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Article Review on Anthracyclines and Anthracycline-Induced Cardiotoxicity

Navin Mathiyalagan*

Department of oncology, Royal College of Physicians, London, UK

***Corresponding author:** Navin Mathiyalagan, Department of oncology, Royal College of Physicians, London, UK, Tel: 7404101313;E-mail: dr.navinmathi@gmail.com

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Abstract

Cancer is rapidly growing to be one of the leading causes of death globally. As of 2018, there were more than 17 million new cancer cases, with a half fold death toll accounting for 9.5 million lives worldwide. Ideally, the statistics highlight an excepted projection in the global burden, leading to the 27.5 million new cancer cases. Despite the adversity of these statistics, recent advancement in the diagnosis and screening of malignant cancerous tumors has significantly lowered cancer mortalities, leading to a 50% and 75% survival rate among adults and children, respectively. Thus, as a future initiative, patients should always undergo constant monitoring of their vitals. Past details on the health history of patients should also be considered before treatment can be adopted. However, this success has led to the recognition of other cancer-treatment related toxicities and a similar need for the identification of early prevention and also mitigation approaches.

Keywords: Anthracyclines; Cardiotoxicity; Cancer-treatment; Chemotherapy

Introduction

Anthracyclines and anthracycline-induced cardiotoxicity

Since their discovery in the 1950s, Anthracyclines have been the most used and trusted chemotherapeutic approach in treating most cancers. Subsequent advancements in the production of Anthracyclines have equally increased their potential, leading to global recognition by the World Health Organization, despite having other potentially beneficial pharmaceutical discoveries [1]. However, these potentially life-saving regimens come with a burden cost on cardiovascular complications. Although other anti-neoplastic therapies are still not free from cardiotoxicity, anthracycline-induced cardiomyopathy is considered the most dominant, considering their indispensable role in the cancer treatment discipline.

Research cites a strong correlation between anthracycline administration and dose-related cardiomyopathies, with the severe cases leading to death from LV dysfunction and heart failure [2]. Results from three studies on 630 patients equally complemented this fact after highlighting a 43% increase in clinical heart incidence rates after a subsequent increase in anthracycline administration by 300 mg/m. The results were clearer on cancer survivors, from which 9% developed an impaired left ventricular ejection fraction following the successful completion of anthracycline therapy. Delayed heart failure was also dominant across this population, with childhood cancer survivors expressing a 12-fold increased proneness to developing congestive heart failure [3].

Over the past decade, the high reliance on anthracycline has implicated a 30% cardiotoxicity incidence in childhood cancer survivors. Ideally, there has been growing concern over the restricted scope of current screening methods to immediate after completion condition, hence missing late chemotherapy-related cardiotoxicity. However, consistent updates in their management promise potential improvement in managing anthracycline-induced cardiotoxicity.

Pathophysiology

Similar to the currently available research regarding the exact mechanisms that anthracyclines work on cancerous cells, it is still not clear the exact mode of action that prompts cardiotoxicity related to the use of anthracyclines in chemotherapy. However, previous proposals on the mechanistic of anthracyclines have been used to account for cardio-myocyte injury. Although anthracyclines express their modes of action in several modes; either by increasing DNA break, through the stabilization of topoisomerase, or preventing synthesis and replication of DNA, cardiotoxicity has been mostly associated with the Reactive Oxygen Species (ROS) from the Quinone evident in most anthracyclines [4]. Recent research suggests otherwise after a study by [5] gave relevance to an alternative model emphasizing the blocking action on topoisomerase. The limited function of topoisomerase is presumed to result in DNA break, causing the release of p53 tumor-suppressor protein. This imbalance is further linked to mitochondrial dysfunction that results in cardiac cell death from the development of ROS. Although ROS is scientifically proven harmful, the aforementioned theory faces opposition from the uncertainty of the relationship between ROS generation and anthracycline-medicated cell injury.

