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ORIGINAL ARTICLE

Discordance of Estrogen & Progesterone Receptors After Neoadjuvant Chemotherapy in Breast Cancer- an Indian Study

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Abstract Neoadjuvant chemotherapy forms the initial modality of treatment for primarily inoperable locally advanced breast cancer (LABC). Breast cancer is characterized by cellular heterogeneity. A change in hormone receptor status after neoadjuvant chemotherapy (NACT) has important therapeutic and prognostic consequences. Data on the influence of neoadjuvant chemotherapy on estrogen receptors (ER) and progesterone receptors (PR) are limited. The primary objective of this study is to compare hormone receptor (HR) status before and after neoadjuvant chemotherapy (discordance) in Indian patients. The secondary objective is to study correlation between tumor response and hormone receptor expression. This is a descriptive study of 78 LABC patients who received neoadjuvant chemotherapy from October 2012 to October 2014. All patients who underwent core biopsy and ER/PR assessment before and after NACT were included in the study. Data was collected prospectively from each patient in a structured proforma. Patients were classified as Group A (ER+, PR+), Group B (ER+, PR-), Group C (ER-, PR+), Group D (ER-, PR-). The HR discordance rate & response to neoadjuvant chemotherapy was assessed. Total HR discordance rate was 21.7 %. The ER discordance was 8.7 % and PR discordance was 13 %. PR positive to PR negative discordance was the predominant one. The pathological complete remission (pCR) rate of endocrine responsive patients was 10.2 % and in the endocrine unresponsive group it was 13.8 %. ER/PR status can change after chemotherapy, hence they need to be re-evaluated after neoadjuvant chemotherapy. This becomes therapeutically important when receptor negative becomes positive.

Keywords Breast cancer · ER · PR · Discordance · Neoadjuvant chemotherapy

Introduction

Breast cancer is a major public health problem for women throughout the world. Worldwide, breast cancer is the most common type of cancer and the most common cause of cancer-related mortality among women [1]. In India as per the ICMR-PBCR data, breast cancer is the commonest cancer among women in urban registries where it constitutes >30 % of all cancers in females [2]. In developing countries more than 50 % of the breast cancer patients present as locally advanced breast cancer (LABC) at diagnosis. Neoadjuvant chemotherapy (NACT) forms the first modality of treatment for LABC patients. Neoadjuvant chemotherapy has shown to alter several biological factors of breast cancer. One of the most important biological factors in breast cancer is hormone receptor (HR) [3]. Estrogen receptor (ER) and progesterone receptors (PR) are both predictive and prognostic markers [4]. Traditionally quantitative assay of ER/PR expression is done by immunohistochemistry (IHC). It forms a part of the initial work up of a breast cancer patient. As they play a crucial role in the treatment of breast cancer, a change in its expression after chemotherapy is of significance. This seems more significant therapeutically, when the discordance is from negative to positive receptor. The aim of this study is to get a better picture of the discordance of the hormone receptor in Indian patients, as studies are sparse in this regard. Another objective is to evaluate the correlation if any, with hormone receptor

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Table 1 Patient and tumour characteristics

Characteristics	Frequency (%)
Age group (yrs)	
≤35	8 (10.3)
36–45	13 (16.7)
46–55	30 (38.5)
56–65	19 (24.3)
66–75	7 (8.9)
76–85	1 (1.3)
Menopausal status	
Postmenopausal	45 (57.7)
Premenopausal	33 (42.3)
Side of breast cancer	
Left side	41 (52.6)
Right side	36 (46.1)
Bilateral	1 (1.3)
Histology	
Invasive ductal carcinoma	76 (97.4)
Lobular carcinoma	2 (2.6)
Grade	
Grade 1	4 (5.1)
Grade 2	46 (59.0)
Grade 3	11 (14.1)
Group A (ER+,PR +)	35 (44.9)
Group B (ER+,PR-)	7 (9.0)
Group C (ER-,PR+)	7 (9.0)
Group D (ER-,PR-)	29 (37.2)
Pathological complete response	
Endocrine responsive (Group A, B, C)	5 out of 49 (10.2 %)
Endocrine non responsive (Group D)	4 out of 29 (13.7 %)

expression and tumor response to primary systemic chemotherapy.

Patients and Methods

Patients Seventy eight patients satisfying the inclusion and exclusion criteria were included in the study from October 2012 to October 2014. Inclusion criteria were, primarily inoperable locally advanced female breast cancer patients, who underwent core biopsy before neoadjuvant chemotherapy, ER/PR assay done by immunohistochemistry as per the recommendations of American Society of Clinical Oncology (ASCO) [5] and those who underwent surgery there after. Exclusion criteria included those patients who did not undergo a core biopsy& ER/PR assay, who had received prior hormonal therapy and those patients who remained inoperable even after neoadjuvant chemotherapy.

