Proceedings of the 4th International Conference on Biological Engineering and Medical Science
DOI: 10.54254/2753-8818/60/20241439

Strategies to Improved Breast Cancer Treatment Associated With Cardiotoxicity

Lai Ka Jerry Chin

Department of PuTuo Clinical, Shanghai University of Traditional Chinese Medicine, Shanghai, China

laikachin88@gmail.com

Abstract. In recent years, breast cancer has developed rapidly. Many women suffer from breast cancer, making the study of its treatment extremely important. The drugs used in breast cancer therapy have shown beneficial effects, but some cause cardiotoxic side effects wich deserve close attention. Cardiotoxicity includes a range of effects, such as arrythmia, cardiac dyfunction and even heart failure, which could be a threaten to life health. Therefore, it is crucial and necessary to deal with the cardiotixicity side effect during breast cancer therapy. Doing so will provide patients better options for their treatment. Three drugs have been proven to have cardiotoxic effects, including anthracyclines(eg:Doxorubicin), HER-2-targeting drug(Tratzutmab), and Cyclophosphamide. Although numerous studies have extensively researched how to mitigate the cardiotoxic effects of anti-breast cancer drugs, few articles have summarized and discussed these findings. This current situation results in a lack of comprehensive treatment plans in clinical practice. Therefore, this paper aims to review these studies and discuss the main drugs used to reduce the toxicity of three commonly used antineoplastic agents, in the hope of providing more comprehensive guidance for clinical medication.

Keywords: Breast cancer, Doxorubicin, Decrazoxane, Carvedilol, Cardiotoxicity.

1. Introduction

Breast cancer has become one of the most common malignant tumors in women globally, and its incidence and mortality rates continue to rise around the world. In 2022, there are 670,000 patients died because of breast cancer while 2.3 million women were diagnosed with breast cancer, which is the most common cancer among women in 157 countries [1]. Women of any age after puberty can develop breast cancer, but the incidence is increasing in older women. Breast cancer has been a threat to female health, the World Health Organization and the public should pay close attention to issues related to breast cancer. The advance of diagnosis of breast cancer and the improved therapy, the incidence of breast cancer and the complications that arise during treatment are still a cause for concern.

There are several common treatments for breast cancer such as chemotherapy and targeted therapy. However, some drugs may cause serious cardiotoxicity during breast cancer treatment, which greatly affects patients' quality of life and health. In chemotherapy, commonly used anthracyclines (e.g., doxorubicin) may cause irreversible myocardial damage and subsequently heart failure while effectively killing cancer cells. Other drugs used in different treatments can also cause serious cardiotoxicity including targeted therapeutic agents for HER2-positive breast cancer as well as cyclophosphamides.

DOI: 10.54254/2753-8818/60/20241439

This review aims to summarize and analyze the mechanisms of cardiotoxicity of common drugs used in breast cancer treatment and to explore the strategies to prevent these cardiotoxicity problems.

2. Common drugs in breast cancer treatment

There are three common drugs used in breast cancer treatment including anthracyclines, HER2-targeted drugs(eg: trastuzumab) and cyclophosphamides. Among anthracyclines, doxorubicin is one of the most common and effective drugs. It is not only used in breast cancer, but also used in other cancers widely. These drugs are capable of inserting into the DNA double helix, interfering with the DNA replication and transcription process, and inducing apoptosis by inhibiting topoisomerase II, which causes DNA strand breaks.

Secondly, HER2-targeted drugs are also used widely in breast cancer therapy, such as Trastuzumab(T-DM1). T-DM1 is a monoclonal antibody directed against the extracellular domain of the tyrosine kinase receptor HER2.This indicates that anti-HER2 therapy may be effective not only in treating breast cancer but also in other affected areas.

Cyclophosphamides is also used to treat breast cancer, which is one of the most widely used drugs against cancer. In addition, it is a potent immunizing agent as well. The synthesis of cyclophosphamides is able to selectively target cancer cells. Cyclophosphamides is an inactive prodrug, while enzymatic and chemical activation is required. After activation, nitrogen mustard induces inter- and intra-strand DNA cross-links, leading to cytotoxicity [2].

