NEW INSIGHTS IN THE PATHOGENESIS OF CISPLATIN-INDUCED NEPHROTOXICITY

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ABSTRACT

Cisplatin (cis-diamminedichloroplatinum II) is a widely used chemotherapeutic agent. However, efficacy and clinical utility of this drug is significantly limited by severe side effects such as nephrotoxicity which develops due to renal accumulation and biotransformation in proximal tubular epithelial cells. Cisplatin-induced nephrotoxicity can be manifested as acute kidney injury (AKI), or as different types of tubulopathies, salt wasting, loss of urinary concentrating ability, and magnesium wasting. The attenuation of cisplatin-caused AKI is currently accomplished by hydration, magnesium supplementation or mannitol-induced forced diuresis. However, mannitol treatment causes over-diuresis and consequent dehydration, indicating an urgent need for the clinical use of newly designed, safe and efficacious renoprotective drug, as an additive therapy for high dose cisplatin-treated patients. Accordingly, we emphasized current knowledge regarding molecular mechanisms responsible for cisplatin-caused nephrotoxicity and we described in detail the main clinical manifestations of cisplatin-induced renal dysfunction in order to pave the way for the design of new therapeutic approaches that can minimize detrimental effects of cisplatin in the kidneys. Having in mind that most of cisplatin-induced cytotoxic effects against renal cells are, at the same time, involved in anti-tumor activity of cisplatin, new nephroprotective therapeutic strategies have to prevent renal injury and inflammation without affecting cisplatin-induced toxicity against malignant cells.

Keywords: *Cisplatin, nephrotoxicity, acute kidney injury, apoptosis, inflam-mation.*

INTRODUCTION

Cisplatin (cis-diamminedichloroplatinum II) is one of the most potent antitumor drugs, which is used to treat various types of malignancies, such as head and neck, gastrointestinal, urogenital, breast and lung cancers (1-13). Nevertheless, efficacy of cisplatin is significantly limited by severe side effects, including nephrotoxicity, ototoxicity and myelosuppression (14,15). Cisplatin-induced nephrotoxicity is a result of renal accumulation and biotransformation of cisplatin and is manifested as acute kidney injury (AKI), or as different types of tubulopathies, salt wasting, loss of urinary concentrating ability, and magnesium wasting (16,17). AKI is dose-dependent complication, noticed in 25-30% of cisplatin-treated patients (18-20). The attenuation of cisplatin-caused renal injury is currently accomplished by hydration, magnesium supplementation or by mannitol-induced forced diuresis (20). However, mannitol treatment may cause over-diuresis and consequent life-treating dehydration (16), indicating an urgent need for the clinical implementation of newly designed, safe and efficacious nephroprotective drug, as an additive therapy for cisplain-treated patients. Until now, amifostine [(ethanethiol, 2-[(3-aminopropyl)amino] dihydrogen phosphate ester)] was most usually used against cisplatin-induced renal injury, but its adverse effects, such as ototoxicity, hypotension, vertigo, hypocalciemia, nausea and vomiting, significantly limited its clinical use (16,17). Accordingly, there still remains an unmet need for the development of new, nephroprotective agent against cisplatin-caused AKI. Having in mind that most of cisplatin-induced cytotoxic effects against renal cells are, at the same time, involved in anti-tumor activity of cisplatin (13), this new, nephroprotective agent will have to prevent AKI without affecting cisplatin-induced toxicity against malignant cells. Design of novel therapeutic strategies against cisplatin-provoked nephrotoxicity requires understanding of molecular mechanisms which are involved in cisplatin-induced renal injury and inflammation and which are responsible for the development of main clinical manifestations and complications of cisplatin treatment. Accordingly, in this review article, we emphasized current knowledge about signaling pathways and cellular mechanisms which are responsible for the development of renal inflammation and activation of detrimental immune response elicited after cisplatin-caused injury of proximal tubular epithelial cells (PTECs). Additionally, herewith we described in detail the main clinical manifestations of cisplatin-induced renal dysfunction in order to pave the way for the design of new therapeutic approaches that can minimize detrimental effects of cisplatin in the kidneys. Our hope is that clinicians and scientists will use information presented herein as a starting point for the design of novel, effective nephroprotective strategies against cisplatin-induced nephrotoxicity.

