Doxorubicin-Cyclophosphamide and Paclitaxel Weekly as Neoadjuvant Chemotherapy in Breast Cancer Patients, with which we start?

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Abstract: Purpose: Chemotherapy regimens containing anthracyclines and taxanes represent the landmark of neoadjuvant systemic therapy of breast cancer. We performed this study in order to compare the efficacy and tolerability of starting neoadjuvant regimens including Doxorubicin-Cyclophosphamide Versus Paclitaxel Weekly in locally advanced or operable breast cancer patients. **Methods:** Fifty two operable or locally advanced, breast cancer patients were identified. Twenty four patients had received 4 cycles of neoadjuvant doxorubicin and cyclophosphamide (AC), followed by definitive surgery then 12 weeks of adjuvant paclitaxel (group A). In 28 patients the reverse sequence was employed, with neoadjuvant 12 weeks of paclitaxol, followed by definitive surgery then adjuvant 4 cycles doxorubicin and cyclophosphamide (AC) (group B).**Results:** We observed 12 pathological complete responses (pCR) (50%) in group A and 3 pCR (11.1%) in group B. Also, we recorded 12 pathological partial response (pPR) in group A (50%) and 19 (70.4%) in group B. Also in group B there were 5 patients (18.5%) with pathological stable disease (pSD) and one patient progressed onto therapy. The patient who progressed was excluded from the study. In the subset of triple negative tumor we had 8 patients (4 in each group) with pCR rate of 75% in group A and 25% in group B with no statistical significance (p = 0.939 and 0.804 respectively). In tumors expressing HER2 positive status pCR was 54.5% (6 patients of 11) in group A and 25% in group B (2 patients of 8), while in HER2 negative tumors pCR was 46.2% in group A (6 patients of 13) and only 1 patient of 19 (5.3%) passed into pCR in group B with no statistical significance (p = 0.682 and 0.128 respectively). In tumors expressing ER and/or PgR receptor status pCR was 50% in group A (p = 1.00) and 0% in group B (p =0.014), while in hormone receptor negative tumors pCR was 25% (3 patients of 12) in group A and 33.3% in group B (3 patients of 9). The significant factors for response in group A were small tumor size (T) and lower stage and for group B were lower grade, small tumor size (T), lower stage and negative hormonal status. The different subsets ranked by pCR rate in group A were triple positive (100%), triple negative (75%), hormone positive HER2 negative (33.3%) then finally hormone negative HER2 positive (0%) while in group B were hormone negative HER2 positive (40%), triple negative (25%), and finally both triple positive and hormone positive HER2 negative (both 0%). The mean relapse free survival (RFS) was 16.5 months for group A and 15.48 months for group B with no statistical significance (p = 0.598) while the mean overall survival (OS) was 16.5 months for group A and 18.22 months for group B with no statistical significance (p = 0.369). Thus starting with anthracycline-based neoadjuvant chemotherapy may be associated with higher rate of pCR if compared to taxane-based neoadjuvant chemotherapy but until now no survival benefit was obtained. Treatments were well tolerated. The most common toxicities were myelosuppression, nausea, vomiting fatigue, alopecia, sensory neuropathy and finally 5 asymptomatic and transient LVEF decrease have been recorded, without any case of clinical cardiotoxicity.**Conclusions:** Both anthracycline-based (namely doxorubicin and cyclophosphamide) versus taxane-based (namely paclitaxel weekly) as a neoadjuvant chemotherapy in locally advanced or operable breast cancer are considered the 'standard' for neoadjuvant setting and we can start with either of them followed by the other.

