BARTKOWIAK, Hanna, GRUBSKI, Damian, ZIARNIK, Kacper, NADOLNY, Filip, JABŁOŃSKI, Jędrzej, KANIA, Martyna, ADAMOWSKA, Agnieszka and ŚNIATAŁA, Alicja. HER2-low breast cancer. Diagnostics, treatment and its adverse events. Journal of Education, Health and Sport. 2024;75:56276. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.75.56276
https://apcz.umk.pl/JEHS/article/view/56276

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).© The Authors 2024;
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The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 18.11.2024. Revised: 29.11.2024. Accepted: 05.12.2024. Published: 05.12.2024.

HER2-low breast cancer. Diagnostics, treatment and its adverse events

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Abstract

Introduction:
Breast cancer is one of the most commonly diagnosed malignant tumors among women worldwide. HER2 receptor is a protein that plays a role in cell growth, division, and repair. Approximately 50% of HER2 –negative breast cancers express low levels of HER2 receptors. HER2-low breast cancer is a newly characterized subtype of breast cancers that express low levels of HER2 receptor but do not meet the criteria for HER2 positivity and HER2 negative

with SCORE - 0 in immunohistochemistry. Recent studies have discovered that HER2-targeted therapies can be effective even at low HER2 expression levels.

Aim of study:

The purpose of this review was to increase awareness of HER2- low breast cancer. The objective was also to underscore the importance of detecting low and very low expression of HER2 receptors. The other goal of this project is to raise awareness of potential new directions in oncological treatments including antibody–drug conjugates.

Materials and methods:

The review was based on the analysis of materials collected in the „Pubmed" and Google Scholar databases. The search was performed using the keywords: „HER2-low breast cancer", trastuzumab deruxtecan antibody–drug conjugates", „HER2-low diagnostic algorithm".

Conclusion:

The results of the DESTINY - Breast04 study shows that trastuzumab-deruxtecan significantly improved both progression-free survival and overall survival among all patients including hormone-positive patients cohort compared to chemotherapy. While trastuzumab-deruxtecan is highly effective, it does come with specific safety considerations that necessitate close monitoring.

Keywords: HER2-low breast cancer, HER2 receptor, trastuzumab-deruxtecan, antibody–drug conjugates

Introduction

Breast cancer is one of the most commonly diagnosed malignant tumors among women worldwide, posing a serious threat to health and life.[1] It is the leading cause of cancer-related deaths, with millions of new cases investigated each year. The frequency of breast cancer has

been steadily rising, generating a growing global health concern.[2] Despite that, in recent years significant improvement has been made in developing new and more effective treatments. Progress in medical research has led to innovative treatments, such as immunotherapy, targeted therapies, and personalized medicine, which have enhanced progression free survival and overall survival.[3] These developments provide better outcomes, even in more advanced stages of the disease. [4] There are four biological subtypes based on receptors' presence: estrogen, progesterone, HER2 and proliferation marker Ki67 status. HER2 breast cancer accounts for approximately 15% of all breast cancers. [5]The presence of HER2 receptors is associated with poor prognosis.[6] Not only is it more aggressive but it is also characterized by metastasis to the other organs and more frequent relapses of the disease. [7]

HER 2 Receptor

HER2 receptor is transmembrane human epidermal growth factor receptor 2, a protein that plays a role in cell growth, division, and repair. [8,9,10] In literature The human protein is also frequently referred to as ErB-2(neuregulin-binding; lacks kinase domain), neu, CD340(cluster of differentiation 340). It is located in chromosome 17 and ist expression depends on the quantity of gene amplification.[11] The structure of HER2 receptor is composed of an extracellular ligand binding domain, a transmembrane domain, and an intracellular tyrosine kinase domain .[12] The extracellular domain comprises four subdomains: two ligand binding regions (LD1 & LD2), two cysteine-rich regions (CR1 & CR2) [13] (Figure 1)

HER2 activation results from heterodimerization and consequent transphosphorylation. HER2 itself does not have a known direct ligand, it plays a crucial role when activated through heterodimerization with other receptors in the ErbB ,leading to conformational change. [14]

Following conformational change, homo- and heterodimeric interactions between the HER receptors , HER2 undergoes autophosphorylation, where phosphate groups are added to specific tyrosine residues on the intracellular kinase domain of HER2.[15] The phosphorylated tyrosine residues serve as docking sites for various intracellular scaffolding proteins, triggering downstream signaling pathways. These include the PI3K/AKT, JAK/STAT, PLCγ/PKC, and Ras/MEK/ERK, that regulate, proliferation, angiogenesis, motility, apoptosis, invasion, differentiation, migration, adhesion, and cell survival. [16]

