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REVIEW ARTICLE

Cisplatin Nephrotoxicity and Sexual Dimorphism: Experimental Trials for Protection

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ABSTRACT

Background: Cisplatin is one of the most commonly used anticancer agents either alone or in combination. Nephrotoxicity is the most common and distressing side effect of its usage. Many mechanisms have been reported for describing the pathogenesis of cisplatin-nephrotoxicity, including a severe inflammatory response, vascular injury, free radicals generation, toxic metabolites, and apoptotic pathways. Many experimental trials were done to prevent or ameliorate cisplatin nephrotoxicity using neutralizing agents, antioxidant agents, or herbal compounds with variable results.

Sex/gender differences have a great role in the process of cisplatin-induced nephrotoxicity. Many experimental studies reported that female rats were more resistant to cisplatin nephrotoxicity than male rats. Many experimental trials were done using a variety of compounds including sex hormones, antioxidants, and plant extracts to discover their preventive effects on cisplatin-induced nephrotoxicity in male and female experimental models with variable results.

Conclusion: There is still a need for further studies to discover effective strategies for combating this dangerous side effect of cisplatin treatment and its sexual dimorphism.

Keywords: Gender difference; Sex difference; Cisplatin-induced nephrotoxicity; Platinum compounds; Antioxidant agents

INTRODUCTION

Cisplatin (cis-diamminedichloroplatinum II, CDDP) is a potent anticancer agent and it is extensively used for the cure of many types of malignant tumors including pulmonary, breast, cerebral, head and neck, leukemia, renal, ovarian, and testicular cancers[1,2]. Nephrotoxicity is the most common and distressing side effect of cisplatin. Many trials attempting to ameliorate or prevent cisplatin-induced nephrotoxicity in patients subjected to chemotherapy were done with variable results [3]. Many experimental trials reported that sex difference had a great role in the process of nephrotoxicity induced by cisplatin with a variety of findings considering the protectant strategies[3,4]. The aim of this article is to review and discuss cisplatin-induced nephrotoxicity, its sexual dimorphism, and the protectant strategies to combat it.

Cisplatin-induced nephrotoxicity

Cisplatin is a platinum compound, with a central platinum atom surrounded by two chloride groups and two ammonia groups[4]. Although cisplatin is very effective against a broad spectrum of malignancies, its use has been associated with many toxic side effects including nephrotoxicity, hepatotoxicity, cardiotoxicity, ototoxicity, gastrotoxicity, myelosuppression and allergic reactions[5]. The kidney is the main route for the excretion of cisplatin and it accumulates and concentrates within the proximal tubular epithelial cells with an approximate concentration of five times that of the serum leading to a high incidence of acute and chronic nephrotoxicity[1,5].

Many mechanisms have been reported for describing the pathogenesis of cisplatin-nephrotoxicity, consisting of severe inflammatory

response, vascular injury, free radicals generation, toxic metabolites, and apoptotic pathways. In general, cisplatin causes damage to the S3 segment of the proximal tubular cells of the corticomedullary region, where it is mainly accumulated[1].

Cisplatin uptake in the epithelial cells of the proximal tubules is mediated by membrane transporters (family 22 member 2 (SLC22A2), SLC22A6, and SLC22A8). The low chloride concentration inside cells facilitates cisplatin hydrolysis by replacing a chloride ion of cisplatin with a water molecule followed by bioactivation of the hydrated cisplatin to the toxic form by a gamma-glutamyl transpeptidase (GGT) and kynurenine aminotransferase 1 (KYAT1)-dependent pathway. The activated toxic form inside the cells of the renal proximal tubules induces DNA damage, mitochondrial damage, and reactive oxygen species (ROS) which trigger oxidative stress, endoplasmic reticulum (ER) stress, autophagy, and cell-cycle regulation. This lead to renal cell death (apoptosis and necroptosis), cell inflammation, and cell senescence, which leads to acute kidney injury and chronic kidney disease[6].

