Correlation of Tumor Infiltrating CD4+ and CD8+ Lymphocytes and Response to Neoadjuvant Chemotherapy in Locally Advanced Breast Cancer

Thesis

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Radwa Mohamed

Dedication

To:

My beloved Dad

My wonderful Mom

My amazing Brother and Sisters

Radiation Oncology Department, Maadi Military Medical Compound

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List of Abbreviations

Abb.	Full term

5-FU *.....5-fluorouracil*
A *.....Doxorubicin*
AD *.....Androgen receptor*
ADCC *.....Antibody Dependent Cell mediated Cytotoxicity*
AI *.....Aromatase Inhibitors*
AJCC *.....American Joint Committee on Cancer*
ASCO *.....American Society of Clinical Oncology*
AUC *.....Area Under the Curve*
BC *.....Breast Cancer*
BCI *.....Breast Cancer Index*
BCT *.....Breast Conservative Treatment*
BL1 *.....Basal-Like 1*
BL2 *.....Basal-Like 2*
BLBC *.....Basal-Like Breast Cancer*
BLIA *.....Basal-Like Immunoactivated*
BLIS *.....Basal-Like Immunosuppressed*
C *.....Cyclophosphamid*
CAP *.....College of American Pathologists*
CBC *.....Complete blood picture*
CDC *.....Centers for Disease Control and Prevention*
CESM *.....Contrast-Enhanced Spectral Mammography*
CISH *.....Chromogenic in situ hybridization*
CRR *.....Clinical Response Rate*
CT *.....Computerized tomography*
CTL *.....Cytotoxic T lymphocytes*
CTLA *.....Cytotoxic T-lymphocyte-associated protein*
D *.....*Docetaxel
DBT *.....Digital Breast Tomosynthesis*
DCIS *.....Ductal Carcinoma Insitu*

List of Abbreviations (Cont...)

Abb.	Full term
DFS	*Disease free survival*
dMFS	*Distant metastasis-free survival*
E	*Epirubicin*
EFPE	*Formalin-fixed paraffin-embedded*
EFS	*Event-Free Survival*
EGFR	*Epidermal growth factor receptor*
EORTC	*European Organisation for Research and Treatment of Cancer*
EPclin	*EndoPredict*
ER	*Estrogen Receptors*
FAS-L	*Fas ligand*
FDA	*Food and Drug Administration*
FDG-PET/CT	*Fluoro-D-glucose positron emission Tomography / Computerized tomography*
FGFR-2	*Fibroblast growth factor receptors-2*
FISH	*Fluorescence in situ hybridization*
GEP	*Gene Expression Profiling*
GGI	*The Genomic Grade Index*
GR	*Glucocorticoid Receptor*
HER-2	*Human Epidermal Growth Factor Receptor- 2*
HMGB1	*High mobility-group box 1*
HR	*Hazard ratio*
HR	*Hormone Receptor*
IBC	*Invasive Breast Cancer*
IFN	*Interferon*
IFN-γ	*Interferon Gamma*
IHC	*Immunohistochemistry*
IL	*Interleukin*
IM	*Immunomodulatory*
IQR	*Inter quartile range*

List of Abbreviations (Cont...)

Abb.	Full term
KFT	*Kidney function test*
LABC	*Locally Advanced Breast Cancer*
LAR	*luminal Androgen Receptor*
LCIS	*Lobular Carcinoma Insitu*
LFT	*Liver function test*
LPBC	*Lymphocyte Predominant Breast Cancer*
LRR	*Local Recurrence Rate*
M	*Mesenchymal*
M	*Methotrexate*
M1	*Metastasis*
MAPK	*Mitogen Activated Protein kinase*
MC	*Molecular Classification*
MDSC	*Myeloid-derived suppressor cells*
MFS	*Metastases-free survival*
MG	*Mammography*
MHC	*Histocompitability Complex*
MNPI	*Modified scores from Nottingham Prognostic Index*
MRI	*Magnetic Resonance Imaging*
MSBR	*Modified Scarff Bloom Richardson grade*
mTOR	*Mammalian target of rapamycin*
N	*Lymph-node*
NA	*Not applicable*
NAC	*Neoadjuvant Chemotherapy*
NET	*Neoadjuvant Endocrine Therapy*
NF-κB	*Nuclear Factor Kappa B*
NK	*Natural Killer*
NR	*Not Reported*
NSABP	*National Surgical Adjuvant Breast and Bowel Project*

List of Abbreviations (Cont...)