Molecular mechanisms responsible for the development of cisplatin-induced nephrotoxicity

Cisplatin is mainly excreted by the kidneys, by both glomerular filtration and tubular secretion (21). During renal excretion cisplatin accumulates in the kidneys, and levels of this drug in PTECs are about five times greater than in the blood (18). Accordingly, toxic effects occur primarily in PTECs (21,22). The copper transporter 1 and 2 (Ctr1 and Ctr2), the P-type copper-transporting ATPases (ATP7A and ATP7B), the organic cation transporter 2 (OCT2), and the multidrug extrusion transporter 1 (MATE1) are the most important membrane transporters involved in the cellular uptake of cisplatin (23). Although cisplatin may enter PTEC through passive diffusion, Ctr1 and OCT2-mediated uptake of cisplatin are mainly responsible for the import of cisplatin in PTECs and for high accumulation of cisplatin in the kidneys (21). Accordingly, genetic deletion of Ctr1 significantly reduced cisplatin-induced apoptosis of PTECs (24). Similarly, deficiency of OCT2 notably attenuated toxicity of cisplatin (25), while cimetidine, an OCT2 substrate, reduced cisplatin uptake by PTECs and alleviated nephrotoxicity (26).

Cisplatin-induced toxicity is a consequence of cisplatin conversion into several nephrotoxic molecules within the PTECs. Several studies have shown that glutathione-conjugate of cisplatin in the kidneys is metabolized via gamma glutamyl transpeptidase (GGT) expressed on the surface of PTECs. These conjugates are further degradated into highly reactive thiols by the activity of aminopeptidase N (APN) and cisteine-S-conjugate beta-lyase (CCBL). Since among all tissues, GGT, APN and CCBL have the highest activity in the kidneys, these enzymes were considered as potential targets for the attenuation of cisplatin-induced nephrotoxicity (20,27). Accordingly, several ongoing experimental and clinical trials investigate potential therapeutic effects of GGT, APN and CCBL inhibition as new approach for alleviation of cisplatin-induced AKI.

Once cisplatin enters the PTECs, it forms intrastrand crosslinks among two adjacent guanine residues within DNA affecting replication and transcription which results in the activation of DNA repair mechanisms. Accordingly, an increased activity of nucleotide excision repair (NER) and mismatch repair (MMR) system has been associated with resistance to cisplatin-induced AKI and enhancement of NER and MMR system activity is considered a new approach for prevention of cisplatin-induced AKI (28).

In addition, regulators of cell cycle play an important role in the development of cisplatin-induced AKI and these molecules could also be taken into account as potential targets for prevention of cisplatin-induced renal injury. After cisplatin administration, normally quiescent kidney cells enter the cell cycle and consequently the cell cycle-inhibitory proteins (p21, 14-3-3 and p27), which coordinate cell cycle and play a protective role against toxicity, become induced. Accordingly, deletion of the p21 or 14-3-3 genes resulted in enhanced nephrotoxicity elicited by cisplatin (29-31). Since cisplatin treatment causes an increased activity of Checkpoint kinase 2 (Cdk2), p21-mediated protection from cisplatin-induced injury is relied on inhibition of Cdk2 (32). Accordingly, several lines of evidence suggested the importance of

Cdk2-inhibitory drugs in prevention of cisplatin-induced nephrotoxicity (32).

Oxidative stress is crucially involved in cisplatin-induced AKI. Within the cell, cisplatin is converted into a highly reactive form, which can rapidly react with thiol-containing antioxidant molecules, such as glutathione, methionine and metallothionein (33,34). Consequently, depletion of glutathione and similar antioxidants leads to increased accumulation of endogenous reactive oxygen species (ROS) resulting in induction of oxidative stress within cisplatin-injured PTECs. ROS may target and modify cell components, including lipids, proteins, and DNA, resulting in cellular stress (35). Additionally, cisplatin may promote ROS generation by direct binding to P450 (CYP) system in microsomes (18,36) or may induce mitochondrial dysfunction by distorting respiratory chain (37). In line with these observations, several studies demonstrated that treatment with antioxidants significantly attenuated cisplatin-induced AKI (38-41), indicating crucial role of oxidative stress in the pathogenesis of cisplatin-induced AKI.

