ONLINE ISSN :3007-309X
PRINT ISSN :3007-3081

Journal of Medical & Health Sciences Review

ANTHRACYCLINE TOXICITY IN CANCER THERAPY: BALANCING EFFICACY AND SAFETY

Sidra[1*], Hina Mumtaz[2], Dania Urooj[3], Abdul Jabbar[2], Faiza Rafique[4], Haeeda Naveed[5], Nimra Riasat[3]

[1]Department of Pharmaceutical Sciences, Government College University, Faisalabad, Punjab, Pakistan, Email: sidrayousaf123@gmail.com
[2]Institute of Pharmaceutical Sciences, University of Veterinary and Animal Sciences, Lahore
[3]Imran Idrees College of Pharmacy, Sialkot
[4]Department of Pharmacy, University of Lahore, Lahore
[5]Department of Pharmacy, Minhaj University, Lahore

ARTICLE INFO

Keywords: Cardiotoxicity, Anthracycline, Doxorubicin, Nephrotoxicity, Neurotoxicity

Corresponding Author: Sidra
Department of Pharmaceutical Sciences, Government College University, Faisalabad, Punjab, Pakistan
Email: sidrayousaf123@gmail.com

ABSTRACT

Toxicity associated with anthracycline derivatives presents significant challenges to cancer therapy. Despite their proven efficacy against various malignancies, possible adverse effects on cardiovascular and hematopoietic systems must be carefully considered when making clinical decisions. Although anthracyclines remain important in cancer therapy, the search for safer alternatives and individualized treatment strategies is of utmost importance to prevent toxicities like cardiotoxicity, nephrotoxicity, and neurotoxicity. Careful monitoring, the addition of cardioprotective measures, and the study of prognostic biomarkers are important factors to reduce the risks associated with the use of anthracyclines. Taken together, the complex interplay between therapeutic benefit and potential toxicity highlights the importance of a nuanced and individualized approach to anthracycline-based therapies. This review highlights the critical need for continued research and development of therapeutic approaches to address their toxicity. By promoting continuous research and adopting innovative solutions, the medical community can strive to optimize the balance between therapeutic efficacy and minimization of unwanted effects of anthracycline derivatives to improve cancer treatment.

1. Introduction

In adult and pediatric patients, anthracyclines are very effective chemotherapeutic medications used to treat a broad range of solid tumors and hematologic malignancies. However, their usefulness is limited by cardiotoxicity, which varies with dosage (1). For the treatment of many malignancies, anthracyclines remain the preferred class of chemotherapeutic drugs (2). This fact is still true despite the advent of numerous new cancer medicines in recent years, including targeted medications and immunotherapies, which have improved the mortality and overall morbidity of a variety of tumors (3). Heart failure (HF) and anthracycline-induced cardiomyopathy are the most common and well-studied, despite the fact that many anti-neoplastic treatments are cardiotoxic. Indeed, mounting data indicates a connection between malignancy and the development of CVD due to shared risk factors in older adults and pediatric patients, as well as the detrimental cardiac consequences associated with cancer treatment (4).

Even though anti-neoplastic medication has a cardiotoxic side effect, reducing, stopping, or stopping it too soon could have a negative impact on overall health. There are no studies that we could find that state that lowering chemotherapy in patients with asymptomatic left ventricular failure improves quality of life over the course of a patient's lifetime by minimizing toxicities and late effects while maintaining oncologic efficacy (5). To provide the current preventative methods, it is necessary to identify the risk factors of toxicities in children cancer survivors through close surveillance (6). A comprehensive study was conducted on four anthracycline compounds doxorubicin (DOXO), epirubicin (EPI), idarubicin (IDA), and methoxymorpholinodoxorubicin (MORPHO) utilizing mouse and rat models. These studies involved various administration routes (intravenous or intraperitoneal) and explored various dosing regimens over different durations. Across all assessments, two distinct types of toxicity emerged, reflecting occurrences in humans as well. Acute toxicity, stemming from cytotoxicity and showcasing the compounds' exaggerated pharmacological activity, affected renewing cell types in the hemolymphopoietic system (HLPS), gastrointestinal (GI) tract, skin, and testes. The second type, chronic progressive toxicity, resulted from sustained disruption of cytoplasmic homeostasis and affected non-renewing cell types. Target sites included the heart (in both animals and humans), kidneys (in rodents), and the peripheral nervous system (PNS) in rodents. The preclinical safety assessment provides a thorough understanding of the acute and chronic toxicities associated with these anthracycline compounds. These findings, spanning various

species and dosing regimens, contribute valuable insights into the potential effects on humans, guiding recommendations for their proper use in clinical settings (7).

