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PREDICTING RESPONSE TO NEOADJUVANT CHEMOTHERAPY IN OPERABLE BREAST CANCER: ROLE OF ER, PR, HER2 AND KI-67 INDEX

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ABSTRACT

Background: Neoadjuvant (anterior or pre-operative) chemotherapy for operable breast cancer helps in down-staging of the tumor and increases the rate of breast conservation surgery. Factors that identify individuals who benefit from chemotherapy have not been clearly established. This study was conducted to assess the role of estrogen receptor, progesterone receptor, HER2 and Ki-67 index in predicting response to a standard anthracycline and taxane-based chemotherapy. **Methods:** The study included 62 women with clinical tumor stage 1-3 and nodal stage 0 or 1. All women received preoperative anthracycline and taxane-based chemotherapy followed by surgery. Clinical and pathological response was assessed using World Health Organization (UICC) and Chevallier's criteria respectively. **Results:** Clinical and pathological complete response rates were 40.3% and 17.7% respectively. The pathological complete response was highest in HER2-enriched patients (45.45%) while basal-like and luminal B subtypes accounted for 27.27% each. Among those that achieved pathological complete response, 90% had Ki-67 >20, 81.8% had grade 3, 72.7% had ER negative status, 81.8% had PR negative status, 63.6% had HER2 positive status. However, there was no statistically significant association between preoperative clinical tumor size(p=0.98), ER(p=0.053), PR(p=0.17), HER2(p=0.17), Ki-67 index(p=0.26) and pathological complete response. **Conclusion:** A high pathological complete response was observed in tumors with high grade, high proliferative activity (high Ki-67), ER/PR negative status, HER2 over-expressing tumors and aggressive molecular subtypes such as basal-like and HER2-enriched breast cancer. However, none of these pre-chemotherapy factors showed statistically significant association with pathological complete response.

KEYWORDS

Neoadjuvant chemotherapy, Ki-67 index, Predictors of response

INTRODUCTION

Advances in the treatment strategies of breast cancer have resulted in improved survival. Chemotherapy is an important component of multimodality management of breast cancer. It results in improved overall survival and disease-free survival by eradicating occult micro-metastases. It can be given either in the adjuvant or neoadjuvant setting without any difference in overall survival as shown by National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 and NSABP B-27 trials [1, 2]. Benefits of neoadjuvant chemotherapy include down-staging of the tumor, increased performance of breast conservation surgery, earlier treatment of possible micro-metastases, in vivo assessment of response to chemotherapy and identification of markers of response to chemotherapy [1].

Individuals who achieve complete pathological response following neoadjuvant chemotherapy are likely to have better survival than those with residual disease. A complete pathological response has been shown to be a surrogate marker for overall survival [1]. This has led to a decrease in the duration of follow up and cost of trials. It is important to identify markers that predict pathological complete response to chemotherapy so that non-responders can be spared the toxic effects of chemotherapy.

Predictive markers are those that identify patients who are more likely to respond to a given therapy. Common predictive markers that are used in the management of breast cancer are estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor (HER2) status which are useful in selecting patients for adjuvant hormonal therapy and targeted therapy respectively. However, no reliable marker has been validated till now that can identify patients who may benefit from chemotherapy. Discordant results have been reported with regard to the predictive nature of various markers possibly because of a heterogeneous patient population, different chemotherapy regimen used and the retrospective nature of most of the studies.

This study was undertaken to study the role of ER, PR, HER2, and Ki-67 index in predicting response to anthracycline and taxane-based neoadjuvant chemotherapy in operable breast cancer. To our knowledge, this is the first prospectively conducted study in South Indian population evaluating response to neoadjuvant chemotherapy and its predictive factors.

MATERIALAND METHODS

The study included 62 consecutive women with invasive breast cancer with clinical tumor (T) stage 1-3 and nodal (N) stage 0 or 1. Patients with a past history of breast cancer, pregnant and those who underwent initial treatment outside our institute including biopsy were excluded from the study. Institutional review board-ethical committee approval was obtained prior to the commencement of the study. Informed consent was obtained from all individual participants.

