The Effect of Hormone Receptor Status on Pathological Response after Preoperative Therapy in Breast Cancer Patients

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ABSTRACT

Background: The pathological complete response of preoperative therapy in breast cancer patients has been correlated with outcome and prognosis in terms of local and distant relapse. Response rates vary according to clinical and pathological prognostic factors of patients including hormone receptor status. This study was performed to assess response in terms of pathological response rates in relation to Estrogen and progesterone receptor status.

Methods: This study analyzed 99 female patients with non metastatic breast cancer who received neoadjuvant chemotherapy +/- targeted therapy during the period of April 2007 to March 2014. Patients were treated at the university hospital of Saarland in Homburg, Germany. Records were reviewed and correlation of response to Estrogen (ER) and Progesterone (PR) status was done. Response was assessed and pathological complete response was defined as absence of invasive and in situ disease in breast and axilla.

Results: Out of 99 patients, 29 (29.3%) patients achieved pathological complete response (pCR). Forty two percent of tumors with negative Estrogen receptor status achieved complete response, versus 18% of ER positive tumors which was found to be of statistical significance (P value 0.009). Similarly 42.6% of tumors with negative Progesterone receptors showed pCR versus only 10% of PR positive tumors which also showed high significance (P value 0.001).

Conclusion: This study confirmed that high pCR rates are achievable in ER and PR negative disease using preoperative chemotherapy. It was concluded that each of the ER, PR status significantly impact pCR rates where ER, PR negative status achieve higher pCR rates.

Keywords Neoadjuvant, Breast cancer, Preoperative, Pathological response.

INTRODUCTION

Preoperative therapy refers to the systemic treatment of breast cancer prior to definitive surgical therapy. The main objective of preoperative therapy is to improve surgical outcomes in patients for whom a primary surgery is technically not feasible and in patients with operable breast cancer who need a mastectomy but desire breast conservation, or in whom a partial mastectomy would result in a poor cosmetic outcome [1,2].

Neoadjuvant (preoperative) treatment can also be regarded as an in vivo test of sensitivity to the used regimen [3] allowing for an early evaluation of the effectiveness of systemic therapy. This can guide the clinician to discontinue the ineffective treatment [4].

The ER-negative genomic profile includes many subtypes, such as basal-like, claudin-low [5], and interferon-rich [6], as well as others. Being also PR negative and HER2 negative, most of these fall under the category of triple negative breast cancers [7].

METHODOLOGY

Study design

This is a retrospective study to assess the efficacy of primary systemic therapy in female patients with non-metastatic breast cancer as shown by pathological complete response. Correlation of response to clinical factors and pathological factors was assessed. All demographic and clinical data were obtained from patients' registry, electronic medical records and surgical pathology reports.

Data selection

The study involved 110 female patients with histologically diagnosed breast cancer who received neoadjuvant (preoperative) chemotherapy +/- targeted therapy during the period of April 2007 to March 2014. Patients were treated at the university hospital of Saarland in Homburg,Germany.

Patients analyzed in the study were 99 patients after exclusion of 11 patients (9 with distant metastases, one with metastases and pregnancy and one due to pregnancy). The patients were considered as 99 subjects when analyzing the patient related factors, however when analyzing tumor related factors they were analyzed as 104 tumors due to bilaterality in 5 patients.

Received: 8 / 03 /2017
Accepted: 18/ 03 /2017
DOI : 10.12816/0036662

All patients were older than 18 years of age and had histologically confirmed invasive breast cancer by core biopsy. Tumors analyzed were clinically T1-4, N0-3 according to the Seventh Edition of the TNM staging criteria of the American Joint Committee on Cancer Staging System [(8).] Unilateral, bilateral, multifocal and multicenteric breast cancers were included and analyzed.

Staging workup was done for all patients before initiation of treatment. Adequate cardiac function and left ventricular ejection fraction were also assessed before treatment. Patients had no comorbidities interfering with therapy initiation.