Similar to other cardiotoxicity modes, the role of topoisomerases in anthracycline-induced arises from its mechanistic mode of action. In this regard, doxorubicin works by forming a top2-DOX-DNA ternary complex, which inhibits polymerase as the topoisomerase 2. Top 2 is composed of Top2 α and Top2 β isoenzymes. While Top2 α holds a significant role in inhibiting DNA replication and chromosomal segregation, the intercalation of Top2 β with DNA exerts cardiotoxicity [6,7]. Ideally, this proposal was ascertained following improved resistance to anthracycline-induced cardiotoxicity on mice that had a Top2 β knockout.

Alternative explanations to anthracycline cardiotoxicity have further focused on their chemical and structural interactions. Toxic metabolites have in this regard been highlighted following a higher incidence in the presence of anthracyclines. The relevance to this notion follows the oxidative stress model of action associated with anti-neoplastic [6]. Anthracyclines, by this concept, induces a release of free radicals as they act as electron acceptors in reactions mediated by oxoreductive enzymes. Thus, the Quinone structure loses electrons,

forming a semi-Quinone radical. Semi-Quinone radicals alter DNA replication by inducing injury or causing damage from their interaction with molecular oxygen. On the other hand, cardiotoxicity through toxic metabolites arises from the electron reduction on the side chain carbonyl moiety, which results in the conversion of anthracyclines to secondary alcohols. Among the highlighted mechanism associated with the anthracyclines' mode of action, research cites their capability in altering iron homeostasis. Subsequent studies have further asserted the role of anthracycline in reducing the production of iron from sub-cellular organelles while increasing iron integration into cells [8].

Across the human body, cardiomyocytes have been ascertained as having the highest mitochondrial density considering their imperative role in respiration. Thus, mitochondria in this region must be kept at an optimal number through autophagy, which aims to maintain the homeostasis of their generation [9]. Autophagy must work in this agreement to eliminate mitochondria damaged by DOX. Anthracyclines, on the other hand, work negatively by inducing an accumulation of major autophagy markers that further reduce ATP levels [10]. Alternatively, anthracycline therapies intensify autophagy, thus degrading autophagolysosomes from the generation of ROS, leading to cell death.

In most of the aforementioned mechanisms, anthracycline was associated with a disruption of several homeostatic physiologies. Anthracycline Cardiotoxicity can, in the same way, be a consequence of the disruptive action of anthracyclines on sarcomere maintenance. Administration of anthracyclines in model animals indicated the down-regulation of several factors related to cardiac sarcomere synthesis. Among them, myocardial GATA4 is important in regulating sarcomere protein expression, which is specific to the cardiac system. Anthracycline administration, on the other hand, suppresses the GATA4 transcriptional factor, thus causing an imbalance regulation on most cardiac genes. This disruptive characteristic on sarcomere further affects its maintenance, thus leading to myocardial dysfunction. Despite literature having several approaches to the mechanistic of anthracycline-induced cardiotoxicity, most researches are hypothesized, lacking clear evidence to their relevance.

Prevention

Since most chemotherapy-induced cardiotoxicity cases often end up in deaths, the field of cardio-oncology recommends prevention as the best treatment. Thus, prior to any chemotherapy engagements, the patient must provide a detailed history focusing on their cardiovascular health status and any previous exposure to chemotherapy. In this regard, strategies aiming at the prevention of anthracycline-induced cardiotoxicity are classified as either primary or secondary. While primary prevention strategies refer to approaches taken prior to or during chemotherapy, secondary approaches are used to prevent further progression to symptomatic stages of diseases [11]. Primary prevention strategies may include the use of cardio protective agents or the reduction of cardiotoxicity potency in the prone regions. In cases involving high-Risk patients, risk reduction can be implemented through interventions such as counseling and appropriate health maintenance.

Prevention might also include the regulation of most technical operations. Research citing to the early 1980s indicate continuous infusion as a possible prevention approach. The study affirmed the potential of continuous infusion in reducing the development of chronic heart failure while limiting its scope impact on tumors. Recent research affirmed that continuous infusion for six hours significantly reduced the occurrence of heart failure. However, the approach is more subjective as the patient will have to bear a prolonged hospitalization.

