** This concludes that PC-18 did not demonstrate significantly greater capacity than placebo for control of hot flashes in women with a history of breast cancer and adjuvant hormone therapy.

Keywords: Breast Neoplasia, Guarana, Hot Flashes, *Paullinia cupana*

Abbreviations

NCCN – National Comprehensive Cancer Network.

SSRIs – Selective Serotonin Reuptake Inhibitors.

CYP2D6 – Cytochrome P450 2D6.

PC-18 – Tablets containing the active ingredient guarana, used as intervention.

ADLs – Activities of Daily Life.

HFRDIS – Hot Flashes Related Daily Interference Scale.

ASEX – Arizona Sex Experience Scale.

BECK – Beck's Depression Inventory.

CHALDER – Chalder Fatigue Scale.

EORTC QLQ-30 – European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30.

CTCAE – Common Terminology Criteria for Adverse Events.

BMI – Body Mass Index.

*Author for correspondence

1. Introduction

Breast cancer is the most prevalent neoplasm in the worldwide female population. In Brazil, the number of new cases was 59,700 for the year 2018, with a risk of 59.7 cases per 100,000 women²⁰. Due to the increased early diagnosis of breast cancer resulting from screening programs⁵ associated with advances in cancer treatment^{32,36}, cure rates and survival rates have increased^{14,24}. The increase in survival is accompanied by a concern for ensuring the survivors' quality of life⁴⁰. Most patients are treated with chemotherapy followed by hormone therapy for at least 5 years, with current data showing the benefit of extending this therapy for up to 10 years in those with high-risk disease³².

Despite the well-documented benefit in overall survival and the decrease in recurrence with such treatments³², the side effects, such as hot flashes and sexual dysfunction, affect the quality of life of this population^{10,17,31}. Approximately 65% of treated women suffer from hot flashes, with 59% of the affected women characterizing the symptom as severe¹⁷.

Hot flashes are vasomotor symptoms³¹ resulting from the dysfunction of the thermoregulatory center, leading to a decrease in the core temperature threshold required to trigger heat waves. Such dysfunction is caused by decreased serum estrogen levels. While premenopausal women have mechanisms to dissipate heat when the temperature of the thermoregulatory nucleus increases by 0.4°C, in menopausal women (or those with hypo-oestrogenism for other reasons), this heat dissipation occurs with much lower temperature increases, leading to hot flashes³⁰.

The most effective treatment for hot flashes is hormone replacement with estrogen, reducing the frequency and intensity of these events by 77% or 2.5 to 3 hot flashes/day^{33,37}. The administration of estrogen restores the thermostat to the neutral position, leading to the inhibition of hot flashes. However, due to the formal contraindication of hormone replacement therapy in breast cancer survivors, it is necessary to attempt to use non-hormonal medications to alleviate the symptoms. Some medications have already shown action in the treatment of menopause-related vasomotor symptoms, such as Selective Serotonin Reuptake Inhibitors (SSRIs) fluoxetine and paroxetine^{26,45}, norepinephrine

and serotonin reuptake inhibitors: venlafaxine^{11,16,25}, desvenlafaxine^{23,44}, anticonvulsants (gabapentin)^{7,19,38}, megestate¹⁸, clonidine^{6,39} and methyldopa^{2,34}. Unfortunately, none of these drugs have achieved the rate of reduction achieved by hormone replacement and still present major drawbacks. Because SSRIs are strong inhibitors of CYP2D6, they decrease the formation of endoxifen and activate the metabolite of tamoxifen, leading to a decrease in the plasma concentration of the drug, directly impacting its efficacy.

Other drawbacks are the withdrawal of venlafaxine treatment due to side effects, and the high required dose of gabapentin (> 900 mg/day) to achieve a response rate, which determines a higher incidence of side effects such as somnolence³⁸. Due to the long-term adverse events associated with a low efficacy in the reduction of hot flashes, many patients and physicians do not use any medications directed against hot flashes, and to date, there is no standard treatment for this symptom.

