

Toxicity and Solution of Trastuzumab Combined Therapy

Yuanxi Ge¹, Yuxin Huang^{2, *}

¹Beijing National Day School, Beijing, 100039, China

²Guangzhou Medical University, Guangzhou, 511436, China

*Corresponding author: 2019123056@stu.gzhmu.edu.cn

Abstract. Trastuzumab is a kind of monoclonal antibody widely used in cancer, especially in breast and stomach cancer. Due to the HER-2 expression in cardiomyocytes, it is most likely to affect normal cardiac function. Although combination therapies can reduce its toxicity to some extent, we still found toxicity in some combination therapies. In this review, we aim to summarize and analyze the toxicity found in combination therapy and give novel solutions to them. We have analyzed the combination toxicity including trastuzumab with ACE inhibitor, premedication, Emtansine, doxorubicin, and anthracycline taxane chemotherapy regimen. And we chose two main solutions as examples, including serum biomarkers and zingerone.

Keywords: Trastuzumab, cancer therapy, combination therapy, HER-2

1. Introduction

Trastuzumab is a kind of monoclonal antibody widely used in cancer, especially in breast and stomach cancer. It is a specific MAb that targets HER2, which is known as a gene amplified in early-stage breast cancer [1].

Trastuzumab acts by binding to a specific region (domain IV) found in the HER2/neu receptor's extracellular portion. This interaction with the receptor has been observed to reverse the characteristics of tumor cells that express HER2/neu [2]. Trastuzumab treatment causes cells to be arrested in the G1 phase of the cell cycle, leading to reduced cell proliferation. Additionally, trastuzumab inhibits angiogenesis, also the formation of new blood vessels, by promoting the production of antiangiogenic factors and inhibiting the expression of proangiogenic factors. The proteolytic cleavage of HER2/neu, as a result of which its extracellular domain is released, may aid in the uncontrolled proliferation observed in cancer. In breast cancer cells, trastuzumab has been demonstrated to impede this cleavage process. One of the notable effects of trastuzumab is the activation of the tumor suppressor called p27 (kip1) [1]. This activation further contributes to the inhibition of tumor cell growth.

Trastuzumab is often combined with other therapies, such as chemotherapy and hormone blockers. Trastuzumab combined with chemotherapy is also proven to have a higher survival rate and response rate compared to independent treatment [3]. Some trastuzumab resistance can be overcome using combination therapies. Lapatinib is a classic example. As a tyrosine kinase blocker, it inhibits nascent signaling through HER gene dimers. It is also smaller than trastuzumab therefore it is more approachable to the central nervous system. Furthermore, the increase of HER2 on the cell surface can boost trastuzumab-dependent ADCC, leading to more content results in PFS and OS [4].

Although the toxicities of trastuzumab combination therapies are rare, it is still an important goal to reduce or even eliminate them. The common side effects are fever, nausea, diarrhea, and cardiomyopathy. And research show that combination treatment sometimes increases the toxicity.

Therefore, in this review we summarize information about the possible toxicities as well as side effects caused by trastuzumab combination therapy, and possible strategies to address them.

2. Trastuzumab toxicity

2.1. Cardiotoxicity

Cardiotoxicity is defined by international oncological guidelines as a drop in left ventricular ejection fraction (LVEF) of exceeding 10% units, coupled by a decline below the usual restriction of 50%. Trastuzumab is frequently linked to an elevated risk of cardiotoxicity. Some form of cardiac dysfunction occurs in 3% to 7% of patients receiving trastuzumab monotherapy in clinical trials [1]. Patients treated with trastuzumab had a significantly increased risk of severe cardiac dysfunction, including congestive heart failure, and a decrease in LVEF, regardless of whether trastuzumab was used as first-line therapy or after disease progression [5].

The pathophysiology of trastuzumab-induced cardiotoxicity remains partially unclear; however, the mechanism of action is known to involve cytotoxicity through suppression of signal transduction, neoangiogenesis, and restoration of DNA damage brought on by other treatments (type 2 cardiotoxicity). The data that are available demonstrate that trastuzumab prevents NRG-1-mediated HER2 activation, reduces essential intracellular mechanisms in cardiomyocytes, and scavenges pro-apoptotic oxidative sub-products of ATP generation in cells with high and sustained ATP demand. Angiotensin II, an inhibitor of NGR-1, can be upregulated in response to oxidative stress. This prevents NGR-1 from binding to additional ErbB family receptors to make up for HER2 blockage, which further inhibits this pathway and increases oxidative stress. Angiotensin II also promotes apoptosis via the AT1 receptor at the same time that it activates NADPH oxidase, which results in mitochondrial malfunction and cell death [6, 7].

