FACTA UNIVERSITATIS
Series **Medicine and Biology** – ONLINE FIRST https://doi.org/10.22190/FUMB230122002D

Review Article

CISPLATIN - AN OVERVIEW OF ITS EFFICIENCY AND TOXICITY

Marija Djordjević[1,2], Jovan Ilić[1,2], Nikola M. Stojanović[3]

[1]University Clinical Center Niš, Niš, Serbia
[2]Faculty of Medicine, University of Niš, Niš, Serbia
[3]Department of Physiology, Faculty of Medicine, University of Niš, Niš, Serbia

Abstract. *Cisplatin is the first heavy metal compound that has been found to possess antineoplastic activity. It is effective in treating testicular, ovarian, head and neck, bladder, cervical, esophageal tumors, and small cell lung carcinoma. Approximately 1% of cisplatin that enters the cell interacts with DNA, forming DNA-cisplatin bonds. Both apoptosis and necrosis can be found in the same population of cells exposed to cisplatin, and the mode of cell death depends on the cisplatin concentration and metabolic state of the target cell. In the bloodstream, the platinum component of cisplatin binds to the blood's proteins (hemoglobin, albumin and transferrin), and other significant portion binds to the glutathione and other cysteine-rich biomolecules. Cisplatin impairs the mitochondrial and cell antioxidant defense system (decreases GSH, NADPH levels, GCH/GSSG ratio, and increases GSSG levels) leading to oxidative stress. There are three main mechanisms of cell resistance to cisplatin: (1) enhanced repair of cisplatin-induced DNA lesions, (2) decrease in uptake and/or increase in efflux and (3) inactivation of cisplatin intracellularly. The usage of cisplatin is limited due to its toxicity and side effects, which include neurotoxicity (numbness and tingling, paresthesia, reduced deep tendon reflexes), nephrotoxicity (renal insufficiency, hypomagnesemia), ototoxicity (tinnitus and bilateral high-frequency hearing loss), cardiotoxicity (changes in electric heart activity, congestive heart failure), gastrotoxicity (nausea, vomiting, and dyspepsia), etc. So far, there has been no effective, clinically administered, therapy for cisplatin-induced toxicity.*

Key words: *cisplatin, oxidative stress, drug resistance, apoptosis, toxicity*

INTRODUCTION

Cis-diamminedichloroplatinum (II) (cisplatin) is the first heavy metal compound that has been found to possess antineoplastic activity. It was discovered in 1965 by accident, when a group of scientists was experimenting with the effects of electric dipoles on cellular growth and division. During the experiments, it was noticed that the compound released from the electrodes was responsible for the inhibition of *Escherichia coli* division [1]. Following this finding, cisplatin was further tested on mice with solid sarcoma tumors and in those experiments cisplatin completely inhibited further tumor growth and development. Clinical testing started in 1971, and the approval from the United States Food and Drug administration (the FDA) was granted in 1978 [2].

Cisplatin is a compound with square planar configuration with a central atom of platinum linked to two chloride, vital groups, and two NH_3 groups [3]. At room temperature, it appears as a white or dark yellow to yellow-orange crystalline powder. Under normal temperature and pressure, cisplatin is found to be stable with a water solubility of 2.53 g/L at 25 °C. Cisplatin has a molecular weight of 301.1 g/mol, a density of 3.74 g/cm^3, a melting point of 270 °C, a log Kow of 2.19 [4].

CISPLATIN AS A CHEMOTHERAPEUTIC OF CHOICE

Cisplatin is the most effective in treating testicular, ovarian, head and neck, bladder, cervical, and esophageal tumors, as well as small cell lung carcinoma (SCLC) [5]. However, its usage is limited due to its toxicity and side effects, which include neurotoxicity, nephrotoxicity, ototoxicity, cardiotoxicity, hepatotoxicity and gastrotoxicity [6,7].

The mode of administration of cisplatin is intravenous as a short-term infusion with normal saline for the treatment of solid malignancies [8]. Cisplatin is used for various types of cancer as a monotherapy or in a combination with other hemiotherapeutic drugs such as docetaxel, cetuximab, paclitaxel, 5-fluorouracil,

Correspondence to: Nikola Stojanović
Department of Physiology, Faculty of Medicine, University of Niš, Bulevar dr Zorana Djindjića 81, 18000 Niš, Serbia
E-mail: nikola.st90@yahoo.com
Received January 22nd, 2023 / Revised April 19th, 2023 / Accepted April 24th, 2023

doxorubicine, vincristine, etoposide, citarabine, etc. As a monotherapy, cisplatin is used in the treatment of gynecological carcinoma, *ie*. cervical carcinoma, ovarian tumors, and cancer of the vulva and vagina in a dose of 40 mg/m^2, weekly in combination with irradiation therapy [9].

Combination therapy regimens are used in the treatment of gastric carcinoma as PF regimen (cisplatin in the dose of 100 mg/m^2 and 5-fluorouracil in the dose of 1000 mg/m^2 for 21 days), pancreatic cancer and hepatobiliary carcinoma as GC regimen (cisplatin in the dose of 75 mg/m^2 and gemcitabin). In the treatment of testicular cancer cisplatin is applied in combination with etoposide (EP), etoposide and ifosfamide (VIP), and etoposide and bleomicine (BEP) [10]. Etoposide and cisplatin (CUP) regimen is also used in the treatment of neuroendocrine tumors, lung tumors, and carcinoma of unknown primary origin. Combination with 5-fuorouracil and docetaxel regimens with cisplatin (PF and TPF) are used in the treatment of head and neck cancers [11]. All of these regimens must include rehydration and gastroprotective drugs applied together with the chemotherapeutics.

Radiotherapy and CP are known to have synergistic effect. Firstly chemotherapy increases the sensitivity of the tumor to radiation. It has been shown that CP inhibits sublethal damage repair caused by previously administered radiotherapy and furthermore, radiotherapy can be used to treat local disease while treating systemic disease with CP [12]. Radiotherapy can be used in combination with CP-protocols for the treatment of cervical cancers, and is mostly effective in Ib stage (before surgery) or Ia stage (after surgery) [13]. But research shows that combination therapy is superior in treatment of locally advanced cervical cancer as opposed to CP alone [12].

Concomitant chemo-radiotherapy was proven to lead to complete response in up to 75% of patients with locally advanced head and neck carcinomas, and this was predominantly used in the case of nasopharyngeal carcinoma [14]. It can be used as a treatment regimen for HPV positive laryngeal carcinoma, while it was shown that HPV positive cancer cells have a satisfactory response to chemo-radiotherapy. The preferred route is 3-weekly CP (100 mg/m2) given on days 1, 22, and 43 of concomitant RT (fractionated – 70Gy) [15,16]. *ESMO* In the treatment of bladder cancer, Eapen and co-workers applied CP arterially with the concomitant use of radiotherapy. Their strategy resulted in a high rate of tumor eradication and normal bladder function thus avoiding cystectomy [17].

MECHANISM OF ACTION OF CISPLATIN

In the bloodstream, where the chloride concentration is high (ranging from 96 to 106 mEq/L), the two chloride groups in the molecule are stable, and the platinum stays coordinated to its chloride ligands. However, after the diffusion of the drug into the intracellular compartment, in an environment with a reduced concentration of chlorides, chloride groups of cisplatin are replaced by the water of hydroxyl groups, thus creating a molecule that can interact with intracellular nucleophilic molecules [3,8]. The resulting aquated cisplatin can react with nucleic material (DNA, RNA), proteins, thiol group-containing molecules such as cysteine, methionine, and glutathione, membrane phospholipids, etc [18].

