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Sex differences in anthracycline cardiotoxicity

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Summary. Anthracyclines are still among the most efficient drugs of cancer chemotherapy used. However, a significant risk of cardiotoxicity limits their use. Cardiotoxicity can be acute during the treatment or may be delayed for a number of years after cessation of the treatment. Chronic cardiotoxicity includes cardiomyopathy and congestive heart failure and may develop in 5-10% of the patients. The molecular mechanisms of the anticancer activity and of the cardiotoxic effects are not completely elucidated yet. Nonetheless, the development of doxorubicin-induced adverse effects is linked to the total cumulative dose, the additional combined treatment, the age and appeared to involve at least mitochondrial dysfunction. Even if there is a clear gender-based discrepancy in the incidence of cardiovascular disease, sparse information is available concerning the difference of doxorubicin-induced cardiotoxicity between male and female. Females live longer than males in many species including humans and develop less cardiovascular diseases, at least until menopause. Moreover, several mitochondria features are prone to sexual dimorphism. Here, we summarize the literature on sex differences in anthracyclines-induced cardiotoxicity in humans and in animal models. Developing sex-based medicine is needed as well as the cooperation between oncologist and cardiologist to improve the understanding of the anticancer drug-related cardiotoxicity.

Key words: anthracycline cardiotoxicity, sex differences, cancer chemotherapy.

Differenze di sesso nella cardiotossicità indotta dalle antracicline

Riassunto. Le antracicline costituiscono tuttora uno dei trattamenti chemioterapici più efficaci, sebbene il loro utilizzo sia limitato dal significativo rischio di cardiotossicità a esse associato. Tale cardiotossicità si distingue in una forma acuta che può presentarsi durante il trattamento, e in una forma cronica che può manifestarsi anche anni dopo la fine della terapia antitumorale. La cardiotossicità cronica prevede una cardiomiopatia e l'insufficienza cardiaca congestizia, e può svilupparsi nel 5-10% dei pazienti. È noto che lo sviluppo degli effetti indesiderati della doxorubicina è legato alla dose cumulativa totale, all'eventuale trattamento combinato e all'età del paziente, e sembra implicare una disfunzione mitocondriale. Tuttavia, il meccanismo molecolare dell'attività antitumorale e degli effetti cardiotossici di questa antraciclina non è stato ancora completamente chiarito. Inoltre, nonostante l'evidente discrepanza nell'incidenza delle malattie cardiovascolari tra individui di sesso diverso, la differenza della cardiotossicità indotta dalla doxorubicina tra maschi e femmine è a tutt'oggi poco conosciuta. Gli individui di sesso femminile vivono più a lungo della controparte maschile in molte specie tra cui l'uomo, e sono meno soggetti alle malattie cardiovascolari, almeno fino al raggiungimento della menopausa. In aggiunta, numerose caratteristiche mitocondriali sono soggette al dimorfismo sessuale. In questo articolo presentiamo un riassunto di quanto noto sulle differenze sessuali nella cardiotossicità indotta dalle antracicline, nella specie umana e in alcuni modelli animali. Riteniamo che lo sviluppo di una medicina di genere e la cooperazione tra le figure dell'oncologo e del cardiologo siano necessarie per migliorare la nostra conoscenza della cardiotossicità associata al trattamento antitumorale.

Parole chiave: cardiotossicità indotta da antracicline, differenze di sesso, chemioterapia antitumorale.

Importance of anthracyclines for cancer treatment and limitation of use

Panel of anticancer therapies has constantly increased for 50 years (surgery, radiotherapy, chemotherapy, hormonotherapy, immunotherapy…). This battery of therapeutics allows increasing the number of durable and complete remissions, hence the survival rate of cancer patients. However, the use of many efficient treatments is limited by long term adverse effects of anticancer medications. Anthracyclines represent one of the most commonly used anticancer drugs. Major side effects associated with anthracycline use are bone marrow suppression, renal dysfunction and a life threatening cardiac toxicity. In a systematic review and meta-analysis on incidence and predictors of anthracycline chemotherapy in patients with cancer overt cardiotoxicity occurred in 6%, whereas subclinical cardiotoxicity developed in 18% of patients[1]. Cardiac toxicity is accentuated by increasing age, combination chemotherapy, mediastinal radiation, previous cardiac disease, hypertension, liver disease and whole body hyperthermia[1-3]. It may present as cardiac insufficiency, arrhythmias, thrombosis, and hypertension.

