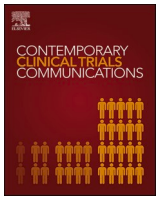
Contemporary Clinical Trials Communications 30 (2022) 101013

Contents lists available at ScienceDirect

Contemporary Clinical Trials Communications

journal homepage: www.elsevier.com/locate/conctc



Study protocol: Randomized, open-label, non-inferiority clinical trial for evaluating the clinical and pathological response rates to neoadjuvant hormone therapy and chemotherapy in patients with luminal-subtype breast tumors

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ARTICLE INFO

Keywords:
Neoadjuvant chemotherapy
Neoadjuvant hormone therapy
Chemotherapy
Radiotherapy
Presurgical treatment
Preoperative endocrine prognostic index

ABSTRACT

Background: Despite neoadjuvant hormone therapy (NHT) is being underused, it is an effective treatment for luminal tumors at a lower cost and with fewer side effects compared to those associated with neoadjuvant chemotherapy (NCT). The lack of robust comparative data between NHT and NCT is a factor that limits its use in clinical practice.

Methods: This study will be a randomized, open-label, non-inferiority clinical trial. Patients diagnosed with HER2-negative luminal-subtype breast cancer will be identified at the time of diagnosis. Menopausal patients randomized for NHT should receive anastrozole for at least six months. Premenopausal women should receive anastrozole associated with subcutaneous goserelin acetate every 12 weeks for at least six months. Patients randomized for NCT will receive a standard institutional regimen based on anthracyclines and taxanes. Sample size was calculated considering the CPS + EG as a method for evaluating response and prognosis, where a score <3 was defined as good. The non-inferiority margin for NHT was set at 15%. The study considered a power of 80%, a significance level of 5%, and an outcome proportion in each group of 69%, resulting in 118 patients in each group. We estimated at 10% of losses, resulting in a sample of 130 patients in each group.

Conclusion: The non-inferiority of NHT in relation to NCT will provide further evidence that replacing NCT with NHT is safe and effective in eligible patients, which is particularly relevant for populations with limited access to health services and for institutions with few available resources.

1. Introduction

Neoadjuvant breast cancer therapy was introduced in the 1970s to reduce locally advanced tumors and make them operable. These tumors were considered unresectable when chemotherapy (CT) and radiotherapy (RT) were the only available methods [1].

Survival outcomes has been proven equally efficacious regarding the use of neoadjuvant and adjuvant chemotherapy; thus, neoadjuvant chemotherapy was consolidated as the method of choice for the presurgical treatment of locally advanced breast cancer–large tumors and/or those exhibiting axillary involvement–and of cases with an unfavorable breast-tumor ratio scheduled to undergo breast-conserving surgery, keeping the prognosis and enabling less invasive surgical procedures [2,3].

Since that time, neoadjuvant CT (NCT) has progressed with advanced drugs, increasing tumor biology knowledge, and improved tumor resectability, resulting in less extensive surgeries in the breast and axilla. In fact, axillary preservation is possible in select cases with no residual disease on sentinel lymph node biopsy [4,5]. A good response to neoadjuvant treatment is considered a good prognostic indicator and can be used to define adjuvant therapies in the HER2-overexpressed and triple-negative subtypes [4,6–8]. A pathological complete response (PCR)–absence of residual disease on histopathological examination of the surgical specimen–is related to a lower recurrence risk, greater survival, and better prognosis in these subtypes [4,9,10]. Despite being widely used, NCT is not the only neoadjuvant strategy available.

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https://doi.org/10.1016/j.conctc.2022.101013
Received 27 April 2022; Received in revised form 19 August 2022; Accepted 1 October 2022
Available online 8 October 2022

Treatment response may vary depending on tumor type; for example, tumors expressing hormone receptors tend to have a lower response rate to CT compared to tumors that do not express hormone receptors, which is not necessarily related to a worse prognosis [3,11,12].