Interaction with nucleic acids and cell death induction

It has been shown that approximately 1 % of cisplatin that enters the cell interacts with DNA.,, Therefore less than 1% of cisplatin-induced damage is caused by DNA-cisplatin bonds [19]. The intrastrand cross-link between cisplatin and DNA is the most frequent damage of the DNA molecule (figure 1). More prone to cisplatin binding are sites containing purine bases, particularly two adjacent guanines (65%), and adenine and guanine (25%) or two guanines separated by any other base (10%) [18, 20]. The most common cisplatin-DNA adduct formation is through the covalent binding of cisplatin to the N7 positions of the imidazole ring (figure 1) [21]. Cells arrested in the corresponding phase of the cell cycle initially attempt to repair the DNA damage, after failing to do so, aberrant mitosis of the cells carrying damaged DNA follow the apoptosis/necrosis pathway. Both types of cell death were found in the same population of cells, depending on the concentration of cisplatin and the metabolic state of the cell [22].

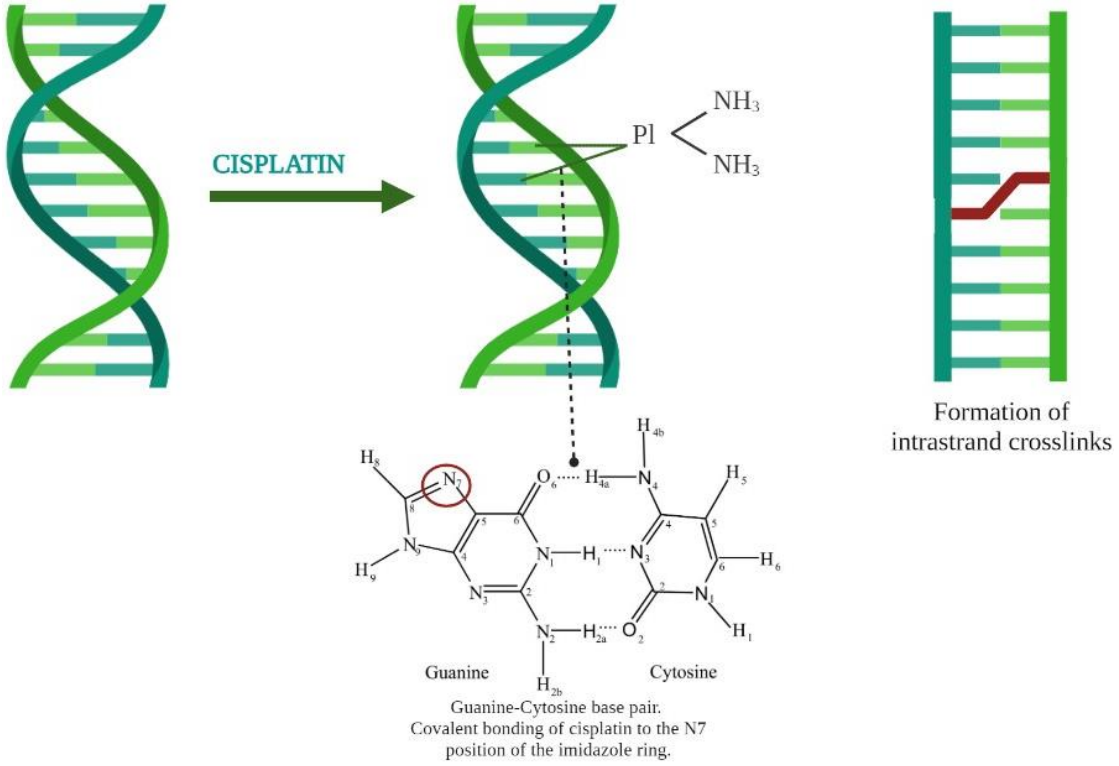


Fig. 1 Formation of cisplatin – DNA adducts.

Apoptosis is induced in cells exposed to lower concentrations of cisplatin (<100 μM) [23]. Cisplatin-induced apoptosis depends on cell type and it mainly involves the activation of tumor protein 53 (p53) and phosphorylation of activator protein (AP-1) leading to cell cycle arrest by down regulating cyclins and cyclin-dependent kinases (p38 mitogen-activated protein kinase, c-jun N-terminal kinases, protein kinase C) [21, 24]. It has been shown that cisplatin activates both intrinsic and extrinsic apoptotic pathways (figure 2). In reaction to proapoptotic stimuli, first, the initiator caspases such as caspase-2, -8, -9, or -10 are activated, and they further activate the executioner caspases (caspase-3 or -7). The intrinsic pathway includes the alteration of the mitochondrial membrane potential, release of cytochrome C (cyt C) and mitochondria-derived activator of caspases such as second mitochondria-derived activator of caspase (Smac/DIABLO) [25, 26]. In the presence of adenosine triphosphate (ATP) and cyt C, the apoptotic protease-activating factor-1 binds to caspase-9, activating it, further leading to the activation of caspase-3 (figure 2) [27]. The extrinsic pathway is activated through the cisplatin interaction with phospholipids in the cell membrane, thus causing cell membrane destabilization, an increase in its permeability, a reduction in the activity of some ion channels and an alteration in cholesterol metabolism [28, 19].

At higher concentrations of cisplatin, apoptosis is activated, but arrested at the level of effector caspases (blocked by cisplatin), when the cell transfers to a different mode of cell death *ie*. necrosis. Necrosis in this case occurs due to NAD^+/ATP depletion when the levels of ATP reach lethal points. This is explained by the damage that cisplatin causes to the molecules involved in cellular energy supply and also to proteins involved in the apoptotic process (p53, Bax, Bcl-2 and caspases) [29].

To date, we have had no complete comprehension of the effects that cisplatin has on RNA. Melnikov and co-workers [30] showed cisplatin-RNA binding when highly distorted folds of an RNA molecule are formed. They have identified nine cisplatin modification sites, specifically on non-Watson-Crick segments of the ribosomal RNA. They also showed that cisplatin does not affect the binding of ribosomal substrates, but stimulates the formation of non-productive ribosomal structures, thus leading to reduced protein production [30,31].

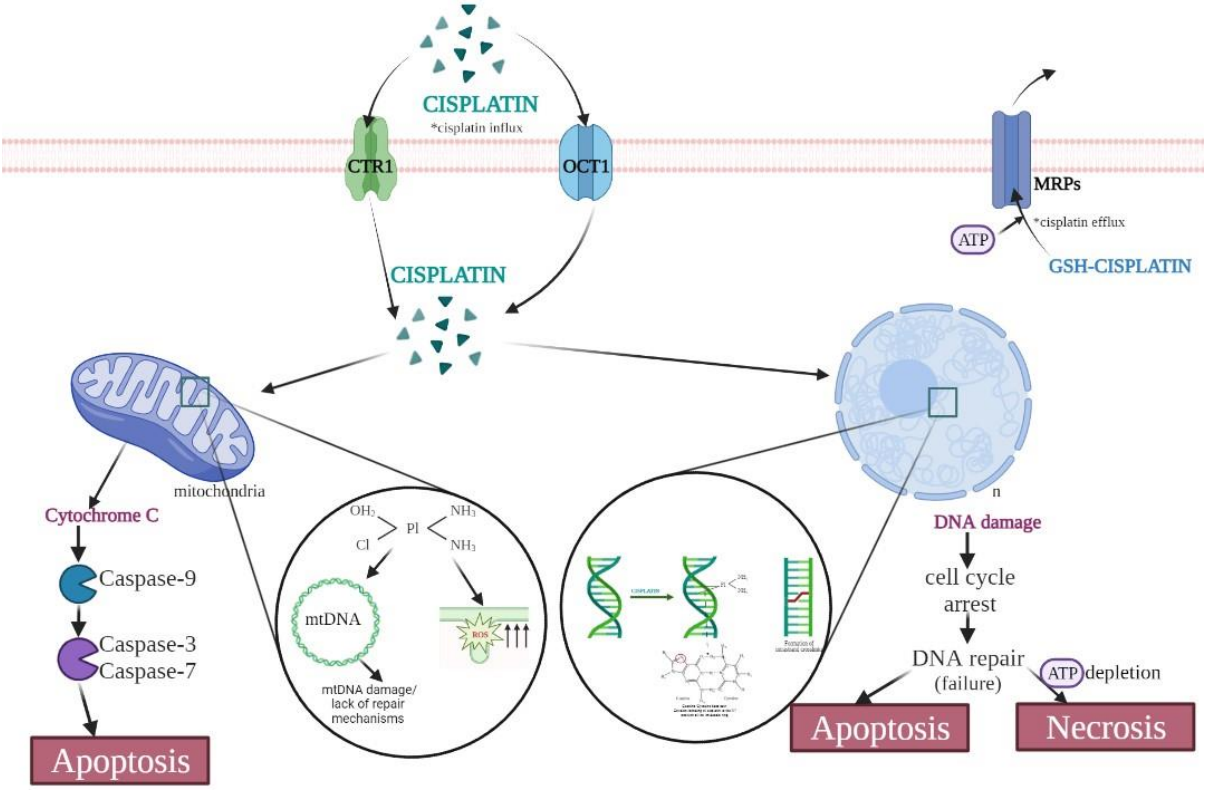


Fig. 2 Effects of cisplatin on mitochondria and DNA. Cell death induction by cisplatin. CTR1 – coper transporter 1; OCT 1 – organic cation transporter 1; MRP - Multidrug-resistance-associated proteins.