2. Survey Methodology

By using multiple databases which includes Google Scholar, PubMed, Research Gate, a comprehensive search for literature review was conducted. The search scheme involved keywords and combinations related to anthracycline toxicity. The search term included anthracycline toxicity, cardiotoxicity by anthracycline, nephrotoxicity, neurotoxicity and associated mechanism. Articles that addressed the toxicities of anthracycline and their detailed mechanisms were considered for inclusion in this review.

3. Toxicities associated with Anthracycline derivatives

3.1. Cardiotoxicity

One might categorize the duration of cardiac damage caused by anthracycline treatment as either early or late cardiotoxicity. Early cardiotoxicity is the term for heart damage that occurs during or within a year after anthracycline therapy. However, late cardiotoxicity does not manifest itself until one year after the cessation of anthracycline therapy. For individuals who have had effective anticancer therapy, heart failure is a persistent issue, particularly for young people and children who have extended life expectancies. Twenty years after receiving anthracycline treatment for pediatric cancer, there is an estimated 5.5% probability of getting clinical heart failure. Clinical and experimental cardiotoxicity are potential human heart damage presentations. Subclinical cardiotoxicity refers to a range of cardiac conditions that are detected by a variety of diagnostic procedures in people who do not exhibit any symptoms (8). For instance, anomalies in the Billingham score for histological abnormalities or abnormalities in heart function are assessed by radionuclide ventriculography or echocardiography. Clinical cardiotoxicity is defined by an abnormal diagnostic test and the presence of heart failure symptoms. The only means of life when cardiac death has reached a critical level is heart transplantation (9). There is a wide range in the frequencies of clinical and subclinical cardiotoxicity reported in the literature. Approximately 57% of children had subclinical cardiac dysfunction at 6.4 years after therapy, and 16% may develop clinical heart failure between 0.9 and 4.8 years after therapy (10). A 2020 study found that after using anthracycline, 36% of patients had subclinical cardiac damage. In 30% of cases, clinical heart failure manifested itself, with a median of 37 months after medication (11). However, we did not conduct in-depth analyses of the prevalence of adult

anthracycline-induced cardiotoxicity. The risk of cardiac complications during anthracycline administration may be increased by radiation therapy directed towards the heart region, tumor type, exposure to cyclophosphamide, phosphamide, amsacrine, trastuzumab, or taxanes, or by the presence of pre-existing heart damage (12). It seems that women, children, and the elderly are the most susceptible.

3.1.1. Cardiotoxicity Mechanisms

The impact on cardiomyocytes is what determines whether a chemotherapeutic agent leads to type 1 or type 2 cardiotoxicity (13). Reversing type I cardiotoxicity is impossible due to the permanent depletion of cardiomyocytes. Reversing type II cardiotoxicity is feasible since it arises from the dysfunction of cardiomyocytes rather than cellular demise. Anthracyclines induce type I cardiac damage due to their long-term impact on cardiomyocyte depletion. With our current understanding of the genesis of cardiotoxicity, we can devise preventive methods to combat the occurrence of persistent heart damage. The primary mechanism by which doxorubicin effectively eliminates rapidly dividing cancer cells is by inducing DNA damage. However, the toxicity experienced by cardiomyocytes from doxorubicin is mostly attributed to the formation of free radicals during metabolism. Within the mitochondrial respiratory complex I, NADH dehydrogenase converts doxorubicin into a radical semiquinone. This radical might potentially react with molecular oxygen to generate a superoxide radical. The hydroxyl radical and hydrogen peroxide are generated as a result of redox cycling (14). In addition, the Fenton reaction may produce reactive oxygen species by converting hydrogen peroxide into hydroxyl radical with the help of Fe^{2+} ions. This process can be enhanced by the formation of doxorubicin-iron complexes. Cardiomyocytes, unlike glycolytic tumor cells, are anticipated to be much more susceptible to the oxidant stress caused by doxorubicin. This is because cardiomyocytes have a higher proportion of mitochondria and rely on oxidative substrate metabolism. To cause oxidative damage in tumor cells, it is necessary to administer doxorubicin at extremely high dosages (15). Controlling the production of reactive oxygen species is essential for improving the harmful effects on the heart caused by doxorubicin, as shown in animal models with altered genes. When mice are given doxorubicin, their left ventricular function improves, and apoptosis decreases if manganese-dependent superoxide dismutase (Mn-SOD) is overexpressed. However, if Mn-SOD is removed, the cardiotoxic effects of doxorubicin are intensified. The lab has recently shown that the activation of the transcription factor aryl hydrocarbon receptor stimulates

