Review

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Cisplatin-induced Kidney Dysfunction and Perspectives on Improving Treatment Strategies

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Cisplatin is one of the most widely used and highly effective drug for the treatment of various solid tumors; however, it has dose-dependent side effects on the kidney, cochlear, and nerves. Nephrotoxicity is the most well-known and clinically important toxicity. Numerous studies have demonstrated that several mechanisms, including oxidative stress, DNA damage, and inflammatory responses, are closely associated with cisplatin-induced nephrotoxicity. Even though the establishment of cisplatin-induced nephrotoxicity can be alleviated by diuretics and pre-hydration of patients, the prevalence of cisplatin nephrotoxicity is still high, occurring in approximately one-third of patients who have undergone cisplatin therapy. Therefore it is imperative to develop treatments that will ameliorate cisplatin-nephrotoxicity. In this review, we discuss the mechanisms of cisplatin-induced renal toxicity and the new strategies for protecting the kidneys from the toxic effects without lowering the tumoricidal activity.

Key Words: Cisplatin, Chemotherapy, Nephrotoxicity, NAD^+

Introduction

Nephrotoxicity is one of the major side effects in the course of chemotherapy with various drugs. It accounts for up to 60% of all cases of hospital-acquired acute kidney injury (AKI) and is associated with considerable morbidity and mortality. There are several mechanisms for the development of nephrotoxicity including oxidative stress, DNA adducts, inflammation, mitochondrial dysfunction, and direct cytotoxicity to the tubular epithelial cells[1]. Cisplatin (*cis*-diamminedichloroplatinum (II), CDDP) is a chemotherapeutic drug used for the treatment of many solid tumors, including those of the breast, head, neck, lung, testis, and ovary. While cisplatin induces various toxicities including gastrotoxicity, myelosuppression, ototoxicity and allergic reactions, the major dose-limiting side effect is nephrotoxicity[2]. The nephrotoxicity of cisplatin has been recognized since its approval for clinical use over 35 years ago. Despite concerted efforts to find less toxic but equally effective alternatives, cisplatin is still widely prescribed in clinical practice. Currently, cisplatin remains the standard drug for the treatment regimens of bladder, head and neck, small-cell and non-small cell lung, ovarian, cervical, and testicular cancers as well as several other forms. Cisplatin is available as a generic drug in the United States. A search of the ClinicalTrials.gov database shows over 500 active treatment trials involving cisplatin, which is indicative of its ongoing widespread clinical use. Cisplatin nephrotoxicity can present with various types of symptoms such as acute kidney injury (AKI), hypomagnesemia, fanconi-like syndrome, distal renal tubular acidosis, hypocalcemia, renal salt wasting, and hyperuricemia[3]. However, the most serious and one of the more common side

effects is AKI, which occurs in 20-30% of patients. This review focuses on the general mechanisms of cisplatin-induced AKI and strategies for protecting the kidneys from the toxic effects without lowering the tumoricidal activity.

Cisplatin Nephrotoxicity

1. Cisplatin and its side effects on the kidney

An estimated 20% of patients receiving high-dose cisplatin have severe renal dysfunction and approximately one third of patients experience kidney injury just days following initial treatment[1]. The pathophysiological phenomena of cisplatin-induced kidney injury include sequential induction of renal vasoconstriction, decrease in renal plasma flow, reduction of glomerular filtration rate, and increase of serum creatinine, as well as a reduction in serum magnesium and potassium levels. The long term effects of cisplatin are not quite understood, but it is believed that cisplatin may lead to a permanent reduction of renal function. The pathophysiological basis of cisplatin-induced nephrotoxicity has been studied over the last few decades. The key pathological occurrences in cisplatin nephrotoxicity are renal tubular cell injury and death. A vigorous inflammatory reaction and activation of inflammasomes are also stimulated, further exacerbating renal damage. In addition, cisplatin may cause renal vasoconstriction through injury on the renal vasculature, which reduces blood flow, causing ischemic damage to the kidney and affects the glomerular filtration rate. Finally, a series of adverse reactions trigger acute renal failure. Even though nephrotoxicity can be controlled by diuretics and adequate hydration of patients, its prevalence is still high.