Guarana (*Paullinia cupana*, family: Sapindaceae) is an Amazonian plant used for centuries by the local population to treat a headache, poor digestion, kidney dysfunction, muscle pain, menstrual cramps, depression and fatigue. Guarana has already been tested in non-oncological populations and has been shown to be beneficial in terms of cognitive performance and mood improvement, being well tolerated at a dose of 75 mg⁴⁶. Studies indicate that the stimulating effect of guarana is not only to the small amount of caffeine, approximately 2.5-5 % present in the dry extract of this plant^{15,48} but perhaps also to other components, such as saponins and tannins²⁹.

Paullinia cupana was also tested in oncology patients and has been beneficial in the treatment of cancer-related fatigue in patients undergoing adjuvant chemotherapy for breast cancer in a randomized double-blind study in which non-purified guarana dry extract was used. It was observed that patients who received guarana had a significant decrease in fatigue compared with placebo. Additionally, there was no severe toxicity and there was no worsening of depression or quality of sleep. The results highlight that guarana is an inexpensive and effective therapeutic alternative for the treatment of fatigue induced by chemotherapy⁸.

A pilot study conducted with women taking adjuvant hormone therapy due to breast cancer who had hot

flashes showed that the use of non-purified dry extract of guarana at a dose of 50 mg twice daily for 6 weeks had significant effects on the amount ($p = 0.0009$) and intensity ($p < 0.0001$) of the hot flashes, with great tolerance and there was no discontinuation due to toxicity³⁵. However, the interpretation of the efficacy of various agents studied for hot flashes, as exemplified above, are subject to the direct influence of the placebo effect, which is responsible for reducing hot flashes 20 to 50 %⁴¹. Women with a high degree of anxiety have an even more pronounced version of this placebo effect, responding even more to placebo. Hence, testing all drugs in a placebo-controlled study is of prime importance. Our primary objective was to evaluate the efficacy of a purified dry extract of guarana (PC-18) in reducing the frequency and intensity of hot flashes in patients with a history of breast cancer and adjuvant hormone therapy, comparing the effects produced with those of a group of patients randomized to receive placebo. The secondary objective was to evaluate the efficacy of PC-18 in improving sexual performance, symptoms of depression, fatigue and eventual repercussions of hot flashes and treatment on the quality of life of these patients.

2. Materials and Methods

The present study consists of a double-blind, placebo-controlled, randomized, uni-institutional, two-arm clinical trial; one is the experimental group, with the purified dried extract of *Paullinia cupana* named PC-18 and another being the placebo group.

The planned sample consisted initially of 70 patients recruited from two hospitals (Mario Covas State Hospital and Padre Anchieta Teaching Hospital) who were being followed up at the oncology services of the referred hospitals. Recruitment was performed essentially by an active search of the patients who met the inclusion criteria and were followed up at any of the hospital services mentioned above.

2.1 Inclusion and Exclusion Criteria

Patients older than 18 years with a previous diagnosis of luminal breast cancer without current evidence of the disease who had completed the surgical, chemotherapeutic and/or radiotherapeutic treatments for at least 3 months, who were also currently using

adjuvant hormone therapy for at least 3 months (either tamoxifen or anastrozole), who reported the presence of at least 1 hot flash per day in the last week or 7 hot flashes per week, who were accessible to study and attended on the scheduled dates for follow-up, who were able to understand the nature and purpose of the study and signed the informed consent form were eligible to participate in the study. Patients with evidence of metastatic disease or local recurrence who had any other cancer diagnosis, with uncontrolled comorbidities, mainly symptomatic hypertension, tachyarrhythmia, hyperthyroidism or heart disease, were excluded from the study.

The study was duly approved by the ethics committee of the School of Medicine of the ABC, to which the two participating hospitals are linked.

