Proceedings of ICBioMed 2025 Symposium: Computational Modelling and Simulation for Biology and Medicine
DOI: 10.54254/2753-8818/2025.LD26536

The Human Epidermal Growth Factor Receptor 2 (HER2) + Breast Cancer Monoclonal Antibody Drugs

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Abstract. In some breast cancers, HER2 genes are overexpressed, which leads to HER2+ BC. Historically, HER2+BC was associated with a more aggressive disease course, faster growth and higher risk of recurrence compared to HER2—BC. Therefore, it used to be a threat to women's health. Currently, diverse treatment methods are developed, including targeted therapy using monoclonal antibodies (mAbs) and antibody-drug conjugates (ADCs). However, there is insufficient data and research about the efficacy of specific ADC drugs, for example Kadcyla, as well as the detailed side effects of different drugs. More experiments may have to be carried out in order to obtain more data. This article mainly focuses on comparing different treatment approaches for HER2+ BC. The mechanisms of mAb and ADCs and effect of immunotherapy combined with drugs are analyzed. This article provides a reference for further research about the development and history of mAbs and ADCs. As for the future of treatment of HER2+ BC, more experiments have to be carried out in order to demonstrate the efficacy and safety of new ADC drugs.

Keywords: HER2+breast cancer, monoclonal antibody, antibody-drug conjugates, immunotherapy.

1. Introduction

Breast cancer (BC) is one of the most common malignant tumors in women, which leads to physiological functional damage and psychological trauma. Globally, 2,296,840 new cases of BC were reported for women in 2022 [1]. The human epidermal growth factor receptor 2 gene (HER2), which is a protein that regulates human cells growth, is overexpressed in about 15-20% cases of BC. In addition, HER2+ BC is the most invasive type of BC since it can grow extremely quickly. Diverse treatment strategies have been developed in recent years, for instance, antibody therapy targeting the HER2 pathway developed in 1998, available first generation of trastuzumab adjuvant trails in 2005 endocrine hormone therapy, chemotherapy, radiation, surgery and etc., all improve the mortality rate and median progression-free survival (PFS) of HER2 BC patients [2].

Among them, the targeted therapies, including utilization of monoclonal antibodies (mAbs) and antibody-drug conjugates (ADCs), are exceptionally effective in cells with lower expression of HER2. Targeted therapies are the cornerstone of treatment of HER2-positive BC, transforming HER2+ BC from a most aggressive and fatal type of BC to one with excellent prognosis, especially

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in early stages. Before the usage of targeted therapies, HER2+ BC is associated with significantly short disease-free survival, high recurrence rates, and poor overall survival (OS). The core targeted therapy mainly involves usage of monoclonal antibodies and ADCs. Trastuzumab, a mAb, targets HER2 extracellular domain. It blocks HER2 signaling and induce antibody-dependent cytotoxicity in early and metastatic stages. The pathologic complete response is increased by 20-30% in early stage and PFS is doubled. As for ADC drugs such as Enhertu (T-DXd) and Kadcyla (T-DM1), they are used at the advanced stage of BC. T-DXd lowers the risk of progression or death by 72%. The prevalent threats because of BC and BC-related death to women worldwide are eliminated.

The aim of this review is to summarize the pathomechanism of HER2+ BC and compare the efficacy of classic mAb drugs and ADCs, as well as the current status of antibody therapy targeting drugs combined with other immunotherapy methods. Furthermore, the different patients' outcomes produced by each method and side effects of each treatment will also be deeply discussed, contextualizing the future development of mAbs and antibody-drug conjugates.

2. Treatments of HER2+BC

2.1. Abnormal expression of HER2

HER2, also known as ERBB2, is a protein located at the surface of cells. In human body, it acts as a dimmer switch, receiving signals that controls and regulates cell growth as well as cell division. The most common cause of HER2 overexpression is because of the amplification of the ERBB2 gene. ERBB2 gene encodes the HER2 protein, which is a critical driver in HER2+ breast cancer. As there are extra copies of the ERBB2 gene on the chromosome, instead of the normal 2 copies, more HER2 mRNA and ultimately more HER2 proteins are produced. Approximately 15-20% of breast cancers are HER2+ BC, which is the most dangerous type of breast cancer. The reason is that amplification of HER2 is an oncogene, and its excess signaling contributes to uncontrolled cancer cell growth, cancer cell division, resistance to cell death as well as metastasis—a key hallmark of cancer. The other significant consequence of HER2 signaling is the formation of pathways involved in invasion and metastasis. This means HER2+ breast cancers often spread to distant organs, for example, bones, liver, lungs, and brain, earlier than other subtypes, even if the primary tumor is small and therefore possesses short PFS and high recurrence rate.

