



Neoadjuvant Therapy in Breast Cancer Patients and Assessment of Response in Relation to Regimen Used and Prognostic Factors

Thesis

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Dedication

*I dedicate this work to my beloved **Parents** for their unconditional love and support. You will always be my source of inspiration. I am very thankful to my dear **Husband** and **Son** for their continuous encouragement, patience and love. I am grateful to **my Sister** and **my Brothers** for always having faith in me. I also dedicate this work to the oncology **patients** in honor of their endurance and in faith for hope.*

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم العظيم

صدق الله العظيم

سورة البقرة الآية: ٣٢

List of Contents

Title	Page No.
Abstract	6
List of Abbreviations	7
List of Tables	10
List of Figures.....	14
Introduction	1
Aim of the Work	4
Review of Literature	
▪ Incidence and Mortality in breast cancer	5
▪ Prognostic and Predictive Factors in Breast Cancer	9
▪ Neoadjuvant Therapy in Breast Cancer	45
▪ Evaluation and Response Assessment in Neoadjuvant Therapy in Breast Cancer	81
Methodology	106
Results	113
Discussion.....	176
Summary	203
Conclusion	206
Recommendations	207
References	208
Appendices	272
Arabic summary	

Abstract

Background: The pathological complete response of neoadjuvant (preoperative) therapy in non metastatic 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 especially molecular subtypes. This study was performed to assess response in terms of pathological response rates in relation to regimen used and prognostic factors.

Methods: This study analyzed 99 female patients with non metastatic breast cancer who received neoadjuvant chemotherapy $\pm$ 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 to assess the regimens given, the toxicity and correlation of response to regimen and prognostic factors was done. Response evaluation was done according to Sinn et al., and was defined as absence of invasive and in situ disease in breast and axilla. Relapse was also correlated to regimen and prognostic factors.

Results: Out of 99 patients, 29 (29.3%) patients achieved pCR. Patients receiving regimens incorporating Anti HER2 agents achieved pCR in 52.6%. Age grouping below versus equal to or above 60 years of age was found to be statistically significant in correlation with pCR (P value 0.05). Similarly pCR was observed in 33.3% of T1/T2 tumors versus 11.5% of T3/T4 tumors which showed statistical significance (P value 0.033). 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 0.000). HER2 receptor status also showed to be of statistical significance when correlated with pathological complete response (P value 0.011). HER2 positive tumors showed complete pathological response in 55% versus 23.5% of HER2 negative tumors.

The molecular subtype showed strong correlation with the pCR rates where HER2 overexpression achieved the highest pCR rate of 60%, followed by Luminal B HER2 positive subgroup which had a PCR rate of 50%. Triple negative tumors achieved 35.9% pCR rate and the lowest rate was observed among the luminal A subgroup which was 5.6% (P value 0.007). Clinical stages cT4a-c and cT4d constituted 30.8% and 38.5% of relapse (P values 0.021 and 0.00) respectively. TAC regimen was shown to be associated with higher relapse incidence in comparison to other regimens used (P value 0.04)

Conclusion: This study confirmed that high pCR rates are achievable in breast cancer patients with HER2 positive and triple negative disease using neoadjuvant (preoperative) chemotherapy and anti HER2 agents (in case of HER2 positive disease). Similarly, it was concluded that each of the ER, PR and HER2 receptor status significantly impact pCR rates where ER, PR negative and HER2 positive status achieve higher pCR rates. Higher pCR rate was also observed in early (T1/T2) tumors in comparison to advanced (T3/T4) tumors, and in ages younger than 60 years old. This was in accordance with the tendency of tumors with an aggressive nature to achieve better pCR rates consistently.

List of Abbreviations

Abb.	Full term
<i>AC</i>	<i>Doxorubicin, cyclophosphamide</i>
<i>AI</i>	<i>Aromatase inhibitor</i>
<i>ALND</i>	<i>Axillary lymph node dissection</i>
<i>AR</i>	<i>Androgen receptor</i>
<i>ASCO</i>	<i>American Society of Clinical Oncology</i>
<i>AUC</i>	<i>Area Under the Curve</i>
<i>BCI</i>	<i>Breast Cancer Index</i>
<i>BCS</i>	<i>Breast conservative surgery</i>
<i>cCR</i>	<i>Clinical complete response</i>
<i>CMF</i>	<i>Cyclophosphamide methotrexate, fluorouracil</i>
<i>CPS+ EG</i>	<i>Clinical stage (C), pathological stage (PS), ER status (E), and grade (G).</i>
<i>DCIS</i>	<i>Ductal carcinoma in situ</i>
<i>DFS</i>	<i>Disease free survival</i>
<i>DNA</i>	<i>Deoxyribonucleic acid</i>
<i>DX</i>	<i>Docetaxel, capecitabine</i>
<i>EBCTCG</i>	<i>Early breast cancer trialists' collaborative group</i>
<i>EC</i>	<i>Epirubicin, cyclophosphamide</i>
<i>ECD</i>	<i>Extracellular domain</i>
<i>EFS</i>	<i>Event-free survival</i>
<i>ER</i>	<i>EndoPredict</i>
<i>ER</i>	<i>Estrogen receptor</i>
<i>FAC</i>	<i>Fluorouracil, doxorubicin, cyclophosphamide</i>
<i>FDA</i>	<i>Food and Drug Administration</i>
<i>FEC</i>	<i>Fluorouracil, Epirubicin, cyclophosphamide</i>
<i>FNA</i>	<i>Fine needle aspiration</i>
<i>GGI</i>	<i>Genomic grade index</i>
<i>HER2</i>	<i>Human epidermal growth factor receptor 2</i>
<i>HP</i>	<i>Trastuzumab plus pertuzumab</i>
<i>HR</i>	<i>Hazard ratio</i>
<i>HR</i>	<i>Hormone receptor</i>
<i>HRT</i>	<i>Hormone replacement therapy</i>