Cisplatin and protein interaction

In the bloodstream, the platinum component of cisplatin binds to the proteins of the blood (hemoglobin, albumin and transferrin), and another significant portion binds to the glutathione and other cysteine-rich biomolecules [32]. Also, cisplatin interacts with transport molecules, responsible for copper transportation, Copper TRansport (Ctr) protein family, like Ctr1 and possibly its homologue Ctr2 [33].

In recent years a good amount of research has been dedicated to the determination of the structure of cisplatin-protein adducts and the exact sites this binding occurs, using mass spectrometry, nuclear magnetic resonance spectrometry, X ray crystallography, and also gel electrophoresis followed by Coomassie blue staining. Using the above-mentioned technics several more cisplatin-binding proteins have been identified, including myosin II A, heat shock protein 90, ribosomal protein L5, and explained the interactions with insulin, cyt C, calmodulin, hemoglobin and myoglobin, ubiquitin, α2-macroglobulin, α1-anti-trypsin, apolipoprotein A1 and A2 [34-36]. Recently it has been found that cisplatin-protein adducts are removed by glutathione (GSH) via the creation of protein-cisplatin-GSH intermediates [37].

Cisplatin and oxidative stress

Previous scientific convictions that the main mechanism of cisplatin cytotoxicity is DNA damage, have now been shown to be secondary to the oxidative damage of cell membrane components and the depletion of energy within the cells. Cisplatin impairs the mitochondrial antioxidant defense system (decreased GSH, NADPH levels, GCH/GSSG ratio, and increased glutathione- disulfide (GSSG) levels). Decreased levels of GSH and the accumulation of GSSG can be secondary to lower levels of glutathione reductase activity. This GSH depletion is a critical event in cisplatin-induced lipo-peroxidation and subsequent toxicity. The oxidation of cardiolipin (CL), an anionic phospholipid in the inner mitochondrial membrane (IMM) responsible for its fluidity and stability, is a key molecule associated with mitochondrial damage. Cardiolipin is an integral part of the mitochondrial bioenergetics process, making contact with membrane transporters, respiratory chain complexes and proteins involved in energy transport, but is also involved in the mitochondrial apoptotic process. Decreased levels of CL lead to rigidity of IMM which can suppress the function of proteins and enzymes in the respiratory chain. The ADP/ATP carrier activity is also dependent on CL. Both of these mechanisms lead to the depletion of ATP [38]. Oxidation of CL also leads to the release of cyt C into the cytosol, which is deemed as an early event the mitochondria-mediated apoptotic cell death [39].

MECHANISMS OF RESISTANCE TO CISPLATIN

Most authors suggest three main mechanisms of resistance to cisplatin action: (1) enhanced repair of cisplatin-induced DNA lesions, (2) decrease in uptake and/or increase in efflux and (3) inactivation of cisplatin intracellularly [40]. Mechanisms of resistance were primarily studied in human ovarian cancer cells and L1210 mouse leukemia cells [41]. It has been shown that all three molecular mechanisms contribute, to a different extent, to the development of resistance, and that in every cell type more than one mechanism is in action.

Enhanced DNA repair

Nucleotides affected by cisplatin are excised from DNA during the process of DNA synthesis, which is mostly done by the nucleotide excision repair (NER) system [42]. This system consists of more than 20 proteins, of which for cisplatin-induced damage, the most important ones are excision repair cross-complementing rodent repair deficiency complementation group 1 (ERCC1), a single-strand DNA endonuclease [43]. Overexpression of ERCC1 is liked to poor survival rates and responsiveness to cisplatin [44]. This correlation has been observed in clinical studies for several human neoplasms including colorectal cancer, head and neck squamous carcinoma, mesothelioma, bladder, esophageal and ovarian cancers and NSLC [45-49]. Since higher levels of ERCC1 have been found in tumors clinically resistant to cisplatin and the fact that we can measure ERCC1 expression, either on mRNA level or protein level, ERCC1 is a valid marker of tumor responsiveness to cisplatin based regimens of treatment [50].

Cisplatin-induced lesions of DNA, such as insertions, deletions, and mismatches, can be detected by mismatch repair (MMR) system (mutL homolog 1 and 2 (MLH 1 and MLH 2)) [51]. These proteins can also detect interstrand adducts. The mechanism is as follows – MMR recognizes the mistake, attempts to repair it; fails in that attempt, thus sending pro-apoptotic signals [52]. Therefore tumor cells under express MMR system proteins to acquire resistance to cisplatin [53, 54]. Methylated MLH1 component is a negative predictor of survival in ovarian cancer patients, and low levels of MSH2 are a negative predictor of the efficiency of cisplatin therapy in patients with resected lung cancer [55].

Decrease in uptake and/or increase in efflux

Until recently it was believed that cisplatin enters the cells via passive diffusion [56], while the uptake is not concentration or time saturated, and also the uptake of cisplatin is slower than of similar compounds that are actively transported through the cell membrane [57]. However, it was observed that cell membrane transporters, primarily copper transporters, CTR1 and CTR2 are important for the uptake of cisplatin. This discovery was first proved in yeast culture, where knocking down CTR1 lowered the levels of transported cisplatin [58]. In the later studies on patients with ovarian cancer and NSCL on cisplatin–regime therapy, authors state that higher levels of CTR1 mRNA expression had a positive correlation with responsiveness and overall survival [59]. Opposite has been seen with CTR2, where lower levels of CTR2 expression are linked to an increased uptake and sensitivity to cisplatin [60]. The expression of these transporters can also be used as a biomarker of tumor sensitivity to cisplatin [61]. In line with this, pre-treatment with copper, protects the cells from cisplatin cytotoxicity, most likely by competitive binding to the transporters thus saturating them completely [62]. In contrast to that, copper chelators facilitate cisplatin intake and cytotoxicity [59]. Its important to note that cisplatin downregulates CTR1 by internalizing the membrane molecule.

Less important cisplatin- transporting molecules are some members of the organic cation transporter family (OCT), most notably OCT1 and OCT2. OCT1 also transports oxaliplatin and carboplatin. There is insufficient data regarding the importance of these transporters in relation to cisplatin resistance [60]. Efflux of cisplatin from the cell is also believed to be occurring via membrane transporters. The authors describe two transporters: P-type ATPase transporters and ATP-binding cassette transporters (ATP7A and ATP7B). Multidrug-resistance-associated proteins (MRPs), part of the ATP binding cassette transporters, are responsible for the efflux of glutathione-platinum conjugates [63].

Cytosolic inactivation of cisplatin

There are two main pathways of cytosolic inactivation of cisplatin: conjugation with GSH and binding with metallothionein proteins.

