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Monoclonal Antibodies Targeting on HER2-positive Cancers

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Abstract:

Trastuzumab can be a therapeutic approach targeting cancers with high expression of human epidermal growth factor receptor 2 (HER2). The market demand for trastuzumab is high, but its large dosage and high price have led to the emergence of many biosimilars. As patents expire, other pharmaceutical companies can develop biosimilars, fostering competition, reducing costs, and increasing patient access to this important therapy. Therapeutic mechanisms of trastuzumab involve binding to the HER2 receptor, inhibiting cancer cell growth signal transduction, inducing antibody-dependent cell-mediated cytotoxicity, and potentially triggering effects such as cell cycle regulation and apoptosis, ultimately suppressing tumor growth. In clinical trials, ABP 980, CT-P6, and PF-05280014 all showed a high level of similarity as their reference drug, trastuzumab. In this review, the potential therapeutic clinical applications of biosimilars are supported by clinical trials through their high similarity to the reference drug, encompassing similarities in safety, structure, efficacy, and mechanism of action. These similarities contribute to the success of biosimilars for patients.

Keywords: Trastuzumab; biosimilar; HER2 positive cancer; ABP 980; CT-P6.

1. Introduction

Trastuzumab, marketed as Herceptin® (Genentech, San Francisco, CA, USA), is a recombinant humanized IgG1 monoclonal antibody targeting the human epidermal growth factor receptor-2 (HER2). The development of biosimilars for trastuzumab is needed to provide more patients with the opportunity to receive treatment for HER2-positive cancers. One of the most common HER2-positive cancer is breast cancer. Breast cancer occurs in every country in the world and it caused 685 000 deaths globally in 2020 [1, 2]. Patients with breast cancer account for 36% of cancer patients. Breast cancer is also one of the first lethal cancer in women. A lot of breast cancer patients are tested as HER2-positive. Previous research showed that chemotherapy together with trastuzumab reduced 40% relative risk of recurrence and 34% of relative risk of death compared to treatment with chemotherapy alone [1, 2].

Although trastuzumab showed significance in breast cancer therapy, the high cost limits its applications, especially in developing countries and areas. As patents expire, other pharmaceutical companies can develop biosimilars, fostering competition, reducing costs, and increasing patient access to this important therapy. Biological medications known as biosimilars exhibit clinical efficacy and safety that are highly comparable to those of their reference drugs [1]. Increased accessibility to biosimilars has broadened the patient population eligible for biological treatments, alleviating the economic strain that cancer imposes on healthcare systems. However, the limited research assessing their clinical efficacy has understandably created uncertainty among healthcare professionals when prescribing biosimilar medications [1]. Thus, it is important to evaluate the manufacturing process of these biosimilars, and the transformative impact of trastuzumab on breast cancer therapy and its economic implications [1]. Therefore, this review outlines HER2-positive cancers and the pharmacological mechanism of trastuzumab and compares the clinical research outcomes of its biosimilars, including ABP980, CP-T6, and PF-05280014. Additionally, this review addresses pertinent concerns related to biosimilar development, regulatory aspects, and, most crucially, their contribution to breast cancer treatment by presenting scientific evidence regarding the clinical utilization of trastuzumab biosimilars.

2. Mechanisms of Trastuzumab and its Biosimilars

2.1 HER2 and Breast Cancer

Trastuzumab holds significant importance due to the high mortality rate of breast cancer. Breast cancer, characterized by uncontrolled cell growth in the breast, has various

types depending on the affected cells. The breast comprises lobules, ducts, and connective tissue, with most cancers originating in ducts or lobules. Metastasis occurs when breast cancer spreads through blood and lymph vessels, posing a threat beyond the breast. Approximately half of breast cancers develop in women without specific risk factors, except for gender and age.

Effectively preventing breast cancer primarily relies on managing risk factors and detecting it early. The identification of breast cancer in its initial phases significantly boosts prognosis and increases the chances of a cure [2]. Effectively averting breast cancer primarily hinges on the management of risk factors and early detection. Detecting breast cancer in its initial stages significantly improves the outlook and heightens the probability of a cure [2]. In a medical setting, breast cancer is categorized based on the hormone receptor expressed in tumor cells, and each subtype presents distinct risk factors for incidence, disease advancement, and sites of metastasis. Furthermore, individualized treatment strategies exist for each subtype, underscoring the importance of identifying the cancer subtype for optimal patient care. Among the hormone receptors associated with breast cancer, human epidermal growth factor receptor 2 (HER2) is frequently excessively expressed, correlated with a more aggressive clinical phenotype. The revelation of HER2 has paved the way for the development and approval of the inaugural biologically targeted therapy: the monoclonal antibody trastuzumab.

