Minireview Article

A review on Anthracycline induced cardiotoxicity- A mechanistic approach

ABSTRACT

Doxorubicin has become one of the most effective chemotherapeutic agents, but its use was complicated by the development of heart failure. Proposed mechanisms for its antitumor effects included intercalation into DNA that caused the prevention of micro molecule synthesis, reactive oxygen species (ROS) generation, DNA binding and cross-linkage, and DNA damage by topoisomerase 2b (TOP2b) suppression and induction of apoptosis. Several drugs such as ACE inhibitors or the angiotensin receptor blockers (ARB), beta-blockers and the CHF therapy are used for the treatment processes. The present brief review of the literature, focuses on literature based on the mechanism of anthracycline-induced cardiotoxicity.

Keywords: *Cytotoxicity, cardiotoxicity, anthracycline, doxorubicin, daunorubicin*

1. INTRODUCTION

Anthracyclines (doxorubicin, daunorubicin, epirubicin, aclarubicin, mitoxantrone and idarubicin) are tremendously important in the treatment of lymphomas, breast cancer, leukemia, and soft tissue sarcomas [1]. They were derived as fermentation products of *Streptococcus verticillus* and exert their anticancer activity by their capability to cause DNA fragmentation [2]. The dose dependant cardiac toxicity induced by anthracyclines restricted their effectiveness as an anticancer agent. Anthracycline administration is associated with dose-related cardiomyocyte injury and death leading to LV dysfunction and heart failure. Table 1 represents the several types of cancer associated to anthracycline chemotherapy. The risk factors for cardiac toxicity induced by anthracycline are cumulative dose, age, radiation therapy, concomitant chemotherapy etc.

Although doxorubicin has become one of the most effective chemotherapeutic agents, but its use was complicated by the development of heart failure [3,4]. In a retrospective analysis of over 4000 patients receiving doxorubicin performed by Von Hoff and colleagues [4], 2.2% of the patients developed clinical signs and symptoms of congestive heart failure.

The present review of the literature, focuses on mechanism of anthracycline-induced cardiotoxicity. A comprehensive literature review has been conducted. A bibliographic search was performed in the sciencedirect, Medline, PubMed, Scopus and Web of Science databases. Databases were searched thoroughly using the key words such as cardiotoxicity, Anthracyclines, risk factors, prevention and treatment, combined with cardiotoxicity, breast cancer, cardiomyopathy or heart failure.

Table 1: Various types of cancer responsive to anthracycline chemotherapy

Carcinoma	Lymphoma	Leukaemia	Sarcoma
Breast [5], small cell lung [6] bladder [7], oesophagus [8,9], stomach [9], liver [10] and thyroid [11]	Hodgkin's disease [12] Non-Hodgkin's Lymphoma [13] Cutaneous T-cell Lymphoma [14]	Acute Lymphoblastic [15] Acute Myeloblastic [16]	Osteogenic bone [17] Soft tissue Ewing [18]

1.1 Mechanism of Cytotoxicity

A major part of the anticancer effect of doxorubicin might be due to irreversible damage of tumour cell DNA. Proposed mechanisms for its antitumor effects included intercalation into DNA that caused prevention of micro molecule synthesis, reactive oxygen species (ROS) generation, DNA binding and cross-linkage and DNA damage by topoisomerase 2b (TOP2b) suppression and induction of apoptosis [19-21]. TOP2b was recently identified as doxorubicin-induced cardiotoxicity mediator in a

rat model [22]. TOP2b unwinds DNA strands during replication, transcription or recombination and is present in all quiescent cells, including cardiomyocytes [23,24]. Doxorubicin has been known as a TOP2b poison that prevented DNA synthesis by intercalation into DNA strands. TOP2b changes DNA topology, which leads to transient breakage of double-strand DNA and DNA supercoil dysregulation that can result in cardiomyocyte death [25].

