MANAGEMENT OF HEREDITARY BREAST CANCER

Essay

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Clinical Oncology and Nuclear Medicine

By

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Amani Saleh Hadi

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رسالة
توطئة للحصول على درجة الماجستير
في علاج الأورام والطب النووي

مقدمة من الطبيب

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LIST OF CONTENTS

LIST OF ABBREVIATIONS

3D-CRT	Three-dimensional Conformal Radiation Therapy
ABC	Abortion-Breast Cancer
ALND	Axillary lymph Node Dissection
APBI	Accelerated Partial Breast Irradiation
ASCO	American Society of Clinical Oncology
ASR	Age Standardized Ratio
ASTRO	American Society for Therapeutic Radiology and Oncology
A-T	Ataxia-Telangiectasia
ATM	Ataxia-Telangiectasia Mutant
BCS	Breast Conservation Surgery
BCT	Breast conservation Therapy
BER	Base Excision Repair
BI-RADS	Radiology Breast Image Reporting and Data System
BMI	Body Mass index
BOADCEA	Breast and Ovarian Analysis of Disease Incidence And Carrier Estimation Algorithm
BRCA1	Breast Cancer gene one
BRCA2	Breast Cancer gene two
BSE	Breast Self Examination
BSO	Bilateral Slapingo-oophercetomy
CA	Cancer
CAT	Cyclophosphamide, Adriamycin, Taxan
CBE	Clinical Breast Examination
CLIA	Clinical Laboratory Improvement Amendments
CMF	Cyclophosphamide, Methotrexate, Fluorouracil
CO60	Cobalt 60
Colon CFR	Colorectal Cancer Family Registry
CS	Cowden Syndrome
CSGE	Conformation Sensitive Gel Electrophoresis
CT	Computed Tomography
CVS	Chorionic Villus Sampling

DCIS	Ductal Carcinoma In Situ
DES	DiEthylStilbestrol
DSBs	Double-Strand Breaks
EBCTCG	Early Breast Cancer Trialist Collaborative Group
EBRT	External Beam Radiotherapy
ELIOT	Electron Intraoperative Therapy
EORTC	European Organization for Research and Treatment of Cancer
ER	Estrogen Receptors
FA	Fanconi Anemia
FBC	Female Breast Cancer
FDR	First-Degree Relative
HBC	Hereditary Breast Cancer
HDR	High Dose Rate
HER2/neu	Human Epidermal growth factor Receptor 2
HNPCC	Hereditary non-polyposis colorectal cancer syndrome
HR	Homologous Recombination
HRR	Homologous Recombination Repair
HRT	Hormone Therapy Treatment
IAPs	Inhibitors apoptosis Proteins'
IBIS	International Breast Cancer Intervention Study
IBTR	Ipsilateral Breast Tumor Recurrence
IMNs	Internal Mammary Lymph Nodes
IMRT	Intensity Modulated Radiation Therapy
INDC	Invasive Ductal Carcinoma
INLC	Invasive Lobular Carcinoma
LCIS	Lobular Carcinoma In Situ
LFS	Li-Fraumeni Syndrome
LINC	Linear accelerator
LN	Lymph Node
LRP6	Lowe-density lipoprotein Receptor-related Protine6
MBC	Male Breast Cancer
MMR	MisMatching Repair

MMTV	Mouse Mammary Tumour Virus
MRI	Magnetic Resonance Imaging
MUFAs	Mono-Unsaturated Fatty Acids
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NER	Nucleotid Excision Repair
NF-kB	Nuclear factor-kB
NHEJ	Non-Homologous End Joining
NSABP	National Surgical Adjuvant Breast and Bowel Project
NSH	Nurses' Health Study
NYU	New York University
OR	odds Ratio
PAHs	Polycyclic Aromatic Hydrocarbons
PARG	PAR Glycohydrolase
PARP	Poly ADP Ribose Polymerase
PBI	Partial Breast Irradiation
PCBs	Poly-Chlorinated Biphenyls
PFS	Progression Free-Survival
PGD	Preimplantation Genetic Diagnosis
PHTS	PTEN Hamartoma Tumor Syndrome
PJS	Peutz-Jeghers Syndrome
pN0	No regional lymph node metastasis histologically and no additional examination for isolated tumor cells (ITCs)
pN0(i-)	No regional lymph node metastasis histologically.-ve immunohistochemical IHC
pN0(i+)	No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2 mm
polβ	Polymerase Beta
PR	Progesterone Receptors
PTEN	Phosphatase tensin homolog on chromsome TEN
PUFAs	Polyunsaturated Fatty Acids
RCTs	Randomize Controlled Trials
RECIST	Response Evaluation Criteria in Solid Tumors

RR	Relative Risk
RRSO	Risk-Reducing Salpingo-Oophorectomy
SAVI	Struts Adjusted Volume Implant
SCF	Supra-Clavicular Field
SDR	Second-Degree Relative
SERM	Selective Estrogen Receptor Modulator
SFAs	Saturated Fatty Acids
SNBx	Sentinel-Node Biopsy
SSA	Signle Strand DNA
SSB	Single-Strand Break
TARGIT	TARGeted Intraoperative Radiotherapy
TNBC	Triple Negative Breast Cancer
TSGs	Tumor Suppressor Genes
USEPA	U.S. Environmental Protection Agency
USPSTF	U.S. Preventive Services Task Force
UV	Ultra Volte
VEGF	Vascular Endothelial Growth Factor
WBI	Whole-Breast Irradiation
WHO	World Health Organization
XP	Xeroderma Pigmentosum
XRCC1	X-Ray Cross-Complementing gene 1

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Breast cancer is one of the most serious diseases, not only because of its high incidence but also because it leads to high death rate in women in the western industrial countries. Approximately more than 700000 breast cancer patients are diagnosed in the whole world annually and it remains the leading cause of death among women aged 40 to 50 years ***(Pazdur et al., 2008)***.

