PHARMACEUTICAL JOURNAL OF INDONESIA 2019. 5(1): 13-20

PHARMACEUTICAL JOURNAL OF INDONESIA

Available online at http://.pji.ub.ac.id

Trastuzumab Induced Cardiotoxicity (TIC) In Patient with Breast Cancer: Pharmacology Aspect, Mechanism of Cardiotoxicity, Risk Factor and Treatment Strategies (Literature Review)

Nur Jaya[1*], Sumarno[2]

[1]*Master of Clinical Pharmacy Programee, Faculty of Pharmacy, Airlangga University, Surabaya,Indonesia*

[2]*Departement of Clinical Pharmacy, Faculty of Pharmacy, Airlangga University, Surabaya, Indonesia*

ARTICLE HISTORY

Manuscript submission : June 04th 2018

Manuscript acceptance for review : July 31th 2018

Aprroval for publication : January 31th 2020

Keywords: Trastuzumab-Induced Cardiotoxicity; Pharmacology, Mechanism of Cardiotoxicity, Breast Cancer, Risk Factor and Treatment Strategies.

A B S T RACT

Background: Breast cancer (BCA) is the most common cancer in women. Systemic threapies for BCA include chemotherapy and homones therapy. Chemotherapy is one of the most important modalities and has become the standard of BCA treatment of in the adjuvant or neoadjuvant setting and was associated with better overall survival rate. One of the chemotherapy for BCA is trastuzumab. Trastuzumab is a monoclonal antibody, that acts as human epidermal growth factor tyrosine kinase HER2 (Erb B2) antagonist. However, it is associated with an increased risk of cardiac dysfunction. Trastuzumab treatment significantly affects the functional and structural characteristics of the heart. The mechanism of trastuzumab-related cardiotoxicity is not fully understood. This review will summarize the pharmacology and mechanism of trastuzumab-induced cardiotoxicity, investigate its risk factors, and consider the appropriate management for the patients.

Discussion: Trastuzumab is not only expressed through the excessive HER2 in positive breast cancer but can also disrupt the cardiomyocytes growth and selectively inhibit the structure and function of the heart causing dilated cardiomyopathy. Increased concern about LV dysfunction early detection triggers the needs to investigate the possible cardioprotective strategy. Some studies recommended angiotensin-converting enzyme inhibitor (ACEI) enalapril, to prevent the late cardiotoxicity and angiotensin receptors blocker (ARB) and also beta-blocker (BB), candesartan and bisoprolol, to significantly reduce left ventricle (LV) dysfunction event, as the management of trastuzumab-induced cardiotoxicity.

Conclusion: Delaying trastuzumab administration after previous anthracycline treatment can prevent or reduce the risk/synergy effect of cardiotoxicity. The temporal withdrawal and reinitiation after LV systolic function stabilization, both spontaneously or using heart failure therapy (eg, ACE inhibitors, angiotensin receptors blockers, beta-blockers), partially succeed in preventing cardiotoxicity. And, monitoring the troponin release was found as the first and the most sensitive test to detect cardiotoxicity early signs, with a proven impact on cardiac prognosis, particularly for trastuzumab (after the previous anthracycline).

* *Corresponding* author: Nur Jaya, *Master of Clinical Pharmacy Programme, Faculty of Pharmacy, University of Airlangga,Surabaya, Indonesia. E*-mail : nurjayamarzuki@gmail.com

1. Introduction

Breast cancer (BCA) is the most common cancer in North America, with approximately 252.710 new cases in 2017 affecting 1 in 8 women (about 12%) in the United States and 26.000 new cases in Canada [2,4,5]. Early detection and improvement in breast cancer screening had increase breast cancer survival rate up to 5 years in nearly 90% of 3 million breast cancer patients [4].

The improvement in chemotherapy and molecular targeted therapy increased breast cancer treatment effectiveness, showed by the increased survival rate. Unfortunately, this achievement was followed by additional treatment-related stress in the cardiovascular system. In America, about 2,3 million women with the history of breast cancer are suffered from a higher congestive heart failure risk due to their previous cancer therapy [3]. Several anticancer agents, such as anthracyclines, taxanes, cyclophosphamide, 5-fluorouracil, tyrosine kinase inhibitors and trastuzumab are associated with an increase in the risk cardiovascular morbidity and mortality[40]. Based on the long term cardiac effect in breast cancer patients, the cancer therapy effect on the cardiovascular system had become the main concern [6].