Finally, trastuzumab causes the pro-apoptotic protein BCL-XS40 to be upregulated and the anti-apoptotic protein BCL-XL to be downregulated. Trastuzumab's cardiotoxicity is typically reversible and dosage independent [6].

2.2. Infusion-related Reactions

The incidence of infusion-related responses is one of the consequences of monoclonal antibody therapy. Acute infusion responses are most common during the initial infusion of chimeric antibody treatment. Their pathomechanism is unclear, and researchers believe it may be related to the activation of the complement system by cells (by Fc-IgG receptors) or through immune complexes. Some typical symptoms occur more frequently when antibodies are detectable [8]. In the retrospective study by Thompson et al, who used the standard dose and administration of trastuzumab, the overall probability of an infusion reaction was 16.2%, with the majority of reactions occurring for the duration of the first dose (91%). Symptoms included chills, pain, rigors, nausea, headache, shortness of breath, vomiting, numbness, and fever. The bulk of reactions were grade 2 (97 percent), while grade 1 reactions occurring and no patients experiencing grade 3 or 4 reactions.

2.3. Interstitial Lung Disease (ILD)

Hypoxemia, dyspnea, and respiratory failure can be symptoms of pneumonitis caused by trastuzumab. A significant neutrophilia is seen in the BAL differential cell count, which supports neutrophilic alveolitis. It was demonstrated in a study by et al. that trastuzumab treatment may cause the development of pneumonia and lung damage. A black box warning for PT is present for trastuzumab, but this side effect is uncommon (1%) and individuals with lung disease or prior lung injury are more likely to experience severe pulmonary responses. The mechanism underlying pulmonary toxic responses might manifest hours to weeks after injection, and HER2 suppression may impede type II lung cells' ability to respond to harm [9, 10].

3. Combination Regimens and Toxicity Management

3.1. Trastuzumab with Angiotensin-converting-enzyme (ACE) Inhibitor

ACEIs raise cardiac output, enhance ventricular geometry, lessen cardiomyocyte apoptosis, and lessen afterload and systolic ventricular wall stress. Nearly all experimental models of cardiac damage result in the induction of cardiac tissue ACEs. The observations by Cardinale et al. demonstrate that enalapril limits the release of any and avoids cardiac dysfunction, even though the exact mechanism by which enalapril reduces the emergence of cardiotoxicity is still unknown [6, 11].

Patients with early breast cancer who tested positive for her2 were allocated at random to one of three treatments: perindopril, bisoprolol, or a placebo (1:1:1) in a double-blind, placebo-controlled experiment by Pituskin et al. during adjuvant therapy with trastuzumab, demonstrating that perindopril and bisoprolol prevented the cancer treatment-related decline in LVEF [6, 12].

According to the National Cancer Institute recommendations: if cardiotoxicity occurs during trastuzumab therapy, trastuzumab can be continued if LVEF is >50%; if LVEF decreases <10% from baseline to 49% to 45% or <44%, trastuzumab should be interrupted and an ACE inhibitor should be initiated. If trastuzumab therapy is interrupted, further LVEF assessment should be performed after 3 weeks, and trastuzumab therapy may be restarted if LVEF returns to normal values or is between 49% and 45% with a <10% decrease from baseline. Interruption of cardioprotective therapy may be considered after normalization of LVEF at the end of cardiotoxic therapy [6].

3.2. Trastuzumab with Premedications

According to Thomson et al.'s reported mean, patients who did not get premedication experienced IRRs more frequently than those who did during the evaluation of the first dosage of trastuzumab. (19% vs 10%, $p=0.065$). The interaction between IRRs and premedication administration is shown in Table 1. The stage, body mass index, and usage of premedication are influencing factors; Even though it wasn't statistically important in univariate analysis, the finding was significant once confounding variables were removed in multivariate analysis. ($p=0.033$) [13].