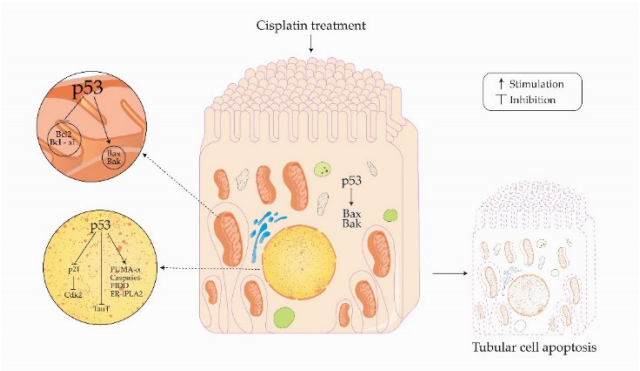
Importantly, cisplatin-induced extensive generation of ROS and free radicals in PTECs accelerate production of advanced glycation end products (AGEs) which further contribute to the progression of renal injury and inflammation (35). Since kidneys have a crucial role in AGEs disposal, cisplatin-induced renal dysfunction increases AGE levels in injured kidneys resulting in the development of glomerulosclerosis, interstitial fibrosis, and tubular atrophy (35).

Treatment with cisplatin *in vivo* causes a great increase in both necrosis and apoptosis of PTECs (42). Extrinsic, intrinsic (mitochondrial) and endoplasmic reticulum (ER)-stress pathway are involved in cisplatin-induced AKI. Cisplatin treatment of PTECs resulted in translocation of Bax to mitochondria and releasing of cytohrome c (43,44), apoptosis-inducing factor (AIF) (45) and endonuclease G (46) from mitochondria, accompanied by activation of caspase-3,-8 and -9 (47) and caspase-12 which has been designated as initiator caspase in ER-stress pathway regulated by the expression of calcium-independent phospholipase A2 (ER-iPLA2) (48-50).

Cisplatin is known to activate all three mitogen-activated protein kinases (MAPKs) in the kidney, including p38, extracellular signal-regulated kinase (ERK), and Jun N-terminal Kinase/Stress-Activated Pathway Kinase JNK/SAPK (51). The ERK was shown to mediate cisplatin-induced nephrotoxicity via phosphorylation of the proapoptotic p66 shc protein (52). Furthermore, inhibition of ERK resulted in attenuated expression and activation of caspase-3, and consequently decreased apoptosis in cisplatin-treated renal cells (51).

P53 protein has an important role in cisplatin-induced AKI (53-55). Cisplatin treatment induces a DNA damage, leading to the activation of molecular sensor for DNA damage- ataxia telangiectasia and Rad3-related protein (ATR), which activates Chk2. Both ATR and Chk2 can phosphorylate p53 for its activation. Also, ROS may promote activation of p53 by inducing DNA damage or through ATR, Chk2, nuclear factor kappa B (NF-kB) or p38 activation (53). Activated p53 increases transcription of pro-apoptotic genes, such as PUMA-α and ER-iPLA2, and down-regulates expression of anti-apoptotic genes (p21 and taurine transporter (TauT)) (53-55). Additionally, p53 promotes apoptosis of PTECs through the interactions with Bcl-XL, Bax, Bak proteins in mitochondria and/or cytosol (53) (Figure 1).

Figure 1. Cisplatin-induced activation of p53 results in apoptosis of tubular cells.



Activated p53 increases transcription of pro-apoptotic genes, such as PUMA-α and ER-iPLA2, and down-regulates expression of anti-apoptotic genes (p21 and taurine transporter (TauT)). Additionally, p53 promotes apoptosis of tubular cells through the interactions with Bcl-XL, Bax, Bak proteins in mitochondria and/or cytosol. **Abbreviations:** Bcl-2: B-cell lymphoma 2; Bcl-xL: B-cell lymphoma-extra large; Bax: Bcl-2-associated X protein; Bak: Bcl-2 homologous antagonist killer; PUMA-α: p53 upregulated modulator of apoptosis; PIDD: p53-induced protein with a death domain; ER-iPLA2: Ca2+-independent phospholipase A2; Cdk2: Cyclin-dependent kinase complex; TauT: taurine transporter.