Methods An informed consent was received from all patients willing for the study. A structured proforma with the variables like age, patient characteristics, histological subtype, tumor size, grade, margins, tumor emboli, nodal status, stage and molecular factors like estrogen receptor, progesterone receptor status were used. Data was collected prospectively, starting from the day of registration for treatment. Patient master files, histopathology reports and hormone receptor IHC reports were analyzed. Any ambiguity in the histopathology and IHC reports were cleared after discussion with the pathologists. Immunohistochemical analysis was done on both core biopsy specimen and post mastectomy specimen for each patient. Before starting chemotherapy trucut biopsy was taken from two cores of the lump and receptor assay was done on both the cores if tumour cells were present. In those cases which did not initially show tumour cells, the truct procedure was repeated before starting chemotherapy. According to ASCO recommendation ER & PR assays are considered positive if there are at least 1 % positive tumour nuclei in the sample on testing in the presence of expected reactivity of internal and external controls [5]. Those patients, who attained complete pathological response, were unable for post-chemotherapy hormone assay due to absence of tumor cells. So that set of patients was excluded from analysis for discordance rate. Patients were classified based on their pre-chemotherapy hormone receptor status as Group A (ER+, PR+), Group B (ER+, PR-), Group C (ER-, PR+), Group D (ER-, PR-). This classification is for the purpose of assessment of response to neoadjuvant chemotherapy in each group and to study correlation between tumor response and hormone receptor status. Statistical analysis was carried out using SPSS version 21.0. software.

Results

The mean age of patients in this study was 51.3 years. 57.7 % of patients were post menopausal, 42.3 % were pre- menopausal. 97.4 % had intraductal carcinoma and remaining were had invasive lobular carcinoma. Histology grade was grade 1 in 5.1 %, grade II in 59 % and grade III in 14.1 % patients (Table 1).

Table 2 Estrogen receptor status before and after chemotherapy

Receptor status	Pre chemo	Post chemo	Change (rate)	ER discordance rate
ER positive	37	34	3/37 (8.1 %)	6/69 (8.7 %) $p = 1.0$
ER negative	32	29	3/32 (9.4 %)	

Table 3 Progesterone receptor status before and after chemotherapy

Receptor status	Pre chemo	Post chemo	Change (rate)	ER discordance rate
PR positive	37	29	8/37 (21.6 %)	9/69 (13.04 %) $p = 0.019$
PR negative	32	31	1/31 (3.2 %)	

Of the 78 patients recruited for the study 9 patients had pathological complete remission. Hence only 69 patients were assessed for the discordance. Before chemotherapy 37 patients were ER positive. Of this 34 (91.9 %) remained as ER positive and 3 (8.1 %) became ER negative after NACT. Out of 32 pre chemotherapy ER-ve patients, 29 (90.6 %) remained ER-ve and 3(9.4 %) became ER + ve. So a total of 6 patients (8.7 %) had change in ER receptor status (ER discordance) following neoadjuvant chemotherapy (p value = 1.0) (Table 2).

Out of 37 pre chemotherapy PR positive patients, 29 (78.4 %) remained positive and 8 (21.6 %) became negative. Of the 32 pre chemotherapy PR-ve patients, 31 (96.9 %) remained negative as such while 1 (3.2 %) became positive. Total change in PR status (PR discordance) following neoadjuvant chemotherapy was in 9 patients (13.04 %) (p value = 0.019). The total discordance rate of ER and PR together is 21.74 % in our study (Table 3).

The positivity staining pattern of tumour cells having more are depicted in Tables 4, 5 and 6. It reveals that the tumours which had discordance showed more than 40 % positive staining, except 1 out of the 15 discordances.

Out of 78 patients, 9 (11.5 %) achieved pCR. Of the 9 patients who achieved pCR 5 were in Group A (ER +, PR+), 4 were in Group D (ER-, PR-). Of the total 49 endocrine responsive patients 5 patients (10.2 %) had pCR. Of the 29 endocrine unresponsive patients, 4 patients (13.8 %) had pCR (p value = 0.910).

Discussion

The objective of this study is to assess the changes in hormone receptor status (i.e. discordance) in patients who had undergone neoadjuvant chemotherapy for breast cancer in our institution. We had a total of 78 patients recruited in our study. As per the literature, the studies that evaluated discordance of ER, PR receptors after NACT, had a study population ranging from a minimum of 18 patients to a maximum of 459 patients (Hirata et al.) [6]. Most patients in this study were in 46–55 years age group. Mean age was 51.3 years. This is approximately a decade younger than the west [7]. This is likely to be due to the different age distribution of Indian population, where only 7 % of the population is above the age of 60 years. Most of the patients were post menopausal (57.7 %) as in most of the previous trials. In Neubauer et al. trial 58 % of patients was post menopausal [8].