2.2 Study Protocol and Medications used

In the first visit, the patients received all of the information about the study in question. If they had complained about hot flashes and agreed to participate, they were given a hot flashes diary. Over the course of one week, the patient was instructed to freely record in the diary the time each hot flash occurred throughout the day, its duration, associated symptoms, how much it interfered with what she was doing and whether anything had to be done to improve the symptoms. From these records, the patient would classify each of her hot flashes as mild, moderate, severe or very severe. At the end of that week, the patient was to complete a scale that assesses how much her hot flashes have interfered in her daily activities and in her quality of life.

The second appointment was scheduled one week after the first appointment (week 1) and consisted of the evaluation of the hot flashes diary. If the patient had presented at least 7 hot flashes throughout the week and agreed to participate in the study, the informed consent form was applied. Next, the following parameters were compiled: demographic characteristics of the patient, such as ethnicity, age, schooling, occupation, marital status, menopausal status, whether the patient had an active sexual life and whether hot flashes interfered with her quality of life. Data on the diagnosis and treatment of breast cancer, such as date of diagnosis, histological type, initial clinical staging, whether the patient had undergone surgery and when, whether chemotherapy

bad been performed and when, whether radiotherapy had been performed and when, date when hormone therapy was initiated and the medication is chosen for this purpose, were also collected. In the second consultation, 4 questionnaires were also provided to the patients.

The PC-18 used was the standardized dry extract of *Paullinia cupana* (PGUR0062F), obtained by extraction in 70% alcohol and after evaporation, the pure extract containing 0.096% of the obromine was obtained. The placebo was given to the patients inside containers and capsules similar to those of PC-18, and it was composed of 100% cornstarch.

Patients were randomized into 2 groups: Group 1 and group 2. Group 1 received treatment with tablets containing the active ingredient of guarana (PC-18) at a dose of 37.5 mg/tablet 2x daily for 4 weeks; group 2 received treatment with placebo tablets for 4 weeks. This dosing was based upon a previous article by Oliveira SS et al that made use of an impurified extract at 50 mg q 12 h daily. Dose was adjusted to 37.5 mg q12h, considering the concentration of the PC-18 compound, against the impurified extract used on the referenced article. The patients received 56 tablets containing guarana or placebo according to the group to which they had been randomly allocated in a double-blind fashion.

For 4 weeks (from the beginning of week 1 to the end of week 4), patients in group 1 and 2, respectively, used PC-18 and placebo. At the third appointment (week 5), the hot flashes diaries that were already completed were delivered by the patient and once again, the questionnaires described below were answered. At that time, the patients returned the medicine bottle; the remaining capsules were counted to determine the lack of use of the medication. There was no crossover (Figure 1).

2.3 Evaluation Tools

The instrument chosen to evaluate the frequency and severity of hot flashes was the same one used by Loprinzi CL^{9,26,42}. Over the course of one week, the patient observed the number of hot flashes, their duration, whether they interfered with their Activities of Daily Life (ADLs) and if anything was needed to improve the symptoms. From this observation, the patient should note how many hot flashes a day she considered mild (without interference

in ADLs), moderate (little interference in ADLs), severe (so uncomfortable that ADLs could not be performed) or very severe (so uncomfortable that ADLs could not be performed and the patient needed to do something to reverse the symptoms) intensity. The frequency was calculated from the average number of hot flashes/day that the patient presented during the week. The severity was calculated from a score obtained by multiplying the number of hot flashes by their respective severity (if light, multiplied by 1; if moderate, by 2; if severe, by 3; and if very severe, by 4). The result of the score corresponds to the sum of these products.

In addition, to evaluate more precisely how hot flashes interfered with daily activities and patient quality of life, a questionnaire was used that evaluates, through a scale from 0 (does not interfere) to 10 (interferes completely), how much the hot flashes interfered in 9 aspects of the patient's life (work, social activities, leisure activities, sleep, mood, concentration, relation with others, sexuality, enjoyment of life) and finally, interference in quality of life as a whole. This scale is the Portuguese version of the scale originally in English (Annex 2) called "The Hot Flashes Related Daily Interference Scale-HFRDIS", created and validated by⁹.

