RESEARCH ARTICLE

Taxane-Based Regimens as Adjuvant Treatment for Breast Cancer: a Retrospective Study in Egyptian Cancer Patients

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Abstract

Background: To evaluate the impact of adding taxanes to anthracycline-based regimens in the adjuvant setting in localized young female breast cancer patients on the overall survival (OS) and the disease free survival (DFS). Materials and Methods: This retrospective study included all female breast cancer patients who were candidates for adjuvant chemotherapy presenting to Kasr Al Ainy centre of clinical oncology and Cairo oncology centre (Cairo Cure) in the period from January 2005 till December 2010. Results: Our study included 865 patients, 732 of whom received anthracycline based regimens and 133 taxane based regimens. The mean age of patients was 39 years. After a median follow up of 50 months the median DFS was 48.4 months. Survival analysis indicated that the tumor size (>5cm *vs.* <5cm) p=0.001), nodal involvement (Yes *vs.* No) p=0.0001) and pathology (invasive lobular *vs.* ductal) p=0.048) affected DFS. As regards hormonal status, ER, PR and HER 2neu positive patients had longer DFS (p=0.001, 0.003, 0.106). On multivariate analysis DFS was affected by tumor size and lymph node involvement (p=0.014, 0.007). Subgroup analysis showed improvement in arms treated with taxanes in terms of DFS with positive Her2neu, ER and PR, but this was not statistically significant. Conclusions: Adding adjuvant taxanes to anthracyclines is beneficial for treatment of localized breast cancer among all subgroups, especially higher risk groups .The type of adjuvant chemotherapy regimens and tumor characteristics have direct effects on DFS.

Keywords: Breast cancer - Egypt - adjuvant chemotherapy - taxanes - her2neu - hormonal status

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Introduction

In Egypt, breast cancer (BC) is the most common cancer among women, representing 18.9% of total cancer cases and 35.1% of cancer in women (Elatar, 2002). Invasive duct carcinoma is the most common pathology constituting 83.4% with high incidence of grade II and III, 66% and 28.6% respectively (El-Bolkainy, 2000).

Breast cancer in Egypt occurs ten years earlier than in developing countries and most of them are premenopausal (Omar et al., 2003). The age-adjusted rate is 49.6 per 100,000 populations (Ibrahim, 2002). The incidence is steadily increasing with a tendency for breast cancer to occur in younger age groups and with advanced stages (Ahmed, 2010). An Australian study found that the Egyptian women had the highest breast cancer rates of all Middle Eastern immigrants to Australia (McCredie, 1994). Egyptian publications conducted in Egypt in the adjuvant breast cancer setting are scarce (Abd-El-Moneim et al., 2011; Hamza et al., 2011; Sakr et al., 2013)

Over three decades Montemurro and Aglietta 2009 summarized adjuvant chemotherapy for BC patients into three eras: first, the era of CMF regimen; then, that of anthracyclines; and more recently taxanes (Montemurro and Aglietta, 2009).

The feasibility of six cycles of either docetaxel plus cyclophosphamide (TC6) or sequential taxane and anthracycline regimen (T-FEC) in Japanese patients with HER2-negative early breast cancer, was assessed (Abe et al., 2014). The study suggested that TC6 is tolerable in Japanese and can be performed in outpatient clinics with slightly lower compliance and appropriate supportive treatment. Another Indian study also showed better tolerance to neoadjuvant sequential docetaxol than concurrent anthracycline and taxane regimen with a similar pathological remission in locally advanced breast cancer patients (Gogia et al., 2014).

In the adjuvant setting taxane-based were more effective than the anthracycline-based regimens in terms of DFS and OS in lymph node positive patients. Its relation to endocrine responsive tumors and Her2neu was limited (Mamounas et al., 2005, Hayes et al., 2007) with

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controversial results (Montemurro and Aglietta, 2009).

The aim of our study is to evaluate the impact of the addition of Taxanes to Anthracycline-based regimens in the adjuvant setting for Egyptian female patients with localized breast cancer in a younger population. The overall survival (OS) and the disease free survival (DFS) were assessed and correlated with the type of adjuvant chemotherapy and the tumor characteristics.

