Egyptian Journal of Surgery Vol 26, No 3, July, 2007

ORIGINAL ARTICLE

RESPONSE OF LOCALY ADVANCED BREAST CANCER TO PRIMARY CHEMOTHERAPY; IS IT ELIGIBLE FOR BREAST CONSERVATION

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Aim: *Assess the eligibility of breast-conserving surgery for large tumours after response to primary chemotherapy (PCT).*
Methods: *50 patients with locally advanced cancer breast presented to Alexandria Surgical Oncology Unit. All patients had complete breast examination, mammography, and US and core biopsies before started of PCT in the form of 4 cycles of either Adryamicine and Cyclophosphamide (AC) or 5-flurouracil, Epirubicin, and Cyclophosphamide (FEC). All responders underwent modified radical mastectomy. Single histopathologist had reviewed all operative specimens. The questionable area which is the difference between pre and post PCT sizes were examined carefully for at least 4 different radial par-tumour areas, searching for any residual tumour tissue.*
Results: *5 patients (10%) achieved complete clinical response (CR) and 38 patients (76%) partial clinical response (PR). Total of 402 slides were examined from questionable areas with positive tumour tissue present in only 22 of them, which belong to 7 patients only out of 43 responders (16.3%). Multivariate analysis showed that: smaller initial tumour size < 5 cm, absence of ductal carcinoma insitue and absence of vascular invasions were the best predictors of absence of tumour tissue in questionable area slides.*
Conclusions: *Those factors were good indicators of eligibility of breast conserving surgery in responders locally advanced breast tumours to PCT.*

Keywords: *Predict, pathological examination, combined therapy.*

INTRODUCTION

The management of breast cancer has undergone remarkable change over the past two decades. A therapeutic revolution has been fuelled by the results obtained from prospective randomized clinical trials. The National Surgical Adjuvant Breast and Bowel Project (NASBP) protocols B-04 and B-06 have clearly demonstrated the efficacy of breast conserving surgery in Stage I and II breast cancer.(1) Neoadjuvant therapy is increasingly being used in the treatment of patients with locally advanced breast cancers.(2) In recent years, the concept of treating patients with primary chemotherapy (PCT) for breast cancer has become more popular.(3) Preoperative PCT is established as the treatment of patients with breast cancer who have a large tumour mass and/or massive regional lymph node involvement.(4)

It was necessary for this method to be evaluated in operable breast tumours too large to be treated immediately by conserving surgery. Preoperative

chemotherapy reduced the size of most breast tumours and decreases the incidence of positive nodes. The greatest increase of lumpectomy after PCT treatment occurred in women with tumours ≥ 4 cm, since women with tumours less than 4 cm were already lumpectomy candidates.[5] There were a lot of debate about the tumour response to PCT and is it eligible to perform breast conserving surgery for large tumour ≥ 4 cm that reduced in size after chemotherapy to < 4 cm.? This study was designed to confirm or to rule out the eligibility of performing breast-conserving surgery for tumours larger than 4 cm which shoed good response to PCT and became less than 4 cm in size after it. The aim of this study was to compare the postoperative pathological finding in cases with large cancer breast who had good response to PCT with the preoperative clinical and mammography finding before PCT.

PATIENTS AND METHODS

50 consecutive patients with locally advanced cancer breast presented to Surgical or Medical Oncology Unit, Alexandria Faculty of Medicine between May 2004 and January 2007 were included in this study. Full medical history and systemic clinical examination and breast examination was done to all patients with emphasis on side, site, size and character of breast masses. All patients had a bilateral breast mammography, US examination and core biopsies before started of PCT. All patients had received preoperative PCT in the form of 4 cycles of one of the following combination: AC: Cyclophosphamide 500 mg/m2 IV day 1, Adryamicin 50 mg/m2 IV day 1, to be repeated every 21 days, or FEC: 5-flourouracil 500 mg/m2 IV day 1, Epirubicin 50 mg/m2 IV day 1, Cyclophosphamide 500 mg/m2 IV day 1, to be repeated every 21 days. After PCT the clinical data of the breast mass as well as mammographic changes were recorded to divide patients into responders (either complete disappearance or partial reduction of ≥ 50% of the tumour size) and none responders (Stationary with reduction < 50% or increase < 25% of the tumour size, or progressive with increase ≥ 25% of the tumour size) according to the UICC criteria.[5]

All responders underwent modified radical mastectomy (MRM) and none responders under went simple palliative mastectomy (SPM) or local palliative radiotherapy. All operative specimens had been immediately emerged in 10% formalin preservative solution. Then specimens were embedded in paraffin wax, cut in 7μm sections and stained with regular H and E stains. Single consultant breast histopathologist has reviewed all the specimens. Full pathological examination including size, multifocality, type, grading, vascular and lymphatic invasion as well as number of total and involved excised axillary lymph nodes. Also the questionable area which is the difference between pre and post PCT sizes were examined carefully for at least 4 different radial par-tumour areas, searching for any tumour tissue. Statistical analysis was done using SPSS (V.9). F-test (ANOVA) was used to compare between means, while X2 test was used to compare between the ratios or proportions.

