A Review on Anthracycline Induced Cardiotoxicity- A Mechanism-based Approach

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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, DNA cross-linkage and binding, DNA damage due to topoisomerase 2b suppression, reactive oxygen species production, and induction of apoptosis. Several drugs such as ACE inhibitors or the angiotensin receptor blockers, 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, aclorubicin, 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 dependent cardiac toxicity induced by anthracyclines restricted their effectiveness as an anticancer agent. Anthracycline use is related to dose-related cardiomyocyte damage and death, resulting in left ventricular 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 [3,4].

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], clinical manifestations of congestive heart failure emerged in 2.2 percent of the individuals. Cardiac event rates on anthracycline treatment are 7%, 18%, and 65%, respectively, at cumulative doses of 150 mg/m2, 350 mg/m2, and 550 mg/m2. In 43,000 women (aged 66-70 years) with breast cancer over a median of 53 months, anthracycline treatment was related with an adjusted hazard ratio of 1.26 (confidence interval, 1.12-1.42) for the development of congestive heart failure. Cardiotoxicity occurred in 9% of 2,625 cancer patients who got anthracyline (74 percent women; 51 percent breast cancer; and 28 percent non-lymphoma), Hodgkin's with 98 percent of instances appearing during the first year (median time 3.5 months). Pediatric populations undergoing anthracycline treatment are still at an increased risk of developing HF decades after their disease has been cured [5].

The present review of the literature, focuses on mechanism of anthracycline induced cardiotoxicity. A thorough study of literature has been undertaken for the present review. A literature review was performed in the science-direct, 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.

2. 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 [20-22]. TOP2b was recently identified as doxorubicin-induced cardiotoxicity mediator in a rat model [23]. TOP2b unwinds DNA strands during replication, transcription or recombination and is present in all quiescent cells, including cardiomyocytes [24,25]. Doxorubicin was characterised as a TOP2b toxin because it intercalated into DNA strands and hindered DNA synthesis. TOP2b changes DNA topology, which leads to transient breakage of double-strand DNA and DNA supercoil dysregulation that can result in cardiomyocyte death [26].

3. MECHANISMS OF CARDIOTOXICITY
Chemotherapeutic cardiac toxicity can be categorized as either type I (early onset) or type II (late onset) [27,28] based on the effect of the agent on cardiomyocytes [29,30]. 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 [31]. Understanding the etiology of anthracycline cardiac toxicity has allowed the development of preventive strategies to prevent the 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 [32]. More recently, topoisomerase 2 has been suggested to be the main mediator of cardiotoxicity [33,34].
Table 1. Various types of cancer responsive to anthracycline chemotherapy

<table>
<thead>
<tr>
<th>Carcinoma</th>
<th>Lymphoma</th>
<th>Leukaemia</th>
<th>Sarcoma</th>
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4. 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 oxidoreductases. In myocardial cells, this is mostly achieved through an enzymatic pathway containing NADH dehydrogenase (complex I) of the mitochondrial electron transport chain [35]. The semiquinone auto-oxidises to produce the parent anthracycline and a superoxide anion in presence of molecular oxygen. [36]. 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 [37]. The doxorubicin-iron complexes form toxic radical and reactive nitrogen species leads to increased nitrosative stress and mitochondrial dysfunction [38].

5. CARDIOTOXICITY THROUGH TOP-OISOMERASE 2β

The topological changes during DNA replication, transcription, recombination and chromatin remodelling regulated by DNA topoisomerases (Top) induce temporary breaks in single or two strands [39]. Top2 is expressed as isoenzymes Top2α and Top2β in humans [40]. 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 [41]. 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 [42] 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 [43], 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 [42]. Animal studies with Top2β knockout mice have demonstrated that the absence of Top2β protects against doxorubicin-induced cardiac toxicity [44,45] partially because of reduced mitochondrial dysfunction [45].

ANTICANCER MECHANISM

- Anthracycline
- Damage to tumor DNA
- Inhibit DNA synthesis
- Intercalation of Anthracycline into DNA
- Inhibit DNA Polymerase Activity
- Inhibit topoisomerases 2
- Programmed Cell Death
CARDIOTOXICITY MECHANISM

Fig. 1. Anticancer and cardiotoxicity mechanism of Anthracycline

6. 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 [46]. 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 [47]. Relentless LVEF monitoring which is noninvasive in nature can be a better cost-effective method through which CHF can be prevented [48]. Dexrazoxane is an iron chelator, which reduces Cardiotoxicity of anthracyclines. However, its usage in clinical practise has been limited because to side effects such as myelotoxicity and issues regarding leukaemia. This is approved for use only in patients receiving >300 mg/m2 of doxorubicin [49].

The role of the clinical diagnosis of cardiotoxicity could be challenging. Therefore, the cardiac imaging with a focus on advanced echocardiography for the detection and management of cancer therapy related cardiovascular complications, in particular, left ventricular dysfunction and heart failure could be beneficial in clinical diagnosis of cardiotoxicity [50,51].

7. CONCLUSION

Anthracyclines are one of the most important drugs in the treatment of breast cancer. As a result, while using such drugs, the risk factors for cardiotoxicity should be recognised, and cardiovascular performance should always be carefully evaluated. To prevent anthracycline induced cardiotoxicity, the cumulative dose should be reduced; alternatively, a novel anthracycline alternative or liposome may be utilised.

DISCLAIMER

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.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.
COMPETING INTERESTS

Authors have declared that no competing interests exist.

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