2. Cisplatin uptake and metabolism in the kidney

Transporters are important mediators of the specific cellular uptake of many drugs including cisplatin. There are several transporters that facilitate the movement of cisplatin across the plasma membranes: copper transporter-1 (CTR1), copper transporter-2 (CTR2), P-type copper-transporting ATPases (ATP7A and ATP7B), organic cation transporter-2 (OCT2), and multidrug extrusion transporter-1 (MATE1)[4]. The renal accumulation of cisplatin is greater than in other organs, and this is a major route for its excretion. While CTR1, CTR2, ATP7A, and ATP7B are ubiquitously expressed, OCTs and MATE1 are highly expressed in secretory organs such as the liver and kidney, and are important as mediators of specific organ toxicities. OCTs transporters have a species- and subtype-specific expression in organs. Human OCT2 (hOCT2) is highly expressed in the basolateral membrane of the renal proximal tubular cells while hOCT1 is locally expressed in the sinusoidal membrane of hepatocytes[5]. Conversely, both OCT1 and OCT2 in rodents show a high level of renal expression particularly in the basolateral membrane of proximal tubular cells, with a higher expression of OCT2 in male animals[6]. In a functional study, Ciarimboli et al. genetically deleted OCT1 and OCT2 genes from mice and investigated the importance of these transporters in the development of acute cisplatin toxicities *in vivo*[7]. OCT1 and OCT2 knockout (KO) mice developed a much milder form of nephrotoxicity under acute conditions with cisplatin compared to wild-type (WT) mice, and they were also protected against cisplatin-related ototoxicity[7,8]. The concept of a protective therapy that reduces cisplatin toxicities by interfering with its uptake by CTRs and OCTs appears very attractive, however, it is important not to compromise the aim of therapy, which is the uptake of the drug into target tumor cells[9].

Once cisplatin is transported into the cell, it may interact with various target molecules and before being converted to a more potent toxin. It has been suggested that the nephrotoxicity of cisplatin in the kidney may depend on metabolic activation involving a pathway that includes glutathione-S-transferase and γ-glutamyltranspeptidase (GGT)[10]. Inhibition of either one of these enzymes leads to the attenuation of cisplatin nephrotoxicity in mice[11]. Notably, prostate cancer xenografts overexpressing GGT, were more resistant to cisplatin chemotherapy, suggesting that inhibition of the cisplatin activation pathway may reduce renal toxicity[12]. As the glutathioneconjugates pass through the kidney, they are cleaved by GGT expressed

on the surface of the proximal tubular cells, to form cysteinyl-glycine conjugates[13]. The cysteinyl-glycine conjugates are further metabolized to cysteine-conjugates by aminodipeptidases, which are also expressed on the surface of the proximal tubular cells. Subsequently, the cysteine conjugates are transported into the proximal tubular cells, where they are further metabolized by cysteine-S-conjugate beta-lyase to highly reactive thiol molecules[14].

3. Mechanisms of cisplatin-induced cytotoxicity

Cisplatin-induced renal injury can be pathophysiologically classified into four types as follows, tubular toxicity (cell death by apoptosis or necrosis), vascular damage (renal vasoconstriction), glomerular injury (damages on glomerular compartments including capillaries, basement membrane, podocytes, mesangial cell, and parietal cells), and interstitial injury (damages by inflammatory responses). The stepwise and complex processes that can result in renal damage are caused by the accumulation of potentially toxic compounds in the tubular fluid, which then diffuse into the highly permeable tubular cells. Cisplatin, a low molecular weight uncharged molecule, is freely filtered at the glomeruli, taken up by renal tubular cells and ultimately reaches its highest gradient in the proximal tubular inner medullae and outer cortices[15]. Therefore, these areas are the dominant sites for cisplatin-induced renal injury, which in turn, causes injury to other tubular areas including the distal and collecting tubules[16].

However, renal damage through tubular cell death is a common histopathological feature of cisplatin nephrotoxicity. The mechanisms of cisplatin-induced nephrotoxicity are complex and involve numerous cellular processes including oxidative stress, apoptosis, and inflammation[17]. For instance, cell death in the form of both necrosis and apoptosis has been identified. Several apoptotic pathways have been implicated in cisplatin-induced renal epithelial cell death. These include the extrinsic pathway activated through the tumor necrosis factor (TNF) and Fas, cell death receptors, as well as the intrinsic mitochondrial and the endoplasmic reticulum (ER) stress pathways.