2.2. The influence of other factors

HER2 interacts with key factors through complex molecular crosstalk that drives tumor aggression and influences treatment response. Firstly, 50% of HER2+ breast cancers are also estrogen receptor-positive (ER+). HER2 and ER pathways crosstalk, promoting mutual activation. HER2 can activate kinases that phosphorylate ER at Ser118, enabling hormone-independent growth. As a result, ER becomes active without estrogen binding and the endocrine therapy resistance is produced. Since tumors ignore estrogen blockers, the hormone therapy fails in 50-70% of HER2+ and PI3K regulates proliferation and apoptosis, somatic PIK3CA mutations activate this process [3,4]. They are reported to be present in about 30% of HER2+ BC [5]. HER2 enhances tumor invasiveness and leads to hormone therapy resistance by interacting with molecules in the ER and PI3K pathways. These mechanisms together weaken the effect of endocrine therapy.

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2.3. Classic monoclonal antibody drugs—trastuzumab

Trastuzumab, the first in the HER class of target agents in HER2+ breast cancer, was FDA-approved in 1998. Mechanistically, it is active in targeting through specific binding with domain IV of the HER2 receptor, blocking downstream activation of signaling pathways (e.g., PI3K/AKT as well as RAS/MAPK pathways), and inducing antibody-dependent cellular cytotoxicity (ADCC) through the Fc region in activation of tumor cell-killing immuno-effector cells [6]. Despite its notable efficacy, medication resistance (e.g., PIK3CA mutations, loss of HER2 epitope) and cardiotoxicities are clinically significant limiting factors. Researchers have been working on newer combination strategies, such as pairing it with antibody-drug conjugates like T-DXd or developing bispecific antibodies targeting other epitopes, to preempt resistance issues. Precision therapy strategies based on biomarkers and individualized dosing regimens also require further study.

2.4. Classic monoclonal antibody drugs—pertuzmab(perjeta)

Approved in 2012 as a second-generation anti-HER2 mAb, pertuzumab selectively targets domain II of the HER2 receptor, effectively blocking heterodimerization of HER2 with other HER family members (e.g., HER3), thereby completely inhibiting HER2 signaling network activation [7]. The landmark CLEOPATRA Phase III trial demonstrated that, in HER2-positive metastatic breast cancer patients, the triple combination of docetaxel, trastuzumab, and pertuzumab significantly improved PFS (median PFS: 18.5 mo vs. 12.4 mo) and OS (median OS: 56.5 mo vs. 40.8 mo) compared to the double combination of chemotherapy and trastuzumab alone [8]. In the adjuvant setting, the APHINITY trial showed that adding pertuzumab to standard chemotherapy and trastuzumab significantly improved the 3-year invasive disease-free survival (iDFS) rate from 93.2% to 94.1% in high-risk patients (those with nodal positivity or hormone receptor negativity) [9]. Like trastuzumab, pertuzumab faces challenges such as resistance and cardiotoxicity, driving research into novel combination therapies and personalized treatment approaches.

ADCs are an innovative and rapidly advancing cancer therapy, particularly in breast cancer. They are composed of a mAb, a linker (cleavable or non-cleavable), and a cytotoxic payload to deliver targeted cell-killing effects to tumors [10].

2.5. Treatment by ADCs

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2.5.1. Enhertu (T-DXd)

Enhertu (trastuzumab deruxtecan, T-DXd), the first targeted therapy approved by U.S Food and Drug Administration (FDA), plays a critical role in the treatment of HER2+ BC because of its extraordinary efficacy, especially in the advanced stage [11]. Enhertu incorporates a mAb derived from trastuzumab, which has high affinity and specificity for HER2. After binding with HER2, the Enhertu complex is taken inside the cancer cell through receptor mediated endocytosis. The payload in Enhertu is called deruxtecan, which is a potent topoisomerase I inhibitor. Deruxtecan stabilizes the "cleavable complex" formed by topoisomerase I and DNA. This prevents the enzyme from resealing the DNA break it created. When the replication fork collides with this stabilized complex, it causes irreversible double-strand DNA breaks, which then triggers cell cycle arrest and ultimately

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lead to cancer cell death. The other important feature of Enhertu is the Bystander effect the linker-payload combination is membrane permeable. Therefore, Enhertu cannot only kill the HER2 overexpressed cells, but also nearby cancer cells.