Trastuzumab is a monoclonal antibody, used in breast cancer therapy, which can disrupt human epidermal growth factor receptor 2 (HER2) [24]. HER2 is a part of transmembrane epidermal growth factor receptor tyrosine kinase (ErbB) that help cell growth, adhesion, migration, differentiation, proliferation, and repairing processes [24,33]. The HER2+ tumor cells have a high proliferative phenotype, increasing their capacity to spread stimulate the HER2+ tumor cells angiogenesis, found in 30% breast cancer cases. They are related to poor hormonal therapy response and the higher metastatic risk, recurrence, and also mortality [1]. So, HER2 signaling inhibition will improve HER2+ breast cancer therapy alongside with the conventional chemotherapy [33].

Trastuzumab significantly increases the overall survival rate in HER2+ breast cancer due to HER2 signaling blockade [25]. HER2 signaling plays an important role in maintaining the function of the cardiomyocytes [26,27]. Recently, the concerns about trastuzumab-induced cardiotoxicity event are emerging, sometimes they can be life-threatening. But, the risk factors and TIC predictor in breast cancer patients are not fully understood [28,29,30].

2. Discussion

Trastuzumab Pharmacology

Trastuzumab is a monoclonal antibody (mAb) that acts in HER2 positive breast cancer. Breast cancer can arise from the overexpression of transmembrane receptor named HER2. Trastuzumab is also indicated for the treatment of patients with HER2 positive early breast cancer following surgery, chemotherapy (neoadjuvant or adjuvant) and radiotherapy (if applicable)[14].

Recent usage: biologic therapy for HER2+ breast cancer tumor. Trastuzumab is a monoclonal antibody that identifies the protein in particular cells and sends a signal for the immune system to destroy them. This agent is more target specific compared to chemotherapy. This can be used as adjuvant therapy in metastatic cases [31].
Pathophysiology: binds to HER2+ cancer cells and sends a signal for the immune system to target them and stop their growth and cell division [31].
Dosage: Loading dose: 4 mg/kg infusion for 90 minutes with Paclitaxel or Docetaxel [14].
Maintenance dose: 2 mg/kg infusion for 30 minutes once a week for 12 weeks, after 1 week followed by (if the chemotherapy was done) 6 mg/kg infusion for 30-60 minutes every 3 weeks for 52 weeks (total therapy duration) [14].
Pharmacokinetics: Half-life and clearance rate decrease with increasing dose. The average half-life is 1,7 and 12 days for 10 mg and 500 mg dose. With 4 mg/kg loading dose followed by 2 mg/kg weekly maintenance dose, the observed half-life is approximately 5,8 days. The average serum concentration of trastuzumab given with paclitaxel increase 1,5 times higher compared with trastuzumab usage with doxorubicin and cyclophosphamide. The use of paclitaxel decreases trastuzumab clearance [14,31].
Administration: IV or infusion access port. The initial dose is administered up to 90 minutes and the following dose is up to 30 minutes [31]. Don't mix with the other drugs, given only via IV (can't be administered via IV push and IV bolus) [15].
Side effect : **Common :** *Rash* (18% to 38%), weight lost (23%), diarrea (7 to 51%), nausea (33% to 76%), stomatitis (24%), vomiting (23 to 53%), anemia *all grades* (4% to 36%), neutropenia *all grades* (6.4%), trombositopenia *all grades* (16%), cough (26% to 43%), dizzines (29.5% to 35%), fever (36% to 56%), trembling (32 to 41%) [15].

