REVIEW

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TRASTUZUMAB AND CARDIOTOXICITY

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Summary

Breast cancer survivors face an increased incidence of cardiac toxicities, which heightens their risk for cardiovascular disease compared to individuals without cancer, leading to poorer overall survival rates. Although trastuzumab has notably improved patient outcomes, its potential to induce cardiotoxicity has become a significant clinical concern. HER2 signaling and neuregulins play critical roles in maintaining cardiac function. Although the exact mechanism behind trastuzumab-induced cardiotoxicity remains unclear, it differs from anthracycline-induced cardiomyopathy, as trastuzumab-induced cardiotoxicity (type II) is mostly reversible. This is because it stems from reduced myocyte contractility, rather than permanent damage to the myocytes. Single-nucleotide polymorphisms (SNPs) – the most common form of genetic variation – are associated with differences in both the effectiveness of systemic treatments and the occurrence of treatment-related toxicities. However, findings regarding the relationship between specific SNPs and cardiotoxicity remain inconclusive. Early detection of trastuzumab-induced cardiotoxicity is crucial for minimizing side effects and enabling the customization of therapeutic strategies for patients at high risk of developing cardiac complications.

KEY WORDS: *breast cancer, trastuzumab, cardiotoxicity*

INTRODUCTION

Breast cancer is known as the most prevalent cancer among women in developed countries and the second major cause of cancer-related deaths worldwide(1). As breast cancer incidence rises, improved early detection and advances in treatment have contributed to an increasing number of survivors(1-3). However, this expanding group faces a heightened risk of developing comorbid conditions, particularly cardiovascular disease(2,3). Breast cancer survivors experience a higher incidence of cardiac toxicities and are consequently at greater risk for cardiovascular disease compared to non-cancer patients, leading to reduced overall survival rates(3). Moreover, cardiovascular disease can diminish the survival benefits achieved through cancer treatment and has already surpassed cancer as the primary cause of death among older survivors(2). Anthracycline-based chemotherapy and trastuzumab are two of the most extensively researched breast cancer treatments, with cardiotoxicity rates noted to reach as high as 27% when used in combination(3-5). Numerous trials have demonstrated the effectiveness of anthracycline-based chemotherapy, while trastuzumab has significantly improved cure rates(5). The concurrent administration of anthracyclines and trastuzumab offers no added benefit over consecutive treatment, which is now the standard due to its association with fewer car-

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diac side effects(5,6). The cumulative incidence of significant cardiac incidents in patients receiving trastuzumab treatment is reported at 4.1% over five years, with severe symptomatic congestive heart failure occurring in 0.8% of cases (3,4). This presents a significant challenge for cardiology and oncology units, as there is no proven strategic approach for managing patients with persistent left ventricular dysfunction even after discontinuing targeted therapy(3). Additionally, traditional cardiovascular risk factors – such as age, smoking, hyperlipidemia, obesity, diabetes, and a genetic predisposition to cardiovascular disease – are linked to an increased risk of cardiac events in these patients(1). While the risk of symptomatic congestive heart failure from trastuzumab is low, moderate forms of cardiac dysfunction are more prevalent and frequently lead to premature pause or cessation of therapy(3,4). In clinical practice, asymptomatic declines in left ventricular ejection fraction (LVEF) have resulted in trastuzumab discontinuation in up to 23% of patients(4). Current guidelines recommend halting or discontinuing trastuzumab if there is a significant decline in LVEF – defined as a 10-15% absolute decrease from baseline or a drop of 10% below the institution's lower limit of normal (typically set at 50%), whether symptomatic or asymptomatic(3-5,7-9). Identifying patients at risk of treatment-associated cardiotoxicity is crucial to prevent chronic side effects while avoiding unnecessary discontinuation of essential anticancer treatments(2).