the synthesis of drug-metabolizing proteins (16), which is crucial for the metabolism of doxorubicin in cardiomyocytes. Studies have shown that mice without the aryl hydrocarbon receptor are at a higher risk of experiencing left ventricular dysfunction, increased formation of reactive oxygen species in cardiomyocytes due to doxorubicin, and cell death. To prevent the decrease in left ventricular function after doxorubicin treatment, it is feasible to eliminate proteins (such as nitric oxide synthase 3) that can encourage the production of free radicals by these medications (17).

Cardiomyocytes undergo doxorubicin metabolism, resulting in the production of reactive oxygen species (ROS). These species subsequently induce cell death via apoptotic mechanisms. Specifically, when cardiomyocytes are exposed to doxorubicin, caspases 9 and 3 are triggered, leading to the opening of the mitochondrial permeability transition pore and the release of cytochrome C into the cytoplasm (18). Doxorubicin may enhance the release of cytochrome C when exposed to oxidative stress by directly binding to the mitochondrial phospholipid cardiolipin. This binding prevents the interaction between inner mitochondrial membrane proteins and cardiolipin.

3.2.Neurotoxicity

The conventional belief that Doxorubicin (DOX) cannot traverse the blood-brain barrier (BBB) has been challenged, revealing unexpected neurotoxic effects associated with its administration. Recent studies propose that DOX might breach the BBB through vascular-associated apical projections of neural stem cells. This revelation coincides with efforts to increase the brain availability of DOX for the treatment of intracranial cancers. In experiments involving rats and rabbits subjected to varying doses of DOX, significant outcomes such as neuronal necrosis, ganglioneuropathy, and degenerative changes in dorsal roots and ganglia have been observed. Quantitative analyses underscore a notable loss of sensory neurons and morphological abnormalities, indicative of a degenerative process. These findings shed light on the intricate ways in which DOX impacts neural tissues, emphasizing the need for comprehensive studies to unravel these mechanisms. The evolving understanding of DOX's potential to induce neurotoxicity underscores the necessity for further in vitro and in vivo investigations. Unraveling the intricacies of how DOX affects the nervous system is crucial not only to identify the mechanisms at play but also to explore potential protective measures for the central nervous system. The quest for experimental and clinical drugs that may mitigate DOX-induced

neurotoxicity is paramount. This evolving comprehension is essential for optimizing cancer treatment outcomes and ensuring the overall well-being of patients undergoing DOX-based therapies (19).

3.3.Nephrotoxicity

Acute renal failure, a significant consequence of drug-induced nephrotoxicity, is a well-recognized side effect associated with Doxorubicin (DOX), a widely used chemotherapy drug. Despite its effectiveness against cancer cells, DOX's clinical use is limited due to its adverse effects, particularly in organs such as the heart, kidneys, lungs, testes, and hematological system. The precise mechanism underlying DOX-induced nephrotoxicity remains elusive, with proposed involvement of free radicals, oxidative damage, apoptosis, and direct renal accumulation. Despite numerous attempts to optimize dosage and explore alternatives, mitigating DOX's side effects has proven challenging (20). A study explored Doxorubicin (DOX) nephrotoxicity in male rats, revealing significant kidney damage marked by increased SUN and creatinine levels, reduced body weight, and elevated oxidative stress indicators. The research highlighted a close correlation between mitochondrial disturbances and the regulation of cell death genes during DOX-induced nephrotoxicity. Notably, pro-apoptotic proteins increased, anti-apoptotic genes decreased, and p53 expression rose while Mdm2 was suppressed. These findings underscore DOX's potential to cause kidney injury alongside its known organ toxic effects during chemotherapy, emphasizing the importance of understanding and mitigating such complications in clinical settings (21).

