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MECHANISM OF RESISTANCE TO TRASTUZUMAB (HERCEPTIN): AN OVERVIEW

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Abstract

This paper performs a comprehensive description of Trastuzumab resistance and possible remedy mechanism. Trastuzumab (Herceptin) is a monoclonal antibody used to treat HER-2 positive breast cancer. However, resistance to Herceptin is a significant clinical challenge. This review discusses the mechanisms of resistance to Herceptin, including increased activity of growth factor receptors, alterations in signaling cascades, and insulin-like growth factor receptor signaling. The role of PTEN loss, PI3K/AKT pathway activation, and HER-2 receptor truncation in Herceptin resistance is also explored. Strategies to overcome resistance, such as combining Herceptin with other therapies or targeting alternative signaling pathways, are discussed. Understanding the mechanisms of resistance to Herceptin is crucial for developing effective therapeutic strategies to improve patient outcomes.

Keywords:
Herceptin resistance, strategies to overcome resistance, signaling pathways, breast cancer, women, Trastuzumab

Introduction

In the view of the Siva et al. (2013) cancer is brought from Greek word "*Karkinoma*" meaning crab, because swollen veins in cancer are identical to crab's limbs. Cancer results from normal cells growing out of control, albeit different types of cancers exist, but all of them are characterized with growth, division, forming new abnormal cells, while defying control cancer may be due to old age, heredity, environment, etc. (Siva et al., 2013).

Cancers are broad or general terms referring to diseases due to cellular alterations elicited by uncontrolled growth and abrupt division of cells. Cancer is a group of diseases that are about 100 disorders affecting biological systems due to uncontrolled growth. Cancer can affect any part of the human body; thus, it is a disorder of concern. Initially, the name cancer was coined by "Hippocrates" about 2,300 years ago (Rajagoplan et al., 2013). In 1800s, living cells were discovered that give rise to other cells in future, and in 1775, it was observed that scrotal cancer spread among workers working in a chimney; lung cancer was observed in about 19th century, others follow in later dates. Normally, the result of normal or healthy cells grow or reproduced as a result of normal instruction given by the genes according to the need of the biological system. However, cancer cells are disobedient cells that are not following the right orders of the great growth control mechanism of the biological system (Rajput, 2022). The cancer was believed to be due to mutation of the genes (carried out in the DNA molecules present in the chromosomes of the cellular nucleus). Genes direct or instruct synthesis of certain amino acids to form proteins upon linking by a peptide bond, bur due to mutation activities genes are perturbed. Tumors occur if there are genetically mutated cells, increased propensity for growth and reproduction of certain cells (mutated cells), then hyperplasia (altered cells appear as normal) and dysplasia (whereby the progeny cells appear abnormal or abrupt and proliferating in reproduction without due cause) (Godoy-Ortiz et al., 2019). After this, the cancer cells may stay in the location, or traverse to other tissues, and may shed cells in blood and lymph, while affecting other parts of the body. This may destroy vital organs and lead to death (Selvam et al., 2011; Rodwell et al., 2017).

Cancer is mainly due to genetic disorders, lifestyle defects (such as smoking, alcoholism), and inheritance. Several types of cancers exist such as bladder, pancreatic cancer, prostate cancer, skin cancer, liver cancer, and breast cancer, etc. (Rajput, 2022) Breast cancer is among the frequently reported cancers in the women folk, in 2008 alone, 184,450 new cases were reported, and 40, 930bceaths were recorded (Siva et al., 2013: American Cancer Society, 2017). Breast cancer remains a major malignant tumor in women. Breast cancer is particularly happening due to social-psychosocial factors, environmental factors, lifestyles, but 5-10% of breast cancers can be attributed to genetic mutation and as well family history (Mathur et al., 2015). Breast cancer begin development from the breast, but tumors from there may reach nearby tissues (Obeagu & Obeagu, 2024). There are numerous approaches to breast cancer prevention or management, but biological approach involves the use of developed monoclonal antibodies targeting human epidermal growth factor receptor (HER-2) among other primary targets. Trastuzumab (Herceptin) is utilized to treat breast cancer due to its antitumor motive; therewith, about 26% of Herceptin was initially applied to treat metastatic form of breast cancer, and the drug show a good interaction along with other antitumor medications utilized (Perez & Dueck, 2103; Nami et al., 2018; Obeagu & Obeagu, 2024). Despite the kinds pf improvements given by cancer therapy using Trastuzumab (Herceptin), resistance to the approach is a major hurdle; therewith, comprehending the mechanism involved in resistance and promulgating

