RESEARCH COMMUNICATION

"Initial Clinical Response" to Neoadjuvant Chemotherapy: An In-vivo Chemosensitivity Test for Efficacy in Patients with Advanced Breast Cancer

Samina Khokher[1]*, Saqib Mahmood[2], Muhammad Usman Qureshi[3], Saeed Akhtar Khan[4], Naseer Ahmad Chaudhry[5]

Abstract

Neoadjuvant chemotherapy (NACT) is well established as the standard of care and initial management of choice for patients with advanced breast cancer (ABC). The response is however not uniform. The present study was an endeavor to develop a clinically applicable tool based on the available clinico-pathological data in the routine clinical setting to predict response to chemotherapy in breast cancer in a developing country. From 1st June 2005 to 30th June 2007, 149 patients registered at INMOL hospital with ABC at initial diagnosis having tumor size 5 cm or more and treated with FAC as NACT were prospectively included in the study to analyze association of response after first cycle of chemotherapy (initial clinical response) with that after the third cycle. Tumor measurements were done at base line (before starting chemotherapy), three weeks after the first course of chemotherapy and three weeks after the third course. Percentage change was calculated for the latter two stages. Clinical response was assessed according to WHO/UICC criteria. Pathological complete response (pCR) was based on the histopathology of the operative specimen after NACT. 67.1% patients (cCR 7.4%+cPR 59.7%) responded to chemotherapy while 32.9% (cSD 23.5%+cPD 9.4%) did not. pCR rate was 4%. No patient had initial clinical complete response while 23% had icPR, 74% had icSD and 3% had icPD. All patients with icPR responded to NACT (cCR 29%+cPR 71%) while 60% of icSD responded to chemotherapy (cCR 1%+cPR 59%) and 40% of icSD failed to respond (cSD 31%+cPD 9%). All patients with icPD developed cPD. The high sensitivity of initial clinical response for prediction of cCR and 100% specificity of icPD for prediction of cPD favors its incorporation in clinical practice, as an early predictor of response to NACT in ABC patients.

Keywords: Advanced breast cancer - neoadjuvant chemotherapy - initial clinical response - in vivo test

Asian Pacific J Cancer Prev, **12**, 939-946

Introduction

Breast cancer is a systemic disease and clinical trials during the last 20 years which included thousands of women with many years of follow up have shown that systemic chemotherapy reduces the risk of recurrence in general by approximately 30%-50% and prolongs overall survival (EBCTCG, 2005). Chemotherapy is recommended for all invasive breast cancers larger than 1.0 cm in size (NCCN, 2011) and/or in node positive disease. Virtually all patients of invasive breast cancer receive chemotherapy at some stage of their disease. The response to chemotherapy is however not uniform. Many patients do not benefit from chemotherapy and about 30% of the early stage patients relapse and about the same percentage of patients in advanced stage disease get cured, when chemotherapy is added to the other modalities of treatment. A combination of drugs has been found to be more effective rather than any single agent. The commonly used drug combinations are CMF, FAC, FEC, TAC, AC followed by T etc. Anthracycline based regimens administered over 6-8 cycles are the current standard (NCCN, 2011) however they are associated with increased risk of cardiomyopathy, congestive heart failure and heart disease (Doyle et al., 2005).

A large proportion of patients in Pakistan present as advanced breast cancer (ABC) at initial diagnosis, with ulcerated bleeding lesions or visually obvious masses in the breast. ABC is a clinical entity (National Breast Cancer Centre 2001) and includes locally advanced breast cancer (LABC) as well as metastatic breast cancer (MBC). Treatment of these patients requires multidisciplinary team approach and the goal is to improve overall survival (OS) and the quality of life. Neoadjuvant chemotherapy (NACT) or primary systemic therapy, is the initial management of choice and tumor shrinkage achieved has the advantage of converting an inoperable disease to operable along with improving the surgical options. It also provides in-vivo assessment of efficacy of chemotherapy. The improvement in OS and quality of life is achieved by reducing the tumor size, growth rate or both, in women with responding tumors. WHO and UICC

*[1]Surgical Division, INMOL Hospital, [2]Department of Human Genetics and Molecular Biology, University of Health Sciences, [3]Nauman associates, [4]Services Institute of Medical Sciences, [5]Pathology, University of health sciences Lahore, Pakistan *For correspondence: drsamkhokher@yahoo.com*

criteria (Hayward et al., 1977; Miller et al., 1981; Pruthi et al., 2007) define four categories of clinical response to NACT as clinical complete response (cCR), clinical partial response (cPR), clinical stable disease (cSD) and clinical progressive disease (cPD). Only a small proportion of advanced breast cancer patients, experience complete disappearance of disease and have cCR. Majority of the patients have either cPR or cSD. A significant proportion however develops disease progression during the course of chemotherapy and is categorized as cPD.