3. Alleviate Doxorubicin-induced cardiotoxicity.

Although anthracyclines are widely used and effective during breast cancer treatment, they can cause a serious side effect that threatens life:cardiotoxicity. For instance, the decline of asymptomatic left ventricular ejection fraction and left ventricular dysfunction, leading to heart failure. Research illustrates that of the 80 women breast cancer patients who accepted doxorubicin treatment, 27 of them developed cardiotoxicity [3]. It also shows the information that using doxorubicin to treat breast cancer has its potential to cause cardiotoxicity. There are three common drugs to improve doxurbicin-induced cardiotoxicity currently, including decrazoxane, Carvedilol and Irbesartan.

3.1. Decrazoxane reduce Doxorubicin-induced cardiotoxicity

Dexrazoxane(DEX) has been proven as a drug to mitigate doxorubicin-induced cardiotoxicity in many cancer therapies.In the study published by Mody H et al, they quantitatively described the doxorubicin-induced cardiotoxicity as well as the protective effects of dexrazoxane by using experimental data with mathematical modeling. They used JIMT-1, MDA-MB-468 cell lines and cultured them,assessed cell viability using the CCK8 cell viability assay, measured absorbance values to determine cytotoxicity, and modeled the pharmacodynamics. The result showed that doxorubicin is more effective than dexrazoxane in two cell lines in anti-cancer aspects as well as its killing rate is higher than dexrazoxane. However, dexrazoxane showed its potential to reduce doxorubicin-induced cardiotoxicity and will not influence the capability of doxorubicinnotably. Additionally, it was shown that a 10:1 dose ratio of dexrazoxane to doxorubicin combined in a three-week regimen maximized protection against the cardiac effects of doxorubicin [4].

To sum up, dexrazoxane can alleviate doxorubicin-induced cardiotoxicity while it should be used in specific dosage and plan. Dexrazoxane reduces the cardiotoxicity effects of doxorubicin without having a highly fluctuating effect on the anticancer effects of doxorubicin. Therefore, dexrazoxane reduce doxorubicin-induced cardiotoxicity in breast cancer treatments and other cancer therapies has its nice prospects and development of clinical.

3.2. Carvedilol reduce Doxorubicin-induced cardiotoxicity

Carvedilol is a non-selective beta-blocker with alpha1-blocking properties. It is widely used in the treatments of hypertension, heart failure, angina pectoris and other diseases. Its main principle of action is to blockβ1, β2 and α1 receptors. Blocking β1 receptor can reduce the contractility and heart rate of

DOI: 10.54254/2753-8818/60/20241439

the heart and lowers the cardiac output. Blocking "Blocking β2 receptors reduces the widening of bronchial and smooth muscles. Also, blocking α1 receptors causes blood vessels to widen, lowering peripheral vascular resistance. Carvedilol's chemical structure is a derivative of carvacrol and includes an aromatic ring.

There is a research published by Karvandi, Mersede, et al, they studied the preventive effect of Carvedilol on right ventricular dysfunction in breast cancer patients treated with anthracyclines. Since anthracyclines in cancer treatment cause cardiotoxicity, but Carvedilol blocks β1、β2 andα receptors and because of its antioxidant may prevent the dysfunction of right ventricular. Their study is a single-blind clinical trial, including 23 breast cancer patients while only 12 accepted anthracyclines treatment (Doxorubicin), the other accepted both anthracyclines and Carvedilol. Their results illustrates that Carvedilol has its ability to improve anthracycline-induced cardiotoxicity [5].

What makes this noteworthy is that Lee, Myunhee et al did a research on the effectiveness of Candesartan and Carvedilol in preventing the breast cancer patients who accept anthryclines. Patients with breast cancer and accepting anthracyclines are their subjects, arranged them to receive Candesartan, Carvedilol or placebo randomly. The study found that the LVEF reduce less in Candesartan and Carvedilol group than the one in placebo group, which illustrates that these two drugs has certain effective to provent anthryclines cardiotoxicity [6].