In the United States, it is the second most common cause of cancer death in women after lung cancer. U.S. women have a one in eight lifetime chance of developing invasive breast cancer and an almost 3% chance of breast cancer causing their death. Breast cancer is the commonest malignancy among Egyptian females, accounting for about 33% of female cancer cases in Egyptian National Cancer Institute (NCI) ***(ELBolkainy et al., 2005)***.

Hereditary breast cancer occurs in all ethnic and racial populations overall prevalence of BRCA1/2 mutations is estimated to be from 1:400 to 1:800. The majority of breast cancer are sporadic occurs randomly and somatic genetic alterations ***(Couch and Weber; 2002)***.

Hereditary breast cancer may eventuate as a result of mutations on several specific gene loci including BRCA1, BRCA2, ATM gene, PTEN and p53. Several other less frequently occurring predisposition genes such as the androgen receptor gene (AR), the HNPCC genes and the

estrogen receptor gene may also be involved, but to a lesser extent. Overall, approximately 5-10% of all breast cancers are thought to involve one of these inherited predisposition genes, with BRCA1 and BRCA2 being responsible for as much as 90% of this group ***(Barrois et al., 2004)***.

Initial reports of BRCA1-linked cases confirmed an excess of cancers with medullary features, lymphocytic infiltration and syncytial growth patterns. BRCA1-linked tumors also tended to be of higher grade than nonhereditary cancers, and are more frequently negative for ERs and progesterone receptors (PRs). C-erbB-2 and cyclin D and are more likely to be positive for p53 over expression. Ductal carcinoma-in-situ (DCIS) is rare in carriers compared with control patients without mutations. Tumors associated with BRCA2 mutations tend to be similar to their nonhereditary counterparts ***(Lakhani et al., 1998)***.

Breast cancers can be classified by different schemata. Every aspect influences treatment response and prognosis Classification aspects include stage (TNM), pathology, grade, receptor status, and the presence or absence of genes as determined by DNA testing. Most breast cancers are derived from the epithelium lining the ducts or lobules, and these cancers are classified as ductal or lobular carcinoma.

Carcinoma in situ is growth of low grade cancerous or precancerous cells in particular tissue compartment such as the mammary duct without invasion of the surrounding

tissue. The most common form of breast cancer is invasive ductal breast cancer, which develops in the cells that line the breast ducts. Invasive ductal breast cancer accounts for about 80% of all cases of breast cancer ***(Romond et al., 2005)***.

Molecular genetic testing for germ line BRCA1 and BRCA2 mutations is available on a clinical basis for individuals who are identified to be at high risk based on their personal and/or family history and for at-risk relatives of an individual with an identified germ line BRCA1 or BRCA2 mutation ***(Frank et al., 2002)***.

Clinical testing of these mutations includes:

1. **Targeted mutation analysis:** Targeted mutation analysis may be population-specific and include mutations known to be found at greater frequencies in individuals of certain ethnic background.

2. **Sequence analysis:** Sequence analysis combined with other methods can detect both common and family-specific BRCA1 and BRCA2 mutations and are recommended when the mutation in a family is not known, except in individuals of Ashkenazi Jewish descent. Both sequence analysis and deletion analysis may be required to detect complex BRCA1 or BRCA2 alleles that have a deletion of an exon or a deletion of several hundred or thousand_nucleotides along with novel inserted sequences.

3.Deletion/duplication analysis: Various methods can be used for the analysis of structural genomic abnormalities, such as large deletions, duplications, or rearrangements ***(Frank et al., 2002)***.

The National Comprehensive Cancer Network (NCCN) has published practice guidelines for the management of individuals with a hereditary breast cancer risk ***(Daly et al., 2010)***.

Breast cancer screening guidelines include:

- Monthly breast self-examination starting in early adulthood.
- Semiannual clinical breast examination beginning at age 25 years
- Annual mammography and breast MRI beginning at age 25-35 years.

Prenatal testing for a BRCA1 or BRCA2 germ line mutation is technically possible by analysis of DNA extracted from fetal cells obtained by amniocentesis usually performed at about 15 to 18 weeks' gestation or chorionic villus sampling (CVS) at about ten to 12 weeks' gestation. Preimplantation genetic diagnosis (PGD) may be available for families in which a BRCA1 or BRCA2 germ line mutation.

Breast cancer is usually treated with surgery and then possibly with chemotherapy or radiation, or both. Hormone positive cancers are treated with long term hormone blocking therapy; treatments are given with increasing