2.2 Mechanism of Trastuzumab

There is a growth in the utilization of antibodies, including trastuzumab, for treating various diseases. These antibodies fall into five isotypes, with IgG antibodies being the most commonly used in clinical approaches. These antibodies have two identical fragment antigen binding (Fab) regions that bind to the antibody target and fragment crystallizable (Fc) regions containing binding sites for Fc receptors in immune cells, platelets, hepatocytes, endothelial cells, etc. (Figure 1). In this context, HER2 is among the identified targets for antibody-based targeted therapy [1].

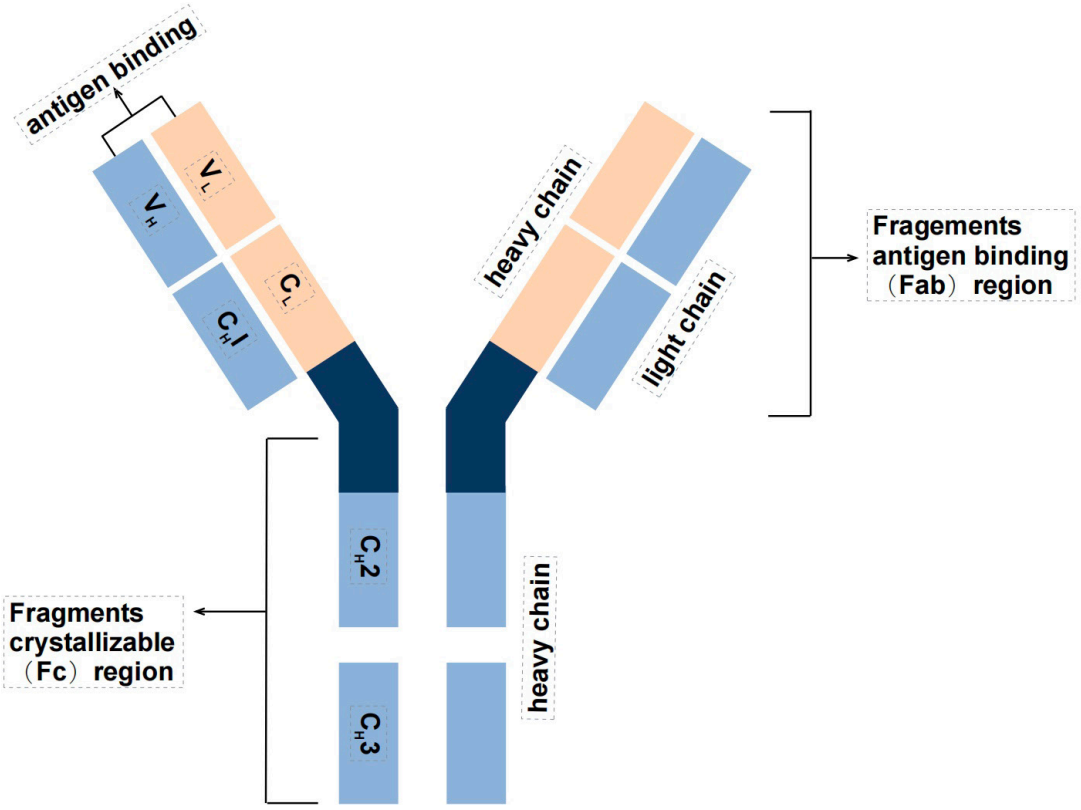

Fig. 1 Structure of trastuzumab. Antibodies have two identical fragment antigen binding (Fab) regions that are bound to the antibody targeting regions and fragment crystallizable (Fc) regions containing binding sites. Figure credit: original.

The IgG1, trastuzumab interacts with the extracellular region of HER2, specifically binding to domain IV, leading to G1 cell arrest through the upregulation of Cdk inhibitor p27 and the inhibition of Akt and MAPK pathways. This

results in the subsequent reduction of HER2 receptors, suppressing cellular survival and growth mechanisms [3]. Impeding dimer formation with HER receptors also blocks extracellular domain cleavage (Figure 2) [3]. Furthermore, trastuzumab induces passive endocytosis, directing the targeted receptor to undergo lysosomal degradation (Figure 2). Additionally, the Fc region of trastuzumab can bind with the Fc γ receptor III of Natural Killer (NK) cells or other immune cells to activate antibody-dependent cell-mediated cytotoxicity (ADCC) signaling pathway so that tumor cells can have cell lysis [3].