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1.Introduction

In women, breast cancer (BC) is the most common cause of cancer and the most common cause of cancer-related death.[1]

Primary chemotherapy (CT) was introduced in the early 1980s and was initially limited to patients with locally advanced BC. Owing to encouraging results in patients with inoperable disease, subsequent pilot studies explored the role of CT delivered before surgery for patients with operable early BC.[2]

The objectives of primary therapy are to improve surgical outcomes in operable BC patients who desire a conservative approach, to convert patients inoperable at diagnosis to operable candidates, and, like systemic therapies used in the

adjuvant setting, to reduce the risk of distant recurrence with the final aim of obtaining a cure. [3]

Furthermore, primary therapy with CT allows for an early evaluation of the *in vivo* responsiveness of the specific tumor to systemic therapy and permits the acquisition of tumor specimens prior to, and during, the preoperative treatment.[1]

There is no significant difference in overall survival (OS) or disease-free survival (DFS) for pre- versus post-operative delivery of systemic therapy. The NSABP B-18 trial randomized 1523 patients with operable BC to receive either four preoperative cycles of doxorubicin and cyclophosphamide or the same CT, given postoperatively. The results of this trial, updated at 9 years of follow-up, did not show any significant difference in OS or DFS between the two treatment arms.[4]

Ideal candidates for primary therapy are patients with locally advanced BC (stage III), but patients with early-stage disease can also be considered as candidates if a surgical breast-conservative approach is not technically feasible at presentation due to small breast size or if the cosmetic outcome following surgery would be suboptimal due to tumor location.[5]

Even with a small tumor, patients with a subtype associated with a high likelihood of response to CT could benefit from a preoperative approach. Indeed, primary therapy is considered appropriate for patients likely to have a good locoregional response, regardless of the tumor size at presentation.[3]

Notably, patients with HER2-positive or triple-negative BC exhibit a higher rate of response to primary therapy with CT compared with patients with HER2-negative, estrogen receptor (ER)-positive BC.[6]

Clinical studies have demonstrated that in patients with HER2-positive disease who receive trastuzumab as part of their neoadjuvant therapy, a pathological complete response (pCR) is associated with higher rates of DFS and OS.[6]The pCR rate among triple-negative BC patients ranges from 27–45%, while the pCR rate for HER2-negative, hormone receptor-positive patients is generally significantly lower (~10%).[7] As pCR is associated with an advantage in DFS and OS in triple-negative BC, it is reasonable that residual disease at surgery confers a higher risk of early disease recurrence.[8]

In defining the systemic treatment before surgery, several terms are used: ‘preoperative‘, focusing on the treatment‘s temporal sequence relative to surgery; ‘primary‘, emphasizing its first position in the temporal sequence of all therapeutic modalities; and ‘neoadjuvant‘, identifying a presurgical treatment with the objectives of reducing the risk of distant recurrence and curing the patient. Accordingly, the term neoadjuvant should only be used to describe treatment of patients with a curable disease.[7]

Current neoadjuvant treatments sequentially combine an anthracycline-based regimen followed or preceded by a taxane. Although an optimal regimen has not yet been established, a combination of four cycles of an anthracycline-based regimen and four cycles of a taxane might produce the higher pCR rate. In regards to the sequential order of administering anthracycline and taxane, no definite data are reported. [7]

Among the most life-threatening side effects of anthracyclines is cardiac toxicity. It has been described since the 1970s, as mainly chronic or late-onset cardiotoxicity, frequently leading to congestive heart failure, and it is well known how the risk of cardiotoxicity increases with higher cumulative doses of anthracyclines.[9]

The incidence and severity of cardiotoxicity is higher when anthracyclines are administered in bolus compared to continuous regimens, possibly related to higher plasmatic peak reached.[4]

Some predisponing factors are described, such as hypertension, age older than 65 years, previous mediastinal radiotherapy, concomitant use of other drugs such as paclitaxel, cyclophosphamide, trastuzumab. Guidelines recommend a maximum cumulative doxorubicin dose of 400-450 mg/m^2, with reported 3-4% of clinical cardiotoxicity, being the incidence of congestive heart failure up to 18% in patients receiving 700 mg/m^2 of doxorubicin. The issue of anthracycline cardiotoxicity still remains a significant challenge, particularly in the neoadjuvant and adjuvant breast cancer settings, where the goal of treatment is cure.[9,10]