Materials and Methods

Our study was a retrospective analysis that included Egyptian Female patients with localized breast cancer presented to 2 Egyptian Centers namely: Kasr Al-Ainy Center of Clinical Oncology, Cairo University and Cairo Oncology Center in the period from January 2005 till December 2010. The study had the institutional ethical review board approval. Inclusion criteria included all female patients with proven pathological diagnosis of breast cancer with localized disease who underwent surgery and were candidate for adjuvant chemotherapy with at least six months follow up.

Metastatic breast cancer cases (proven by chest X-ray, bone scan or abdominal ultrasound) at presentation was excluded from the study. Patients receiving neoadjuvant or non- anthracycline-based chemotherapy and followed up for less than six months were also not included.

Surgery consisted of modified radical mastectomy with axillary dissection of level I and II lymph nodes or conservative breast surgery in the form of lumpectomy and axillary evacuation.

The adjuvant chemotherapy regimens for patients in the study were Anthracycline-based regimens or Taxane + anthracycline-based regimen. The most common Anthracycline-based regimen used was FAC (5-Flurouracil 500mg/m^2, Doxorubicin 50mg/m^2, Cyclophosphamide 500mg/m^2) given every 3 weeks for 6 cycles. Taxanes used in combined Taxane-Anthracycline-based regimens were either weekly Paclitaxel or 3-weekly Docetaxel for 3 cycles proceeded by Anthracycline-based regimen in the first 3 cycles.

Patients who underwent lumpectomy and axillary evacuation received local radiation to the breast after completion of chemotherapy. Patients who underwent mastectomy received radiation to the chest wall in case of positive or close margins, tumors 4 cm or more in maximum dimension or node positive disease. Patients with positive axillary lymph nodes (LN) received radiotherapy to the supraclavicular LN.

Hormone receptor assays were performed in the histopathology department by immunohistochemistry (IHC). Estrogen and progesterone receptors were considered positive if >1% of tumor cells showed expression by IHC. HER 2neu positive patients had either scored 3+ by IHC or are positive by fluorescence in situ hybridization FISH or Silver in situ hybrization (SISH). Premenopausal women with ER or PR positive tumors received 5 years of adjuvant tamoxifen 20 mg/day. Postmenopausal women with ER or PR positive tumors were assigned to 5 years of sequential aromatase inhibitor

Table 1. Clinico-Pathological Characteristics in Both Groups

Variables		Anthracycline No=477		Taxane No=133		P value
		N0	%	No	%	
Age	<35 years	43	9%	12	9%	0.984
	35-50	250	52.4%	68	51.1%	
	>50	184	38.5%	53	39.9%	
Menopausal status	Premenopausal	253	55.1%	76	58.9%	0.443
	Postmenopausal	206	44.9%	53	41.1%	
	Missing	18		4		
Type of surgery	MRM	346	72.5%	89	66.9%	0.205
	BSC	131	27.5%	44	33.1%	
Tumor size (T)	T1-2	343	80.9%	102	81.0%	0.989
	T3-4	81	19.1%	24	19%	
	Missing	53		7		
Nodal status (N)	N0	38	8.5%	10	7.5%	0.757
	N+	410	91.5%	121	92.4%	
	Missing	29		2		
Pathology	IDC	389	81.7%	108	81.8%	0.98
	ILC	87	18.3%	24	18.2%	
	Missing	1		1		
Grade	I	10	2.6%	4	3.6%	0.833
	II	305	79.2%	87	79.1%	
	III	70	18.2%	19	17.3%	
	Missing	92		23		
ER	Negative	149	32.6%	42	32.6%	0.874
	Positive	308	67.4%	87	67.4%	
	Missing	20		4		
PgR	Negative	191	43.1%	56	43.8%	0.898
	Positive	252	56.9%	72	56.2%	
	Missing	34		5		
Her2	Negative	231	73.6%	76	66.1%	0.128
	Positive	83	26.4%	39	33.9%	
	Missing	163		18		
Relapse	No	212	44.4%	97	73.0%	<0.001
	Yes	265	55.6%	36	27.0%	

and tamoxifen. Herceptin was not offered to HER 2neu positive patients due to its unavailability in our centre at that time.