4. Recommendation

Considering the difficulties presented by anthracycline derivatives and their potential toxicity, the following recommendations guide clinical practice and future research:

Creation and execution thorough risk stratification models that identify those at higher risk based on features unique to each patient for the harmful effects of anthracycline. The patient's overall health, any current ailments, and potential susceptibility to certain side effects should all be taken into consideration when designing treatment plans (22). Cardioprotective measures are applied to patients undergoing anthracycline treatment as well as therapy regimens. To identify early indications of cardiotoxicity, this may involve frequent cardiac surveillance and the use of medications known to be cardioprotective, such as dexrazoxane (23). Investigation and creation of substitute treatment approaches that are less harmful yet just as effective or even more

effective should be done. Finding more about targeted treatments, immunotherapies, and other innovative approaches that could be helpful substitutes for an anthracycline-based regimen (24). Extending earlier research to find biomarkers with predictive value that can be utilized to find people who are more likely to encounter specific toxicities. This makes it possible to choose patients more precisely, which permits treatment plan modifications and preventative measures.

To get informed consent, better inform patients about the possible dangers and advantages of anthracycline-based therapy (25). Assist patients in making educated decisions with their healthcare providers by providing them with a complete understanding of the potentially harmful effects that these medications may have. Offering cancer patients who have undergone anthracycline-based therapy long-term follow-up services to identify and address late toxicity, this involves routine cardiovascular evaluations, hematologic monitoring, and general health monitoring (26). Facilitating cooperation between cardiologists, hematologists, oncologists, and other pertinent specialists, as well as guaranteeing complete and thorough access to patient care plays an important part. Multidisciplinary teams can work collaboratively to handle the challenges associated with treating anthracycline-induced toxicity (27).

5. Conclusion

In conclusion, the toxicity associated with anthracycline derivatives represents a major obstacle in the field of cancer therapy. Although they are effective in several cancers, possible negative effects on the hematological and cardiovascular systems must be carefully considered when making treatment decisions. To address their toxicity, this study highlights the urgent need for further research and improved therapies. The search for safer substitutes and individualized treatment plans is essential, although anthracyclines remain important in cancer therapy. Implementation of cardioprotective measures, careful monitoring and search for predictive biomarkers are key components to reduce the risks associated with anthracycline use. Taken together, the complex interactions between potential toxicities and therapeutic benefits highlight the importance of an individualized and nuanced approach to anthracycline-based therapy. In the pursuit of better cancer care, the medical community can strive to maximize the balance between therapeutic efficacy and reduction of anthracycline side effects by supporting continued research and implementing creative solutions.

Abbreviations:

DOXO: Doxorubicin,
EPI: epirubicin,
IDA: idarubicin,
MORPHO: methoxymorpholinodoxorubicin
HLPS: hemolymphopoietic system
PNS: peripheral nervous system
Mn-SOD: manganese-dependent superoxide dismutase

References

1. Martins-Teixeira MB, Carvalho I. Antitumour Anthracyclines: Progress and Perspectives. ChemMedChem. 2020;15(11):933-48.
2. Valcovici M, Andrica F, Serban C, Dragan S. Cardiotoxicity of anthracycline therapy: current perspectives. Archives of Medical Science. 2016;12(2):428-35.
3. Ganatra S, Neilan TG. Immune checkpoint inhibitor-associated myocarditis. The oncologist. 2018;23(8):879-86.
4. Bansal N, Adams MJ, Ganatra S, Colan SD, Aggarwal S, Steiner R, et al. Strategies to prevent anthracycline-induced cardiotoxicity in cancer survivors. Cardio-Oncology. 2019;5:1-22.
5. Colan SD, Lipshultz SE, Sallan SE. Balancing the oncologic effectiveness versus the cardiotoxicity of anthracycline chemotherapy in childhood cancer. Progress in Pediatric Cardiology. 2014;36(1-2):7-10.
6. Lipshultz SE, Law YM, Asante-Korang A, Austin ED, Dipchand AI, Everitt MD, et al. Cardiomyopathy in children: classification and diagnosis: a scientific statement from the American Heart Association. Circulation. 2019;140(1):e9-e68.
7. Mazue G, Iatropoulos M, Imondi A, Castellino S, Brughera M, Podesta A, et al. ANTHRACYCLINES - A REVIEW OF GENERAL AND SPECIAL TOXICITY STUDIES. Int J Oncol. 1995;7(4):713-26.
8. Avagimyan A, Kakturskiy L, Heshmat-Ghahdarijani K, Pogosova N, Sarrafzadegan N. Anthracycline Associated Disturbances of Cardiovascular Homeostasis. Current Problems in Cardiology. 2022;47(5):100909.
9. Sawicki KT, Sala V, Prever L, Hirsch E, Ardehali H, Ghigo A. Preventing and Treating Anthracycline Cardiotoxicity: New Insights. Annual Review of Pharmacology and Toxicology. 2021;61(Volume 61, 2021):309-32.
10. Nishi M, Wang P-y, Hwang PM. Cardiotoxicity of Cancer Treatments: Focus on Anthracycline Cardiomyopathy. Arteriosclerosis, Thrombosis, and Vascular Biology. 2021;41(11):2648-60.
11. Bhagat A, Kleinerman ES. Anthracycline-Induced Cardiotoxicity: Causes, Mechanisms, and Prevention. In: Kleinerman ES, Gorlick R, editors. Current Advances in Osteosarcoma : Clinical Perspectives: Past, Present and Future. Cham: Springer International Publishing; 2020. p. 181-92.
12. Russo M, Della Sala A, Tocchetti CG, Porporato PE, Ghigo A. Metabolic Aspects of Anthracycline Cardiotoxicity. Current Treatment Options in Oncology. 2021;22(2):18.
13. Zhao J, Zhang N, Ma X, Li M, Feng H. The dual role of ferroptosis in anthracycline-based chemotherapy includes reducing resistance and increasing toxicity. Cell Death Discovery. 2023;9(1):184.
14. Trapani D, Zagami P, Nicolò E, Pravettoni G, Curigliano G. Management of Cardiac Toxicity Induced by Chemotherapy. Journal of Clinical Medicine. 2020;9(9):2885.
15. Hulst MB, Grocholski T, Neefjes JJC, van Wezel GP, Metsä-Ketelä M. Anthracyclines: biosynthesis, engineering and clinical applications. Natural Product Reports. 2022;39(4):814-41.