In the case of GSH, it is known that GSH can aid in lowering the cytotoxicity by extinguishing DNA-platinum adducts before their transformation to cytotoxic cross-links, or by forming complexes with cisplatin, thus reducing the available intracellular cisplatin [64]. Also, GSH as an antioxidant maintains the redox potential. The formation of these chelate complexes between cisplatin and GSH leads to faster elimination of cisplatin. A study by Godwin et al. [65] has shown that cisplatin-resistant cell lines of ovarian cancer show higher expression of γ-glutamylcysteine synthetase and y-glutamyl transferase, thereby showing the importance of GSH metabolism in cisplatin resistance. Thus, lower levels of GSH in cancer cells lead to higher cytotoxicity of cisplatin [66].

Metallothionein proteins are cysteine-rich proteins that bind metals such as copper, zinc, cadmium, and mercury. Their function is in the regulation of cellular metal homeostasis and as detoxifiers of heavy metals. The second role is their involvement in cisplatin resistance. Overexpression of these proteins leads to cisplatin resistance [67-69].

SIDE EFFECTS AND TOXICITY OF CISPLATIN

Nephrotoxicity

Cisplatin is eliminated by the kidneys via glomerular filtration and tubular secretion [70]. The process of cisplatin elimination begins with the formation of glutathione conjugates. These conjugates transform into cysteine glycine conjugates by glutamyl-transpeptidase (GGT), found on the brush border of proximal tubule cells. They are further metabolized into cysteine conjugates by cysteine-S-conjugate beta lyase, also found on the surface of proximal tubule cells. In the proximal tubule cells they are metabolized to highly reactive thiols (figure 3) [71-73], which react with macromolecules finally leading to the cell death. Hannigan and co-authors have shown that mice deficient in GGT were resistant to nephrotoxicity induced by cisplatin, and that inhibition of GGT by acivicin protects against cisplatin nephrotoxicity [74]. The inhibition of cysteine-S-conjugate beta lyase with aminooxyacetic acid is also found to protect mice exposed to cisplatin in a dose of 15 mg/kg [73]. Also, the concentration of cisplatin in the tubule cells is greater than the concentration in the blood, which suggests an accumulation of the drug in the renal tubule cells.

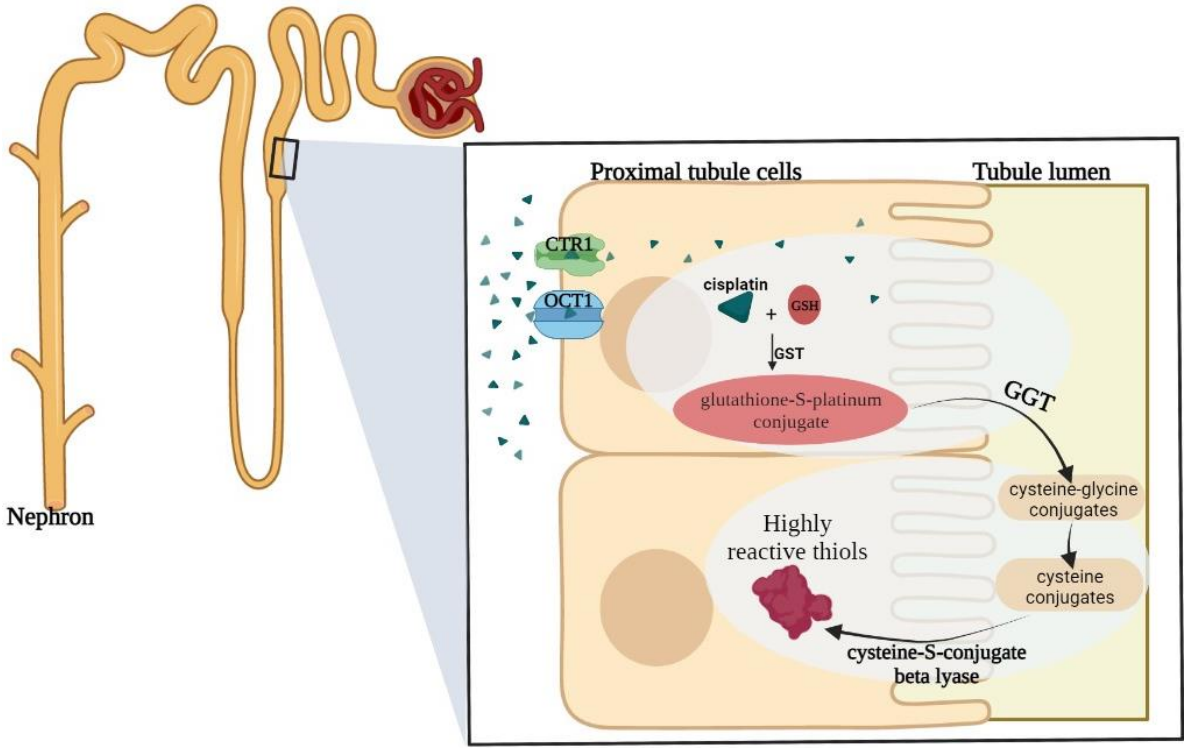
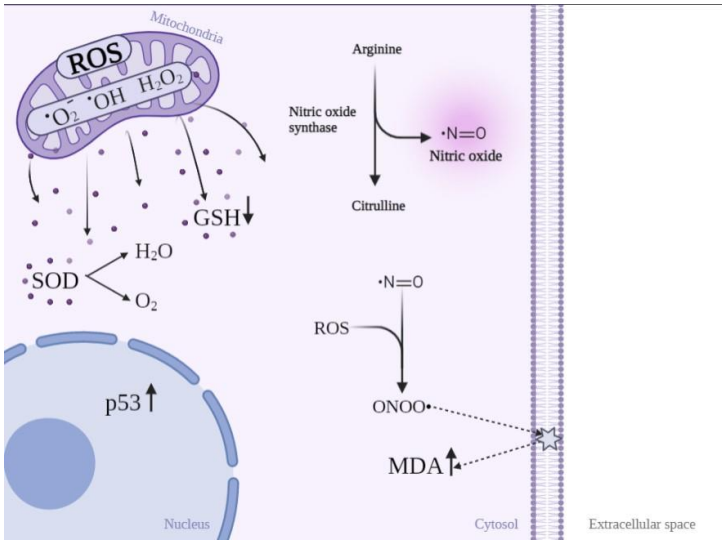


Fig. 3 Cisplatin effects on proximal tubule cells of the kidney. Metabolism and elimination of cisplatin.

Substantial evidence indicates that oxidative stress is involved in cisplatin-induced nephrotoxicity. Production of reactive oxygen species (ROS), depletion of antioxidant systems and stimulation of accumulation of lipid peroxidation products in the kidney are listed as the main mechanisms associated with cisplatin-nephrotoxicity. Oxidative metabolism is stimulated by cisplatin and the production of ROS in the damaged mitochondria, including superoxide anions ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2) and hydroxyl radicals ($OH^{\cdot}$), increases (figure 4). The produced ROS can impair antioxidant defense mechanisms such as GSH and SOD [75]. It is assumed that nitrosative stress is also involved in cisplatin-nephrotoxicity. Studies have shown that the cellular effects of ROS are enhanced by the production of nitric-oxide (NO), most likely as a consequence of the induced production by the inducible form of NOS, which leads to the continuous formation of peroxynitrite (ONOO), which further reacts with $O_2^{\cdot-}$ contributing to kidney damage by cisplatin (figure 4) [75]. One of the mechanisms of cisplatin toxicity and cell death involves the activation of p53 in renal cells, which has been proven to occur both in *in vivo* and *in vitro* conditions [76, 77].



Fig, 4 Schematic overview of oxidative stress and nitrosative stress in proximal tubule cells induced by cisplatin. Cisplatin induces elevation of ROS in mitochondria, which are released into the cytosol resulting in depletion in levels of GSH and SOD. ROS increases the production of NO, thus leading to increased production of ONOO, that damages the cell membrane, which leads to increased levels of MDA. SOD – superoxide dismutase; GSH – glutathione; ROS – reactive oxygen species; MDA - malondialdhyde; ONOO – peroxynitrite.