Severe : Cardiac dysrhythmia (3%), Heart failure (Adjuvant breast cancer, 0.4% to 3.2%; metastatic breast cancer, 7% to 28%), Left ventricular cardiac dysfunction (5% to 18.5%), Myocardial ischemia, Grade 3 or 4. **Other:** Infusion reaction (21% to 40%), Tumor lysis syndrome [15].
Contra Indikation: history of active cardiac disease, abnormal electrocardiogram, abnormal chest rontgen, left ventricle function decrease, or uncontrolled hypertension [31].
Major interaction: Doxorubicin/anthracycline - Trastuzumab: increase cardiomyopathy risk. Warfarin - Trastuzumab: increase bleeding risk [15].
Monitoring: cardiac status through multi gated acquisition scanning or echocardiography before starting doxorubicin, after doxorubicin, before trastuzumab, 3 months after initial therapy, 6 months after initial therapy, and 15 months after initial therapy. Care modification is conducted if there are a sign and symptom of heart failure with >10% left ventricle function decrease [31].

Figure 1. Trastuzumab Prescribing Information
Note: Based on information from [14,15,31].

The Mechanism of Trastuzumab-induced Cardiotoxicity

Although trastuzumab can promote HER2 positive breast cancer prognosis, trastuzumab induced cardiotoxicity (TIC) is still becoming an important problem. The exact mechanism of TIC is not fully understood, yet some mechanisms had been suspected. Trastuzumab is a monoclonal antibody that acts as HER2 receptor (ErbB2) antagonist, that disrupts neoangiogenesis and cell adaptation on physiologic and pathologic stress. This is not only overexpressed in HER2 positive breast cancer [22] but also selectively inhibits in the animal study that initiates the structural and functional alteration causing dilated cardiomyopathy [36].

Some studies showed that ErbB2 has an important role in cardiac function and development. In cardiac tissue, ErbB2 acts as a co-receptor of tyrosine receptor ErbB, ErbB4, and neuregulin peptide 1 ligand (NRG1). In cardiomyocyte, NRG1 binds the ErbB4 and facilitates ErbB4/ErbB2 heterodimerization, triggers heterodimer autophosphorylation, increases tyrosine kinase activity, and induces ERK-MAPK and PI3K-Akt pathway that enhances the cardiomyocyte proliferation, contractile function, and survival rate. HER2 blockade is related to the alteration of anti-apoptotic / pro-apoptotic protein ratio, due to anti-apoptotic protein BCL-XL down-regulation and pro-apoptotic protein BCL-XS upregulation. Since they are the main mediator of mitochondria and apoptotic function, the shifting ratio of pro-apoptotic protein is related to mitochondrial dysfunction that leads to cardiomyocyte death [13].. The cardiotoxicity of trastuzumab is based on its ability to prevent the formation of NRG1 / ErbB2 / ErbB4 complex, that important to cardiomyocyte survival [13].

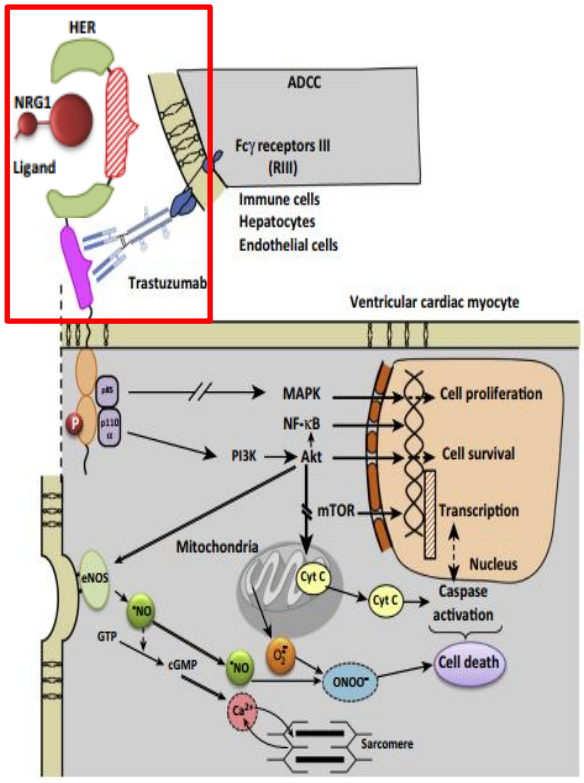

Figure 2. Neuregulin (NRG)/ErbB signaling on cardiomyocyte and endothelium. NRG-1 is expressed and released by endothelium and microvascular endothelial. ErbB is expressed in ventricular cardiac myocytes. ErbB receptor is also localized in caveolae by eNOS. NRG-1 releases its paracrine effect through ErbB receptor. The heterodimer is a downstream pathway stimulator, such as PI3K/Akt and MAPK. Trastuzumab activity is related to these blockades, that leads to the increased of cell cycle arrest, cell proliferation, and cell survival suppression. The mechanism of trastuzumab is to attract immune cells to the tumor sites that overexpress HER2 by antibody-dependent cellular cytotoxicity (ADCC). Abbreviation: Cyt C, cytochrome c. eNOS, endothelial nitric oxide synthase. MAPK, mitogen-activated protein kinase. PI3K, phosphatidylinositol-3-kinase [32].