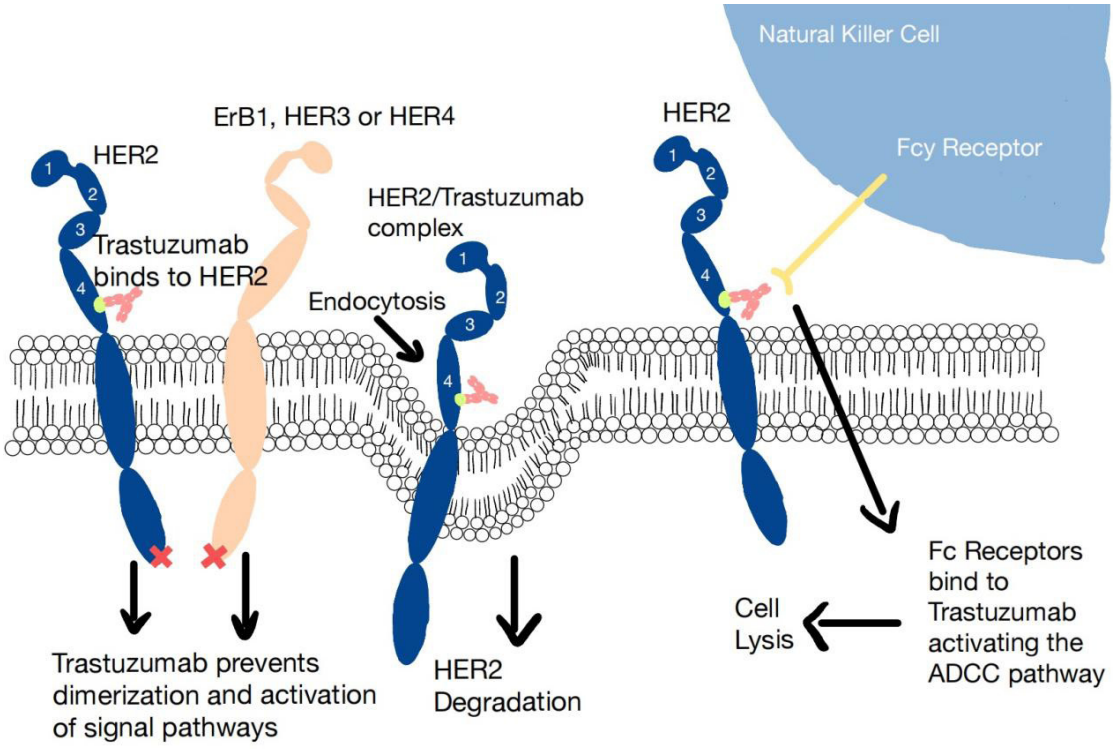

Fig. 2 Mechanisms of action and resistance for trastuzumab. It primarily works by inhibiting HER2 signaling by blocking dimerization and promoting the internalization and degradation of HER2. Additionally, the Fc region's interaction with immune cells, like Natural Killer cells, triggers antibody-dependent cell-mediated cytotoxicity (ADCC), contributing to the destruction of tumor cells expressing HER2. Figure credit: original.

3. Applications of Trastuzumab Biosimilars

3.1 ABP 980

Using surface plasmon resonance, the similarity is estimated between ABP 980 and its reference drug. ABP 980 and its reference drug, trastuzumab RP, both exhibit similarity in terms of at-rate, off-rate, and relative affinity with the extraterrestrial domain of human epidermal growth factor receptor 2 (HER2). ABP 980 and trastuzumab RP underwent competitive assessment binding SK-BR-3 breast cancer cells [4]. The outcome illustrated that the average combination of POSITIVE HER2 cells across all lotions and products tested was about 100%, validating the comparable activity of binding in both. Analysis of the cytometric flow of HER2-treated HER2 cells with ABP 980 and trastuzumab RP showed analog levels of post-binding HER2 internalization. In addition, proliferation in NCI-N87 gastric cancer cells is prohibited with high HER2 expression and MCF7 breast cancer cells block deficiency with stable low HER2 levels between ABP 980 and RP, confirming bio-similarity [4].

The clinical effects of ABP 980 were examined in a randomized, single-blind, single-dose Pharmacokinetic (PK) equivalence study involving healthy participants. It was found that ABP 980 and trastuzumab RP have similar pharmacokinetics [4]. Furthermore, both groups experienced similar rates of treatment-related adverse events, and none of the patients developed antibodies against ABP 980 during the study [4].

In conclusion, ABP 980 showed similar therapeutic effectiveness and comparable outcomes in terms of efficacy measures between ABP 980 and the reference drug.