possible remedies is an important stride (Zhang et al., 2024). This paper performs a comprehensive description of Trastuzumab resistance and possible remedy mechanism

Mechanism of Resistance

Increased activity of growth factors receptors, and that of human epidermal growth factor (HER) signaling cascade, is one of the factor leads to continued proliferation in the presence of Herceptin. Increasing levels of phosphorylated epidermal growth factor activating ligand, and EGFR such as, transforming growth factor-alpha and heparin-binding epidermal growth factor (EGF), has been detected in HER-2positive breast cancer cell line with decrease response to HERCEPTIN (Armould et al., 2006; Ashok & Kefah, 2008; William et al., 2013). Clinically, the efficacy of Herceptin seems to be limited in breast cancer that overexpressed HER-2 as measured intense membranes staining in most of the tumor cells with HER-2 IgG 3+immunochemistry or high number HER-2 gene determined by Fluorescence In Situ Hybridization (FISH) (Tseng et al., 2006; Sharial et al., 2012; Labaran, 2014; Stratikopoulos & Parsons, 2016). Nonetheless, overexpression of HER-2 by Fluoresce In Situ hybridization, or immunochemistry is the biomarker predictive as a better response to the therapeutic with the antibody. Most of the women with HER-2 gene-amplified metastatic breast cancer do not respond to Herceptin, suggesting both de Novo and required mechanisms of resistance to Herceptin. For instant overexpression of IGF-R1 or increase levels of HER/heteromodimers (Arpino et al., 2008). This potentiate the activation of phosphatidylinositol 3-kinase (P13) and the Akt which act as downstream effectors which is very important in Herceptin action when transfected into antibody responsive to human barest cancer cells (Leqque-Cabal et al., 2016; Luque-Bolivar et al., 2020; Łukasiewicz et al., 2021). As a result of low level or loss of phosphatase (P10), the implication of the important pathways (P13K) in primary tumour was associated to the lower response to Herceptin. Knowing the mechanisms behind the Herceptin resistant is a critical step in the development of anti-HER-2. The important contributors to the mechanisms of resistant are; the truncation of human epidermal growth factor receptor (HER-2), by fragmentation of P95HER-2 exhibit resistance to Herceptin due to lack of Herceptin resistance, binding epitope can increase photolytic cleavage of epidermal growth factor receptor (HER-2) which change the translation and initiating site of HER-2 protein (Baselga & Aklbanell, 2001; Brader & Eccles, 2004). Various alteration of the receptor- antibody interaction and the binding that occur, may act as the main mechanisms for the resistance. Therefore, increased expression of protein like mucin4 and its membrane associated with glycoprotein which inhibit the action of human epidermal growth facyor2 and prevent binding of Trastuzumab (Herceptin) to the human epidermal growth factor2 (HER-2) (Labaran, 2014; Łukasiewicz et al., 2021).