The role of appropriate anthracycline administration in the prevention of cardiotoxicity is not only limited to infusion. Instead, pharmacology cites the choice agent as a possible strategy, considering that different anti-neoplastic have a wide range of cardiotoxicity. In this regard, liposomal encapsulation can be applied to reduce Cardiotoxicity [12,13]. This approach alters the bio distribution of the drug, thus creating a defined target on the cancer cells. Several studies have equally highlighted a reduced risk of heart failure development in patients treated using liposomal encapsulated anthracycline as opposed to the conventional approach.

The high relevance of oxidative stress in cardiotoxicity has increased the focus on drugs with antioxidant properties. Among them, dexrazoxane is the only FDA approved pharmaceutical agent in preventing anthracycline-induced cardiotoxicity. The cardio protective agent works by chelating iron and converting the O^2 and H^2O^2 into a more potent hydroxyl. Although this mechanism in the cardio-protective approach has been successful in mitigating the progression and incidence of anthracycline-induced cardiotoxicity, it might not be the only prevailing approach. Indeed, there has been considerable research suggesting the role of dexrazoxane in precluding the intercalation of DNA with TOP2 ß, thus preventing cardiomyocyte damage or death. However, this approach further incorporates a possible burden of later tumor developments and a compromise of the anthracycline efficacy. Recent research on the efficacy of dexrazoxane highlights a higher benefit scope from its use. Practically, an exponential delay in cardiotoxicity risk in the presence of dexrazoxane was evident in doses of more than 400 mg/ m2 as opposed to the 200 mg/ m^2 recorded in the absence of dexrazoxane.

In most cases, a neuro hormonal cascade is a primary condition that further progresses to heart failure and other cardiovascular diseases. In this regard, research has identified the potential equally implemented benefits of beta-blockers in blocking early neuro hormonal cascade, thus preventing heart failure. Recent studies that base the use of beta-blockers in preventing anthracycline cardiotoxicity rely on additional antioxidant activity of carvedilol and nebivolol. Literature concerning the use of blockades has grown to further include ACEi and ARBs as part of the primary approaches to anthracycline-induced cardiotoxicity. Ideally, similar randomized trials with different blockades have highlighted a similar protective mechanism on left-ventricular dysfunction attributed to chemotherapy.

On the other hand, ACEIs and ARBs improve cardiac functioning by working as blockades to angiotensin. They further rely on blood pressure to regulate the afterload. Similar studies on rats indicated an improvement when using zofenopril in reducing the risk of developing doxorubicin-induced cardiomyopathy. Similar results were identified in patients using enalapril, as LVEF was significantly decreased. In one of the largest clinical trials for the efficiency of beta-blockers for the prevention of cardiotoxicity, carvedilol was linked to a reduction in troponin levels and diastolic dysfunction, which further reduced the risk of developing anthracycline-induced Cardiotoxicity.

Despite the relevance of using ARBs and ACEIs in reducing the risk of anthracycline-induced toxicity, there have been concerns over its long-term use. In a recent study aimed at assessing the role of

candesartan on cardiotoxicity, patients undergoing candesartan treatment reported a higher incidence of developing fatal neoplastic diseases. Ideally, this long-term use was attributed to an increased risk of recurrence. The adversity associated with the use of ARBs and ACEIs is not only limited to the recurrence of cancer conditions but can also increase the risk for patients without a history of some specific cancer type. For instance, a cohort study found an increased risk of basal and squamous cell carcinoma in patients undergoing treated exposure to ACEI, ARB, or thiazide with no history of skin cancer.

A final proposal to the primary prevention of anthracycline-induced toxicity is the use of statin. This approach relies on the anti-inflammatory characteristics of statin. Model studies using animals have indicated reduced myocardial fibrosis and cell death after the administration of anthracycline. Ideally, the same results were evident in humans following a cohort study on 201 women. In the study, women who underwent statin therapy while being treated with anthracycline had a lower risk of developing heart failure compared to the control group [14]. In all these studies, statin was not beneficial when working independently but required an equally increased use of ACE inhibitors. The use of statin is relatively new in oncology. Thus, there are proposals and ongoing research on the role of atorvastatin in the prevention of anthracycline cardiotoxicity.