In Hematology Oncology Department, Saad Specialist Hospital, Al-Khober, Saudi Arabia, in collaboration with Ain Shams University Clinical Oncology Department, Cairo, Egypt, We performed a phase III study in order to evaluate efficacy and tolerability of starting with anthracycline containing regimens namely Doxorubicin-Cyclophosphamide (AC) or taxanes namely paclitaxel weekly as neoadjuvant treatment in operable or locally advanced, breast cancer patients without contra-indication to conventional anthracyclines.

2.Patients and methods

Patient clinical information, tumor characteristics, response rate and toxicity information were recorded. From January 2012 to June 2014, a total of 52 patients with operable or locally advanced breast cancer were identified in Hematology Oncology Department, Saad Specialist Hospital, Al-Khober, Saudi Arabia in collaboration with Ain

Shams University Clinical Oncology Department, Cairo, Egypt.

All primary breast cancers had undergone a core biopsy prior to neoadjuvant treatment, and staging work-up included complete blood count, chemistry, chest radiography, liver ultrasound or computed tomography (CT) scan of the liver and bone scan. In advanced breast cancer (stage IIIA or more), Fluro-Deoxy-Glucose (FDG) Positron Emission Tomography (PET) with CT scan was performed. Cardiac function evaluation included clinical history, a baseline left ventricular ejection fraction (LVEF) evaluation by echocardiogram, and an electrocardiogram, all repeated after 4 cycles, at the end of neoadjuvant chemotherapy, and during the follow up period, every 6 months or whenever indicated. All the evaluated patients had normal organ functions, aged > 18 years, and ECOG performance status (PS) ≤2.

The assessment of estrogen receptor (ER), progesterone receptor (PgR) and HER2 were determined by standard methods on pre-treatment core-biopsy, and evaluation was repeated, whenever feasible, at definite surgery. ER and PgR were considered positive when >1% of the neoplastic cells showed distinct nuclear immunoreactivity, whereas Patients were considered HER2 positive when cells express Dako 3+, or 2+ but amplified by FISH or SISH.

Patients were randomized into two groups: the first group will receive 4 cycles of AC protocol of neoadjuvant chemotherapy, and the second group will receive neoadjuvant paclitaxel weekly for 12 weeks.

After standard premedication, 24 patients were incorporated in the first group and received Doxorubicin (60 mg/m^2) in combination with cyclophosphamide (600 mg/m^2) to be repeated every three weeks for 4 cycles. The remaining 28 patients were enrolled in the second group and received paclitaxel weekly (80 mg/m^2) for 12 weeks. Prophylactic granulocyte colony stimulating factors (G-CSF) were administered in the majority of patients, and all the patients received G-CSF in case of severe myelosuppression.

Toxicity was assessed at each treatment cycle using the National Cancer Institute Common Toxicity Criteria for Adverse Events (version 4.03).

Pathological response was evaluated in all enrolled patients at definite surgery. Pathological complete response (pCR) was defined as no residual invasive tumor in both breast and axilla.

Surgery procedures included breast conserving surgery or mastectomy, and complete axillary or sentinel node dissection. After surgery, patients of the first group who received 4 cycles of AC protocol received adjuvant paclitaxel weekly (80 mg/m^2) for 12 weeks, while in the second group who received paclitaxel weekly for 12 weeks received adjuvant AC protocol with Doxorubicin (60 mg/m^2) in combination with cyclophosphamide (600 mg/m^2) to be repeated every three weeks for 4 cycles.

After that, patients were treated with standard radiotherapy, adjuvant trastuzumab, and adjuvant hormonal therapy, whenever indicated.