In the DESTINY-Breast03 study in people with HER2+ metastatic breast cancer, treatment with Enhertu lengthened the amount of time people lived without their cancer getting worse by 72% when compared to Kadcyla [12].

However, although it is innovative and effective, the side effects of Enhertu is still inevitable. The common adverse reaction in patients includes nausea, reduced appetite, vomiting, musculoskeletal pain, fatigue, diarrhea, alopecia, and constipation. 28% of the patients attending the trial of Enhertu had adverse reactions and 16% of the patients had to permanently stop receiving Enhertu [12].

2.5.2. Kadcyla (T-DM1)

KAdcyla, (T-DM1) is another ADC drug used to treat HER2+ BC, whereby trastuzumab is linked to mertansine, primarily in the adjuvant setting for residual disease and in the metastatic setting. It is currently undergoing multicentered phase 3 trials, exploring its full role in the treatment of HER2 overexpression BC, with promising early results [8].

The key trial of Kadcyla is called EMILIA. The result of the trial shows that PFS of Kadcyla is 9.6 months, OS is 30.9 months and the response rate is 43.6%. Thus, Kadcyla offers robust efficacy in HER2+ BC treatment [13].

Similarly, its common side effects include fatigue, nausea, musculoskeletal pain, thrombocytopenia (low platelets), increased liver enzymes, neuropathy, and headache. Cardiac toxicity is less common than with trastuzumab alone, but monitoring is still requiredThe heading of a sub subsection title should be in 12-point bold with initial letters capitalized, aligned to the left with a linespace single and an additional spacing of 10-point before and 10-point after.

2.6. Combined with other immunotherapy methods

2.6.1. Anti-HER2 bispecific antibodies + immunomodulation

New bispecific antibodies ZW25 (against ECD4/ECD2 of HER2) and KN026 (against HER2/HER3 heterodimer) elicit HER2 pathway inhibition and activate immune cells through their novel spatial architecture [14]. Preclinical data verify that these drugs not only suppress proliferation and metastasis of HER2+ tumor cells but also significantly reconstruct the tumor's immune microenvironment. Clinical trial data from a recently reported Phase II study reveal that ZW25 combined with pembrolizumab achieves a 45% objective response rate in advanced HER2+ breast cancer, significantly superior to monotherapy (28%), with 2-3 times increased CD8+ T-cell infiltration in tumor tissue [15].

2.6.2. Antibody-drug conjugates (ADCs) + immunotherapy

Third-generation ADCs such as trastuzumab deruxtecan (T-DXd) offer an excellent platform for combination regimens due to their powerful "bystander effect" and induction of immunogenic cell death (ICD). The DESTINY-Breast12 trial revealed that combining T-DXd with durvalumab achieves a median PFS of 12.1 months in HER2-low metastatic breast cancer, significantly outperforming monotherapy (6.8 months). In TROP2-targeted ADC therapy, sacituzumab govitecan (SG) combined with atezolizumab achieves a 52% objective response rate in HR+/HER2- breast cancer with excellent tolerability [16]. Future research focuses on: 1) Establishing predictive

DOI: 10.54254/2753-8818/2025.LD26536

biomarker signatures (e.g., PD-L1 CPS score, TMB, MSI); 2) Optimizing dosing schedules and sequences; 3) Exploring novel immune checkpoint inhibition mechanisms in combination with ADCs [17].

3. Conclusion

This review provides the up-to-date developments in the management of HER2+BC, where the focus was placed on the mAbs trastuzumab and pertuzumab and on the ADCs T-DXd and T-DM1. Therapies with the agents have transformed the face of the illness from the aggressive disease with grim outcome in the past into one with significantly better potential for survival. Why the drug has been beneficial is the targeted therapy where the cells are targeted by disrupting the cells' HER2 receptors' pathway towards cytotoxicity and in the ADCs by conveying the deadly payload into the tumor cells. Of future potential interest are new agents including bispecifics and immunoprotein combinations.

The observation reveals the value added by targeted therapy in enhancing patient results in concert with the original focus on the aggressiveness and historically dismal results for HER2+ BC. The results pave the way for subsequent research with the focus on breaking through the causes of resistance and toxicity and maximizing the efficacy of combinational therapy.

One significant limiting factor is the variation in patient response caused by genetic heterogeneity and side effects from therapy potentially limiting wider applications. Greater attention should go towards customized methods of medicine according to the employment of biomarkers in treatment outcome prediction and new combinations in resistance overcoming attempts. Eventually, targeted therapy development against the HER2 forms the future of precision oncology and has the potential for even more effective treatment even more tailored.

Authors contribution

All the authors contributed equally and their names were listed in alphabetical order.

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