Starting from 2008, the human epidermal growth factor receptor (HER2) was assayed by immunohistochemistry. It was considered positive if score 3+, and considered negative for score 0, 1+ while score 2+ was considered equivocal. No patients with amplified HER2, in either groups received adjuvant trastuzumab.

After completion of adjuvant chemotherapy and radiotherapy, patients were planned for follow up visits every 3 months during the first year, every 4 months in the second year, then every 6 months until the end of the fifth year and yearly thereafter. Patients underwent a history and physical examination at each follow-up, a mammogram and echocardiography were performed yearly. Chest X ray, Abdomino-pelvic ultrasonography, bone scan and labs were requested as clinically indicated.

Patients were divided into 2 groups according to the type of adjuvant chemotherapy regimen received: anthracycline based regimen and taxane based regimen. The primary end point of this study was disease-free survival (DFS), which was defined as the time from surgery to disease progression in the form of local breast (including ductal carcinoma in situ) or nodal recurrence and metastatic disease. Patients who had contralateral breast cancer after 2 years, a second malignancy, or non-disease-related death were not considered relapsing.

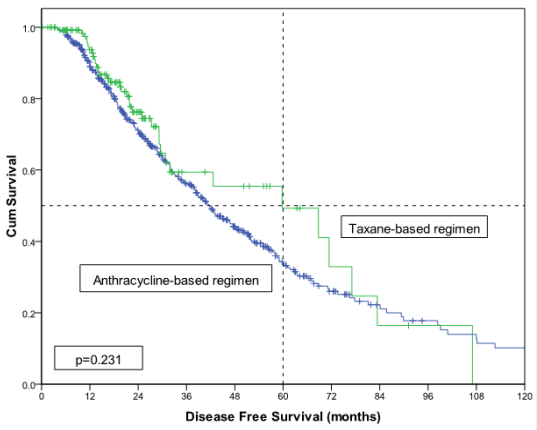

Figure 1. Kaplan-Meier Curve for DFS Among Patients with Early Breast Cancer According to Regimen Received

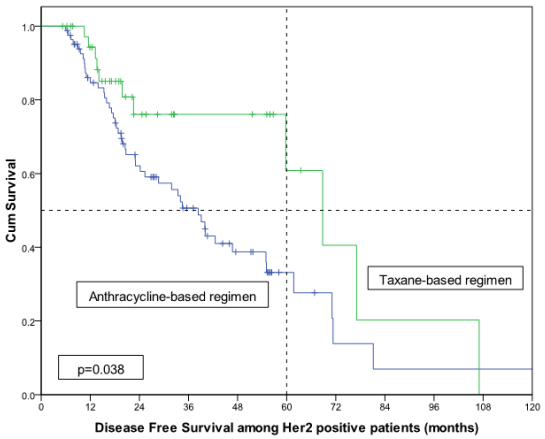

Figure 2. Kaplan-Meier Curve for DFS in Patients with Her2 +ve According to Regimen Received

Statistical analysis

All data were tabulated and statistically studied by descriptive analysis as well as survival analysis in relation to different prognostic factors. Comparison between groups was done using Student t test for continuous data and Chi square test for categorical data. Survival analysis was done according to Kaplan-Meier method and both groups were compared by log-rank test for significance. Multivariate analysis using Cox regression module was performed to test the power of relation between the independent variables and survival. Differences were considered significant if p value is less than 0.05. All statistical calculations, data management and analysis were performed using computer programs Microsoft Excel version 7 (Microsoft Corporation, NY, USA) and SPSS version 17 (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA).

Results

During the period from January 2005 till December 2010, 865 patients fulfilling the inclusion criteria were included in this study.