The clinicians in limited resource countries face multiple challenges because on average only 5% of the amount spent in the west (Lancet, 2009), is available for cancer patients here and pathological complete response (pCR) reported is low; 3.6% (Khokher et al., 2010) compared with up to 29% (El-Saghir et al 2008) in the advanced stage patients of breast cancer in the developed world. In the low income countries the human and economic resources are limited, the disease is advanced or incurable and palliative care facilities are not established (Farmer et al., 2010).

The increasing knowledge of breast cancer histopathology, molecular biology, as well as the diversity of clinical presentations, course of the disease and the variable response to therapy points to the heterogeneity of breast cancer. The geographical, racial and ethnic differences add to the complexity of the problems faced in the clinical decision making. Hormone therapy and molecular targeted therapies are guided by the respective receptor status of the disease. The response to even these therapies is not 100% predictable (Labianca et al 2008). Based on clinical judgment and current standard guidelines the response to general chemotherapy however is far lower. In a metaanalysis (Mauri et al., 2005) of NACT studies, clinical complete response (cCR) was reported as 7% to 65% and pCR as 4% to 29% in different patient populations. Another review (Rustogi et al., 2005) reports 10% to 30% clinical complete response in the studies reviewed. There is no clinically applicable in-vivo or in-vitro test available to predict this variable response to chemotherapy in an individual patient of breast cancer. There is a dire need to search for an accurate, clinically applicable and cost effective tool to predict response to chemotherapy. Nearly all the research in the developed countries is focused on early stage breast cancer where they are trying to identify the patients with good prognostic markers so that overtreatment of these patients with chemotherapy can be avoided. Gene signatures are being used to identify subsets of early breast cancer (EBC) patients with good prognosis in whom chemotherapy can be avoided. The clinical trial TAILORx is based on OncotypeDx assay and MINDACT is based on Mammaprint gene signature assay (Dowsett and Dunbier, 2008; Cianfrocca and Gradishar, 2009). For us in a developing country it is important to save the advanced stage patients from toxicity of the ineffective treatment, where when ineffective, not only it is waste of resources but it also adds the agony of treatment toxicity to the misery of disease. Current approach to decision making includes integration of classical, clinical and pathological factors but no specific model exists to predict the treatment response in an individual patient. Prediction of the efficacy of chemotherapy in an individual patient is an important research goal so that treatment options can be individualized and patients are saved from the toxicity of ineffective treatment. In a web based survey of current research topics, the highest priority was to identify molecular signatures of efficacy of chemotherapy in breast cancer (Dowsett et al., 2007).

The best prediction of response or resistance is before the initiation of NACT. Many studies have however shown that so far it is not possible to predict it with any single or combined marker (Untch and von-Minckwitz 2009; Osako et al., 2010; Rakha et al., 2010). Response to NACT is generally evaluated after two to four cycles of chemotherapy (Smith et al., 2002; von Minckwitz et al., 2008a; Beslija et al., 2009). A prospective study was conducted at INMOL hospital to identify predictors of response to neoadjuvant chemotherapy in patients with advanced breast cancer, in the routine clinical setting. The study was approved by the advanced research and studies board and ethical committee of University of Health Sciences and INMOL hospital, Lahore. Part of this study has already been reported (Khokher et al., 2010). The prospectively collected data of this study was analyzed to see association of response after first cycle of chemotherapy (called initial clinical response) with the response after the third cycle of chemotherapy. We here present the analysis of this data.

Materials 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 the ulcerated lesions and core needle biopsy in the lesions with intact skin. Receptor (ER, PgR, HER2 Neu) studies on tumour tissue by Immunohistochemistry were done on formalin fixed paraffin embedded biopsy specimens. Hercep Score 3+was taken as Positve,0 or 1+ as Negative and 2+ as equivocal for HER 2. ER and PgR were considered positive when > 10% cells stained positive. Complete blood count, renal function test, liver function test, blood sugar, echocardiography, chest X-ray, mammography or sonomammography, abdominal and pelvic ultrasound and bone scan were done prior to treatment.

Chemotherapy Regimen

Chemotherapy regimen was advised by the oncologist independent of the study. FAC (5-Fluorouracil, Adriamycin and Cyclophosphamide intravenously every 3 weeks) being the standard. The other regimens were administered on specific indications on individual basis.

Measurements of Tumors

All measurements were made by the Breast Surgeon in centimeters using calipers and a tape measure according to the standard procedure (Kuerer et al 2000) and were

recorded prior to the first cycle, 3 weeks after the first cycle and 3 weeks after the third cycle of NACT. 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 diameters were measured and recorded. In case of multiple or bilateral lesions measurements of the largest lesion alone were recorded. Photographic record was made whenever patient gave consent for it.