Historically, neoadjuvant hormone therapy (NHT) has been reserved for patients with hormone receptor-positive tumors and important comorbidities that increase the risk of first-choice surgery or NCT. These patients are generally women aged 70 years or older [11,13]. However, recent evidence suggests the beneficial use of NHT in a wider spectrum of younger patients, including premenopausal women eligible for initial surgical treatment [12,14,15].

Some benefits of NHT in patients with tumors expressing hormone receptors are increased breast-conserving surgery rates and *in vivo* tumor response assessment, thus increasing the number of patients who may benefit from adjuvant chemotherapy or hormone therapy (HT) follow-up to avoid potentially ineffective treatments with a higher incidence of side effects [16–19].

The difficulty in determining a unified method to assess tumor response to different neoadjuvant therapies is a primary limiting factor in the design of the studies comparing them [20–23].

Considering that consistent and detailed information on pathological tumor response can improve prognostic assessment and provide subsidies for adjuvant therapy, a dichotomization into PCR and residual disease (RD) has become insufficient [8]. A new, more specific classification system is the residual cancer burden (RCB), which evaluates tumor size, tumor bed cellularity, and lymph node tumor burden. Further, RCB divides patients with RD into three categories correlated with five-year disease-free survival: I – mild, II – moderate, and III – severe [8]. Despite its thoroughness, the RCB has not been validated for tumors receiving NHT, and its prognostic correlation is more accurate for HER2-overexpressed and triple-negative tumors [8,24].

Luminal-subtype tumors are susceptible to both NCT and NHT. Based on the assumption that a good response to neoadjuvant treatment suggests a lower five-year recurrence risk, a method for evaluating the pathological response after NHT had to be validated as this therapy acts on tumor cells differently from NCT [25].

Based on this need, the preoperative endocrine prognostic index (PEPI) was developed to standardize the NHT response assessment and to estimate the five-year recurrence risk for patients undergoing this treatment. The PEPI calculation considers tumor size, lymph node involvement, Ki67, and estrogen receptor positivity after NHT (Table 1) [25,26].

The clinical and pathologic stage and estrogen receptor status and histologic grade (CPS + EG) scoring system was developed to facilitate the prognostic assessment of breast cancer patients undergoing neoadjuvant therapies [22,27,28].

The CPS + EG system helps the prognostic assessment of patients undergoing both NHT and NCT and assesses the pre-therapy clinical staging and post-therapy pathological staging, in addition to providing information on ER and NG biomarkers [27]. The stratification of these patients according to prognosis is fundamental for recommending them to new therapies or to clinical trials (Table 2) [27].

Table 1
PEPI scoring criteria [25,26].

PEPI		
	Score	
	Recurrence	Overall survival
Residual tumor size		
ypT1/2	0	0
ypT3/4	3	3
Residual lymph node impairment		
Negative	0	0
Positive	3	3
Residual Ki67		
0–2.7%	0	0
>2.7–7.3%	1	1
>7.3–19.7%	1	2
19.7%–53.1%	2	3
>53.1%	3	3
Residual ER by Allred staining		
0–2	3	3
3–8	0	0

PEPI, Preoperative Endocrine Prognostic Index.

2. Justification

Several studies have attempted to demonstrate the best HT option and its ideal duration; however, few clinical trials have investigated the non-inferiority of NHT compared to that of NCT in patients diagnosed with luminal tumors without HER2-overexpression. Previous studies have included a small number of patients, most of whom were post-menopausal [16,19,22,29,30].

In 2020, the need to reduce the number of hospital admissions for elective surgeries due to COVID-19 led to an increase in NHT. This treatment was used more intensively to postpone surgical procedures for breast cancer treatment in eligible patients with luminal tumors without affecting disease progression [31,32].

The longer time elapsing between therapy initiation and clinical response through tumor reduction is a factor that discourages NHT prescription. However, even with a less-evident clinical response than that observed with NCT, this lower response does not directly correlate with worse survival for patients treated with NHT [22].

