ORIGINAL ARTICLE

A phase II trial of neoadjuvant doxorrubicin plus gemcitabine, followed by weekly paclitaxel in locally advanced breast cancer: an analysis of effectiveness and toxicity

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Abstract

Background: Neoadjuvant chemotherapy is a therapeutic strategy for patients with locally advanced breast cancer. To evaluate the toxicity and clinical efficacy of the combination of Gemcitabine plus doxorubicin followed by paclitaxel in neoadjuvancy.

Methods: A phase II trial, in which 19 patients, ages 37 to 65, with pathologically proven breast cancer, were included. They received four cycles of doxorubicin 50mg/m^2 on day 1 and Gemcitabine 1000 mg/m^2 on days 1 and 8, every 21 days; followed by four cycles of paclitaxel 80 mg/m^2 on days 1, 8, and 15, every 28 days. The follow-up was performed with mammography and clinical examination.

Results: The planned regimen was completed in 17 (89.4%) of the 19 patients. Thirty seven percent of the patients presented mucositis grades 3-4 and 15% had diarrhea grades 3-4. Hematologic toxicities grades 3-4 were seen in 31.5% of the cases (6 patients). Complete clinical response was observed in 9 (47%) patients; of whom four showed complete pathological response after surgery.

Conclusion: The response rate (clinical and pathological) in this study was similar to the one observed in the usual regimen of neoadjuvancy using doxorubicin, cyclophosphamide, and paclitaxel. However, the toxicity profile of the combination regimen containing gemcitabine was exceedingly high, causing the interruption of the protocol.

Key words

Breast neoplasms, Neoadjuvant chemotherapy, Gemcitabine, Doxorubicin, Paclitaxel

1 Introduction

The number of Brazilian women with the diagnosis of locally advanced or metastatic breast cancer is considerably high. It is estimated that 28% of the new diagnosed cases in the country are stage III disease [1]. Locally advanced breast cancer is generally treated with a combination of cytotoxic drugs before the surgical procedure (neoadjuvancy). The neoadjuvancy not only increases the chances of a later conservative surgery of the breast, but also permits the evaluation of the objective response and chemosensitivity to the drugs that are being used. Moreover, it is possible that this therapeutic modality acts in a way to attack early micrometastatic disease. Complete pathological response is observed in one out of every five or six patients and is directly correlated to survival advantage, which makes it a very important endpoint in the evaluation of new neoadjuvant treatment strategies in breast cancer [2, 3, 4].

The most appropriate drug combination for neoadjuvancy is still under debate. Over the years, the combination of an alkylant and anthracyclin followed by a taxane has become the most popular choice of neoadjuvancy worldwide. The main study to support this option of therapy stems from the NSABP B-27 trial, which compared the use of doxorubicin and cyclophosphamide (AC) followed by docetaxel (T) before and after the surgery. The patients who received triplet therapy before surgery fared better [5]. More recently, the results of neoadjuvancy seemed to improve with the use of weekly paclitaxel after AC, with significant gains in disease-free-survival and overall survival [6].

Gemcitabine is a pyrimidine analogue with well-known activity in advanced breast cancer, providing responses in 25-46% of the patients, with a mild toxicity profile [7, 8, 9]. Previous studies combining gemcitabine to anthracyclins (AG) in advanced breast cancer have indicated clinical benefit in 25-55% of the cases [10, 11, 12]. Based on these reports, the AG combination was moved to the neoadjuvant setting, showing a promising response rate. On the other hand, the toxicity profile is a matter of debate, since mucositis and neutropenia are common and intense. For this reason, some authors advocate for the use of granulocyte stimulating factor, while others do not [13, 14, 15]. The response rates were similar to the ones previously described in the combination of anthracyclin and taxanes [16, 17].

The aim of the present study was to evaluate the toxicity profile of a neoadjuvant combination of gemcitabine plus anthracyclin, followed by weekly paclitaxel (AG-T) in advanced breast cancer patients treated in the Brazilian Public Health System ("Sistema Único de Saúde" – SUS). Clinical responses were also observed to decide if there are grounds for a further phase III study.

2 Materials/patients and methods

This phase II clinical trial was designed to evaluate the toxicity profile of AG-T neoadjuvant in a series of patients with locally advanced breast cancer (stages IIB or III). The inclusion criteria were: women ages 18 and up, Karnofsky´s performance status score over 80%, neutrophils > 1,000/mm^3, platelets over 100,000/mm^3, hemoglobin > 10.0g/dl, normal hepatic and renal function, and no previous history of malignant tumors.

