RESEARCH COMMUNICATION

Response to Neoadjuvant Chemotherapy in Patients with Advanced Breast Cancer: A Local Hospital Experience

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Abstract

A large proportion of women present with advanced breast cancer in the developing countries with limited resources. Many of these patients have ulcerated, bleeding lesions or visually obvious masses in the breast. Neoadjuvant chemotherapy is well established as the standard of care and initial management of choice for these patients. Tumor shrinkage achieved with neoadjuvant chemotherapy has the advantage of converting an inoperable disease to an operable condition, with the option of breast conservation surgery where mastectomy is the only initial option for loco-regional control. Neoadjuvant chemotherapy also provides the earliest possible treatment of micrometastases and thus improves survival. In the present study, 165 advanced breast cancer female patients registered at the Institute of Nuclear Medicine and Oncology, Lahore, Pakistan, between 1st July 2005 and 30th June 2007 were evaluated for response to neoadjuvant chemotherapy. Tumor measurements were made and recorded prior to the first cycle of chemotherapy and 3 weeks after the third cycle. A clinical complete response was seen in 7.3%, a partial response in 60%, stable disease in 24% and progressive disease in 9%. A complete pathological response was only seen in 3.6% of evaluable patients. We conclude that breast cancer in patients presenting for neoadjuvant chemotherapy at our facility is more aggressive, generally presents as more advanced and bulky local disease, affects a younger population and features a low and unpredictable response to neoadjuvant chemotherapy.

Keywords: Breast cancer - neoadjuvant chemotherapy - advanced malignancies - clinical response

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Introduction

A large proportion (40% to 80%) of women present with Advanced Breast Cancer (ABC) in the developing countries with limited resources (Chopra 2001; Malik 2002; Yip et al., 2006; Aziz et al., 2008; Eniu et al., 2008). Many of these patients have ulcerated, bleeding lesions or visually obvious masses in the breast. On the other hand ABC accounts for only 7 to 10 % of breast cancers in the developed world (SEER, 2000).

ABC is a clinical entity including all Stage III and Stage IV cases of Breast Cancer at initial diagnosis. These cases can also be labelled as Locally Advanced Breast Cancer (LABC) and Metastatic Breast Cancer (MBC). Locally advanced breast cancer is a relatively nonspecific term and refers to large (≥5cm) invasive tumors with varying degrees of involvement of skin and/or chest wall (T3, T4) or large or matted (N2, N3) regional lymph nodes (Newman, 2009). It includes all patients with clinical stage III which is further classified as IIIA (T3N1M0, T3N2M0), IIIB (T4N0M0, T4N1M0 and T4N2M0) and IIIC (T3N3M0, T4N3M0) according to AJCC Staging System (Singletary et al., 2002). LABC also includes some patients in stage IIB (T3N0). Evidence of metastasis with any tumor or nodal status puts the breast cancer in Stage IV. Neoadjuvant chemotherapy (NACT) also called preoperative, induction or primary systemic chemotherapy is well established as the standard of care and initial management of choice for these patients (Giordano 2003; Shenkier et al., 2004). Tumor shrinkage achieved with NACT in these patients has the advantage of converting an inoperable disease to operable and option of breast conservation surgery in the operable disease where mastectomy is the only initial option for loco-regional control. NACT also provides the earliest possible treatment of micro metastases and thus improves survival. Another advantage is objective evaluation of response in vivo which can have impact on therapeutic decisions aiming at individualization of chemotherapy rather than one shoe fits all approach. This treatment approach also provides a living model for different types of research activities especially to address questions related to breast cancer biology and response to treatment (Rastogi et al., 2008; Wolff et al., 2008). It is hoped that research in this setting will ultimately lead to individualization of breast cancer treatment (Gralow et al., 2008).

