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Pharmacogenetics of Trastuzumab Review of literature

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Abstract

Trastuzumab (Herceptin) is a monoclonal antibody that targets the human epidermal growth factor receptor 2 (HER2), improving survival rates in patients with HER2-positive breast cancer. Despite its efficacy, treatment responses vary widely among patients, with approximately 23% of early-stage HER2-positive breast cancer patients experiencing no response or recurrence within a decade. This review explores the pharmacogenetic landscape influencing trastuzumab efficacy, focusing on genetic polymorphisms that affect drug metabolism and therapeutic outcomes. Key genetic factors, including variations in the FCGR3A, TP53, HER2, BARD1, FGFR1, MDM2, and ATM genes, are examined for their roles in modulating the immune response and resistance to therapy. Understanding these genetic influences is crucial for optimizing trastuzumab treatment strategies and personalizing therapy to enhance patient outcomes in HER2-positive breast cancer.

Keywords

Pharmacogenetics, Trastuzumab, HER2-positive breast cancer, Genetic polymorphisms

Introduction

Trastuzumab (Herceptin), a model of targeted cancer treatment, inhibits the overexpressed or amplified receptor tyrosine kinase HER2 in 10-30% of gastric cancers and 15-20% of breast cancers [1].

Trastuzumab has greatly improved survival rates in HER2-positive cancers since it was approved. Clinical experience, however, has shown significant variation in treatment response: about 23% of patients with early-stage HER2-positive breast cancer who receive adjuvant trastuzumab either do not respond or have a recurrence within 10 years [2].

Pharmacogenetics, which is used frequently with pharmacogenomics, is the study of how a patient's genetic composition affects their response to medication therapy, including toxicity and efficacy. Gene expression and function can now be quickly evaluated through technological advancements. This involves evaluating both host (germline) and tumor (somatic) genetic diversity. For instance, tissue microarrays enable the assessment of expression patterns of thousands of tumor genes, which have been crucial in providing prognostic and predictive data for specific biologic subtypes of cancer. DNA changes, such as nucleotide repeats, insertions, deletions, or substitutions, may represent genetic variants. A single-nucleotide change, known as a single-nucleotide polymorphism (SNP), can result in either no enzyme activity or altered enzyme activity, which can have a major effect on a drug's disposition and/or response. Variations in the coding region of DNA may result in amino acid substitutions in the translated protein, whereas alterations in the noncoding regions of DNA might affect several aspects of protein function compared with a wild-type protein. Pharmacogenomic studies seek to identify genetic alterations, such as SNPs, that substantially affect the production or function of proteins involved in the pharmacokinetics or pharmacodynamics of medications [3].

Background and Theoretical Foundation

History of trastuzumab

(MAbs) Monoclonal antibodies are defined as "laboratory-produced molecules engineered to preserve as substitute antibodies that can restore, enhance, or mimic the immune system's attack on cancer cells [4].

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In the 18th century, Dr. Edward Jenner found out that the fluid taken out of a small pustule, which was injected into an individual, offered protection against the contraction of the disease. This was in the initial steps of antibody development. The ideas behind monoclonal antibodies (mAbs) were developed in the 1930s and 1940s by several different scientists, such as the isolation of agglutinins by McMaster and Hudack, as well as the finding of lymphocytes as the major source of antibody production [5]. However, it wasn't until 1975 that the first monoclonal antibody intended for human use was produced, and it wasn't until 1986 that it was properly licensed. The process of isolating a single plasma cell clone that produced a homogeneous antibody and multiplying it by repeatedly passing spleen cells into irradiated syngeneic mice was described in the first report of laboratory-created mAbs in 1970 [6].

Only in 1986 did the first monoclonal antibody obtain a complete license. In 1984, Milstein and Kohler were awarded the Nobel Prize in Physiology or Medicine because they were the first to successfully manufacture large quantities of mAb in vivo, this signaled the introduction of the "hybridoma" and changed how mAbs were made. The initial monoclonal antibodies (mAbs) were made from murine (derived from mice) protein and were not well tolerated by humans over long periods of time. In order to produce fully humanized antibodies, technical advancements forced a reevaluation and eventual modification of the manufacturing procedures. Muromonab-CD3, an anti-rejection drug, was the first monoclonal antibody authorized by the US Food and Drug Administration. The first monoclonal antibody discovered to be successful in treating solid tumors was trastuzumab [7].

