Genetics In Breast Cancer

RED: Important
GREEN: Doctors notes
Gray: Just go through it

OBJECTIVES

1-Know the prevalence of breast cancer and its relation to specific inherited genes .

2-know the factors which affect the prognosis of breast cancer .

3-know ERS and HER2 effect on breast cancer .

4-know the molecule Herceptin (trastuzumab) and its uses .

Introduction

Carcinoma of the breast is one of the leading causes of cancer morbidity among women worldwide. In the USA alone , there are more than 200,000 newly diagnosed cases of invasive breast cancer and in excess of 40,000 cancer related deaths each year.

When a new diagnosis of breast cancer is made , the most immediate issue of the patient involve :

1- What the diagnosis means for her future, whether or not she will survive.

2- Whether therapies beyond primary surgery might be of additional benefit.

There has been an encouraging decline in mortality from breast cancer over the past years , which can be attributed to several factors :

1- Largely related public education.

2- Screening programs that lead to the discovery of the disease at an earlier and more treatable stage.

In addition, there have been several significant and important treatment advances with improvements in hormonal therapies, the development of more effective combination chemotherapy regimens and the development of biologic therapeutics such as the targeted therapy against the human epidermal growth factor receptor 2 (HER2).

Genetic and family history of breast cancer

- About 5% to 10% of breast cancers are related to specific inherited mutations.
- Women are more likely to carry a breast cancer susceptibility gene if they develop breast cancer before menopause, have bilateral cancer, have other associated cancers (e.g. ovarian cancer), have a significant family history (i.e. multiple relatives affected before menopause), or belong to certain ethnic groups.
- About half of women with hereditary breast cancer have mutations **in gene BRCA1** (located on chromosome 17q 21.3), and an additional one-third have mutations **in BRCA2** (located on chromosome 13q 12-13). The exact location is very important
- Although their exact role in carcinogenesis and their relative specificity for breast cancer are still being elucidated, **both of these genes are thought to function in DNA repair**.
- **They act as tumor suppressor genes**, since cancer arises when both alleles are inactive or defective - one caused by a germline mutation and the second by a subsequent somatic mutation.
- Most carriers "70-80%" of the mutations will develop breast cancer by the age of 70 years (post-menopause), as compared with only "7-8%" of women who do not carry a mutation and might develop breast cancer by the age of 70.
- The role of these genes in nonhereditary sporadic breast cancer is less clear, because mutations affecting BRCA1 and BRCA2 are infrequent in these tumors.

Family history is an important risk factor If you carry BRCA1 & BRCA2 and you have strong family history that means you WILL get breast cancer

Cont.

Hormone receptors

- The first of the prognostic and predictive biomarkers in breast cancer to enter routine clinical use.
- 60% to 70% of breast carcinomas express estrogen receptors (ERs) and progesterone receptors (PRs).
- tumors that express these receptors depend on estrogen, progesterone, or both for growth
- The ERs became the first target for either treatment by therapeutic hormonal manipulations with **ER antagonists such as tamoxifen or treatment with aromatase inhibitors**, which will decrease the local concentrations of estrogen within the tumor microenvironment of mammary tissue or within metastatic deposits.
- The presence of ERs in breast cancer is a weak prognostic factor; however, it is optimally useful as a predictive factor for the benefit of adjuvant (additional or supportive) tamoxifen or aromatase inhibitors therapy.

Why is it important to know them? Because they play a role in prognosis and treatment

Molecular prognostic predictive factors HER2

- Normal cells have one copy of the HER2 gene on each chromosome 17 (CHR l7), as it normally transmits signals regulating cell growth and survival.
- In approximately 15 to 25% of breast cancers , the HER2 gene in the nucleus is found to be amplified 2 to 20 fold.
- HER2 - positive breast cancer is known to be aggressive since it is significantly correlated with several unfavorable pathologic tumor characteristics including: larger tumor size, positive axillary nodes, higher nuclear grade, higher proliferative index
- HER2 over expression may have a predictive role for response to adjuvant chemotherapy and endocrine therapy.

- The Herceptin molecule (Herceptin is the drug used against HER2 positive tumor cells) has been shown to demonstrate a high specificity and affinity for the HER2 protein.

Diagnostics

Demonstration of HER2 neu receptors can be done by using the following techniques:-

1-Immunohistochemistry antibodies against HER2 are applied to the tissue and if the antigen (HER2) is present a reaction is visualized by means of a dye or a color producing enzyme, which is used to label antibody.

2-Fluorescent or silver in situ hybridization (FISH or SISH)

Immunophenotyping as a Surrogate for Molecular Category Using Estrogen Receptor, Progesterone Receptor and HER2 Status

	Molecular Category			
	Luminal A	Luminal B	HER2	Basal-like*
ER	+	+	−	−
PR	+	+	−	−
HER2	−	+	+	−

Important to note the difference between Luminal A and B Breast cancer with regards to HER2 status

