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Cisplatin; nephrotoxicity and beyond

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Abstract

Cisplatin is one of the most extensively administered and highly effective substances for the treatment of several solid tumors; however, it shows dose-dependent renal side effects. This review was aimed to summaries and present the recently published papers on the toxicities of cisplatin, focussing on its nephrotoxicity. Directory of Open Access Journals (DOAJ), Google Scholar, PubMed, EBSCO, and Web of Science have been searched. Renal toxicity is clinically the most important and well-known side effect of cisplatin. Various investigations suggested that several mechanisms including oxidative stress, DNA injury, and inflammatory responses, are involved in cisplatin-induced renal toxicity. In recent years, much interest has been directed towards a gender difference in renal toxicity of cisplatin. The literature on gender-related cisplatin toxicity shows conflicting results even on the same tissues. Cisplatin induced renal toxicity maybe sex related probably due to differences in kidney circulation. Because of ill-understood mechanisms, it requires further investigations.

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Introduction

Renal toxicity is one of the main side effects in the course of chemotherapy with different drugs. Cisplatin is a chemotherapeutic agent administered for the treatment of various solid tumors including tumors of head and neck, lung, testis, breast, and ovary. Cisplatin shows various side effects including myelosuppression, ototoxicity, gastrointestinal toxicity, allergic reactions and renal toxicity. The major dose-limiting side effect of cisplatin is renal toxicity and its reduction has been a matter of concern in recent years (1-8). This review was aimed to summaries and present the recently published papers on the toxicities of cisplatin, focusing on its nephrotoxicity.

Core tip

Several mechanisms such as oxidative stress, DNA injury, and inflammatory responses are involved in cisplatin-induced renal toxicity. In recent years, much interest has been directed towards a gender difference in cisplatin induced renal toxicity. The literature on gender-related cisplatin toxicity shows conflicting results even on the same tissues. Cisplatin induced renal toxicity maybe sex-related even though the underlying mechanisms are ill-understood. Gender differences in kidney circulation may be an important factor contributing to this difference; however, understanding the underlying mechanism requires further investigations.

Materials and Methods

Directory of Open Access Journals (DOAJ), Google Scholar, PubMed, EBSCO and Web of Science were searched with key words relevant to cisplatin, gender, acute renal failure, nephrotoxicity.

Results and Discussion

Several types of drugs accumulate in kidney tissue, either in the early or in the forms of metabolites, result in critical dysfunction of kidney. Nephrotoxicity is the main side-effect of cisplatin that occurs in 20%-30% of patients. Although cisplatin is a potent chemotherapeutic agent, but it induces acute renal failure (9-11). Cisplatin renal toxicity can present with features such as acute hypomagnesaemia (12,13), distal renal tubular acidosis, renal salts wasting, Fanconi-like syndrome, hypocalcaemia, hyperuricemia and finally acute renal failure (9,12). Kidney is one of the most susceptible target organs for drug-associated toxicity due to its high perfusion rate and high ability for drugs up-

take and metabolism (14-16).

Cisplatin-induced renal toxicity may become a life threatening condition for hospitalized patients. Intensive efforts have been put into development of new strategies to minimize drug-induced renal toxicity. To extend novel strategies and to prevent and/or diminish drug-induced renal toxicity, various pharmacological and molecular approaches have been proposed; but, the clinical use of these preventive modalities is still limited (17-21).

Cisplatin, an uncharged low molecular weight molecule, is freely filtered through the glomerular capillaries, taken up by kidney tubular cells, finally reaching its highest gradient in renal proximal tubules, inner medulla and outer stripes. Hence, these areas are the main sites for cisplatin-induced kidney damage, which eventually leads to damages on different areas including distal and collecting renal tubular cells (10-15). Glomerular atrophy, degeneration of the tubular epithelial cells and interstitial inflammatory cells infiltration are the main histological findings in cisplatin treated kidney tissues. However, glomerular injuries have not been identified in the majority of cisplatin treated animals (10-16).

The features of cisplatin-induced renal damage includes progressive vasoconstriction, decrease in kidney plasma flow and glomerular filtration rate, a rise in serum creatinine, and also a decrease in serum magnesium and potassium levels. Long-term side effects of cisplatin on kidney are not well known, but it is thought that cisplatin may leads to a permanent decline in kidney function (17-21). Although the main pathological findings in cisplatin renal toxicity is tubular cell damage and death, a strong inflammatory reaction and activation of inflammasomes is also accelerated in this condition, which further aggravates kidney injury.