NACT although accepted as the current standard for LABC is a toxic and expensive treatment and response is not uniform in the patient population. Different regimens using different cytotoxic drugs are being used, majority

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include an anthracyclin (Shenkier et al., 2004). Clinical Complete Response (cCR) according to UICC criteria is reported in 4 to 62% of patients while Pathological Complete Response (pCR) is reported only in 3 to 46% (Mathew et al., 2009). In a recent review of focus group for developing guidelines for treatment of LABC in low and middle income countries (El Saghir et al., 2008), it has been noted that not only there is enormous variability and heterogeneity in the range of response rates in the trials of NACT for LABC ranging from 7% to 65% cCR and 4% to 29% pCR but also that all these trials (nine trials with a total of 3,946 patients) were conducted in the developed countries with maximal resources. No such trial was available from developing countries with limited resources. This is so in spite of the fact that LABC accounts for up to 80% of the patients at the time of presentation in the developing countries compared to 7 to 10% in the developed world. Moreover, Breast Cancer is well known as a heterogeneous disease biologically, genetically and clinically with enormous variations in different geographical, racial and ethnic groups (Carey et al., 2006; Chia et al., 2008).

This paper is based on a prospective study conducted over a period of two years at Institute of Nuclear Medicine & Oncology Lahore (INMOL); a public sector cancer hospital in Lahore, Pakistan to evaluate the clinical response to NACT in patients with Advanced Breast Cancer (ABC). This study was approved by advanced research board and ethical committee of University of Health Sciences, Lahore and INMOL hospital Lahore and was part of a study on prediction of response to chemotherapy in breast cancer. Informed consent of the patients was taken to be included in the study.

Subjects and Methods

All female patients registered at INMOL with ABC at initial diagnosis having tumor size 5 cm or more (Clinically Evaluable Breast Tumor) with plan of NACT between 1st July 2005 and 30th June 2007 were prospectively included in the study group. Provisional diagnosis was based on triple assessment and histopathological diagnosis was established by incisional biopsy in ulcerated lesions and core needle biopsy in lesions with intact skin. Receptor (ER, PR, HER 2 Neu) studies on tumour tissue by immunohistochemistry were done on formalin fixed paraffin embedded biopsy specimens. Hercep Score 3+ was taken as positive, 0 or 1+ as negative and 2+ as equivocal for HER 2.

Chemotherapy regimen was advised by the oncologist independent of the study. FAC with 5-fluorouracil, adriamycin and cyclophosphamide intravenously every 3 weeks being the standard. The other regimens were administered on specific indications on individual basis. All tumor measurements were made by the breast surgeon or her assistant in centimeters using calipers and a tape measure according to standard procedure (Kuerer et al., 2000) and were recorded prior to the first cycle of chemotherapy and 3 weeks after the third cycle. The tumor was grasped between thumb and index finger of left hand and compressed gently, calipers in the other hand was used as a gauge of the diameter. The width of the calipers was then translated into centimeters by the measuring tape or scale. The procedure was repeated in the other dimension and thus two largest perpendicular diameters were measured and recorded. In case of multiple or bilateral lesions measurements of the largest lesion alone were recorded. Clinical response was assessed according to WHO/UICC criteria (Miller et al., 1981; Therasse 2002). According to this criteria, Clinical Complete Response (cCR) is defined as no residual clinically detectable tumor, Clinical Partial Response (cPR) is defined as a reduction of 50% or more in the product of the maximum perpendicular diameters of the tumor, Clinical Stable Disease (cSD) as less than 50% decrease or less than 25% increase in the product of the tumour dimensions and Clinical progressive Disease (cPD) is defined as 25% or more increase in the product of tumor dimensions. cCR & cPR are grouped as "Responders" and cSD & cPD are grouped as "Non Responders". Pathological Complete Response (pCR) is based on the histopathology of the operative specimen after NACT labelled as pCR when there is no residual invasive tumor in the breast and axilla. Evaluation was made by the oncologist and surgeon three weeks after three cycles of chemotherapy. Decision was made for surgery if disease was operable, further chemotherapy and/or radiotherapy if disease was resistant and/or still inoperable or in stage IV. Adjuvant hormone therapy was given to all hormone receptor positive cases.

Results

During the period of 1st June 2005 to 30th June 2007, 215 patients were registered for treatment with plan of NACT at INMOL and their base line workup was done. Fifty patients were excluded from the study as their final response data was not available. Of these fifty patients, 28 were lost to follow up at different stages before the final evaluation three weeks after the third course of chemotherapy, 19 expired during this time, 2 developed complications and NACT was stopped and one patient had neo-adjuvant hormone therapy rather than cytotoxic drugs.