The rate of reabsorption of the proximal tubules decreased significantly due to its damage by cisplatin and this led to alteration of renal hemodynamics, attenuation of glomerular filtration rate, increasing plasma renin activity and renal vascular resistance (RVR) without affection on mean arterial pressure. Also, cisplatin causes alteration in the renin-aldosterone system as it reduces mineralocorticoid receptor binding[7].

Approaches for prevention or amelioration of cisplatin nephrotoxicity

These approaches can be classified into four categories including (a) neutralizing agents, (b) antioxidant agents, (c) cisplatin analogues, and (d) herbal compounds[8].

(a) Neutralizing agents: One example of neutralizing agents is sodium thiosulfate which improved the clinical tolerance dose of cisplatin from 120mg/m^2 per injection to 225 mg/m^2[9]. Another cytoprotective agent; amifostine ameliorated the renal damage caused by cisplatin as demonstrated by many studies[10-12]. But due to severe side effects (severe hypotension and nausea), the use of amifostine in clinical practice was limited and the safety of amifostine needs large, randomized, and controlled trials to be well examined[13].

(b) Antioxidant agents: Antioxidant agents act by reducing reactive oxygen species (ROS) production and oxidative stress[8]. There is growing evidence for the protective effects of antioxidants on cisplatin-induced nephrotoxicity. Vitamin E administration alone or in combination with other antioxidant agents could ameliorate oxidative stress resulting in reducing serum creatinine, serum urea, and kidney tissue damage[14]. Chen et al. 2014 and Mohamed et al. 2019[15,16] demonstrated the effective role of the antioxidant vitamin C for the protection from cisplatin nephrotoxicity in their experimental studies on rats.

(c) Cisplatin analogues: In trials to decrease cisplatin nephrotoxicity, novel cisplatin analogues such as carboplatin and oxaliplatin were introduced as alternatives to cisplatin chemotherapy for some tumors such as cervical cancer[17], ovarian cancer[18]، and colorectal cancer[19]. There are many limitations to the use of these analogues as carboplatin was reported to cause significant myelotoxicity, particularly thrombocytopenia[20] and oxaliplatin was reported to cause severe peripheral neuropathy[21].

(d) Herbal compounds: Recent studies showed that many herbal compounds such as Wogonin, Ginsenoside, Mallow extract, Plantago major extract, Curcumin, and Nigella sativa have antioxidant, anti-inflammatory, and anti-apoptotic properties that regulate the pathways of cisplatin-induced nephrotoxicity leading to amelioration of kidney damage[22].

Sexual dimorphism of Cisplatin-induced nephrotoxicity

Sexual dimorphism in the process of tumor growth and the response to antitumor agents is one of the important research work that is highlighted in experimental and clinical research[23]. Marcu LG [4] in his review on gender and sex-related differences in normal tissue effects induced by platinum compounds concluded that tissue toxicity induced by platinum drugs including cisplatin is sex/gender-dependent and requires further experimental and clinical studies to combat this variation.

The sex difference has a great role in the process of nephrotoxicity induced by cisplatin and most of the experimental studies reported that female rats are more resistant than male rats to cisplatin-induced nephrotoxicity because of the protective effects of estrogen and the greater antioxidant defense they have[3]. Shi and Coworkers[24] reported that male rats treated with cisplatin develop more severe kidney injury than female rats in both acute kidney injury (AKI) and chronic kidney disease models.

Zamani et al.[25] and Nematbakhsh et al.[26] reported that both sexes treated with cisplatin showed a significant increase in serum levels of creatinine and blood urea nitrogen with a higher level in male rats compared to female rats. On the other hand, Jilanchi et al.[29] reported that female rats showed significantly higher serum creatinine and blood urea nitrogen levels than male rats after cisplatin injection.

Nematbakhsh et al.[26] reported that there was an increase in serum magnesium, and kidney malondialdehyde (MDA) in male rats compared to female rats after cisplatin injection. Also, Stakisaitis et al.[28] showed that the 24 h urinary excretion of sodium after the repeated injection of cisplatin at a dose of 2.5 mg/Kg for 3 subsequent days was higher in the male rats than the female rats.