Left breast cancers were more common (52.6 %) in our study and this is at par with the literature. Invasive ductal carcinoma (IDC) was the predominant histology (97.4 %). Only 2.6 % had invasive lobular carcinoma. In the Neubauer et al. trial 71 % were IDC, 19 % lobular, and 10 % other subtypes.

In our study 49 % patients belonged to Group A (ER+, PR+ group) followed by Group D 37.2 % (ER-, PR-) Group B (ER+, PR-group) & Group C (ER- PR+ Group) 9 % each. Therefore, the incidence of endocrine responsive breast cancer patients (pre-chemotherapy) in our study was 62.8 %. When compared to western population the endocrine responsiveness of Indian population is less [9, 10]. In Hirata et al. study, Group A constituted 50 %, group D 34 % Group B & Group C together constituted 16 %. Thus endocrine responsive tumors constituted 66 % which is almost similar to our study.

In our study change in ER receptor status (ER discordance) following NACT was 8.7 %. Change was more or less similar in ER positive and ER negative subgroup. Change in the PR status (PR discordance) following NACT was 13 % which is statistically significant ($p = 0.019$). Change was higher in PR positive to PR negative (21.6 %) when compared to PR negative to PR positive (3.1 %) In the Neubauer et al. study, the ER discordance noted was 8 % and PR discordance was 18 %. Our results are nearly similar with this study. But in Hirata et al. study, which was the largest study conducted ER discordance rate, was 14.9 % and PR discordance rates 29.1 %. It is observed that PR discordance is significantly higher in all the studies reviewed, of which PR positive changing to PR negative was the predominant one [11]. Indian study by Tanuja et al. also reveals that PR discordance is higher, that is 20.5 % while ER discordance was only 12.8 % [12].

Hirata et al. study showed that prognosis of patients with change in HR status after NACT but who did not receive endocrine therapy (ET) accordingly was worse than that who received ET. In our study the impact of long term out come in change in HR following NACT was not a study

Table 4 Tumour cells positive for ER/PR before chemotherapy for all receptor positive tumours

Receptor	1–39 % positivity	40–59 % positivity	60–79 % positivity	80–100 % positivity
ER ($n = 37$)	6 (16.2 %)	7 (18.9 %)	9 (24.3 %)	15 (40.5 %)
PR ($n = 37$)	8 (21.6 %)	9 (24.3 %)	11 (29.7 %)	9 (24.3 %)

Table 5 Tumour cells positive for ER/PR for discordant tumours before chemotherapy

Receptor	Before chemotherapy			
% cells stained	1–39 %	40–59 %	60–79 %	80–100 %
ER discordance ($n=3$)	–	1	1	1
PR discordance ($n=8$)	1	2	2	3

objective. This aspect will be addressed in our follow up future study.

In our study, pathological complete remission was higher in non-endocrine responsive than endocrine responsive group which was statistically not significant ($p=0.910$). Several other studies like Guarneri et al. and Ring et al. [13] has also shown that pCR rate is high in endocrine nonresponsive patient.

Conclusions

The hormone receptor status of breast cancer patients may change after neoadjuvant chemotherapy. Thus, hormone receptor status should be evaluated, not only in the biopsy specimen obtained before initiation of neoadjuvant chemotherapy (NACT), but also in specimens obtained after neoadjuvant chemotherapy. Our study has shown significant discordance in hormone receptor status following primary systemic therapy. The reason for this discordance is not well understood. This study throws light to the fact that tumour biology may change with treatment. It is also well studied that tumour biology may change when patient becomes metastatic. This explains why when a patient becomes metastatic, it is better to rebiopsy from the metastatic site and repeat ER, PR and Her -2 assay. Discordance may be due to chemotherapy either directly or indirectly changing biology of the tumour cells or causing selection of resistant tumour cells in the residual disease. A change in receptor status might have important clinical consequences for adjuvant systemic treatment especially when hormone negative patient become positive. So this study justifies retesting of receptor status in residual disease after NACT. Retesting of receptor status should definitely be considered in situations where this might be of clinical relevance, particularly in ER negative and/or PR negative tumors. More randomized controlled trials with more number of patients must be done for exploring the possible mechanisms of hormone receptor discordance. This study also reveals the fact that hormone receptor negative patients have got more pCR than hormone receptor positive patients.

Table 6 Tumour cells positive for ER/PR for discordant tumours after chemotherapy

Receptor	After chemotherapy			
% cells stained	1–39 %	40–59 %	60–79 %	80–100 %
ER discordance ($n=3$)	–	2	–	1
PR discordance ($n=1$)	–	–	1	–

Compliance with Ethical Standards

Disclosure The authors have declared no conflicts of interest.

Ethical Approval The study was approved by the institutional human ethics committee and institutional review board. All procedures performed in the study were in accordance with the ethical standards of the institutional ethics committee and with the 1964 Helsinki declaration and comparable ethical standards.

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