RESULTS

This study was carried on 50 locally advanced cancer breast female patients (median age 50, range 26-70). Forty-four % of all patients were premenopausal. At their first time of presentation, none of them had clinical, radiological or laboratory evidence of distant metastases (M0). The mean initial tumour size were 7.3±2.2cm with range of 4-13 cm. Negative clinical examination of axilla (N0) had been detected in 56%, while 28% had mobile mass in the axilla (N1) and 16% had fixed one (N2). Clinically lymph nodes enlargement was more common in larger tumours (>5 cm) than with a smaller (<5 cm), 66.2% and 45.8% respectively. (P= 0.076) Skin changes in the form of peau d' orange, buckering and ulceration were presented in 34%, 26% and 18% respectively. Overall assessment of all patients by TNM classification system revealed that 25.9% of the patients had stage I disease, 48.3% had stage II and 25.8% had stage III.

The most common histological type was infiltrative ductal carcinoma (IDC) where it presented for 88% of studied tumours. Infiltrative lobular carcinoma (ILC) was presented in 12% of the tumours. In addition, 8 patients had ductal carcinoma in situ (DCIS) component beside IDC type (16%). The chemotherapy regimen used for all patients was AC for 70% of all patients, while EFC was used in 30%. In our study AC had better response rate (88.6 %) than FEC, which had response rate of (80%), with no significant difference. (P= 1.82) Of the 50 patients who started PCT, 5 patients (10%) achieved complete clinical remission (CR) and 38 patients (76%) partial clinical response (PR), giving overall objective response of 86%. On the other hand, 4 patients (8%) had a static disease and another 3 patients (6%) had a progressive disease on chemotherapy. The later two groups were subsequently had SPM supplemented by either pre, or/and, post operative radiotherapy.

The clinical response was matched with mammography and ultrasonography (US) response in all cases (Fig. 1). Only 2 in responder group were still had extensive PDO as well as 5 in none responder group who had either fungating ulcer or extensive PDO, all seven patients had musculocutaneous flap to close skin defect after either MRM or SPM. Patient age failed to predict the clinical response of breast tumour to PCT (P=0.35). All static and

progressive tumours were belonged to patients with large primary breast carcinoma (> 5 cm). Table 1. Shows the clinical features comparison between responders and non-responders to PCT. Response was observed to occur more in premenopausal patient more than in post menopausal one. Initial tumour size was smaller in responder group but it was not statistically significant. There was no difference in clinical lymph node enlargement in both groups. (Fig. 2)

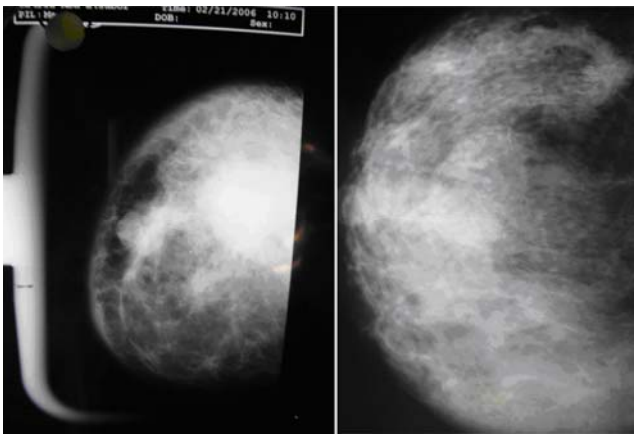

Fig 1. Pre & post PCT mammography for responder patient.

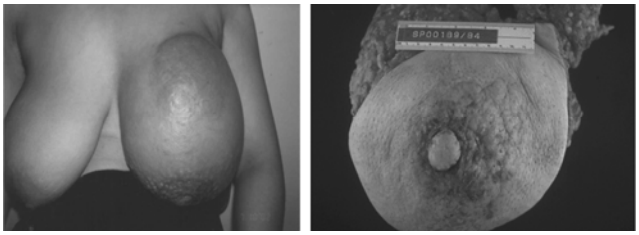

Fig 2. Pre treatment large size tumour & its mastectomy specimen after good respond to PCT.