Clinical and Pathological Response

Clinical response was assessed according to WHO/ UICC criteria (Hayward et al 1977, Miller AB et al 1981). 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) is defined as less than 50% decrease or less than 25% increase in the product of the tumor dimensions. Clinical progressive Disease (cPD) is defined as 25% or more increase in the product of tumor dimensions. cCR and cPR are grouped as "Responders" and cSD and cPD are grouped as "Non Responders". Response after the first cycle of chemotherapy was assessed from the measurements of tumor 3 weeks after the first cycle of chemotherapy and was called "Initial Clinical Response". Initial Clinical Response is abbreviated by "i" which is added as a prefix to the four WHO/UICC response categories; Initial clinical Complete Response (icCR), Initial clinical Partial Response (icPR), Initial clinical Stable Disease (icSD) and Initial clinical Progressive Disease (icPD).

Pathological Complete Response (pCR) was based on the histopathology of the operative specimen after NACT labeled as pCR when there was no residual invasive tumor in the breast and axilla.

Follow up Therapy

Evaluation was made by the oncologist and surgeon after 03 cycles of chemotherapy and decision made for surgery if disease was operable, further chemotherapy and/or radiotherapy if disease was resistant and/or still inoperable or stage IV. Adjuvant hormone therapy was given to all hormone receptor positive cases.

Statistical Analysis

Statistical analysis was done using descriptive statistics on MS Excel. p values were calculated by Fischer's exact test. The sensitivity, specificity and predictive values (Altman and Bland 1994a, Altman and Bland 1994b) were calculated by Mc Nemar test for the diagnostic performance of initial clinical response in the prediction of clinical response to NACT.

Results

Patient and Tumor Characteristics

From 1st June 2005 to 30th June 2007, 215 patients were registered for treatment with plan of NACT at INMOL and base line workup was done. Due to unavailability of response data, fifty patients were excluded from the study for evaluation of response to NACT. Of these fifty patients twenty eight were lost to follow up at different stages before the final evaluation three weeks after the third course of chemotherapy, nineteen patients expired during this time, two patients developed complications and NACT was stopped and one patient had neo-adjuvant hormone therapy rather than cytotoxic drugs. Of the remaining 165 patients 16 received chemotherapy regimens other than standard FAC and were excluded for the present study. The base line patient and tumor characteristics of the 149 patients included in the present study are summarized in Table 1.

Response to Neoadjuvant Chemotherapy.

Tumor measurements were available at base line

Table 1. Baseline Characteristics of the Patients

Parameter	Group	Frequency	Percentage
Age	20-29	8	5.4%
	30-39	38	25.5%
	40-49	47	31.5%
	50-59	36	24.2%
	>60	20	13.4%
Menopausal status	Pre	90	60.4%
	Post	59	39.6%
Family History	Positive	10	6.7%
	Negative	139	93.3%
Side	Right	72	48.3%
	Left	64	43.0%
	Bilateral	13	8.7%
Base line Tumor size (cm)	5 to 10	49	32.9%
	10.1-15	58	38.9%
	15.1-20	33	22.1%
	>20	9	6.0%
Lymph Node Status	N0	7	4.7%
	N1	99	66.4%
	N2	23	15.4%
	N3	20	13.4%
Stage	II B	3	2.0%
	III A	21	14.1%
	III B	43	28.9%
	III C	19	12.8%
	IV	63	42.3%
Histopathology	IDC	132	88.6%
	ILC	13	8.7%
	Mixed	2	1.3%
	Unknown	2	1.3%
Grade	I	1	0.7%
	II	35	23.5%
	III	60	40.3%
	Unknown	53	35.6%
ER	Positive	33	22.1%
	Negative	62	41.6%
	Unknown	54	36.2%
PgR	Positive	30	20.1%
	Negative	64	43.0%
	Unknown	55	36.9%
HER 2	Positive	27	18.1%
	Equivocal	10	6.7%
	Negative	28	18.8%
	Unknown	84	56.4%
Total		149	100%

Table 2. The Predictive Value of the Initial Clinical Response for NACT Response

Initial Response	Prediction of cCR				Prediction of cPD			
	Sensitivity	Specificity	PPV	Accuracy	Sensitivity	Specificity	PPV	Accuracy
icPR	91%	83%	29%	83%	0%	75%	0%	68%
icSD	9%	20%	1%	19%	71%	25%	9%	30%
icPD	0%	97%	0%	90%	29%	100%	100%	93%

PPV, positive predictive value

(before starting chemotherapy), three weeks after the first course of chemotherapy and three weeks after the third course of chemotherapy. The percentage change was calculated for the latter two stages.