In addition to the regulation of apoptosis, p53 may contribute to the development of cisplatin-caused nephrotoxicity by modulating autophagy which, as an adaptive mechanism, promotes PTECs survival during AKI (56). Within hours after cisplatin administration, markers of autophagy, such as Beclin 1, LC3, and Atg5 are significantly up-regulated in injured PTECs (56-58). Importantly, DNA damage, activation of p53, and mitochondrial injury are increased in proximal tubules of autophagy-deficient mice, suggesting protective role of autophagy in cisplatin-injured kidneys (57,59-62).

It is important to highlight that, in addition to apoptosis and autophagy, necroptosis was also detected in renal tubules after injection of cisplatin (63,64). Receptor-interacting protein 1 (RIP1) and mixed lineage kinase domain-like protein (MLKL) – deficiency, as well as pharmacological inhibition of necroptosis, significantly reduced cisplatin-induced AKI (63,64).

The important role of inflammation in the development of cisplatin-induced aki

Inflammation plays a key role in the progression of cisplatin-induced AKI (65-72). After cisplatin treatment, several alarmins are produced by injured renal cells such as mesangial cells, glomerular cells, endothelial and renal tubular cells which can initiate enhanced production of inflammatory cytokines (70). Among them, tumor necrosis factor alpha (TNF-α) was significantly elevated in the serum as well as urine of cisplatin-treated animals, indicating important pathophysiological role of TNF-α in cisplatin-induced nephrotoxicity (65,66). The biological activities of TNF-α are mediated by two different receptors, TNFR1 and TNFR2 (71,72). Although TNFR1 was responsible for TNF-α-induced systemic and anti-tumor effects (71), several lines of evidence demonstrated that TNFR2 rather than TNFR1 mediates cytotoxic and inflammatory actions of TNF-α in cisplatin-injured kidneys (72). Accordingly, inhibition of TNFR2 should be further explored in up-coming experimental studies as a potentially new therapeutic approach that could reduce AKI without affecting anti-tumor effects of cisplatin mediated by TNF-α.

Some research demonstrated an important role of TLR-4 for enhanced production of TNF-α in resident and renal-infiltrating immune cells. One of possible endogenous molecules which can bind TLR-4 and initiate an innate immune response after cisplatin-treatment is gp96, which is increased after cisplatin administration (68). Activation of TLR-4 promotes p38 MAPK dependent signaling which induces enhanced secretion of TNF-α in cisplatin-injured kidneys (67,68). In addition to TLR-4 dependent production of TNF-α, cisplatin treatment also activates inflammasome complex in renal infiltrated leukocytes, resulting in enhanced secretion of interleukin (IL)-1β (69).

Elevated levels of TNF-α and IL-1β are isially accompanied with enhanced production of other inflammatory cytokines, particularly IL-18, and IL-6 resulting in the increased recruitment of circulating immune cells into cisplatin-injured kidneys (73-76). Intercellular adhesion molecule-1 (ICAM-1) has been considered a crucially important adhesion molecule for migration of immune cells into cisplatin-injured kidneys since the inhibition of this integrin significantly reduced total number of renal-infiltrated leukocytes (77).

Although expression of IFN-γ, well known inflammatory cytokine, is increased in cisplatin-injured kidneys, neutralization of this cytokine had no impact on renal dysfunction, suggesting the existence of IFN-γ-independent development of cisplatin-induced AKI (78). Recently published studies indicated important pathogenic role of IL-33 in cisplatin-induced AKI. Serum levels of IL-33 were increased in cisplatin-injured animals. Mice with cisplatin-induced AKI injected with fusion protein, which neutralized IL-33, had a significant decrease in creatinine, pathohistological score, and showed reduced apoptosis of cisplatin-induced PTECs, while injection of recombinant IL-33 notably aggravated cisplatin-induced AKI (79).