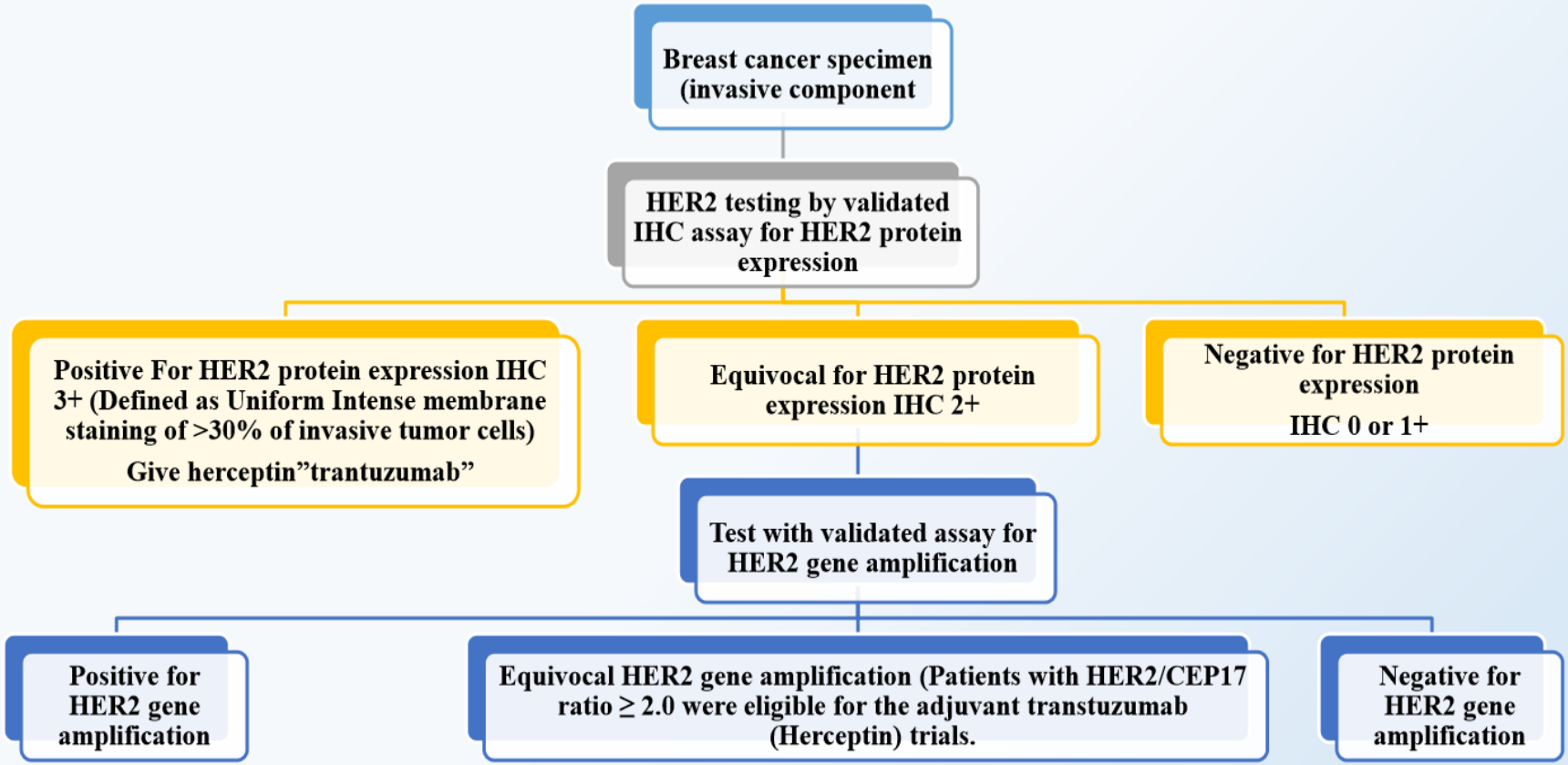
Fluorescent or silver in situ hybridization (FISH or SISH)

For your knowledge

- In FISH, fluorescently tagged DNA or RNA probes are used to identify genomic sequences of interest.
- FISH may be used to identify sequences of interest in tissue sections, an advantage that permits correlation of probe hybridization with tissue morphology.
- When coupled to conventional cytogenetics, FISH provides high resolution for identification of specific abnormalities, e.g., gene amplification, deletions, and translocations.
- FISH requires denaturation (transfer double stranded DNA into single stranded DNA), hybridization with a probe, and washing.
- First, a probe specific for the target of interest (eg. Cancer cells) is applied to the slide, along with a nuclear counterstain and reagents or heat that enhance denaturation of target DNA and reduce background. The slides are sealed and incubated in a humid environment under conditions that denature the DNA, allowing hybridization to occur between the probe and its cDNA sequence. The unbound probe is then removed by washing, and patterns of fluorescence are interpreted by fluorescence microscope.

In other words we take a sample from the breast tissue and we do denaturation (by Heating or Alkalinizing substance and the results is separation of the strands of DNA) and hybridization with probes (strands) and these strands have marker for HER2/neu gene on chromosome 17 and we see these markers on adding fluorescence, and if HER2/neu amplified it will bind with it and produce a light which I can see in the Immunofluorescence.

ASCO/CAP Guideline recommendations for the optimal algorithm for HER2 testing by IHC



Check your understanding

1. Which of the following is mutated in breast cancer?

A. BRCC1
B. BRCA3
C. BRCC2
D. BRCA2

2. What do we use to assess the levels of HER2 protein expression at the tumor cell membrane?

A. Immunohistochemistry
B. Cytology smear
C. Both are correct
D. Neither is correct

3. Which of the following is a weak prognostic factor in breast cancer?
A. HER2
B. ERS
C. HPV
D. ESR

4. Which of the following chromosomes carries the HER2 gene?

A. Chromosome 15
B. Chromosome 16
C. Chromosome 17
D. Chromosome 18

5. Which of the following receptors will most likely be expressed in breast cancer?

A. Estrogen and testosterone receptors
B. Estrogen and progesterone receptors
C. Progesterone alone
D. Testosterone alone

6. Where can we find BRCA1 & 2 respectively?

A. 17q 21.3 & 13q 12-13
B. 13q 12-13 & 17q 21.3
C. 17q 21.6 & 21q 17.3
D. None of the above

Answers: 1.D 2.A 3.B 4.C 5.B 6.A

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