

Assessment of Cardiotoxicity in Hormone Positive Postmenopausal Breast Cancer Patients Receiving Aromatase Inhibitors

A Thesis

*Submitted For Partial Fulfilment of Master Degree in
Clinical Oncology and Nuclear Medicine*

By

Rehab Gamal Shaaban

M.B.B.C.H.

Under Supervision of

Prof. Dr. Eman Aly El- Shaarawy

*Professor of Clinical Oncology and Nuclear Medicine
Faculty of Medicine – Ain Shams University*

Ass. Prof. Dr. Dina Ahmed Salem

*Assistant Professor of Clinical Oncology and Nuclear Medicine
Faculty of Medicine – Ain Shams University*

Dr. Reham Mohamed Faheim

*Lecturer of Clinical Oncology and Nuclear Medicine
Faculty of Medicine – Ain Shams University*

*Faculty of Medicine
Ain Shams University*

2017

List of Contents

Title	Page No.
List of Tables	i
List of Figures.....	vi
List of Abbreviations	ix
Introduction	1
Aim of the Work	4
Review of Literature	
▪ Epidemiology and Etiological Factors.....	5
▪ Clinical Presentation and Diagnostic Workup	15
▪ Treatment Modalities & Effect on Cardiac Safety.....	40
▪ Aromatase Inhibitors in Hormone Positive Post-Menopausal Patients	84
▪ Cardiotoxicity in Breast Cancer Patients Receiving Aromatase Inhibitors.....	115
Patients and Methods.....	143
Results	147
Discussion.....	190
Summary and Conclusions	206
Recommendations	208
References	210
Arabic Summary	

List of Tables

Table No.	Title	Page No.
Table (1):	BI-RADS Assessment Categories.....	18
Table (2):	Clinical and pathologic staging of breast cancer according to AJCC 7th edition.....	24
Table (3):	Clinical and pathologic staging of breast cancer according to AJCC 7th edition.....	25
Table (4):	Surrogate definitions of intrinsic subtypes of breast cancer.....	29
Table (5):	Prospective randomized trials comparing conservative surgery and radiation with mastectomy for early-stage breast cancer.....	46
Table (6):	Radiation therapy oncology group consensus definitions for breast cancer radiation therapy planning.....	51
Table (7):	Treatment policy for regional nodes.....	58
Table (8):	Systemic treatment recommendations for early breast cancer subtypes.....	60
Table (9):	Review of trials evaluating adjuvant trastuzumab with chemotherapy for patients with HER2/NEU-positive breast cancer.....	67
Table (10):	Summary of cardiac safety with trastuzumab in early breast cancer.....	69
Table (11):	Local and systemic treatment in percentage of patient in relation to age groups.....	83
Table (12):	The different criteria for identifying menopause.....	86
Table (13):	The major trials of adjuvant A.I.	93

List of Tables (cont...)

Table No.	Title	Page No.
Table (14):	Efficacy of aromatase suppression by three generations of AIs	105
Table (15):	Incidence of gynecologic symptoms in patients receiving aromatase inhibitors versus tamoxifen or placebo in randomized phase III trials	110
Table (16):	Pathophysiology of CV Toxicities observed with breast cancer treatment.....	116
Table (17):	Indirect systemic effects of estrogens	117
Table (18):	Direct effects of estrogens	117
Table (19):	Framingham Risk Score of cardiac events.....	125
Table (20):	Criteria for consideration of post anthracycline echocardiography according to National Comprehensive Cancer Network Guidelines	127
Table (21):	Imaging modalities in the detection of HF	130
Table (22):	Univariate and logistic models associating electrovar diagram changes to left ventricular systolic dysfunction.....	132
Table (23):	Classification of blood pressure (BP)	144
Table (24):	Patients and tumor characteristics in study population (no. = 123pts)	148
Table (25):	Stage of tumor in study population.....	149
Table (26):	Pathology and IHC of the tumor in study population	150
Table (27):	Received treatment in study population	151

List of Tables (cont...)