Despite being underused, NHT is an effective treatment for luminal tumors at a lower cost and with fewer side effects compared to those associated with NCT [33]. The lack of robust comparative data between NHT and CT is a factor that limits its use in clinical practice.

3. Hypothesis

The clinicopathological response to NHT is non-inferior to that of NCT in patients with HER2-negative luminal-subtype breast tumors; The five-year prognostic assessment of patients undergoing NHT is non-inferior to that of those undergoing NCT; Some patients could be spared from CT in neoadjuvant therapy, leaving the decision on the use of CT for a post-surgical time.

Table 2
CPS + EG scoring system criteria [27,38,39].

CPS + EG scoring system criteria	
	Score
Clinical staging	
I	0
IIA	0
IIB	1
IIIA	1
IIIB	2
IIIC	2
Pathological staging	
0	0
I	0
IIA	1
IIB	1
IIIA	1
IIIB	1
IIIC	2
Tumor marker	
ER[a] negative	1
NG[b] 3	1

CPS, clinical and pathologic stage; EG, estrogen receptor status and histologic grade.
[a] Estrogen Receptor.
[b] Nuclear Grade.

4. Patients and methods

Patients diagnosed with HER2-negative luminal-subtype breast cancer will be identified at the time of diagnosis at a breast cancer outpatient clinic and referred for eligibility (Table 3).

Those eligible for inclusion in the study will receive an explanation about the research and procedures in the Informed Consent From (ICF) and assigned into one of the two treatment groups using randomized blocks of four patients each.

During treatment, patients will be seen and evaluated by the principal investigator or one of his trained assistants every three months. Clinical tumor response (breast and axilla) will be assessed. Adherence to treatment will be assessed in patients under NHT.

Menopausal patients randomized for HT should receive anastrozole 1 mg tablet per day for at least six months. Premenopausal women should receive anastrozole 1 mg tablet per day associated with subcutaneous goserelin acetate 3.6 mg every 12 weeks for at least six months.

Postmenopause will be defined at the time of diagnosis by a period of at least 12 months since the last menstruation or by follicle stimulating hormone (FSH) dosage $\geq$30 mIU/mL. Patients aged below 60 years who underwent hysterectomy will have menopause defined by FSH dosage.

Patients randomized for NCT will receive a standard institutional regimen based on anthracyclines and taxanes, with doses based on individual body surface areas: doxorubicin 60 mg/m^2 concomitant with cyclophosphamide 600 mg/m^2 every 21 days for four cycles followed by paclitaxel 80 mg/m^2 weekly for 12 cycles.

A blood sample will be collected at the breast care or oncology department and stored in the translational research laboratory on the day neoadjuvant therapy begins in order to investigate circulating biomarkers. New samples must be collected three months after the beginning and end of neoadjuvant therapy.

Circulating biomarkers will be evaluated in patients at the end of the proposed treatment. The markers to be tested and the form of analysis will be defined according to the most current and promising evidence available at the end of the study.

At the end of the neoadjuvant treatment, the patients will be referred for surgery according to the availability of the assistant breast surgeon designated by the Breast Care Service at the time of diagnosis. The surgical procedure should not exceed six weeks after the end of neoadjuvant therapy.

RCB, PEPI and CPS + EG will be estimated for all patients included in the study for subsequent correlation between the scores, the objective will also be to evaluate the applicability of the RCB for patients with luminal tumors undergoing NHT, and the applicability of the PEPI score for patients with luminal tumors undergoing NCT (Fig. 1).

Table 3
Eligibility criteria.

Inclusion criteria	Exclusion criteria
Histological diagnosis of invasive breast carcinoma	Metastatic disease
ER > 50%	Inflammatory breast carcinoma
PR > 20%	Impossibility of treatments due to comorbidities
Ki67 $\leq$ 35%	Hemoglobin <7.0 g /dL
Tumor $\geq$ 2 cm using US	AP $\geq$ 1.5 times the reference value
Tumor <2 cm using US with impaired lymph node[a]	Neutrophil count <1500 U /mm^3
	Platelet count <100,000 U /μL
	Serum creatinine> 1.5 mg/dL
	Score >2 on the ECOG Scale
	Ongoing pregnancy

ER: Estrogen receptor; **PR**: Progesterone receptor; **US:** Ultrasonography; **AP:** Alkaline phosphatase; **ECOG:** Eastern Cooperative Oncology Group.