Insulin like growth factor receptor signaling

Signaling pathways of insulin-growth factor (IGF-IR), and HER-2 are the major mechanisms for Herceptin resistance and human anti insulin-like growth factor receptor (IGFR-IR) IgG, CP-751871, and small-molecule selective IGF-1R TKI, NVP-AEW541 has demonstrated antitumor activity against Herceptin resistance in breast cancer tumor models (Bruce et al., 2010; Cleveland Clinic, 2021). High levels expression of insulin-like growth factor receptor (IGFR-IR) and human epidermal growth factor receptor2 (HER-2), amplified cell lines and are connected to reduce the response to Herceptin. This determination is as result of crosstalk between insulin growth factor-like receptor (IGFR-IR) and HER-2, with the stimulation of IGR-1 leading to phosphorylation of HER-2 and the activation of phosphatidylinositol-3 kinase (P13K) (Lavaud & Andre, 2014; Richard et al., 2016). However, the inhibition of insulin-like growth facyor1 (IGFR-IR) signaling block the phosphorylation of HER-2 and restore the sensitivity of Herceptin. The signaling of insulin-like growth factor receptor1 activates MAPK-

RAS and AKT-P13K pathways, this implicate Herceptin (Trastuzumab) resistance. Cell lines that co-express insulin-like growth factor receptor1 (IGF-1R), and HER-2 are less potent to Herceptin. Trastuzumab (Herceptin) is associated with the increased signaling of IGF-1R therefore increased expression of growth factor receptor1 were shown to decrease Herceptin-mediated growth and attack human epidermal growth factor2 that overexpress cancer cells (Labaran, 2014; Ma, 2015; Dong et al., 2022).

P13K pathways up-regulation

The activation of Mtor-akt AND P13Kinase, are precursors leadings to cell proliferation and growth in different types of tumor. The current study shows that there is strong relationship between mutational activation of this important pathways and the resistance to therapies targeted over Erb-B2 kinase like Herceptin (Crowder et al., 2004; Zhang et al., 2024). Two important mechanisms occur as a result of activation of P13K: when phosphatase, and ten-sin homologen (P10) loss function or activates of mutational gene change the catalytic subunit of the Phosphotidylinositol-3-kinase P13K (P13KCA). Deficiency of P10 in women who had tumor show significant low levels compared to overall response in Herceptin with taxane treatment than women with the P10 positive tumor, statistically (35.7 vs 66.7%) was identified as the probability of Herceptin response reduced as P10 decreased (Harahap et al., 2017; Hunter et al., 2020). However, lack of standard assay, the study of immunochemistry has been generalized when coupled with data based on Herceptin responses in laboratory models on human epidermal growth factor 2 (HER-2), amplified P10 hypothesis breast cancer, these show that P10 ultimately served to predict the main catalyst in this scenario. Although the resistance to Herceptin thought to be mediated through mtor/P13K/Akt pathways (Rakha et al., 2015; Sobolewski & Legrand, 2021) In preclinical trials loss of Erb-B2 resistance has resulted in the acquisition of the tumor suppressor gene P10 which stop spread of P13K or lead to mutation in P13K cancer, and resulted in the breakdown of phosphotidylinositol-3-kinase, via the activation of the mtor (Ahamd et al., 2014; Labaran, 2014; Richard et al., 2016; Girish et al., 2024).

The signaling of growth factor -dependent, recruitment of P13K subunits catalyzes the phosphorylation of the inositol ring converted PIP2 to PIP3 these terms as inositol lipids products change wide set of signaling proteins downstream of P13K.PIP3 is tightly regulated by phosphatase (P10) (SHIP1 and 2) (Hudis, 2007; Hole et al., 2023). However, P10 reverts PIP3 and come back to PIP2 so that it stops downstream signaling, but SHIP specific enzymes convert P IP3 into phosphotidylinositol (PtdIns). However, the activation of AKT/P13K pathways has been frequently point out the main mechanisms of resistance to targeted treatment. The main regulator to AKT/P13K, pathways activates, the role of P10 has been indicated in resistance to any HER treatment in many cancer cells. The most mutated human genes in cancer cells are P10 because it antagonizes P13K, by preventing PDK1 activation of AKT through PIP3. Regulation of MAPK on pathways has been established by inhibiting Shc-mediator and Ras activation (Holbro & Hynes, 2004; Abarn, 2014). Nonetheless modulation of P10 in AKT, P13K, and MAPK is critical, in order to impair proliferation and cell survival. P10 has also implicated in limiting of cells cycle and progression from G0/G1 to S. Therefore, loss of P10 expression takes longer for the activation of signal protein in order to provide advantage in terms of cell proliferation and survival. In HNCC tumors, loss of P10 expression in 10-30% of the cases occurs (Jin et al., 2003; Hynes & Lane, 2005; Zhang et al., 2024).

