The Role of Targeted Therapy in Breast Cancer

Essay

Submitted for partial fulfillment of master degree in Clinical Oncology and Nuclear Medicine

By

Mai Abd El-Baset Mohamed Ali

M.B.B.Ch

Under Supervision of

Prof. Dr. Tarek Hussein

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

Prof. Dr. Hesham Ahmed El-Ghazaly

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

Dr. Amr Shafiek

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

Faculty of Medicine
Ain Shams University
2012

First, I wish to express my deep thanks, sincere gratitude to

ALLAH

who always helps me, care for me and grunted me the ability to accomplish this thesis. I would like to express my deepest gratitude, thanks and gratefulness to **Prof. Dr. Tarek Hussein,** *Professor of Clinical Oncology and Nuclear Medicine, Faculty of Medicine- Ain Shams University, for his enthusiastic support, encouragement valuable scientific advices, and great help through out of the accomplishment of this work. May God bless him.*

My sincere thanks to **Prof. Dr. Hesham Ahmed El-Ghazaly,** *Assistant Professor of Clinical Oncology and Nuclear Medicine, Faculty of Medicine- Ain Shams University, for his kind and meticulous supervision, support, help, valuable supervision all through the work.*

Many thanks, and sincere gratitude to **Dr. Amr Shafiek,** *Lecturer of Clinical Oncology and Nuclear Medicine, Faculty of Medicine- Ain Shams University, for her kind supervision encouragement and meticulous revision of this work.*

Words can never express my sincere thanks to ***my parents, my sister, my brother, my husband and my dear son for*** *their generous support and continuous encouragement.*

I would like to express my over lasting gratitude to all ***my dear colleagues, friends*** *and all who offered me any kind of help, encouragement wishing them the best of all.*

Mai Abdel Baset Mohamed

List of Contents

List of Abbreviations

ABC	Advanced breast cancer
ACR	The American College of Radiology
ADCC	Antibody-dependent cellular cytotoxicity
ALTTO	The Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization
AP	Activator protein
ASCO/CAP	The American Society of Clinical Oncology/College of American Pathologists
BCIRG	Breast Cancer International Research Group
BCPT	The Breast Cancer Prevention Trial
BSE	Breast self exam
CB	Clinical benefit
CBE	Clinical breast exam
CBR	Clinical benefit rate
CDKs	Cyclin-dependent kinases
CISH	Chromogenic in situ hybridization
CMF	Cyclophosphamide, methotrexate, and 5-fluorouracil
DCIS	Ductal carcinoma in situ
DVT	Deep venous thrombosis
EGFR	Epidermal growth factor receptor

Epo B	Epothilone
ER	Estrogen receptor
FDA	The Food and Drug Administration
FGFR1	Fibroblast growth factor receptor 1
FISH	Fluorescence in situ hybridization
FTIs	Farensyltransferase inhibitors
HDACi	Histone deacetylase inhibitors
HDACis	Histone deacetylase inhibitors
HER2	Human epidermal growth factor receptor 2
HER2 ECD	Extracellular domain HER2
HERA	Herceptin® Adjuvant
HSP	Heat shock proteins
IAPs	Inhibitors of apoptosis proteins
IGF-1	Insulin-like growth factor-1
IHC	Immunohistochemistry
MAbs	Monoclonal antibodies
MAPK	Mitogen activated protein kinase
MDR	Multidrug resistance
MMPs	Matrix metalloproteinases
MRI	Magnetic resonance image
mTOR	The protein mammalian target of rapamycin
mTOR	Mammalian target of rapamycin inhibitors
NCCN	The National Comprehensive Cancer Network