[a] Metastatic involvement should be defined by cytology (US-guided fine needle aspiration (FNA) of the suspected lymph node) or histology (core biopsy of the suspected lymph node or biopsy of the sentinel lymph node before neoadjuvant therapy).

5. Sample calculation and statistical considerations

Sample size was calculated using the R Core Team software (2020) [34–36] considering the CPS + EG as a method for evaluating response and prognosis, where a score <3 was defined as good and $\geq$3 as unfavorable (85,98). The non-inferiority margin for NHT was set at 15% (106,107). The study considered a power of 80%, a significance level of 5%, and an outcome proportion in each group of 69%, resulting in 236 patients (118 in each group). The possibility of losses was estimated at 10%, resulting in a sample of 260 patients (130 in each group).

For both clinical and pathological responses, 95% confidence intervals will be determined for success proportions in each treatment group. Bilateral 95% confidence intervals will also be constructed for determined in clinical and pathological response proportions between NHT and NCT treatments, respectively. The hypothesis of the non-inferiority of the clinical response to NHT in relation to NCT will be accepted if the lower limit of the confidence interval for the difference in this response is greater than −15%. Similarly, the hypothesis of the non-inferiority of the pathological response to NHT in relation to NCT will be accepted if the lower limit of the confidence interval for the difference in this response is greater than −15%.

An interim analysis of the data will be performed at the end of the first 12 months of recruitment to assess the speed of recruitment and the possibility of including new centers in the research, with the possibility of recalculating the sample with power adjusted to 90%.

6. Ethical aspects and monitoring

This research will follow the resolution 466/2012 of the National Health Council of the Brazilian Ministry of Health. Eligible patients will be included in the study after signing the ICF. The project was approved by the *Instituto de Medicina Integral Professor Fernando Figueira* (IMIP) Research Ethics Committee under CAAE no. 48932821.8.0000.5201. The research protocol was registered at the Brazilian Clinical Trials Registry (*Registro Brasileiro de Ensaios Clínicos* - REBEC) under approval no. RBR-7wjw5z6.

An external monitoring committee will be formed to periodically review research data and immediately discontinue the study if one of the treatments is too superior or too inferior in the interim data analysis.

The study will be discontinued if more than 30% of patients experience disease progression while receiving one of the chosen therapies. Each patient will be evaluated every three months by the researchers, in addition to monthly appointments with the attending physicians.

Disease progression will be defined according to the RECIST 1.1 criteria [37]:

- $\geq$ 20% increase in the dimension of the largest diameter of the largest lesion;
- Onset of new lesions;
- Unmistakable progression of other lesions.

7. Final considerations

If our study demonstrates the non-inferiority of NHT in relation to NCT, it will provide further evidence that replacing NCT with NHT is safe and effective in eligible patients, which is particularly relevant for populations with limited access to health services and for institutions with few available resources.