Pathology

Tumor size was determined through clinical examination and the initial sonomammography to categorize the T stage of tumors. Tumor size was determined using the longest dimension. In case of multicentricity (5 tumors) the dimensions of the largest tumor was used.

Patients were categorized to either having positive or negative lymphatic involvement. Patients with clinically negative axilla underwent sentinel lymph node biopsies before starting therapy. Biopsies were performed for Patients with clinically positive axilla to confirm involvement and patients who had positive results underwent axillary lymph node dissection as part of the surgery. Clips were used in all patients to mark the tumor bed before start of preoperative therapy.

ER/ PR/ HER2 and Ki 67 were performed using core biopsies obtained before initiation of therapy. They were not repeated again postoperatively.

Treatment types

A. Chemotherapy

All patients were planned to receive 6-8 cycles of chemotherapy (all anthracyclin and Taxane containing regimens except eight patients three of whom received anthracyclin only and five received Taxane only) ± targeted agents for patients with HER2 positive tumors.

Regimens used were either TAC (docetaxel 75 mg/m2, Doxorubicin 50 mg/m2 and Cyclophosphamide 500 mg/m2 /21d) for 6 cycles or EC (Epirubicin 90mg/m2 D1 +cyclophosphamide 600mg/m2 D1/21d) for 4 cycles followed by Docetaxel (100mg/m2 D1/21d) for 4 cycles. A group of patients received other regimens which were less common and thus were grouped together and represented separately as a group. The different regimens they received will be further addressed in the results. Laboratory tests including complete blood picture, liver and kidney functions tests were assessed before each cycle.

B.Targeted therapy

For HER2 positive patients, trastuzumab was given at a dose of 8 mg/kg as a loading dose then 6 mg/kg every 3 weeks which was continued postoperatively to a total duration of one year. Pertuzumab was given at a dose of 840 mg (loading dose) followed by 420 mg every 21 days for 8 cycles in combination with Trastuzumab in the preoperative setting. Lapatinib was given at a dose of 1250mg/d for 24wks preoperatively.

Response evaluation

Clinical examination and ultrasonography recorded every 2-3 cycles were reviewed to gather data regarding response or progression. Pathological complete response was assessed according to Sinn et al and was defined as absence of invasive and in situ disease in breast and axilla [(9).]

Patients who showed progressive disease on anthracyclines were shifted to Taxanes. Patients who were on Taxanes after anthracyclines and showed progression were referred to surgery.

Patients who underwent breast conservative surgery or who were candidates for postoperative radiotherapy were referred to the radiotherapy department.

The study was done after approval of ethical board of Al-Azhar university and an informed written consent was taken from each participant in the study.

Data Analysis

Statistical Analysis Software (IBM SPSS, version 20) was used for data analysis. First, descriptive analysis for the whole sample was done using counts and percentage for categorical variable and mean ± SD for quantitative variables. Univariate frequency analysis was performed using chi square test and fisher exact test for categorical variables and independent t test and paired t test for quantitative variables. Statistical significance was established at a p-value of less than 0.05.

RESULTS

Patient demographics

The patients' ages ranged between 33 and 79 years. The mean age was 53.59 ±SD 10.692. Forty three patients (43.4 %) were premenopausal and 56 patients (56.6 %).

Tumor characteristics

Our study included 104 tumors. The mean tumor size was 29.6 mm (sd±13.7) ranging in size between 3.2mm (in one of the patients with T4d tumor) and 80 mm. The size of the tumor was not documented in 4 cases. Multifocality was recorded in 8 patients and multicentric disease in 5 patients. The tumor characteristics are described in table (1).