Among responders group (n=43) 17 of them (39.5%) had clinical enlargement of axillary lymph nodes before starting of treatment. After responding to PCT only 4 of them (23.5%) still had a clinically palpable axillary lymph nodes. (P = 0.001) On the other hand, among non-responders group (n=7) 5 of them (71.4%) had clinical enlargement of axillary lymph nodes before starting of treatment. After non-responding to PCT 6 of them (86%) had a clinically palpable axillary lymph nodes. Table 2. Shows the histopathological features of responders and non-responders tumours. It is clearly reasonable that the mean histological size of responders was statistically smaller than non-responders. (p=0.001) 95% of responders' tumours were IDC while only 5% were ILC. Most of ILC did not respond to PCT (4 out of 6) 67 %. (p= 0.01) There was no relationship between histological tumour grades and its response to PCT. The responders group showed only 16 out of 43 tumours with lymph node involvement in compared with 5 out of 7 in non-responders. (P= 0.003)

All post mastectomy specimens from responder patients (n=43) were examined for presence of tumour tissue in the para-tumour (questionable) area. At least 2 slides were prepared from 4 different radial sites, in the area lie between pre and post PCT sizes determined by pre and post PCT mammography examinations. Total of 402 slides were examined with positive tumour tissue present in only 22 of them (Fig. 3). Those 22 positive slides belong to 7 patients only out of 43 responders (16.3%). Positive one slide only in one patient and 2-4 positive slides in the other 6 patients. Table 3. Shows the relation between positive questionable area slides and the pathological characters of original tumours. Multivariate analysis showed that: smaller initial tumour size < 5 cm, absence of DCIS and absence of vascular invasions were the best predictors of absence of tumour tissue in questionable area slides.

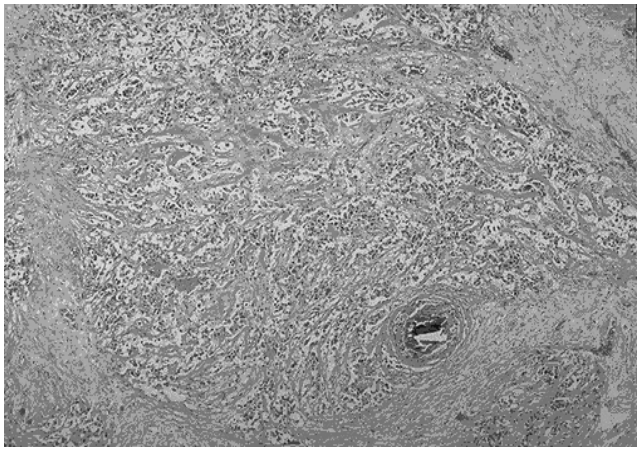

Fig 3. Focal island of IDC in a patient with positive questionable area. (H&E stain, 10^3 Power of magnofication)

Table 1. Pre-treatment clinical features of responder and non-responder groups.

		Responders (n = 43)	Non-responders (n = 7)	P value
Number of patients		43	7	
Clinical Features	Mean age (years)	43.3	49.8	0.35
	Premenopausal	74%	39%	0.03
	Menopausal	26%	61%	
	Mean initial size (mm.)	39.6	76.5	0.33
TNM	T1	26%	33%	0.73
	T2	74%	58%	
	T3	0%	9%	
	N0	27%	42%	0.67
	N1	67%	49%	
	N2	6%	9%	

Table 2. Postoperative pathological features of responder and non-responder groups.

		Responders (n = 43)	Non-responders (n = 7)	P value
Mean histological size (mm.)		32.7	56.7	0.07
Histological type (%)	IDC	41 (95%)	3 (43%)	0.65
	ILC	2 (5%)	4 (57%)	
	DCIS	2 (5%)	6 (86%)	
SBR grade (%)	I	21 (49%)	1 (14%)	
	II	18 (42%)	2 (28%)	
	III	4 (9%)	3 (44%)	
	IV	0 (0%)	1 (14%)	
ER +ve		33 (77%)	4 (57%)	
PR +ve		23 (53%)	2 (28%)	0.03
Vascular invasion		7 (16.3%)	5 (71.4%)	0.001
Lymphatic invasion		9 (20.9%)	5 (71.4%)	0.07
Lymph nodes involved		16 (37%)	5 (71%)	0.68

Table 3. Pathological features of tumours in patients with Positive Q. area compared to patients with Negative Q. area.