Trastuzumab mechanisms of action

Antibody-dependent cellular cytotoxicity (ADCC) activation: due to its IgG1 Fc structure, trastuzumab can bind to Fcγ receptors on immune effector cells, especially natural killer (NK) cells [8].

Trastuzumab is a full humanized IgG1 antibody with an Fc domain that allows it to bind to various Fc receptors (FcRs). Human immune cells, such as B cells, NK cells, macrophages, and neutrophils, express a variety of FcRs, including both activating and inhibitory receptors. FcR expression across a wide range of important immune effectors raises the possibility that trastuzumab's therapeutic activity involves several immunologic pathways. The functional modification of trastuzumab's binding affinity by common polymorphisms in FCGR genes suggests that, from a clinical standpoint, FcRs play an important role in each patient's response to trastuzumab [9,10].

Blocking of proteolytic HER2 extracellular domain (ECD) cleavage: In preclinical models, trastuzumab has been shown to inhibit both basal and induced cleavage of the HER2 extracellular domain (ECD). This inhibition stops the formation of phosphorylated p95, which is a truncated variant of HER2. Trastuzumab can decrease HER2 ECD cleavage, but it does not have a direct impact on p95 phosphorylation because p95 does not possess the trastuzumab binding epitope [8].

Trastuzumab prevents aggressive tumor microenvironments from developing: Vascular endothelial growth factor (VEGF) is released in response to both neuregulin 1 (NRG1) and hypoxia-inducible factor 1 (HIF-1) when HER2 is overexpressed. In order to increase the transport of nutrients and oxygen, HER2+ breast tumors promote VEGF-mediated vascular formation. However, the disordered vascular network created by the high amounts of VEGF production leads to the selection of more aggressive and invasive cells that are resistant to cytotoxic treatment. Trastuzumab dramatically increases perfusion while suppressing VEGF release. Additionally, trastuzumab may prevent the production of other angiogenesis mediators, such as Ang-1, PAI-1, and TGF [11,12].

Trastuzumab modifies the cellular physiology of tumor cells overexpressing HER2: Trastuzumab-treated cells have a decrease in proliferation along with an arrest during the G1 phase of the cell cycle. Reduced expression of proteins involved in the sequestration of the cyclin-dependent kinase (cdk) inhibitor p27kip1, such as cyclin D1, is associated with cell cycle arrest. As a result, p27kip1 is released, enabling it to attach to and prevent cyclin E/cdk2 complexes [12].

Trastuzumab interferes with MAPK and PI3K/Akt pathway: Trastuzumab's most well-known action is the inhibition of the PI3K/Akt and MAPK pathways, which increases cell cycle arrest and suppresses cell growth and proliferation. It is generally acknowledged that trastuzumab reduces Akt phosphorylation and inhibits HER2 activation by interfering with HER2 dimerization. Trastuzumab can disrupt tyrosine kinase Src signaling by binding to HER2, which increases PTEN levels and activity, as other groups have critically demonstrated. Additionally, PI3K/Akt signaling is suppressed, and cell growth and survival are inhibited [13].

Pharmacogenetics

Genetic polymorphisms are variations in each person's DNA that don't change over the course of a person's lifetime. The human genome includes 1.4 million single-nucleotide polymorphisms (SNPs), many of which influence pharmacokinetic and pharmacodynamic processes of medications. Only specific cells experience genetic mutations, which are acquired alterations in gene sequences. Compared with host tissues, tumor cells may experience mutations more frequently. These genetic polymorphisms affect cellular targets, signaling pathways, drug metabolism and transport and response of cells to treatment [14].

DNA changes such as nucleotide repeats, insertions, deletions, or substitutions are examples of genetic variants. One nucleotide change, known as a single nucleotide polymorphism (SNP), can result in the absence or modification of enzyme activity, which can have a major effect on a drug's disposition and/or reaction. These changes may have several effects on the toxicity and effectiveness of drugs. Changes in the noncoding regions of DNA can modify several elements of protein function in comparison to a wild-type protein, while changes in the coding area of DNA may lead to amino acid substitutions in the protein [3].