Doxorubicin ($C_{27}H_{29}NO_{11}$, trade name Adriamycin), the leader of the anthracycline family, is a natural compound isolated from the actinobacterium *Streptomyces*

peucetius var. *caesius*. Doxorubicin belongs to the World Health Organization model list of essential medicines (updated in 2015). This 19th list is characterized by the most efficacious, safe and cost–effective medicines for priority conditions. Doxorubicin is one of the most active agents for the treatment of both solid tumors and hematological malignancies. However its use is hampered by its severe dose-dependent cumulative cardiotoxicity inducing cardiomyopathy that can evolve to congestive heart failure (CHF). Cardiotoxicity can be acute during the treatment or may be delayed for a number of years after cessation of the treatment. The chronic type of anthracycline cardiotoxicity develops gradually with time and can result in severe and irreversible toxic damage to the myocardium. It has been calculated that 10% of patients treated with doxorubicin or its derivatives will develop cardiac complications up to 10 years after the cessation of chemotherapy[4].

Anthracycline-induced cardiotoxicity: a multiplex system

The molecular mechanisms responsible for anticancer anthracycline activity as well as those underlying anthracycline-induced cardiotoxicity are incompletely understood and are subject of intense research and debate in the literature. The anticancer activity has been ascribed to nuclear DNA intercalation, topoisomerase II inhibition and drug-DNA adducts formation while the cardiotoxic effects have been attributed mainly to oxidative stress and mitochondrial dysfunction[5]. Anthracycline cardiotoxicity is considered as a complex multifactorial process. Early and late phases of cardiotoxicity have been described, early events taking place at the time of treatment whereas late events develop years later. However, it appears that these two phases may not be as distinct, pointing to a continuum from the first cardiac insult during or early after treatment and leading years after to cardiac disease[6]. Doxorubicin is lipophilic and this influences its cellular uptake, retention, duration, protein and lipid targets as well as pharmacokinetic/pharmacodynamics properties which may be involved in side effects appearing after therapy termination[6]. Many of the evidence have pointed out the role of free radicals. The chemical structure of doxorubicin is prone to the generation of free radicals generating oxidative stress and cellular damages. Several cardiac targets have been proposed like mitochondrial dysfunction[7,8], disturbed energy fluxes[9], ion dysregulation[10], and alteration of cardiac-specific signaling pathways[6]. However, the separation of anticancer and cardiotoxic effects of anthracycline may not be so divergent[11]. They both involve oxidative stress and the common endpoint is cell death. Mitochondria are emerging as one of the major cellular targets of both effects owing to the pivotal role they play in cell death, oxidative stress, energy provision and calcium homeostasis[5,9]. Alteration in myocardial energy metabolism includes a fall in high energy phosphate levels, ATP and phosphocreatine, reduction in oxidative capacity of mitochondria, altered mitochondrial biogenesis, decrease in mitochondrial protein content, marked reduction in fatty acid utilization, disturbances in energy transfer between sites of energy production and energy utilization by creatine kinase, as well as defects in AMPK signaling[5,7-9,12-15]. In human hearts, it was demonstrated that the mitochondrial membrane transition pore opening, that triggers cell death, is involved in the development of doxorubicin cardiotoxicity[16]. The main targets of anthracycline, mitochondrial function, bioenergetic and signaling pathways as well as oxidative stress, lead to cell dysfunction and cell death which accumulate over years and induce, in worst cases, heart failure with cavity dilatation and increasing fibrosis. Interestingly, these targets are known to exhibit sexual dimorphism. For examples, important gender-associated "redox features" of cells have already been described in the literature[17-19]; sexual dimorphism has been shown in the expression of mitochondria-related genes in rat heart at different ages[19]; the interplay between mitochondria and sex steroid hormones may influence lifespan[20]. Knowing that sex differences exist in cardiovascular diseases (see below), the possible sexual dimorphism in doxorubicin-induced cardiotoxicity deserves further investigation.

