

Review Article

Potential Ameliorating Role of Spironolactone in Trastuzumab-induced Cardiotoxicity: A Narrative Review



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Citation Ghabousian A, Alizadehasl A, Ansari N, Haghazali M. Potential Ameliorating Role of Spironolactone in Trastuzumab-induced Cardiotoxicity: A Narrative Review. *International Journal of Medical Toxicology and Forensic Medicine*. 2022; 12(2):E36127. <https://doi.org/10.32598/ijmtfm.vi.36127>

doi <https://doi.org/10.32598/ijmtfm.vi.36127>



Article info:

Received: 15 Sep 2021

First Revision: 10 Oct 2021

Accepted: 29 Oct 2021

Published: 21 Jun 2022

Keywords:

Spironolactone, Trastuzumab; cardiotoxicity, Heart failure, Cardio-oncology, Chemotherapy, Mitochondria, Oxidative stress

ABSTRACT

Background: Around 20% of breast cancers (BCs) overexpress Human Epidermal Growth Factor Receptor 2 (HER-2). HER-2 overexpression is associated with increased tumor aggressiveness and poor prognosis. Trastuzumab (an anti-HER2 monoclonal antibody) has been reported to improve overall survival in early-stage and metastatic BCs, but at the expense of increasing cardiac morbidity. In the current review study, we aim to discuss the pathogenesis of trastuzumab-induced cardiotoxicity and the potential ameliorating role of spironolactone in this regard.

Methods: The search strategy aimed to identify both published and unpublished studies. First off, we identified keywords and index terms, including trastuzumab, cardiotoxicity, heart failure, and spironolactone to conduct a broad search in PubMed, Embase, Scopus, and Web of Science, using the aforementioned keywords either individually or in combination. Lastly, the reference list of all identified articles was also evaluated. Our study included observational and interventional studies, case-reports, and systematic reviews and meta-analyses.

Results: Trastuzumab could deteriorate mitochondrial function and subsequently leads to the accumulation of Reactive Oxygen Species (ROS) in cardiomyocytes. Published clinical studies offered conflicting results regarding the efficacy of angiotensin-converting enzyme inhibitors and beta-blockers in respect of trastuzumab-induced cardiotoxicity. On the other hand, spironolactone was found to have both antioxidant and anti-inflammatory properties. Recent in-vivo studies supported the cardioprotective effect of spironolactone through maintaining mitochondrial ultrastructure and reducing ROS production.

Conclusion: Although spironolactone mitigates oxidative stress and mitochondrial dysfunction, there is a lack of clinical evidence to support the effectiveness of spironolactone in trastuzumab-induced cardiotoxicity. Design and implementation of clinical trials are recommended to determine the potential beneficial effects of spironolactone on trastuzumab-induced cardiotoxicity.

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1. Introduction

Breast Cancer (BC) is the most common malignant tumor in women worldwide [1]. Nowadays, with significant advances in early diagnosis and management of BC, patients' survival has markedly improved. However, the increased life span and the use of cardiotoxic chemotherapeutic agents have led to increased incidence of cardiovascular diseases and subsequent morbidity and mortality [2]. Human Epidermal Growth Factor Receptor-2 (HER-2), previously termed ErbB2, is a transmembrane proto-oncogene receptor and serves as a signal-transducing tyrosine kinase [3]. HER-2 activation exerts modifying impact on cell growth, proliferation, and survival by activating the Phosphatidylinositol 3-Kinase (PI3K) and Mitogen-Activated Phosphor Kinase (MAPK) signaling pathways [4]. Noteworthy, the overexpression of HER-2 receptor has been observed in approximately one-fifth of BC patients and is associated with a significantly worse prognosis [5]. However, HER-2 glycoprotein upregulation is not merely confined to BC; it can also occur in different epithelium-derived tumors [6, 7].