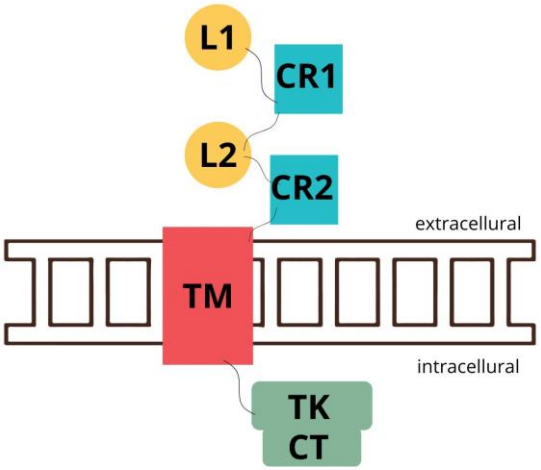

Figure 1. Structure of the HER2 receptor. The extracellular domain structure consist of two ligand binding regions (LD1 & LD2), two cysteine-rich regions (CR1 & CR2), a short transmembrane domain (TM), a catalytic tyrosine kinase domain (TK), and a carboxy terminal tail (CT). [12]

The HER2 receptor can contribute to tumorigenesis primarily through HER2 gene amplification that leads to the complete HER2 protein overexpression on the cellular membrane. It leads to excessive signaling that drives uncontrolled cell growth, proliferation, and survival.[17]

HER2 receptor diagnostics

Approximately 50% of human epidermal growth factor receptor 2 –negative breast cancers express low levels of HER2 receptor. [18] Currently there are many available methods to assess the HER2 status in tumor cells. [19] However, the only approved and recommended protocols for clinical use include chromogen-based immunohistochemistry (IHC) and the ratio of HER2/neu/CEN17 DNA probe–based in situ hybridization (ISH) using diverse visualization reagents. [20]

Immunohistochemistry

Immunohistochemistry (IHC) is the method of detecting the expression status of the HER2 receptor on the cell membrane. Test assay with the anti-HER2 antibodies 4D5 and CB11 on formalin-fixed, paraffin-embedded tissue, assay identified staining patterns for HER2 as negative (0) HER2-low (1+ and 2+ ISH-) or positive (2+ ISH+ and 3+). [20]

This receptor also is the target of trastuzumab therapy. It may seem that the actual detection of the HER-2 receptor would predict response to trastuzumab therapy. However, there are numerous factors that affect the results of HER2 IHC analysis such as storage,fixation, the specific antibody and its domain,reagent optimization,antigen retrieval, controls, and interobserver variability in interpretation. Taken together, these results imply lack of correlation between trastuzumab treatment and immunohistochemical findings. [21]

Table 1 shows the description of HER2 receptor expression by immunohistochemistry (IHC) assay of the invasive component of a breast cancer specimen according to the ASCO/Cap guidelines.[22]

HER2 score 0	No staining is observed or Membrane staining that is incomplete and is faint/barely perceptible and within ≤ 10% of tumor cells
HER2 score 1+	Incomplete membrane staining that is faint/barely perceptible and within > 10% of tumor cells
HER2 score 2+	Circumferential membrane staining that is incomplete and/or weak/moderate and within > 10% of tumor cells

	or Complete and circumferential membrane staining that is intense and within ≤ 10% of tumor cells
HER2 score 3+	Circumferential membrane staining that is complete, intense, and within > 10% of tumor cells

Table 1. Interpretation of IHC results [22]

HER2-low diagnostic process algorithm

If the result of expression of the HER2 receptor in IHC testing is HER2 score 2+, the in situ hybridization must be performed. The ISH must be ordered using the same specimen. If the result of the ISH gene to chromosome 17 is amplified with an HER2/CEP17 ratio ≥2.0 and an average HER2 gene (ERBB2) copy number ≥4.0 signals/cell, HER2 positive can be identified. [23]

HER2-low can be identified when expression of HER2 receptor in IHC is on HER2 score 1+ or HER2 score 2+ and lack of ERBB2 amplification by in situ hybridization. Figure 2 presets the algorithm of HER2- low identification pathway. [24]

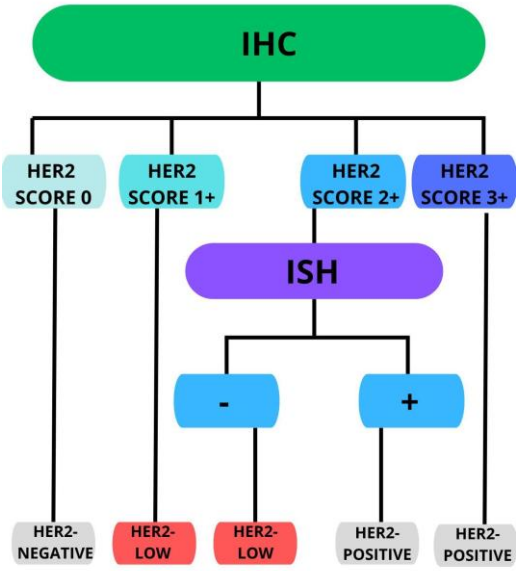

Figure 2. Presenting the pathway algorithm of HER2-low diagnostic process
IHC- immunohistochemistry ISH - in situ hybridisation