Sex differences in cardiovascular diseases

Cardiovascular diseases (CVD) are the major cause of morbi-mortality in both men and women. There is a significant gender difference in incidence, diagnosis, and prognosis of cardiovascular diseases, in part because of differences in risk factors and hormones. Several lines of evidence demonstrate that CVD clearly display significant gender differences in terms of onset, progression and outcome[21]. Women have less cardiovascular disorders than men in the premenopausal period with risks increasing in the postmenopausal period reaching and even exceeding that of men. In the EuroHeart Failure survey on the quality of care among patients with heart failure in Europe, 51% of men but only 28% of women had a left ventricular ejection fraction <40%[22]. Yet, cardiovascular diseases are the leading cause of death in women and the mortality rate of women is higher than that of men. In addition, the clinical presentation as well as outcome after therapeutic interventions differ between women and men[23]. Women have more frequently diastolic HF, associated with the major risk factors of diabetes and hypertension and men have

more frequently systolic HF because of coronary artery disease[24]. Under stress, male hearts develop more easily pathological hypertrophy with dilatation and poor systolic function than female hearts[24]. Among 8592 patients from the PREVEND study studied for sex-specific incidence and risk of new-onset heart failure, women had higher risk for heart failure with preserved ejection fraction with atrial fibrillation being a specific female risk factor compared to men[25].

Some sex-specific pathways of CVD have been identified. Female-specific pattern of gene expression was shown in patients with idiopathic dilated cardiomyopathy involving energy metabolism and regulation of transcription and translation while male pattern involved genes related to muscular contraction[26]. Sex differences is also exemplified in genetically modified mice were sex has been shown to influence cardiac phenotype development[27]. For example, male specific cardiac phenotypes have been observed in mice with deficiency in insulin growth factor-I or expression of mutant troponin T or with muscle limited overexpression of myostatin[27]. Important gender-associated "redox features" of cells have already been described that are often associated with the pathogenesis of several human morbidities[17]. After transverse aortic constriction in mice, better preserved cardiac function in females is associated with lower alteration of mitochondrial function and biogenesis, as well as fatty acid oxidation[28]. Women with aortic stenosis have more concentric hypertrophy with better systolic function, less upregulation of extracellular matrix genes and better reversibility after unloading, while stressed female hearts maintain energy metabolism better than male hearts and are better protected against calcium overload[24]. Maladaptive LV remodeling occurs more frequently in men and is associated with greater activation of profibrotic and inflammatory markers[29]. Sexually dimorphic gene expression in the heart of mice and men has been identified by gene expression profiling[30].

The reasons for sex dimorphism in the cardiovascular system are multiple. Cardiovascular cells contain functional estrogen (ER) and androgen (AR) receptors and are targets for sex hormone action, which can influence many physiological and pathological processes, including vascular and myocardial cell homeostasis. Two ERs, ERα and ERβ, have been described. 17β-estradiol (E2) may have genomic and non-genomic effects. The genomic effects involve binding of hormones on hormone responsive elements and regulate the expression of cardiac specific genes[31]. Non genomic effects involve rapid, within seconds or minutes, signaling effects through activation of non-nuclear membrane-associated ERs[32]. The relative importance of genomic and non-genomic effects and of ERα and ERβ in the cardiomyocyte are still matter of debate[33-35].

In addition to hormones and receptors, other genetic and epigenetic factors are also involved[36]. A sex-specific cardiac expression of some miRNAs may be related to sex differences in fibrosis after pressure overload[37]. In humans, beyond these biological aspects, differences in lifestyle between women and men like smoking status, alcohol consumption or dietary habits could also partly explain this sexually dimorphic gene expression, habits which are known to be associated with incidence of HF[38].