Statistical design

Patient and disease characteristics were analyzed using descriptive statistics, and expressed as either relative frequency [percentages] for discrete variables and for continuous variables mean with standard deviation (SD) or median are used. The association between qualitative variables was tested by the Pearson Chi-Square, while the association between quantitative variables was tested by unpaired Student t-test and analysis of variance [ANOVA] test with p-value was calculated for both being significant if less than 0.5 and highly significant if less than 0.001. The association bet Relapse-free survival (RFS) were calculated from date from definite surgery to local or distant invasive relapse, death, or last follow-up are plotted. The SPSS (version 17.0) statistical program was used for all analyses.

3.Results

Patient's characteristics

From January 2012 to June 2014, a total of 52 patients with operable or locally advanced breast cancer were identified in Hematology Oncology Department, Saad Specialist Hospital, Al-Khober, Saudi Arabia in collaboration with Ain Shams University Clinical Oncology Department, Cairo, Egypt. Main patient characteristics are listed in Table 1. Median age was 44 (range, 26-65); median PS status was 1 (range, 0-2); 31 tumors (84%) were ER and or PgR positive, 8 tumors were triple negative (TN). Clinical stage at baseline ranged from IIA to IIIC; 65.4% of the patients (34 patients) had stage III disease. Forty-three tumors were invasive ductal carcinoma, 9 tumors were invasive lobular carcinoma and 3 patients had inflammatory breast cancer. As regards comorbidities, 1 patient had synchronous thyroid cancer (papillary thyroid cancer) with the breast cancer and was treated first with near total thyroidectomy followed by radioactive iodine ablation before stating neoadjuvant chemotherapy and 1 patient had chronic idiopathic thrombocytopenic purpura (ITP) with platelet count around 60000 to 70000 and she was under maintenance steroid therapy. Neoadjuvant treatment regimens are listed in Table 2.

Efficacy

Forty-six patients had an objective clinical response to neoadjuvant treatment, 5 patients had a stable disease, and 1 patient developed progression in the form of contralateral lymph node metastasis. A pCR at surgery was observed in 15 patients (28.9%); in 31 patients a partial response (pPR) was observed (59.6%), 5 patients had pathological stable disease (pSD) at surgery (9.6%), whereas 1 patient progressed onto therapy (after 8 weeks of paclitaxel) and developed contralateral lymph node metastasis. That patient was considered as failure of paclitaxel, shifted to AC protocol, surgery was cancelled and patient was excluded from the study. In the first group (group A), a pCR at surgery was observed in 12 patients (50%), and a pPR was found in the remaining 12 patients (50%). No pSD or progressive disease (PD) in this group. In the second group (group B), a pCR was achieved in only 3 patients (10.7%), a pPR was found in the remaining 19 patients (67.9%), 5 patients had pSD (17.8%) and 1 patient (3.6%) developed progressive disease (Table 3).

Table 1 : Main baseline patient characteristics in 52 patients

Characteristics	N (%)		
	Total	Group A	Group B
Age			
Median	44	44	44.5
Range	26-65	26-65	38-61
Performance status			
ECOG 0	0 (0)	0 (0)	0 (0)
ECOG 1	51 (98.1)	24 (100)	27 (96.4)
ECOG 2	1 (1.9)	0 (0)	1 (3.6)
Menopausal status			
Pre	42 (80.8)	20 (83.3)	22 (78.6)
Post	10 (19.2)	4 (16.7)	6 (21.4)
Histology			
Ductal	43 (82.7)	21 (87.5)	22 (78.6)
Lobular	9 (17.3)	3 (12.5)	6 (21.4)
Tumor size			
T1	0 (0)	0 (0)	0 (0)
T2	21 (40.4)	15 (62.5)	6 (21.4)
T3	24 (46.1)	6 (25)	18 (64.3)
T4	7 (13.5)	3 (12.5)	4 (14.3)
Clinical stage			
IIA	12 (23.1)	9 (37.5)	3 (10.7)
IIB	6 (11.5)	3 (12.5)	3 (10.7)
IIIA	24 (46.1)	9 (37.5)	15 (53.6)
IIIB	7 (13.5)	3 (12.5)	4 (14.3)
IIIC	3 (5.8)	0 (0)	3 (10.7)
Grading			
G1	3 (5.8)	0 (0)	3 (10.7)
G2	27 (51.9)	15 (62.5)	12 (42.9)
G3	22 (42.3)	9 (37.5)	13 (46.4)
Hormone receptor status			
Positive	31 (59.6)	12 (50)	19 (67.9)
Negative	21 (40.4)	12 (50)	9 (32.1)
HER2 status			
Positive	19 (36.5)	11 (45.8)	8 (28.6)
Negative	33 (63.5)	13 (54.2)	20 (71.4)
Triple negative status			
Positive	8 (15.4)	4 (16.7)	4 (14.3)
Negative	44 (84.6)	20 (83.3)	24 (85.7)
Surgery			
Lumpectomy	12 (23.1)	9 (37.5)	3 (10.7)
Mastectomy	39 (75)	15 (62.5)	24 (85.7)
No surgery	1 (1.9)	0 (0)	1 (3.6)