The renal cellular pathways affected by cisplatin injury have been examined primarily *in vitro* using freshly isolated and cultured renal tubular epithelial cells. *In vitro*, low concentrations of cisplatin result in apoptotic cell death while necrosis ensues at higher concentrations[18]. *In vivo*, nephrotoxic doses of cisplatin generate a large increase in both necrosis and apoptosis in the kidney[19]. In the extrinsic pathway, ligands bind to the death receptors on the plasma membrane, with recruitment and activation of caspase-8, which further activates downstream caspases inducing apoptosis[20]. It is known that the major death receptors are Fas, TNF-alpha (TNF-α) and TNF-receptor (TNFR) 1 and 2. There is ample evidence supporting the activation of death receptor pathway by cisplatin. Tsuruya et al. observed that TNFR1- and Fas-deficient renal epithelial cells are resistant to cisplatin-induced cell death[21]. Seth et al. identified that cisplatin increases the activity of caspase-8[22]. Takeda et al. showed that inhibition of caspase-8 reduces cisplatin-induced cell death in *vitro*[23]. In addition, there is also considerable evidence that cisplatin activates the intrinsic mitochondrial pathway. The involvement of the intrinsic apoptotic pathway in cisplatin-induced renal injury was initially suggested by studies showing Bax accumulation in mitochondria, cytochrome c release, activation of caspase-9, and apoptosis in cultured renal cells[24]. In addition, the endoplasmic reticulum (ER) stress pathway involves activation of caspase-12 and Ca^{2+}-dependent phospholipase A2, and pharmacological inhibition of these enzymes reduces cisplatin-related apoptosis[25].

However, cell cycle regulators also play a pivotal role in renal cell injury[26]. In brief, many normally quiescent kidney cells enter the cell cycle following acute kidney injury. Control of the cell cycle is determined by the sequential activation and inhibition of cyclin-dependent kinases (CDK), like CDK2. The CDK inhibitor p21is upregulated by cisplatin and plays a protective role against cisplatin toxicity. Therefore, overexpression of p21 inhibits cisplatin-induced apoptosis *in vitro* while mice lacking the p21 gene are more susceptible to cisplatin renal toxicity *in vivo*[27]. p53 is known as a major mediator of cisplatin-induced cell death, and p53 tumor suppression induces

cell cycle arrest or apoptosis in response to DNA damage, oncogene activation, and hypoxia[28]. Cisplatin induces activation of p53 in the kidney *in vivo*[29], and the renal epithelial cells *in vitro*[22]. Pharmacological or genetic inhibition of p53 activation reduces the activation of caspases, induction of apoptosis, and renal injury by cisplatin *in vitro*, and *in vivo*[30].

In addition, cellular stress induced by cisplatin activates mitogen-activated protein kinases (MAPK) pathways including extracellular signal-regulated kinases (ERK), p38, and c-Jun N-terminal kinases (JNK). Specific inhibition of p38, MAPK, ERK or JNK reduces caspase activation, apoptosis, the inflammatory response, and renal injury[31]. Cisplatin-induced generation of reactive oxygen species (ROS) is directly related to its cytotoxicity. Cisplatin-induced injury associated with ROS generation can be improved by free radical scavengers[32], iron chelators[33], superoxide dismutase (SOD)[34], catalase[35], selenium, Vitamin E[36], and heme oxygenase-1 induction[37].

ROS directly target the lipid components of the cell membrane causing peroxidation and denaturation of proteins, which finally leads to enzymatic inactivation. ROS are produced by the xanthine-xanthine oxidase system, mitochondria, and NADPH oxidase in cells. Following treatment with cisplatin, ROS are produced throughout these systems and are implicated in the pathogenesis of acute renal injury[38]. Cisplatin triggers enzymatic activation of glucose-6-phosphate dehydrogenase (G6PD) and hexokinase, which raise the free radical production and deplete the antioxidant production[39]. Also, cisplatin increases the intracellular calcium level, which activates NADPH oxidase and stimulates ROS production by damaged mitochondria[38]. In addition, free radicals can also cause mitochondrial dysfunction[39]. Cisplatin has negative inhibitory effects on antioxidant enzymes, and therefore significantly decreases the renal activities of SOD, glutathione peroxidase, and catalase[40]. Reactive nitrogen species (RNS) have also been studied in cisplatin-induced nephrotoxicity. Cisplatin increases the production of peroxynitrite and nitric oxide in the kidney tissues of rats[41]. Peroxynitrite induces changes in the structure and function of proteins, lipid peroxidation, chemical cleavage of DNA, and a reduction in cellular defenses by oxidation of thiol pools.