Sex differences in toxicity and pharmacology

Sex-specific differences in pharmacokinetics and pharmacodynamics have been reported to have important clinical consequences. Sex can influence the absorption, the distribution, the metabolism and the excretion of drugs leading to various efficacy and side effects. Although not taken into account in a systematic manner, sex- and gender-based differences in pharmacological parameters is demonstrated by the increasing available data on gender variation in drug efficacy and toxicity profiles. This includes sex-based differences in pharmacodynamics and pharmacokinetics parameters[39]. Male versus female drug processing can turn up with difference in the efficacy and on the side effect level[40]. Because women were/are not always included in clinical trials or preclinical tests, information in how safe and effective a given blood level of a drug is are missing for half of the population[40].

As an example, pharmacokinetics and pharmacodynamics of anti-hypertensive drugs is sex-specific. In many cases, female sex is a risk factor for adverse effects or attenuated clinical responses of anti-hypertensive drugs because of lower clearance, smaller distribution volumes, higher activity of some metabolic enzymes, or presence of sex hormones[41]. Regarding doxorubicin and its main metabolite doxorubicinol, important intra- and inter-patient variations of pharmacodynamics and pharmacokinetics parameters have been observed[42]. In clinics, intravenous bolus injection is the main way of doxorubicin administration[43].

Sex differences in anthracycline-related cardiotoxicity in animal studies

The question then emerges as to whether anthracycline cardiotoxicity may exhibit sex and gender differences. Indeed, in animal studies, although most studies have been conducted in males, some show that females develop less cardiomyopathy and nephropathy than males[44-46] after chronic administration of anthracyclines.

In LOU/M/Wsl rats, doxorubicin-induced nephropathy develops faster in male than females but no difference was found between males or females for the development and severity of cardiomyopathy[44]. Studying the influence of chronic Adriamycin treatment on cellular defense mechanisms against free radicals, it appears that liver of female rats was far less susceptible to *in vivo* treatment than liver of male rats. No signs of biochemical damage was observed in heart of both sexes but histological lesions were evident only in males[45].

In spontaneously hypertensive rats (SHRs), treated males had significantly more severe cardiomyopathy scores and higher levels of cardiac troponin T than females[46]. This was associated with increased number of cardiac mast cells and of degranulated mast cells. Protection offered by female sex was abrogated after ovariectomy suggesting the protective role of female hormones.

In adult tumor-bearing male SHRs, cardio-sensitivity to doxorubicin is higher than in females or hormone-deficient male animals. It is suggested that reproductive hormones negatively regulate doxorubicin-induced cardiotoxicity and that the selective cytotoxic mechanism involves oxidative stress and apoptosis in male SHRs[47].

One of the cardiotoxic effects of doxorubicin is an excessive production of free radicals of oxygen. Female adult cardiomyocytes have a greater survival advantage when challenged with oxidative stress-induced cell death[48]. 17-β-estradiol confers protection against oxidative stress and cardiac injury in ovariectomized rats treated with Adriamycin[49].

Another feature of doxorubicin cardiotoxicity is related to mitochondrial dysfunction and down-regulation of energy metabolism signaling pathways. Recently we investigated the bioenergetics and signaling pathways defects following doxorubicin treatment in male and female Wistar rats. Doxorubicin treatment resulted in males in important weight loss and decrease in survival rate, strong alterations of myocardial function, decrease in energy signaling pathways, downregulation of mitochondrial biogenesis, decrease in cardiolipin content, decrease in mitochondrial DNA content, and alteration of mitochondrial respiration[14]. Alterations in mitochondrial function were independent of changes in cytoplasmic milieu as they were recorded in permeabilized cells with controlled pH, calcium, and non-limiting concentration of oxygen and substrates suggesting intrinsic changes. This was associated with a decreased content of AMPK. All parameters appeared unaffected or remarkably preserved in treated females. No sex differences were found for the oxidative stress response or for death markers. These results evidence a clear sexual dimorphism of doxorubicin cardiotoxicity. Moreover, mitochondrial dysfunction and energy metabolism signaling pathways seems thus associated with early cardiotoxicity in males but not in females[14]. Growing evidence links phospholipid alterations especially cardiolipins to defects in mitochondrial function and energy metabolism in heart failure. In search for a mechanism explaining altered mitochondrial function and sexual dimorphism of doxorubicin cardiotoxicity, we further examined lipid and phospholipid profiles. We showed that doxorubicin has a sex-specific impact on the heart phospholipidome especially on cardiolipin, an essential mitochondrial lipid[15].