The median age of the whole group was 49 years (21 - 73 years). Regarding the type of surgery, 70% underwent MRM. Less than 20% of patients were presenting with T3-4 tumors while lymph nodes were positive in more than 90% of patients, two thirds of them had 4 or more positive nodes. As expected, IDC was the main pathological subtype (81.7%); with 80% of them Grade II. Among those with available immunohistochemistry, ER was positive in more than two thirds of patients, while Her2 was positive

Table 2. Multivariate Analysis Among Group Study Patients

Variable		HR	95.0%CI Lower	Upper	P value
Tumor stage	T3-4 *vs* T1-2	1.707	1.112	2.621	0.014
Nodal stage	N+ *vs* N0	1.937	1.198	3.132	0.007
Regimen	Taxane *vs* Anthra	0.716	0.439	1.168	0.181
Age	>35 *vs* < 35 yrs	1.042	0.602	1.804	0.882
Pathology	IDC *vs* ILC	1.011	0.126	8.116	0.992
Grade	III *vs* I, II	1.326	0.929	1.893	0.12
ER	+ve *vs* -ve	0.821	0.515	1.311	0.409
PgR	+ve *vs* -ve	0.774	0.484	1.236	0.283
Her2	+ve *vs* -ve	1.187	0.815	1.728	0.371

Table 3. Median DFS (in months) According to Regimen Received Among Different Subgroups

Subgroup	Anthracycline	Taxane	P value
Age < 35 yrs	28.6	59.7	0.241
Age > 35 yrs	41.9	68.7	0.465
T1-2	48.4	59.7	0.467
T3-4	29.4	71.4	0.449
N+	43.5	68.7	0.62
N1	61.7	59.7	0.973
N2-3	40	68.7	0.402
ER-ve	32.2	Not reached	0.206
ER+	50	68.7	0.248
Her2 –ve	43.5	71.4	0.068
Her2 +ve	38.3	68.7	0.038

in less than one third of them.

Patients were divided into 2 groups according to adjuvant chemotherapy regimen received. Among 610 patients, 477 patients received anthracycline-based regimen (Group 1) while 133 patients received taxane-based regimen (Group 2). Both groups were balanced regarding their clinicopathological characteristics with no statistical significant difference Table 1.

At a median follow up period of 40 months (6-180 months), the relapse rate was 55.6% for Group 1 compared to 27.1% for Group 2 (p<0.001).The median DFS for the whole population was 42.5 months (95%CI 37.7-47.3 months). Comparing the 2 groups, the median DFS for Group 1 was 41.7 months versus 59.7 months for Group 2 but this difference did not reach statistical significance (p=0.231) Figure 1.

Multivariate analysis was done for different risk factors affecting disease free survival. The only independent variable affecting DFS in our group study was tumor size and lymph node status Table 2.

Subgroup analysis was done to identify subgroups benefiting from adding Taxanes. The only subgroup that showed a statistically significant benefit from the addition of Taxanes were Her2 positive patients with median DFS of 68.7 months compared to 38.3 months for those received anthracycline-based regimens (p=0.038). Although there was a benefit of adding taxanes in other subgroups but it did not reach a statistical significance Table 3.

Discussion

This study supports the use of a Taxane drug as part of the adjuvant chemotherapy regimen following surgery for early stage breast cancer patients as it provides a statistically significant improvement in relapse rate.

Our findings revealed that tumor size of 5 cm and above and positive lymph node status was significantly associated with a higher risk of relapse and decreased survival in breast cancer patients. This results was consistent with (Cihan, 2014) that showed that stage including tumor size and nodal status remained the strongest prognostic factors in long term survival. This was confirmed by an Iranian study done by (Faradmal et al., 2010) and an Egyptian study by (Sedhom et al., 2011).

Our study reported that positive axillary lymph nodes decreased the median survival of breast cancer patients. This coincides with (Kim et al., 2005) that found that the most important prognostic factor affecting local control, disease-free survival, and overall survival was axillary lymph node metastasis.

The results of this study showed an improvement of DFS in favor of taxane-based regimens, but the difference compared to anthracycline-based regimens was not significant (59.7 *vs* 41.7 months, HR=0.716, 95% CI: 0.439-1.168, p=0.181). The 5 years DFS was 50% and 37% for the taxanes and the anthracycline regimen respectively with 28.5% reduction in the risk of relapse which was statistically significant (p<0.001).