The monoclonal antibody trastuzumab is primarily used to treat HER2-positive breast cancer. Following its binding to the HER2 receptor, the monoclonal antibody is broken down by intracellular protein breakdown mechanisms. Their metabolism is less affected by CYP450 enzymes than that of many conventional chemotherapy drugs. Rather, the HER2 gene and immune response-related genes have a major influence on the effectiveness and metabolism of the monoclonal antibody. The HER2 gene encodes the HER2 receptor protein, which is the target of pertuzumab and trastuzumab. Therefore, the therapeutic efficacy of these antibodies is closely correlated with the overexpression or amplification of the HER2 gene. Their distribution and effectiveness in vivo may be affected by changes in the HER2 gene status [15].

Genetic Polymorphisms in HER2-Positive Breast Cancer Affecting Trastuzumab Response

About 15-20% of instances of breast cancer have HER2 overexpression. The prognosis for HER2-positive breast cancer is poorer due to its high histological grade and increased likelihood of metastasis. However, HER2 activity can be blocked by anti-HER2-targeted medications like trastuzumab, which lessens tumor aggressiveness and increases patient survival. Patients who relapse or acquire metastases during treatment were shown to have different responses to anti-HER2-targeted therapy. Predicting a patient's response to HER2-targeted therapy is therefore essential for preventing unwanted side effects and selecting better options for them [16].

FCGR3A polymorphism and ADCC

FcγR polymorphisms refer to genetic variations found in genes encoding Fcγ receptors, such as FCGR1A, FCGR2A, FCGR2B, FCGR2C, FCGR3A, and FCGR3B, located on chromosome 1q23.3-q24.3. These variations include single- nucleotide polymorphisms (SNPs) and copy number variations (CNVs), which can potentially alter ligand binding. As a result, they may affect receptor function, alter the degree of receptor expression, and influence the magnitude of immune responses, especially in mAb-based treatments. The FCGR3A gene is reported to be highly polymorphic, with approximately 40 variants located in exon 4. The FcγRIIIa-158V/F polymorphism results in either valine (V) or phenylalanine (F) at position 158 of the receptor's extracellular domain. The change from F to V at 158 increases Fc- FcγR binding affinity and increases response rate [17].

ADCC potency is impacted by variations in the FCGR3A gene, particularly the FCGR3A-V158F variant, which results in distinct signaling functions and varying affinities for immunoglobulin G. An improved response to trastuzumab treatment has been linked to the FCGR3A-158 V allele's increased binding to IgG1 immune complexes at low concentrations. Patients with FCGR3A-158 V-V genotypes have higher antibody-mediated ADCC activity than those with F-F genotypes, which is further associated with this improved response. This is probably because the Fc region in the V variant has a higher affinity [18].

In a study of 54 Italians with HER2-positive metastatic breast cancer, Musolino, et al. found that patients with the FCGR3A-158 mutant V-V genotype responded better to trastuzumab and taxane. Additionally, Tamura, et al. examined the FCGR3A-V158F polymorphism in the Japanese population and found a strong correlation between FCGR3A-158 V-V and response rate in patients with early and metastatic breast cancer [9,19].

However, additional research that was repeated across different ethnic groups concluded that having the FCGR3A-158 V allele did not improve disease-free survival or response rates in breast cancer patients. Hurvitz, et al.'s cohort study of 1189 patients receiving trastuzumab-based treatment found no relationship between FCGR3A genotypes and disease-free survival [20].

TP53 gene polymorphism in her2 positive breast cancer

The p53 signaling pathway is triggered when cells experience stress, such as damage to their DNA. The p53 protein functions as a transcription factor when it is activated, transactivating several target genes that start cell cycle arrest, apoptosis, DNA repair, and prevent metastasis. According to reports, the most prevalent malignancy among women with pathogenic TP53 mutations is breast cancer (25.5%). Furthermore, 70% of individuals with HER2-positive breast cancer may have TP53 mutations, which are associated with a poor prognosis [21].

Patients with HER2-positive breast cancer have a worse prognosis when they have TP53 mutations, especially pathogenic ones. Resistance to cytotoxic anticancer medications has been linked to TP53 mutations that cause loss of function. Multiple trastuzumab-resistant patients were found to have two TP53 variants, p. Ser241Phe and c.376-2dup.Two resistant patients had the p. Ser241Phe variant, which is thought to be likely pathogenic. Two resistant patients also had the splice site variant c.376-2dup, which has varying interpretations of pathogenicity. One resistant patient had a novel allele in exon 4 of the TP53 gene, c.407A > G (p. Gln136Arg). In this missense variation, arginine is substituted for glutamine at codon 136 [17].

