ENDOCRINE RESISTANCE IN HORMONE RECEPTOR POSITIVE ADVANCED BREAST CANCER (A RETROSPECTIVE STUDY)

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List of Abbreviations

Abbr.	Title
AP1	: Activator protein 1
AdCCs	: Adenoid cystic carcinomas
ABC	: Advanced breast cancer
AIB1	: Amplified in breast cancer 1
AJCC	: American Joint Committee on Cancer
AKT	: Serine/threonine-specific protein kinase
AE	: Anti-estrogen
AIs	: Aromatase inhibitors
ATP	: Adenosine tri phosphate
ADH	: Atypical ductal hyperplasia
ALH	: Atypical lobular hyperplasia
BC	: Breast cancer
BCL-2	: B-cell lymphoma 2 gene
BM	: Bone metastasis
BMI	: Body mass index
BRCA1, BRCA2	: Breast cancer 1, 2
BI-RADS®	: Breast Imaging Reporting and Data System
TCGA	: Cancer Genome Atlas
CBR	: clinical benefit rate
CISH	: Chromogenic insitu hybridization
CTs	: Computed tomography
CI	: Confidence interval
CNB	: Core Needle Biopsy
CC	: Craniocaudal projection
CDK4/6	: Cyclin dependent kinases 4/6
CYP2D6	: Cytochrome enzymes

CK7 CK5 : Cytokeratin
DCIS : Ductal carcinoma insitu
DBT : Digital breast tomosynthesis
DFI : Disease-free interval
DNMT1 : DNA methyltransferase 1
EGFR : Epidermal growth factor receptor
ER : Estrogen receptor
PR : Progesterone receptor
ESR1 : Estrogen receptor protein 1 gene
ERR : Estrogen related receptors
ERE : Estrogen-response element
ET : Endocrine therapy
EMA : European Medicines Agency
ECM : Extracellular matrix
ERK : Extracellular signal regulated kinase
FGFR : Fibroblast growth factor receptor
FNAB : Fine Needle Aspiration Biopsy
FNAC : Fine needle aspiration cytology
FISH : Fluorescent insitu hybridization
FDG-PET)/CT: Fluorodeoxyglucose positron emission tomography
FDA : Food and Drug Administration
FFPE : Formalin-fixed paraffin-embedded tissues
FFDM : Full-field digital mammography
HRT : Hormone replacement therapy
HR : Hazard ratio
HR : Hormone receptor
HER2 : Human epidermal growth factor receptor-2
ICC : Invasive cribriform carcinoma
IGF-1 : Insulin-like growth factor-1
IHC : Immune histochemical

IDC : Infiltrating ductal carcinoma
IBC : Inflammatory breast cancer
ILC : Invasive lobular carcinoma
LCIS : lobular carcinoma in situ
LFS : Li-Fraumeni syndrome
LD : Loading-dose
LHRH : Luteinizing hormone-releasing hormone analogs
LNR : Lymph node ratio
MRI : Magnetic resonance imaging
MAPK : Mitogen activated protein kinase
MBC : Metastatic breast cancer
MLO : Mediolateral oblique projection
mRNA : Messenger RNA
miRs : MicroRNAs
MKI67 : Monoclonal antibody Ki-67
mtor : Mammalian target of rapamycin
NE : Neuroendocrine
NF-kB : Nuclear factor kB
nCOA3 : Nuclear receptor co-activator 3
OBC : Occult breast cancer
OCP : Oral contraceptive pills
ORR : Objective response rate
OS : Overall survival
PAX2 : Paired box 2 gene product
PAS : Periodic Acid Schiff staining
PI3K : Phosphatidyl inositol 3 kinases
PIK3CA : phosphatidyl inositol 3 kinases catalytic subunit
PIP3 / PIP2 : Phosphatidylinositol (3,4,5)-triphosphate, Phosphatidylinositol (4,5)-bisphosphate
PCR : Polymerase chain reaction

PFS	: Progression free survival
PTEN	: Phosphatase and tensin homolog
qRT-PCR	: Quantitative reverse transcriptase polymerase chain reaction
RTK	: Receptor tyrosine kinase
RS	: Recurrence score
RR	: Relapse rate
SEER	: Surveillance, Epidemiology, and End Results
SERDs	: Selective estrogen receptor downregulators
SERMs	: Selective estrogen receptor modifiers
SISH	: Silver insitu hybridization
SREs	: Skeletal-related events
SRC1, 2, 3	: Steroid receptor coactivator-1, 2, 3
PBL	: The primary breast lymphoma
TTP	: Time to progression
TNM	: Tumor-Node-Metastasis breast cancer staging system
uPA	: Urokinase-type plasminogen activator
UICC	: Union Internationale Contre le Cancer
VEGF	: Vascular endothelial growth factor
WHO	: World Health Organization
WBRT	: Whole-brain radiation therapy