The age of 165 evaluable patients ranged from 22 to 80 years with a mean of 45.7±11.3 years. Majority (59%) of them were in the premenopausal stage of their lives. The maximum pretreatment tumor size was 28.2 cm and the mean of tumor diameters of these patients at baseline was 12.7± 4.9 cm. Large sized tumors with size ≥ 10cm was present in 71% of patients and 32% had tumor size ≥15cm. Majority of patients had invasive ductal carcinoma and tumor of grade III and stage III while status of all the three hormone receptors was known only in 76 patients and 31% (18/64) had Triple Negative Disease (TND) by virtue of being negative for all the three receptors (Table 1).

FAC chemotherapy was offered to 149 (90%) of patients (Table 2). Clinical complete response (cCR) was seen in 12 (7.3%) and Clinical partial response (cPR) in 99 (60%) patients with an overall objective response (cCR plus cPR) observed in 111 (67 %) patients. Clinical stable disease (cSD) was seen in 40 (24%) and Clinical

Table 1. Baseline Data and Tumor Characteristics for Evaluable Patients

Parameter	Group	Frequency	%
Age	20-29	8	4.8%
	30-39	42	25.5%
	40-49	52	31.5%
	50-59	38	23.0%
	≥60	25	15.2%
Menopausal status	Pre	98	59.4%
	Post	67	40.6%
	Total	165	100.0%
Side	Right	82	49.7%
	Left	69	41.8%
	Bilateral	14	8.5%
Histopathology	IDC	146	88.5%
	ILC	15	9.1%
	Mixed	2	1.2%
	Unknown	2	1.2%
Grade	I	1	0.6%
	II	42	25.5%
	III	66	40.0%
	unknown	56	33.9%
Stage	II B	3	1.8%
	III A	25	15.2%
	III B	48	29.1%
	III C	20	12.1%
	IV	69	41.8%
ER	Positive	40	24.2%
	Negative	68	41.2%
	Unknown	57	34.5%
PR	Positive	35	21.2%
	Negative	72	43.6%
	Unknown	58	35.2%
HER 2	3 positive	28	17.0%
	Negative	36	21.8%
	2positive/Equivocal	12	7.3%
	Unknown	89	53.9%
Baseline T size	5 -10 cm	60	36.4%
	10.1 – 15 cm	61	37.0%
	15.1-20 cm	34	20.6%
	>20 cm	10	6.1%
	Total	165	100.0%

Table 2. Patient Numbers in Relation to the Chemotherapy Regimen

Group	Frequency	%
FAC	149	90.3%
FEC	3	1.8%
AC	2	1.2%
TAC	2	1.2%
GEMZAR CISPLATIN	1	0.6%
GEMZAR CARBOPLATIN	1	0.6%
XELODA	1	0.6%
CMF	5	3.0%
CAP	1	0.6%
Total	165	100.0%

progressive disease (cPD) in 14 (9%) patients. This means 54 (33%) (cSD plus cPD) patients did not respond to the treatment (Figure 1).

Of the 12 patients showing cCR, 6 underwent Modified Radical Mastectomy, 2 had breast conservation surgery, 2 evaded surgeries, surgery was deferred in one patient and one patient was offered radiotherapy. Both patients with