Overall objective response (cCR 7.4% + cPR 59.7%) was observed in 100 (67.1%) patients, While 49 (32.9%) patients did not respond to the treatment (cSD23.5% + cPD9.4%). Out of the 11 patients with complete clinical response 6 patients underwent Modified Radical Mastectomy and two had breast conservation surgery. Both patients with breast conservation and 4 with mastectomy had pathological complete response with no residual disease in breast or axilla documented on histopathology of the operated specimen. One patient with mastectomy had no residual disease in the breast but had two axillary lymph nodes with metastatic deposits, the other patient had residual invasive lobular carcinoma in the breast as well as metastatic deposits in 4 axillary lymph nodes. One patient with cCR evaded surgery and disease came back in 6 month's time. It is assumed that this patient 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 7 cycles of FAC .One patient having Clinical Complete Response was Stage IV initially with bone metastasis. Her bone 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 them. She had no evidence of breast disease at that time. Histologic correlation of Clinical Complete Response with Pathological Complete Response was thus possible in 8 patients only and 6/8 (75%) of cCR and 6/149 patients (4%) overall had pCR.

The percentage change in the tumor size three weeks after the first cycle of chemotherapy was used to categorize the patients into four response groups on the principles of UICC/WHO similar to the response after three cycles. Prefix of "i" (initial) was added to cCR, cPR, cSD and cPD to differentiate it from the final response group. None of the patients had complete disappearance of disease on examination done at three weeks after the first cycle of chemotherapy and 4/149 had 25% or more increase in the product of two tumor diameters. However icSD was observed in 111 and icPR was observed in 34 patients.

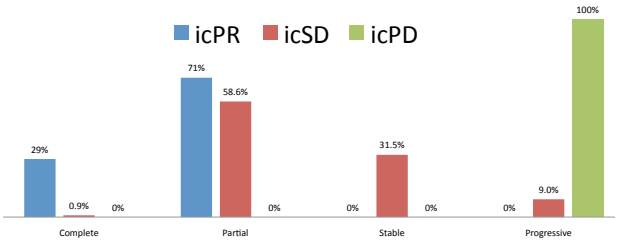

Figure 1. Distribution of Initial Clinical Response in the NACT Response Groups

Association of Initial Clinical Response with Response to NACT

No patient was found to have icCR. Distribution of the icPR, icSD, icPD were 23%, 74% and 3% respectively. The p-value for initial clinical response was found to be highly significant; 2.2*exp(-16) when grouped as initial responder (icCR + icPR) Vs initial non-responder (icSD + icPD) and even more significant; 4.41*exp(-18) when taken as a continuous variable. No patient was found to have icCR so the icPR was labeled as initial responder and icSD and icPD as initial non responders. The initial response to NACT was evaluated as a parameter for prediction of two extreme groups of NACT response (cCR and cPD) and the sensitivity, specificity, positive predictive value and accuracy of the three initial response groups was calculated. Table 2 shows these values on evaluation of initial clinical response as a predictive factor for the two extreme groups of response to NACT. Taken as a group icPR has high sensitivity (91%) for cCR and icPD has the highest specificity for cPD (100%)

Discussion

This study shows a heterogeneous group of advanced breast cancer patients with a range, from low grade ER, PgR 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 (32.9%) of our patients not only failed to respond to chemotherapy but actually had disease progression (9.4%). In the reports of NACT general emphasis on cCR and pCR masks the smaller but significant number of non-responders to chemotherapy. A review of NACT studies including 1549 assessable women (Raut and Chordiya, 2010) showed, down staging of disease and breast conservation in 397 women; however in 66 women tumor progression necessitated more radical surgery than originally planned. All treatments are associated with some side effects but chemotherapy is particularly known to have serious toxic side effects. 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 in Pakistan is forced to make decisions on individual basis with minimum diagnostic workup 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). Resources can be allocated for these drugs only if we can save the cost by giving chemotherapy to potential responders only.

Cancer is on the rise worldwide, but is growing most quickly in the developing countries. An estimated 1.7 million women will be diagnosed with breast cancer in 2020, a 26% increase from the current levels, and 60% of them will be in the developing countries where only 5% resources are available for its treatment (Lancet, 2009). Because of financial constraints it is nearly impossible in the limited resource countries, to treat these patients according to the guidelines developed by the scientific bodies of the developed world (Aziz, 2008; Deo, 2010) and it is crucial to reserve the chemotherapy for the patients most likely to respond. This is required to save the non-responders from cost and toxicity of ineffective medicines and direct these resources to the potential responders. There is lack of a specific marker which can predict the efficacy of chemotherapy and different chemotherapy regimens are being used without any clear indications for a particular regimen (Goldhirsch et al., 2009). The theme "Personalizing cancer care" adopted by the annual meeting of American Society of Clinical Oncology in 2009 (Alexander, 2009) shows that it is an important research topic in the developed countries as well. It has been stated that;

"The time for one-size-fits-all medicine is ending, and an era of tailoring treatments to patient's and tumor's unique biology is arriving. The goal is to match the right treatment to the right patient at the right time".