The other mechanisms of trastuzumab-induced cardiotoxicity are due to mitochondrial dysfunction and cellular energy disruption from BCL-XL / BCL-XS ratio alteration. These events lead to mitochondrial membrane loss and the alteration of its intracellular components including electron transport loss, generation of free radicals, oxidative phosphorylation that reduce the ATP, and pro-apoptotic protein release such as cytochrome C [(13)].

Trastuzumab-associated cardiotoxicity was confirmed in vitro through cardiac cells culture and in vivo through animal studies using rats. Those studies showed that trastuzumab treatment significantly affects the functional and structural characterization of the heart. This mechanism involves genes alteration that related to cardiac function, adaptation capability to the stress, vasodilatation and contractility (Myl4, Myl7, Mhy1, Rxfp1, Ttn, Nppa, Acta1), calcium and sodium regulation (FGF12 and Sln), and mitochondrial function, apoptotic, and DNA repairing genes (Fbxl7 and Atf3). Trastuzumab also increases myocardial risk at 4-hydroxynonenal (4-HNE) and 3-nitrotyrosine (NT) level, oxidative and nitrate stress, that causing mitochondrial dysfunction and other cardiac tissue damage[(13)].

Cardiac damage has been observed also by electron microscopy imaging. Trastuzumab treatment causes cardiomyocyte ultrastructure alteration, associated with ultrastuctural damages of heart tissues in mice. In particular, alterations in intermitochondrial distance, thickness of myofibers and number of mitochondria have been observed[(39)]. It is noteworthy that both oxidative stress and structural alterations have been similarly found to be the main pathways in doxorubicin related cardiotoxicity[(13)].

Cardiotoxicity Risk Factors

Breast cancer therapy-induced cardiotoxicity is multifactorial. Radiotherapy is effective to reduce the local recurrence of breast cancer but it increases ischaemic heart disease and coronary artery disease risk in 20 years or more after treatment [(7)]. The anthracycline-based chemotherapy regimen, as adjuvant therapy for BCA, was found to be effective to increase the overall survival rate but it has dose-dependent cardiomyopathy risk due to irreversible anthracycline-induced cardiotoxicity [(8)]. The targeted agent, such as trastuzumab, can increase clinical outcome in 20% women with HER2 overexpressed BCA but its usage with anthracycline in metastatic cases is related to a high risk of heart failure (28%) [(9)].

Trastuzumab-induced cardiotoxicity is not dose-dependent and usually reversible, these features are different from anthracycline-induced cardiotoxicity. In a BCA adjuvant therapy study using anthracycline and trastuzumab, the risk relative of the heart failure (HF) was 7.19 (95%CI: 5.00 to 10.35) and the absolute risk of HF approximate 4% increase [(19,20)]. Nowadays, it is hard to predict which patients will have the highest risk of trastuzumab-induced cardiotoxicity [(6)].

In a meta-analysis, including the cohort conducted by Mantarro et al. 2016 [(16)], in 29.000 patients, the severe trastuzumab-induced cardiotoxicity was seen in 3% patients, with an increased event up to 19% particularly in the elderly, smoker, and also diabetic, hypertension, and cardiovascular disease patients. One of the most relevant implications of trastuzumab-induced cardiotoxicity is treatment cessation, that in turn can increase cancer recurrence [(17,18)].

So, we concluded that the risk factors of trastuzumab-induced cardiotoxicity are history of previous anthracycline treatment, short duration between anthracycline and anti-HER2 treatment, age >65 years, high body mass index (>30 kg/m2), history of left ventricle (LV) dysfunction, arterial hypertension, and history of previous radiotherapy [(19,20,21)].