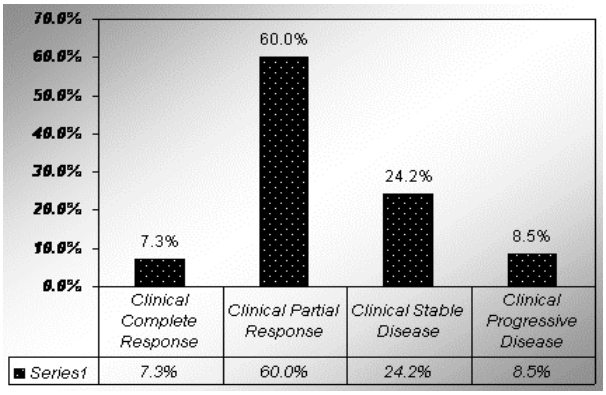

Figure 1. Frequency of Clinical Response Rates to NACT

breast conservation and 4 out of 6 patients who underwent mastectomy had pathological complete response with no residual disease in breast or axilla documented on histopathology of operated specimen. One out of 6 patients who underwent mastectomy had no residual disease in breast but had two axillary lymph nodes with metastatic deposits; the other patient had residual invasive lobular carcinoma in breast as well as metastatic deposits in 4 axillary lymph nodes. Two patients with cCR who evaded surgery had recurrence of disease in 2 & 6 months time. It is assumed that these patients did not have pCR and had some residual disease which progressed without treatment. One patient was found to develop bone metastases during treatment for which surgery was deferred. This patient had relapsed local disease after seven cycles of FAC. One patient initially had Stage IV tumor with bone metastasis. Her bony metastases also responded to chemotherapy. No surgery was done in this patient and only radiotherapy was added for local control. One year later she presented with brain metastasis and succumbed to it. She had no evidence of breast disease at that time. Histological correlation of Complete Clinical Response with Complete Pathological Response was thus possible in 8 patients only and 6/8 (75%) of cCR and 6 out of the total 165 (3.6%) evaluable patients actually had Complete Pathological Response.

Discussion

In this study, we found that only 3.6% of our advanced breast cancer patients had pathological complete response and 7.3% had clinical complete response to neoadjuvant chemotherapy. Pathological complete response to NACT is considered as a surrogate marker for survival and it has been suggested that these patients with pCR have the best long term outcome (Fisher et al., 1998; Kuerer et al., 1999; Wolmark et al., 2001; Heys et al., 2002). However the response rates vary from population to population and in the same population with different chemotherapy regimens and certain patient and tumor characteristics. This is because breast cancer is a heterogeneous disease from clinical, biological, genetic and molecular point of view with disparities across racial and ethnic groups (Bonadonnna 1998; Fisher et al., 1998; Kuerer et al., 1999; Mauriac et al., 1999). In a recent review of nine trials of NACT on 3946 LABC patients, enormous variability in response has been reported, with 7% - 65%

cCR and 4%-29% pCR (El Saghir et al., 2008). All these trials have been conducted in the developed world and included the operable cases of breast cancer. Our study with inclusion of mainly inoperable LABC and use of FAC in the majority (90.3%) shows cCR of 7.3% which is close to the minimum cCR reported and worse pCR rate of 3.6% compared to the minimum pCR of 4% reported in the literature. The reason may be the high frequency of biologically aggressive large sized tumors with markers for resistance to therapy (Mauriac et al., 2007; Gralow et al., 2008) in our studied population.

The mean age (45.7±11.3years) of presentation in our studied population is less than that of patient populations in reports and trials of invasive breast cancer from other regions and supports the similar findings from our region (Malik 2002; Gilani et al., 2003). The average age reported for United States is 61 years (SEER 2005; American Cancer Society 2007). A recent report of a database from 1998 to 2006 of a diverse population with invasive breast cancer at Boston University Medical School (Stead et al., 2009) had 30% of patients equal to or less than 50 years in age compared to 70.7% in our study and median of 58 years compared to 45 years in our study.

The mean tumor size (12.7±4.9cm) in our study is larger than the other reported studies and trials of NACT in LABC patients. Majority of studies from other population report tumors of ≥3cm in size (Bonadonna et al., 1998; Garimella et al., 2007; Tiezzi et al., 2007), only one study includes tumors up to 20 cm in diameter (Chen et al., 2008). In our study 71% of evaluable patients had tumor size of 10 cm or more and 32.1% had tumor size of ≥15cm. The largest tumor in our study was of 28.2cm size. These types of patients are generally reported as case reports (Ishikawa T et al 2002) or described as Locally Far-Advanced cases of breast cancer (Ardavanis et al., 2006).

Even with the application of well defined TNM categories there are variations in the groupings used to identify LABC patients (Newman 2009). Patients in our study were few Stage IIB (T3N0) cases, all Stage III cases and those Stage IV cases who had T3 or T4 disease as well (T3 with any N&M1,T4 with any N&M1). A previous study from INMOL has reported 71% of breast cancer patients presenting at Stage III or IV (Gilani et al., 2003). These patients are candidates for neo-adjuvant chemotherapy mostly to achieve operability and only occasionally to conserve breast. This is in contrast to the developed world where the latter is the usual case as is evident by different studies (Vander Hage et al., 2001; Lebowitz et al., 2004; Mieog et al., 2007).