List of Abbreviations Cont...

Abb.	Full term
IV	<i>Intravenous</i>
LPBC	<i>Lymphocyte predominant breast cancer</i>
MAPK	<i>Mitogen activated protein kinase</i>
MRI.....	<i>Magnetic resonance imaging</i>
mtor.....	<i>Mammalian target of rapamycin (mTOR)</i>
NAC	<i>Neoadjuvant chemotherapy</i>
NAT	<i>Neoadjuvant therapy</i>
NSABP.....	<i>National Surgical Adjuvant Breast and Bowel Project</i>
OR.....	<i>Odds ratio</i>
OS	<i>Overall Survival</i>
PAI.....	<i>Plasminogen activator inhibitor</i>
PALB2	<i>Partner and localizer of BRCA2</i>
PAM50	<i>Predictor Analysis of Microarray 50</i>
PARP	<i>Poly ADP ribose polymerase</i>
pCR.....	<i>Pathologic complete response</i>
PEPI.....	<i>Preoperative endocrine prognostic index</i>
PET.....	<i>Positron-Emission Tomography</i>
pN0ITC.....	<i>Isolated tumor cells</i>
pN1 _{mic}	<i>Micrometastases</i>
PR	<i>Progesterone receptor</i>
PR	<i>Progesterone receptor</i>
PTEN.....	<i>Phosphatase and tensin homolog gene</i>
RCB.....	<i>Residual cancer burden</i>
ROR	<i>Risk of relapse</i>
RS	<i>Recurrence score</i>
RT PCR.....	<i>Reverse transcription polymerase chain reaction</i>
SLN.....	<i>Sentinel lymph node</i>
SLNB.....	<i>Sentinel lymph node biopsy</i>
STK11mutations	<i>Serine /threonine protein kinase 11</i>
TAC.....	<i>Docetaxel, doxorubicin, cyclophosphamide</i>
TC	<i>Docetaxel, cyclophosphamide</i>

List of Abbreviations Cont...

Abb.	Full term
<i>TILs</i>	<i>Tumour-infiltrating lymphocytes</i>
<i>TNBC</i>	<i>Triple negative breast cancer</i>
<i>TP53</i>	<i>Gene tumor suppressor gene</i>
<i>upa</i>	<i>Urokinase plasminogen activator</i>
<i>uPAR</i>	<i>Urokinase plasminogen activator receptor</i>
<i>US</i>	<i>Ultrasound</i>

List of Tables

Table No.	Title	Page No.
Table (1):	Molecular subtypes classification.....	109
Table (2):	Descriptive analysis of patient characteristics (99 patients).....	114
Table (3):	Descriptive analysis of tumor characteristics (104 tumors).....	117
Table (4):	Descriptive analysis of molecular subtypes for 103 tumors.....	118
Table (5):	Treatment regimens received in the study.....	122
Table (6):	Descriptive data of patients categorized according to whether they received single versus double anti HER2 therapy or neither	123
Table (7):	Regimens received by patients with HER2 positive disease.....	124
Table (8):	Regimens received by patients in the fourth group labeled as others	125
Table (9):	Illustrates the number of patients who completed their cycles for every treatment group.	126
Table (10):	Types of toxicities encountered in patients' records.	127
Table (11):	Comparison of the occurrence of toxicity among patients who received the TAC regimen in comparison to all other treatment groups.....	129
Table (12):	Toxicity recorded with EC/ Docetaxel regimen in comparison to all other regimens.	132
Table (13):	Toxicities encountered by patients receiving regimens containing anti HER2 agents.....	133

List of Tables cont...