Overcoming Resistance to Herceptin (Trastuzumab)

Various studies carried out in order to find out how to overcome the resistance of Herceptin are on the way. However, there is no actual mechanism that overcomes the resistance which is seen in breast cancer patients whose tumors have developed (Hurvitz & Kakkar, 2012). However, vascular Hplus-ATPase (V-ATPase), a part of the proton pump, could be an interesting mechanism in targeting HER-2 positive breast cancer because it regulates potential hydrogen (pH), homeostasis in eukaryotic cells which consists of membrane protein translocated V0 subunit as well as cytoplasmic V1 subunit were adenosine triphosphate (ATP) is hydrolyzed (Lemmon et al., 2010; Labaran, 2014). As vacuolar -ATPase is known for its role in many steps for recyclic pathways and endocytotic pathways. The inhibition of vacuolar -ATPase would lead to high disturbance of endocytotic pathways. Mucin4 is one of the associated membranes found in the extracellular domain of the human epidermal growth factor receptor 2(HER-2), based on this finding the expansion of MUCIN4 over expression is one of the primary mechanisms of resistance to Herceptin that is done by NSCLC (Fiszman & Janis, 2011: Labaran, 2014) However, the percentage of NSCLC that express MUCIN4, is 80-85% and Aden squamous and adeno in cancerous, which is characterized by greater stars in MUCIN4 expression (68-75% at the same time). Nonetheless analysis showing that, MUCIN4 and expression of human epidermal growth factor 2 could be involved in differentiation and apoptosis. Therefore, the primary resistance to Herceptin in some cancers such as, prostate cancer involves other mechanisms like expression of MUCIN4, is not presented in malignancy of prostate tissue. When epidermal growth factor receptor and HER3 are activated, radiation targets MEHD7945A out of all the receptors in order to overcome the resistance of Herceptin in clinical treatment, strategies using both epidermal growth factor receptor and radiation (Junttila et al., 2009; Mayer, 2013; Labaran, 2014). The actual mechanisms lead to acquired resistance to radiation and epidermal growth factor receptor are not clear. But indicates that interaction between members of human epidermal growth factor represent as pacemakers, affecting the high levels in clinical therapies that target human epidermal growth factor (Slamon et al., 2001; Labaran, 2014).

Based on the evidence gathered on human epidermal growth factor receptor 3 (HER-3) and epidermal growth factor as key player in order to acquire resistance on human epidermal growth factor 2 targeting agent (Wang & Hung, 2012; Tauber et al, 2024). However, the human epidermal growth factor receptor 3 (HER-3), play a crucial role of signaling, in the other family members that lead to a compensatory pathway for epidermal growth factor receptor inhibitors. These elicited, indicates the possible value in order to inhibit the functions of different members of human epidermal growth factor receptor in order to achieve clinical efficacy to overcome acquired resistance to epidermal growth factor receptor inhibitor treatment (Rubin & Yarden, 2001; Richard et al., 2016). The ability of MEHD7945A in order to overcome the elementary resistance to epidermal growth factor receptor (EGFR) inhibitor treatment needed, the actual role of human epidermal growth factor receptor 3 HER-3) in regulating elementary resistance to human epidermal growth factor receptor (EGFR) inhibitors is not characterized (Wheeler et al., 2008). SRC activation act as a key junction point of multiple Trastuzumab resistance to its mechanisms. Combinations of Saracatinib (SRC) inhibitor plus Herceptin are efficient in dealing with a range of De Novo and acquired resistance mechanisms. These results, indirectly improved Erb-B2 treatment in breast cancer patients (Winer & Harris, 2014; WHO, 2022; Zhu et al., 2024).