To evaluate the possible interference of PC-18 in sex drive, depression, quality of life and fatigue, the respective questionnaires ASEX^{27,28}, the BECK scale^{3,4}, EORTC QLQ-30^{1,43,12}, previously validated for Portuguese, were used.

ASEX was developed to evaluate psychotropic medication-induced sexual dysfunction. This instrument has previously been validated for use in Brazilian cancer patients²². ASEX is a five-question short questionnaire designed to measure sexual functioning in 5 domains. The items are scored on a 6-point scale, ranging from 1 (hyperfunction) to 6 (hypofunction), with a total score ranging from 5 to 30. A total score > 18, a score \geq 5 (very difficult) on any of the items or three items with an individual score \geq 4 are indicative of clinically significant sexual dysfunction^{27,28}.

The Beck Depression Scale consists of a self-report questionnaire with 21 multiple choice items and is one of the instruments most used to measure the severity of depressive episodes. It covers 21 premises referring to the current moment of the subject that are quantified on a scale of 4 intensity points (0 to 3). The instrument is

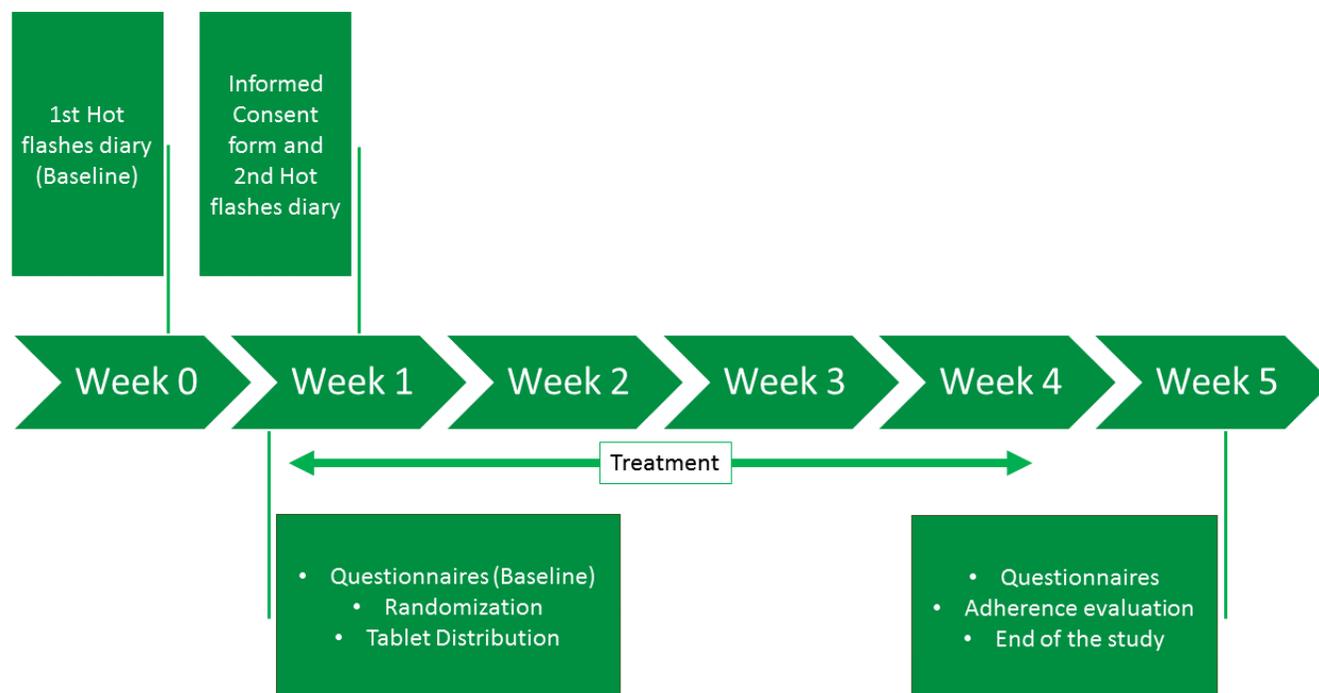


Figure 1. Protocol for the study.

easy to manipulate and apply and has great acceptance. The scores range from 0 to 63, where zero indicates there is no trace of depression and higher scores indicate greater severity of depression. The interpretation guide is as follows: 1. 0 = Minimal score, no depression; 2. 10 to 16 = Mild to moderate state of depression; 3. 17 to 29 = moderate to severe state of depression; and 4. 30 to 63 = Indicates a severe state of depression^{3,4}.