Table No.	Title	Page No.
Table (28):	Pervious and current hormonal treatment in study population.....	152
Table (29):	<i>Blood pressure</i> in study population.....	153
Table (30):	Blood pressure was classified according to	153
Table (31):	<i>Lipid profile</i> in study population.....	155
Table (32):	Evaluation of study population by <i>ECHO</i>	156
Table (33):	Evaluation of study population (n=123pts.) by <i>ECG</i>	158
Table (34):	<i>High risk group</i> in our study:.....	160
Table (35):	Correlation between measured blood pressure with patients and tumor characteristics in study population	162
Table (36):	Correlation between measured blood pressure and previously received treatment in study population	164
Table (37):	Correlation between measured blood pressure and current A.I in study population.....	165
Table (38):	Correlation between lipid profile with patient and tumor characteristics in study population.....	166
Table (39):	Correlation between lipid profile with patient and previously received treatment in study population	169
Table (40):	Correlation between lipid profile with current A,I in study population	170

List of Tables (cont...)

Table No.	Title	Page No.
Table (41):	Correlation between cardiotoxicity by ECHO with patient and tumor characteristics in study population	171
Table (42):	Correlation between cardiotoxicity by ECHO with previously received treatment in study population	173
Table (43):	Correlation between cardiotoxicity by ECHO with current A.I in study population.....	174
Table (44):	Sub-anylsis for significant correlation between cardiotoxicity in ECHO (n=71pts) and current treatment with A.I.....	176
Table (45):	The presence of ECHO cardiotoxic findings in relation to patient and tumor characteristics.....	177
Table (46):	The presence of ECHO cardiotoxic findings in relation to previously received treatment.....	179
Table (47):	Logistic regression analysis for correlation between between LVD and previous treatment with Taxans.....	180
Table (48):	The presence of ECHO cardiotoxic findings in relation to current A.I.....	180
Table (49):	Correlation between cardiotoxicity ECG findings with patient and tumor characteristics in study population	181
Table (50):	Correlation between cardiotoxicity ECG findings with previously received treatment in study population.....	183

List of Tables (cont...)

Table No.	Title	Page No.
Table (51):	Correlation between cardiotoxicity ECG findings with current A.I in study population.....	184
Table (52):	Correlation between high risk patients with tumor and patient characteristics in study population.....	185
Table (53):	Correlation between high risk patients with previously received treatment in study population.....	188
Table (54):	Correlation between high risk patients with current A.I in study population	189

List of Figures

Fig. No.	Title	Page No.
Figure (1):	Most common cancers among women	5
Figure (2):	Trends in Incidence Rates for Selected Cancers by Sex, United States, 1975 to 2013	6
Figure (3):	Calculated age specific incidence rates for breast cancer in Egypt 2008–2011	7
Figure (4):	Trends in In Situ and Invasive Female Breast Cancer Incidence Rates by Age, US, 1975-2012	8
Figure (5):	Global breast cancer mortality 2012.....	13
Figure (6):	Surveillance, Epidemiology, and End Results (SEER) Program SEER of breast cancer	14
Figure (7):	Overview of multidisciplinary breast cancer management.....	16
Figure (8):	A hyperdense mass with an irregular shape and a speculated margin with the focal skin retraction BI-RADS -5.....	19
Figure (9):	Mammography typical microcalcifications in DCIS	19
Figure (10):	Clinical and pathologic staging of breast cancer according to AJCC 7th edition.....	25
Figure (11):	Relapse free survival according to breast cancer TNM stage	33
Figure (12):	The Decision Tree for Ductal Carcinoma in Situ	45

List of Figures (Cont...)

Fig. No.	Title	Page No.
Figure (13):	Computed tomography simulation images used to determine arrangement of tangent beams in prone breast irradiation.....	50
Figure (14):	Shielding of LAD coronary in breast radiotherapy	53
Figure (15):	Dose distribution to the breast with intensity modulated radiation therapy	54
Figure (16):	Early breast cancer treatment algorithm	77
Figure (17):	Female breast cancer treatment patterns	82
Figure (18):	(Neo) adjuvant systemic treatment choice by biomarker expression and intrinsic phenotype.....	84
Figure (19):	Mechanism of action of hormonal therapy	102
Figure (20):	Metabolic pathways differentially targeted by aromatase inhibitors (AIs)	104
Figure (21):	Characteristic ECG changes in left systolic dysfunction	133
Figure (22):	Distribution of classes of blood pressure measured in study population.	154
Figure (23):	Classification of lipid profile changes.	155
Figure (24):	Classes representing cardiotoxicity appearing in the ECHO.	157
Figure (25):	Classification of study population according to ECG findings.....	159
Figure (26):	Percentage of high risk group population.	160
Figure (27):	The relation between lipid profile changes and history of HTN and DM.	167

List of Figures (cont...)