There is growing recognition of the importance of inflammation in cisplatin-induced nephrotoxicity and cellular toxicity. Over the past decades, a number of mediators of inflammatory renal injury have been identified including direct injury by cisplatin, damage-associated molecular patterns (DAMPs) through Toll-like receptor 4 (TLR4), vicious cycle with NF-κB activation and cytokines/chemokines, as well as activation of immune cells[3]. TNF-α is the typical inflammatory cytokine and plays a central role in many infectious and inflammatory diseases. An increase in the renal expression of TNF-α was demonstrated in mouse models of cisplatin nephrotoxicity[42]. More recently Oh et al. identified the pivotal role of TNF-α and other inflammatory cytokines like IL-1β and IL-6 in the cisplatin-induced nephrotoxicity model[43]. To address the functional role of TNF-α in the pathogenesis of cisplatin-induced acute renal failure, renal function and histology were examined in mice treated with cisplatin in the presence or absence of TNF-α inhibitors as well as in TNF-α KO mice[44]. TNF-α inhibitors reduced cisplatin-induced renal dysfunction and histological evidence of injury. Moreover, TNF-α KO mice sustained less kidney injury than WT mice and had markedly higher survival rates following cisplatin injection[44]. These results have been confirmed by a number of other studies[45] and establish an important role for TNF-α in the pathogenesis of cisplatin nephrotoxicity. TNF-α can be produced by a variety of non-immune cells as well as immune cells. However, Zhang et al. were able to determine the source of the TNF-α that was responsible for cisplatin-induced renal damage. They created chimeric mice in which TNF-α could be produced by resident kidney cells or by circulating immune cells, and evaluated kidney function, histology, and cytokine expression in these chimeric mice following cisplatin administration. In this study, they demonstrated that the local production of TNF-α by resident kidney cells, probably the renal epithelial cells themselves, was crucial to cisplatin-induced nephrotoxicity[46]. The produc-

tion of TNF-α by cisplatin is highly dependent upon ROS, NF-κB activation and activation of p38 MAPK[47]. The biological activities of TNF-α are mediated by two distinct receptors, TNFR1 (p55) and TNFR2 (p75) while many of the cytotoxic and proinflammatory activities of TNF-α are mainly mediated by TNFR1[48]. However, studies using TNFR1- or TNFR2-deficient mice revealed that the cisplatin-induced nephrotoxicity is mediated mainly through TNFR2 rather than TNFR1[49].

The expression of a number of inflammatory cytokines and chemokines is increased in the kidney following cisplatin treatment. Faubel et al.[50] and Lu et al.[51] determined that the expression of IL-1β, IL-18, CX3CL1, and IL-6 in kidney tissue were increased by cisplatin administration, in mice. Additionally, deletion of caspase-1, which is responsible for the formation of active IL-1β and IL-18 through activation of inflammasomes, reduced cisplatin induced renal injury and neutrophil infiltration in the kidney *in vivo*[52].

Protection against cisplatin-induced renal dysfunction

1. Renoprotective approaches

Active hydration with saline and simultaneous administration of mannitol before, during and after cisplatin treatment, significantly reduce cisplatin nephrotoxicity and this strategy has been accepted as the standard of care for reducing the associated side effects[53]. The detailed mechanism surrounding the benefits of salt is uncertain, but volume expansion with saline or hypertonic saline may increase the rate of cisplatin excretion. In addition, salt provides a high concentration of chloride ions that competitively prevent the dissociation of the chloride ions from the cisplatin molecule, thereby reducing the formation of the reactive form of cisplatin[54]. A recent study demonstrated that saline does not reduce the cellular accumulation of cisplatin but instead, activates a stress response within the cell that modifies sensitivity to cisplatin. The osmotic stress decreases the accessibility of cisplatin to DNA, induces proximal tubular cell resistance to the apoptotic pathway, and changes the metabolic activation of nephrotoxins. However, this approach may interfere with the antineoplastic activity of cisplatin by blocking tumoricidal effects.