The long-term risk of trastuzumab-associated cardiotoxicity remains uncertain. While some clinical trials have shown no increased risk of cardiac insufficiency beyond the first 2-3 years(10-12), observational studies suggest a higher incidence – up to 20% – with a longer duration of risk(13-15). As 5-year breast cancer survival rates now exceed 85% in developed countries, the long-term cardiac sequelae of treatment are becoming increasingly important(10,15-17). Cardiovascular comorbidities, in particular, are thought to play a critical role in shaping long-term survival outcomes.

HER2 RECEPTOR AND TRASTUZUMAB

Human epidermal growth factor receptor 2 (HER2) was discovered at the beginning of the 1980s and is overexpressed in almost 25% of breast cancers(6). HER2 plays a key role in an especially invasive breast cancer subtype, which led to the development of trastuzumab, a monoclonal antibody targeting the HER2 receptor(4,6). Trastuzumab became the standard first-line treatment for HER2-positive breast cancers in both early-stage and metastatic contexts(4,6). The development of HER2-targeted treatment followed the realization that HER2 is a tyrosine kinase receptor, a member of the human epidermal growth factor receptor (HER) family, encoded by the ERBB2 gene(6). The name *neu* indicates its initial identification as a proto-oncogene in rat neuroblastoma cells(6). The human epidermal growth factor receptor family includes four closely related transmembrane receptors – HER1/ErbB1, HER2/ErbB2, HER3/ErbB3, and HER4/ErbB4 – frequently overexpressed in solid tumors and crucial for regulating normal cell growth and development(18). These receptors influence cell behavior by dimerizing in response to extracellular ligands(19-23). HER3 is a preferred dimerization partner for HER2(19-23). Under normal conditions, HER2 signaling is tightly regulated, but in cases of overexpression, it leads to continuous signal generation, overwhelming the body's cell regulatory mechanisms(19-23). HER2 overexpression in breast cancer is strongly related to rapid disease progression and increased mortality(6). Unlike other oncogenes, HER2-driven tumorigenesis occurs through overexpression rather than mutations or structural alterations(19). However, activating mutations in the HER2 receptor domain have been observed in a subset of advanced HER2-positive cancers, especially in patients who have developed resistance to targeted therapy with trastuzumab(19,24). Although these findings warrant further investigation, the current evidence shows that most HER2-positive breast cancers result from the overexpression of HER2 in its unmutated form(19,25). This understanding, along with insights into HER2's molecular pathways, suggested that inhibiting HER2 activity could enhance outcomes for patients with HER2-positive breast cancer(6). Trastuzumab, the first HER2-targeted therapy approved by the U.S. Food and Drug Administration (FDA), is a recombinant humanized monoclonal antibody that binds to the extracellular region of HER2(6,9,18). It triggers tumor-suppressive effects through various mechanisms, including activation of antibody-mediat-

ed cellular toxicity, HER2 breakdown, antibody-induced cell death by recruiting natural killer cells, and disruption of downstream signaling pathways like MAPK and PI3K/Akt, which are included in cell proliferation(6,9,18). Trastuzumab also disrupts HER2 receptor dimerization and increases levels of the cell-cycle inhibitor p27kip1, promoting cellular division arrest and apoptosis(26-29). Adding trastuzumab, along with other HER2-directed agents such as pertuzumab, T-DM1, and lapatinib, to standard chemotherapy has significantly reduced the risk of relapse, improved prognosis, and extended overall survival in patients with HER2-positive breast cancer, which historically had an unfavorable prognosi (4,6,8). HER2 amplification has also been discovered in other cancers, including gastric and gastroesophageal junction cancers(6). Despite trastuzumab's success and generally favorable tolerance, cardiotoxicity has emerged as a significant clinical concern(4).