All patients were evaluated clinically and radiologically using sonomammogram. Calipers were used to measure bidimensional tumor size. A core needle biopsy was done for histological confirmation of invasive breast cancer. Histological grading was done based on Scarff-Bloom Richardson grading system.

Immunohistochemical analysis for ER, PR, HER2, and Ki-67 index were performed on sections of formalin fixed paraffin embedded tissue from core needle biopsies using standard immunohistochemical methods. ER and PR were considered positive if at least 1% of tumor cells showed nuclear staining [3]. With respect to HER2 status, all 3+ reactions were considered to be positive results. HER2 status of 0 and 1 were considered negative. If Her2 status was 2+, Fluorescent in Situ Hybridization (FISH) was performed [4].

Assessment of Ki-67 index was made according to the recommendations proposed by International Ki-67 in Breast Cancer Working Group (IKBCWG) [5]. MIB1 was used as an antibody for IHC. Counting was done in 3 randomly selected high power fields. Tumor cells which showed nuclear staining were counted irrespective of the intensity of staining. A total of 500 tumor cells were counted and the Ki-67 index was described as the percentage of the total number of tumor cells with nuclear staining. It was categorized into high and low levels based on a cut-off of 20% which was obtained using the Receiver Operating Characteristic (ROC) curve having area under the curve as 59.2% with a sensitivity of 90.9% and 1-specificity of 72.5% (Figure 1).

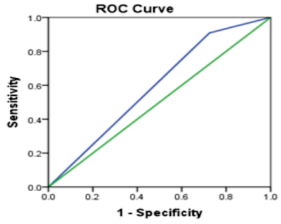

Fig. 1 Receiver Operating Characteristic (ROC) Curve For The

Pathologic Complete Response To Chemotherapy Using Ki-67 Index. Area Under Roc Curve Was 0.592.

We divided breast cancer into different molecular subtypes based on ER, PR, and HER2 status. Tumors with positive ER and/or PR receptor and negative HER2 receptor were classified as luminal A subtype. Those with positive ER and/or PR receptor and positive HER2 receptor were classified as luminal B subtype. Tumors which were ER and PR receptor negative and HER2 receptor positive were labeled as HER2-enriched tumors. Tumors which were negative to ER, PR, and HER2 were classified as the basal-like subtype.

All patients received anthracycline and taxane-based neoadjuvant chemotherapy. The common neoadjuvant chemotherapy regimen used were 3 cycles of FEC [5-Fluorouracil (600 mg/m2), Epirubicin (60 mg/m2), Cyclophosphamide (600 mg/m2)] IV every 3 weeks plus 3 cycles of Docetaxel (75 mg/m2) IV every 3 weeks or 4 cycles of AC [Doxorubicin (60 mg/m2), Cyclophosphamide (600 mg/m2)] IV every 3 weeks plus 4 cycles of Docetaxel (75 mg/m2) IV every 3 weeks. Endocrine therapy wasn't a part of neoadjuvant therapy. In patients whose tumor was HER2 receptor positive, Trastuzumab was given along with neoadjuvant chemotherapy (loading dose of 8 mg/kg IV over 90 min followed by 6 mg/kg IV over 30 min every 3 weeks). Trastuzumab was omitted in patients who were not affordable.

Evaluation Of Response To Chemotherapy

Calipers were used to measure bidimensional tumor size before initiating chemotherapy, after every two cycles and at the completion of chemotherapy. Clinical response assessment was made based on World Health Organization (UICC) criteria [6]. Complete response (CR) was defined as no residual palpable or radiological abnormality. Partial response (PR) was defined as greater than 50% decrease in bidimensional tumor size. Those tumors which didn't show any decrease in tumor size or decreased by less than 50% were defined as having stable disease (SD). Tumors which showed an increase in tumor size by greater than 25% were defined as progressive disease (PD).

Pathological response assessment was made using Chevallier method [7]. Tumors with no evidence of invasive cancer or ductal carcinoma in situ (DCIS) either in the breast or axillary lymph nodes were graded as Grade 1. Residual DCIS in tumor with no focus of invasive tumor or DCIS in axillary nodes were labeled as Grade 2. Grade 3 tumors were those with a residual component of the invasive tumor with stromal fibrosis. Tumors that showed no or few modifications were classified as Grade 4. Pathological complete response (pCR) definition included Grade 1 and Grade 2 tumors. Grade 3 tumors corresponded to partial response (PPR) while Grade 4 tumors were those having stable disease (PSD).