Several studies have also defined the role of antioxidants in reducing the risk of anthracycline-induced cardiotoxicity. However, the use of cardio protective anti-oxidants is restricted to some flavonoids, especially monoHer. While studies found other antioxidants as being ineffective, flavonoids have been identified to hold the antioxidant's properties while also inhibiting iron chelation and carbonyl reeducates inhibition. Thus, these antioxidants can be used to prevent the cardiotoxicity of anthracyclines while protecting their anti-tumor activity. Although subsequent monoHER derivatives have highlighted higher protection in animals, most clinical settings rely on the use of monoHER.

Further from the pharmacological approaches to reducing the risks of anthracycline cardiotoxicity, patients can also implement exercise prior to treatment. In one study on rats, endurance training provided prior to treatment with anthracycline significantly increased cardiac activity within the mitochondria-localized ATP-Binding Cassette (ABC) transporter protein. Thus, exercise may control the transport of anthracyclines like doxorubicin from mitochondria and the heart, thus preventing cardiotoxicity. Currently, no single prevention strategy works on all cardiotoxicity cases, considering that they all occur at different degrees and on a limited population.

Over the last two decades, a better understanding of the molecular pathways leading to tumor progression has increased the comprehensions and analysis scope of mechanism-based therapies. In this regard, new cancer therapies have been identified to target a specific condition, thus improving the prognosis. These therapies specifically target the cardiovascular system during chemotherapy treatment by limiting the risk of developing later cardiotoxicity conditions. However, these approaches are still new and lack enough evidence to highlight their role in reducing the risk of anthracycline-induced cardiomyopathy.

Management

In most cases, the best treatment for anthracycline-induced cardiotoxicity is prevention. Thus, in cases of early detection, patients should be restrained from the administration or use a different antineoplastic. On the other hand, in cases of later diagnosis, especially when the condition has already developed to congestive heart failures, common cardio protective and anti-heart failure interventions like the use of beta-blockers, diuretics, and ACEI should be adopted. All of the aforementioned approaches to treatment only work by limiting the effect of a condition but not eliminating it. There hence lacks a definite treatment approach to this condition [15-17].

In regard to the lack of a definite treatment approach in dealing with anthracycline-induced cardiotoxicity, future approaches in mitigating cardiotoxicity must consider a collective responsibility of both cardiovascular physicians and oncologists. Since various mechanisms contribute to cardiotoxicity, patients should only be treated if they reach a threshold in all their health status. Thus, as a future initiative, patients should always undergo constant monitoring of their vitals. Past details on the health history of patients should also be considered before treatment can be adopted. Thus, prior treatment should work to identify the best approaches that minimize the development of anthracycline-induced Cardiotoxicity [18].

Conclusion

Anthracycline continues to hold an indispensable role in the treatment of cancers, hematological malignancies, and sarcoma. However, its use is highly associated with an increased risk for the development of cardiotoxicity following treatment. Anthracycline-induced cardiotoxicity is in this regard dose-dependent. Concern over the increased risk of developing heart failure and other neoplastic diseases is still considered a top priority in the oncological field of cancer patients, especially considering the improved survival rate among this population. In reference to the mechanistic that base the etiology of cardiotoxicity, several strategies, including the use of beta-blockers, ARBs, and ACEIs, can be adopted a primary prevention approaches. Secondary prevention strategies, on the other hand, work to regulate the progression of the diseases to the symptomatic stage. Prevention can also be implanted through a technical manipulation of the anthracycline administration. In this regard, continuous infusion and the use of liposomal encapsulated anthracycline work to limit the development of doxorubicin-induced cardiotoxicity. Although the treatment of anthracycline-induced cardiotoxicity is not well defined in the field of oncology, several studies suggest the use of cardio protective and interventions similar to those for other types of heart failure. Future studies should create a greater focus on the mechanistic of cardiotoxicity in a bid to identify better prevention and mitigation strategies.

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