



Review Article

An Overview of Her 2 Neu Positive Breast Cancer

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ABSTRACT

The term "cancer" encompasses a wide range of diseases that share the common feature of abnormal cell growth and uncontrolled spread within the body. In HER2- positive breast cancer, there is an amplification or overexpression of the HER2 gene, leading to increased production of the HER2 protein on the surface of cancer cells. By 2050, it is estimated that the number of breast cancer cases will reach 3.2 million. Breast cancer arises from a combination of genetic and environmental factors, making its etiology multifactorial in nature. BRCA1 and BRCA2, genes increase the risk. Hormonal factors, age, reproductive history, lifestyle choices, obesity, radiation exposure, and certain environmental factors contribute to the development of breast cancer. Possible signs and symptoms of breast cancer encompass a breast lump or thickening, alterations in breast size or shape, nipple discharge or inversion, skin dimpling or puckering, redness or scaliness of the breast skin, and enduring breast or nipple discomfort. Diagnostic tests for breast cancer include mammography, ultrasound, magnetic resonance imaging (MRI), and breast biopsy. The management of HER2-positive breast cancer involves a multimodal approach. It includes targeted therapies like trastuzumab, pertuzumab, and ado- trastuzumab emtansine, chemotherapy, surgery (lumpectomy or mastectomy), radiation therapy, and hormonal therapy.

INTRODUCTION

The term "cancer" encompasses a wide range of diseases that share the common feature of abnormal cell growth and uncontrolled spread within the body. These cells have the ability to invade and destroy normal tissues, and they can also spread to other parts of the body through a process called metastasis. [1]

BREAST CANCER:

Breast cancer is a type of cancer that originates in the breast tissue, typically starting in the cells lining the milk ducts or the lobules that produce milk. It is characterized by the uncontrolled growth and division of abnormal cells in the breast, which can invade surrounding tissues and potentially spread to other parts of the body. [2] [3].

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HER 2 NEU POSITIVE BREAST CANCER:

HER2-positive breast cancer is a specific subtype of breast cancer characterized by the overexpression or amplification of the human epidermal growth factor receptor 2 (HER2/neu) gene. This genetic alteration leads to an increased production of the HER2 protein on the surface of cancer cells. The overexpression or amplification of HER2/neu receptors results in increased HER2 protein signalling within the cancer cells, promoting abnormal cell growth and division. [4] HER2-positive breast cancer is associated with more aggressive tumor behavior and a higher risk of tumor progression and metastasis compared to HER2-negative breast cancer. [5]

EPIDEMIOLOGY OF BREAST CANCER:

Breast cancer is a significant global health issue with varying incidence rates across different countries and regions. Here are some epidemiological facts about breast cancer:

Global Incidence:

According to the Global Cancer Statistics 2018 report, breast cancer is the most commonly diagnosed cancer among women worldwide, with an estimated 2.1 million new cases in 2018. [6]

Incidence in the United States:

Breast cancer is the most frequently detected cancer among women in the United States, with an anticipated 281,550 new cases of invasive breast cancer projected for 2021. [7]

Incidence in India:

In India, breast cancer exhibits the highest incidence and mortality rates among all cancers. As per the Globocan 2020 survey, breast cancer accounted for 13.5% of all cancer cases in India. [8] The number of cancer diagnoses in the country ranged from 1.3 to 2.5 million in recent years, with breast cancer being the most prevalent type. [9]

Impact in India:

One woman is diagnosed with breast cancer every four minutes in India, and a breast cancer-related death occurs every thirteen minutes. [10]

ETIOLOGY OF BREAST CANCER:

The etiology of HER2-positive breast cancer involves various factors, including genetic, hormonal, and environmental influences. Here are some key factors associated with the development of HER2-positive breast cancer:

Genetic Factors:

HER2 (human epidermal growth factor receptor 2) gene amplification or overexpression is a hallmark of HER2-positive breast cancer. Genetic alterations in the HER2 gene lead to an increased production of HER2 protein on the surface of cancer cells. [11] Other genetic factors, such as mutations in BRCA1 and BRCA2 genes, are also associated with an increased risk of developing HER2-positive breast cancer. [12]