Surgery, either modified radical mastectomy (MRM) or breast conservation surgery (BCS), was performed at least four weeks after the last chemotherapy cycle. Adjuvant Chemotherapy and Radiotherapy was given to all patients according to institution policy. Adjuvant Endocrine therapy was given to those with either ER or PR positive receptor status. According to institution policy Trastuzumab is given to all patients with HER2 positive tumors. However, Trastuzumab was omitted in patients who could not afford the drug.

Statistical Analysis

Statistical analysis was performed using IBM SPSS v20 software. Chi-square test or Fisher's exact test was used to assess the relationship between predictive factors and clinical/pathological response. A p value of <0.05 was considered significant.

RESULTS

Overall, 62 patients were included in the study (Table 1). The average age of the patient was 50.38 years ranging from 23 to 80 years. Average Ki-67 index was 36.59 ranging from 7 to 90. Most (75.8%) of the patients had a high Ki-67 index.

Table 1: Patient Characteristics

	n= 62 (%)
Age	
<50 years	28 (45.1)
>50 years	34 (54.8)
Clinical Tumor Size	
T1 = <2 cm	0 (0)
T2 = 2-5 cm	28 (45.1)
T3 = >5 cm	34 (54.8)
Clinical Stage	
1	0 (0)
2	33 (53.2)
3	29 (46.7)
Surgery	
Modified radical mastectomy	52 (83.8)
Breast conservation surgery	10 (16.1)
Pathological Tumor Stage (ypT)	
T0 = 0	16 (25.8)
T1 = <2 cm	12 (19.3)
T2 = 2-5 cm	28 (45.1)
T3 = >5 cm	6 (9.6)
Pathological Nodal Status	
Involved	38 (61.2)
Uninvolved	24 (38.7)
Pathological Nodal stage	
0	24 (38.7)
1	22 (35.4)
2	11 (17.7)
3	5 (8.06)
Pathological Stage	
0	12 (19.3)
1	4 (6.4)
2	25 (40.3)
3	21 (33.8)
Clinical Response	
Complete Response	25 (40.3)
Partial Response	30 (48.3)
Stable Disease	7 (11.2)
Progressive Disease	0 (0)
Pathological Response	
Chevallier Grade 1	10 (16.1)
Chevallier Grade 2	1 (1.6)
Chevallier Grade 3	51 (82.2)
Chevallier Grade 4	0 (0)
Estrogen Receptor	
Positive	34 (54.8)
Negative	28 (45.1)
Progesterone Receptor	
Positive	25 (40.3)
Negative	37 (59.6)
Human epidermal growth factor receptor	
Positive	26 (41.9)
Negative	36 (58.06)
Molecular Subtype	
Luminal A	5 (8.06)
Luminal B	30 (48.3)
HER2-enriched	16 (25.8)
Basal-like	11 (17.7)
Grade	
1	0 (0)
2	19 (30.6)
3	43 (69.3)
Ki-67 Index	
<20	15 (24.1)
>20	47 (75.8)

All the patients completed their chemotherapy. The regimens used were FEC plus Docetaxel in 77.4% (48/62) of patients and AC plus Docetaxel in 22.5% (14/62) of patients. The regimen was not changed midway for any of the patients. None of the HER2 expressing patients received Trastuzumab along with neoadjuvant chemotherapy due to financial constraints.

Following neoadjuvant therapy, 40.3% (25/62) of patients had complete clinical response while 48.3% (37/62) of patients had a partial response. None of the patients progressed during chemotherapy while 11.2% (7/62) of patients had stable disease.