Version 3.0 of the QLQ-C30 consists of 5 functional scales, 2 symptom scales, 1 global health status scale and 6 unique items. All scales range from 0 to 100; thus, a high score for a functional scale represents a high level of healthy functioning and a high score for the overall health status represents a high quality, but a high score for a scale/item of symptom represents a high level of symptomatology, which translates into a poor response. The answers are coded in the same way as in items 1 to 28, i.e., “No”, “Little”, “Yes” and “Very Much”; questions 29 and 30 are scored on a numerical scale from 1 to 73^{1,43}.

The Chalder scale consists of 11 questions. Questions 1-10 have the standardized responses of “Less than usual”, “No more than usual”, “More than usual” and “Much

more than usual”; question 11 has the standardized responses “Better than usual”, “No worse than usual”, “Worse than usual” and “Much worse than usual”. The score is assigned from 0 to 33 points (Chalder et al., 1993). Toxicities were assessed according to CTCAE version 4.0 (CTCAE versao 4.0).

3. Statistical Analysis

First, the sample calculation was based on the prevalence of hot flashes among post-breast cancer women of 65%¹⁷, with a possible variation of this frequency of 10%, with a study power of 80% and a significance level of 5%, considering the possibility of 20% loss. The sample planning also contemplated an interim analysis when the recruitment reached 50% of the predicted number, that is, 35 patients.

We analyzed the means of the frequency of the hot flashes and the product of the frequency by the intensity of the hot flashes, which were compared between the groups that received PC-18 and placebo by Student’s T-test or the Wilcoxon test, depending on the normality or otherwise of the samples. Likewise, we analyzed the differences between groups for the Quality of Life EORTC

QLQ C-30, Beck, ASEX and Chalder questionnaire scores. We considered the values of p that were less than or equal to 0.05 as significant.

4. Results

In our study, after reaching 40 patients, an interim analysis was performed, as predicted in the statistical planning. Of the 40 patients, 2 were followed up for neoplasia at the Mario Covas State Hospital, Santo Andre-SP and 38 were followed up for neoplasia at the Padre Anchieta Teaching Hospital, Sao Bernardo do Campo-SP. The analysis of the demographic characteristics showed that

Table 1. Table of characteristics

	PC-18	Placebo
Age		
Average (Range)	53 (37-70)	52.2 (43-77)
St Dev	9,5	7,9
BMI		
Average	26 (19,5-45,3)	29,5 (17-45,3)
Median	25,7	28,8
St Dev	4	6,1
Menopause		
Yes	18	16
No	2	4
Medication		
Anastrozol	10	5
Tamoxifen	10	15
Chemotherapy		
Yes	16	18
No	4	2
Radiotherapy		
Yes	14	14
No	6	6
Tabagism		
Yes	1	3
No	19	17
Ethnicity		
White	9	14
Brown	10	4
African Decendent	1	2

both arms were comparable; there was no significant difference between them (Table 1).

The mean ages were 53 years in the intervention group and 52.25 in the control group. Regarding medication, most patients in the control group used tamoxifen as hormone therapy, 15 (75%) compared with only 10 (50%) in the intervention group, but with no significant difference between them ($p = 0.1$).

All questionnaires were answered by all patients, with the exception of the hot flashes diary, which was not answered by only 1 patient.