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Abstract

Background: Breast cancer is considered the most frequently diagnosed cancer and the second cancer death leading cause in American women (following lung cancer). Despite the advances in the diagnosis and management of breast cancer, 6–10% of affected patients present metastatic breast cancer at diagnosis and 30–40% will develop metastases during the evolution of their disease. **Aim of the Work:** Firstly to review the literature on endocrine therapy for treatment of hormone receptor positive advanced breast cancer, mechanisms of endocrine resistance and how to overcome them and secondly to analyze retrospectively data of hormone receptor positive advanced breast cancer patients in the last 5 years. **Patients and Methods:** The department of clinical oncology and nuclear medicine, Ain Shams University hospitals, patients with a histologically and IHC confirmed diagnosis of endocrine positive advanced breast cancer female patients who received endocrine therapy in their metastatic setting during the period from January 2010 to December 2014, were included in this retrospective study. **Results:** The current study revealed multiple factors that can predict endocrine therapy response such as age, menopausal status, ER expression and site of distant metastasis **Conclusion:** The current retrospective study together with other clinical studies has changed the focus from a ‘‘one size fits all’’ treatment strategy, to the idea of tailored breast cancer therapies for which new predictive markers are currently being explored. **Recommendations:** The biological characteristics of breast cancer are important to determine the benefit from endocrine treatment in the metastatic setting, and the assessment of biomarkers from metastatic sites allows for a better prediction of this benefit than from primary tumor features. This indicates that it may be clinically important to biopsy distant metastases to assess hormone receptor and HER2 status whenever possible. Furthermore, this necessitates the identification of novel biomarkers through undergoing multiple studies and their introduction to be standard of care such as gene expression profiling.

Key words: breast cancer, endocrine therapy, hormonal receptors

Introduction

Breast cancer is the most frequently diagnosed cancer and the second leading cause of cancer death among American women. It is estimated that 1 in 8 women alive today in the United States will be diagnosed with breast cancer during her lifetime. An estimated 232,670 women will be diagnosed with breast cancer, of whom 40,000 women will die of cancer of the breast in 2014 ***(Howalder et al., 2014).***

"Advanced breast cancer" usually refers to recurrent breast cancer or metastatic breast cancer, also called Stage IV breast cancer ***(Poll, 2014).***

Breast cancer is a heterogeneous disease and is divided into five subtypes including (luminal A, luminal B, basal like, normal like breast tumor, and HER2-amplified) ***(Martin et al., 2014).***

Approximately 75% of breast cancers express either or both the estrogen receptor (ER) and progesterone receptor**.**

ER signaling pathway is the major driver in promoting proliferation, survival and invasion of ER-positive breast cancer cells.

Endocrine therapy is the mainstay of treatment for patients with ER-positive breast cancer, especially those with metastatic disease. Endocrine therapies include treatments

which target ER by blocking receptor binding with an antagonist or by depriving the tumor of estrogen. The three broad groups of currently approved anti-estrogen therapies are selective estrogen receptor modulators (SERMs) which block activity of ER; selective estrogen receptor down regulators (SERDs) which induce destabilization and degradation of ER; aromatase inhibitors (AIs), including steroidal/irreversible and nonsteroidal/ reversible inhibitors, which decrease estrogen production in peripheral tissues and within the tumors through inhibition of the enzyme aromatase ***(Zhao et al., 2014).***

Despite the fact that these therapies allow a significant decrease of breast cancer mortality, a large number of patients fail to respond to initial therapy (primary resistance) or develop resistance after prolonged treatment (acquired resistance) that limit the usefulness of these drugs ***(Bianco et al., 2012).***

Primary resistance in breast cancer is characterized by loss of ER (the ERα isoform) expression and ER gene mutations such as deletion and point mutation. By contrast, multiple mechanisms have been detected to account for the acquired resistance to endocrine therapies.

The ER can also be activated by ligand independent fashion, as a consequence of signaling events downstream of membrane receptor tyrosine kinases (RTKs). The bidirectional crosstalk between the RTK signaling and ER pathways has been implicated in the development of