Hormonal Factors:

Hormonal influences play a role in breast cancer development, including HER2-positive subtype. Prolonged exposure to estrogen and progesterone hormones is associated with an increased risk of breast cancer, including HER2-positive breast cancer. [13][14] Hormone receptor status, particularly estrogen receptor (ER) and progesterone receptor (PR) status, may also be linked to HER2-positive breast cancer. [15][16]

Lifestyle and Environmental Factors:

Certain lifestyle factors have been associated with an increased risk of breast cancer, but their direct influence on HER2-positive breast cancer is not yet fully understood.

Factors such as physical inactivity, obesity, excessive alcohol consumption, and smoking have been linked to an increased risk of breast cancer overall. [17]

Hormone-related Factors:

Early menarche (onset of menstruation) and late menopause have been associated with an increased risk of breast cancer, but their specific impact on HER2-positive subtype requires further investigation. [18]

SIGNS AND SYMPTOMS OF BREAST CANCER:

The signs and symptoms of breast cancer can vary, and not all individuals with breast cancer will experience the same symptoms. Some common signs and symptoms of breast cancer include:

Breast Lump or Thickening:

A lump or mass in the breast or underarm area is one of the most common and noticeable signs of breast cancer. The lump may feel hard, irregular in shape, and different from surrounding breast tissue.

Changes in Breast Size or Shape:

Breast cancer may cause changes in the size, shape, or appearance of one or both breasts. Swelling or distortion of the breast may be observed.

Skin Changes:

Breast cancer may cause skin changes on the breast, such as redness, dimpling, puckering, or thickening of the skin. The skin may resemble an orange peel in texture (referred to as "peau d'orange").

Nipple Changes:

Changes in the nipple, such as inversion (turning inward), flattening, or changes in direction, may be indicative of breast cancer. Unexplained nipple discharge, other than breast milk, may also occur.

Breast Pain or Discomfort:

Some women with breast cancer may experience breast pain or discomfort. However, it's important to note that not all breast cancers cause pain.

Unexplained Weight Loss:

In advanced cases of breast cancer, unexplained weight loss and loss of appetite may occur.

Enlarged Lymph Nodes:

Swollen or tender lymph nodes in the underarm or around the collarbone may indicate the spread of breast cancer to nearby lymph nodes.

DIAGNOSTIC TESTS OF BREAST CANCER:

Early detection is key to improving the prognosis and successful treatment of breast cancer. Regular breast self-examination, clinical breast examination by a healthcare professional, and age-appropriate mammography screening are important in detecting breast cancer at an early stage.

Immunohistochemistry (IHC):

Immunohistochemistry is a widely used method to assess the HER2 protein expression levels in breast cancer tissue samples. It involves staining the tissue samples with specific antibodies that target the HER2 protein. The staining intensity and extent of staining in cancer cells are evaluated under a microscope. The results are reported as 0, 1+, 2+, or 3+ based on the intensity and percentage of stained cells. A score of 3+ indicates strong HER2 protein overexpression and is considered positive for HER2 status, while scores of 0 or 1+ are considered negative, and 2+ is considered equivocal and often requires further testing, such as fluorescence in situ hybridization (FISH). [20]

Fluorescence In Situ Hybridization (FISH):

FISH is a molecular technique used to detect HER2 gene amplification in breast cancer cells. It involves the use of fluorescent DNA probes that specifically bind to the HER2 gene region. The probes emit fluorescent signals, which are visualized under a fluorescence microscope. The HER2/CEP17 ratio is calculated by comparing the number of HER2 gene copies to the number of copies of a reference gene called CEP17. A HER2/CEP17 ratio of ≥ 2.0 is considered positive for HER2 amplification. [21]

Silver In Situ Hybridization (SISH):

SISH is an alternative to FISH for detecting HER2 gene amplification in breast cancer cells. It uses a chromogenic method instead of fluorescent signals for visualizing the gene copies. The SISH assay provides similar information as FISH but with different staining characteristics. [22]

Dual In Situ Hybridization (DISH):

DISH is a method that combines the detection of HER2 gene amplification and HER2 protein expression within the same tissue section. It allows simultaneous visualization of both HER2 gene and protein status, providing comprehensive information for determining HER2 positivity.