For the primary outcome, the hot flashes diary was the main score. In week 0, all 20 patients in the placebo group and 19 in the study group completed the questionnaire; these numbers decreased with the progression of the week, with 16 and 13 at week 1; 15 and 13 at week 2; 15 and 12 at week 3; and 15 and 12 at weeks 4 and 5.

In our study, both arms showed significant reductions in the number and intensity of hot flashes, showing, as already mentioned above, the weight of the placebo effect in this population. The frequency and intensity curves with each week of medication use, showed a progressive decrease, with greater expression in the first week of intervention (Figures 2 and 3).

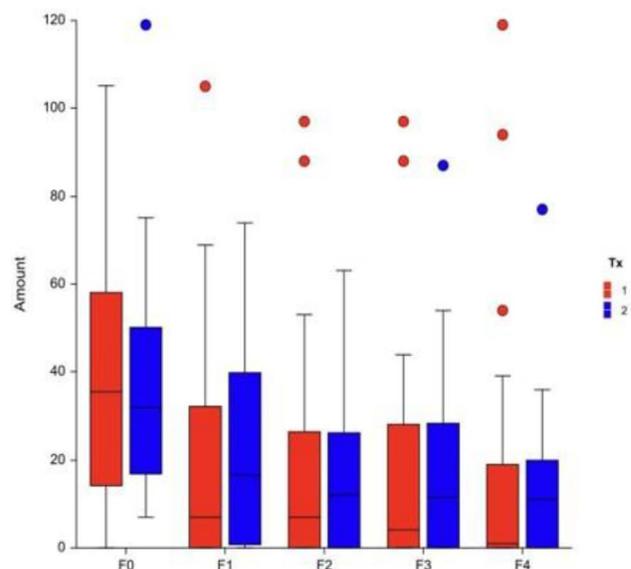
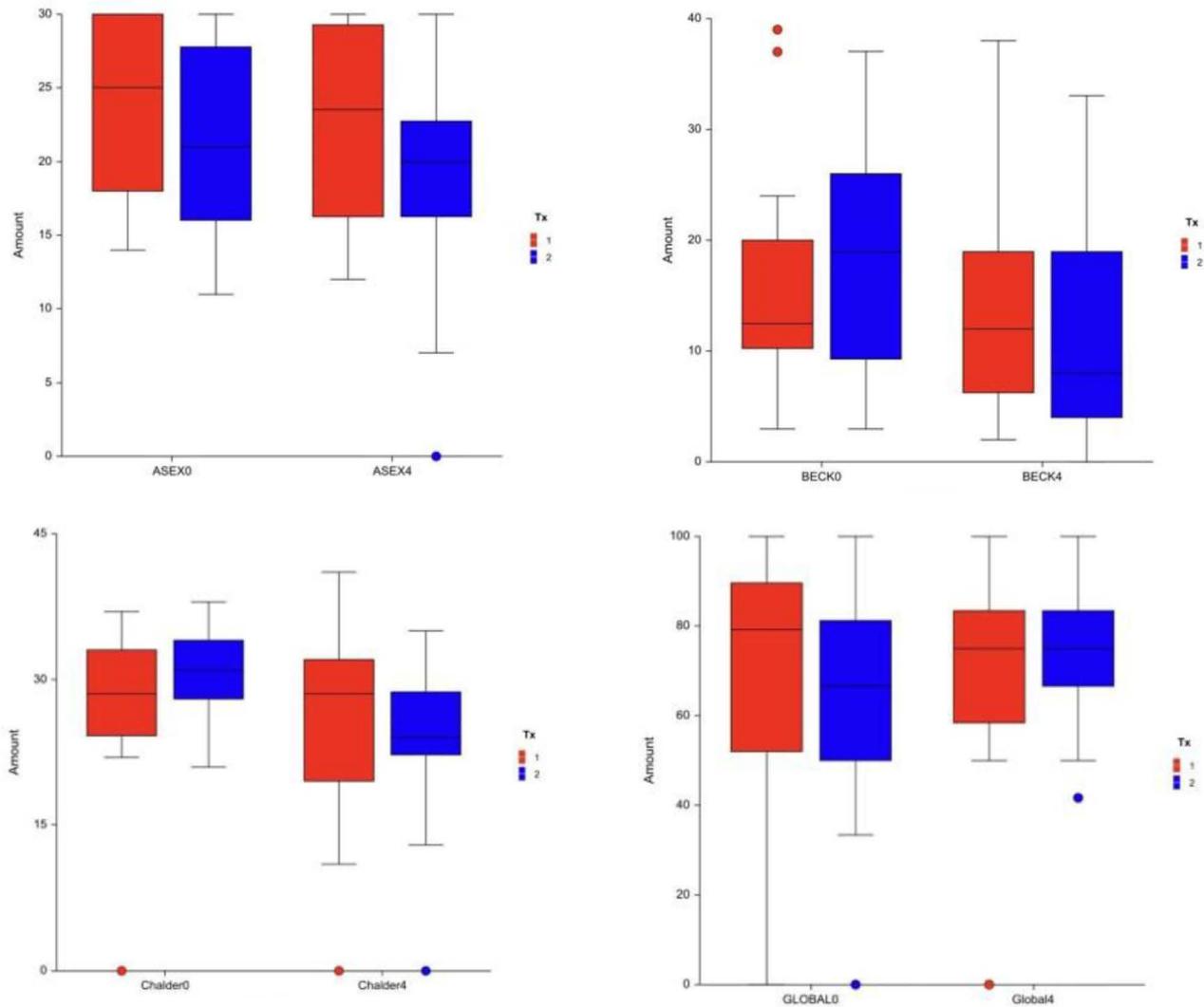


