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Review

Mechanisms of Cardiotoxicity of Cancer Chemotherapeutic Agents: Cardiomyopathy and Beyond

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ABSTRACT

Tremendous strides have been made in the treatment of various oncological diseases such that patients are surviving longer and are having better quality of life. However, the success has been tainted by the iatrogenic cardiac toxicities. This is especially concerning in the younger population who are facing cardiac disease such as heart failure in their 30s and 40s as the consequence of the anthracycline's side effects (used for childhood leukemia and lymphoma). This resulted in the awareness of cardiotoxic effects of anticancer drugs and emergence of a new discipline: oncocardiology. Since then, numerous anticancer drugs have been correlated to cardiomyopathy. Additionally, other cardiovascular effects have been identified, which includes but is not limited to myocardial infarction, thrombosis, hypertension, arrhythmias, and pulmonary hypertension. In this review

RÉSUMÉ

Le traitement des diverses maladies oncologiques a connu des avancées remarquables de telle sorte que les patients survivent plus longtemps et ont une meilleure qualité de vie. Cependant, les toxicités cardiaques iatrogènes ont entaché ces progrès. Cette situation est particulièrement préoccupante chez la population jeune qui fait face au cours de la trentaine et de la quarantaine aux cardiopathies comme l'insuffisance cardiaque en raison des effets secondaires de l'anthracycline (utilisée contre la leucémie et le lymphome de l'enfant), mais a permis la sensibilisation aux effets cardiotoxiques des médicaments anticancéreux et l'émergence d'une nouvelle discipline : la cardio-oncologie. Depuis, une corrélation a été établie entre les nombreux médicaments anticancéreux et la cardiomyopathie. De plus, d'autres effets cardiovasculaires, notamment, mais non exclusivement, l'infarctus du myocarde,

The National Cancer Institute defines cardiotoxicity as "toxicity that affects the heart" (http://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=44004). It is quite a simplistic explanation, which essentially describes the word "cardiotoxicity" rather than defines it. One of the more accurate clinical descriptions of cardiotoxicity has been formulated by the cardiac review and evaluation committee supervising trastuzumab clinical trials, who defined drug-associated cardiotoxicity as 1 or more of the following: (1) cardiomyopathy characterized by a decrease in left ventricular ejection fraction (LVEF) globally or due to regional changes in interventricular septum contraction; (2) symptoms associated with congestive heart failure (CHF); (3) signs associated with heart failure, such as S3 gallop, tachycardia, or both; (4) decline in initial LVEF of at least 5% to <55% with signs and symptoms of heart failure or asymptomatic decrease in LVEF of at least 10% to <55%.[1] This definition has a limited scope because it does not include subclinical cardiovascular damage that might occur early in response to some of the chemotherapeutic agents. Other cardiac factors such as coronary artery disease and rhythm disturbances or other affected cardiovascular organ system such as pulmonary hypertension also has been excluded. Thus, this definition, although ideal for cardiomyopathy, does not encompasses the broad scope of unwanted cardiovascular effects of anticancer drugs. Although a recent upsurge in the interest of cardiotoxicity mediated by anticancer drugs has been due to an increased incidence of cardiomyopathy and consequent heart failure in oncological patients,[2] newer anticancer drugs have a different array of cardiovascular effects (Table 1). Therefore, collaborative efforts between the oncologists and the cardiologists are clearly warranted to screen, identify, and manage our cancer patients for cardiac disease so that early intervention can provide a boon to this highly specialized population cohort.

In this review we discuss chemotherapeutic-mediated cardiomyopathy and beyond. It is not an exhaustive review of all of the anticancer medications or regimens but it is an attempt to provide examples of cardiovascular toxic effects of some of the prominent anticancer drugs. We outline a clinical perspective and molecular mechanism involved with each anticancer drug. The research effort to attenuate, if not to ameliorate, cardiotoxic effects lies in the deeper understanding of the mechanism(s) behind anticancer-mediated cardiotoxicity.

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we examine some of the anticancer agents that mitigate cardiotoxicity and present current knowledge of molecular mechanism(s). The aim of the review is to ignite awareness of emerging cardiotoxic effects as new generations of anticancer agents are being tested in clinical trials and introduced as part of the therapeutic armamentarium to our oncological patients.

la thrombose, l'hypertension, l'arythmie et l'hypertension pulmonaire, ont été observés. Dans cette revue, nous examinons certains médicaments anticancéreux qui atténuent la cardiotoxicité et présentons les connaissances actuelles sur le ou les mécanismes moléculaires. L'objectif de cette revue vise à accroître la sensibilisation aux effets cardiotoxiques émergents alors que les nouvelles générations de médicaments anticancéreux font l'objet d'essais cliniques et sont introduites dans l'arsenal thérapeutique proposé à nos patients en oncologie.