NDGA	Nordihydroguaiaretic acid
NF-κB	The nuclear transcription factor nuclear factor-κB
NSAIDs	Non-steroidal anti-inflammatory drugs
PARP-1	Poly(ADP-ribose) polymerase-1
pCR	Pathological complete response
pCR	Pathologic complete response
PFS	Progression-free survival
PI3K	Phosphatidyl-inositol 3-kinase
PR	Progesterone receptor
PST	Primary systemic chemotherapy
PTEN	Phosphatase and tensin homologue loss
RTK	A receptor tyrosine kinase
SOLD	The synergism or long duration
STAR	The Study of Tamoxifen and Raloxifene trial
TAMs	Tumour-associated macrophages
TEACH	Tykerb® Evaluation After Chemotherapy trials
TKI	Tyrosine kinase inhibitor
TNBC	Triple negative breast cancer
TNM	Tumor, lymph nodes, metastasis
uPA	Urokinase-type plasminogen activator
US	United States
VEGF	The vascular endothelial growth factor

List of Tables

List of Figures

Epidemiology:

Excluding skin cancers, breast cancer is the most common malignancy among women, accounting for nearly 1 in 3 cancers diagnosed among women in the United States, and it is the second leading cause of cancer death among women ***(Howlader et al., 2011).***

Approximately 230,480 new cases of invasive breast cancer are diagnosed and 39,520 breast cancer deaths are expected to occur among US women in 2011. Breast cancer incidence rates were stable among all racial/ethnic groups from 2004 to 2008 ***(Jemal et al., 2011).***

Breast cancer is more than 100 times more common in women than breast cancer in men, although males tend to have poorer outcomes due to delay in diagnosis ***(Buchholz et al., 2009)***.

Despite advances in diagnosis and treatment, breast cancer is the most frequent cause of death in women ages 35 to 55 ***(Stanley et al., 2010).***

In Egypt, it is the most common cancer among women, representing 18.9% of total cancer cases (35.1% in women and 2.2% in men ***(EL-Bolkainy et al., 2006)***.

Risk factors:

1. Gender:

Simply being a woman is the main risk factor for developing breast cancer. The main reason they develop more breast cancer is because their breast cells are constantly exposed to the growth-promoting effects of the female hormones estrogen and progesterone. Men can develop breast cancer, but this disease is about 100 times more common among women than men ***(Jarde et al., 2011).***

2. Age:

About 1 out of 8 invasive breast cancers are found in women younger than 45, while about 2 of 3 invasive breast cancers are found in women age 55 or older ***(Colditz et al., 2009).***

3. Genetic risk factors:

About 5% to 10% of breast cancer cases are thought to be hereditary, resulting directly from gene defects.

BRCA1 and BRCA2: The most common cause of hereditary breast cancer is an inherited mutation in the BRCA1 and BRCA2 genes. In normal cells, these genes help prevent cancer by making proteins that keep the cells from growing abnormally ***(Stoddard et al., 2009).***

The risk may be as high as 80% for members of some families with BRCA mutations. Women with these inherited mutations also have an increased risk for developing other cancers, particularly ovarian cancer ***(Hendrick et al., 2010).***

Other gene mutations can also lead to inherited breast cancers. These gene mutations are much rarer and often do not increase the risk of breast cancer as much as the BRCA genes ***(Dunning et al., 2009).***

ATM: The ATM gene normally helps repair damaged DNA. Inheriting 2 abnormal copies of this gene causes the disease ataxia-telangiectasia. Inheriting one mutated copy of this gene has been linked to a high rate of breast cancer in some families ***(Filho et al., 2011).***

p53: Inherited mutations of the p53 tumor suppressor gene cause the Li-Fraumeni syndrome**.** People with this syndrome have an increased risk of developing breast cancer, as well as several other cancers such as leukemia, brain tumors, and sarcomas. This is a rare cause of breast cancer ***(Cavalieri et al., 2010).***

CHEK2: The Li-Fraumeni syndrome can also be caused by inherited mutations in the CHEK2 gene. Even when it does not cause this syndrome, it can increase breast cancer risk about two folds when it is mutated ***(Wiseman et al., 2010)***.