Patients received four cycles of AG every 21 days (doxorubicin 50mg/m^2 on day 1 and Gemcitabine 1000 mg/m^2 on days 1 and 8) followed by four T cycles every 28 days (paclitaxel 80 mg/m^2 on days 1, 8, and 15). The surgical procedure (mastectomy or lumpectomy) was carried out 4 to 6 weeks after the end of the last paclitaxel cycle. The choice of surgical procedure and treatment after surgery were at the attending physician's discretion.

Mammography and breast ultrasound were originally planned to be performed before the beginning of the chemotherapy, after the first four cycles of AG and after the end of the last paclitaxel cycle. However, the protocol could not be followed, because the study was conducted in patients treated in the Brazilian Public Health System (SUS) and those exams were not

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available to be executed as planned. All patients were submitted to at least one mammography before the beginning of the chemotherapy. Breast Magnetic Resonance Imaging was not performed because the Brazilian Public Health System does not offer it to patients. All women were followed with physical examination performed at every medical consultation, when the tumor size was clinically accessed and toxicity was evaluated by Common Toxicity Criteria (CTC version 3.0).

Complete clinical response was defined as no evidence of tumor on the physical exam, whereas partial clinical response was defined as a reduction in tumor size greater than 50%. Reduction of less than 50% or an increase up to 20% was considered stable disease and an increase of more than 20% in tumor size was considered progression disease.

The protocol was approved by the institutional committee of ethics in research and by the Brazilian national committee of ethics in research. All patients were required to give written consent to enter the study.

3 Results

Table 1. Baseline patients and tumors characteristics

Patients and tumors characteristics	N (%) / median (range)
Age (years)	52.5 (35-57)
Pre-chemotherapy TNM stage	
T3N0M0	5 (26.4%)
T4N0M0	1 (5.2%)
T3-4N1M0	6 (31.6%)
T2-4N2M0	6 (31.6%)
T2-4N3M0	1 (5.2%)
Hormone receptor status	
Positive	10 (52.6%)
Negative	9 (47.4%)
Cerb-B2	
Cerb-B2 +++	5 (26.4%)
Cerb-B2 ++	2 (10.4%)
Cerb-B2 + or 0	12 (63.2%)
Total	19 (100%)

From November 2005 to February 2007, 19 patients with invasive ductal carcinoma stages IIB and III were selected for the study. The patient's baseline clinical characteristics are displayed in Table 1. It is very important to state that the four patients classified as having T2 had a clinically positive axilla before initiating the study protocol. The neoadjuvant treatment was not thoroughly applied in two patients. Patient number five presented grade 3 long-lasting hepatotoxicity after the fourth cycle of AG. Patient number six achieved maximum tumor response at the first paclitaxel cycle, but presented an increase in her tumor dimensions during the third paclitaxel cycle, at which time she was immediately sent to surgery. The reduction of the tumors' largest diameters can be verified for each patient in Figure 1.There was no significant difference in clinical response between patients with positive and negative hormonal receptors.

Nine patients (47.3%) had a complete clinical response after AG-T, and four (21%) of those patients with complete clinical response also presented complete pathological response. The other ten patients had partial responses (47.3%). Nevertheless, as it was previously described, one of those patients with partial response had her treatment stopped because of liver toxicity and another one was sent to surgery before the end of the chemotherapy because her tumor increased in diameter during the taxane cycles. This patient did not meet criteria to progressive disease (increase higher than 20% in tumor diameter); however, this decision was on her attending physician discretion. Table 2 shows the clinical and

pathological stagings before and after chemotherapy, the tumor's largest diameters before and after chemotherapy, and the surgical procedure that each patient was submitted to. It is important to state that all patients were submitted to axillary lymph node dissection and not to sentinel lymph node dissection due to technical conditions at the institution where the study was carried out.