There is also some evidence that inflammatory cascades could contribute to cisplatin-induced nephrotoxicity. The expression of numerous inflammatory cytokines and chemokines increases in the kidney tissue after the application of cisplatin 78]. However, evidence for a functional role for many of these cytokines is missing. For example, some studies have determined that the expression of IL-1β, IL-18, CX3CL1 and IL-6 increases in cisplatin nephrotoxicity [79, 80].

Cisplatin causes tubule damage that leads to acute renal failure, vascular damage of small and medium arteries resulting in decreased blood flow, glomerular damage and long term use leads to chronic renal failure [81].

Part of the nephrotoxicity of cisplatin is due to vascular damage and vasoconstriction, which arise mainly from endothelial dysfunction and disorders of vascular autoregulation. Cisplatin may have direct toxic effects on the vascular endothelium and microangiopathy can cause a decrease in blood flow through the kidney, which can further lead to a decrease in glomerular filtration (GF) and hypoxic tubule damage [82]. Prolonged exposure to cisplatin lead to glomeruli damage. Cisplatin causes damage to the cells of glomerulus directly thus leading to morphological changes of the glomeruli and impaired permeability of the glomerular membrane causing proteinuria. Cisplatin alters glomerular filtration rate, mainly by decreasing permeability of the filtration membrane, which occurs as a result of the contraction of mesangial cells [83]. Cisplatin damages the proximal tubules, specifically the S3 segment of the outer medullary stripe. Intracellularly, we can detect the changes in the mitochondria and nuclear pallor in the distal nephron. On the glomeruli, there are no obvious morphological changes [70]. Electron microscopic studies show changes in the pars recta including profound thinning or focal loss of brush border, cellular swelling, condensation of nuclear chromatin, vacuolization of the cytoplasm, rounding of mitochondria with swollen cristae, increased number of pinocytotic vesicles and lysosomal bodies in the apical region bordering the lumen [84].

Cisplatin nephrotoxicity presents itself as renal insufficiency, several days after the dose administration, and can be found in 20-30% of patients. Renal insufficiency is manifested with high levels of creatinine, urea and uric acid in serum, and with lower serum creatinine clearance. More common kidney manifestations are hypomagnesiemia, *ie*. Falconi like syndrome [81]. The primary line in reducing nephrotoxicity is volume expansion with sodium chloride. In animal models many anti-inflammatory agents have been found to reduce nephrotoxicity, preventing inflammation and cell damage, like caffeic acid phenethyl ester and melatonin that prevent the overproduction of ROS and also alter GSH metabolism [85, 86]. There is some evidence that anti-TNF-α agents could reduce cisplatin nephrotoxicity [87].

Cardiotoxicity

Cisplatin cardiotoxicity is primarily associated with the changes in electric heart activity and are most commonly in the form of ventricular arrhythmias, supraventricular tachycardia, occasional sinus bradycardia, and atrial fibrillation [88]. Some authors have reported acute myocardial infarction, myocarditis, and pericarditis, as a manifestation of cisplatin toxicity. They concluded that the possible mechanism of cisplatin induces cardiac arrhythmias is due to the drugs effect on sodium ion channels [89]. Cisplatin also induces coronary vasospasm (a

step into the development of coronary artery disease) and increases von Willebrand factor which leads to endothelial injury. All of the above-mentioned changes due to cisplatin toxicity ultimately result in congestive heart failure and sudden cardiac death.

The underlying mechanism of cisplatin-induced cardiotoxicity is most likely oxidative stress. In cells, cisplatin shifts the redox balance by conjugation and depletion of glutathione, and induces damage to the mitochondria, therefore increasing ROS production [90]. Experimental studies on rat hearts treated with cisplatin showed increased levels of ROS and lipid peroxidation and decreased GSH levels and SOD activity [91].

Cisplatin also induces a destabilization and depolarization of mitochondrial membranes in cardiomyocites with visible mitochondrial ultrastructural abnormalities. As previously stated, cisplatin damages DNA in the nucleus, but cisplatin can also damage DNA in mitochondria. This damage to the mitochondria DNA, due to the sheer number and essential role in energy production causes damage in cardiomyocytes [92]. Cardiomyocytes of mice hearts treated with cisplatin showed signs of endoplasmatic reticulum stress and increased caspase-3 activity, with early apoptotic events happening at the level of mitochondrial transmembrane potential [93]. Cisplatin accumulates in the mitochondria where it causes an increase in ROS production. This leads to the development of mitochondrial dysfunction and damage, as well as the activation of pro-apoptotic molecules [94]. Energy depletion that happens due to mitochondrial dysfunction is also, a key component that leads to the death of cardiomyocytes. It has been shown that cisplatin inhibits fatty acid oxidation, a major energy source, and also inhibits cytochrome C oxidase, an important enzyme in mitochondrial respiratory function.

A small amount of research has been devoted to explaining the role of myocardial inflammation induced by cisplatin, but from the literature review, we can state that cisplatin activates pro-inflammatory factors that promote inflammation and cell injury in cisplatin-induced cardiac toxicity. Cisplatin induces the production of myocardial TNF-α and increases myocardial myeloperoxidase activity. Formed TNF-α then binds to its receptors and induces the recruitment of immune cells, mainly neutrophils and macrophages. Immune cells produce various cytokines and chemokines, as well as ROS, in total contributing to the cytotoxic effects of cisplatin [94, 95].

Disruption of cell membranes caused by cisplatin administration leads to a release of intracellular proteins such as cardiac troponin, lactate dehydrogenase, and creatine kinase.These biomarkers are used to detect myocardial damage caused by cisplatin. Some authors have reported a significant increase in serum levels of these biomarkers after only one dose was administered [96].

Neurotoxicity

Cisplatin predominantly affects the neurons of the dorsal root ganglia leading to symptoms such as numbness and tingling, paresthesia, reduced deep tendon reflexes, and leg weakness. Cisplatin accumulates in the dorsal root ganglia, thus causing abnormalities in the nucleoli of spinal root ganglion cells. After chronic application of cisplatin, spinal root neurons and peripheral neurons showed significant damage in relation to the reduction in cell size. The first onset appears after a cumulative dose of 300-600 mg/m^2 is administered. The most severe form of cisplatin neurotoxicity is expected 1-4 months after the end of weekly cisplatin administration. In most patients, the resolution of symptoms happens over the next 12 months [97]. Because nerve damage can only partially be reversed, effective neuroprotective therapies have been studied. Most effective have been GSH, N-acetylcisteine, vitamin E, oxcarbazepine and some chelators such as calcium and magnesium infusions. Pace and co-workers have reported that vitamin E as an antioxidant can prevent neurotoxicity [98]. Also, N-acetylcisteine can increase the concentration of GSH, which prevents the accumulation of cisplatin [99].

Ototoxicity

Ototoxicity is usually seen in younger patients, where a cisplatin administration in dose of 50 mg/m^2 affects around 31% of patients after the initial dose, leading to tinnitus and bilateral high-frequency hearing loss. Higher doses (150 mg/m^2) given over a shorter period of time, and higher cumulative doses, lead to bilateral, progressive, and irreversible hearing disorders [100]. Risk factors include previous cranial irradiation, renal dysfunction or inner ear damage, or concomitant exposure to other ototoxic agents, such as aminoglycosides, loop diuretics. Cisplatin-induced ototoxicity is thought to be due to the damage to the inner ear, via increased concentration of ROS and depleting the concentration of GSH. So far, there has been no effective treatment for this cisplatin side effect. Although the preventive use of antioxidants has been studied, their clinical use has not been fully accomplished. [101].

Gastrointestinal and hepatotoxicity

Gastrointestinal toxicity caused by cisplatin includes emetic effects, i.e. chemotherapy nausea and vomiting (CINV) and dyspepsia. Some patients can develop anorexia which can lead to cachexia [102]. The co-administration of radiotherapy can increase the incidence of CINV. Treatment is based on the combination of antiemetic drugs such as ondasetron, dexamethasone, and olanzapine [103].