The development of HER-2 inhibitors has changed the landscape of treatment for patients suffering HER-2 positive tumors [8]. Adding HER-2-directed agents to the standard chemotherapeutic regimen has demonstrated survival benefits in several malignant tumors, including BC, gastric cancer, and gastroesophageal junction adenocarcinoma [9-11]. Trastuzumab is a prototype of humanized anti-HER-2 monoclonal therapeutic antibodies that selectively target the extracellular domain of the HER-2 receptor [12]. Trastuzumab is believed to mediate antibody-dependent cellular cytotoxicity and trigger natural killer cells activation against tumor cells [13, 14]. Besides, the amount of HER-2 receptors tends to diminish after exposure to trastuzumab [15]. As previously mentioned, trastuzumab can also hinder the proliferation-promoting signaling pathways [16]. In a meta-analysis study that included 1497 patients with HER-2 positive metastatic BC, trastuzumab administration promoted overall survival rate (Hazard Ratio (HR)=0.79, 95% Confidence Interval (CI)=0.67-0.94), but elevated the risk of heart failure (Relative Risk (RR)=3.49, 90% CI=1.88-6.47) [17]. Similar findings have been reported in the setting of adjuvant therapy [18, 19]. Accordingly, the clinical benefits of trastuzumab in BC treatment have been overshadowed by the emerging cardiovascular sequels [20-22].

The present review study aims to discuss the pathogenesis of trastuzumab-induced cardiotoxicity and the potential role of spironolactone in ameliorating cardiac injury.

2. Materials and Methods

A broad search was carried out in reliable databases, including PubMed, Embase, Scopus, and Web of Science, using the following keywords either individually or in combination: trastuzumab, cardiotoxicity, heart failure, and spironolactone. We did not limit the publication date. Relevant published articles in English were scrutinized.

The current narrative review was conducted to elaborate the potential impact of spironolactone administration on ameliorating trastuzumab-induced cardiotoxicity. The search strategy aimed to identify both published and unpublished studies. First off, we identified keywords and index terms, including trastuzumab, cardiotoxicity, heart failure, and spironolactone to conduct a broad search in PubMed, Embase, Scopus, and Web of Science, using the aforementioned keywords either individually or in combination. Lastly, the reference list of all identified articles was also evaluated. Our study included observational and interventional studies, case-reports, and systematic reviews and meta-analyses.

3. Results

Trastuzumab-induced cardiotoxicity

It has been proposed that trastuzumab-induced cardiotoxicity affects 15-20% of patients [23, 24]. Despite long-running endeavors, the precise underlying molecular mechanisms of trastuzumab-induced cardiotoxicity have not yet been fully explicated [25, 26]. HER-2 downstream signaling is the sine qua non of embryonic cardio-genesis, and has a pivotal role in the regulation of cardiac homeostasis [27]. Ventricular-limited deletion of HER-2 in a mice model has given rise to the characteristics of dilated cardiomyopathy, including diminished contractility [28]. In spite of anthracycline-induced cardiomyocyte injury and according to the biopsy specimen, there is no apparent ultrastructural remodeling attributable to trastuzumab [29]. Moreover, cardiac dysfunction triggered by trastuzumab is not dose-dependent, and appears to be predominantly reversible upon holding off the agent [16]. However, a few studies have recommended that exposure to trastuzumab may increase irreversible changes in cardiac tissue [30, 31].

Currently, undermining mitochondrial components via Reactive Oxygen Species (ROS) generation and im-

pairing metabolic pathways have garnered increasing attention in the pathogenesis of trastuzumab-induced cardiotoxicity [32, 33]. Trastuzumab was found to interfere with the expression of several myocardial genes involved in mitochondrial function, metabolic pathways, global cardiac function, and contractility [34].

Trastuzumab is deemed to block Neuregulin1 (NRG1), an epidermal growth factor that promotes HER-2/HER4 heterodimerization [35]. The NRG-1/ErbB signaling pathway is essential for cardiomyocyte development and mitochondrial activity [36, 37]. Animal studies have revealed that NRG1 knockout during embryogenesis is incompatible with life [38]. Another in-vivo study has found that NRG-1 injection in rats alleviates oxidative stress and preserves mitochondrial function [39]. Besides, NRG-1 seems to exert an anti-apoptotic feature and facilitates the cardiomyocyte repairing process [40]. Notably, trastuzumab upregulates pro-apoptotic molecules such as Bcl-xS while downregulating anti-apoptotic proteins such as Bcl-xL [41, 42].