A meta-analysis in 100,000 women in 123 randomized trials was conducted by (Peto et al., 2012) to compare between different polychemotherapy regimens for breast cancer. In trials adding 4 separate cycles of a taxane to a fixed anthracycline based control regimen , the extension of treatment duration reduced breast cancer mortality (RR 0.86, SE 0.04, two sided significance [2p]= 0.0005) . Eight years follow up of the French trial PACS01 trial demonstrated a benefit for DFS and OS rates with the sequential administration of docetaxel after FEC100 (Fluorouracil 500mg/m^2, Epirubicin 100mg/m^2, and Cyclophosphamide 500mg/m^2) for patients with node-positive, operable breast cancer. Eight-year DFS rates were 65.8% with FEC alone and 70.2% with FEC-D. OS rates at 8 years were 78% with FEC alone and 83.2% with FEC-D. Cox regression analysis adjusted for age and number of positive nodes showed a 15% reduction in the relative risk of relapse and a 25% reduction in the relative risk of death in favor of FEC-D. Significant relative risk reductions were observed in the hormone positive, HER2-positive, and Ki67 ≥20% (Coudert et al., 2012). This is consistent with an Egyptian study done by (Sakr et al., 2013) using the same regimen as the French trial. Five-year DFS rates were 74 % with FEC and 78 % with FEC-D (p=0.013). Multivariate analysis adjusted for prognostic factors showed a 17 % reduction in the relative risk of relapse with FEC-D. Five-year overall survival rates were 85 % with FEC and 89.4 % with FEC-D, demonstrating a 27 % reduction in the relative risk of death (p=0.014). Another Malaysian study showed similar but earlier response to FEC as regard tumor size reduction in all stages of breast cancer when compared to docetaxol (Hassan, 2013).

The results of subgroup analysis of this work indicated also that there were favorable gains in DFS in the taxane-based treatment arm but no statistical difference between the 2 treatment arms except for Her2 positive patients taking into consideration that none of them received adjuvant Trastuzumab. The DFS was 68.7 months compared to 38.3 months for those receiving anthracycline-based regimens (p=0.038).

Eleven trials reported subgroup results of ER status. For ER-positive subgroup the pooled HR of 0.83 (95% CI 0.76-0.90) for DFS indicated a 17% reduction in the risk of recurrence presented in the taxanes-based treatment arm, and for the ER-negative subgroup the pooled HR of 0.80 (95%CI 0.73-0.88) for DFS indicated a 20% reduction in the risk of recurrence presented among patients receiving taxanes (Berry et al., 2004; Citron et al., 2013). However M.D. Anderson Cancer Center (MDACC) trial In the MDACC trial (Madarnas et al., 2011), a subgroup analysis found no significant difference in Disease-free survival (DFS) by estrogen receptor (ER) status (p=0.07 for ER negative, p=0.39 for ER positive).

The benefit of addition of Taxanes in Her2 positive disease shown in our study was also demonstrated by (Hayes et al., 2007) that found that the addition of Paclitaxel to doxorubicin plus cyclophosphamide improved DFS compared to doxorubicin plus cyclophosphamide in HER2 positive patients. Five year DFS rate was approximately 75% in taxane arm *vs* 55% in the anthracycline arm. These results were inferior to Tai et al., (2013) showing a mean estimated disease free survival of 80.2 months when adjuvant trastuzumab was added with a mean DFS

of 93.1% at 7 years.

The DFS in this Egyptian study was lower than that in developed countries. This may be due to the young age, high percent of Her2+ not receiving trastuzumab and high lymph node involvement.

This study is limited by the relative small number of patients, lack of number of events and shorter follow up among the group receiving taxanes. Also the unavailability of trastuzumab at that time in our Centre affected the results. We conclude from this study that the type of adjuvant chemotherapy regimens and tumor characteristics have direct effects on DFS. Adding taxanes to anthracyclines is beneficial for treatment of localized breast cancer after surgery among all subgroups especially higher risk groups. If Trastuzumab is not affordable for Her2 positive patients, use of Taxane-based regimen in adjuvant setting significantly improve DFS.

In Egypt, raising awareness about early detection of breast cancer by breast self-examination and screening programs should be accentuated to improve treatment results and survival.

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