Studies are still sparse investigating sexual dimorphism of anthracycline cardiotoxicity. Yet, growing evidence mainly obtained in experimental studies points to a sexual dimorphism of doxorubicin cardiotoxicity, females being protected compared to males (Figure 1). This protection includes the essential targets of doxorubicin i.e. energy metabolism, energetic signaling path-

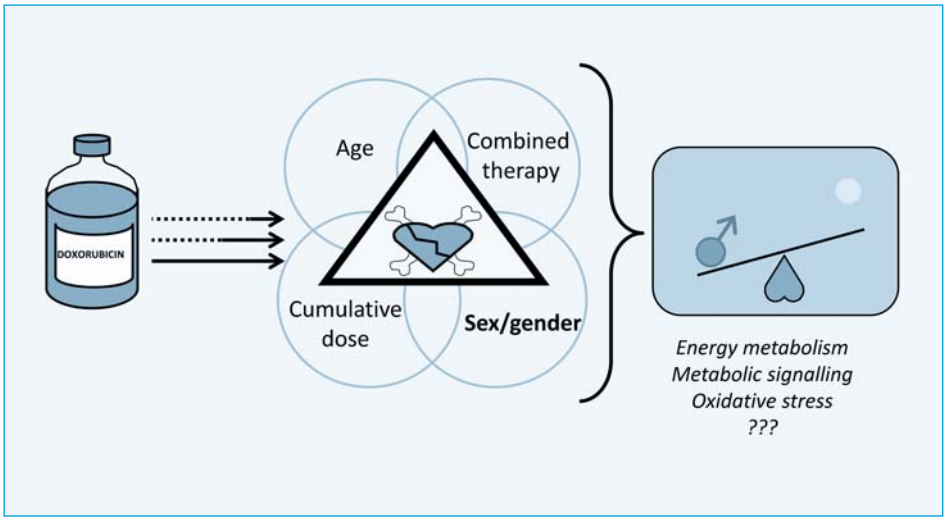

Figure 1. Sex/gender as risk factors for doxorubicin cardiotoxicity. Implication of energy metabolism.

ways and oxidative stress. Further studies are needed to understand in more details the mechanistic background of female protection.

Sex differences in anthracycline-related cardiotoxicity in humans

Doxorubicin-related sex differences in cardiotoxicity have been under-evaluated in humans. Even if there is a significant sex difference in incidence of cardiovascular disease at the adult stage, it is not known whether a difference in doxorubicin-related cardiotoxicity between men and women also exists. Several risk factors for cardiotoxicity induced by anthracyclines have been identified, such as total cumulative dose, additional treatment, existing cardiomyopathy, age, and sex. But the reasons for including sex as a risk factor are not clear. Indeed, studies have mainly been devoted to young children receiving anticancer drugs for hematological malignancies. A study investigated the late cardiotoxic effects of doxorubicin treatment in childhood for leukemia or osteogenic sarcoma (a mean of 8.1 years earlier) and found that female sex and higher cumulative doses were associated with depressed contractility with an interaction between the two variables[3,50]. This suggests that doxorubicin cardiotoxicity is higher in prepubertal girls[3]. Another study evaluated the early cardiotoxicity of anthracycline in children. Although rare, in this study also female sex and high dosage were found to increase the risk for anthracycline cardiotoxicity[51]. A study aimed at determining the long-risk of cardiac disease after Adriamycin therapy for a cancer in childhood and the influence of radiotherapy, evidenced a trend towards a greater interaction for a greater increase in the risk of cardiac failure per amount of the Adriamycin cumulative dose among boys than girls[52]. Altogether these results suggest however that prepubertal girls are more susceptible to develop early or late cardiac toxicity than boys of the same age. May be this is due to absence of female hormones at this age.