Treatment Strategies

Increased concern about LV dysfunction early detection triggers the needs to investigate the possible cardioprotective strategy [(34)]. Over the past decades, some studies were conducted to find out the possible role of congestive heart failure conventional therapy to treat and prevent LV dysfunction in cancer patients [(33)]. Cardinale et al. recommended angiotensin-converting enzyme inhibitor (ACEI), enalapril, to prevent late cardiotoxicity in patients

with an increased troponin I (TNI) after the high dose of chemotherapy. TNI is a biomarker of early cardiotoxicity risk detection in patients treated with trastuzumab [35].

The PRADA (Prevention of cArdiac Dysfunction during Adjuvant breast cancer therapy) [38] randomized, placebo-controlled, double-blinded trial was conducted in 130 women with early BCA treated with adjuvant regimen using anthracycline with/without trastuzumab, and also radiotherapy. The subjects, without any significant cardiovascular comorbidity, randomly treated with candesartan (an angiotensin receptors blocker), metoprolol (a selective beta blocker), as a combination or monotherapy, and placebo. After three years follow up, in the candesartan group there was a significant decreased of LV dysfunction, compared to the placebo group. While in the metoprolol group, there was no protective effect observed.

Recently, in a randomized placebo-controlled trial, Boekhout et al. [10] found that there was a significant decreased of LV dysfunction in the patients treated with trastuzumab that given candesartan as a preventive treatment, compared with placebo. Furthermore, Bosch et al. in OVERCOME (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies)[11] trial recommended the combination of enalapril and carvedilol as an additional protective agent to chemotherapy-induced cardiotoxicity compared with placebo.

The data from MANTICORE [12], randomized trial of perindopril, bisoprolol, and placebo in patients treated with trastuzumab, showed that bisoprolol significantly prevented left ventricular ejection fraction (LVEF) reduced compared with both perindopril or placebo. Ongoing research (NCT01009918) evaluates a prophylactic role of lisinopril and carvedilol in preventing trastuzumab-induced cardiotoxicity [33].

Despite the appealing results from these randomized trials, it is very important to note that all of these studies use a small sample and only followed up in short duration. Furthermore, all of these trials recruited women without any cardiovascular comorbidity so many bigger trials are needed to understanding the optimal cardioprotective strategy. Based on the updated evidence, prophylactic cardioprotective treatment is highly recommended in patients with a high risk of cardiotoxicity (for example the patients with a history of cardiovascular disease or uncontrolled cardiovascular risk factors) [33].

During monitoring, it is recommended to start cardioprotective treatment when there is a TNI increase or subclinical LV dysfunction found in echocardiography examination [28]. If there is heart failure (HF) progression during chemotherapy, the comprehensive HF treatment should be given according to the guidelines. The patients should be evaluated multidisciplinary bu cardiologist and oncologist to determine the need and duration of interruptive chemotherapy [33]. If cardiotoxicity develops during trastuzumab treatment, the National Cancer Research Institute [37] recommended this algorithm: trastuzumab is continued if LVEF>50%; ACEI is added in trastuzumab treatment if LVEF falls <10% from the baseline, between 45 - 49%; start ACEI and stop trastuzumab if LVEF falls >10% from the baseline, between 45 - 49% or <44%. In case of trastuzumab interruption, a further assessment of LVEF should be performed after 3 weeks and if restored to normal values or between 49 and 45% with a drop <10% from baseline trastuzumab treatment can be restarted [33]. At the end of the cardiotoxic treatment, cardioprotective therapy interruption can be considered after normalization LVEF [23].

3. CONCLUSION

Delaying trastuzumab administration after previous anthracycline treatment can prevent or reduce the risk/synergy effect of cardiotoxicity. The temporal withdrawal and reinitiation after LV systolic function stabilization, both spontaneously or using heart failure

therapy (eg, ACE inhibitors, angiotensin receptors blockers, beta-blockers), partially succeed in preventing cardiotoxicity. And, monitoring the troponin release was found as the first and the most sensitive test to detect cardiotoxicity early signs, with a proven impact on cardiac prognosis, particularly for trastuzumab (after the previous anthracycline).

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