N: Number of patients

Table 2 : Neoadjuvant chemotherapy regimens in 52 patients

Group	Neoadjuvant chemotherapy regimens	N [%]
A (First group)	Doxorubicin/cyclophosphamide (4 cycles) → surgery	24 (46.1)
B (Second group)	Paclitaxel weekly (12 weeks) → surgery	28 (53.9)

N: Number of patients

Table 3 :Pathological responses in 52 patients

Responses	Total		Group A		Group B	
	N	%	*N*	%	*N*	%
Complete response*	15	28.9	12	50	3	10.7
Partial response	31	59.6	12	50	19	67.9
Stable disease	5	9.6	0	0	5	17.8
Progressive disease	1	1.9	0	0	1	3.6

* Pathological complete response (pCR) was defined as no residual invasive tumor in both breast and axilla

Among the small subset (8 patients) with triple negative (TN) tumors, we observed 4 pCR (50%), 3 patients from 4 in the first group (75%) and 1 patient from 4 in the second group (25%). In tumors expressing ER and or PgR, 6 patients of 12 (50%) and no patient (0%) of 18 in had pCR in groups A and B respectively while in hormone negative patients, 3 patients of 12 (25%) had pCR in group A and 3 patients of 9 (33.3%) had pCR in group B. After making mixing of both subsets the following was discovered; in hormone positive and HER2 negative tumors, 3 pCR (33.3%) and 6 pPR (66.7%) in group A and no pCR (0%), 10 pPR (66.7%) and 5 patients SD (33.3%) in group B. In hormone negative and HER2 positive tumors; no pCR (0%), 8 pPR (100%) in group A while 2 pCR (40%) and 3 pPR (60%) in group B. Finally in triple positive patients, all the 3 patients developed pR in group A (100%) while all the 3 patients in group B developed pPR (100%).

In regards to surgery procedures, 39 patients (75%) underwent mastectomies, whereas 12 (23.1%) patients had breast conserving surgery, and for the patient that developed progressive disease surgery was cancelled (1.9%). A complete axillary dissection was performed in 49 patients (94.2%), whereas a sentinel node biopsy was performed in only 2 patients (3.8%). Thirty-one patients with tumor expressing hormonal receptors at baseline biopsy received adjuvant hormonal therapy for 5 years. Postoperative radiotherapy was administered as clinically indicated and 19 patients with HER2 positive were treated with adjuvant trastuzumab for 1 year.

After exclusion of the patient who developed progressive disease on therapy and with a median follow up of 22 months (range, 6 to 34 months), 6 recurrences were observed: 3 in bone, 3 visceral. As expected, no recurrences were observed in the 15 patients who achieved a pCR in both groups. Among the 31 patients that achieved pPR, 3 patients developed recurrences all of them in group B. In patients developed stable disease (5 patients) all were located in group B, 3 recurrences occurred. No reported deaths until now. The mean relapse-free survival (RFS) for group A was 16.5 months and for group B was 15.48 months with no statistical significance (p = 0.598) (Figure 1). For overall survival (OS), the means were 16.5 months and 18.22 months for both groups respectively with no statistical significance (p = 0.396) (Figure 2).