1.2 Mechanisms of Cardiotoxicity

Chemotherapeutic cardiac toxicity can be categorized as either type I (early onset) or type II (late onset) [26,27] based on the effect of the agent on cardiomyocytes [28,29]. Type I cardiotoxicity is produced by cardiomyocyte death, either through apoptosis or necrosis, and as a result is irreversible usually caused by anthracyclines and chemotherapeutics. Type II cardiotoxicity is reversible caused by cardiomyocyte dysfunction rather than cell death [30]. Understanding the etiology of anthracycline cardiac toxicity has allowed the development of preventive strategies to combat the development of permanent cardiac damage.

The precise mechanism of anthracycline-induced cardiac toxicity remains unclear. The most commonly accepted hypothesis was that anthracyclines interfered with redox cycling, resulting in DNA damage due to reactive oxygen species (ROS) production [31]. More recently, topoisomerase 2 has been suggested to be the main mediator of cardiotoxicity [32,33].

1.3 Cardiotoxicity through Reactive Oxygen Species

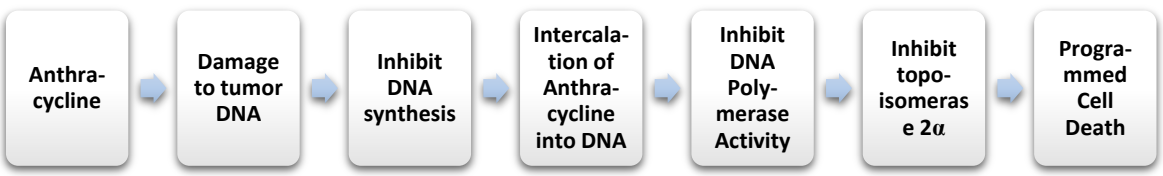
The molecular base of drug cardiac toxicity is the production of ROS in heart cell mitochondria. The quinone moieties of anthracyclines are subject to univalent reduction to a semiquinone radical by a several cellular oxido-reductases. In myocardial cells, this is mostly achieved through an enzymatic pathway containing NADH dehydrogenase (complex I) of the mitochondrial electron transport chain [34]. The semiquinone auto-oxidises to produce the parent anthracycline and a superoxide anion in presence of molecular oxygen. [35]. The non-enzymatic pathway permits a self- perpetuating redox cycle to be established, leads to the accumulation of superoxide anions. ROS levels may also be increased by free cellular iron and potentiating ferrous-ferric cycling of molecular iron [36]. The doxorubicin-iron complexes form toxic radical and reactive nitrogen species leads to increased nitrosative stress and mitochondrial dysfunction [37].

1.4 Cardiotoxicity through Topoisomerase 2β

The topological changes during DNA replication, transcription, recombination and chromatin remodelling regulated by DNA topoisomerases (Top) induce temporary single or double-stranded breaks [38]. Top2 is expressed as isoenzymes Top2α and Top2β in humans [39]. Among both the isoenzyme, Top2α is the most predominant and is greatly expressed in proliferating non-malignant and malignant cells. It is crucial for chromosomal segregation and its expression fluctuates through the cell cycle, peaking during G2/M phases [40]. On the contrary, Top2β is more abundant in quiescent cells, for example adult mammalian cardiomyocytes, and its expression rests constant during the cell cycle.

Doxorubicin exerts its anticancer activity by intercalating DNA. Topoisomerase 2 and DNA bind with doxorubicin forming a Top2-doxorubicin-DNA ternary complex, which leads to double-stranded DNA breaks. When bound to Top2α, the ternary complex arrests the cell cycle in G1/G2; inhibits DNA replication and induces apoptosis [41] as proposed in proliferating malignant cells. Conversely, when bound to Top2β, peroxisome proliferator-activated receptor (PPAR) which controls oxidative metabolism gets suppressed and results in mitochondrial dysfunction [42], In adult mammalian cardiomyocytes, this leads to an activation of altered P53 tumour suppressor pathway, impaired calcium handling, β-adrenergic signalling, mitochondrial dysfunction and increased apoptosis. Doxorubicin cannot bind directly to DNA without Top2β [41]. Animal studies with Top2β knockout mice have demonstrated that the absence of Top2β protects against doxorubicin-induced cardiac toxicity [43,44] partially because of reduced mitochondrial dysfunction [44].