HER2-Low Breast Cancer Treatment

For many years patients with HER2-low breast cancer had no specifically designed treatments such as antibodies targeting this receptor. Treatments such as Trastuzumab were efficient only in high expression (score 3+) of HER2 receptor. Women with HER2-low expression had limited targeted treatment options and were treated with single-agent palliative chemotherapy.[25]

Recent study III trial of DESTINY - Breast04 has shed light on new methods of treatment previously treated HER2-low advanced breast cancer with an antibody–drug conjugates. [26] This clinical trial involved patients with HER2-low metastatic breast cancer who had received one or two previous lines of chemotherapy. Participants were randomized to receive either trastuzumab deruxtecan or a physician's choice of chemotherapy, which was the standard treatment at the time.[26]

Trastuzumab-deruxtecan

Trastuzumab-deruxtecan (T-DXd) is an antibody–drug conjugates(ADCs). These molecules consist of a humanised antibody against the antigen HER2, a novela, self-immolative, enzyme-cleavable linker covalently bound to a topoisomerase I inhibitor payload cytotoxic agent. They are designed for specific delivery of cytotoxic agents to malignant cells. [27]
Cleavable linkers are sensitive to lysosomal proteases such as cathepsins. In cancer cells cathepsins level is elevated.[28] After the linker is selectively cleaved,cytotoxic agent DXt is released intracellularly where it can cause cytotoxic effect and in consequence lead to apoptosis of targeted cell. [29] Furthermore the cytotoxic agent is then taken up and kills surrounding cells, which themselves may or may not express the ADC target antigen.This is called "bystander effect."[30] The bystander effect depends largely on factors such as the extent of ADC internalization after binding to the target antigen and the hydrophobicity of the armed cytotoxic payload.[30] This bystander killing can also occur if the cytotoxic drug is released from the antibody after antigen binding just before internalization.[31]

Destiny - Breast04 study

The results of the DESTINY - Breast04 study shows that trastuzumab - deruxtecan significantly improved both progression-free survival and overall survival compared to chemotherapy. In the hormone receptor–positive cohort, the median progression-free survival was 10.1 months in the trastuzumab - deruxtecan group and 5.4 months in the physician's choice group (hazard ratio for disease progression or death, 0.51; $P<0.001$) and overall survival was 23.9 months and 17.5 months, respectively (hazard ratio for death, 0.64; $P=0.003$). Among all patients, the median progression-free survival was 9.9 months in the trastuzumab - deruxtecan group and 5.1 months in the physician's choice group (hazard ratio, 0.50; $P<0.001$), and overall survival was 23.4 months and 16.8 months, respectively (hazard ratio for death, 0.64; $P=0.001$). [26]

Adverse events

While trastuzumab deruxtecan is highly effective, it does come with specific safety considerations that necessitate close monitoring. Drug-related adverse events occur in most

treated Patients.[32] The majority of treatment emergent adverse events with trastuzumab deruxtecan is gastrointestinal or hematological in nature. [33]Nausea and vomiting were two of the most frequent treatment emergent adverse events that occurred during trials. Some of the most dangerous events such as pneumonitis, interstitial lung disease and pneumonia lead to drug discontinuation, dose reduction, or dose interruption. Trastuzumab deruxtecan has been associated with some serious adverse events, including a small number of drug-related adverse events associated with death cases. [34]

adverse events	**DESTINY-Breast01[[34]**	**DESTINY- Breast03 [32]**	**DESTINY-Breast04[26]**
Nausea	77,7%	72,8%	73%
Fatigue	49,5%	44,7%	47,7%
Alopecia	48,4%	36,2%	37,7%
Vomiting	45,7%	44%	34%
Neutropenia	34,8%	42,8%	33,2%
Thrombocytopenia	21,2%	24,9%	23,7%
Pneumonitis	15,8%	10,5%	12,1%

Table 2. Includes the most common drug-related adverse events in three trials: Destiny-breast01, Destiny-breast03, Destiny-breast04

Conclusion

The introduction of effective HER2-targeted therapy for HER2-low breast cancer patients not only enlarged the therapeutic options but also changed the traditional classification of HER2

status . HER2-low represents a unique biological and therapeutic subgroup. The aim of the further research will improve treatment strategies and investigate additional targeted therapies for HER2-low patients, which may lead to developing personalized care for this group of Patients. This review underlines the importance of establishing new therapies to better reach the diverse molecular profiles within breast cancer.

1. Patient consent:

Not applicable

2. Data were obtained from

PubMed and Google Scholar.

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Receiving funding: not applicable

All authors read and approved the final manuscript.

4. Funding:

This research received no external funding.

5. Ethical Assessment and Institutional Review Board Statement:

Not applicable. As this article involves a review and synthesis of existing literature, rather than original research involving human subjects, ethical assessment and institutional review board statements are not applicable.

6. Data availability statement:

Not applicable

The authors declare no conflicts of interest.

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