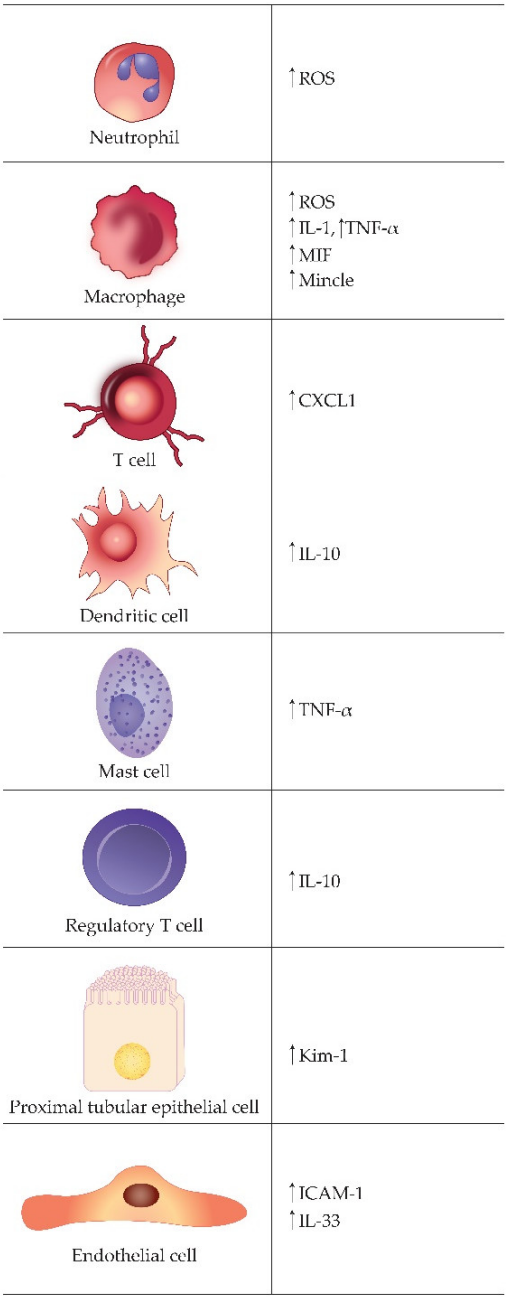
IL-10 is a cytokine with potent anti-inflammatory properties that suppresses the activation of leukocytes and the production of proinflammatory cytokines and chemokines in cisplatin-injured kidneys (80). Several studies demonstrated that IL-10, secreted mainly by regulatory T cells (Tregs), tolerogenic dendritic cells, and alternatively activated macrophages, reduces cisplatin nephrotoxicity, and may act, in part, by inhibiting the maladaptive activation of genes that cause leukocyte activation and adhesion, and induction of iNOS (78,80-82).

Different types of immune cells, including neutrophils, macrophages, mast cells, natural killer (NK) cells, T and B cells produce inflammatory cytokines or anti-inflammatory IL-10 and other immunomodulatory factors which play an important role in the pathogenesis of cisplatin-induced AKI (Figure 2).

Mast cells have important pathogenic role in cisplatin-induced nephrotoxicity. Depletion of mast cells resulted in significantly reduced renal injury in cisplatin-treated mice (82). Deficiency of mast cells was accompanied by lower number of renal-infiltrated leukocytes and notably down-regulated serum levels of TNF-α, suggesting that mast cells mediated cisplatin-induced AKI by promoting recruitment of circulating immune cells in the kidneys in TNF-α-dependent manner (82,83).

Renal-infiltrated neutrophils produce large amounts of ROS, proteases, and inflammatory cytokines, leading to renal epithelial injury (84-86). In contrast, an inhibition of TNF-α or TLR-4 signaling pathways, administration of IL-10 as well as inhibition of ICAM-1 (68,77,80,87) are associated with a decreased number of activated neutrophils in renal parenchyma of cisplatin-treated animals which corresponds to the attenuation of renal injury and inflammation. It has to be noted that neutrophils, which infiltrate cisplatin-injured kidneys, may alter their inflammatory phenotype depending on the cross-talk with immunosuppressive cells (86).

Figure 2. Immunomodulatory molecules which expression is enhanced in renal parenchymal and immune cells upon cisplatin treatment.



Cisplatin treatment induces enhanced expression of reactive oxygen species (ROS), inflammatory cytokines and chemokines as well as integrins in the kidneys enabling crosstalk between cisplatin-injured proximal tubular epithelial cells, endothelial cells and renal-infiltrated innate and adaptive immune cells.
***Abbreviations*:** ROS: Reactive oxygen species; IL: Interleukin; TNF-α: Tumor necrosis factor alpha; MIF: Macrophage migration inhibitory factor; Mincle: Macrophage-inducible C-type lectin; CXCL1: Chemokine (C-X-C motif) ligand 1; Kim-1: Kidney injury molecule-1; ICAM-1: Intercellular adhesion molecule-1.