High histological grade, negative ER and/or PR status and positive HER 2 receptors are established markers of biologically aggressive breast cancer. In our study, 60.6% of patients were of GIII and only 2.2% were of GI compared to 42% and 14% respectively, reported in the database of a diverse breast cancer population (Stead et al., 2009). NCCN guidelines recommend the three receptor evaluation (ER, PR, HER2) as essential for the initial workup of all newly diagnosed breast cancer patients (NCCN 2002). In our series of 165 patients all the three basic Immunohistochemistry (IHC) receptor studies were available only in 76 (40%) patients and ER, PR were available in 107(65%) patients. Of the known cases of HER 2 in our study, 41.2% were positive compared to 15 to 25% reported in the literature. We also found higher number of ER, 61.4% (84/137) and PR, 67.6% (92/136) negative patients in our study as compared to 30% and 38% respectively reported in the database of diverse population with multiple races and ethnicity (Lee et al., 2007).

The Triple Negative Disease (TND) lacking expression of ER, PR and HER2 is considered to be biologically equivalent to the basal type of breast cancer and racial differences with regard to tumor biology and TND frequency have been reported. TND was seen in 31% of our evaluable patients compared to 10-17% reported in the literature (Chen et al., 2008; Ries-Filho and Titt 2008; Linderholm et al., 2009). Black women and Africans are reported to have significantly higher percentage of basal type of breast cancers (21 to 39%) compared to white Americans (8 to 16%) (Newman, 2009). The reason for the higher proportion of TND in our study is partly selection bias as our case series consists of locally advanced breast cancer patients only and partly because breast cancer is known to be biologically more aggressive in this part of the world (Aziz et al., 2008; AzizunNisa et al., 2008).

Our study shows a heterogeneous group of advanced breast cancer patients ranging from low grade ER, PR positive tumor presenting as advanced cases only because of neglect, socioeconomic and cultural constraints to rapidly progressing high grade triple negative disease. When subjected to the neo-adjuvant chemotherapy this biological heterogeneity is expressed by the varying response ranging from complete clinical response in a stage IV patient to clinical progressive disease in an earlier stage patient. A considerable proportion (32.7%) of our patients not only failed to respond to chemotherapy but actually had disease progression (8.5%). The case of the progressive disease is like adding fuel to fire and that too with appreciable cost and toxicity. If we add the 19 patients from the initial group who died during the course of NACT and were thus not evaluable, the overall picture is of great concern. Management of these patients with advanced disease is challenging because of limited resources and financial constraints; with no uniform resource availability or health insurance for comprehensive diagnostic workup and therapeutic interventions. The treating clinician is forced to make decisions on individual basis with minimum diagnostic workup (Aziz, 2008) and cheapest possible medicines. Different trials have shown that inclusion of expensive new medicines like Taxanes and monoclonal antibodies in NACT improves the pCR rates as well as survival in breast cancer patients (Heys et al., 2002; Bear et al., 2003; Lyons et al., 2006; Gianni et al., 2007). Only 1.2% of our patients received Taxanes and no one of HER 2 positive cases received Trastuzumab. The reasons are cost issues which need to be taken care of, for the optimum treatment of patients on current standards. Research is essentially needed to identify the biological markers to predict response and resistance to chemotherapy in our population. This would save the cost and toxicity as well as direct the meager resources

available to the potential responders of NACT exclusively.

In conclusion, breast cancer in patients presenting for NACT at our facility is more aggressive, generally presents as more advanced and bulky local disease, affects younger population and has low and unpredictable response to NACT. There is need to further study the biology of disease and its response to different therapeutic regimens in our population.

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References

American Cancer Society (2008). Breast Cancer Facts 2007. Atlanta, USA.

Ardavanis A, Scorilas A, Tryfonopoulas D, et al (2006). Multidisciplinary therapy of locally far-advanced or inflammatory breast cancer with fixed perioperative sequence of epirubicin,vinorelbine,and fluorouracil chemotherapy, surgery, and radiotherapy : long term results. *Oncologist*, **11**, 563-73.

Aziz Z (2008). Across generations: cancer treatment in developing countries. *J Clin Oncol*, 26, 4990-1.

Aziz Z, Iqbal J, Akram M (2008). Effect of social class disparities on disease stage, quality of treatment and survival outcomes in breast cancer patients from developing countries. *Breast*, **14**, 372-5.

Azizunisa, Bhurgri Y, Raza F, et al (2008). Comparison of ER, PR & HER 2/Neu (C-erb B2) reactivity pattern with histologic grade, tumor size and lymph node status in breast cancer. *Asian Pac J Cancer Prev*, **9**, 553-6.