MECHANISMS OF TRASTUZUMAB-ASSOCIATED CARDIOTOXICITY

The significance of HER2 signaling in comprehending the underlying mechanisms of cardiac function became apparent when it was discovered that some breast cancer patients treated with trastuzumab developed synergistic cardiac dysfunction, especially when combined with anthracyclines(18). Although the precise mechanism of trastuzumab-induced cardiotoxicity is not fully cleared, multiple theories have been suggested(6,18). It is widely known that the HER2 and ErbB receptor families play a critical role in cardiomyocyte growth and development(6,30). Recent studies using human-induced stem cell cardiomyocyte models have shown that mitochondrial impairment and changed cellular energy metabolism are crucial factors in trastuzumab-related cardiotoxicity(6,30). HER2 signaling is crucial for maintaining cardiomyocyte function and blocking downstream intracellular pathways can lead to impaired cellular metabolism, sarcomere disruption, and cell death(6,31,32). A *double-hit* hypothesis emerged to explain the combined cardiotoxic effects of trastuzumab and anthracyclines: anthracyclines initiate oxidative damage, while trastuzumab inhibits neuregulin and HER2 signaling necessary for cardiomyocyte repair(6,33). This theory also resulted in the differentiation between type I and type II cardiomyopathy(6,34). Type I cardiomyopathy, caused by anthracyclines, is dose-dependent and characterized by irreversible cardiomyocyte necrosis(6,34). In contrast, trastuzumab-induced cardiotoxicity (type II) is generally reversible because it results from a reduction in myocyte contractility rather than irreversible damage to the myocytes(5,6,34). It is neither dependent on dosage nor cumulative and cardiomyocytes show no structural changes, such as vacuolization or cell loss(5,6,34). Although both types of cardiomyopathy share common risk factors, such as age, pre-existing cardiac conditions (e.g., hypertension, diabetes), and a history of heart failure or baseline reduced LVEF, there are differences in specific risk factors: for type I (anthracycline-induced) cardiomyopathy, the cumulative dose of anthracyclines is a primary determinant, whereas for type II (trastuzumab-induced) cardiomyopathy, prior exposure to anthracyclines notably elevates the risk(1-6,34). Since both agents can contribute to cardiomyopathy and are often used sequentially, no single test can definitively distinguish between trastuzumab– and anthracycline-induced cardiotoxicity. However, a combination of factors – including the patient's drug history, the timing of symptom onset, imaging findings (such as fibrosis, which may be visible on MRI and is less common with trastuzumab-induced damage), and the response to discontinuation – can offer important insights in determining the cause(3-6,31-34). However, this aforementioned distinction has been debated, as trastuzumab-related cardiac dysfunction can range from asymptomatic left ventricular dysfunction to congestive cardiac failure, which in some cases does not improve even after treatment cessation(4,6,35,36). Neuregulins (NRG), particularly NRG-1, play an essential role in cardiovascular health(18). Widely expressed in the circulatory system, NRG-1 is produced by the microvascular endothelium and sends signals through interactions with the HER receptor family, including cardiomyocytes(18). In cardiomyocytes, HER2/ErbB2-HER4/ErbB4 heterodimer signaling is crucial for cell growth during development and maintaining contractility in adulthood(18). Studies in mice with ErbB2 knockouts demonstrated that although these mice seemed normal at birth,

they developed cardiomyopathy as adults, emphasizing the role of HER2 signaling in cardiac function(18,37). Cardiac microvascular endothelial cells express multiple NRG-1 isoforms, including both alpha (α) and beta (β) variants, but only β variants are active in cardiomyocytes(18,38). NRG-β1 plays a protective role by promoting antioxidant and antiapoptotic pathways, helping to prevent atherosclerosis and oxidative stress-induced damage(18). Oxidative stress triggers the release of NRG-1 from endothelial cells, potentially explaining why HER2 blockade exacerbates cardiomyocyte injury from other sources(18). Additionally, inhibition of key downstream pathways – such as mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K/Akt) – further contributes to cardiomyocyte damage(18). While the MAPK pathway drives cell proliferation, the PI3K/Akt pathway supports cell survival(18). NRG-β1 stimulates nitric oxide (NO) production in adult cardiomyocytes via the PI3K/Akt pathway, which protects them from oxidative injury(18). HER2 blockade disrupts this pathway, leading to the accumulation of oxidative species and free radicals in cardiomyocytes, resulting in myocardial dysfunction(18).