Fig. No.	Title	Page No.
Figure (28):	The relation between lipid profile changes and history IHD and vascular accidents.....	168
Figure (29):	The correlation between cardiotoxicity and history of DM and HTN.	172
Figure (30):	The relation between types of currently used A.I and number of patients with cardiotoxicity in ECHO.	175
Figure (31):	Correlation between ECG findings and history of IHD.	182
Figure (32):	The correlation between high risk group and history of HTN.	186
Figure (33):	The correlation between high risk group and history of DM.	186
Figure (34):	The correlation between high risk group and history of IHD.	187
Figure (35):	The correlation between high risk group and history of vascular accidents.	187

List of Abbreviations

Abb.	Full term
<i>AI</i>	<i>Aromatase inhibitors</i>
<i>AJCC</i>	<i>American Joint Committee on Cancer</i>
<i>ALN</i>	<i>Axillary lymph nodes</i>
<i>ALNs</i>	<i>Axillary Lymph Nodes</i>
<i>APBI</i>	<i>Accelerated Partial Breast Irradiation</i>
<i>ASTRO</i>	<i>American Society for Radiation Oncology</i>
<i>BCS</i>	<i>Breast Conservative Surgery</i>
<i>BMI</i>	<i>Body Mass Index</i>
<i>CALGB</i>	<i>Cancer and Leukemia Group B</i>
<i>CSR</i>	<i>Cancer Statistics Review</i>
<i>DCIS</i>	<i>Ductal Carcinoma in Situ</i>
<i>DIBH</i>	<i>Deep Inspiration Breath-Hold</i>
<i>E2</i>	<i>Estradiol</i>
<i>ER</i>	<i>Estrogen Receptor</i>
<i>ET</i>	<i>Endocrine Therapy</i>
<i>EUSOMA</i>	<i>European Society of Breast Cancer Specialists</i>
<i>FDG-PET</i>	<i>Fluorodeoxyglucose Positron Emission Tomography</i>
<i>FNA</i>	<i>Fine Needle Aspiration</i>
<i>GnRH</i>	<i>Gonadotropin-Releasing Hormone</i>
<i>HBOC</i>	<i>Hereditary Breast Ovarian Cancer</i>
<i>HER2</i>	<i>Human Epidermal Growth Factor Receptor 2</i>
<i>HR</i>	<i>Hormone Receptor</i>
<i>IBTR</i>	<i>Ipsilateral Breast Tumor Recurrence</i>
<i>IBTR</i>	<i>Ipsilateral Breast Tumor Recurrence</i>
<i>IDC</i>	<i>infiltrating Ductal Carcinoma</i>
<i>IHC</i>	<i>Immunohistochemistry</i>
<i>ILC</i>	<i>Infiltrating Lobular Carcinoma</i>
<i>IMRT</i>	<i>Intensity-Modulated Radiation Therapy</i>

List of Abbreviations (Cont...)

Abb.	Full term
<i>ITA</i>	<i>Italian Tamoxifen Anastrozole</i>
<i>LAD</i>	<i>Left Anterior Descending</i>
<i>LCIS</i>	<i>Lobular Carcinoma in Situ</i>
<i>LHRH</i>	<i>Luteinizing-Hormone-Releasing Hormone</i>
<i>LV</i>	<i>Left Ventricular</i>
<i>M</i>	<i>Metastasis</i>
<i>MBC</i>	<i>Metastatic Breast Cancer</i>
<i>MLC</i>	<i>Multi-Leaf Collimator</i>
<i>N</i>	<i>Nodal Involvement</i>
<i>NCRP</i>	<i>National Cancer Registry Program</i>
<i>OS</i>	<i>Overall Survival</i>
<i>OS</i>	<i>Overall Survival</i>
<i>PFS</i>	<i>Progression-Free Survival</i>
<i>PFS</i>	<i>Progression-Free Survival</i>
<i>PMRT</i>	<i>Post-Mastectomy Radiation</i>
<i>PR</i>	<i>Progesterone</i>
<i>PR</i>	<i>Progesterone Receptor</i>
<i>RS</i>	<i>Recurrence Score</i>
<i>SERMs</i>	<i>Selective Estrogen Receptor Modulators</i>
<i>SIOG</i>	<i>Society of Geriatric Oncology</i>
<i>SLN</i>	<i>Sentinel Lymph Node</i>
<i>SREs</i>	<i>Skeletal-Related Events</i>
<i>T</i>	<i>Tumor Size</i>
<i>TG</i>	<i>Triglyceride</i>
<i>TLI</i>	<i>Thymidine Labeling Index</i>
<i>WBI</i>	<i>Whole Breast Irradiation</i>