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 the developed world with a lot of money available as research grants as well as the developed infrastructure for research and development of new biomarkers, the current research is almost completely based on genes and focused at the molecular level. Moreover with the established screening programs majority of the patients are diagnosed either at asymptomatic stage or at early symptomatic stage. This has led to more emphasis and more research on early stage breast cancer. The breast cancer patients in Pakistan however differ not only in their disease but also in their resources. They need a clinically useful predictive tool for easy application and crucial clinical decisions with regard to the treatment of their disease, with minimum added cost or morbidity. Similarly there are no grants for the expensive gene based research in the local population of patients with advanced breast cancer. The present clinical study is a reflection of both these aspects.

Prediction of efficacy of chemotherapy is very important at the two extremes of NACT response categories (cCR and cPD). Potential cCR patients need to be identified as early as possible because maximum effort and maximum resource should be allocated to them as they are most likely to benefit from chemotherapy. We also need to identify potential cPD patients because continued administration of ineffective chemotherapy will not only be a waste of resources but it will also add toxicity of drugs to the misery of disease. The locally advanced patients in developing countries can best be classified as locally far advanced (Ardavanis et al., 2006). They generally present with either inoperable or borderline operable disease. Only rarely they have operable disease when NACT is given to improve the surgical option in favor of the breast conservation surgery. In the present study only 2/86 patients with LABC underwent breast conservation surgery. Among patients with non-responding or progressing tumors, continued ineffective chemotherapy may negate the possibility of surgical ablation of disease. These patients may best be managed by timely switch over to some alternative modality of treatment if possible or to palliative supportive care only. The test for identification and diagnosis of potential cCR should be highly sensitive because no patient should be missed out or negated the opportunity of a potentially effective chemotherapy. However the test for identification or diagnosis of potential cPD should be very specific because this will infer cessation of chemotherapy with switch over to either some other modality of treatment or no active treatment at all.

Comparison of physical examination with sonography and mammography has shown (Herrada et al., 1997; Fiorentino et al., 2001; Sperber et al., 2006) that physical examination correlates best with the pathological findings for assessment of breast tumor size after NACT. However MRI has higher accuracy (Shin et al., 2010; Park et al., 2011) with the surgical pathology findings. The present study was conducted by an experienced breast surgeon who made the tumor measurements herself. These tumor measurements were available at base line, 3 weeks after the first cycle of chemotherapy and 3 weeks after the third cycle of chemotherapy.

The tumor measurements after the first course of chemotherapy were evaluated as a predictor of response to chemotherapy and it was called "INITIAL" clinical response to differentiate it from the term "EARLY" clinical response. The term early has been used by others for response evaluated after two courses of chemotherapy in their trial reports and studies (Minckwitz et al 2005; 2008a; 2008b; Beresford et al., 2008; Esteva and Hortobagyi, 2008; Ishitobi et al 2009). In another study (Moon et al., 2005) early response referred to the maximum clinical response within three cycles of NACT. It has been demonstrated that reliable prediction of pCR is not possible with the routinely determined clinical and biological factors before the NACT, and the response after two cycles of chemotherapy is a strong, although a dependent predictor (von-Minckwitz et al., 2008b).

The present study is a report of evaluation of clinical response after the first cycle of NACT as a predictor of response to NACT. It is termed as initial clinical response

and prefix "i" is added to the response group of NACT according to WHO/UICC criteria (icCR, icPR, icSD, icPD). The initial clinical response in the present study was found to be highly significant as a predictor of response to NACT. icCR has very high sensitivity (91%), to identify cCR and high specificity (75%) to identify cPD . icPD at the other extreme has 100% specificity for cPD. None of the initial responding patient in this study had cPD while 29% of initial responding patients had clinical complete response. The remaining 71% of initial responding patients had clinical partial response. All the patients with icPD progressed to clinical progressive disease while only 9% of the icSD progressed to cPD. No other parameter or tumor marker has been reported with this level of sensitivity for cCR and specificity for cPD. These are the most desired features of a predictive parameter for prediction of the response to NACT. Its only disadvantage is that it is not available prior to treatment. However there is a good old dictum that "The earlier the better" and "Better late than never". In the study of von-Minckwitz already cited, the clinical response after two cycles of chemotherapy was found to be the only factor with significant predictive value among many tumor and host factors, on univariate as well as multivariate analysis. The same was found true for initial clinical response reported in the present study.

Molecular functional imagings have also been used early in the course of NACT to predict response to chemotherapy (Meisamy et al., 2004; Schwarz et al., 2005; Padhani et al., 2006; Rousseau et al., 2006) However these techniques are very expensive and require high tech equipment. In a study of MRI measurements of tumor size and pharmacokinetic parameters as early predictors of response to NACT, early tumor size change on MRI was found to be a better response predictor rather than the pharmacokinetic parameters on MRI (Yu et al., 2007). A report of early assessment of tumor response by molecular profiling has been conducted on core biopsy specimens (Sharma et al., 2009) but this technique is invasive and involves expensive molecular profiling technology. The clinical evaluation is inexpensive as well as reasonably accurate. The clinical evaluation at three weeks after the first cycle requires only an additional appointment of the patient with someone having basic clinical skills and is timed around the second cycle of chemotherapy. In the present study this evaluation was done either a day prior to the course of chemotherapy when patients had appointment for laboratory tests or on the day of administration of chemotherapy.