Table 2. Description of TNM clinical staging, clinical largest tumor diameter before chemotherapy, largest tumors' diameter after chemotherapy, surgical procedure and axillary pathological status

Patient identi-fication number	TNM clinical staging	TNM pathological staging	Clinical largest palpable tumor diameter before chemotherapy (cm)	Clinical largest palpable tumor diameter after chemotherapy (cm)	Surgery
1	T2N+	NA****	3.0	NP*	Patient declined procedure
2	T3N0	CPR*****	5.0	NP*	BCS + ALND **
3	T3N+	NA****	5.0	1.4	Patient declined procedure
4	T4N+	NA****	4.6	2.0	MRM + ALND ***
5	T3N+	T2N+	6.5	4.0	MRM + ALND ***
6	T3N+	CPR*****	8.0	NP*	MRM + ALND ***
7	T4N0	T2N+	11.3	4.5	MRM + ALND ***
8	T2N+	CPR*****	4.8	NP*	MRM + ALND ***
9	T4N+	TxN+	7.0	NP*	MRM + ALND ***
10	T3N0	NA****	9.4	1.5	BCS + ALND **
11	T4N+	T2N+	15.0	5.0	MRM + ALND ***
12	T4N+	T2N+	4.0	3.5	MRM + ALND ***
13	T4N+	T2N+	9.5	2.5	MRM + ALND ***
14	T3N0	CPR*****	6.5	NP*	BCS + ALND **
15	T3N+	TxN+	9.5	NP*	MRM + ALND ***
16	T3N+	T1N+	10.5	1.5	BCS + ALND **
17	T3N+	TxN+	7.0	NP*	BCS + ALND **
18	T2N+	TxN+	3.0	NP*	BCS + ALND **
19	T3N0	TxN+	5.0	NP*	MRM + ALND ***

* NP: non-palpable tumor

** BCS + ALND: breast conserving surgery plus axillary lymph node dissection

*** MRM + ALND: modified radical mastectomy plus axillary lymph node dissection

**** NA: not-available

***** CPR: complete pathological response

The adverse effects related to the treatment are shown in the Table 3. As mentioned, Grade 3 liver toxicity was observed in one patient. Six patients (31.5%) presented hematologic toxicity grades 3 and 4, with severe neutropenia in five of them. Mucositis was reported in all patients, seven (36.8%) of which had grades 3 and 4. Thirteen patients complained of periods of nausea, but it was considered as intense (Grades 3 and 4) in only three of them. Grades 3 and 4 diarrhea, were reported in 3 patients (15.7%).

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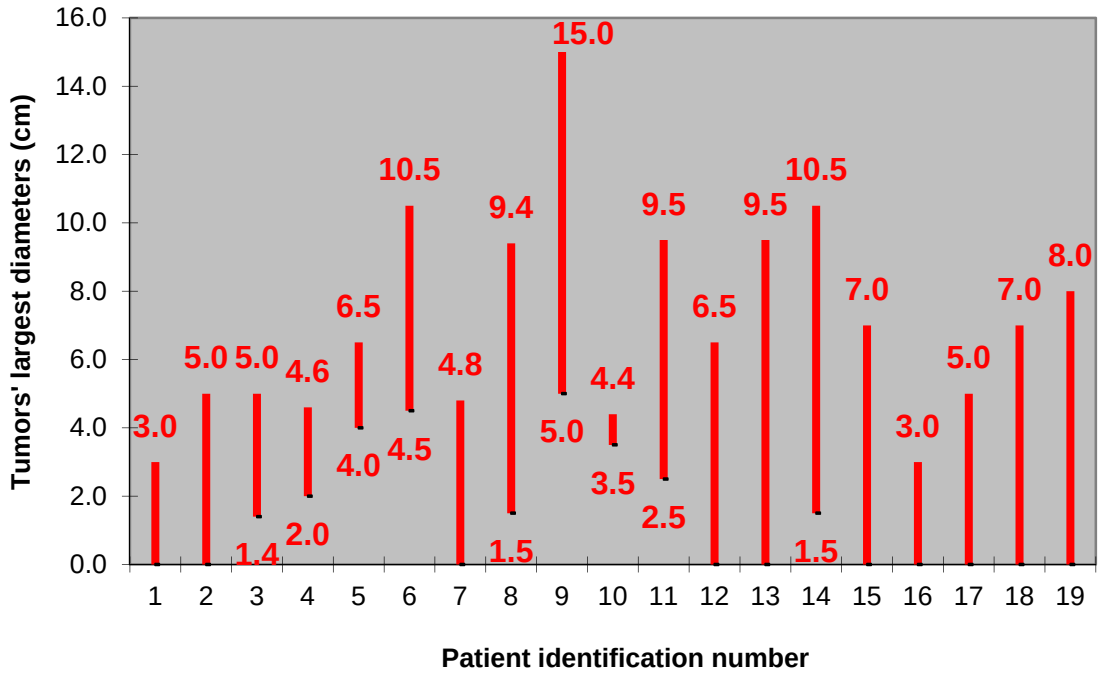

Figure 1. Tumors' largest diameters before (at the top of the lines) and after (at the bottom of the lines) neoadjuvant chemotherapy for each patient incuded in the study. * Data regarding patient number six refers to her best response.