Pathogenesis pathways involved in cisplatin induced renal toxicity

Oxidative and nitrosative stress

Cisplatin-induced renal toxicity is directly associated with an increase in oxidative stress in renal tissues (12-19). Cisplatin induces reactive oxygen species generation in renal tissue. Reactive oxygen species directly act on multiple cell components, including lipids, proteins, and DNA (20-24). Increased reactive oxygen species production can increase mitochondrial dysfunction. Besides injured mitochondria also increase reactive oxygen species generation. Because of pivotal role of mitochondrial dysfunction in apoptosis induction, the protective effect of antioxidants against mitochondrial impairment could reduce apoptosis in cisplatin-induced renal toxicity (20-28).

Furthermore, the endoplasmic reticulum stress pathway involves in activation of caspase-12 and Ca^{2+}-dependent phospholipase A2, therefore pharmacological inhibition of these enzymes reduces cisplatin-related apoptosis (19-28). On the other hand, reactive oxygen species straightly target the lipid components of the cell membrane causing peroxidation and denaturation of proteins, which leads to enzymatic inactivation. Reactive oxygen species are made by the xanthine-xanthine oxidase system, mitochondria, and nicotinamide adenine dinucleotide phosphate-oxidase in cells. Following treatment with cisplatin, reactive oxygen species are produced throughout these systems and are implicated in the pathogenesis of acute kidney damage. Cisplatin triggers enzymatic activation of glucose-6-phosphate dehydrogenase and hexokinase, which increase the free radical production and deplete the antioxidant content. Importantly, cisplatin raises the intracellular calcium level, which activates nicotinamide adenine dinucleotide phosphate-oxidase and stimulates reactive oxygen species production by damaged mitochondria (18-28). Cisplatin has negative inhibitory influence on antioxidant enzymes, and thus considerably decreases activity of superoxide dismutase, glutathione peroxidase, and catalase in the kidney. Interestingly reactive nitrogen species have also been investigated in cisplatin-induced renal toxicity (22-29). When cisplatin is transported into the cells, it can interact with several target molecules and may transform to a more potent toxin. Cisplatin has been shown to increase the production of peroxynitrite and nitric oxide in renal tissues in experimental studies. Peroxynitrite provokes changes in the structure and function of proteins, chemical cleavage of DNA lipid peroxidation, and a diminution in cellular defenses by oxidation of thiol pools (28-34).

Apoptosis

Cisplatin-induced renal toxicity depends on several signaling pathways that lead to apoptosis and necrosis of renal tubular epithelial cells (29-36). Increased reactive oxygen species production can increase mitochondrial dysfunction and the consequent activation of the caspases cascade. Multiple studies have shown that mitochondrial damage is the main apoptotic pathway for cisplatin induced kidney tubular cell death (35-39). Multiple studies have shown that a low concentration of cisplatin may lead to apoptotic cell death whereas necrosis happens at higher concentrations. Other mechanisms of cisplatin induced renal toxicity include the activation of extrinsic pathway by tumor necrosis factor (TNF), as well as the intrinsic mitochondrial and endoplasmic reticulum stress pathways. It is well known that the major death receptors are TNF-alpha and TNF-receptor 1 and 2. Additionally, there is substantial evidence that cisplatin activates the intrinsic mitochondrial pathway. The engagement of the intrinsic apoptotic pathway in cisplatin-induced kidney damage was initially suggested by investigations showing BAX accumulation in mitochondria, activation of caspase-9, cytochrome c release and apoptosis in cultured kidney cells (28-39).

Activation of glutathione-S-transferase and γ-gamma-glutamyl transpeptidase

More precise findings are proposed that renal toxicity of cisplatin in the renal tissue may depend on activation of metabolic pathway that comprises glutathione-S-transferase and γ-gamma-glutamyl transpeptidase. Inhibition of each of these enzymes resulted in a decrease in cisplatin renal toxicity in experimental studies (24-31). As the

glutathione conjugates pass across the renal tubules, they are cleaved by gamma-glutamyl transpeptidase that is expressed on the surface of the proximal tubular cells, and form cysteinyl-glycine conjugates. Then cysteinyl-glycine conjugates are further metabolized in to cysteine-conjugates by aminodipeptidases, which are also expressed on the surface of the renal proximal tubular cells. The cysteine conjugates are transported into the renal proximal tubular cells, where they are metabolized by cysteine-S-conjugate beta-lyase to highly reactive thiol molecules (25-31).