Cisplatin and other platinum- based drugs can cause damage to sinusoid vessels of the liver. This damage to the sinusoids can result in nodular hyperplasia and benign tumors of the liver [104, 105]. Patients develop

symptoms that include abdominal pain and edemas. The nderlying mechanism is the overproduction of ROS and damage to mitochondria of the epithelial cells lining the sinusoids. There is no known treatment to prevent cisplatin-induced hepatotoxicity [106, 107].

CONCLUSION

Cisplatin is still a widely used chemotherapeutic agent, used alone and/or in combination with other drugs in a large number of tumors, despite proven toxicity. Today, a great effort is being made on the development of new types of platinum-based drugs, which have less side effects, but the fact is that more research is needed on the application of preventive drugs that could target ever-present side effects. We also see potential in examining specific factors in patients that would predispose them develop some of the toxic effects of cisplatin, i.e specific genetic markers.

REFERENCES

1. Loehrer PJ, Einhorn LH. Drugs five years later. Cisplatin. Ann Intern Med 1984;100(5):704-13.
2. Arnesano F, Natile G. Mechanistic insight into the cellular uptake and processing of cisplatin 30 years after its approval by FDA. Coord Chem Rev 2009;253(15-16):2070–81.
3. Macciò A, Madeddu C. Cisplatin: an old drug with a newfound efficacy – from mechanisms of action to cytotoxicity. Expert Opin on Pharmacoth 2013;14(13):1839–57.
4. Dasari S, Tchounwou PB. Cisplatin in cancer therapy: molecular mechanisms of action. Eur J Pharmacol 2014;740:364-78.
5. Gómez-Ruiz S, Maksimović-Ivanić D, Mijatović S, Kaluđerović GN. On the discovery, biological effects, and use of Cisplatin and metallocenes in anticancer chemotherapy. Bioinorg Chem Appl 2012;2012:140284.
6. Giaccone G. Clinical perspectives on platinum resistance. Drugs 2000;59 Suppl 4:9–17: discussion 37-8.
7. Fuertes MA, Alonso C, Perez JM. Biochemical ´modulation of cisplatin mechanisms of action: enhancement of antitumor activity and circumvention of drug resistance. Chem Rev 2003;103(3):645–62.
8. Aldossary SA. Review on pharmacology of cisplatin: clinical use, toxicity and mechanism of resistance of cisplatin. Biomed Pharm J 2019;12(1):7-15.
9. Lukka H, Hirte H, Fyles A, et al. Concurrent Cisplatin-based Chemotherapy plus Radiotherapy for Cervical Cancer–a Meta-analysis. Clin Oncol 2002; 14(3):203–2.
10. De Vries G, Rosas-Plaza X, van Vugt MATM, Gietema JA, de Jong S. Testicular cancer: Determinants of cisplatin sensitivity and novel therapeutic opportunities. Cancer Treat Rev 2020;88:102054
11. Posner MR, Hershock DM, Blajman CR, et al. TAX 324 Study Group. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007:357(17):1705-15.
12. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman M A, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. N Engl J Med 1999: 340(15):1144-53.
13. Lukka H, Hirte H, Fyles A, Thomas G, Elit L, Johnston M, et al. Concurrent Cisplatin-based Chemotherapy plus Radiotherapy for Cervical Cancer–a Meta-analysis. Clinical Oncology 2002:14(3):203–12.
14. Kranjc Brezar S, Prevc A, Niksic Zakelj M, Brozic A, Cemazar M, Strojan P, et al. Synergistic effect of cisplatin chemotherapy combined with fractionated radiotherapy regimen in HPV-positive and HPV-negative experimental pharyngeal squamous cell carcinoma. Sci Rep 2020:10(1):1-9.
15. Noronha V, Joshi A, Patil VM, Agarwal J, Ghosh-Laskar S, Budrukkar A, et al. Once-a-week versus once-every-3-weeks cisplatin chemoradiation for locally advanced head and neck cancer: a phase III randomized noninferiority trial. J Clin Oncol 2018:36(11):1064-1072.
16. Machiels JP, Leemans CR, Golusinski W, Grau C, Licitra L, Gregoire V. Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS–ESMO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2020:31(11):1462-75.
17. Eapen l, Stewart D, Collins J, Peterson R. (2004). Effective bladder sparing therapy with intra-arterial cisplatin and radiotherapy for localized bladder cancer. J Urol 2004:172(4);1276–80.
18. Wang D, Lippard SJ. Cellular processing of platinum anticancer drugs. Nat Rev Drug Discov 2005;4:307-20.
19. Rebillard A, Lagadic-Gossmann D, Dimanche-Boitrel MT. Cisplatin cytotoxicity: DNA and plasma membrane targets. Curr Med Chem 2008;15:2656-63.
20. Burstyn JN, Heiger-Bernays WJ,Cohen SM, Lippard SJ. Formation of cis-diamminedichloroplatinum (II) 1, 2-intrastrand cross-links on DNA is flanking-sequence independent. Nucleic Acid Res 2000;28:4237-43.
21. Tchounwou PB, Dasari S, Noubissi FK, Ray P, Kumar S. Advances in Our Understanding of the Molecular Mechanisms of Action of Cisplatin in Cancer Therapy. J Exp Pharmacol 2021;13:303-328.
22. Sorenson CM, Eastman A. Influence of cis-diamminedichloroplatinum(II) on DNA synthesis and cell cycle progression in excision repair proficient and deficient Chinese hamster ovary cells. Cancer Res 1988;48:6703-7.
23. Sancho-Martínez SM, Piedrafita FJ, Cannata-Andía JB, López-Novoa JM, López-Hernández FJ. Necrotic concentrations of cisplatin activate the apoptotic machinery but inhibit effector caspases and interfere with the execution of apoptosis. Toxicol Sci 2011;122(1):73-85.
24. Kumar S, Tchounwou PB. Molecular mechanisms of cisplatin cytotoxicity in acute promyelocytic leukemia cells. Oncotarget 2015;6(38):40734–46.
25. Zeng H, Zhang S, Yang KY, Wang T, Hu JL, Huang LL, Wu G. Knockdown of second mitochondria-derived activator of caspase expression by RNAi enhances growth and cisplatin resistance of human lung cancer cells. Cancer Biother Radiopharm 2010;25(6):705-12.
26. Parrish AB, Freel CD, Kornbluth S. Cellular mechanisms controlling caspase activation and function. Cold Spring Harb Perspect Biol 2013;5(6):a008672.
27. Gonzalez VM, Fuertes MA, Alonso C, Perez JM. Is cisplatin-induced cell death always produced by apoptosis? Mol Pharmacol 2001;59(4):657-63.
28. Jensen M, Bjerring M, Nielsen NC, Nerdal W. Cisplatin interaction with phosphatidylserine bilayer studied by solid-state NMR spectroscopy. J Biol Inorg Chem 2010;15:213-23.