Table 3. Adverse events with doxorubicin plus gemcitabine followed by weekly paclitaxel

Effect	Grade 1 (n)	Grade 2 (n)	Grade 3 (n)	Grade 4 (n)
Alopecia	2	11	-	-
Anemia	8	9	2	-
Anorexia	1	1	-	-
Diarrhea	2	2	3	-
Fatigue	3	3	-	-
Febrile neutropenia	-	2	-	2
Mucositis	3	9	7	-
Myalgia/arthralgia	1	2	-	-
Nausea/vomiting	7	8	-	-
Neutropenia	5	3	1	1
Thrombocytopenia	3	-	-	-
Total	35	50	13	3

4 Discussion

Despite the small number of recruited patients for the study, we could observe that the combination of gemcitabine with doxorubicin followed by weekly paclitaxel is capable of producing clinical and pathological responses in neoadjuvancy in locally advanced breast cancer. In this group of patients with extensive tumors, the complete pathological response rate was slightly over 20%, a figure close to the one reported in more classical combinations such as AC-T (cyclophosphamide with doxorubicin followed by docetaxel). Other phase II studies that evaluated the efficacy of gemcitabine in neoadjuvant treatment have presented similar rates of pathological response. For instance, three recent trials obtained 18-23% of complete pathological response. One of these combined gemcitabine, epirubicin, and docetaxel, while the others used gemcitabine with epirubicin and paclitaxel or dose-dense gemcitabine, epirubicin and albumin-bound paclitaxel [14, 18, 19].

Data from studies conducted in women with advanced disease in which the same three-drug combination was used in different dosing schedules also suggests that this regimen is highly active, but at expense of high hematological toxicity. The overall response rates, including partial and complete responses, ranged from 55.2 to 82.9%, while grades III-IV neutropenia ranged from 41 to 69%. In a phase II trial conducted by Passardi and colleagues, 27% of patients required the use of granulocyte colony-stimulating factor [20-23].

In our data, the most concerning toxic effects of the combination studied were neutropenia and mucositis, requiring the hospitalization of seven over 19 patients (36.8%). This type of complication had been reported with gemcitabine combinations for neoadjuvant treatment in significantly variable rates (10 to 54%), making some authors to advocate for the use of granulocyte stimulating factor during the AG phase, while others do not [9, 13-15, 18, 19] .In our study, the use of weekly paclitaxel seemed not to have potentiated the neutropenic effect, which was more related to the AG combination, as observed in other studies [14, 24, 25]. Mucositis was much more frequent in our study than reported in other gemcitabine-combination strategies. Grade 3 and 4 mucositis have been reported in 0.5 to 3% of cases in these studies. We have observed this complication in 36.8% of our patients. Grade 3 and 4 diarrheas were also more frequent in our group of patients: 15.7% versus 3-5% in previous studies. It is conceivable that the higher rate of severe hematologic and non-hematologic complications could be related to the type of anthracycline used: epirubicin versus doxorubicin. Further evidence showing that the use of sequential gemcitabine and doxorubicin has a highly toxic hematological profile came from an Indian study published soon after we had terminated the accrual of our study. The use of different schedules of gemcitabine and doxorubicin in this study demonstrated that a subgroup of patients that had received gemcitabine on days 1 and 8 and doxorubicin on day 2 presented an unacceptable rate of severe neutropenia and mucosites (80% of the cases) [14]. It is possible that the use of prophylactic granulocyte colony-stimulating factor may reduce the toxicities of AG-T, and this strategy may be worthy of evaluation in further phase III studies, since the efficacy of the combination seems to be equivalent to the therapies presently recommended for neoadjuvancy.

Despite the fact that previous studies showed evidence that positive hormonal receptors is a predictor of bad response to neoadjuvant chemotherapy, our data does not corroborate this finding, since there was no difference between those groups, probable due to the lack of power of our study. Many recent studies, conducted in very different settings of neoadjuvant chemotherapy protocols, show that the tumors' genotype and phenotype profile are important response predictors [26-30].

5 Conclusion

Despite the limitations of the study, the efficacy data from this trial, regarding clinical and pathological responses rates, was similar to the one observed in the usual regimen of neoadjuvancy using doxorubicin, cyclophosphamide, and paclitaxel. However, the toxicity profile of the experimental regimen used in our study was exceedingly high, causing the interruption of the protocol.

Competing interests

The authors don't have any competing interests to declare.

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