Tolerogenic renal DCs and T regulatory cells (Tregs), in juxtracrine and paracrine manner, promote enhanced expression of IL-10 in renal-infiltrated neutrophils resulting in their differentiation into immunosuppressive and anti-inflammatory cells. Accordingly, depletion of neutrophils as well as their adoptive transfer may result in either alleviation or aggravation of cisplatin-induced AKI, depending on the cellular-make up and microenvironment of the cisplatin-injured kidneys (86).

Macrophages play an important inflammatory role in the initial phase of cisplatin-caused AKI. Cisplatin treatment induces activation of inflammasome, p38 MAPK and NF-kB pathways in renal macrophages resulting in enhanced production of superoxide anions, nitric oxide (NO), IL-1 and TNF-α (73,89). In addition, cisplatin-induced activation of TLR-4 induces expression of macrophage-inducible C-type lectin (Mincle) in renal infiltrating macrophages. Mincle promotes generation of inflammatory M1 macrophages which are capable to produce large amounts of inflammatory cytokines. Accordingly, cisplatin-induced activation of Mincle on macrophages results in exacerbation and progression of renal inflammation (90). In line with these findings, suppressed expression of Mincle on renal macrophages completely abrogates their inflammatory phenotype and adoptive transfer of Mincle-silenced macrophages protects against cisplatin-induced nephrotoxicity (90). Accordingly, Mincle is considered a potential molecular target for macrophage dependent attenuation of cisplatin-induced AKI and its therapeutic potential is going to be explored in future experimental studies. In addition to Mincle, macrophage migration inhibitory factor (MIF) plays an important pathogenic role in cisplatin-induced nephrotoxicity. Deletion of MIF suppressed influx of M1 macrophages and reduced concentration of macrophage-derived inflammatory cytokines and chemokines in the kidneys, attenuated recruitment of circulating immune cells in the cisplatin-injured kidneys which resulted in alleviation of AKI (91).

CD4+ and CD8+ T cells are crucially important in orchestrating immune response during cisplatin-induced AKI (66,79,92). Cisplatin-injured renal cells release IL-33 which activates CD4+ T cells and increase production of inflammatory cytokines, such as TNF-α, and chemokine CXCL1 (79). CXCL1 induces enhanced recruitment of neutrophils and may directly induce apoptosis of tubular epithelial cells (66,79). Cisplatin treatment increases expression of Fas receptor on renal tubular cells enabling apoptosis of these cells due to their interaction with FasL expressing renal infiltrating CD8+ T lymphocytes and NK cells (92).

Cisplatin treatment provokes enhanced expression of T cell immunoglobulin mucin 1 (Tim-1) on PTECs which acts as a costimulatory molecule for activation of renal-infiltrated T cells (93). Consequently, use of Tim-1-blocking antibody suppressed activation of renal-infiltrated CD4+ helper T cells and their cross-talk with CD8+ cytotoxic T cells, significantly reduced apoptosis of PTECs and protected against cisplatin-induced AKI (93). Due to its important role in the development and progression of AKI, Tim-1 was designated as kidney injury molecule-1 (Kim-1) and has been considered

as potential molecular target for the attenuation of T cell-driven renal inflammation (93).

Among immunosuppressive cells, Tregs and tolerogenic DCs have the most important role for the attenuation of detrimental inflammatory response in cisplatin-injured kidneys (94-96). Soon after cisplatin injection, forkhead box P3 (FoxP3)-expressing CD4+CD25+ circulating Tregs migrate into the injured kidneys where, in IL-10 dependent manner, suppress activation of M1 macrophages, inflammatory neutrophils, Th1 and Th17 cells (94). Accordingly, adoptive transfer of Tregs significantly attenuated renal dysfunction and mortality of cisplatin-treated T cell–deficient mice (94). Treg-induced alleviation of cisplatin-caused AKI was accompanied by down-regulated serum levels of inflammatory cytokines (TNF-a and IL-1b), reduced number of M1 macrophages and inflammatory IFN-γ and IL-17-producing leukocytes in the injured kidneys, indicating therapeutic potential of Treg-based therapy for attenuation of cisplatin-induced nephrotoxicity.