Cardiomyopathy

Anthracyclines

Clinical perspective. In a retrospective analysis of >4000 patients treated with doxorubicin (DOX), Von Hoff and colleagues[3] reported that 2.2% of the patients developed clinical signs and symptoms of CHF. Because the study identified CHF on the basis of clinical assessment, incorporation of subclinical left ventricular dysfunction would result in greater incidence of the cardiovascular disease in DOX patients; as acknowledged by the authors themselves.[3] This study went on to conclude that the prevalence of heart failure markedly increased with a cumulative dose of 550 mg/m^2 of DOX,[3] which is now recognized as one of the greatest determinants in the development of anthracycline-mediated heart failure.[4]

Subsequently, the cardiotoxicity in DOX-treated patients was prospectively assessed in 3 clinical trials (2 in breast and 1 in non-small-cell lung cancer) conducted between 1988 and 1992. The studies showed that the rate of conventional DOX-related CHF was 5% at a cumulative dose of 400 mg/m^2, 16% at a dose of 500 mg/m^2 and 26% at a dose of 550 mg/m^2.[4] Although there is a clear dose-response associated with cardiotoxicity, histopathologic changes can be seen in endomyocardial biopsy specimens from patients who have received as little as 240 mg/m^2 of DOX.[5] Moreover, subclinical events occurred in approximately 30% of the patients, even at doses of 180-240 mg/m^2,[6] although they were observed 13 years after the treatment was received. Even doses as low as 100 mg/m^2 have been associated with reduced cardiac function.[5,7] These findings suggest that there is no safe dose of anthracyclines. Conversely, early studies suggested that some patients had no significant cardiac complications despite achievement of the doses as high as 1000 mg/m^2.[8] Therefore, individual susceptibility to cardiomyopathy might vary. However, the current consensus is that DOX causes cardiomyopathy.

Potential molecular mechanisms. Anthracycline-mediated cardiomyopathy has been studied extensively. Among the pathways implicated in anthracycline-mediated toxicity, production of reactive oxygen species and formation of iron complexes are involved, resulting in intracellular damage. However, we identified a direct target of DOX that provides a unifying mechanism encompassing most of the implicated pathways.

It has been well studied that one of the mechanisms of DOX-induced tumour-cytotoxic effect is mediated by topoisomerase II α inhibition.[9] Toposiomerase II α is an enzyme that regulates the overwinding or underwinding of DNA during its repair process.[10] They play an important role in regulating cellular processes such as replication, transcription, and chromosomal segregation by altering DNA topology.[10] However, topoisomerase II β (Top II B) serves the same function in quiescent cells. Because they share catalytic mechanisms and have a high degree of amino acid similarity (approximately 70% identity at the amino acid level)[11]; we embarked on a project to study the role of Top II B in murine cardiac cells treated with DOX. We successfully showed that[12]: (1) in rats, the molecular phenotype of acute and chronic DOX cardiomyopathy is characterized by the formation of a ternary DNA-Top II B-DOX cleavage complex that triggers double-strand breaks in the DNA; (2) the acute stage is characterized by upregulation of the apoptotic pathway signalling, specifically *Apaf-1*, *Bax*, *Mdm-2*, and *Fas*. In chronic conditions, (3) the genes implicated in mitochondrial dysfunction and oxidative phosphorylation were activated by downregulation of peroxisome proliferator-activated receptor γ, coactivator 1 α and β.[12] This downregulation resulted in (4) a decrease in the key components of the electron transport chain such as *Ndufa3*, *Sdha*, and *Atp5a1*, thus culminating into (5) ultrastructural mitochondrial damage with vacuolization.[12] The mitochondria were also (5) dysfunctional, measured according to oxygen consumption and changes in mitochondrial membrane potential. The end result was (6) an increase in end-systolic and end-diastolic volumes with a decrease in ejection fraction.[12] The formation of the ternary complex is also responsible for the production of most (70%) DOX-induced reactive oxygen species. Therefore, the oxidative stress is preferentially a result of the DOX-induced DNA damage and of the consequent changes in the transcriptome rather than of the redox-cycling of DOX. Transgenic mice with cardiomyocyte-specific deletion of Top II B were indeed protected from the acute and progressive or chronic DOX-induced heart failure, and did not exhibit the severe cardiomyopathic phenotype of the wild type mice. Therefore, Top II B is required to initiate the entire phenotypic cascade of DOX-induced cardiomyopathy (Fig. 1).[12] Other studies also identified the activation of the p53 pathway to DNA damage and the consequent apoptosis and mitochondrial dysfunction in cultured cardiomyocytes treated with DOX.[13,14]

The corroborating evidence of the Top II B mechanism is provided by the use of dexrazoxane (DEX). In vivo, DEX has shown significant cardioprotection against DOX in various preclinical models such as mouse, rat, hamster, rabbit, and dog.[15-18] In addition, the cardioprotective effects were evident