

Sexual Dimorphism of Doxorubicin-Induced Cardiotoxicity

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Doxorubicin is a potent chemotherapeutic agent widely used to treat both hematologic malignancies and solid tumours in paediatric and adult cancer patients. Unfortunately, the clinical utility of this effective agent is limited by dose-dependent cardiotoxicity that may progress to cardiac dysfunction and heart failure. Even after 40 years of preclinical and clinical research, the exact mechanism of doxorubicin-induced cardiotoxicity is not completely understood. Similarly, the best prevention and/or treatment strategy to mitigate cardiotoxicity has not been identified yet [1]. Nevertheless, there are several factors that have been demonstrated to increase the risk of doxorubicin-induced cardiotoxicity including: total cumulative dose, pre-existing cardiovascular disease, and administration of other cardiotoxic chemotherapeutic agents such as trastuzumab [2]. However, there is inconclusive evidence about the role of sex as a risk factor of doxorubicin-induced cardiotoxicity.

In general, the risk of cardiovascular diseases is lower in premenopausal women than in men of the same age [3]. Nevertheless, female sex has been considered as a risk factor for doxorubicin-induced cardiotoxicity in paediatric cancer patients [4]. Female breast cancer patients are also very sensitive to doxorubicin-induced cardiotoxicity, especially when combined with other cardiotoxic chemotherapeutic agents such as trastuzumab [5]. On the other hand, some studies have shown that men are more sensitive to doxorubicin-induced cardiotoxicity than women [6,7]. Interestingly, recent experimental studies have unequivocally demonstrated that adult female rats are protected against doxorubicin-induced cardiotoxicity [8-11].

In this brief report, we will try to unravel the reasons behind the apparent discrepancy between experimental and clinical data, discuss the potential mechanisms of sexual dimorphism of doxorubicin-induced cardiotoxicity, and identify gaps of knowledge in this research area. In our opinion, the age and the menopausal state of the female patients are the two most important determinants of the sexual dimorphism observed in the clinical setting. For instance, the female sex has been considered as a risk factor for doxorubicin-induced cardiotoxicity mainly in female paediatric cancer patients [12,13], the majority of whom are pre-pubertal. Similarly, the majority of breast cancer patients are post-menopausal [14]. Pre-pubertal girls and post-menopausal women have low levels of female sex hormones that may play the key role for protection against doxorubicin-induced cardiotoxicity. To support this notion, male Hodgkin lymphoma patients have been shown to be more susceptible to doxorubicin-induced cardiac adverse effects than female patients in their 20s-40s years of age [6]. Female patients in this age group are likely to have high levels of sex hormones which are known to protect against cardiovascular diseases. Nevertheless, doxorubicin treatment is also likely to cause premature ovarian failure, and sharp decline in female sex hormones [15]. Therefore, the proposed protective effect of female sex hormones is most likely against the first exposure to doxorubicin. The protection may actually be conferred by the good overall baseline cardiovascular health of female patients in this age group. In agreement with this opinion, male rats were more sensitive to doxorubicin-induced cardiotoxicity than female rats, despite the sharp decline in sex hormone levels after doxorubicin administration in these animals [10]. Ovariectomy prior to doxorubicin administration has also been shown to exacerbate doxorubicin-induced cardiotoxicity in female experimental animals [8,16,17].

The mechanisms of sexual dimorphism of doxorubicin-induced cardiotoxicity are not completely understood. Sex-related differences in mast cell activity, oxidative stress, cardiolipin remodelling, and cardiac energy metabolism have been proposed to play a role in the sexual dimorphism of doxorubicin-induced cardiotoxicity [8,9,11,17]. In response to other cardiac stressors, estrogen has been shown to be cardioprotective through its anti-apoptotic, anti-fibrotic, and anti-hypertrophic effects [18-20]. It is still to be determined whether these properties can also contribute to the protective effects of estrogen against doxorubicin-induced cardiotoxicity.

The uncertainty about the role of sex in the risk stratification of doxorubicin-induced cardiotoxicity constitutes a serious gap of knowledge. From a clinical perspective, it is critical to design studies that investigate the effect of sex on doxorubicin-induced cardiotoxicity in clearly defined groups of pre-pubertal girls, women of child-bearing age, and post-menopausal women in comparison to age-matched men. From the preclinical perspective, sexual dimorphism should be studied in juvenile pre-pubertal models of doxorubicin-induced cardiotoxicity to explore whether pre-pubertal female animals will also be more sensitive to doxorubicin-induced cardiotoxicity than juvenile male animals similar to the findings in paediatric cancer patients. In addition, female animals should be included in all experimental protocols that examine the potential protective effect of a new drug and/or strategy against doxorubicin-induced cardiotoxicity.

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