Tolerogenic DCs represent specific sub-population of resident renal immune cells which have important immunosuppressive and nephroprotective role in cisplatin-induced AKI (95,96). Damage associated molecular patterns (DAMPs) and alarmins, released from cisplatin-injured PTECs, down-regulate expression of costimulatory molecules and enhance expression of anti-inflammatory IL-10 in renal DCs (78,88,95,96). These immunosuppressive DCs, mainly in IL-10 dependent manner, inhibit activation of M1 macrophages, inflammatory neutrophils and Th17 cells in the cisplatin-injured kidneys contributing to the alleviation of inflammation (78,88,95,96). Accordingly, depletion of tolerogenic DCs significantly enhanced inflammatory response in the kidneys and aggravated cisplatin-induced AKI (88,95).

Clinical manifestations of cisplatin-induced renal injury

Acute renal failure, thrombotic microangiopathy, hypomagnesemia, anemia, salt wasting and Fanconi-like syndrome have been the most usually observed clinical manifestations of cisplatin-induced nephrotoxicity (97).

Generally, acute renal failure begins a few days after cisplatin treatment. It is manifested by an increase in the blood urea nitrogen and serum creatinine concentrations and decrease of glomerular filtration rate. Cisplatin-treated patients usually develop non-oliguric AKI, and glucosuria and minimal proteinuria might be observed as a result of PTEC injury (20).

Significant decrease in renal blood flow occurs three hours after cisplatin administration, resulting in deterioration in glomerular filtration rate (GFR). Increased sodium chloride delivery to macula densa and tubulo-glomerular feedback are related to an increased vascular resistance and reduced GFR (98).

The proximal renal tubules are the major site of sodium and water reabsorption (98). Cisplatin treatment causes reduction activity of ATPase, disturbed transport of water and electrolytes, mitochondrial dysfunction and altered cation balance in PTECs, leading to the decreased reabsorption of sodium and water and increased salt and water excretion (98). Accordingly, renal salt wasting syndrome occurs in 10% patients and represents one of the most usually observed complication of cisplatin therapy (99). Renal salt wasting syndrome is associated with intensive polyuria, hyponatremia, hypovolaemia, severe orthostatic hypotension, and prerenal AKI accompanied by dysfunction of the renin-aldosterone system which regulate salt and water wasting in the kidneys (98-101).

Also, cisplatin treatment may decrease the reabsorption of the filtered magnesium which causes refractory hypomagnesemia. This complication occurs in 90% of patients, and depends on the cumulative dose of administered cisplatin (17,99). Having in mind that hypomagnesemia may be observed in some patients 6 years after initial cisplatin treatment, there is a possibility that cisplatin-induced hypomagnesemia has been developed in two phases. The first phase, which is manifested by malabsorption of magnesium, happens due to the cisplatin-caused damage of calcium/magnesium-sensing receptor (99), while the second phase, characterized by patchy necrosis of tubular cells, is manifested by progressive renal injury and extensive magnesium loss (99). It has to be noted that magnesium deficiency may be associated with hypokalemia and hypocalcemia and, accordingly, malignant cardiac arrhythmias and neuromuscular dysfunction may be observed in cisplatin-treated patients (99).

Renal Fanconi syndrome has also been reported in some of cisplatin-treated patients (20). This syndrome is characterized by glycosuria, urinary lack of low molecular weight proteins (β2- microglobulin, retinol- binding protein and α1-macroglobulin), aminoaciduria (loss of amino acids such as alanine, valine, leucine, methionine), proximal tubular acidosis, phosphate and potassium wasting (97,98,102,103). Additionally, long-term exposure to cisplatin may result in the development of tubulointerstitial injury and interstitial fibrosis which may be life-thretening complication of cisplatin (98,104).

CONCLUSIONS

Cisplatin treatment induces apoptosis and oxidative stress in PTECs eliciting strong inflammatory response in the injured kidneys. Having in mind that these cisplatin-induced effects are, at the same time, involved in anti-tumor activity of cisplatin, newly designed renoprotective strategies against cisplatin-caused nephrotoxicity should rely on the identification of the structural and functional differences between cisplatin-injured renal and tumor cells. In that way, the prevention of cisplatin-induced nephrotoxicity will not affect antitumor effects of cisplatin and will significantly improve its clinical utility.

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CONFLICT OF INTEREST

The authors declare no financial or commercial conflict of interest.

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