In a rat model, the combination of allopurinol and ebselen reduces cisplatin nephrotoxicity and ototoxicity[55]. Allopurinol, which is a xanthine oxidase inhibitor, potentially reduces ROS generation. Ebselen, a glutathione peroxidase mimetic, is a scavenger of peroxynitrite and can protect against lipid peroxidation in the presence of glutathione or other thiol molecules. In addition, ebselen has been evaluated in clinical trials for the treatment of acute ischemic stroke. Erdosteine, an enzymatic activator of G6PD, helps maintain the proper intracellular redox state and protects against oxidative stress[39]. Anedaravone and N-acetylcysteine can replete intracellular storages of reduced glutathione[56]. Slymarin, naringernin, vitamin C, and vitamin E are antioxidant compounds that have also been found to have renoprotective functions in animal studies[40].

Salicylates are typical anti-inflammatory drugs for the treatment of a broad range of inflammatory disorders. Their anti-inflammatory action is attributed to the inhibition of cyclooxygenase activity and prostaglandin synthesis. Moreover, high doses of salicylates can stabilize the inhibitor of kppa B (IκB) enzyme as well as reduce NF-κB transcriptional activity, and these effects attenuate TNF-α generation and reduce renal inflammatory response in the cisplatin toxicity models. Salicylates do not disturb the anti-neoplastic activity of cisplatin. No reduction in tumor killing is found when cisplatin is administered in conjunction with sodiumsalicylate[19]. This may be explained by the fact that cisplatin renal toxicity is mediated via TNFR2, whereas the anti-tumor effect of TNF-α is mediated by TNFR1. Moreover, inhibition of NF-κB as a cell survival factor, by salicylate, might improve the effectiveness of chemotherapy[41]. α-Melanocyte stimulating hormone (α-MSH) and IL-10, which suppress TNF-α production, attenuate cisplatin-induced renal injury in animal models[57]. Fibrates inhibit accumulation of free fatty acid and suppresses apoptosis by preventing the release of cytochrome

c from mitochondria and by inhibiting the transfer of Bax proteins from the cytoplasm to mitochondria in the *in vitro* model. Fibrates have been shown to prevent cisplatin-induced renal toxicity in an animal study[58].

Resveratrol (3, 5, 4'-trihydroxystilbene) is a polyphenolic phytoalexin that naturally exists in many plant parts and products, such as berries, grapes, peanut skins and red wine[59] and has numerous beneficial effects on health. Resveratrol has been postulated to explain the protective effects of red wine on the cardiovascular system, and the effects of this compound are exerted by several mechanisms including antioxidant[60]. Especially, resveratrol has shown the protective activities for cisplatin induced cytotoxicity and nephrotoxicity through reduction of oxidative stress and deacetylation of p53, free radicals, and inhibition of inflammatory responses *in vitro* and *in vivo*[61-63]. Conversely, sirtuin 1 (SIRT1), an NAD^+-dependent deacetylase, is implicated in calorie restriction (CR)-induced extension of the lifespan and delay of age-related diseases[59]. The enzymatic activation of SIRT1 exerts cytoprotective effects through several mechanisms including anti-apoptosis, antioxidative and anti-inflammatory effects as well as the regulation of mitochondrial biogenesis, autophagy and metabolism in response to cellular energy and redox status[64]. Resveratrol has been shown to activate SIRT1[65] and numerous studies have shown that resveratrol can prevent many diseases, such as cancer, cardiovascular disease, cognitive disorders, diabetes, neurodegenerative disorders, and kidney diseases through by this mechanism[66]. Thus, resveratrol exerts cytoprotective effects through at least two mechanisms, which are antioxidant activity and SIRT1 activation.