Author declaration

1) We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant

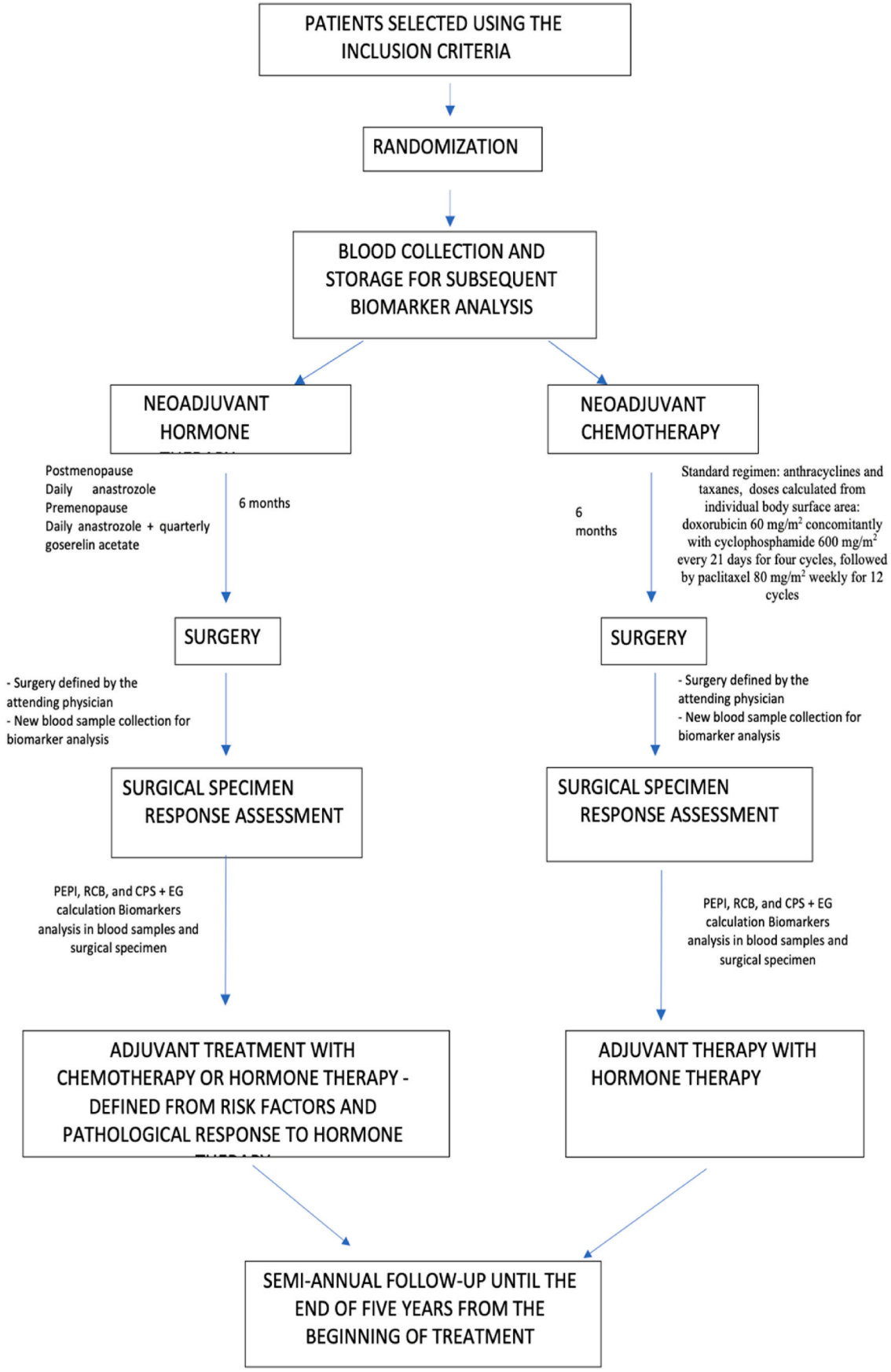

Fig. 1. Study Flowchart.

financial support for this work that could have influenced its outcome.

2) We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.
3) We confirm that neither the entire paper nor any of its content has been submitted, published, or accepted by another journal. The paper will not be submitted elsewhere if accepted for publication in the Journal.
4) We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.
5) We confirm that any aspect of the work covered in this manuscript that has involved either experimental animals or human patients has been conducted with the ethical approval of all relevant bodies and that such approvals are acknowledged within the manuscript.
6) We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He/she is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs.

Funding

This research has not yet received any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

Thanks to the breast surgery and the clinical oncology teams at IMIP, who were willing to collaborate to the recruitment and to the follow-up of patients during the study.

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