Figure 2 Chart for Frequency of Episodes. PC-18 = 1; Placebo = 2



Figures 4 to 7: Charts for score outcomes, each chart target score specified on the x axis. PC-18 = 1; Placebo = 2

is formally contraindicated. Thus, one can make use of non-pharmacological measures (in cases of mild to moderate episodes) and/or therapeutic interventions (in severe to very severe cases), many of which have several adverse effects and may even lead to the decreased action of tamoxifen, as with SSRIs.

The use of tamoxifen was associated with hot flashes in up to 80% of patients, 30% of which classified such episodes as severe¹⁷. Genetic characteristics of estrogen receptors may also influence the risk and intensity of tamoxifen-induced hot flashes. Aromatase inhibitors may also lead to hot flashes, but they tend to be less frequent and less severe^{21,22}, as also observed in this study.

The great influence of the placebo effect on hot flashes cannot be ruled out, underscoring the need for placebo-controlled trials. In fact, the interpretation of the efficacy of the various agents studied for hot flashes is influenced by the placebo effect, which is responsible for reducing the frequency of hot flashes from 20 to 50%⁴⁸. This effect is even more significant in women with a high degree of anxiety, suggesting that even active agents with proven statistical significance can act, at least in part, through the placebo effect mechanism.

In this study, although the group of patients receiving PC-18 had significant decreases in the number and intensity of hot flashes during the study, the decreases were not significantly greater than those seen in the

placebo group. Likewise, we did not observe significant changes in the scores of the other questionnaires analyzed (ASEX, Chalder, QLQ C-30 and Beck) among patients receiving PC-18 and placebo. This fact reinforces the need to always include a placebo group in studies that seek pharmacological relief of symptoms, as we did in this study.

The absence of a trend favoring PC-18 led us to suspend this study in the first interim analysis, scheduled for when the study reached half of the total planned sample. Based on the results obtained in this study, we could not suggest the use of guarana to reduce hot flashes in this patient population.

Supplementary Data



6. Funding

Funding for this study was provided through the Centre for Study and Research in Haematology and Oncology (CEPHO), an institution related to the ABC Medical School and Haematology/ Oncology chair.

7. Role of the Funding Source

CEPHO assisted on providing the funding for intervention and placebo elaboration. All other costs were funded by the authors themselves.

8. Declarations of Interest

The authors confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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