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.*

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

List of Abbreviations Cont…

Abb.	Full term
IV	*Intravenous*
LPBC	*Lymphocyte predominant breast cancer*
MAPK	*Mitogen activated protein kinase*
MRI	*Magnetic resonance imaging*
mtor	*Mammalian target of rapamycin (mTOR)*
NAC	*Neoadjuvant chemotherapy*
NAT	*Neoadjuvant therapy*
NSABP	*National Surgical Adjuvant Breast and Bowel Project*
OR	*Odds ratio*
OS	*Overall Survival*
PAI	*Plasminogen activator inhibitor*
PALB2	*Partner and localizer of BRCA2*
PAM50	*Predictor Analysis of Microarray 50*
PARP	*Poly ADP ribose polymerase*
pCR	*Pathologic complete response*
PEPI	*Preoperative endocrine prognostic index*
PET	*Positron-Emission Tomography*
pN0$_{ITC}$	*Isolated tumor cells*
pN1$_{mic}$	*Micrometastases*
PR	*Progesterone receptor*
PR	*Progesterone receptor*
PTEN	*Phosphatase and tensin homolog gene*
RCB	*Residual cancer burden*
ROR	*Risk of relapse*
RS	*Recurrence score*
RT PCR	*Reverse transcription polymerase chain reaction*
SLN	*Sentinel lymph node*
SLNB	*Sentinel lymph node biopsy*
STK11mutations	*Serine/threonine protein kinase 11*
TAC	*Docetaxel, doxorubicin, cyclophosphamide*
TC	*Docetaxel, cyclophosphamide*

List of Abbreviations Cont…

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

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