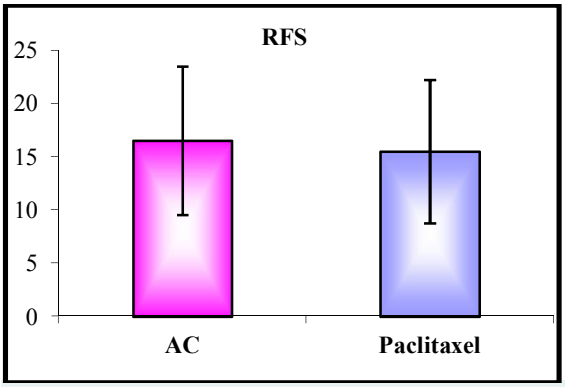

Figure 1 :Mean relapse free survival for both groups.

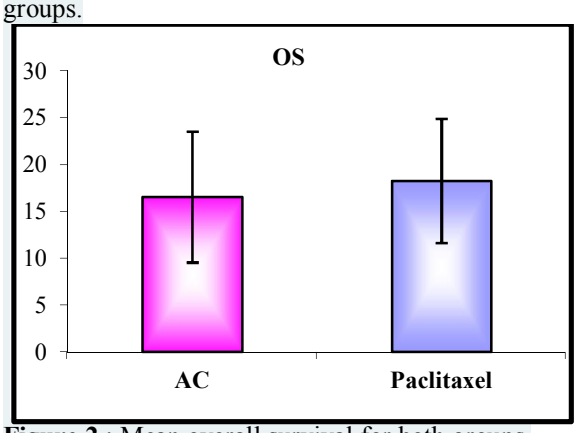

Figure 2 : Mean overall survival for both groups.

Toxicity

Regarding treatment tolerability, regimens were quite well tolerated overall. Fifty-one (98.1%) patients completed neoadjuvant treatment without any life threatening conditions or observed toxic deaths, with 1 patients discontinuing paclitaxel regimen after 8 weeks due to development of new lesions, namely contralateral axillary lymph node enlargement. That patient was considered as failure of paclitaxel, shifted to AC protocol, surgery was cancelled and patient was excluded from the study. As regards the rest of the patients (51 patients), they all did surgery either lumpectomy or modified radical

mastectomy and then completed adjuvant treatment followed by radiation therapy, hormonal therapy for 5 years and adjuvant trastuzumab for 1 year as indicated.

The safety of the regimens is reported in Table 4. The main toxicity observed during treatment administration was myelosuppression (namely neutropenia and anemia), nausea, vomiting, alopecia, and fatigue occurring in all patients without any life threatening conditions reported. Grade 3 neutropenia was seen in 4 patients (2 in each group) and was associated with febrile neutropenia in all patients. Anemia that requested packed red blood cells (RBCs) transfusion (grade 3) occurred in 5 patients (2 in group A and 3 in group B). Mucositis was seen more in group A (20 patients, 83.3%) compared to group B (12 patients, 44.4%) with statistical significance (p = 0.004). All cases were grade 1 or 2 except 1 patient who developed grade 3 mucositis. Diarrhea occurred mostly in group B (16 patients, 59.3%) compared to group A (8 patients, 33.3%) but with no statistical significance all grade 1 or 2 with 1 patient grade 3. Sensory neuropathy, allergic reaction, and elevated hepatic transaminases were all observed more in group B but with no statistical significance when compared to group A except in neuropathy with 14 patients affected in group B (51.9%) compared to 3 patients in group A (12.5%) with statistical significance (p = 0.003) all grade 1 or 2. As to cardiotoxicity, treatments were very well tolerated, with no cases of clinical cardiotoxicity. All the patients had at least a baseline echocardiogram and 2 subsequent evaluations. The median cardiac follow-up period was 22 months (range, 6- 34 months). We recorded only 5 cases (9.8%) of asymptomatic grade 2 left ventricular ejection fraction (LVEF) decrease (ranging from 10% to 19%), 4 in the first group (16.7%) and only 1 patient in the second group (3.7%) with no statistical significance.