In the research published by Jahangir, Emrana, et al, they studied whether Carvedilol can prevent Doxorubicin-induced heart failure in mice. They use mice as their research model. The result turned out that DOX group mice showed a significant heart failure symptoms including cardio function decline and histopathological changes. But those mice in combination group showed the improvement of their cardio function notably. Meanwhile, the symptoms of heart failure were prevented and relieved, and histopathologic analysis showed reduced myocardial damage [7].

In conclusion, Carvedilol shows its benefit to prevent and improve DOX-induced cardiotoxicity. It can alleviate cardiac contractility, heart rate, and also to protect LVEF from declining too rapidly as well as other data shows that Carvedilol can protect heart. In particular, it has an attenuating and preventive effect on DOX-induced cardiotoxic side effects.

3.3. Irbesartan reduced Doxorubicin-induced cardiotoxicity

Irbesartan(IRB) is angiotensin II receptor blocker with broad activities of biological. IRB exerts its effects primarily through selective blocking AT-1 receptor and the consequent pressure-lowering effects of angiotensin II [8]. One of the possible mechanisms of Doxorubicin-induced cardiotoxicity may be the activation of renin-angiotensin system and production of angiotensin II,and inhibition of angiotensin II receptors has the potential to reduce DOX-induced cardiotoxicity.

In the recent research, they studied IRB modulate pathways to inhibit DOX-induced cardiotoxicity. They used mice as their research model, Combination group(IRB and DOX). Their result turned out that combination of IRB and DOX provides cardioprotection by inhibiting oxidative/nitrative stress in the first place. Additionally, IRB has effects to against inflammatory, reducing TNF-alpha levels and so on. IRB also exhibited anti-apoptotic effects as well as cleaved caspase-3 levels were reduced. Meanwhile, IRB alleviated DOX-induced TGF-β1 and increasing phosphorylation p38-MAPK expression [9]. This shows that IRB can reduce and protect DOX-induced cardiotoxicity.

In summary, these three drugs shows their advantages to improve DOX-induced cardiotoxicity through different aspects. But what should be pay close attention on is the dosage and usage of these three drugs to ensure that less influence on DOX treatment and also can protect cardio function. Therefore, specific therapeutic dosages and ratios needed to be explored in further study.

4. Reduce HER-2-induced cardiotoxicity

HER-2 targeted drug is one of the first choices used in breast cancer treatment, but its cardiotoxicity side effect brings serioud problems. Speakin of Trastuzumab(TZM), which is a representative drugs in HER-2 targeted drugs, there are researches illustrate that it will bring cardiotoxicity side effect through Notch2/JAK2/STAT3 pathways to induce myocardial cell damage [10]. For example, TZM treatment

DOI: 10.54254/2753-8818/60/20241439

will lower LVEF and increase cardiac enzyme biomarkers. It is crucial to study on prevent and improve HER-2-induced cardiotoxicity. In this review, it will mention four drugs which could improve HER-2-induced cardiotoxicity including CoQ10, Beta-blockers, ACE and Carvedilol.

4.1. Coenzyme Q10 reduce HER-2-induced cardiotoxicity

Coenzyme Q10(CoQ10) is one of the most common drug used in cardio disease with its advantage to prevent cardiovascular ailment. CoQ10 is essential human compounds, which is synthesized in the inner mitochondrial membrane. A group of healthy elderly participants treated with selenium and CoQ10 showed a significant reduction in cardiovascular mortality after a 4-year treatment [11].

In the research published by Al-Hammadi, Nawal et al, they studied that CoQ10 is able to prevent the breast cancer patients with TZM therapy from cardio toxicity. They found out that, CoQ10 protect those patients from rising ejection fraction and reducing inflammation biomarkers and cardiac enzyme levels [12]. It illustrates that CoQ10 has its benefit to protect cardiac function, which is useful to improve cardiotoxicity. Meanwhile, their result comes out that CoQ10 can effectively prevent patients from TZM-induced cardiotoxicity by rising EF. Therefore, CoQ10 not only protect cardiac function, but also reversal and alleviate HER-2-induced cardiotoxicity.