In HER2-positive early breast cancer patients, the prevalence of TP53 mutations and p53 protein immunopositivity seems to be a positive predictor of trastuzumab efficacy, improving disease-free survival [22].

Another study reports that TP53 mutations are reported in HER2-positive breast cancer and are related to low levels of efficacy of the anti-HER2 antibody drugs, such as trastuzumab, which causes shorter progression-free survival. This indicates that TP53 mutation has the potential to act as a biomarker of resistance against anti-HER2 antibody therapy in patients who are HER2-positive [23].

HER2 gene polymorphism

Human epidermal growth factor receptor 2 (HER2), also known as Erb-B2 receptor tyrosine kinase 2 (ERBB2), is one of the 20 families of tyrosine kinase receptors that are

known to be changed in conditions involving unchecked proliferation. It is also known to be a carcinogenic driver.

The HER2 gene, located in chromosomal region 17q21, can encode the transmembrane tyrosine kinase GFR. It is usually expressed in the breast tissue's epithelial cells. Even in the absence of a ligand, the tyrosine kinase binding partners may interact with HER2 [24].

Research on the relationship between HER2 gene polymorphisms and trastuzumab responsiveness has produced contradictory findings:

A 2015 study found no association between six different HER2 single-nucleotide polymorphisms (SNPs) (rs1810132 STR C>T, -1985 G>T, ---3444C>T, P1170A C>G, and I655A A>G) and stable disease or time to treatment failure in patients receiving trastuzumab-lapatinib-bevacizumab combination therapy [25].

Han, et al. found that HER2-positive patients with the Val/Ile and Val/Val genotype had a significantly lower DFS score than those with the Ile/Ile genotype, suggesting that the Ile655Val HER2 polymorphism is linked to trastuzumab resistance. Tyrosine kinase activity may be reduced when Val is converted to Ile at codon 655. The combination showed a lower rate of apoptosis and an increased growth capacity in an in vitro study, in which the Ile655Val HER2 polymorphism (rs1136201) results from the substitution of isoleucine for valine [26,27].

Also, Furrer, et al. found that the rs1136201 SNP in the HER2 gene may influence the trastuzumab response, with Val rather than Ile being linked to a decrease disease disease-free survival [28].

Another HER2 gene polymorphism is the Ala1170Pro polymorphism, which results in the substitution of Alanine for Proline. In a cohort of 237 women with early HER2-positive BC receiving trastuzumab, Furrer, et al. discovered no correlation between the HER2Ala1170Pro SNP and disease-free survival [29].

BARD1 gene polymorphism

The gene BARD1 (BRCA1-associated RING domain 1) is crucial for the development of breast cancer because it produces a protein that interacts with BRCA1's N-terminal region. Homologous recombination deficit is most frequently caused by mutations in the tumor suppressor gene BRCA1 or in any associated gene [30].

Previously believed that the rs2070096 SNP in the BARD1 gene, which causes a C > G substitution leading to the synonymous protein Thr351Thr, had little effect on protein function. Recent research indicates that synonymous variants may have an impact on treatment responses, cancer cell functionality, and translation efficiency. The variant allele rs2070096 was found to be significantly associated with a pathological complete response (pcr) in patients, especially those receiving a combination of trastuzumab and pertuzumab. On the other hand, Coté, et al. study discovered that patients who were heterozygous for this SNP had a higher chance of relapsing after receiving trastuzumab and chemotherapy compared with non-trastuzumab and chemotherapy-based treatment [29,31].

FGFR1 gene polymorphism

The fibroblast growth factor receptor 1 gene (FGFR1, chromosomal region: 8p11.2-p12) is another possible biomarker in breast cancer. It is a member of a family of receptor tyrosine kinases that affect the downstream MAPK, PI3K-AKT-mTOR, and STAT pathways when activated by fibroblast growth factors. Physiologically, FGFR1 stimulation promotes angiogenesis, migration, survival, and proliferation [32].

Cell cycle regulation is largely dependent on the PI3K/AKT pathway, which includes FGFR1 and HER2. FGFR1 gene amplification can cause aberrant activation of this pathway, which promotes cell cycle progression and inhibits apoptosis. According to the study, trastuzumab monotherapy and combination therapy with pertuzumab are examples of neoadjuvant anti-HER2 treatments for which FGFR1 gene amplification is a significant predictor of poor response [33].

