ORIGINAL ARTICLE

Correlation between Neoadjuvant Chemotherapy Response and ER, PGR and Her-2 Expression in Breast Cancer

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ABSTRACT

Aim: To evaluate predictive values of histopathologic markers Estrogen receptors (ER), Progesterone receptors (Pgr) and Her2 in clinical and pathologic response of breast cancers treated with neoadjuvant anthracycline based chemotherapy (NAC).
Study design: Comparative Cross-sectional Study
Place and duration of study: FMH College of Medicine & Dentistry and Ittefaq Hospital, Lahore between 2011 and 2012.
Methods: Pretreatment core biopsy was obtained on 56 patients with unresected breast cancer. Histologic features and immunohistochemical stains for ER, Pgr, and Her2 were obtained. All patients received anthracycline-based chemotherapy regimen with 5-fluorouracil, adriamycin or epirubicin, and cyclophosphamide 4 to 6 cycles before surgery. The pathologic response in the surgical excision specimen was assessed using Miller Pyane System of classification for neoadjuvant chemotherapy.
Results: Tumors with negative ER and Pgr status responded better to neoadjuvant therapy as compared to ER and Pgr positive tumors.
Conclusions: The prediction of the efficacy of chemotherapy based on evaluation of hormonal receptor status can help us select patients who are likely to respond well to this mode of treatment. It can also predict patients who are unlikely to benefit from the treatment and thus save them from undesired chemotherapy effects.
Keywords: Breast Cancer, Estrogen Receptors, Progesterone Receptors, Her2, NAC.

INTRODUCTION

Neoadjuvant chemotherapy has been used as a primary treatment for locally advanced breast cancer; recently it's been extended to operable breast cancer[1,2,3]. Neoadjuvant chemotherapy for locally advanced breast cancer has become a model for testing novel therapeutic regimen, as pathologic complete response (pCR) in an excellent intermediate end point (surrogate marker) to test effectiveness of therapy[1]. It is important to identify factors (predictive markers) that may predict the response to neoadjuvant therapy. These factors should identify patients who will benefit mostly from treatment, and would permit a tailored approach in selecting the initial therapy that may yield the best clinical and pathological response and subsequent overall survival[4]. This study was designed to evaluate predictive values of histopathologic markers Estrogen receptors (ER), Progesterone receptors (Pgr) and Her2 in clinical and pathologic response of breast cancers treated with neoadjuvant anthracycline based chemotherapy (NAC). The pathological complete response (pCR) is an indicator of favorable of predicting a pCR, such as the endocrine markers ER, Pgr and Her2, may be helpful in improving our understanding of the drug response and its effect on the prognosis.

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METHODS

Fifty six patients were included in the study. Inclusion criteria were patients with breast cancer. All patients had unresected disease and were considered candidates for preoperative chemotherapy. Pretreatment core biopsy was done. The histologic features including tumor type and histologic grade (Nottingham grading system) were recorded. Immunohistochemical stains for ER, Pgr, and Her2 were obtained on the initial core biopsy. HER2 positivity is defined as 3+ markedly positive in more than 30% of tumor cells. All patients received anthracycline-based chemotherapy regimen with 5-fluorouracil, adriamycin or epirubicin, and cyclophosphamide (FAC/FEC) 4 to 6 cycles before surgery. Tumor measurements were performed by physical examination at the baseline and after final cycle of neoadjuvant chemotherapy. The pathologic response in the surgical excision specimen was performed using Miller Pyane System of classification for neoadjuvant chemotherapy which is divided into 5 grades. Grade 5 complete pathological response

(pCR): no residual invasive tumor identified either in the breast or the lymph nodes, grade 4> 90% response, grade 3, 30-60% response, grade 2, upto 30% response, grade 1 less than 5%.

RESULTS

After 4-6 cycles of chemotherapy (pCR) was seen in 21% of patients and partial response was observed in 79% of the patients. Tumors with negative hormone receptor status responded better to neoadjuvant therapy as compared to ER and Pgr positive tumors. Therefore according to our observation negative hormone receptor status can be a predictive marker for response to neoadjuvant chemotherapy. HER2 positive status is not a consistent predictor of response to neoadjuvant chemotherapy.