Bear DB, Anderson S, Brown A, et al (2003).The effect on tumor response of adding sequential preoperative docetaxel to preoperative doxorubicin and cyclophosphamide; Preliminary results from National Surgical Adjuvant Breast and Bowel project protocol B27. *J Clin Oncol*, **21**, 4165-74.

Bonadonna G, Valagussa P, Brambilla C, et al (1998).Primary chemotherapy in operable breast cancer: Eight year experience at Milan Cancer Institute. *J Clin Oncol*, **16**, 93-100.

Carey LA, Perou CM, Livasy CA, et al (2006). Race, breast cancer subtypes and survival in the Carolina Breast Cancer Study. *JAMA*, 295, 2492-502.

Chen S, Chang, Lin Y, et al (2008). High pathologic complete response in HER 2-positive locally advanced breast cancer after primary systemic chemotherapy with docetaxel and epirubicin. *Jpn J Clin Oncol*, **38**, 99-105.

Chia S, Swain SM, Byrd DR, et al (2008). Locally advanced and inflammatory breast cancer. *J Clin Oncol*, 26, 786-90.

Chopra K (2001). The Indian scene. *J Clin Oncol*, **19**, 106-11.

El Saghir NS, Eniu A, Carlson RW, et al (2008). Locally advanced breast cancer treatment guideline implementation with particular attention to low and middle income countries. *Cancer*, **113**, 2315-24.

Eniu A, Carlson RW, Aziz Z, et al (2008). Breast cancer in limited resource countries: treatment and allocation of resources. *The Breast*, **12**, S38-53.

Fisher B, Bryant J, Wolmark N, et al (1998). Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol*, **16**, 2672-85.

Garimella V, Watson MB, Cairns H, et al (2007). Assessment of apoptotic markers as predictors of response to neoadjuvant FEC chemotherapy in locally advanced breast cancer. *Cancer Therapy*, **5**, 239-42.

Gianni L, Semiglazov V, Manikhas GM, et al (2007). Neoadjuvant Trastuzumab in locally advanced breast cancer (NOAH): antitumor and safety analysis. *J Clin Oncol*, **25 (18 Suppl)**, 532.

Gilani GM, Kamal S, Akhter AS (2003). A differential study of breast cancer patients in Punjab, Pakistan. *J Pak Med Assoc*, **53**, 478-80.

Giordano SH (2003). Update on locally advanced breast cancer. *Oncologist*, 8, 521-30.

Gralow JR, Zujewski JA, Winer E (2008). Preoperative therapy in invasive breast cancer: Reviewing the state of the science and exploring new research directions. *J Clin Oncol*, **26**, 696-7.

Heys SD, Hutcheon AW, Sarkar TK, et al (2002) .On behalf of the Aberdeen Breast group. Neoadjuvant Docetaxel in Breast cancer: 3 year survival results from the Aberdeen Trial. *Clin Breast Cancer*, **Suppl 3**, 69-74.

Ishikawa T, Hamaguchi Y, Ichikawa Y, et al (2002). Locally advanced mucinous carcinoma of the breast with sudden growth acceleration: a case report. *Jpn J Clin Oncol*, **32**, 64-7.

Kuerer HM, Hunt KK, Newman LA, et al (2000). Neoadjuvant chemotherapy in women with invasive breast carcinoma: conceptual basis and fundamental surgical issues. *J Am Coll Surg*, **190**, 350-63.

Kuerer HM, Newman L, Smith T, et al (1999). Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin based neoadjuvant chemotherapy. *J Clin Oncol*, **17**, 460-9.

Lebowitz PF, Eng-Wong J, Swain SM, et al (2004). A phase II trial of neoadjuvant docetaxel and capecitabine for locally advanced breast cancer. *Clin Cancer Res*, **10**, 6764-9.

Lee MC, Patel-Parekh L, Bland KI, et al (2007). Increased frequency of Estrogen Receptor (ER) Negative and Aneuploid Breast Cancer in African American women at all stages of disease: First analysis from the National Cancer Database.(NCDB), Society of Surgical Oncology Breast Cancer Symposium Abstract 121.