Vasoconstriction

Cisplatin induces kidney vasoconstriction via damaging in the kidney vasculature, which decreases blood flow, triggering ischemic injury to the renal tissue and eventually changes the glomerular filtration rate. Finally, a series of adverse reactions trigger acute kidney injury (18-22).

Inflammation

Another cause of cisplatin-induced renal toxicity and cellular toxicity is inflammation. In the recent years, various inflammatory mediators effective in kidney damage have been recognized. These mediators acts in different pathways including direct damage by cisplatin, damage-associated molecular patterns by Toll-like receptor 4, vicious cycle of nuclear factor kappa-light-chain-enhancer of activated B-cells (NF-κB) activation and chemokines/cytokines, and also activation of immune cells. TNF-α is the typical inflammatory cytokine and plays a major role in many infectious and inflammatory diseases. An increase in the expression of TNF-α in the kidney was found in experimental investigations. Following cisplatin treatment in conclusion, the expression of various inflammatory cytokines and chemokines is increased in the kidney (30-38).

Inhibition of protein synthesis

Cisplatin is cytotoxic through its equated metabolite. When blood chloride concentration is moderately high, cisplatin remains unchanged. On the contrary, when cisplatin enters the cell, it undergoes hydrolysis due to low intracellular chloride concentrations, and the two chloride ions are replaced by water. Then, the equated form attaches to N7 positions of guanine and forms the intra-strand cross links characterizing the cytotoxic mechanism of cisplatin. Cisplatin specially accumulates in cells of the S3 segment of the kidney's proximal tubule. Inhibition of protein synthesis is the initial manifestation of cisplatin toxicity (38-42).

Renal histomorphological damages induced by cisplatin

Cisplatin-induced kidney damage can be categorized into four types: (*a*) tubular cell toxicity defined as cell death through apoptosis or necrosis, (*b*) vascular injury via kidney vasoconstriction, (*c*) glomerular damage by injury to the glomerular compartments consisting of capillaries, basement membrane, mesangial cells, parietal cells and podocytes, and (*d*) interstitial nephritis through inflammatory responses. The gradual and complex processes that can lead to renal damage are caused by the collection of potentially toxic substances in the tubular fluid that diffuses through the highly permeable membranes of tubular cells (23-29,34-36).

In addition to the morphological findings by light microscopy, prominent ultrastructural changes were identified in the renal proximal tubular epithelial cells. Marked tubular degeneration with distinct apoptotic changes, loss of apical microvilli, ramification of cytoplasm, irregularity of basement membrane, vesiculation in the mitochondria, marginal condensation of nuclear chromatin and presence of many lysosomes were identified in cisplatin treated kidney tissues. Irregular glomerular basement membrane, increased mesangial matrix, proliferation of mesangial cells and fusion of podocytes foot processes, may also be found in the electron microscopic examination of cisplatin treated rats' kidneys (38-43).

Amelioration of cisplatin nephrotoxicity based on inhibition of its pathogenesis

Induction of oxidative stress with rather high concentrations of the drug in the kidney transport system explains renal toxicity of cisplatin. In fact, many pathways involved in cisplatin renal toxicity have been defined and considered as targets for kidney protection, and several new potentially protective substances have been reported. The multiple pathways leading to kidney injury and kidney cell death have points of convergence and share some common modulators (35-43). The most frequent event amongst all the expressed pathways is the oxidative stress that works as both a trigger and a consequence. It is possible that various natural antioxidants especially those found in fruits and herbs could effectively scavenge cisplatin-induced reactive oxygen species generation directly and/or indirectly by antioxidant properties and attenuating renal p53 expression and subsequent inhibition of renal tubular cell death (22-28,32-36).

In fact, natural herbal products and medicinal plants have potential antioxidant activity (33-39) and are thus frequently administered along with chemotherapeutic drugs to deliver better protection against their toxic side effects. Hence, to increase the clinical usefulness of cisplatin, several free radical scavengers have been used to ameliorate cisplatin induced renal toxicity (36-42).