Table 4 : Main toxicities in 51 patients according to National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03

Toxicity	Grade 1 N (%)			Grade 2 N (%)			Grade 3 N (%)			Grade 4 N (%)		
	T	A	B	T	A	B	T	A	B	T	A	B
Hematologic												
Neutropenia	35 (68.6%)	16 (66.7%)	19 (70.4%)	12 (23.5%)	6 (25%)	6 (22.2%)	4 (7.9%)	2 (8.3%)	2 (7.4%)	0 (0%)	0 (0%)	0 (0%)
Febrile neutropenia (FN)	-	-	-	-	-	-	4 (7.9%)	2 (8.3%)	2 (7.4%)	0 (0%)	0 (0%)	0 (0%)
Thrombocytopenia	18 (35.3%)	8 (33.3%)	10 (37%)	2 (3.9%)	1 (4.2%)	1 (3.7%)	1 (2%)	0 (0%)	1 (3.7%)	0 (0%)	0 (0%)	0 (0%)
Anemia	25 (49%)	12 (50%)	13 (48.1%)	21 (41.2%)	10 (41.7%)	11 (40.7%)	5 (9.8%)	2 (8.3%)	3 (11.1%)	0 (0%)	0 (0%)	0 (0%)
Nonhemathologic												
Nausea	31 (60.8%)	19 (79.2%)	12 (44.4%)	19 (37.2%)	4 (16.7%)	15 (55.6%)	1 (2%)	1 (4.2%)	0 (0%)	-	-	-
Vomiting	25 (49%)	14 (58.3%)	11 (40.7%)	25 (49%)	9 (37.5%)	16 (59.3%)	1 (2%)	1 (4.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Mucositis	20 (39.2%)	11 (45.8%)	9 (33.3%)	11 (21.6%)	8 (33.3%)	3 (11.1%)	1 (2%)	1 (4.2%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Diarrhea	15 (29.4%)	5 (20.8%)	10 (37%)	8 (15.7%)	3 (12.5%)	5 (18.5%)	1 (2%)	0 (0%)	1 (3.7%)	0 (0%)	0 (0%)	0 (0%)
Alopecia	25 (49%)	12 (50%)	13 (48.1%)	26 (51%)	12 (50%)	14 (51.9%)	-	-	-	-	-	-
Fatigue	43 (84.3%)	20 (83.3%)	23 (85.2%)	7 (13.7%)	3 (12.5%)	4 (14.8%)	1 (2%)	1 (4.2%)	0 (0%)	-	-	-
Neurotoxicity (sensory)	12 (23.5%)	2 (8.3%)	10 (37%)	5 (9.8%)	1 (4.2%)	4 (14.8%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hypertransaminases	10 (19.6%)	4 (16.7%)	6 (22.2%)	2 (3.9%)	1 (4.2%)	1 (3.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Hypersensivity	0 (0%)	0 (0%)	0 (0%)	2 (3.9%)	0 (0%)	2 (7.4%)	3 (5.9%)	1 (4.2%)	2 (7.4%)	0 (0%)	0 (0%)	0 (0%)
Cardiac toxicity	-	-	-	5 (9.8%)	4 (16.7%)	1 (3.7%)	0 (0%)	0(0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

T: Total, A: Group A, B: Group B.

4.Discussion

Anthracyclines comprise of a group of the most active cytotoxic agents in breast cancer which are routinely administered in the pre-operative treatment for operable or locally advanced breast cancer [11].