Overcoming Herceptin Resistances by osu-03012 Compound

Research has shown that anti-inflammatory drug mediated cell death, in cancer cells, such as COX-2 inhibitor, by blocking the signal of phosphoinositide-dependently kinase one, for example Celecoxin as

an important step in manufactured a novel class phosphotidylinositide kinase one inhibitor devoid the work of COX-2 (Wu et al., 2022). Osu-03012 is a novel compound that exhibits high potency by inducing apoptosis and deactivating AKT low microM concentration in cancer cells via phosphotidylinositide kinase one inhibitor. Since phosphotidylinositide kinase one act as a mediator of phosphoinositol3 (PI3K) pathway and can potentially provide better treatment in HER-2 positive breast cancer. Clinically varied treatments are attempted in order to overcome Herceptin resistance. Continued treatment of Herceptin resistance with alternative chemotherapy rule overcome Herceptin resistance (). Even though the actual time of Herceptin treatment remains unclear, preclinical studies show that, the synergistic effect of Herceptin with many cytotoxic agents results in clinicians to administer Herceptin over progression, in combined with 2nd and 3rd line of therapeutics agent. Resistance to Herceptin leads to various molecular changes occurring at different stages of the downstream effectors in phosphoinositol3kinase (PI3K) pathways which lead to maintenance of signal transduction (Slamon et al., 2001; Labaran, 2014; Vasantha et al., 2022; Wang et al., 2022).

However, using Everolimus inhibits the pathways that send signal for cells to survive, proliferate, and grow. The main downstream effectors for these pathways may overcome Herceptin sympathy. Everolimus reverse Herceptin resistance leading to an up regulation of insulin -like growth factor receptor 1R (IGF-1R/ expression, another signaling pathway, allowing insulin-like growth factor 1 to drive proliferation, and cells growth (Spector & Blackwell, 2009).

Data suggests that, activation of (Akt/mtor and PI3K) pathways in clinical trial might play a crucial role towards the resistance of hormones under attack therapy. These processes are shown by proteomic gene expression profiling to be up regulated in MCF-7 in human breast cancers cell subjected to extend estrogens scarcity. Signaling of overactive EGF mediates hormone to target resistant treatment (Labaran, 2014; Wu et al., 2022). The interaction between estrogens receptor and Akt/mtor/PI3K pathways, and that of epidermal growth factor re eptor-2 is a future means of endocrine treatment resistance. Estrogens deprived in long-term MCF-7 which activates IGF-1R in human breast cancer cells, and IR was correlated with PI3K pathways. The activation of epidermal growth factor, or IGF-1 and PI3K pathways enhance estrogens receptor alpha transcription in MCF-7 cells. Combination of tamoxifen inhibitors with mtor inhibitors has been shown in preclinical tests of estrogen receptor showing positive hormone response in hormone-resistant breast cancer. Nonetheless, activity of temsirolimus inhibited Mtor activity, and bring back feeling to tamoxifen via initiation of cell death. Thus, proposed Akt encourage tamoxifen resistance may be intervening the signaling Mtor pathways. Combination of letrozole with temsirolimus, when given daily in postmenopausal breast cancer patients (30 milligrams for five days each and every two weeks) may overcome the resistance. The randomization of some patients was carried out in a clinical trial, and suggested that the combination of aromatase inhibitor, with monoclonal antibody extensively prolonged progression and free survival in women with metastatic breast cancer and HER-2 positive breast cancer (Wheeler et al., 2008; Wang et al., 2022).

Conclusion

In conclusion, the mechanisms of resistance to Trastuzumab (Herceptin) in breast cancer are complex and multifaceted. Understanding these mechanisms is crucial for developing effective treatment strategies for HER2-positive breast cancer. Further research is needed to elucidate the molecular mechanisms underlying Trastuzumab resistance and to identify potential therapeutic targets. By combining

Trastuzumab with other targeted therapies or chemotherapy, it may be possible to overcome resistance and improve treatment outcomes for patients with HER2-positive breast cancer.

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