Next-Generation Sequencing (NGS):

NGS is an emerging technique that can assess multiple genes, including HER2/neu, simultaneously in breast cancer tissue samples. It provides a comprehensive genetic profile of the tumor, which may aid in selecting targeted therapies based on multiple molecular alterations. [23]

PATHOPHYSIOLOGY OF HER 2 NEU BREAST CANCER:

Activation of HER2 Signalling: The HER2 protein belongs to the HER family of receptor tyrosine kinases, which regulate essential cellular processes such as cell growth, differentiation, and survival. In HER2/neu positive breast cancer, the overexpression of HER2 leads to an increased number of HER2 receptors on the surface of cancer cells. This, in turn, results in hyperactivation of HER2 signalling pathways. [24]

Activation of Downstream Signalling Pathways:

The overexpression of HER2 protein in HER2/neu positive breast cancer cells leads to the activation of downstream signalling pathways, particularly the PI3K/AKT/mTOR and MAPK/ERK pathways. These pathways are involved in promoting cell proliferation, survival, and angiogenesis. [25]

Increased Cell Growth and Division:

Abnormal HER2 signalling in HER2/neu positive breast cancer cells leads to uncontrolled cell growth and division. This unregulated cellular proliferation contributes to the formation of tumor masses and the rapid progression of the disease.

Aggressive Clinical Behavior:

HER2/neu positive breast cancer tends to be more aggressive than HER2-negative breast cancer. It is associated with a higher risk of tumor progression, recurrence, and metastasis. Therefore, accurate determination of HER2/neu status is essential for guiding appropriate treatment strategies. [26]

MANAGEMENT:

The management of HER2/neu positive breast cancer involves a multidisciplinary approach, and treatment decisions are based on the stage of cancer, tumor characteristics, and the patient's overall health.

Surgery:

Breast Cancer Surgery: Options include breast-conserving surgery (lumpectomy) or mastectomy, depending on the tumor size and location.

Lymph Node Evaluation: Axillary lymph node dissection or sentinel lymph node biopsy may be performed to assess lymph node involvement. [27]

Radiation Therapy:

Postoperative Radiotherapy: Radiation therapy is used after breast-conserving surgery to reduce the risk of local recurrence. [28]

Systemic Therapy:

Chemotherapy: Chemotherapy may be recommended for early-stage HER2/neu positive breast cancer or for patients with advanced-stage disease. [29]

Targeted Therapy: HER2-targeted therapies are used to specifically target HER2/neu positive breast cancer cells. Trastuzumab (Herceptin) is one of the most effective targeted therapies. [30]

Hormone Therapy:

Hormone therapy may be used in combination with HER2-targeted therapy if the cancer is also hormone receptor-positive (expressing estrogen or progesterone receptors). [31]

Follow-up and Supportive Care:

Regular follow-up visits with the oncologist are essential to monitor treatment response and detect any signs of recurrence or side effects. [32]

CONCLUSION



HER2-positive breast cancer represents a subtype of breast cancer wherein cancer cells exhibit an overexpression of the human epidermal growth factor receptor 2 (HER2) protein on their surface. The prognosis for HER2-positive breast cancer has significantly improved over the years, thanks to targeted therapies specifically designed to inhibit the HER2 protein. Trastuzumab (Herceptin) and other HER2-targeted therapies have been instrumental in improving outcomes for patients with this subtype of breast cancer. Treatment for HER2-positive breast cancer often involves a combination of surgery, chemotherapy, radiation therapy, and targeted therapies. Neoadjuvant and adjuvant therapies are commonly used to shrink the tumor before surgery or to prevent cancer recurrence after surgery. In recent years, there have been significant advancements in HER2-targeted therapies, and research continues to find more effective treatment options and combinations.

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