We assessed pathological response using Chevallier's criteria. There was a complete pathological response in 17.7% (11/62) patients. Among those who achieved pCR 90.9% (10/11) had a Ki-67 index greater than 20. With respect to the hormone receptor status, 72.7% (8/11) and 81.8% (9/11) of the patients had a negative expression for ER and PR respectively. The HER2 receptor was over-expressed in 63.6% (7/11) of patients who achieved pCR. Most (81.8%) of the patients who achieved PCR had a higher grade (9/11). Tumor size did

not differ much in those who achieved PCR as compared to those who did not (45.45% in T2 vs 54.55% in T3). The pCR was highest in HER2-enriched patients (45.45%) (5/11) while basal-like and luminal B subtypes showed a response rate of 27.27% each (3/11). None of the patients with luminal A subtype achieved PCR (0/11). The association between tumor size (p= 0.983), grade (p= 0.478), ER (p= 0.053), PR (p= 0.174), HER2 (p= 0.177), Ki-67 index (p= 0.268) and molecular subtype (p= 0.167) with pathological response was not significant. Similarly, these factors did not show any significant association with a clinical response either (Table 2 & 3).

Table 2: Prediction of Clinical Response

	Complete Response n=25	Partial Response n=37	p
Clinical Tumor Stage			0.502
1= <2 cm	0	0	
2= 2-5 cm	19	18	
3= >5 cm	15	19	
Grade			0.849
1	0	0	
2	8	11	
3	17	26	
Ki-67 index			0.977
<20	6	9	
>20	19	28	
Estrogen Receptor			0.712
Positive	13	21	
Negative	12	16	
Progesterone Receptor			0.568
Positive	9	16	
Negative	16	21	
Human epidermal growth factor receptor			0.065
Positive	14	12	
Negative	11	25	
Molecular Subtype			0.852
Luminal A	1	4	
Luminal B	13	17	
HER2-enriched	7	9	
Basal-like	4	7	

Table 3: Prediction of Pathological Response

	Complete Response n=11	Partial Response n=51	p
Clinical Tumor Stage			0.983
1= <2 cm	0	0	
2= 2-5 cm	5	23	
3= >5 cm	6	28	
Grade			0.478
1	0	0	
2	2	17	
3	9	34	
Ki-67 index			0.268
<20	1	14	
>20	10	37	
Estrogen Receptor			0.053
Positive	3	31	
Negative	8	20	
Progesterone Receptor			0.174
Positive	2	23	
Negative	9	28	
Human epidermal growth factor receptor			0.177
Positive	7	19	
Negative	4	32	
Molecular Subtype			0.167
Luminal A	0	5	
Luminal B	3	27	
HER2-enriched	5	11	
Basal-like	3	8	

DISCUSSION

Clinical and pathological complete response rates following neoadjuvant chemotherapy have been shown to vary between 50-85% and 15-40% respectively in various studies [1, 2, 8]. The variation in response rates is mainly due to the heterogeneous patient population and different chemotherapy regimen. In our study, clinical and pathological complete response rates were 40.3% and 17.7% respectively. Clinical assessment frequently under or overestimates tumor response and does not correlate well with the histological response. It has also not been shown to correlate well with prognosis and hence cannot be used as a surrogate endpoint. In our study, none of the prechemotherapy factors were able to predict clinical response.

Most of the studies have shown that larger size tumors respond poorly to chemotherapy [9, 10, 11]. Most of these studies included locally advanced tumors. We restricted the study to operable breast cancer and the patient population was equally distributed between T2 and T3 status. There was no difference in pCR in both (45.45% in T2 vs 54.55% in T3). High-grade tumors supposedly respond better to chemotherapy as shown by multiple studies [10-13]. We found that those who achieved pCR, the majority (81.8%) had grade 3 tumors however it didn't reach statistical significance.

Tumors that do not express hormone receptors (HR) have a better response to preoperative chemotherapy and a higher PCR as shown by the largest trial NSABP B27. In this landmark trial the PCR was 16.7% in HR-negative patients as compared to 8.3% HR-positive patients (p = 0.001) [2]. A large prospective study by Colleoni et al. that looked into the hormone receptor expression of tumors and response to chemotherapy showed that high PCR was achieved in those who lacked ER/PR expression (43%) as compared to those with ER/PR activity (20%) (n= 399, p <0.0001) [13]. Similar results were echoed by Ring et al., Kuerer et al., and Jones et al. [9, 10, 12]. Though most of the individuals who achieved pCR in the present study lacked ER and PR expression we did not find any association between hormone receptor expression and response to chemotherapy.