Table 1. interaction between IRRs and premedication administration

Dose	Premedication	No premedication
All doses (n=1788)	10/1319 (0.8%)	23/469(5%)
First dose(n=197)	8/82(10%)	22/115(19%)
Subsequent dose(n=1591)	2/1237(<1%)	1/354(0%)

Table 1. lists reactions to infusions with or without premedication. In the Thomson et al. experiment, there was no written prescription for a premedication prior to trastuzumab. According to Tanz et al., two patients who experienced severe infusion reactions were successfully desensitized using an antihistamine and a corticosteroid premedication before receiving a very slow rate of infusion. They utilized aspirin and montelukast as premedics for cutaneous responses, such as flushing. Bronchospasm was treated with a glucocorticoid and montelukast. Premedications included acetaminophen and a glucocorticoid were used for fever and chills. One delayed reaction was noticed within 24 hours of desensitization after all desensitization, and it was light and handled over the phone [12–14].

3.3. Trastuzumab with Emtansine (T-DM1)

Ado-trastuzumab emtansine, brentuximab vedotin and some other ADCs are the FDA-approved ADCs that are currently available. Others are proven not having a deep associated connection with pulmonary toxicity. In a study, the researchers identified index cases by using dyspnea, cough, fever, and hypoxia imaging as clinical symptoms to reassure that pneumonitis was not caused by infection or progressive metastatic disease.

Consequently, the toxic effect of T-DM1 is pneumonitis, although with sample size. In the study, the researchers looked into a variety of potential risk factors for pulmonary damage. Taxanes are known to be associated with pulmonary toxicity, but in their review, they did not find a higher incidence of toxicity in patients with prior taxane use. It is important to highlight, however, that the number of patients who developed pneumonitis following a previous reaction to trastuzumab was quite low, and the documentation of such reactions was limited. As a result, drawing definitive conclusions based on the small sample size is difficult. Nevertheless, this finding could indicate that an immune reaction to the antibody component could potentially contribute to the development of symptoms. The researchers also looked at whether the location of the ADC cytotoxic payload delivery could affect its toxicity, however they found no statistically significant increase in pneumonitis in patients with lung metastases [15].

3.4. Trastuzumab with Doxorubicin

Cardiotoxicity can be observed more often when trastuzumab is given in conjunction with doxorubicin. A study shows that when trastuzumab is given together with doxorubicin it often leads to cardiotoxicity. This means that it can cause damage to the heart, which can result in ventricular dysfunction in up to 25% of patients, chronic heart failure, and even death. In a prior trial, trastuzumab was used to treat 27% of patients with HER2-positive metastatic breast cancer, and they revealed some level of cardiac impairment, including a decrease in the ability of the left ventricle to pump blood, and 19% reported signs of heart failure. This trial involved the simultaneous administration of trastuzumab and doxorubicin. However, subsequent large-scale trials showed that the number of cardiac incidents linked to trastuzumab was not as high as in the initial trial, ranging from 1-4%. In these trials, patients were carefully screened to ensure normal heart function and were closely monitored throughout the study. To minimize the risk of synergistic toxicities, the concurrent administration of doxorubicin and trastuzumab is no longer recommended in clinical practice. Instead, the two agents are given one after the other [16].

Possible mechanisms for the development of cardiotoxicity caused by anthracyclines include the regulation of signaling pathways that control gene expression [17]. The inhibition of topoisomerase 2 through the formation of a covalent Top2-Doxorubicin-DNA ternary complex, resulting in the breakage of double-stranded DNA. Additionally, oxidative stress and oxidation of mitochondrial DNA, in addition to the activation of the proinflammatory transcription factor NF κ B and inducible nitric oxide synthase (iNOS), may contribute to the cardiotoxic effects. Overexpression of ErbB2 has the capacity to increase the action of antioxidant enzymes, cut down the amount of reactive oxygen species (ROS), and provide protection against doxorubicin cardiotoxicity. However, trastuzumab can worsen this condition [16].