2. New approach to overcoming nephrotoxicity

There is no special treatment to protect cancer patients against cisplatin-induced renal dysfunction or injury. These patients need to be carefully monitored to ensure adequate hydration and electrolyte treatment to avoid renal injury. However, there are reports of the remarkable beneficial effects of the enzymatic activation of NADH: quinone oxidoreductase 1 (NQO1) by β-lapachone (3, 4-dihydro-2, 2-dimethyl-2H-naphto [1, 2-b] pyran-5, 6-dione), The NQO1-mediated effects are evident on several characteristics of metabolic syndromes including, the prevention of health decline in aged mice, amelioration of obesity or hypertension, prevention of arterial restenosis, protection against salt-induced renal injury and cisplatin-induced nephrotoxicity and ototoxicity[43,67-73]. NQO1 is a cytosolic antioxidant flavoprotein that catalyzes the reduction of quinones to hydroquinones and detoxifies by utilizing NADH as an electron donor, which consequently increases intracellular NAD^+ levels[74]. Additionally, there is evidence that NQO1 has a role in other biological effects, including anti-inflammatory processes, scavenging of superoxide anion radicals, and stabilization of p53 and other tumor-suppressor proteins[75-77]. β-Lapachone (3, 4-dihydro-2, 2-dimethyl-2H-naphto [1, 2-b] pyran-5, 6-dione) is a well-known substrate of NQO1[78]. Meanwhile, cellular NAD^+ and NADH have been shown to be important mediators of energy metabolism and cellular homeostasis[43]. Since NAD^+ is used as a cofactor for various enzymes such as cyclic ADP-ribose synthases, poly (ADP-ribose) transferases, and SIRTs[79], the regulation of NAD^+ may have therapeutic potentials through its effect on NAD^+-dependent enzymes.

There are seven homologs of SIR2 (SIRT1-7) in mammals, which show differential subcellular localizations[80]. Nuclear-localized SIRT1 is activated under energy stress conditions including, fasting, exercise, or low glucose availability. SIRT1 has a pivotal role in hormone responses, metabolism, neurogenesis, development, stress response, and apoptosis[81] by deacetylation of target substrates, such as FOXO, histones, NF-κB p65, FOXO and p53[82]. In addition, recent studies suggest that SIRT1 regulates inflammatory responses through NF-κB p65 deacetylation. Mitochondrial SIRT3 regulates adaptive thermogenesis, cellular survival upon stress, energy homeostasis, and mitochondrial functions[83]. SIRT3 exerts antioxidative effects through the deacetylation and activation of mitochondrial isocitrate dehydrogenase 2 (IDH2), and the enhancement of the glutathione anti-

oxidant defense system. Furthermore, SIRT3 abrogates the p53 function through direct interaction and deacetylation of p53 inmitochondria[84].

Recently, we reported that β-lapachone prevents cisplatin nephrotoxicity. Our data showed that NQO1 enzymatic activation by β-lapachone suppresses cisplatin-induced renal injury by down-regulation of potential mediators of renal damage[43]. Cisplatin causes renal injury through a sequence of events that include tubular cell death and tissue damage by inflammatory cytokine TNF-α secretion, and a vicious cycle of oxidative stress, NF-κB activation, and inflammatory responses. Mechanistically, the cellular level of NAD^+ was elevated by NQO1 enzymatic action using β-lapachone, which in turn activated the deacetylase enzymes SIRT1 and SIRT3. The activated SIRT1 and SRT3 enzymes further deacetylated p65 and p53 in the nuclei and mitochondria, and thereby attenuated inflammation and tissue damage. Furthermore, β-lapachone did not interfere with the tumoricidal effect of cisplatin *in vivo*[43]. Therefore, we strongly suggest that direct modulation of cellular NAD^+ levels by pharmacological agents could be a promising therapeutic approach for the treatment of various diseases, including cisplatin nephrotoxicity.

Conclusion

In this review, we focused on the pathophysiology of renal injury caused by cisplatin, an important chemotherapeuticagent. Cisplatin has been administered for the treatment of several malignancies, such as head and neck cancer, ovarian cancer, testicular cancer, and in particular, lung cancer. Numerous studies have shown its efficacy, but the side effects such as nephrotoxicity, ototoxicity and neuropathy have been a problem. Hydration was beneficial, but its efficacy was still limited in a high percentage of patients. Cisplatin-induced renal cell death involves multiple pathways including activation of intrinsic and extrinsic apoptotic pathways, oxidative stress, inflammatory responses, etc. Unfortunately, many of these pathways contribute to the cisplatin-induced cytotoxic actions on tumor cells. However, recently reported our work, may seems to be one of the best ways to protect renal tissue from cisplatin induced injuries without the reduction of tumoricidal activity of the drug, which is utilizing enzymatic activation and subsequent regulation of intracellular metabolites and signaling molecules[43]. Thus, specialized strategies targeted at attenuating cisplatin-induced renal injury may have the unintended consequence of reducing its anti-tumor actions. The design of preventive strategies must, therefore, be carefully considered to overcome this risk.

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