Table (1): descriptive analysis of tumor characteristics (104 tumors)

		Number of tumors 104 (%)
Laterality (5 bilateral)	Right	**46** (44.2)
	Left	**58** (55.8)
Pathological type	IDC	**94** (90.39)
	ILC	**8** (7.69)
	Clear cell	**1** (0.96)
	medullary ca	**1** (0.96)
Tumor grade	G1	**2** (2)
	G2	**49** (47)
	G3	**53** (51)
clinical T stage* (Total 100)	T1	**15** (15)
	T2	**59** (59)
	T3	**6** (6)
	T4 (a,b,c)	**11** (11)
	T4d	**9** (9)
clinical N stage (Total 101)**	N0	**32** (31.7)
	N+	**69** (68.3)
ER (total 103)	Negative	**52** (50.5)
	Positive	**51** (49.5)
PR (total 103)	Negative	**63** (61.2)
	Positive	**40** (38.8)
HER2 (total 103)	Negative	**83** (80.6)
	Positive	**20** (19.4)
Ki 67 (total 104)	<20	**29** (27.9)
	20 and more	**75** (72.1)

*T stage missing for 4 tumors

**N stage missing for 3 tumors

Lymph node fine needle aspiration cytology for patients with clinically positive axilla was done for 58 patients (84.1%) of which 36 (62.1%) showed positive cytology of malignant involvement and 22 (37.9%) showed negative results.

Neoadjuvant therapy regimens used in 99 patients

A. Type of therapy

All patients received chemotherapy. Seventy nine patients (79.8%) received chemotherapy alone and 20 patients (20.2%) received chemotherapy and anti HER2 targeted therapy.

B. Chemotherapy

1) Combinations used

Ninety one patients (92%) out of 99 patients received anthracyclin and Taxane containing regimens. Three patients (3%) received anthracyclin only, and five patients (5%) received Taxane only (± targeted agents for patients with HER2 positive tumors).

2) Type of regimen received

Patients were categorized into 4 groups as shown in table (2). The first group(13.1% of patients) received 6 cycles of Taxotere, Adriamycin and cyclophosphamide (TAC). The second group (43.4% of patients) received 4 cycles of Epirubicin and cyclophosphamide (EC) followed by 4 cycles of Docetaxel.

The third group consisted of 20 patients (20.2%) who had HER2 positive disease, and thus in addition to the anthracyclin/Taxane based regimen they also received an anti HER2 targeted therapy. This was further divided into two subgroups according to whether the patient received a single agent Trastuzumab (15 patients) or double therapy with either Tastuzumab ± Pertuzumab ± Lapatinib (5 patients). The regimens they received are listed in table (3).

Table (2) treatment regimens received in the study

Treatment regimen	Number of patients (total 99)	%
TAC	**13**	**13.1%**
EC / Docetaxel	**43**	**43.4%**
anti_HER2 neu	**20**	**20.2%**
Others*	**23**	**23.2%**

*details of regimens received by this group is mentioned in table (3)

Table (3) regimens received by patients in the fourth group labeled as others

Regimen	**Number of patients** total 23/99 (% out of 99)
EC	3 (3)
EC+bevacizumab / Docetaxel+ bevacizumab	5 (5.1)
EC / paclitaxel weekly	4 (4)
weekly paclitaxel	3 (3)
nabpaclitaxel weekly foll. by EC	5 (5.1)
EC foll.by 1 Docetaxel foll. By Paclitaxel	1 (1)
paclitaxel weekly + bevacizumab	1 (1)
1 EC foll by EC/ paclitaxel+addition of bevacizumzb	1 (1)

Pathological Response

Out of the 99 patients, 29 patients achieved pathological complete response and 68 showed less than complete response (29.3% and 68.7% respectively) with 2 patients showing missing response data. For patients with bilateral tumors pathological response was only considered to be complete if achieved bilaterally. Accordingly, one patient with bilateral disease achieved pCR unilaterally (i.e. total pCR was observed in 30 tumors), but was not considered to have pCR.

Forty two percent of tumors with negative Estrogen receptor status achieved complete response versus 18% of ER positive tumors as shown in table (4) . This was found to be of statistical significance (P value 0.009).

Similarly 42.6% of tumors with negative Progesterone receptors (86.7% of all cases) showed pathological complete response versus only 10% of PR positive tumors which also showed high significance (P value 0.001).