3.5. Trastuzumab with Anthracycline Taxane Chemotherapy

Genuino and co-workers conducted a systematic review and meta-analysis, a regimen of chemotherapy with the addition of adjuvant trastuzumab in patients with HER2-positive EBC respectively lowered the risk of death and recurrence by 33% and 35%. Nevertheless, it may raise the hazard of CHF and LVEF loss by a factor of three and two, respectively. The clinical application requires both stake and advantage assessment of the net clinical benefit, weighed against the patient's assessment of cardiovascular function prior to initiation of therapy, as well as the need for ongoing monitoring of cardiovascular function during treatment [18].

4. Emerging Strategies to Reduce Toxicity

4.1. Serum Biomarkers

Cancer patients who have received specific cancer treatments (chemotherapy, targeted therapy, biology, etc.) are more likely to suffer from cardiovascular disease due to various factors. Therefore, a patient's cardiovascular health status can be assessed before cancer treatment is initiated. For cancer

patients undergoing cardiotoxic cancer therapy, Serum biomarkers are a useful tool for determining baseline risk and diagnosing cardiovascular disease. The HFA Cardiac Oncology Study Group proposes to specifically assess serum cardiac biomarkers' effect in cancer patients both pre-treatment and post-treatment. The effects during the treatment are also analyzed.

Biomarkers are proteins or other biochemical entities circulating in the bloodstream that measure and quantitatively respond to a patient's dynamic CV physiopathology, with characteristics such as objectivity and reproducibility.

Two biomarkers that have fulfilled the requirements and are widely used in clinical practice over the past 30 years of research are cardiac troponin (cTn) and natriuretic peptide (Nps).

Cardiac troponin (cTn) is a structural protein specific to people's heart and is an organ-specific marker. Temporal alterations in the short term in cTn concentration can distinguish between acute disease and chronic cardiomyocyte injury, and plasma concentrations of cTn have been associated with a progressive decline in LVEF.

Nps is a quantitative marker of HF that calculates intracardiac filling pressures as well as end-diastolic wall stress, and its concentration can aid in the diagnosis of HF. In addition, Nps has a higher accuracy in differentiating between heart failure and other reasons to dyspnoea: the greater the NP value, the more likely dyspnea due to heart failure. In populations including risk factors for CV, Nps screening may detect patients who will be more likely to suffer cardiotoxicity, allowing for focused preventive actions [19].

4.2. Zingerone

Zingerone is one of the active constituents of ginger with anti-inflammatory, antioxidant, and anti-apoptotic properties. Trastuzumab treatment reduces the activity of oxidative and antioxidant enzymes, which reduces the heart's free radical- quenching capacity, leading to oxidative stress and cardiotoxicity. Also, trastuzumab treatment leads to a significant increase in IL-2 and TNF- α levels, and elevated expression of these pro-inflammatory cytokines also induces cardiotoxicity. In the controlled experiment by Khan et al, the cellular changes (sarcoplasmic reticulum inflammation, cytoplasmic vacuolization, loss of myofibrils, etc.) treated with zingerone were successfully restored to normal, as well as the levels of pro-inflammatory cytokines and serum cardiac markers enzyme levels, the glutathione levels of the experimental rats were elevated, and the levels of the antioxidant enzymes were normalized, which effectively mitigated the trastuzumab-mediated cardiotoxicity. However, their study used an animal model, and further exploration in humans is needed [9].

5. Conclusion

The toxicity we found with trastuzumab, although very weak, should be a point of concern. Trastuzumab can cause cardiotoxicity in combination with chemotherapy, trastuzumab combined with Emtansine can cause lung toxicity, and trastuzumab combined with doxorubicin can cause cardiac toxicity. Due to the urgency and severity of cancer, these possible side effects can occur in the reality of cancer treatment, so it is important to pay attention and understand the mechanisms and solutions. Monoclonal antibodies are still a widely-used and efficient treatment for cancer. As the possibility that trastuzumab alone may cause toxicity is more prominent, discovering and resolving the toxicity of trastuzumab in combination with other treatments is imminent, and the toxicity treatments that we have identified contain serum biomarkers and Zingerone, which can be used as a reference in the context of current developments. In order to provide safer and more efficient treatments for cancer patients, additional safe combination strategies still need to be investigated and developed.