To sum up, CoQ10 plays a vital role to improve HER-2-induced cardiotoxicity. It is important to study that the dosage and usage of how to use CoQ10 and HER-2 targeted drugs at the same time will achieve better results and will not affect each other.

4.2. ACE reduce HER-2-induced cardiotoxicity

The main pharmacological effect of Angiotensin-converting enzyme(ACE) is the inhibition of ACE activity, reducing the generation of vasoilatory effects, alleviating the hydrolysis of bradykinin, blood volume reduction in blood pressure. It shows its positive effects on cardiovascular, usually used to prevent or improve hypertension and atherosclerosis.

In the research published by Oliva, Stefano et al, their experiments results illustrated that the breast cancer patients who also accepted TZM therapy occurs cardiotoxicity, such as heart failure(HF) or a decline of LVEF. However, it was improved after stop using TZM then use ACE and beta-blockers to recover cardiovascular functions. They also gave the information that, this treatment mainly used in patients with severe hypertension and a significant decline in LVEF within the first 3 months of TZM therapy [13]. It shows that TZM-induced cardiotoxicity is reversible, which is different with Dox-induced cardiotoxicity. Its reversibility makes it promising for patients to address this type of cardiotoxicity with medication.

4.3. Carvedilol reduce HER-2-induced cardio toxicity

As it mentioned before in DOX-induced cardiotoxicity, it will also reduce HER-2 induced cardio toxicity. Beiranvand, Elham et al studied Carvedilol against TZM-induced cardiotoxicity. They used rats as their research subject, the result showed that TZM therapy negatively affect Left ventricular dysfunction,Intraventricular systolic diameters (LVIDs) and other markers, while using carvedilol reduced these data [14]. It illustrates that Carvedilol has its ability to protect TZM-induced cardiotoxicity.

In the research published by Beiranvand, Elham et al, they investigated the toxicity of TZM in the H9c2 cell line and the antagonistic effect of Carvedilol on it. Their results indicated that complete or partial restoration of trastuzumab-induced expression levels of DAPs in proteomic analysis of cardiomyocytes treated with carvedilol combination therapy. Carvedilol inversed the protein down-regulation of translational biological processes induced by TZM [15]. Therefore, Carvedilol is crucial to improve TZM-induced cardio toxicity and clarifying the usage of carvedilol in it is what should be studied next.

5. Cyclosporamyide-induced cardio toxicity

Cyclophosphamide (CP) is an alkylating agent used to treat different types of tumors and self-immunity diseases. CP connected with DNA through its metabolites, causing DNA strand breaks and cell cycle

DOI: 10.54254/2753-8818/60/20241439

arrest, thereby inhibiting DNA replication and transcription. This effect is obvious in rapidly processing cells so that it has significant killing effect to cancer cells. It is widely used in breast cancer, Ovarian cancer and other disease. But its side effect brings serious influence, while Acrolein is the main metabolite that causes CP-induced toxicity. Nowadays, there are two drugs shows there effects to alleviate CP-induced cardio toxicity, including Levocabastine, VE and Glutathione S-transferase P.

5.1. Levocabastine reduce CP-induced cardiotoxicity

Levocabastine(LEV)has potent antihistamine activity. Histamine H1 and neurotensin NTS2 receptor is inhibited by LEV so that it is broadly used in allergies to reduce the uncomfortable symptoms such as water eyes.

According to the research published by Akram, Wasim, et al, CP-induced cardio toxicity decreased notably under LEV treatment. For instance, LEV(100 μg/kg) dramatically reduced CP-induced LDH as well as values of markers of cardiac inflammation. However, LEV(50 μg/kg) did not illustrate any significant protection of CP-induced cardio toxicity [16].

5.2. Vitamin E reduce CP-induced cardiotoxicity

There is a research illustrates that VE has protective effects on CP-induced cardio toxicity in male rats.The results by Attia, A. A., et al shows the information of VE is able to return cardiac enzyme biomarkers near normal level. It also protects the complete function and structure of muscle cell as well as reduces CP-induced cardio toxicity and degenerative change through keeping the structure of myocardial fibers intact, which shows its defensive role to CP-induced cardio toxicity. Meanwhile, VE can protect regular organization of myofibril from CP-induced cardio toxicity [17].