Table1: ER/Pgr/ Her2 and pCR

Baseline Feature	=n	pCR	P
Overall	58	18 (31%)	
ER/Pgr Absent	16	10 (63%)	
ER/Pgr weak Positive	42	8 (19%)	0.029
Her2 Negative	36	12 (33%)	0.724
Her2 Positive	22	6 (27%)	

Fig 1: Nuclear positive staining for estrogen receptor.

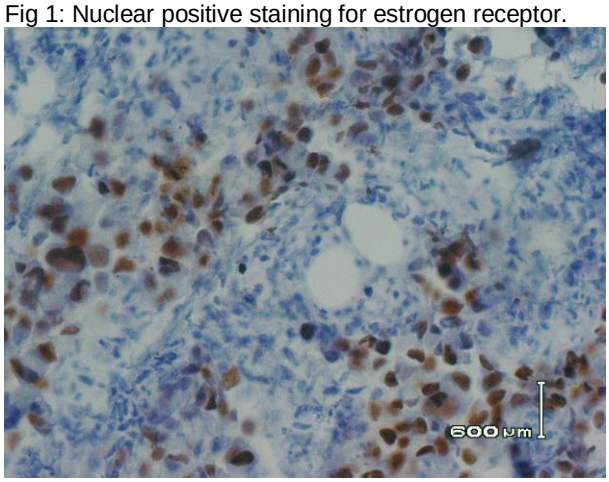


Fig 2: Nuclear positive staining for progesterone receptor.

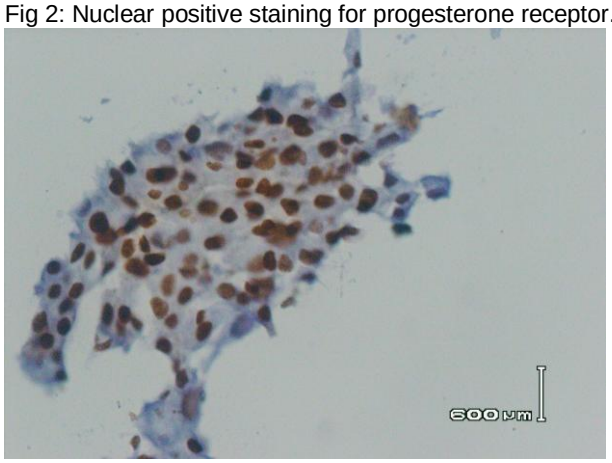
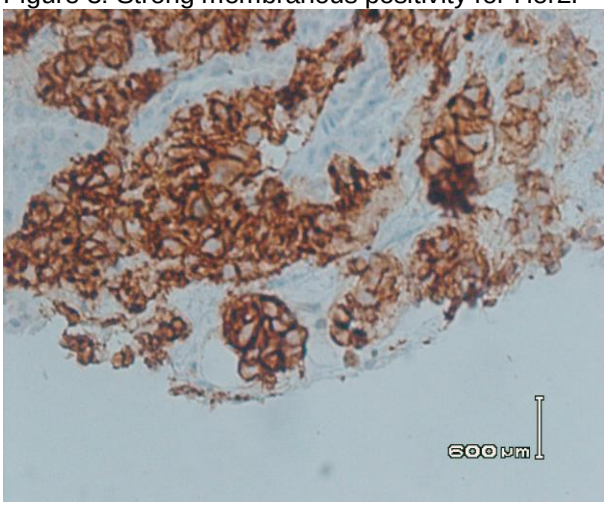


Figure 3: Strong membranous positivity for Her2.