TRASTUZUMAB AND GENETIC FACTORS

Studies have confirmed that alterations in the HER2 gene are linked with breast cancer development(39). As a proto-oncogene with innate tyrosine kinase activity, the HER2 gene is located on chromosome 17q21 and produces a transmembrane protein(39). Single-nucleotide polymorphisms (SNPs) – the most prevalent type of genetic variation – are defined as variations at a single nucleotide position in the DNA sequence(40-43). These variations can occur in protein-coding genes (multiple allele genes) and noncoding regions of DNA(40-43). Polymorphisms are defined as DNA sequence variations that occur in at least 1% of the population(42). SNPs have been linked to variations in the efficacy of systemic treatments as well as treatment-related toxicities(40,42). However, the role of SNPs in treatment outcomes and responses in HER2-positive breast cancer is not yet clarified(40-42). One of the most studied polymorphisms in the HER2 gene is Ile655Val, which is associated with variable expression of the HER2 transmembrane protein and may impact treatment outcomes, overall survival, and the incidence of cardiotoxicity(42,44). This polymorphism occurs at codon 655, resulting in three genotypes: Ile/Ile (59%), Ile/Val (34.4%), and Val/Val (6.6%) (42,44). Conflicting results have emerged regarding the impact of the Ile655Val polymorphism on breast cancer risk and treatment toxicity in heterozygotes (Ile/Val) and homozygotes (Val/Val) (42,44). While smaller population studies suggested that populations with a higher prevalence of the Val allele may face an increased risk of breast cancer and trastuzumab-related cardiotoxicity, larger studies have not supported this theory(42). Another SNP, Pro1170Ala, has been linked to trastuzumab-induced cardiotoxicity and overall survival, although the data remains inconsistent and further investigation is warranted(40,45,46). Limited studies suggest that the Pro/Pro genotype may be associated with a higher risk of cardiotoxicity in contrast to the Pro/Ala and Ala/Ala variants (40,45,46). Some studies have reported statistically significant differences in HER2 protein expression on tumor cell surfaces associated with the Pro1170Ala polymorphism, but additional research is needed, particularly in Caucasian populations(40,45,46). Two other SNPs, FCGR2A-H131 and FCGR3A-V158F, are known to influence treatment outcomes and trastuzumab-related cardiotoxicity(47). These polymorphisms, found in genes coding for Fc gamma receptors, are believed to contribute to the immunological response to antibody-dependent cytotoxicity – one of the proposed mechanisms of trastuzumab's action(47). However, the findings related to these SNPs remain conflicting(47). Additionally, several studies have identified uridine diphosphate-glucuronosyltransferase 2B7 (UGT2B7) as a significant factor in inactivating antitumor drugs through various mechanism (48,49). The transformation of the UGT2B7-161 SNP from the C allele to the T allele has been shown to affect the metabolism, side effects, and effectiveness of anthracycline-based chemotherapy, with a negative association with the risk of cardiotoxicity(48,49). Some studies have suggested that the UGT2B7-161 polymorphism may also be linked to trastuzumab-induced cardiotoxicity, especially in combination with pertuzumab, showing that individuals with the CC homozygous genotype experienced a substantially greater incidence of drug-induced cardiotoxici-

ty compared to those with the TT or CT genotypes(48). In summary, more extensive studies are needed to reach clearer conclusions about the impact of these genetic variations on trastuzumab-related cardiotoxicity.

