Management of Hormonal Resistant Breast Cancer

An Essay

Submitted for Partial Fulfillment of the Master Degree in Oncology and Nuclear Medicine

BY

Sara Essam Mohamed Zaki

M.B.B.CH

Supervised by

Prof. Dr. Nivine Mahmoud Ahmed Gado

Professor of Oncology and Nuclear Medicine
Faculty of Medicine- Ain Shams University

Dr. Khaled Abdel Karim Mohammed

Assistant Professor of Oncology and Nuclear Medicine
Faculty of Medicine- Ain Shams University

Dr. Nagy Samy Goubran

Assistant Professor of Oncology and Nuclear Medicine
Faculty of Medicine- Ain Shams University

Faculty of Medicine
Ain Shams University
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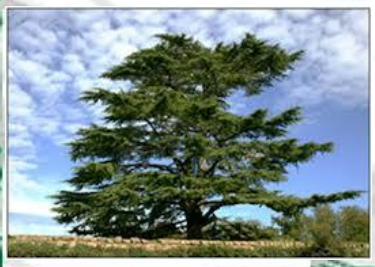
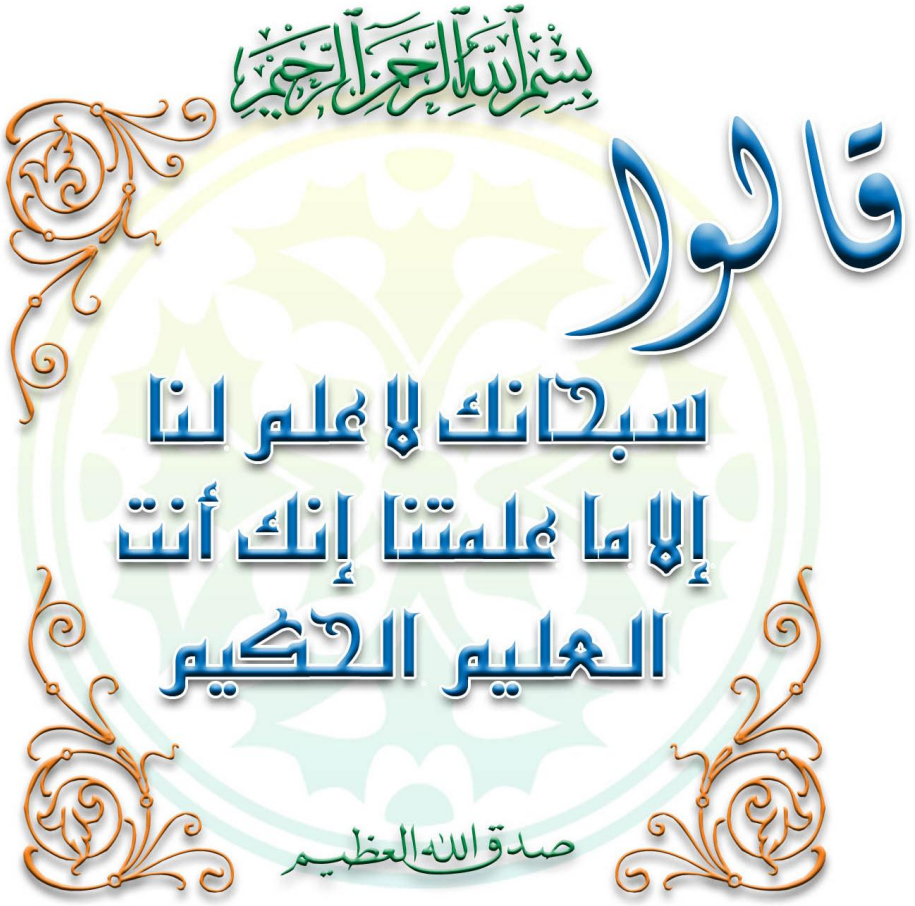
Dedication

Words can not express my thanks, gratefulness, respect and love to my **parents**, and all members of my family. Without their help, support, patience and encouragement, I would have never achieved any success.





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Sara Essam

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List of Abbreviations

Abb.	Meaning
ACS	American Cancer Society
AF1	Acivity Function 1
AIs	Aromatase Inhibitors
ALN	Axillary Lymph Node
AMPK	Adnosine Monophosphate kinase
AP1	Activator Protein 1
ATAC	Arimidex Tamoxifen Alone or in Combination trial
AUC	Area Under Curve
BCS	Breast Conservative Surgery
BMI	Body Mass Index
BRCA	Breast Cancer gene
CBE	Clinical Breast Examination
CDK	Cyclin Dependant Kinase
CK	Cytokeratin
CR	Complete Response
CSC	Cancer Stem Cell
DMBA	7,12 Di Methyl Benz Anthracene
DNA	Deoxyribonucleic acid
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
EGRFs	Epidermal Growth Factors
ER	Estrogen Receptor
ET	Endocrine Therapy
FGFR	Fibroblast Growth Factor Receptor
FISH	Flourescent In Situ Hybridization
GnRHAs	Gonadotropin Releasing Hormone Analogs
HDAC	Histone DeActylase