Glutathione depletion is another important mechanism causing cisplatin nephrotoxicity. Intracellular binding to sulfhydryl groups leads to glutathione depletion, resulting in lipid peroxidation and eventually mitochondrial injury. In addition to its DNA binding property, cisplatin also causes mitochondrial injury resulting in production of reactive oxygen species. Tubular cell injury is recognized as major pathological changes in cisplatin-induced renal toxicity. The highest concentration of cisplatin in the kidney is seen in the proximal tubule, leading to kidney toxicity, tubular injury, and cell death, depending on the duration and dosage administered. Many studies have identified multiple signaling pathways that are responsible for renal

tubular cell damage and death in cisplatin renal toxicity. Hence, renal proximal tubule cell death is seemed to be the major pathological change in cisplatin renal toxicity. Various pathways are responsible for renal tubular cell apoptosis in cisplatin-induced kidney toxicity and inhibition of those pathways is usually necessary for global therapeutic properties (28). Both basolateral organic cation transporters (OCT1 and OCT2) are involved in cisplatin transport, accumulation, and its toxicity (8,29). Although some studies have suggested methods to diminish cisplatin-induced kidney toxicity, the protection is usually partial, highlighting the need for combined or novel strategies (30-43). Therefore, alternative modalities are required that are less toxic and produce more global therapeutic properties (31-37).

Gender difference in cisplatin nephrotoxicity

In recent years, much interest has been directed towards the gender difference in renal toxicity of cisplatin (7-14,43-46). The literature on gender-related cisplatin toxicity shows conflicting results even on the same tissues (40,41). Studies of cisplatin toxicity on renal tubular epithelial cell cultures in both genders of monkeys and rats showed that, rat cells were more sensitive than monkey cells with no gender-related differences in either species (35-40). Another investigation showed that, female rats were more susceptible to cisplatin toxicity than males. These differences may be related to the effect of estrogen. Estrogen is found to have protective properties on heart and kidney (39-44). However, in our previous study conducted on ovariectomized rats estrogen replacement resulted in increased cisplatin renal toxicity. It is postulated that high estrogen levels may cause an increase of oxidative stress by means of nitrous oxide production (40-44). Interestingly our recent investigation revealed protective effects of recombinant erythropoietin against cisplatin renal toxicity might also differ between sexes (45-48).

Recently Kirkim et al (46) conducted a study on the gender-related susceptibility for cisplatin ototoxicity. Rats were divided into four groups; a male control, a female control, male cisplatin and a female cisplatin group. For the cisplatin groups 16 mg/kg of cisplatin was administered. They found that hearing in the female rat cisplatin group to be disturbed more widely than the hearing in the male rat cisplatin group. Morphological evaluation showed more serious injuries in the spiral ganglion and brain stem tissues of female rats. The difference in hearing can be attributed to the more severe injury found in neuronal tissues like spiral ganglion cells and brainstem neurons (40-49). Gender difference in nephrotoxicity has also been investigated in previous study. They have been shown that males tend to suffer more from kidney damage caused by amphotericin B (48-50) and Tobramycin than female rats (35-39). Moreover, the possibility of renal toxicity induced by phenobarbital is greater in male rats than females (38-42). Male animals seem to be less resistant to ischemic acute kidney injury than females (40-45). It has also been reported that the neuropathy induced by cisplatin is gender related (38-42). Recently Nematbakhsh et al, investigated the role of gender in cisplatin induced kidney toxicity. They administered a low dose of cisplatin (1 mg/kg/day; ip) daily to male and female rats for 15 consecutive days. They found that serum levels of blood urea nitrogen, creatinine, magnesium, kidney malondialdehyde levels, kidney weight and renal damage scores were significantly greater in males than in females ($P<0.05$). They concluded that cisplatin-induced nephrotoxicity is gender related and further studies need to be carried out to determine the underlying mechanisms for it (40). Similarly, in a study difference between sexes was observed in protective effect of recombinant human erythropoietin against cisplatin-induced renal toxicity. Administration of recombinant human erythropoietin were found to significantly decrease changes in serum creatinine, blood urea nitrogen, and malondialdehyde levels in male rats, but not in females. However, no significant differences were found in the renal histological damage scores between the groups. The mechanism underlying these observations has not been yet clear, and it may not be solely related to female sex hormone, even though estrogen itself promotes cisplatin induced renal toxicity. Sex differences in kidney circulation are a possible reason for gender-related cisplatin renal toxicity. Additionally simulation of angiotensin system receptors leads to different responses in the sexes (40-50) with more vasodilator property in female, which affects kidney blood flow. The renal blood flow on the other hand disturbed by cisplatin (48-52). Hence, possibly the female renal blood flow is diminished less by cisplatin than male, which causes less injury. The affinity and the drug binding, pharmacokinetic effectiveness of drugs, and genetic nature are the factors that may also attribute to the gender-related different responses (50-54).

Conclusion

Cisplatin induced renal toxicity maybe sex related probably due to differences in kidney circulation. Because of ill-understood mechanisms, it requires further investigations.

Authors' contribution

Searching of the papers conducted by AB and MRA. AB and MT wrote the primary draft. MRK edited the paper.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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