CARDIAC FUNCTION MONITORING

Early detection of treatment-induced cardiotoxicity is crucial for minimizing the side effects of antineoplastic therapy and provides an opportunity to tailor therapeutic strategies to the individual needs of patients at high risk for developing cardiac complications(5,42). According to the European Society of Medical Oncology (ESMO), the standard approach for monitoring cardiac function involves measuring left ventricular ejection fraction (LVEF) through either transthoracic echocardiography (TTE) or radionuclide ventriculography(5,42). LVEF is determined by calculating left ventricular end-diastolic and end-systolic volumes, utilizing the geometric principles of the modified Simpson's rule(5,42). This method is safe, widely available, and does not involve radiation exposure(6). However, there are limitations to this technique, including intraobserver and interobserver variability, which can lead to missed subtle abnormalities(5,50,51). Since a decrease in LVEF is often noted later, global longitudinal strain (GLS) has been proposed as an echocardiographic indicator of early heart dysfunction, although its clinical applicability remains uncertain(6). Additionally, several studies have suggested the use of three-dimensional echocardiography (3De) to enhance the precision lacking in traditional 2D TTE(5). Research indicates that 3De is a reproducible method for measuring LVEF and left ventricular volume; however, it requires high-quality imaging and skilled operators, which may not be readily available(5). Due to potential limitations in echocardiographic windows, cardiac MRI can serve as a complementary diagnostic tool(5,6). It can confirm a diagnosis of cardiotoxicity or rule out other forms of cardiomyopathy(5,6). However, this approach faces challenges, including high costs, technical demands, limited accessibility, and known contraindications such as metallic implants, high body mass index (BMI), and claustrophobia(5). The most accurate method for assessing cardiac tissue is endomyocardial biopsy; however, its invasive nature limits its routine use(5). The frequency of cardiac imaging assessments should be tailored according to each patient's estimated baseline risk, and an examination should be performed promptly if the patient exhibits newly developed heart symptoms(52). Serum biomarkers offer an accessible method for screening and diagnosing cardiotoxicity, as well as guiding therapy(6,52). The most extensively studied biomarkers include cardiac troponin (cTn) and B-type natriuretic peptide (BNP), which serve as indicators of myocyte death and myocardial stress, respectively(5). The release patterns of biomarkers vary with different cancer treatments, and any increase in their levels should be evaluated in light of established risk factors such as age, sex, kidney function, obesity, and infections(5,52). Although assessing troponin elevations in patients undergoing chemotherapy is essential, some studies have not been able to confirm the predictive value of troponin elevation specifically in those treated with trastuzumab(42). Nevertheless, persistent increases in troponin levels may help identify patients who could benefit from cardioprotective measures, such as angiotensin-converting enzyme (ACE) inhibitors, and those unlikely to recover after discontinuing targeted therapy(42). Additionally, as previously mentioned, BNP levels tend to increase with age, which could affect the interpretation of BNP results in patients undergoing trastuzumab treatment(5,42). According to the ESC Guidelines on cardio-oncology, it is recommended to assess cardiovascular toxicity risk prior to initiating cancer treatments known to carry significant cardiovascular risk. For therapies such as anthracyclines and HER2-targeted treatments, baseline measurements of cTn and BNP are suggested for risk stratification, particularly in high and very high-risk patients(52). For patients in the high and very high-risk categories receiving anti-HER2-targeted therapies, monitoring of BNP and cTn is recommended every 2-3 cycles during treatment and again at 3– and 12-months following therapy discontinuation. For those in the low and moderate risk groups, cTn measurement can be considered after anthracycline chemotherapy and prior to starting anti-HER2-targeted therapies. In these patients, BNP and cTn monitoring every 3 months during treatment and at 12 months post-treatment may be considered, though this approach has a lower level of evidence(52).