It is well-established that inhibition of the HER-2 signaling is a remarkable contributor to the intensification of oxidative stress, which appears to be a rational explanation for an elevated risk of cardiac dysfunction after concomitant use of trastuzumab and anthracyclines [43]. Additionally, the extraordinary ROS levels lead to the activation of mitochondrial permeability transition pore located in the inner mitochondrial membrane and cause significant mitochondrial osmotic damage by increasing permeability [33, 44]. Interestingly enough, a recent experimental study on rabbit cardiac tissue has demonstrated that mitochondrial cristae tend to become disorganized due to edema, and mitochondrial membranes integrity could be disrupted in response to trastuzumab therapy [45]. Another recent study of human-induced pluripotent stem cell-derived cardiomyocytes has shed new light on the pathogenesis of trastuzumab-induced contractile dysfunction in cardiomyocytes. Overall, this study found that trastuzumab therapy did not affect cell viability, which precludes the possibility of irreversible cardiac injury. Besides, trastuzumab led to a significant diminution in cellular Adenosine Triphosphate (ATP) content, ATP-linked respiration, proteins involved in oxidative phosphorylation, and mitochondrial DNA levels per cell [46]. The clinical presentation of trastuzumab-associated cardiac dysfunction ranges from asymptomatic reduction in left ventricular ejection fraction (LVEF) to advanced heart failure [47].

Cardioprotective agents in trastuzumab-induced cardiotoxicity

There is no clinically effective therapeutic approach to prevent trastuzumab-induced cardiotoxicity yet [48]. More importantly, the cardioprotective efficacy of Angiotensin-Converting-Enzyme Inhibitors (ACEI) and beta blockers in trastuzumab-induced cardiotoxicity has been called into question, with the studies indicating conflicting results [49]. A randomized, double-blind, placebo-controlled trial that included 94 patients with HER-2 positive BC receiving adjuvant trastuzumab has shown that perindopril and bisoprolol cannot prevent the remodeling associated with trastuzumab [50]. In another similar study conducted on 210 patients, candesartan failed to preserve LVEF during trastuzumab adjuvant therapy [51]. On the other hand, in a cohort study of 6542 patients with BC who received trastuzumab/anthracyclines, it became evident that ACEI or beta blocker exposure has association with a significantly decreased risk of all-cause mortality, that is, 21% (HR=0.79; 95% CI: 0.70-0.90) [52]. A randomized, double-blind, multi-central trial conducted on 468 patients with HER-2 positive BC receiving trastuzumab and had a history of anthracycline exposure revealed that both lisinopril (HR=0.49, 95% CI=0.27-0.89) and carvedilol (HR=0.53, 95% CI=0.30-0.94) could improve cardiotoxicity-free survival [53]. Studies on the cardioprotective effect of statins in BC patients are limited. In a retrospective case-control study about the efficacy of statins on trastuzumab-related cardiotoxicity, patients with statin exposure had a lower risk of cardiac dysfunction (Odds Ratio (OR) =0.32, P=0.049) [54]. In another recent retrospective cohort of patients with BC who received trastuzumab, the statin receiving group (2.7%) had a non-significant lower 5-year cumulative incidence of symptomatic heart failure in comparison with the statin-naive group (3.7%) (pv=0.09) [55].

Potential role of spironolactone in trastuzumab-induced cardiotoxicity

Spironolactone, a potassium-sparing diuretic, competitively antagonizes mineralocorticoid receptors and exhibits antioxidant and anti-inflammatory properties [56-58]. Spironolactone mitigates the deleterious effects of the last component of the renin-angiotensin-aldosterone system on cardiomyocytes [59, 60]. It should be pointed out that aldosterone is inclined to promote inflammatory response, fibrosis, and ROS formation in cardiac tissue, particularly in the vulnerable myocardium [61, 62]. Furthermore, spironolactone barricades the androgen receptors and interferes with steroidogen-

esis [63]. Due to its diverse functions, it has been in broad clinical use for many years [64]. Spironolactone has been shown to be effective in the management of resistant hypertension and reduced ejection fraction heart failure [65]. Moreover, it has been recently supposed that the anti-inflammatory role of spironolactone might occur due to the suppression of NF- κ B signaling. NF- κ B is considered to be one of the crucial promoters of proinflammatory cytokines [66]. Spironolactone treatment puts up roadblock on apoptosis in endothelial cells by decreasing caspase 3 activity, a major executioner caspase, and cytochrome c leakage [67].