16. Stansfeld A, Radia U, Goggin C, Mahalingam P, Benson C, Napolitano A, et al. Pharmacological strategies to reduce anthracycline-associated cardiotoxicity in cancer patients. Expert Opinion on Pharmacotherapy. 2022;23(14):1641-50.
17. Kim Y, Seidman JG, Seidman CE. Genetics of cancer therapy-associated cardiotoxicity. Journal of Molecular and Cellular Cardiology. 2022;167:85-91.
18. Koczurkiewicz-Adamczyk P, Gąsiorkiewicz B, Piska K, Gunia-Krzyżak A, Jamrozik M, Bucki A, et al. Cinnamamide derivatives with 4-hydroxypiperidine moiety enhance effect of doxorubicin to cancer cells and protect cardiomyocytes against drug-induced toxicity through CBR1 inhibition mechanism. Life Sciences. 2022;305:120777.
19. Kamińska K, Cudnoch-Jędrzejewska A. A Review on the Neurotoxic Effects of Doxorubicin. Neurotoxicity Research. 2023;41(5):383-97.
20. El-Sayed E-SM, Mansour AM, El-Sawy WS. Protective effect of proanthocyanidins against doxorubicin-induced nephrotoxicity in rats. Journal of Biochemical and Molecular Toxicology. 2017;31(11):e21965.
21. S. Lahoti T, Patel D, Thekkemadom V, Beckett R, D. Ray S. Doxorubicin-Induced In Vivo Nephrotoxicity Involves Oxidative Stress- Mediated Multiple Pro- and Anti-Apoptotic Signaling Pathways. Current Neurovascular Research. 2012;9(4):282-95.
22. Perry TR, Roberts ML, Sunkara B, Maddula R, McLeish T, Gomez J, et al. Modeling precision cardio-oncology: using human-induced pluripotent stem cells for risk stratification and prevention. Current Oncology Reports. 2021;23:1-16.
23. Omland T, Heck SL, Gulati G. The role of cardioprotection in cancer therapy cardiotoxicity: JACC: CardioOncology state-of-the-art review. Cardio Oncology. 2022;4(1):19-37.
24. Principe DR, Kamath SD, Korc M, Munshi HG. The immune modifying effects of chemotherapy and advances in chemo-immunotherapy. Pharmacology & therapeutics. 2022;236:108111.
25. Monteiro AR, Garcia AR, Póvoa S, Soares RF, Macedo F, Pereira TC, et al. Acute toxicity and tolerability of anthracycline-based chemotherapy regimens in older versus younger patients with breast cancer: real-world data. Supportive Care in Cancer. 2021;29:2347-53.
26. Henriksen PA. Anthracycline cardiotoxicity: an update on mechanisms, monitoring and prevention. Heart. 2018;104(12):971-7.
27. Johnson M, Keyes D. Anthracycline toxicity. StatPearls [Internet]: StatPearls Publishing; 2024.