29. Pérez JM, Montero EI, González AM, Alvarez-Valdés A, Alonso C, Navarro-Ranninger C. Apoptosis induction and inhibition of H-ras overexpression by novel trans-[PtCl2(isopropylamine)(amine')] complexes. J Inorg Biochem 1999;77(1-2):37-42.
30. Melnikov SV, Söll D, Steitz TA, Polikanov YS. Insights into RNA binding by the anticancer drug cisplatin from the crystal structure of cisplatin-modified ribosome. Nucleic Acids Res 2016;44(10):4978-87.
31. Chapman EG, DeRose VJ. Site-specific platinum(II) cross-linking in a ribozyme active site. J Am Chem Soc 2012;134:256–62.
32. Messori L, Merlino A. Cisplatin binding to proteins: A structural perspective. Coord Chem Rev 2016;315:67-89.
33. Kuo MT, Chen HH, Song IS, Savaraj N, Ishikawa T. The roles of copper transporters in cisplatin resistance. Cancer Metastasis Rev 2007;26(1):71-83.
34. Messori L, Marzo T, Merlino A. Interactions of carboplatin and oxaliplatin with proteins: Insights from X-ray structures and mass spectrometry studies of their ribonuclease A adducts. J Inorg Biochem 2015;153:136-142.
35. Zhang N, Liu H, Cui M, Du Y, Liu Z, Liu S. Direct determination of the binding sites of cisplatin on insulin-like growth factor-1 by top-down mass spectrometry. J Biol Inorg Chem 2015;20(1):1-10.
36. Will J, Wolters DA, Sheldrick WS. Characterisation of cisplatin binding sites in human serum proteins using hyphenated multidimensional liquid chromatography and ESI tandem mass spectrometry. Chem Med Chem 2008;3(11):1696-707.
37. Peleg-Shulman T, Gibson D. Cisplatin−Protein Adducts Are Efficiently Removed by Glutathione but Not by 5‘-Guanosine Monophosphate. J Am Chem Soc 2001;123(13):3171–2.
38. Santos NA, Catão CS, Martins NM, Curti C, Bianchi ML, Santos AC. Cisplatin-induced nephrotoxicity is associated with oxidative stress, redox state unbalance, impairment of energetic metabolism and apoptosis in rat kidney mitochondria. Arch Toxicol 2007;81(7):495-504.
39. Martins NM, Santos NAG, Curti C, Bianchi MLP, Santos AC. Cisplatin induces mitochondrial oxidative stress with resultant energetic metabolism impairment, membrane rigidification and apoptosis in rat liver. Journal of Applied Toxicology 2008;28(3):337–44.
40. Amable, L. Cisplatin resistance and opportunities for precision medicine. Pharmacol Res 2016;106:27-36.
41. Richon VM, Schulte N, Eastman A. Multiple mechanisms of resistance to cis-diamminedichloroplatinum(II) in murine leukemia L1210 cells. Cancer Res. 1987;47(8):2056–61.
42. Wood RD, Araujo SJ, Ariza RR, et al. DNA damage recognition and nucleotide excision repair in mammalian cells. Cold Spring Harb Symp Quant Biol 2000;65:173–82.
43. Ahmad A, Robinson AR, Duensing A, et al. ERCC1-XPF endonuclease facilitates DNA double-strand break repair. Mol Cell Biol 2008;28:5082–92.
44. Bellmunt J, Paz-Ares L, Cuello M, et al. Gene expression of ERCC1 as a novel prognostic marker in advanced bladder cancer patients receiving cisplatinbased chemotherapy. Ann Oncol 2007;18:522–8.
45. Shirota Y, Stoehlmacher J, Brabender J, et al. ERCC1 and thymidylate synthase mRNA levels predict survival for colorectal cancer patients receiving combination oxaliplatin and fluorouracil chemotherapy. J Clin Oncol 2001;19:4298–304.
46. Metzger R, Leichman CG, Danenberg KD, et al. ERCC1 mRNA levels complement thymidylate synthase mRNA levels in predicting response and survival for gastric cancer patients receiving combination cisplatin and fluorouracil chemotherapy. J Clin Oncol 1998;16:309–16.
47. Kim MK, Cho KJ, Kwon GY, et al. Patients with ERCC1-negative locally advanced esophageal cancers may benefit from preoperative chemoradiotherapy. Clin Cancer Res 2008;14:4225–31.
48. Dabholkar M, Bostick-Bruton F, Weber C, Bohr VA, Egwuagu C, Reed E. ERCC1 and ERCC2 expression in malignant tissues from ovarian cancer patients. J Natl Cancer Inst 1992;84:1512–7.
49. Olaussen KA, Dunant A, Fouret P, et al. DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. N Engl J Med 2006;355: 983–91.
50. Olaussen KA. A new step ahead for the consideration of ERCC1 as a candidate biomarker to select NSCLC patients for the treatment of cetuximab in combination with cisplatin. Cancer Biol Ther 2009;8:1922–3.
51. Kunkel TA, Erie DA. DNA mismatch repair. Annu Rev Biochem 2005;74:681–710.
52. Vaisman A, Varchenko M, Umar A, et al. The role of hMLH1, hMSH3, and hMSH6 defects in cisplatin and oxaliplatin resistance: correlation with replicative bypass of platinum-DNA adducts. Cancer Res 1998;58:3579-85.
53. Fink D, Aebi S, Howell SB. The role of DNA mismatch repair in drug resistance. Clin Cancer Res 1998;4:1–6.
54. Kamal NS, Soria JC, Mendiboure J, et al. MutS homologue 2 and the long-term benefit of adjuvant chemotherapy in lung cancer. Clin Cancer Res 2010;16:1206–15.
55. Gifford G, Paul J, Vasey PA, Kaye SB, Brown R. The acquisition of hMLH1 methylation in plasma DNA after chemotherapy predicts poor survival for ovarian cancer patients. Clin Cancer Res 2004;10:4420–6.
56. Galluzzi L, Senovilla L, Vitale I, et al. Molecular mechanisms of cisplatin resistance. Oncogene 2012;31(15):1869-83.
57. Eichholtz-Wirth H, Hietel B. The relationship between cisplatin sensitivity and drug uptake into mammalian cells in vitro. Br J Cancer 1986;54(2):239–43.
58. Hall MD, Okabe M, Shen DW, Liang XJ, Gottesman MM. The role of cellular accumulation in determining sensitivity to platinum-based chemotherapy. Annu Rev Pharmacol Toxicol 2008;48:495-535.
59. Ishida S, McCormick F, Smith-McCune K, Hanahan D. Enhancing tumor-specific uptake of the anticancer drug cisplatin with a copper chelator. Cancer Cell 2010;17(6):574-83.
60. Blair BG, Larson CA, Rafraei R, Howell SB. Copper transporter 2 regulates the cellular accumulation and cytotoxicity of cisplatin and carboplatin. Clin Cancer Res 2009;15(13);4312–21.
61. Yoshida H, Teramae M, Yamauchi M, et al. Association of copper transporter expression with platinum resistance in epithelial ovarian cancer. Anticancer Res 2013;33(4):1409-14.
62. More SS, Akil O, Ianculescu AG, Geier EG, Lustig LR, Giacomini KM. Role of the copper transporter, CTR1, in platinuminduced ototoxicity. J Neurosci 2010;30:9500–9.
63. Burger H, Loos WJ, Eechoute K, Verweij J, Mathijssen RH, Wiemer EA. Drug transporters of platinum-based anticancer agents and their clinical significance. Drug Resist Updat 2011;14(1);22–34.
64. Ishikawa T, Ali-Osman F. Glutathione-associated cis-diamminedichloroplatinum(II) metabolism and ATP-dependent efflux from leukemia cells. Molecular characterization of glutathione-platinum complex and its biological significance. J Biol Chem 1993;268(27):20116-25.
65. Godwin AK, Meister A, O'Dwyer PJ, Huang CS, Hamilton TC, Anderson ME. High resistance to cisplatin in human ovarian cancer cell lines is associated with marked increase of glutathione synthesis. Proc Natl Acad Sci U S A 1992;89(7):3070-4.
66. Yang YY, Woo ES, Reese CE, Bahnson RR, Saijo N, Lazo JS. Human metallothionein isoform gene expression in cisplatin-sensitive and resistant cells. Mol Pharmacol 1994;45(3):453-60.
67. Kasahara K, Fujiwara Y, Nishio K, et al. Metallothionein content correlates with the sensitivity of human small cell lung cancer cell lines to cisplatin. Cancer Res 1991;51(12):3237-42.