Table (4) correlation between hormonal and HER2 receptor status and response

Receptor status	Incomplete response	%	Complete response	%		P value
ER –ve (50/101)	**29**	**58.0%**	**21**	**42.0%**	**6.857**	**.009***
ER +ve (51/101)	**42**	**82.0%**	**9**	**18.0%**		
PR –ve (61/101)	**35**	**57.4%**	**26**	**42.6%**	**12.313**	**.001***
PR +ve (40/101)	**36**	**90.0%**	**4**	**10.0%**		

DISCUSSION

The current study has highlighted the significant correlation between hormone receptor status and pCR rates as 42% of tumors with negative Estrogen receptor status achieved complete response, which represent 70% of all cases versus 18% of ER positive tumors. This was found to be of statistical significance (P value 0.009).

Similarly 42.6% of tumors with negative Progesterone receptors (86.7% of all cases) showed pathological complete response versus only 10% of PR positive tumors which also showed high significance (P value 0.001).

These results were consistent with the pooled analysis by von Minckwitz et al where 13% of positive hormone receptor tumors achieved pCR while 36% of negative hormone receptor tumors showed pCR (P value <0.001) [10] .

This was also similar to another pooled analysis [11], which compared the pCR rates in correlation with ER and PR receptor status each separately as in our study and was also found to be of high statistical significance (P value <0.001 for both). ER negative tumors showed a pCR of 26% versus 7.6% in ER positive tumors, and 22.9% of PR negative tumors versus 7.4% only in PR positive tumors have achieved pCR.

Also in the case of HER2 positive tumors ER negative subgroup achieved better pCR rates as observed in the NeoSphere Phase II randomized trial of neoadjuvant therapy comparing trastuzumab/docetaxel, trastuzumab/pertuzumab/docetaxel, trastuzumab/ pertuzumab and pertuzumab/docetaxel. The pathological complete response rates (no invasive tumor in breast) were 29%, 46%, 17% and 24%, respectively. When patients were analyzed based on estrogen receptor status, a 63% pathological complete response rate was seen in those with ER-negative disease treated with trastuzumab/ pertuzumab /docetaxel and 27% in those with ER-negative disease treated with trastuzumab/pertuzumab [12] .

In a Japanese study of 129 female patients with HER2 positive invasive breast cancer, the patients received neoadjuvant chemotherapy consisting of 12 cycles of paclitaxel (80 mg/m2) every week or 4 cycles of docetaxel (75 mg/m2) every 3 weeks followed by 4 cycles of FEC-75 (5-fluorouracil, 500 mg/m2, epirubicin, 75 mg/m2; and cyclophosphamide, 500 mg/m2) every 3 weeks, all patients also received 4 mg/kg trastuzumab on day 1of the treatment and 2 mg/kg trastuzumab every week thereafter for a total of 24 cycles. Pathological complete response rates were significantly higher in patients with ER negative 78.6% (p < 0.001), and PgR negative 75.3% (p < 0.001) tumors than in those with ER-positive 40%, and PgR positive 38.9% tumors [13].

The most favorable outcomes after pCR were recorded in patients with HER2 positive, hormone receptor negative tumors who received trastuzumab (event free survival: HR 0.15, CI 0.09-0.27; Overall survival: HR 0.08, CI 0.03-0.22) and in the triple negative subgroup (overall survival HR 0.16, CI 0.11-0.25) [14].

In this study 58 patients (56.3%) underwent breast conservative surgeries whereas 45 patients (43.7%) underwent mastectomies. Precisely 69% of patients with complete response were amenable for breast conservative surgery. On the other hand 20.5% of the patients who had mastectomies had a pCR. Breast conservative surgery was however still possible for 48.5% of patients with incomplete response. The correlation between response and type of operation showed a tendency towards statistical significance (P value 0.077). It is therefore important to specify the appropriate candidates for preoperative therapy based on the patient and tumor characteristics especially hormonal status and molecular subtypes. This would increase the chance for pCR and possibility for better surgical outcome and opportunity for conservative surgery.

CONCLUSION

It was concluded that each of the ER and PR receptor status significantly impact pCR rates where ER, PR negative status achieve higher pCR rates after preoperative therapy in breast cancer.

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