ANTICANCER MECHANISM



CARDIOTOXICITY MECHANISM

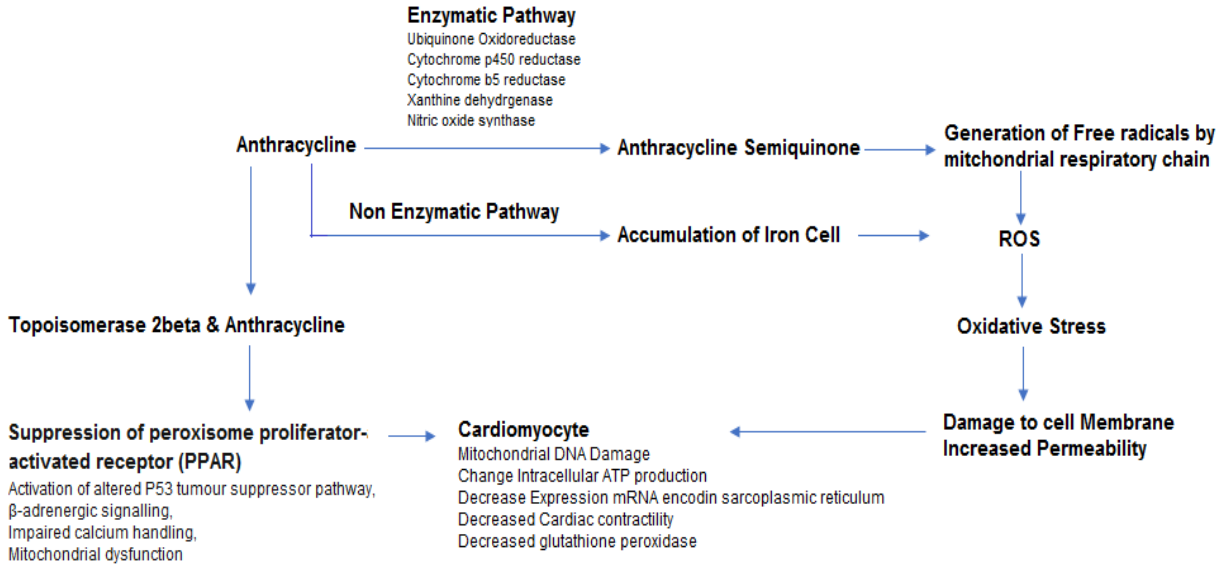


Fig. 1. Anticancer and cardiotoxicity mechanism of Anthracycline

1.5 Treatment of anthracycline cardiotoxicity

Several drugs such as ACE inhibitors or the angiotensin receptor blockers (ARB), beta-blockers and the CHF therapy are used for the treatment processes. The use of these agents can help to stabilize the LV systolic functioning [45]. Only nebivolol or carvedilol beta-blockers can be used but any ACE inhibitor or ARB can be used for anthracycline cardiovascular toxicity. Experts of the domain opine that an early diagnosis can always lead to better treatment. Such treatment often involves a high expenditure [46]. Relentless LVEF monitoring which is noninvasive in nature can be a better cost-effective method through which CHF can be prevented [47]. Dexrazoxane is an iron chelator, which reduces Cardiotoxicity of anthracyclines. However, adverse effects including myelotoxicity and concerns about leukemia have limited its use in clinical practice. This is approved for use only in patients receiving >300 mg/m2 of doxorubicin [48].

2. Conclusion

Anthracyclines are one of the most important drugs in the treatment of breast cancer. Therefore, while using these drugs, the risk factors associated with cardiotoxicity should be considered, cardiac function should be accurately measured and the cumulative dosage should be limited; otherwise, a new anthracycline alternative or liposome may be used to reduce anthracycline-induced cardiotoxicity.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that no competing interests exist. The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

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