Authors Contribution

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

References

- [1] Le X-F, Pruefer F, Bast R C. HER2-targeting Antibodies Modulate the Cyclin-dependent Kinase Inhibitor p27Kip1 via Multiple Signaling Pathways. *Cell Cycle*, Taylor & Francis, 2005, 4(1): 87–95.
- [2] Drebin JA, Stern DF, Link VC, Weinberg RA, Greene MI. Monoclonal antibodies identify a cell-surface antigen associated with an activated cellular oncogene. *Nature*, 1984, 312(5994): 545–548.
- [3] Nahta R, Esteva F J. HER-2-targeted therapy: lessons learned and future directions. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*, 2003, 9(14): 5078–5084.
- [4] A D, Z R, H S, et al. Overcoming trastuzumab resistance in HER2-positive breast cancer using combination therapy. *Journal of Cellular Physiology*, *J Cell Physiol*, 2020, 235(4): 3142–3156.
- [5] Jerusalem G, Lancellotti P, Kim SB. HER2+ breast cancer treatment and cardiotoxicity: monitoring and management. *Breast Cancer Res Treat*, 2019, 177(2): 237–250.
- [6] Nicolazzi MA, Carnicelli A, Fuorlo M, et al. Anthracycline and trastuzumab-induced cardiotoxicity in breast cancer. *Eur Rev Med Pharmacol Sci*, 2018, 22(7): 2175–2185.
- [7] Nakagami H, Takemoto M, Liao J K. NADPH oxidase-derived superoxide anion mediates angiotensin II-induced cardiac hypertrophy. *Journal of Molecular and Cellular Cardiology*, 2003, 35(7): 851–859.
- [8] Pichler W J. Adverse side-effects to biological agents. *Allergy*, 2006, 61(8): 912–920.
- [9] Mo H, Jazieh K A, Brinzovich D, et al. A Review of Treatment-Induced Pulmonary Toxicity in Breast Cancer. *Clinical Breast Cancer*, 2022, 22(1): 1–9.
- [10] Vahid B, Mehrotra A. Trastuzumab (Herceptin)-associated lung injury. *Respirology*, 2006, 11(5): 655–658.
- [11] Cardinale D, Colombo A, Sandri M T, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. *Circulation*, 2006, 114(23): 2474–2481.
- [12] Brennan P J, Rodriguez Bouza T, Hsu F I, et al. Hypersensitivity reactions to mAbs: 105 desensitizations in 23 patients, from evaluation to treatment. *The Journal of Allergy and Clinical Immunology*, 2009, 124(6): 1259–1266.
- [13] Goto E, Hata T, Nishihara M, et al. Preventive effect of dexamethasone premedication on the development of infusion-related reaction in breast cancer patients receiving trastuzumab. *British Journal of Clinical Pharmacology*, 2023, 89(7): 2102–2112.
- [14] Rombouts M D, Swart E L, VAN DEN Eertwegh A J M, et al. Systematic Review on Infusion Reactions to and Infusion Rate of Monoclonal Antibodies Used in Cancer Treatment. *Anticancer Research*, 2020, 40(3): 1201–1218.
- [15] Egloff H, Kidwell K M, Schott A. Ado-Trastuzumab Emtansine-Induced Pulmonary Toxicity: A Single-Institution Retrospective Review. *Case Reports in Oncology*, 2018, 11(2): 527–533.
- [16] Milano G, Biemmi V, Lazzarini E, et al. Intravenous administration of cardiac progenitor cell-derived exosomes protects against doxorubicin/trastuzumab-induced cardiac toxicity. *Cardiovascular Research*, 2020, 116(2): 383–392.
- [17] Ghigo A, Li M, Hirsch E. New signal transduction paradigms in anthracycline-induced cardiotoxicity. *Biochim Biophys Acta*, 2016, 1863: 1916–1925.
- [18] Genuino AJ, Chaikledkaew U, The DO, et al. Adjuvant trastuzumab regimen for HER2-positive early-stage breast cancer: a systematic review and meta-analysis. *Expert Rev Clin Pharmacol*, 2019, 12(8): 815–824.
- [19] Pudil R, Mueller C, Čelutkienė J, et al. Role of serum biomarkers in cancer patients receiving cardiotoxic cancer therapies: a position statement from the Cardio-Oncology Study Group of the Heart Failure Association and the Cardio-Oncology Council of the European Society of Cardiology. *European Journal of Heart Failure*, 2020, 22(11): 1966–1983.