In a study conducted on the vascular tissue of Ren2 rat models, NADPH oxidase activity, a crucial source of oxidative stress, and lipid peroxidation were significantly decreased after spironolactone administration. More importantly, spironolactone upregulated the anti-apoptotic Bcl-xL protein and suppressed the activation of caspase 3, which executes apoptosis [68]. It should be noted that caspase-3 and caspase-7 activation can be induced by trastuzumab administration [69].

Connexin 43(Cx43) is a transmembrane gap junctional protein which involves in cardiomyocytes' cell-cell communication [70]. On the other hand, Cx43 can be expressed on the mitochondrial membrane and is thought to have a vital role in controlling mitochondrial respiration [71]. The overexpression of mitochondrial Cx43 has been reported as a measure to counteract the detrimental impacts of trastuzumab on mitochondrial function [72]. In addition, available evidence suggests that spironolactone has a positive influence on the expression of Cx43 [73, 74].

In an experimental study carried out on the streptozotocin-mediated diabetic rats, treatment by spironolactone was associated with the increments in the cardiac levels of vitamin E and decrements in nitrite production [75]. It is well understood that vitamin E acts as a potent antioxidant, which can reduce superoxide and hydrogen peroxide formation within the mitochondria [76, 77]. Liu et al. recently explored the cardioprotective effect of spironolactone in rats with diabetic cardiomyopathy. Twenty-four rats were classified into three groups: Non-diabetic control, diabetic 1 (treated by spironolactone), and diabetic 2 (treated by normal saline). They detected that treatment with spironolactone caused a significant decline in NADPH Oxidase 4 (NOX4) expression while increased Nuclear Respiratory Factor 1 (NRF-1) expression. It is worth mentioning that loss of NRF-1 creates a significant elevation in ROS levels. Moreover, NOX4 serves as ROS producing enzyme. Spironolactone also

promoted the expression of crucial proteins within the electron transport chain, namely, cytochrome c oxidase subunit 5B (COX5b) and ATP synthase 5a (ATP5 α 1) [78]. In other words, spironolactone therapy maintained both mitochondria ultrastructure and metabolic pathways. In an experimental study involving 80 female rats, the efficacy of spironolactone in cardiotoxicity induced by trastuzumab and radiotherapy was evaluated. In rats that received trastuzumab with concomitantly applied radiotherapy, spironolactone mitigated the expression of TGF- β and cardiac fibrosis score. However, it had no significant impact when trastuzumab was administered alone. Nevertheless, this study's limitation was the use of a light microscope, which poses an important obstacle to evaluating ultrastructural changes [79].

The role of spironolactone in doxorubicin-induced heart failure has been brought to light by several studies [80]. In a meta-analysis that included 12 studies about cardioprotective approaches in doxorubicin-induced cardiotoxicity, spironolactone was found to be the first appropriate therapeutic opportunity to prevent cardiac dysfunction based on LVEF changes [81]. Nonetheless, there is a shortage of clinical studies to evaluate the efficacy of spironolactone to this end. Taken together, it is evident that the deleterious impact of trastuzumab on the function of cardiomyocytes is mediated through mitochondrial dysfunction and ROS generation. Current experimental studies have illustrated that spironolactone can substantially attenuate mitochondrial morphologic changes, oxidative stress, and inflammation in cardiomyocytes. Therefore, spironolactone seems to be a good candidate for further clinical investigations with the aim of ameliorating trastuzumab induced-cardiotoxicity.

4. Conclusion

Treatment of HER-2-positive BC by trastuzumab may impair mitochondrial function and metabolic pathways within the cardiomyocytes. Overproduction of ROS seems to have a critical role in trastuzumab-induced cardiotoxicity. Recent experimental studies have suggested that spironolactone can attenuate mitochondrial dysfunction and ameliorate oxidative stress. Nonetheless, there is a lack of clinical evidence to support the effectiveness of spironolactone in this regard. Further clinical studies are recommended to determine the efficacy of spironolactone in the protection against trastuzumab-induced cardiotoxicity.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors have no conflict of interest to declare.

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