ABSTRACT

Major studies shown a significant DFS and OS advantage for different schedules of A.I treatment, including upfront AIs or sequential use of tamoxifen and AIs, have been shown to improve disease-free survival and overall survival compared with tamoxifen alone. The benefit of AIs on breast cancer recurrence and mortality far outweigh the risks of adverse events, and this should be taken into account when considering treatment options for patients. Nevertheless, cardiovascular events reported in clinical trials with AIs raise potential concerns that suggest the need for additional follow-up and studies.

Our cross sectional study that assessed cardiotoxicity for adjuvant and metastatic breast cancer patients at Ain-Shams university clinical oncology department in the interval from August 2016 to June 2017, a total of 123 hormone receptor positive postmenopausal women were treated with Aromatase Inhibitors (AIs) showed evidence of cardiotoxicity by ECHO in 71 patients (57.7% of study population) (P value=0.016). However, it was not detected by blood pressure measurement, lipid profile, ECG. So, ECHO represents an important tool for screening cardiotoxicity that seems to be associated with use of A.I in postmenopausal patients. With the goal of early detection of cancer treatment-related cardiac toxicity, leading to early treatment that results in better survival outcomes.

Keywords: Selective Estrogen Receptor Modulators - Recurrence Score - Post-Mastectomy Radiation

INTRODUCTION

Breast cancer is the leading cause of death among women, and its incidence is increasing with age. The average age at diagnosis is 61 years, and most of deaths occurs beyond the age of 65 years. The best approach to elderly women with breast cancer is still a big challenge. Those patients should have at least a brief general assessment to detect treatable problems, which are not adequately evaluated by the oncologists. The most effective treatment should be provided, unless there are explained reasons against it (*Tesarova, 2016*).

Breast cancer is considered the second most common cancer overall (1.7 million cases, 11.9%). In females, breast cancer is the most common cancer diagnosed in more and less developed regions, with more cases occurring in less developed (883, 000 cases) than more developed regions (794, 000) (*Erlay et al., 2012*).

In Egypt, breast cancer is the most common type of cancer which counts for 38.8% of all cancers in women (*Ibrahim et al., 2014*).

High endogenous estrogen levels increase the risk of breast cancer (particularly hormone receptor-positive) in both premenopausal and postmenopausal women. In postmenopausal women, the correlation between an increased risk for breast

cancer and increased hormone levels (eg: estradiol, estrone) has been fairly consistent (*Farhat et al., 2011*).

In postmenopausal women, most breast cancers are hormone receptor positive. So, endocrine therapies designed to prevent estrogen driven proliferation, could induce tumor regression (*Darby et al., 2005*).

Aromatase inhibitors (AI) are used in adjuvant treatment for post-menopausal women with hormone receptor positive breast cancer to reduce the risk of recurrence, and in the metastatic cases to improve overall survival (*Prince et al., 2016*).

Breast cancer is commonly diagnosed in postmenopausal women who are liable to have 1 or more cardiovascular disease which has a significant competing risk for morbidity and mortality among non-metastatic breast cancer survivors. After treatment completion, adjuvant systemic therapies may result in late-cardiac toxicity after decades. After some adjuvant breast cancer therapies the cumulative incidence of treatment-related cardiotoxic outcomes may be as high as 33%. Treatment-induced cardiotoxicity may manifest as cardiomyopathy, arrhythmias, coronary ischemia, thromboembolism, conduction abnormalities, valvular and pericardial disease (*Kathryn et al., 2012*).