The highly significant predictive power of initial clinical response is comprehendible if we look at the enormous heterogeneity and diversity reported for breast cancer by the recent genomic and proteomic studies (Asakawa et al., 2010; Graeser et al., 2010; Mc Dermott et al., 2011) added on to the heterogeneity of patient population. Initial results from the studies sequencing the genome of human breast cancers show that an average tumor contains 90 mutated genes (Sjoblom et al 2006). This translates to thousands of different combinations which emphasizes the enormous molecular diversity of breast cancer. All these high profile expensive assays miss out the variations in the drug metabolism inside the patient, which is unrelated to the tumor's molecular profile. The Pharmacogenetics (Assfalg et al 2008, Caraco 2004, Tan et al 2008) on the other hand miss out the variations in the tumor, a patient is encountering. It was hoped that the genomic analyses of cancer tumors would be able to identify in advance that which patients will benefit from chemotherapy and which will not. A lot of work has been done and a number of articles have been published but still there is no clinically useful tool to tell how the patient's cancer cells will react to the chemotherapy. In other words the efficacy of chemotherapy cannot be determined or predicted before the actual interaction of chemotherapy and tumor cells takes place in vivo. We lack the in-depth knowledge of the biological processes resulting in the tumor response or the resistance to chemotherapy and with the present day knowledge, no single or combinatorial tumor parameter can predict with accuracy the drug versus tumor interaction in vivo (Rakha et al 2010, Osako et al 2010, Untch and von-Minckwitz 2009). It is therefore suggested that for the optimum use of NACT in patients with advanced breast cancer, the clinical assessment should be done after the first course rather than the current practice (Beslija et al 2009, Smith et al 2002) of two to four courses of NACT. The increasing knowledge and high powered studies hold promise for the future but till then the response to the first course of the NACT (Initial Clinical Response) should be considered as a real time test of chemosensitivity of the tumor which can predict the individual's response with accuracy. It has the advantage assessing the drug versus tumor interaction in an individual patient in a direct manner and provides early information on the clinical response to NACT. It is easier, cheaper and ethical to be used and can be relied upon for clinical decision making in patients with advanced breast cancer. The clinical response evaluation after first cycle of NACT has the potential of improving the quality of care in these patients in accordance with the current recommendations (Peppercorn et al 2011) of American Society of Clinical Oncology.

We conclude that the initial clinical response evaluation three weeks after the first course of neoadjuvant chemotherapy is a good predictor of response. The initial clinical progressive disease has 100% specificity and 93% accuracy for clinical progressive disease. The initial partial response has 91% sensitivity for clinical complete response and 100% sensitivity for overall response. The high sensitivity of initial clinical response for prediction of cCR and specificity for prediction of cPD favors its incorporation in clinical practice, as an early predictor of response to NACT in patients with advanced breast cancer. There is a need to study the biology of breast cancer, its response to different therapeutic regimens and the molecular and genetic predictors of its response to chemotherapy in the local population of patients.

References

Alexander W (2009). Meeting highlights: American Society of Clinical Oncology, 45th Annual Meeting. *PandT*, **34**, 379-82.

Altman DG, Bland JM (1994). Diagnostic tests 1: sensitivity and specificity. *BMJ*, **308**, 1552.

Altman DG, Bland JM (1994). Diagnostic tests 2:Predictive values. *BMJ*, **309**, 102

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. *The Oncologist*, **11**, 563-73.

Asakawa H, Koizumi H, Koike M, et al (2010). Prediction of breast cancer sensitivity to neoadjuvant chemotherapy based on status of DNA damage repair proteins. *Breast Cancer Res*, **12**, 17.

Assfalg M, Bertini I, Colangiuli D, et al (2008). Evidence of different metabolic phenotypes in humans. *PNAS*, **105**, 1420-4.

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.

Aziz Z, Sara S, Akram M, et al (2004). Socioeconomic status and Breast Cancer Survival in Pakistani Women. *J Pak Med Assoc*, 54, 448-53.

Aziz Z (2008). Across Generations: Cancer Treatment in Developing Countries. *J Clin Oncol*, **26**, 4990-1.

Beresford MJ, Stott D, Makris A (2008). Assessment of clinical response after two cycles of primary chemotherapy in breast cancer. *Breast Cancer Res Treat*, **109**, 337-42.

Beslija S, Bonneterre J, Burstein HJ, et al (2009). Third consensus on medical treatment of metastatic breast cancer. *Ann Oncol*, **20**, 1771-85.

Bhurgri Y, Bhurgri A, Nishter S, et al (2006). Pakistan - Country Profile of Cancer and Cancer Control 1995-2004. *J Pak Med Asso,* **56,** 124-30.