Regarding histological alteration, Pinches et al. [27] and Wei et al.[30] showed more histopathological lesions in male rats than in female rats after administration of cisplatin.

The cause of sex-dependent nephrotoxicity is not fully detected, but the differences in renal circulation between males and females could be a factor. Experimental studies showed that the renal vasculature in males depends on nitric oxide more than that of females and the availability of nitric oxide in males reduced over time and this led to a decrease in renal plasma flow and acceleration of pre-existent kidney disease[4]. Another hypothesis is related to cisplatin uptake by the kidneys. The membrane transporter, organic cation transporter (OCT2), that act as a mediator for cisplatin uptake into renal tubular cells were reported to be significantly higher in male kidneys than female kidneys as sex hormones have a role on the level of organic cation transporter (OCT2) [31]. Urakami et al. [32] demonstrated that testosterone intake increased the level of organic cation transporter (OCT2) in both male and female rats, but estradiol intake moderately decreased the level of OCT2 in both sexes. Kander et al. [33] demonstrated that females have lower oxidative stress and reactive oxygen species (ROS) formation than males and Eshraghi-Jazi and Nematbakhsh[3] postulated that this variation has a role in the more resistance of females to the toxic effect of cisplatin.

Experimental trials of protective effect of different compounds on sexual dimorphism of Cisplatin-induced nephrotoxicity

Many experimental studies were done using a variety of compounds including sex hormones, antioxidants, and plant extracts to discover their preventive effects on cisplatin-induced nephrotoxicity in male and female experimental models with variable results[3].

Jilanchi et al.[34] in a study on the effects of pomegranate flower extract as an antioxidant on nephrotoxicity induced by cisplatin in female rats demonstrated that the level of serum creatinine, blood urea nitrogen, and kidney tissue damage score increased by cisplatin injection and pomegranate flower extract failed to ameliorate these effect on the kidney. Mazaheri et al.[35] reported that fennel essential oil as a phytoestrogen source failed to ameliorate nephrotoxicity induced by cisplatin in ovariectomized female rats. Jilanchi et al.[36] in their study on the role of vitamin E in the prevention of cisplatin nephrotoxicity found that the level of serum creatinine and blood urea nitrogen in male rats treated with cisplatin was nearly equal to that of the control group, but it was significantly higher in the female rats. Also, they found that the kidney tissue damage score was much higher in female rats indicating that Vitamin E may have a nephroprotective effect against cisplatin-induced nephrotoxicity in male rates and it has not such effect in female rats. Haghighi et al.[37] in their study on the role of losartan (angiotensin II receptor 1 blockade) in cisplatin-induced nephrotoxicity in rats concluded that losartan could prevent cisplatin-induced nephrotoxicity in male rats, but it exaggerated kidney damage in females, and this may be related to the renin-angiotensin system receptors in the kidneys.

Alsuhaibani's study [38] demonstrated the positive protective role of Nigella sativa against cisplatin-induced nephrotoxicity in adult male rats. But, considering the studies [34-37] that demonstrated differences in the protective effects of drugs and natural products against cisplatin-induced nephrotoxicity according to the gender of the rats, Nematbakhsh[39] recommended future studies to be done to show the protective role of Nigella sativa against nephrotoxicity induced by Cisplatin considering the difference in response according to the gender.

CNCLUSION

Cisplatin induces nephrotoxicity according to experimental studies on both male and female models and its intensity is related to sex. The female rats appeared more resistant to cisplatin nephrotoxicity than the male rats. Many experimental studies were done using a variety of compounds including sex hormones, antioxidants, and plant extracts to discover their preventive effects

on cisplatin-induced nephrotoxicity in male and female experimental models with variable results. Further investigations and studies are needed to discover effective strategies to ameliorate or prevent cisplatin-induced nephrotoxicity considering its sexual dimorphism.

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