		Positive Q. area (n = 7)	Negative Q. area (n = 36)	P value
Mean initial size (mm.)		40.7	42.5	3.2
Histological type (%)	IDC	5 (71.4%)	36(100%)	0.6
	ILC	2 (28.6%)	0 (0%)	< 0.0001
	DCIS	2 (28.6%)	0 (0%)	< 0.0001
SBR grade (%)	I	1 (14.3%)	20(55.6%)	0.04
	II	2 (28.6%)	16 (44.4%)	0.07
	III	4 (57.1%)	0 (0%)	0.001
	IV	0 (0%)	0 (0%)	0.00
ER +ve		3 (42.8%)	30 (83%)	0.001
PR +ve		3 (42.8%)	20(56%)	0.56
Vascular invasion		5 (71.4%)	2 (5.6%)	0.003
Lymphatic invasion		6 (85.7%)	3 (8.3%)	0.08
Lymph nodes involved		6 (85.7%)	10 (27.8%)	0.003

Q = questionable

DISCUSSION

PCT as treatment for locally advanced breast carcinoma enables reduction in tumour size, facilitate operation and enable conservative breast surgery in some cases. Previous studies have clearly established that neoadjuvant therapy causes significant tumour regression, thus allowing more breast-conserving surgery to be performed.[6-8] Adriamycin based regimens was the commonest combination in our study similarly to most published studies until now. Although the regimens are varied, the response rates range between 63% and 87% among different series.[9]

Bonadonna et al. Had shown that the response rate may not be related to the drug regimens but may be related to dose intensity of the chosen regimen. In his study 60-80% of patients with stage III disease could be treated by breast conservative procedure after applying PCT.[10] Although recent results suggested that FAC combination has a higher response rate to PCT in cancer breast,[11] our results showed that AC combination has a marginal better rate than FAC. 86% of tumours with DCIS showed poor response to PCT. Also all responders with DCIS component showed positive slides in questionable area, which confirm multi-focality characters.

The clinical response was matched with mammography and US response in all cases. It was very helpful to measure the tumour size both pre and post PCT treatment accurately by mammography. That helped in determine the questionable zone, which is the difference between the pre, and post PCT sizes. Preoperative treatment reduces the tumour's dimensions substantially in most patients, regardless of tumour size. However, such a response is much more likely to be sufficient to allow breast-conserving surgery for relatively smaller tumours than for larger ones.[12] In our study, Although it was not significant, response to PCT was related to pre treatment tumour size, where the smaller the tumour the better response. Another very interesting results of our study that the very large primary tumours >10 cm had a poor response to PCT. Thus, PCT is better to applied to median size cancer breast 4-10 cm where we could obtain the best results of down staging the size to allow conserving of patient's breast and to avoid high non-responsiveness rate.

(Feldman et al. 1986) found that absence of macroscopic evidence of residual gross cancer was a better indicator of improved survival than clinically assessed complete response. However they did not use mammography to complement clinical assessment.13 Clahsen et al.[14] showed that localised control of breast cancer was better in women treated with preoperative chemotherapy, and they also had a longer disease free survival (DFS). Bernard Fisher et al. showed those younger patients with clinically positive nodes and smaller tumours were most likely to have a complete clinical response.15. That was not evident in our study were age could not predict response to PCT.

A disadvantage of preoperative systemic therapy is the potential psychological morbidity induced by leaving the tumour in situ while initial systemic therapy is undertaken.

In general this did not prove to be a problem even in patients with non responsive disease. This was probable due to the fact that surgical removal of the tumour, still regarded by many patients as the critical step in their management, is still possible. Formal examination of psychological morbidity was not however undertaken during this study but should be part of any future work.

After studying 340 patients in MD Anderson Cancer Institute, they concluded that breast conservation therapy after neoadjuvant chemotherapy results in acceptably low rates of local recurrence in appropriately selected patients, even those with T4 disease. Advanced nodal involvement at diagnosis, residual tumour larger than 2 cm, multi-focal residual disease, and lympho-vascular invasion predict higher rates of local tumour recurrence.[15]

Each individual patient should be discussed in consultation with medical and radiation oncologist, to reach a consensus for treatment. Surgical oncologist should recognise that a large size of primary tumour is not an absolute contraindication for breast conservation procedure. Patients can have more options for their local treatment after discussion with surgical oncologist. Our results challenge the classical indication for primary mastectomy by showing that use of PCT, sequentially combined with conservative surgery and radiation in selective tumours with special pathological characters, can offer an effective and safe alternative to women concerned about the preservation of body integrity.

From our results we could conclude that: delivery of PCT in large-size but resectable breast cancer can induce down staging of primary tumour to less than 4 cm to allow breast conservation. Small primary tumour size, absence of DCIS, and absence of vascular invasions are best indicators of absence of tumour tissue in post PCT para-tumour (questionable) area. Those factors were good indicators of eligibility of breast conserving surgery in responders locally advanced breast tumours to PCT.

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