PTEN: The PTEN gene normally helps regulate cell growth. Inherited mutations in this gene cause Cowden syndrome, a rare disorder in which people are at increased risk for both benign and malignant breast tumors, as well as growths in the digestive tract, thyroid, uterus, and ovaries. Defects in this gene can also cause a different syndrome called Bannayan-Riley-Ruvalcaba syndrome that is not thought to be linked to breast cancer risk ***(Jarde et al., 2011).***

CDH1: Inherited mutations in this gene cause hereditary diffuse gastric cancer, a syndrome in which people develop a rare type of stomach cancer at an early age. Women with mutations in this gene also have an increased risk of invasive lobular breast cancer ***(Pritchard et al., 2011).***

STK11: Defects in this gene can lead to Peutz-Jeghers syndrome. People affected with this disorder develop pigmented spots on their lips and in their mouths, polyps in the urinary and gastrointestinal tracts, and an increased risk of many types of cancer, including breast cancer ***(Robb et al., 2009).***

4. Family history of breast cancer:

Breast cancer risk is higher among women whose close blood relatives have this disease. Having one first-degree relative with breast cancer approximately doubles a woman's

risk. Having 2 first-degree relatives increases her risk about 3-fold ***(Rohan et al., 2008).***

Altogether, less than 15% of women with breast cancer have a family member with this disease ***(Plomteux et al., 2006).***

5. Personal history of breast cancer:

A woman with cancer in one breast has a 3- to 4-fold increased risk of developing a new cancer in the other breast or in another part of the same breast ***(Norton et al., 2009).***

6. Previous chest radiation:

Women who had radiation therapy to the chest area as treatment for another cancer (such as Hodgkin disease or non-Hodgkin lymphoma) have a significantly increased risk for breast cancer. This varies with the patient's age when they had radiation. If chemotherapy was also given, it may have stopped ovarian hormone production for some time, lowering the risk. The risk of developing breast cancer from chest radiation is highest if the radiation was given during adolescence, when the breasts were still developing. Radiation treatment after age 40 does not seem to increase the breast cancer risk ***(Anton-Culver et al., 2010).***

7. Race and ethnicity:

Overall, white women are slightly more likely to develop breast cancer than are African-American women, but African-American women are more likely to die of this cancer.

However, in women under 45 years of age, breast cancer is more common in African-American women. Asian, Hispanic, and Native-American women have a lower risk of developing and dying from breast cancer ***(Ajani et al., 2009).***

8. Dense breast tissue:

Women with denser breast tissue have more glandular tissue and less fatty tissue, and have a higher risk of breast cancer ***(Shimizu et al., 2005).***

9. Menstrual period:

Women who have had more menstrual cycles because they started menstruating at an early age (before age 12) and/or went through menopause at a later age (after age 55) have a slightly higher risk of breast cancer. The increase in risk may be due to a longer lifetime exposure to the hormones estrogen and progesterone ***(Swanson et al., 2008).***

10. Oral contraceptive use:

Studies have found that women using oral contraceptives have a slightly higher risk of breast cancer than women who have never used them ***(Florescu et al., 2011).***

11. Hormone therapy after menopause:

Hormone therapy with estrogen (often with progesterone) has been used for many years to help relieve symptoms of menopause and to help prevent osteoporosis may have a role as a risk factor ***(Weir et al., 2008.)***

12. Breast-feeding:

Some studies suggest that breast-feeding may slightly lower breast cancer risk, especially if breast-feeding is continued for 1½ to 2 years ***(Hortobagyi et al., 2010)***.

13. Alcohol:

The use of alcohol is clearly linked to an increased risk of developing breast cancer ***(Thomsen et al., 2009)***.

14. Obesity:

Being overweight or obese has been found to increase breast cancer risk, especially for women after menopause ***(Ghadirian et al., 2009).***

15. Physical activity:

Evidence is growing that physical activity in the form of exercise reduces breast cancer risk ***(Chlebowski et al., 2011).***