Linderholm BK, Hellborg H, Johansson U, et al (2009). Significantly higher levels of vascular endothelial growth factor (VEGF) and shorter survival times for patients with primary operable triple-negative breast cancer. *Ann Oncol*, **20**, 1639-46.

Lyons JA, Silverman P, Remick S, et al (2006). Toxicity results and early outcome data on a randomized phase II study of Docetaxel + or – Bevacizumab for locally advanced unresectable breast cancer. *J Clin Oncol*, **24**, 3049.

Malik IA (2002). Clinicopathological features of breast cancer in Pakistan. *J Pak Med Assoc*, **52**, 100-4.

Mathew J, Asgeirsson KS, Cheung KL, et al (2009). Neoadjuvant chemotherapy for locally advanced breast cancer. A review of literature and future directions. *EJSO*, **35**, 113-22.

Mauriac L, Keshaviah A, Debled M et al (2007). Predictors of early relapse in postmenopausal women with hormone receptor positive breast cancer in BIG 1-98 trial. *Ann Oncol*, **18**, 859-67.

Mauriac L, McGregor G, Avril A (1999). Neoadjuvant chemotherapy for operable breast carcinoma larger than 3 cm: A unicentre randomized trial with a 124 month median followup. *Ann Oncol*, **10**, 47-52.

Mieog JSD, Vanderhage JA, VandeVelde CJH (2007). Neoadjuvant chemotherapy for operable breast cancer. *Br J Cancer*, **94**, 1189-200.
Miller AB, Hoogstraten B, Staquet M, et al (1981). Reporting results of cancer treatment. *Cancer*, **47**, 207-14.
National Comprehensive Cancer Network (2002). Practice Guidelines in Oncology. Breast Version 2. 2002.
Newman LA (2009). Epidemiology of locally advanced breast cancer. *Semin Radiat Oncol*, **19**, 195-203.
Rastogi P, Anderson SJ, Bear HD, et al (2008). Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Projects B-18 and B-27. *J Clin Oncol*, **26**, 778-85.
RiesFilho JS, Tutt ANJ (2008). Triple negative tumors: a critical review. *Histopathology*, **52**, 108-18.
SEER (2000). National Cancer Institute DCCPS, Surveillance Research Program, Cancer Statistics Branch. SEER Program Public use data tapes 1973 – 1998, November 2000 submission, issued April 2001.
SEER Cancer Statistics Review 1975-2005, National Cancer Institute [http://seer.cancer.gov/csr/1975-2005/]
Shenkier T, Weir L, Levine M, et al (2004). Clinical practice guidelines for the care and treatment of breast cancer: 15. Treatment for women with stage III or locally advanced breast cancer. *CMAJ*, **170**, 983-94.
Singletary SE, Allred C, Ashley P, et al (2002). Revision of the American joint committee on cancer staging system for breast cancer. *J Clin Oncol*, **20**, 3628-36.
Stead LA, Lash TL, Sobieraj JE, et al (2009) Triple-negative breast cancers are increased in black women regardless of age or body mass index. *Breast Cancer Res*, **11**, R18.
Therasse P (2002). Measuring the clinical response. What does it mean? *Eur J Cancer*, **38**, 1817-23.
Tiezzi DG, Andrade JM, Ribeiro-Silva A, et al (2007). Her-2, p53, p21 and hormonal receptors protein expression as predictor factors of response and prognosis in locally advanced breast cancer treated with neoadjuvant docetaxel plus epirubicin combination. *BMC Cancer*, 7, 36.
VanderHage JA, VaderHage CJH, Julian J, et al (2001). Preoperative chemotherapy in primary operable breast cancer: results from the European organization for research and treatment of cancer trial 10902. *J Clin Oncol*, **19**, 4224-37.
Wolff AC, Berry D, Carey LA, et al (2008). Research issues affecting preoperative systemic therapy for operable breast cancer. *J Clin Oncol*, **26**, 814-9.
Wolmark N, Wang J, Mamounas E, et al (2001). Preoperative chemotherapy in patients with operable breast cancer:nine year results from National Surgical Adjuvant Breast and Bowel Project B-18. *J Natl Cancer Inst Monogr*, **30**, 96-102.
Yip CH, Taib NAM, Mohamed I (2006). Epidemiology of breast cancer in Malaysia. *Asian Pac J Cancer Prev*, **7**, 369- 74.