Abb.	Meaning
HDIs	Histone DeActylase Inhibitors
HDPP	Her 2 Derived Prognostic Predictor
Her 2	Human Epidermal Growth Factor 2
HRT	Hormone Replacement Therapy
IGF-1	Insulin like Growth Factor 1
IGFR-1R	Insulin like Growth Factor 1 Receptor
IHC	Immuno Histo chemistry
IKK	IκB kinase
INPP4B	INositol Poly Phosphate 4 phosphatase
IRS	Insulin Receptor Substrate
JNK	Jun-N Terminal Kinase
LTED	Long Term Estrogen Deprivation
MAPK	Mitogen Activated Protein Kinase
MBC	Metastatic Breast Cancer
MCF 7	Michigan Cancer Foundation 7
mTOR	Mammalian Target of Rapamycin
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
OS	Overall Survival
PAK1	P21-Activated kinase
PARP 1	Poly ADP- Riboseo Polymerase 1
PCR	Pathological Complete Response
PDGFR	Platelet Derived Growth Factor Receptor
PFS	Progression Free Survival
PI3K	Phosphoinositide-3 kinase
PI3KCA	PI3K Catalytic subunit
PKA	Protein Kinase A
PKA	Protein Kinase A

Abb.	Meaning
PMRT	Post Mastectomy RT
PR	Progeterone Receptor
PTEN	Phosphatase and Tensin homologue deleted on chromosome ten
RFS	Relapse Free Survival
RT	Radiation Therapy
RTK	Receptor Tyrosine kinase
RT-PCR	Reverse Transcription Polymerase Chain Reaction
SABCC	Southern Arizona Buffelgrass Coordination Center
SERMs	Selective Estrogen Receptor Mudulators
SP 1	Specifity Protein 1
STED	Short Term Estrogen Deprivation
TGF	Transforming Growth Factor alpha
TK	Tyrosine Kinase
TKIs	Tyrosine Kinase Inhibitors
TN	Triple Negative
TNM	Tumor-Node-Metastases
VEGF	Vascular Endothelial Growth Factor
WBRT	Whole Breast Radiation Therapy
WHO	World Health Organization

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Introduction

Breast cancer is one of the most frequently diagnosed cancers in women worldwide, it accounts for 26 % of all malignancies in women and it's the most common cause of cancer death in women **(Jemal et al., 2011).**

Breast cancer is a clinically heterogeneous disease. Global gene expression analyses using high throughput technologies have helped to explain much of the heterogeneity of breast cancer and have provided important new molecular classifications. In the last decade, genomic studies have identified five major breast cancer intrinsic subtypes (Luminal A, Luminal B, HER2-enriched, Basal-like and a Normal Breast-like group). These groups of tumors are associated with critical clinical differences and may further provide important knowledge on the biology of breast cancer initiation and progression **(Weigelt et al., 2010).**

The treatment of breast cancer includes the treatment of local disease with surgery, radiation therapy, or both, and the treatment of systemic disease with cytotoxic chemotherapy, endocrine therapy, biologic therapy, or combinations of these. The need for and selection of various local or systemic therapies are based on several prognostic and predictive factors **(NCCN Guidelines, 2013).**

According to the 2011 and 2013 St Gallen guidelines, the decision on systemic adjuvant therapies should be based on the surrogate intrinsic phenotype determined by ER/PR, HER2 and Ki67 assessment **(Goldhirsch et al., 2013).**

All luminal cancers should be treated with Endocrine Therapy (ET). Most luminal A tumors, except those with highest risk of relapse (e.g; extensive nodal involvement), require no chemotherapy, whereas luminal B HER2-negative cancers constitute a population of the highest uncertainty regarding chemotherapy indications. Indications for chemotherapy within this subtype depend on the individual risk of relapse, taking into account the tumor extent and features suggestive of its aggressiveness (grade, proliferation, vascular invasion), presumed responsiveness to ET and patient preferences **(Wishart et al., 2011).**

The ER signaling pathway is an example of a complex biological pathway that controls a variety of functions, such as cell proliferation, apoptosis, invasion, and angiogenesis, and is exploited by breast cancer cells to serve as a major survival pathway driven by the female hormone estrogen. The classic function of ER is its nuclear function, also referred to as genomic activity, to alter the expression of genes important for normal cellular function and tumor growth and survival. ER modulates the expression of hundreds of genes, some by

upregulation and others by down regulation.**(Schiff et al., 2009).**

Coregulators serve as a fine-tuning mechanism by increasing or reducing the transcriptional activity of the receptor. Several coregulators have been implicated in cancer, most notably AIB1 **(Osborne et al., 2003).**

The ER signaling pathway is also regulated by membrane receptor tyrosine kinases, including EGFR, HER2, and IGF1-R. These membrane kinases activate signaling pathways that eventually result in phosphorylation of ER as well as its co-activators and co-repressors at multiple sites to influence their specific functions **(Schiff et al., 2003).**

Resistance to endocrine therapy can occur de novo (existing before any treatment is given) or be acquired (developing during a given therapy after an initial period of response). Some tumors lose estrogen dependence with loss of ER expression, although preclinical data suggest that ER can sometimes be re-expressed during subsequent treatment, other tumors lose estrogen dependence while still expressing ER, indicating that an escape pathway has developed to replace ER **(Lopez-Tarruella and Schiff, 2007).**

Multiple pathways and molecules have been implicated in the diverse mechanisms responsible for endocrine resistance. These pathways and their gene networks, recently reviewed

elsewhere, have mostly been investigated in the preclinical setting with a focus on Tamoxifen. Several alternative pathways have been shown or suggested to play a general role in resistance to various other forms of endocrine therapy. Deregulation of these pathways most often arises from genetic or epigenetic changes in the tumor cells themselves. These changes influence uptake and metabolism of the endocrine agents and cellular responses to their inhibitory effects **(Musgrove and Sutherland, 2009).**

Targeted agents to reverse resistance to endocrine therapy include: EGFR inhibitors, mTOR inhibitors, PI3K inhibitors, hystone deacetylase inhibitors, Src inhibitors and IGF-1R Inhibitors **(Rocio-Garcia et al., 2013).**

Aim of the Work

The aim of the work is to review the molecular basis of resistance to hormonal treatment and the recent advances concerning the management of hormonal resistant breast cancer.