To sum up, it is crucial to use Vitamin E during CP therapy to improve CP-induced cardio toxicity. It is also worthy to confirm the dosage of VE in cancer therapy, which will not affect the treatment of CP.

6. Conclusion

Breast cancer has been one of the most threaten diseases to female around the world. In the recent years, there are more and more drugs used in the treatment of breast cancer with the development of medical technical,while they bring cardiotoxicity side effects, which is a problem we should focus on. When choosing a treatment for breast cancer patients, the efficacy and side effect should be under concern to make sure the quality of life for patients after treatment. For the breast cancer long-term survivors, it is more important to do some cardiac function check earlier to prevent cancer-therapy drugs induced cardiac dysfunction with regular testing and follow up to select a better treatment. Anti-cancer drugs cause changes in many biomarkers that can pave the way for early detection of cardiac dysfunction in preparation. There are amounts of researches indicate that certain drugs can protect breast cancer therapy drugs induced cardiotoxicity, it is imminent to study next step in clinical research, which is an issue author will keep an eye on. Meanwhile, lage-scale trials of cardioprotective drug interventions can continue to advance and bring new drugs to the forefront to prevent cardiac dysfunction. With the increasing cardiotoxicity associated with breast cancer treatment, but progress has continued to be made in terms of mechanisms and other aspects, there is a need to continually improve and update cardioprotectives strategies to achieve the ultimate goal of reducing the morbidity and mortality form this growing cardiovascular disease.

References

[1] Rashid, F A, Anwar, W, Kandakurti, P K & Hazari, A 2024 Physical rehabilitation program for cardiorespiratory health and quality of life among breast cancer survivors in UAE: protocol for a randomized control trial. In Trials (Vol. 25, Issue 1). Springer Science and Business Media LLC. https://doi.org/10.1186/s13063-024-08192-9

[2] Gordon, M Y, Goldman, J M & Gordon-Smith, E C 2009 Cyclophosphamide and cancer: Golden anniversary. Nature Reviews Clinical Oncology, 6(11), 638-647. https://doi.org/10.1038/nrclinonc.2009.146

[3] Pestana, R M C, Teixeira-Carvalho, A, Dos Santos, L I, de Oliveira, A N, Soares, C E, Sabino, A P, Simões, R & Gomes, K B 2024 Microparticles and cardiotoxicity secondary to doxorubicin-based chemotherapy in breast cancer patients. International journal of cardiology, 395, 131435. https://doi.org/10.1016/j.ijcard.2023.131435

[4] Mody, H, Vaidya, TR & Ait-Oudhia, S In vitro to clinical translational pharmacokinetic/pharmacodynamic modeling of doxorubicin (DOX) and dexrazoxane (DEX) interactions: Safety assessment and optimization. Sci Rep 13, 3100 (2023). https://doi.org/10.1038/s41598-023-29964-4

[5] Karvandi, M, Ghadyani, M, Mohebbi, N, Tabarraee, M & Salari, S 2023 Evaluation of the Effect of Carvedilol in Preventing Right Ventricular Dysfunction in Breast Cancer Patients Receiving Anthracycline. Advanced biomedical research, 12, 5. https://doi.org/10.4103/abr.abr_134_21

[6] Lee, M, Chung, W B, Lee, J E, Park, C S, Park, W C, Song, B J & Youn, H J 2021 Candesartan and carvedilol for primary prevention of subclinical cardiotoxicity in breast cancer patients without a cardiovascular risk treated with doxorubicin. Cancer medicine, 10(12), 3964–3973. https://doi.org/10.1002/cam4.3956

[7] Tashakori Beheshti, A, Mostafavi Toroghi, H, Hosseini, G, Zarifian, A, Homaei Shandiz, F & Fazlinezhad, A 2016 Carvedilol Administration Can Prevent Doxorubicin-Induced Cardiotoxicity: A Double-Blind Randomized Trial. Cardiology, 134(1), 47–53. https://doi.org/10.1159/000442722