68. Siegsmund MJ, Marx C, Seemann O, et al. Cisplatin-resistant bladder carcinoma cells: enhanced expression of metallothioneins. Urol Res 1999;27(3):157-63.
69. Yao X, Panichpisal K, Kurtzman N, Nugent K. Cisplatin nephrotoxicity: a review. Am J Med Sci 2007;334(2):115-24.
70. Townsend DM, Tew KD, He L, King JB, Hanigan MH. Role of glutathione S-transferase Pi in cisplatin-induced nephrotoxicity. Biomed Pharmacother 2009;63(2):79-85.
71. Townsend DM, Deng M, Zhang L, Lapus MG, Hanigan MH. Metabolism of Cisplatin to a nephrotoxin in proximal tubule cells. J Am Soc Nephrol 2003;14(1):1-10.
72. Townsend DM, Hanigan MH. Inhibition of gamma-glutamyl transpeptidase or cysteine S-conjugate beta-lyase activity blocks the nephrotoxicity of cisplatin in mice. J Pharmacol Exp Ther 2002;300(1):142-8.
73. Zhang L, Hanigan MH. Role of cysteine S-conjugate beta-lyase in the metabolism of cisplatin. J Pharmacol Exp Ther 2003;306(3):988-94.
74. Hanigan MH, Gallagher BC, Taylor PT Jr, Large MK. Inhibition of gamma-glutamyl transpeptidase activity by acivicin in vivo protects the kidney from cisplatin-induced toxicity. Cancer Res. 1994;54:5925-9.
75. Chirino YI, Pedraza-Chaverri J. Role of oxidative and nitrosative stress in cisplatin-induced nephrotoxicity. Exp Toxicol Pathol 2009;61(3):223-42.
76. Wei Q, Dong G, Yang T, Megyesi J, Price PM, Dong Z. Activation and involvement of p53 in cisplatin-induced nephrotoxicity. Am J Physiol Renal Physiol 2007;293(4):F1282-91.
77. Jiang M, Yi X, Hsu S, Wang CY, Dong Z. Role of p53 in cisplatin-induced tubular cell apoptosis: dependence on p53 transcriptional activity. Am J Physiol Renal Physiol 2004;287(6):F1140-7.
78. Nishikawa M, Nagatomi H, Chang BJ, Sato E, Inoue M. Targeting superoxide dismutase to renal proximal tubule cells inhibits mitochondrial injury and renal dysfunction induced by cisplatin. Arch Biochem Biophys 2001;387:78:84.
79. Faubel S, Lewis EC, Reznikov L, et al. Cisplatin-induced acute renal failure is associated with an increase in the cytokines interleukin (IL)-1beta, IL-18, IL-6, and neutrophil infiltration in the kidney. J Pharmacol Exp Ther 2007;322(1):8-15.
80. Lu LH, Oh DJ, Dursun B, He Z, Hoke TS, Faubel S, Edelstein CL. Increased macrophage infiltration and fractalkine expression in cisplatin-induced acute renal failure in mice. J Pharmacol Exp Ther 2008;324(1):111-7.
81. Manohar S, Leung N. Cisplatin nephrotoxicity: a review of the literature. J Nephrol 2018;31(1):15-25.
82. Yatsu T, Aoki M, Inagaki O. Preventive effect of zelandopam, a dopamine D1 receptor agonist, on cisplatin-induced acute renal failure in rats. Eur J Pharmacol 2003;461(2-3):191-5.
83. Delbancut A, Lagroye I, Cambar J. Renal cytotoxicity of cisplatin in cultured glomerular mesangial and proximal and distal tubular cells. Toxicol In Vitro 1994;8(4):517-9.
84. Goldstein RS, Mayor GH. Minireview. The nephrotoxicity of cisplatin. Life Sci. 1983 Feb 14;32(7):685-90. doi: 10.1016/0024-3205(83)90299-0.
85. Potić, M, Ignjatović I, Nickovic V, et al. Two different melatonin treatment regimens prevent an increase in kidney injury marker-1 induced by carbon tetrachloride in rat kidneys. Can J Physiol Pharmacol 2009;97(5):422-8.
86. Mitić BP, Mitić DM, Radić MS, et al. (2022). Honeybee Propolis Phenol, Caffeic Acid Phenethyl Ester, Attenuates Cisplatin-Induced Kidney Damage-a Multitarget Approach. Records of Natural Products 2022;*16*(4).
87. Miller RP, Tadagavadi RK, Ramesh G, Reeves WB. Mechanisms of Cisplatin nephrotoxicity. Toxins (Basel) 2010;2(11):2490-518.
88. Raja W, Mir MH, Dar I, Banday MA, Ahmad I. Cisplatin induced paroxysmal supraventricular tachycardia. Indian J Med Paediatr Oncol 2013;34:330-2.
89. Altena R, Hummel YM, Nuver J, et al. Longitudinal changes in cardiac function after cisplatin-based chemotherapy for testicular cancer. Ann Oncol 2011;22:2286-93.
90. Patanè, S. Cardiotoxicity: anthracyclines and long term cancer survivors. Int J Cardiol 2014;176(3):1326-8.
91. Rosic G, Selakovic D, Joksimovic J, et al. The effects of N-acetylcysteine on cisplatin-induced changes of cardiodynamic parameters within coronary autoregulation range in isolated rat hearts. Toxicol Lett 2016;242:34-46.
92. Dugbartey GJ, Peppone LJ, de Graaf IA. An integrative view of cisplatin-induced renal and cardiac toxicities: Molecular mechanisms, current treatment challenges and potential protective measures. Toxicology 2016;371:58-66.
93. Marrer E, Dieterle F. Impact of biomarker development on drug safety assessment. Toxicol Appl Pharmacol 2010;243:167-179.
94. El-Sawalhi MM, Ahmed LA. Exploring the protective role of apocynin, a specific NADPH oxidase inhibitor, in cisplatin-induced cardiotoxicity in rats. Chem Biol Interact 2014;207:58-66.
95. Chowdhury S, Sinha K, Banerjee S, Sil PC. Taurine protects cisplatin induced 25 cardiotoxicity by modulating inflammatory and endosplasmic reticulum stress responses. Biofactors 2016;42(6):647-64.
96. El-Awady el-SE, Moustafa YM, Abo-Elmatty DM, Radwan A. Cisplatin-induced cardiotoxicity: mechanisms and cardioprotective strategies. Eur J Pharmacol 2011;650:335-41.
97. Albers JW, Chaudhry V, Cavaletti G, Donehower RC. Interventions for preventing neuropathy caused by cisplatin and related compounds. CDSR 2014;(3).
98. Pace A, Savarese A, Picardo M, et al. Neuroprotective effect of vitamin E supplementation in patients treated with cisplatin chemotherapy. J Clin Oncol 2003;21(5):927-31.
99. Lin PC, Lee MY, Wang WS, et al. N-acetylcysteine has neuroprotective effects against oxaliplatin-based adjuvant chemotherapy in colon cancer patients: preliminary data. Support Care Cancer 2006;14(5):484-7.
100. Rademaker-Lakhai JM, Crul M, Zuur L, et al. Relationship between cisplatin administration and the development of ototoxicity. J Clin Oncol 2006;24(6):918-24.
101. Rybak LP, Whitworth CA, Mukherjea D, Ramkumar V. Mechanisms of cisplatin-induced ototoxicity and prevention. Hear Res 2007;226(1-2):157-67.
102. Crawford J. Cancer cachexia: Are we ready to take a step forward?. Cancer 2018;124(3):456-8.
103. Rapoport BL, Molasiotis A, Raftopoulos H, Roila F. Chemotherapy-Induced Nausea and Vomiting. Biomed Res Int 2015;2015:457326.
104. Oun R , Moussa YE , Wheate NJ . The side effects of platinum-based chemotherapy drugs: a review for chemists. Dalton Trans 2018;47(19):6645-53.
105. Waseem M, Bhardwaj M, Tabassum H, Raisuddin S, Parvez S. Cisplatin hepatotoxicity mediated by mitochondrial stress. Drug Chem Toxicol 2015;38(4):452-9.
106. Chun YS, Laurent A, Maru D, Vauthey JN. Management of chemotherapy-associated hepatotoxicity in colorectal liver metastases. Lancet Oncol 2010;10(3):278-86.
107. Cüre MC, Cüre E, Kalkan Y, et al. Infliximab Modulates Cisplatin-Induced Hepatotoxicity in Rats. Balkan Med J 2016;33(5):504-11.