MDM2 gene polymorphism

The MDM2 protein, the main negative regulator of the p53 protein, is encoded by the mouse double minute 2 (MDM2) gene. Tumor cells undergo EMT (epithelial-to-mesenchymal transition) due to MDM2 overexpression, which renders them chemotherapy-resistant. Overexpression of MDM2 is associated with resistance to trastuzumab regimens in HER2-positive breast cancer [34].

ATM gene polymorphism

(Ataxia telangiectasia mutated), ATM may resist apoptosis due to low levels of DNA double-strand breaks, which may lead to early senescence. ATM regulates the level of the ARF (alternative reading frame) tumor suppressor protein, which in turn controls cell proliferation and the apoptotic response. On the other hand, RB1 influences cell proliferation and treatment response by controlling the course of the cell cycle through interactions with E2F transcription factors. Therefore, the resistance of HER2-positive breast cancer cells to trastuzumab may be mostly due to the dysregulation of ATM and RB1. Important insights into the mechanisms underpinning treatment resistance in breast cancer can be gained from the roles of ATM and RB1 in cell cycle regulation and cellular senescence, as well as their relationship to trastuzumab resistance [35,36].

Other gene mutations that predict the response to trastuzumab

Gene overexpression or deletion: After anti-HER2 treatment, changes in the target itself may result from overexpression or deletion of related genes, which lowers or eliminates HER2 expression and decreases the medication's efficacy. Studies on trastuzumab resistance have revealed mutations in genes like CDH1, GNAS,

MLH1, RB1, SMARCB1, SMO, and VHL [36].

Aim of the study: The purpose of this research is

to investigate the pharmacogenetic variables affecting trastuzumab's effectiveness in patients with HER2-positive breast cancer. The study specifically looks for genetic polymorphisms that influence drug response.

Method

With an emphasis on important genetic polymorphisms in genes like FCGR3A, TP53, HER2, BARD1, FGFR1, MDM2, and ATM, this review summarizes the body of research on the pharmacogenetics of trastuzumab. A thorough examination of peer-reviewed research, clinical trials, and genetic studies that look at the connection between these genetic variations and trastuzumab response is part of the methodology. Data were gathered from multiple databases, and conclusions were assessed to ascertain how they might affect individualized treatment plans for HER2-positive breast cancer.

Study design

The research is structured as a review of the literature. It focuses on the genetic polymorphisms that affect trastuzumab's effectiveness and resistance in patients with HER2-positive breast cancer, methodically analyzing and synthesizing the body of research on the drug's pharmacogenetics. In order to provide a thorough understanding of how genetic variations affect treatment outcomes, this design enables the integration of findings from multiple studies. In order to improve patient responses to trastuzumab therapy, the review seeks to identify important genetic factors that can guide individualized treatment plans.

Source of data

Peer-Reviewed Journals: Articles that were published in well-regarded scientific journals that concentrate on pharmacogenetics, oncology, and the treatment of breast cancer. These articles present empirical findings and clues about the genetic variables that determine the efficacy of trastuzumab.

Clinical trials: The information about the clinical trials that study the efficacy of trastuzumab in patients with HER2-positive breast cancer, with references to research on genetic variations and their influence on treatment reactions.

Genetic studies: Studies that investigate genetic polymorphisms in trastuzumab response, in particular studies on genes such as FCGR3A, TP53, HER2, BARD1, FGFR1, MDM2, and ATM.

Medical and scientific databases: The data were collected in databases including PubMed, Scopus, and Web of Science that allow access to a wide variety of studies, reviews, and meta-analyses on the pharmacogenetics of trastuzumab.

Conclusion

The efficacy of trastuzumab in the management of HER2-positive breast cancer patients is greatly affected by the pharmacogenetic situation. The differences in genes like FCGR3A, TP53, and HER2 are important in the regulation of treatment responses and resistance mechanisms. These genetic factors are crucial to the optimization of trastuzumab therapy and tailoring treatment strategies to ensure better patient outcomes and reduced adverse effects. In the future, the research attention should be made to verifying these genetic markers in other populations to enhance the predictive value of pharmacogenetic testing in the clinical setting.

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