DISCUSSION

Breast cancer is the most frequent malignancy in women worldwide, it accounts for 20-25% of malignant tumors in women with annual incidence of about 800 - 1000 cases. Neoadjuvant chemotherapy is the standard of care for locally advanced breast cancer and is now being used increasingly for even operable breast cancers. It has improved breast conservation rates by 5-10% and allowed early assessment of treatment. It seems that it will become standard of care even for operable breast cancers. It shows better results in terms of the rate of response to treatment and a reduction in the requirement of mastectomy[1,2]. In future we would be looking to have optimal markers for various breast cancer phenotypes. Our interest is to allow therapy adjustments to improve outcome. So question is when to do therapy, how to determine the need for it, and the need to change treatment?

This study is merely an effort to establish an association between marker, treatment, and clinical outcome, in which marker mediates relationship between clinical outcome and treatment. Not all markers are appropriate for surrogate role so how to look for markers appropriate for this role. Patients who achieved pCR clearly have better survival rates than patients who do not[5].

Symmon in one of his articles stated that, the role of pathological response as a surrogate for survival can be refined by the use of standardized pathology measures after PST[6].

So if pCR rate increases, will survival rate increase too? Is pCR of prognostic value in patients with ER+ breast cancer or those treated with endocrine therapy? And the most important question, patients who achieve pCR be treated with less therapy?

In our study we focused on ER, Pgr and Her2 and tried to assess the role of these markers as predictive markers as a way of identifying tumor subtypes in breast cancer. The key is selection of patient population for various therapy options.

Alvarado et al[2] reported in a study of 205 patients that a reduction in tumor size occurred in 40% of patients, 12% had a cCR, and 28% a cPR, only 8% had no histologic evidence of residual invasive primary breast carcinoma or axillary metastases after 4 cycles of NAC (pCR), this result is comparable with our study. The pCR rates by neoadjuvant chemotherapy reported in the past were around 20% or less[7,8,9,10,11,12]; if we give neoadjuvant chemotherapy only for patients who are likely to benefit from it, we could obtain a high pCR rate and avoid the undesirable side effects of chemotherapy.

Neoadjuvant chemotherapy provides an excellent model for evaluation of potential predictive factors. Information on the differential histologic response of primary breast tumors and axillary metastases to NAC is limited[4].

In the present series, 31% of the patients had a pCR. There is a paucity of published data concerning the incidence and outcome of patients with a pCR in the primary tumor and axillary lymph nodes after NAC.

Fisher et al[14] found a 7% rate of pCR in the primary tumor and axillary lymph nodes in 185 patients with local operable breast cancer and clinically positive axillary lymph nodes. There is data that suggests that steroid receptor negativity predicts chemosensitivity. Colleoni et al[14] have demonstrated, like in our study, that tumors negative for ER and Pgr receptors demonstrated clinical and pCR rates superior to that of ER-positive tumors. Several other studies have also demonstrated a statistically greater response rate to NAT in steroid-receptor-negative patients[15]. Kuerer et al [16] reported, like in our study, that ER-negative patients obtained a higher pCR rate than ER-positive patients with doxorubicin-containing neoadjuvant chemotherapy.

Data in the neoadjuvant settings are conflicting when it comes to HER2 and its effect on NAT. Estevez et al[17] found no association between overexpression of HER-2 and the clinical and, pathological response

Four randomized studies in the adjuvant setting showed that HER2-positive patients obtained more benefit from anthracycline-containing chemotherapy than HER2-negative patients[18]. In contrast, Zhou B et al[4] reported that overexpression of HER2 and negative hormonal receptor status is much more likely to respond to neoadjuvant chemotherapy. It is clear that the impact of HER2 on response to NAT should be tested in a greater number of prospective trials to make a final conclusion.

The prediction of the efficacy of chemotherapy can properly select good candidates who will respond well to the treatment and also can exclude poor candidates who will have undesirable side effects instead of the benefits by the treatment[16].

CONCLUSIONS

Limited information is available regarding tailoring treatment for an individual patient. Response to neoadjuvant therapy varies in different tumor subpopulations. Major contrast is between endocrine responsive and endocrine non-responsive tumors. Definition of specific predictors of response is the key for future trials.

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