HER2 is over-expressed in 20-30% of breast cancer patients and is thought to predict chemoresponsiveness to anthracyclines [14]. In a large multicenter prospective study by Huober et al. HER2 status was not predictive of response to anthracycline and taxane-based chemotherapy (pCR = 23.6% in HER2 +ve vs 20% in HER2 -ve, p= 0.09) [15]. Similar results were reported by Colleoni et al., Petit et al., Fanayte et al., and Arpino et al. [13,16-18]. Whereas Penault Llorca et al. showed HER2 positive tumors had 4.5 times more chances of attaining a PCR than HER2 negative tumors (p <0.005) [19]. Fasching et al. and Jones et al. also reported better responses in HER2 over-expressing tumors [11, 12]. In our study, HER2 positive patients responded better to chemotherapy but it didn't reach statistical significance. It is controversial whether the actual predictor of chemoresponsiveness to anthracyclines is HER2 status or topoisomerase amplification. It is well known that anthracyclines mainly act by inhibiting topoisomerase 2 enzyme. Topoisomerase and HER2 genes are located in proximity on chromosome 17 and both are frequently co-amplified. In a prospective study by Di Leo et al. anthracyclines were more effective in HER2-amplified topoisomerase-amplified tumors than HER2-amplified topoisomerase-non-amplified tumors [24].

The Ki-67 index is the most commonly used method to assess the rate of proliferation of the tumor. It is thought that rapidly proliferating tumors respond better to chemotherapy. The results from various studies regarding the predictive potential have been contradictory [11-13, 17, 18, 20]. One of the factors for this is the difference in cut-offs used in studies ranging from 15-50%. Even IKBCWG failed to conclude the optimal cut-off to be used in clinical decision making [5]. We have used ROC curve analysis similar to Kim et al. for identifying cut-off value. We did not find a high Ki-67 index predictive of better response to chemotherapy [21]. However, of 11 patients who achieved PCR more than 90% had Ki-67 index >20%. A recent meta-analysis by Chen et al. showed that a high Ki-67 index could predict PCR to anthracyclines with or without taxanes in univariate as well as multivariate analysis [22].

Aggressive molecular subtypes such as basal-like and HER2-enriched tumors have a better response to chemotherapy while luminal A and B subtypes have low PCR rates. According to a prospective study by Rouzier et al. PCR was 45% in both basal-like subtype and HER2-

enriched subtype whereas luminal subtypes had a pCR of 6% [23]. In our study, HER2-enriched subtype had a better PCR of 45.45% and no patients with luminal A subtype achieved pCR. None of the molecular subtypes in our study could predict a better response to chemotherapy.

There are potential limitations in this study. First, is a small sample size. Since the pathological complete response is an uncommon event a large sample size is required for identifying significant outcomes. Second, the neoadjuvant chemotherapy chosen was heterogeneous and was based on factors such as the age and performance status of the patient, receptor status and tumor characteristics. Third, none of the HER2 expressing patients received Trastuzumab along with neoadjuvant chemotherapy due to patient's financial constraints. It has been shown that addition of trastuzumab to chemotherapy in HER2 expressing tumors significantly increases PCR.

To our knowledge, this is the first prospective study in South Indian population evaluating predictive factors of chemotherapy in breast cancer and has been conducted on a homogeneous population of operable breast cancer. With regard to evaluating the predictive efficacy of Ki-67 index the cut-off value was not chosen arbitrarily, instead ROC analysis was done to choose the optimum value. Further assessment of Ki-67 index was based on recent international recommendations overcoming the limitations which were seen in earlier studies. None of the clinical or pathological factors could predict response to neoadjuvant chemotherapy in our study. Perhaps a similar study with a larger sample size would be able to provide better information.

CONCLUSION

In our study, we observed a high pathological complete response rate in tumors with high grade, high proliferative activity, ER/PR negative status, HER2 over-expressing tumors and aggressive molecular subtypes such as basal-like and HER2-enriched breast cancer. However, none of these prechemotherapy factors showed statistically significant association with pathological complete response possibly due to a small sample size.

Conflicts of Interest - none
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Disclosures - none

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