Caraco Y (2004). Genes and the response to drugs. *N Engl J Med*, **351**, 2867-9.

Cianfrocca MO, Gradishar W (2009). New molecular classifications of breast cancer. *CA Cancer J Clin*, **59**, 303-13.

Deo AVS (2010). Challenges in the treatment of breast cancer in developing countries. *Natl J Med India*, **23**, 129-31.

Doyle JJ, Neugut AI, Jacobson JS, et al (2005). Chemotherapy and Cardiotoxicity in Older Breast Cancer Patients: A Population-Based Study. *J Clin Oncol*, **23**, 8597-8605.

Dowsett M, Dunbier AK (2008). Emerging biomarkers and new understanding of traditional markers in personalized therapy for breast cancer. *Clin Cancer Res*, **14**, 8019-26.

EBCTCG (2005). Early breast cancer trialists collaborative group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15 years survival; an overview of randomized trials. *Lancet*, **365**, 1687-1717.

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.

Esteva FJ, Hortobagyi GN (2008). Can early response assessment guide neoadjuvant chemotherapy in early-stage breast cancer. *JNCI*, **100**, 521-3.

FarmerP, Frenk J, Knaul FM, et al (2010). Expansion of cancer care and control in countries of low and middle income: a call for action. *Lancet*, **376**, 1186-93.

Fiorentino C, Berruti A, Bottini A, et al (2001). Accuracy of mammography and echography versus clinical palpation in the assessment of response to primary chemotherapy in breast cancer patients with operable disease. *Breast Cancer Res Treat*, **69**, 143-51.

Gilani GM, Kamal S, Akhter AS (2003). A Differential Study of Breast Cancer Patients in Punjab, Pakistan. *J Pak Med Assoc*, **53**, 478-80.

Goldhirsch A, IngleJN, Gelber RD, et al (2009). Threshholds for therapies: Highlights of the st.Gallen International expert consensus on the primary therapy of early breast cancer. *Ann Oncol*, **20**, 1319-29.

Graeser M, McCarthy A, Lord CJ, et al (2010). A marker of homologous recombination predicts pathologic complete response to neoadjuvant chemotherapy in primary breast cancer. *Clin Cancer Res*, **16**, 6159-68.

Hayward JL, Carbone PP, Heuson JC, et al (1977). Assessment of response to therapy in advanced breast cancer; a project of the programme on clinical oncology of the international union against cancer, Geneva, Switzerland. *Cancer*, **39**, 1289-94.

Herrada J, Iyer RB, Atkinson EN, et al (1997). Relative value of physical examination, mammography, and breast sonography in evaluating the size of the primary tumor and regional lymph node metastases in women receiving neoadjuvant chemotherapy for locally advanced breast carcinoma. *Clin Cancer Res*, **3**, 1565-9.

Ishitobi M, Komoike Y, Motomura K, et al (2010). Early response to neo-adjuvant chemotherapy in carcinoma of the breast predicts both successful breast-conserving surgery and decreased risk of ipsilateral breast tumor recurrence. *The Breast Journal*, **16**, 9-13.

Khokher S, Mahmood S, Khan SA (2010). Response to Neoadjuvant chemotherapy in patients with advanced breast cancer: A local hospital experience. *Asian Pac J Cancer Prev*, **11**, 303-8.

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.

Labianca R, Gariassino M, Torri V (2008). Predicting response of molecularly targeted therapies: a still possible challenge? *Ann Oncol*, **19**, 829-30.

Lancet (2009). Breast cancer in the developing countries. *Lancet*, **374**, 1567

Mauri D, Pavlidis N, and Ioannidis JPA (2005). Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. *J Natl Cancer Inst*, **97**, 188-94.

McDermott U, Downing JR, Statton MR (2011). Genomics and the continuum of cancer care. *N engl J Med*, **364**, 340-50.

Meisamy S, Bolan PJ, Baker EH, et al (2004). Neoadjuvant chemotherapy of locally advanced breast cancer: Pridicting Response with in vivo 1H MR spectroscopy-A pilot study at 4 T1. *Radiology*, **233**, 424-31.

Miller AB, Hoogstraten B, Staquet M, et al (1981). Reporting results of cancer treatment. Cancer, **47**, 207-14.

Moon YW, Rha SY, Jeung HC,et al (2005). Neoadjuvant chemotherapy with infusional 5-fluorouracil, adriamycin and cyclophosphamide (iFAC) in locally advanced breast cancer: an early response predicts good prognosis. *Ann Oncol*, **16**, 1778-85.

National Breast Cancer Centre. Clinical practice guidelines for the management of advanced breast cancer. Canberra: Commonwealth of Australia:2001

NCCN (2011). National Comprehensive Cancer Network. NCCN Practice Guidelines in Oncology. Breast. Version 2. http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf accessed on 18 january 2011.