Neoadjuvant chemotherapy has been widely used in patients with operable and locally advanced

breast cancer in order to increase the rate of breast conserving surgery and to obtain a better long-term outcome, and sequential regimens of anthracycline-based schemes followed or preceded by a taxane are considered the "standard" even outside clinical trials [12].

The biological heterogeneity of breast cancer is well known, and the identification of markers predictive of therapeutic response is a major challenge in breast cancer, mainly in the neoadjuvant setting, as well as incorporation of biological agents in primary treatment regimens. Significant encouraging results are achieved mainly in HER2 positive tumors, whereas in TN or in ER and/or PgR positive tumors established and efficacious targeted agents are lacking, being chemotherapy and endocrine therapy still the mainstay of treatment [13].

The results of our study suggest that starting with anthracycline-based neoadjuvant chemotherapy may be associated with higher rate of pCR if compared to taxane-based neoadjuvant chemotherapy but until now no survival benefit was obtained. The significant factors for response in group A were small tumor size (T) (p = 0.030) and lower stage (p = 0.046) and for group B were lower grade (p = 0.046), small tumor size (T) (p < 0.001), lower stage (p < 0.001) and negative hormonal status (p = 0.014). The different subsets ranked by pCR rate in group A were triple positive (3 patients of 3, 100%), triple negative (3 patients of 4, 75%), hormone positive HER2 negative (3 patients of 9, 33.3%) then finally hormone negative HER2 positive (no patient of 8, 0%) while in group B were hormone negative HER2 positive (2 patients of 5, 40%), triple negative (1 patient of 4, 25%), and finally both triple positive and hormone positive HER2 negative (both 0%). Also, neoadjuvant chemotherapy regimen AC was associated with a significant pCR rate than paclitaxel weekly group (p = 0.003). HER2 status and triple negative status were both non-significant for the 2 groups (p = 0.682 and 0.128 for HER2 and 0.273 and 0.428 for triple negative). Those results are not similar if compared with the Collaborative Trials in Neoadjuvant Breast cancer, 12 randomized trials that comprised approximately 13,000 patients, presented at 2012 San Antonio Breast Cancer Symposium, Texas, USA, the most significant groups that demonstrated significant pCR and event-free survival rates were hormonal receptor-positive, HER2-negative, grade 1–2: 7% (HR for event-free survival: 0.63; p = 0.07); hormonal receptor-positive, HER2-negative, grade 3: 16% (HR: 0.27; p < 0.001); hormonal receptor-positive, HER2-positive (treated with a trastuzumab-containing regimen): 30% (HR: 0.58; p = 0.001); and hormonal receptor-negative, HER2-negative (triple-negative): 34% (HR: 0.24; p < 0.001); and hormonal receptor-negative, HER2-positive (treated with a trastuzumab-containing regimen): 50% (HR: 0.25; p < 0.001). This meta-analysis confirms the relationship between pCR and survival outcomes for patients treated with neoadjuvant CT, particularly for women with HER2-positive, triple-negative, or hormonal receptor-positive grade 3 tumors [2,14,15].

The mean relapse free survival (RFS) was 16.5 months for group A and 15.48 months for group B with no statistical significance (p = 0.598) while the mean overall survival (OS) was 16.5 months for group A and 18.22 months for group B with no statistical significance (p = 0.369).

It is too early to evaluate whether achieving a pCR will result in predicting long-term favorable outcome, since the follow-up period is still too short, even if, to date, recurrences observed have only been in patients not experiencing a pCR.

In conclusion, the results from this study on comparing the effect of starting anthracycline-based (namely doxorubicin and cyclophosphamide) versus taxane-based (namely paclitaxel weekly) as a neoadjuvant chemotherapy in locally advanced or operable breast cancer patients confirms that both regimens are considered the 'standard' for neoadjuvant setting and any of them can be started with followed by the other, even with the limitations of the small sample size and further data are required. Also, our study confirmed a favorable toxicity profile.

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