[8] Darwish, I A, Darwish, H W, Bakheit, A H, Al-Kahtani, H M & Alanazi, Z 2021 Irbesartan (a comprehensive profile). Profiles of drug substances, excipients, and related methodology, 46, 185–272. https://doi.org/10.1016/bs.podrm.2020.07.004

[9] El-Said, NT, Mohamed, EA & Taha, RA Irbesartan suppresses cardiac toxicity induced by doxorubicin via regulating the p38-MAPK/NF-κB and TGF-β1 pathways. Naunyn-Schmiedeberg's Arch Pharmacol 392, 647–658 (2019). https://doi.org/10.1007/s00210-019-01624-3

[10] Su, Z, Liu, S, Zou, Y, Shan, L, Yu, M, Xie, S, Li, X & Jin, Y 2023 Trastuzumab-induced human cardiomyocyte damage through the Notch2/JAK2/STAT3 pathway. Clinics (Sao Paulo, Brazil), 78, 100268. https://doi.org/10.1016/j.clinsp.2023.100268

[11] Zozina, V I, Covantev, S, Goroshko, O A, Krasnykh, L M & Kukes, V G 2018 Coenzyme Q10 in Cardiovascular and Metabolic Diseases: Current State of the Problem. Current cardiology reviews, 14(3), 164–174. https://doi.org/10.2174/1573403X14666180416115428

[12] Al-Hammadi, N, AlSabri, E, Kudhair, A H, Qassam, H & Hadi, N R 2023 Coq10 for preventing cardiotoxicity in breast cancer patients treated with trastuzumab. Journal of medicine and life, 16(8), 1188–1193. https://doi.org/10.25122/jml-2023-0098

[13] Oliva, S, Cioffi, G, Frattini, S, Simoncini, E L, Faggiano, P, Boccardi, L, Pulignano, G, Fioretti, A M, Giotta, F, Lestuzzi, C, Maurea, N, Sabatini, S, Tarantini, L & Italian Cardio-Oncological Network 2012 Administration of angiotensin-converting enzyme inhibitors and β-blockers during adjuvant trastuzumab chemotherapy for nonmetastatic breast cancer: marker of risk or cardioprotection in the real world?. The oncologist, 17(7), 917–924. https://doi.org/10.1634/theoncologist.2011-0445

[14] Beiranvand, E, Ostad, S N, Ardakani, E M, Torkashvand, F, Sardari, S & Vaziri, B 2020 In Vivo Evaluation of Carvedilol Cardiac Protection Against Trastuzumab Cardiotoxicity. Drug research, 70(4), 165–169. https://doi.org/10.1055/a-1110-7034

[15] Beiranvand, E, Torkashvand, F, Ostad, S N, Mirzaie, M, Ardakani, E M, Zandi, F, Sardari, S, Salekdeh, G H, Shokrgozar, M A & Vaziri, B 2020 Proteomics Analysis of Trastuzumab Toxicity in the H9c2 Cardiomyoblast Cell Line and its Inhibition by Carvedilol. Current

pharmaceutical biotechnology, 21(13), 1377–1385. https://doi.org/10.2174/1389201021666200515135548IF: 2.2 Q3

[16] Akram, W, Najmi, A K, Alam, M M & Haque, S E 2024 Levocabastine ameliorates cyclophosphamide-induced cardiotoxicity in Swiss albino mice: Targeting TLR4/NF-κB/NLRP3 signaling pathway. Toxicology and applied pharmacology, 483, 116838. https://doi.org/10.1016/j.taap.2024.116838IF: 3.3 Q2

[17] Attia, A A, Sorour, J M, Mohamed, N A, Mansour, T T, Al-Eisa, R A & El-Shenawy, N S 2023 Biochemical, histological, and ultrastructural studies of the protective role of Vitamin E on cyclophosphamide-induced cardiotoxicity in male rats. Biomedicines, 11(390). https://doi.org/10.3390/biomedicines11020390