3.2 CT-P6

Activation of the phosphatidylinositol 3 kinase/Akt pathway by HER2 and HER3 heterodimers can stimulate tumor cell proliferation [5, 6]. Trastuzumab, by binding to HER2, hinders HER3 phosphorylation and the activation of the phosphatidylinositol 3 kinase/Akt pathway, thereby efficiently interrupting this signaling cascade [7-10]. The assessment of CT-P6's influence on Akt1 and HER3 phosphorylation in BT-474 cells, conducted through quantitative sandwich ELISA, unveiled a concentration-dependent decline in phosphorylation levels [11].

Conducting a comparative assessment of the suppressive impacts on Akt1 and HER3 phosphorylation, signifying pathway restraint, revealed marginal distinctions among CT-P6, the European Union-endorsed trastuzumab, and the trastuzumab accredited in the United States. In the juxtaposition of standardized optical density (OD) values with the CT-P6 benchmark, scant fluctuation was observed among the trio of products concerning the hindrance of Akt1 phosphorylation (average relative activity remains steady at 99% for all three) and HER3 phosphorylation (average relative activity is within the range of 103–105%) [11].

Briefly, the animation illustrates CT-P6's mechanism of action, highlighting its interference with HER2 and HER3 heterodimers to inhibit the phosphatidyl inositol 3 kinase/Akt pathway, disrupting tumor cell proliferation signaling. As comparative analysis indicates, CT-P6 showed similar efficacy to trastuzumab.

3.3 PF-05280014

The clinical effectiveness of PF-05280014 against trastuzumab has been evaluated. The current Phase 3 equivalence study, a randomized, double-blind trial, aims to assess PF-05280014's effectiveness in treating women with metastatic HER2+ breast cancer. A total of 707 patients were randomly selected to be administered either PF-05280014 weekly or trastuzumab sourced from the EU weekly. The drug Paclitaxel was given on the 1st, 8th, and 15th days of each 28-day period, starting with an initial dose of 80 mg/m2, then potentially decreasing to 70 and 60 mg/m2 as required, and maintained for at least 33 weeks until the disease advanced [12].

Preliminary findings indicate that the effectiveness of PF-05280014 matches that of the benchmark trastuzumab. Utilizing RECIST version 1.1 guidelines and a blinded radiology analysis, the risk ratio for an objective response rate (either partial or complete up to 25 weeks, verified up to 33 weeks; the main outcome) between PF-05280014 and trastuzumab stood at 0.94 (95% CI 0.84-1.05). The specified ratio lies within the established equivalence range of 0.80 to 1.25. A similarity among those receiving PF-05280014 and trastuzumab is shown by the projected one-year rate of survival without disease progression (56 vs.52%) and the total survival rate (89 vs. 88%) [12].

PF-05280014 showed effectiveness similar to trastuzumab in the initial neoadjuvant therapy for HER2-positive breast cancer. In the PF-05280014 and trastuzumab groups, 99.0% and 96.6% of patients, respectively, received surgical interventions [13]. Around half of the patients in each group experienced a total pathological response, marked by the lack of invasive cancer cells in both breast and lymph nodes. Most patients experienced a pathological reaction, evidenced by total response rates of 46.5% for PF-05280014 and 48.3% for trastuzumab and partial response rates of 50.5% and 44.9%, respectively. It was noted that 2.0% of individuals receiving PF-05280014 and 3.4% of those on trastuzumab show no pathological reaction [13]. Furthermore, a considerable portion of patients across both treatment cohorts showed an objective response (either complete or partial) as assessed by central radiology review, either at the 6th cycle or upon treatment completion [13].

To sum up, PF-05280014 closely resembles its benchmark medication, trastuzumab, in effectiveness. Upcoming clinical studies are necessary to explore the widespread use of PF-05280014 in extensive populations.

4. Conclusion

Trastuzumab has elevated the treatment efficiency and safety for HER2+ breast cancer, but the accessibility to this biological medicine is constrained by its expensive manufacturing. As the patent for the reference product expires, the emergence of trastuzumab biosimilars generates anticipations of cost reduction, potentially facilitating access to biological therapies. This, in turn, could provide patients with a more affordable anti-HER2 therapy. ABP980, CT-P6, PF-05280014.Further clinical trials are required to verify the efficiency and safety of these biosimilars, to explore more applications, and to compose better biosimilars based on current research. In summary, the significance of comparing trastuzumab with its various biosimilars lies in demonstrating, through clinical trials, the broad patient drug options, higher curability rates, and the ability to achieve equivalent effects with lower costs. Moreover, it is a primary driver for the research and development of biosimilars. Additionally, these biosimilars contribute to the sustainable growth and diversity of the drug market for treating HER2-positive cancers.

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