Abb.	Full term
OS	*Overall survival*
P	*Pertuzumab*
PAM 50	*Prediction Analysis of Microarrays 50*
pCR	*Pathological Complete Responses*
PD-1	*Programmed cell death-1*
PDL-1	*Programmed cell death ligand-1*
PDL-2	*Programmed cell death ligand-1*
PFS	*Progression free survival*
PI3K	*Phosphoinositide 3- kinase*
PIK3CA	*Phosphatidylinositol-4,5-Bisphosphate 3-kinase catalytic subunit alpha*
PgR	*Progesterone Receptors*
PTEN	*Phosphatase and tensin enzyme*
QNBC	*Quadruple Negative Breast Cancer*
RCB	*Residual Cancer Burden*
RECIST	*Response Evaluation Criteria in Solid Tumors*
RFS	*Relapse-free survival*
ROR	*Risk-of-Recurrence*
RS	*Recurrence Score*
RTK	*Receptor tyrosine kinases*
SD	*Stable disease*
SEER	*Surveillance, Epidemiology, and End Results program*
T	Trastuzumab
TAA	*Tumor-Associated Antigens*
T-DM1	*Trastuzumab Emtansine*
TGF-β	*Transforming growth factor*
Th-1	*T helper cell -1*
TIL	*Tumor Infiltrating Lymhocytes*

List of Abbreviations (Cont...)

Abb.	Full term

TLR**.....***Toll-Like Receptor*
TNBC**.....***Triple Negative Breast Cancer*
TNF**.....***Tumor Necrosis Factor*
Tregs**.....***Regulatory T cells*
US **.....***Ultrasound*
V**.....***Vincristine*
Vs. **.....***Versus*
X**.....***Capecitabine*

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INTRODUCTION

Breast cancer is the most common invasive malignancy and the second most common cause of death from cancer in women ***(Hiatt and Brody, 2018).***

Over 1.5 million women (25% of all women with cancer) are diagnosed with breast cancer every year throughout the world. In America, it is estimated that 30% of all new cancer cases among women are breast cancer ***(Sun et al., 2017).***

Breast cancer has not traditionally been considered as an immunogenic disease; however, a large body of evidence has shown the presence of significant immune cell infiltration in patient tumors ***(West et al., 2013).***

Breast cancer is capable of stimulating the immune system. Furthermore, the intensity of tumoral immune response influences the effectiveness of cancer therapy, and is correlated with favorable clinical outcome. Some breast tumors have substantial lymphocytic infiltration, and tumor-infiltrating lymphocytes (TILs) have been recently proposed as a surrogate marker of adaptive immune response. The interaction of the immune system with tumor cells in breast cancer appears to be associated with triple negative breast cancer (TNBC) and HER2-positive breast cancer, and they are thought to be more immunogenic than luminal A carcinomas ***(García-Teijido et al., 2016).***

Several studies have stated that these tumors are infiltrated by a heterogeneous population of immune cells, namely T cells, B cells, natural killer (NK) cells and macrophages. Tumor infiltrating lymphocytes (TIL) are of helper (CD4+) and cytotoxic (CD8+) pheno-types, and express activation markers such as CD25 and the transferrin receptor ***(Gisterek et al., 2008).***

CD8+ cytotoxic T lymphocytes are the primary effector cell type, because they exhibit cytotoxic activity towards tumor cells expressing tumor-associated antigens (TAAs). Where they induce tumor cell death directly upon recognition of tumor peptides presented in association with major histocompitability complex (MHC) class I molecules on tumor cells ***(Melichar et al., 2014).***

CD4+ lymphocytes eliciting its antitumor response through the activation and regulation of many facets of the adaptive immune response as interferon gamma (IFN-γ) production, NK and macrophages activation ***(Gu-Trantien et al., 2013).***

Tumor infiltrating lymphocytes (TILs) is a prognostic indicator for higher rates of pathological complete responses (pCR) to neoadjuvant chemotherapy (NAC) ***(Dieci, et al., 2014).***

Preclinical studies have suggested that cytotoxic agents may partly exert their antitumor activity by inducing immune response against tumor cells ***(André et al., 2013).*** Denkert et al., were able first to show in a large-scale analysis of 1058 patients' biopsies that TIL+ tumors achieved a pCR rate of 40–42 % following NAC, whereas TIL− tumors achieved a pCR of only 3–7% ***(Denkert et al., 2015).***