Table No.	Title	Page No.
Table (14):	Toxicities encountered by single versus double anti HER2 agents.....	135
Table (15):	Postoperative pathological staging.	138
Table (16):	The relation between the initial clinical T stage and the occurrence of downstaging.....	140
Table (17):	Correlation between response and type of operation.	141
Table (18):	Rate of relapse.	143
Table (19):	Correlation between reponse achieved and relapse occurrence.....	144
Table (20):	Kaplan Meier product limit analysis of DFS comparison between complete and incomplete response among all studied patients.....	145
Table (21):	Correlation between surgery type and incidence of relapse.....	146
Table (22):	Correlation between Menstrual status and relapse.....	147
Table (23):	Comparison between the five molecular subtypes as regards occurrence of relapse.....	148
Table (24):	Comparison between molecular subtypes and type of relapse.	149
Table (25):	Comparison between each molecular subtype against the other subtypes combined and the type of relapse.	150
Table (26):	Kaplan Meier product limit analysis of DFS comparison between patients with complete and incomplete response among cases with Triple negative subtype.....	151

List of Tables cont...

Table No.	Title	Page No.
Table (27):	Kaplan Meier product limit analysis of DFS comparison between complete and incomplete response among cases with luminal B HER2 negative patients.....	152
Table (28):	Correlation between clinical T stage and relapse.....	154
Table (29):	Correlation between pathological T stage and relapse.....	155
Table (30):	Correlation between clinical N status and relapse.....	156
Table (31):	Correlation between pathological N stage and relapse.....	157
Table (32):	Correlation between regimen received and occurrence of relapse.....	158
Table (33):	Correlation between regimen received and type of relapse.....	159
Table (34):	Correlation between response and regimen received.....	161
Table (35):	Correlation between single or double anti HER2 agents containing regimens and response.....	162
Table (36):	Mean age, parity and age at first birth correlated with response.....	162
Table (37):	Correlation between age and response.....	163
Table (38):	Correlation between Menstrual status and response.....	164
Table (39):	Correlation between T stage (categorized as early and late) and response.....	165
Table (40):	Correlation between different T stages and response.....	165
Table (41):	Correlation between each T stage against all other stages and response.....	166

List of Tables cont...

Table No.	Title	Page No.
Table (42):	Correlation between laterality and response.....	167
Table (43):	Correlation between bilaterality and response.....	168
Table (44):	Correlation between initial clinical nodal status and response.	168
Table (45):	Correlation between pathological type and response.	169
Table (46):	Correlation between tumor grade and response.....	170
Table (47):	Correlation between each tumor grade against other grades and response.....	170
Table (48):	Correlation between ki67 and response.	171
Table (49):	Correlation between hormonal and HER2 receptor status and response.....	172
Table (50):	Correlation between all molecular subtypes and pathological response.....	173
Table (51):	Correlation between each molecular subtype in relation to the other subtypes and pathological response.....	174

List of Figures

Fig. No.	Title	Page No.
Figure (1):	Top ranked cancers by absolute death for all ages in females, 2013	5
Figure (2):	Age specific incidence rates for breast cancer in Egypt 2008–2011.....	7
Figure (3):	Mechanism of action of trastuzumab and pertuzumab. NK: natural killer; Fcγ R III: Fcγ receptor III	55
Figure (4):	Algorithm used at Moffitt Cancer Center for axillary assessment in patients with invasive breast cancer larger than 2 cm in diameter.....	83
Figure (5):	Patients' age group representation.	115
Figure (6):	Patients' Menstrual status representation.	115
Figure (7):	Representation of tumor molecular subtypes in 103 tumors.	119
Figure (8):	Type of therapy received.	120
Figure (9):	Representation of number of patients who received Anthracyclin and Taxane containing regimens, Anthracyclin only and Taxane only regimens.....	121
Figure (10):	Treatment regimens received.....	122
Figure (11):	Anti HER2 therapy received by 20 patients (20.2%).....	123
Figure (12):	Number of patients in relation to completion of cycles.....	126
Figure (13):	Toxicity among patients who received the TAC regimen in comparison to all other treatment groups.....	130
Figure (14):	Incidence of peripheral neuritis with EC/ Docetaxel regimen in comparison to all other regimens.....	131
Figure (15):	Type of surgery.....	136

List of Figures cont...

Fig. No.	Title	Page No.
Figure (16):	Preoperative T3-T4 and N positive percentage versus postoperative.....	137
Figure (17):	Representation of complete and incomplete pathological response rates.	138
Figure (18):	Percentage of patients who achieved T stage downstaging versus patients who showed stable disease or progression.	139
Figure (19):	Correlation of response with type of surgery.	142
Figure (20):	Kaplan Meier curve of DFS comparison between patients who achieved pathological complete versus incomplete response	146
Figure (21):	Kaplan Meier curve for DFS in patients with triple negative disease.....	151
Figure (22):	Kaplan Meier curve for DFS in patients with luminal B HER2 negative disease.....	152
Figure (23):	Age in relation to response.	163
Figure (24):	Response in relation to molecular subgroup.	175