CARDIOPROTECTIVE STRATEGIES

According to the ESC Guidelines on cardio-oncology, the optimal time to implement preventive measures is at cancer diagnosis, before starting anticancer treatment(52). This proactive approach allows the oncology team to assess cardiovascular (CV) risks, educate patients about their CV risk factors, and adjust surveillance and follow-up strategies as needed(52). For patients classified as high or very high risk, a referral to a cardiology unit should be strongly considered. A thorough review of traditional risk factors – such as age, family history, and lifestyle choices – is essential, along with obtaining a baseline electrocardiogram (ECG)(52). Targeted pharmacological strategies can be utilized to prevent cardiotoxicity linked to anthracycline and radiation therapies(52). Secondary prevention strategies involve regular clinical assessments, including physical examinations and cardiovascular evaluations, such as 12-lead ECGs, transthoracic echocardiograms (TEE), and monitoring of cardiac biomarkers, as previously mentioned(52). There is growing research interest in determining the most effective methods for preventing trastuzumab-induced cardiotoxicity before and during treatment(6). Several trials indicate that medications like beta blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) can help mitigate declines in LVEF in patients undergoing trastuzumab therapy(6). It's important to recognize that prevention strategies for anthracycline-induced cardiotoxicity differ from those for trastuzumab-induced cardiotoxicity, as the mechanisms that cause cardiac injury are distinct(42). However, medications that are foundational in treating heart failure with reduced ejection fraction (HFrEF) may assist in reducing the risk of cardiotoxicity(3). While some studies involving breast cancer patients treated with trastuzumab have shown benefits from beta blockers and ACE inhibitors, others have reported contrasting results(42). Rechallenging with trastuzumab requires careful consideration of individual risks and benefits, although there is growing evidence indicating the relative safety of resuming trastuzumab treatment(3,5). Data from large clinical trials suggest that neurohormonal inhibition and beta-blockers are associated with reduced troponin levels and may have a slight impact on preventing the deterioration of cardiac function(3,52). Despite extensive research, significant gaps remain in our understanding, particularly in predicting the development of cardiotoxicity, identifying novel biomarkers for early detection of cardiovascular adverse events, distinguishing between different types of cardiotoxicity, and developing targeted cardioprotective strategies for anti-HER2 therapies(52). The ESC Guidelines on cardio-oncology emphasize the importance of personalized decision-making, particularly in cases of significant asymptomatic reductions in LVEF or the onset of heart failure symptoms, to guide decisions on whether to discontinue treatment(3,5,52). Implementing cardioprotective measures should be a priority in these scenarios(3,52).

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Sažetak

TRASTUZUMAB I KARDIOTOKSIČNOST

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Kod bolesnica koje su preboljele rak dojke, povećava se učestalost onkološkom terapijom uzrokovane kardiotoksičnosti što dovodi do povećanog rizika za razvoj kardiovaskularnih bolesti te posljedično lošijeg ukupnog preživljenja. Iako je trastuzumab značajno poboljšao ishode HER2-pozitivnog raka dojke, kardiotoksičnost uzrokovana ovom terapijom postaje sve veći klinički izazov. HER2 signalizacija i neuregulini ključni su za održavanje srčane funkcije. Iako točan mehanizam kardiotoksičnosti izazvane trastuzumabom nije potpuno razjašnjen, razlikuje se od one izazvane antraciklinima. Kardiotoksičnost izazvana trastuzumabom (tip II) obično je reverzibilna te nastaje zbog smanjene kontraktilnosti kardiomiocita, a ne njihovog trajnog oštećenja. Jednonukleotidni polimorfizmi najčešći su oblik genetskih varijacija, a povezani su s razlikama u učinkovitosti sustavnog antineoplastičnog liječenja ali i terapijskom toksičnosti. Ipak, rezultati istraživanja povezanosti specifičnih jednonukleotidnih polimorfizama i kardiotoksičnosti i dalje su oprečni. Rano otkrivanje kardiotoksičnosti izazvane trastuzumabom ključno je za smanjenje rizika od nuspojava i prilagodbe preventivnih strategija, posebno za pacijente s visokim rizikom od razvoja srčanih komplikacija.

KLJUČNE RIJEČI: *rak dojke, trastuzumab, kardiotoksičnost*