Despite a clear gender-based difference in the incidence of cardiac diseases, to the best of our knowledge, no survey has been conducted to specifically assess gender differences in the occurrence of anthracycline cardiotoxicity in adults. Studying the cardiac status of the long-term survivors (at least 5 years after therapy) and estimating the features of subclinical cardiotoxicity induced after conventional treatment of lymphoma with doxorubicin, the group of B. Coffier in France[53] found evidence of subclinical cardiomyopathy in the absence of CHF. Interestingly they could identify that male sex contributed to the decrease in fractional shortening as did older age, high dose of doxorubicin, associated radiotherapy or overweight. In population–based cohort studies, the predicted 10-year cumulative incidence of CHF for males without or with preexisting cardiac disease is higher in males than in females[54,55]. Thus only few data are available to establish whether a gender-based difference exists in anthracycline cardiotoxicity. A more direct assessment of gender-based doxorubicin cardiotoxicity is thus urgently needed. Advances in this domain could help to find adjuvant therapy to cancer medication and specially anthracyclines.

Sex differences in other cancer therapies

Sexual dimorphism has also been described for other anticancer therapies like tyrosine kinase inhibitors. Tyrosine kinase (TK) inhibitors are a novel class of anticancer drugs for certain forms of cancers. However, the use of these drugs is also limited by their cardiotoxicity. Tyrosine kinase inhibitors, small molecules that occupy the ATP binding site of the tyrosine kinase receptor, inhibit abnormal high kinase activity and uncontrolled cell growth. Some of these drugs induce cardiotoxicity in a significant number of patients[56]. Interestingly, sunitinib, one of TK inhibitors, exhibits cardiotoxicity that also involves mitochondrial abnormalities and inhibition of AMPK[56,57] as well as other off-target kinases[58]. However, in this case females appear more sensitive than males to the toxicity of sunitinib. A retrospective study identified that female patients were more susceptible to multi-organ system toxicity than male patients[59] but without studying specifically cardiotoxicity. Similarly old age and female sex have been identified as risk factors for severe toxicity of 5-fluorouracil-based chemotherapy[60]. Sexually dimorphic cardiotoxicity was observed in mice and cardiomyocytes. It was shown that estrogen enhances cardiotoxicity of sunitinib through modulation of drug transport and metabolism[58]. These effects may be mediated by the well-described sex-specific hepatic drug metabolism that implicates sex-specific expression of the cytochrome P450s[61].

Consequences and conclusions

There is no specific treatment for the cardiomyopathy related to anti-cancer treatment. According to the European Society of Cardiology, the cardiovascular status of these patients should be adequately monitored and the treatment for symptomatic patients should follow the standard treatment for CHF that may include angiotensin converting enzyme inhibitors, β-blockers, diuretics, cardiac glycosides and aldosterone antagonists[62,63]. Attempts to reduce doxorubicin toxicity have been to decrease the cumulative doses, develop less cardiotoxic analogs or to give erythropoietin or iron chelators like dexrazoxane, however with mitigated success until now[43,64].

Doxorubicin-related adverse effects are a real public health issue because cardiomyopathy may not be developed directly after the treatment, but silently years later and remains a life-threatening condition[4]. Additionally patients with antecedent of cardiovascular disease or at risk cannot benefit from this effective treatment. Thus it is important and necessary to understand the cardiotoxicity so as to develop anti-cancer therapies with less cardiovascular side-effects. The fact that females seem to be protected may help to understand the basis for cardiotoxicity and thus to define new therapeutic approaches. The sexual dimorphism of the response to pharmacological treatments deserves larger attention. In the era of personalized medicine it is time to take into account half of the population diverging for an entire chromosome from the other one.

Key messages

- Due to the increasing efficacy of anti-cancer therapy, the anti-cancer drug induced cardiotoxicity is becoming a health problem.
- Despite our knowledge of a sexual dimorphism in cardiovascular diseases, data are lacking for anti-cancer cardiotoxicity.
- Some animal studies have been conducted and point to a better resistance of females towards cardiotoxicity with involvement of mitochondria and oxidative stress.
- Very few studies have been conducted in humans and suggest a better protection of adult females but a higher susceptibility of prepubertal girls.
- Retrospective and prospective human studies as well as basic studies are needed in order to understand the basis for the sexual dimorphism of anti-cancer drug cardiotoxicity and thus to develop new therapeutic approaches.

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