Osako T, Horji R, Matsuura M, et al (2010). Common and discriminative clinicopathological features between breast cancers with pathological complete response or progressive disease in response to neoadjuvant chematheraoy. *J Cancer Res Clin Oncol*, **136**, 233-241.

Park JS, Moon WK, Lyou CY, et al (2011). The assessment

of breast cancer response to neoadjuvant chemotherapy: comparison of magnetic resonance imaging and18F-fluorodeoxyglucose positron emission tomography. *Acta Radiologica*, **52**, 21-8

Parkin DM, Bray F, Ferlay J, et al (2005). Global Cancer Statistics 2002. *CA. Cancer J Clin*, **55**, 74-108.

Padhani AR, Hayes C, Assersohn L, et al (2006). Prediction of clinicopathologic response of breast cancer to primary chemotherapy at contrast-enhanced MR imaging: initial clinical results. *Radiology*, **239**, 361-74.

Peppercorn JM, Smith TJ, Helft PR, et al (2011). American Society of clinical oncology statement: Toward individualized care for patients with advanced cancer. J Clin Oncol DOI:10.1200/JCO.2010.33.1744.

Rakha EA, Reis-Filho JS, and Ellis IO (2010). Combinatorial biomarker expression in breast cancer. *Breast Cancer Res Treat*, **120**, 293-308.

Raut NV and Chordiya N (2010). Neo adjuvant chemotherapy in breast cancer: What have we learned so far? *Indian J Med Paediatr Oncol*, **31**, 8-17.

Rousseau C, Devillers A, Sagan C, et al (2006). Monitoring of early response to neoadjuvant chemotherapy in stage II and II breast cancer by [18F]Fluorodeoxyglucose Positron Emission Tomography. *J Clin Oncol*, **24**, 5366-72.

Pruthi S, Boughey JC, Brandt KR, et al (2007). A Multidisciplinary Approach to the Management of Breast Cancer, Part 2; Therapeutic Considerations, Mayo Clin Proc. **82**, 1131-40.

Rustogi A, Budrukkar A, Dinshaw K, et al (2005). Management of locally advanced breast cancer: evolution and current practice. *J Cancer Res Ther*, **1**, 21-30.

Sharma S, Hiran KR, Pavithran K, et al (2009). A pilot study to assess the feasibility of evaluation of markers of response to chemotherapy at one day and 21days after first cycle of chemotherapy in carcinoma of breast: a prospective non-randomized observational study. World Journal of Surgical Oncology.7:35 doi:10.1186/1477-7819-7-35.

Schwarz JD, Bader M, Jenicke L, et al (2005). Early prediction of response to chemotherapy in metastatic breast cancer using sequential 18F-FDG PET. *J Nucl Med*, **46**, 1144-50.

Shin HJ, Kim HH, Ahn JH, et al (2010). Comparison of mammography, sonography, MRI and clinical examination in patients with locally advanced or inflammatory breast cancer who underwent neoadjuvant chemotherapy. The British Journal of Radiology. doi:10.1259/bjr/74430952.

Sjoblom T, Jones S, Wood LD, et al (2006). The consensus coding sequences of human breast and colorectal cancers. *Science*, **314**, 268-74.

Smith IC, Heys SD, Hutcheon AW, et al (2002). Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. *J Clin Oncol*, **20**, 1456-66.

Sperber F, Weinstein Y, Sarid D, et al (2006). Preoperative clinical, mammographic and sonographic assessment of neoadjuvant chemotherapy response in breast cancer. *IMAJ*, **8**, 342-6.

Tan SH, Lee SC, Goh BC, et al (2008). Pharmacogenetics in breast cancer therapy. *Clin Cancer Res*, **14**, 8027-41.

Von Minckwitz G, Blohmer JU, Raab G, et al (2005). In vivo chemosensitivity-adapted preoperative chemotherapy in patients with early-stage breast cancer: the GEPARTRIO pilot study. *Ann Oncol*, **16**, 56-63.

Von Minckwitz G, Kummel S, Vogel P, et al (2008). Intensified neoadjuvant chemotherapy in early-responding breast cancer: Phase III randomized GaperTrio Study. *JNCI*, **100**, 552-62.

Von Minckwitz G, Sinn HP, Raab G, et al (2008). Clinical response after two cycles compared to HER2, Ki-67, p53, and bcl-2 in independently predicting a pathological complete response after preoperative chemotherapy in patients with operable carcinoma of the breast.Breast Cancer Res.10:R30 doi:10.1186/bcr1989.

WHO Screening for breast cancer. [Online] (2008). Available from: http://www.who.int/cancer/detection/breastcancer/en/. Accessed on 25-11-2010.

Yu HJ, Chen JH, Mehta RS, et al (2007). MRI measurements of tumor size and pharmacokinetic parameters as early predictors of response in breast cancer patients undergoing neoadjuvant anthracycline chemotherapy. *Journal of Magnetic Resonance Imaging*, **26**, 615-23.