REVIEW

Advances in Our Understanding of the Molecular Mechanisms of Action of Cisplatin in Cancer Therapy

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Abstract: Cisplatin and other platinum-based chemotherapeutic drugs have been used extensively for the treatment of human cancers such as bladder, blood, breast, cervical, esophageal, head and neck, lung, ovarian, testicular cancers, and sarcoma. Cisplatin is commonly administered intravenously as a first-line chemotherapy for patients suffering from various malignancies. Upon absorption into the cancer cell, cisplatin interacts with cellular macromolecules and exerts its cytotoxic effects through a series of biochemical mechanisms by binding to Deoxyribonucleic acid (DNA) and forming intra-strand DNA adducts leading to the inhibition of DNA synthesis and cell growth. Its primary molecular mechanism of action has been associated with the induction of both intrinsic and extrinsic pathways of apoptosis resulting from the production of reactive oxygen species through lipid peroxidation, activation of various signal transduction pathways, induction of p53 signaling and cell cycle arrest, upregulation of pro-apoptotic genes/proteins, and down-regulation of proto-oncogenes and anti-apoptotic genes/proteins. Despite great clinical outcomes, many studies have reported substantial side effects associated with cisplatin monotherapy, while others have shown substantial drug resistance in some cancer patients. Hence, new formulations and several combinational therapies with other drugs have been tested for the purpose of improving the clinical utility of cisplatin. Therefore, this review provides a comprehensive understanding of its molecular mechanisms of action in cancer therapy and discusses the therapeutic approaches to overcome cisplatin resistance and side effects.

Keywords: cisplatin, molecular mechanisms of action, combination therapy, cancer treatment

Introduction

In 1844, Peyrone synthesized cisplatin for the first time. In 1893, Alfred Werner contributed towards designing the structure of cisplatin with a firm basis of coordination chemistry.[1] The identification of cisplatin and its bioactivity evolved from laboratory experiments of Professor Rosenberg along with significant contributions by Loretta Van Camp, Tom Krigas, Eugene Grimley, and Andrew Thomson from the biophysics department at Michigan State University.[2,3]

Cisplatin is structurally a coordination compound with square planar geometry. It appears as white or deep yellow to yellow-orange crystalline powder at room temperature.[4,5] Under normal temperature and pressure, cisplatin is found to be stable with a water solubility of 2.53g/L at 25°C.[6]

Cisplatin has been widely used against human cancers following its first usage by the National Cancer Institute for clinical trials.[7] It is well established as an anti-cancer drug agent based upon its therapeutic implications. The molecular structure

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of cisplatin determines the anticancer activity in a dose-dependent fashion inhibiting Deoxy Ribonucleic Acid (DNA) synthesis. However, therapeutic efficacy has been challenging beyond the comprehensive drug development as neurotoxicity, ototoxicity and renal toxicity, etc., have been observed. Thus, strategies need to be developed to address cisplatin-related toxicities and drug resistance. An extensive search for less toxic analogs of cisplatin, combination therapy with other cancer drugs and nanotechnology can be used to combat the side effects. This review provides a perspective on the advances in our understanding of the molecular mechanisms of action of cisplatin for targeted cancer therapy.

Molecular Mechanisms of Action
Overview of Mechanisms
Cisplatin's cytotoxicity has been attributed to DNA binding, tailed by single-stranded DNA breaks.[8] Cisplatin is activated upon its entry into the cytoplasm by displacing chloride atoms with water molecules forming an electrophile with affinity towards sulfhydryl groups on proteins and nitrogen donor atoms on nucleic acids.[9] This selective binding to 1, 2-intrastrand cross-links of purine bases with cisplatin triggers blockage in cell division and induces apoptotic cell death.[10] The most common cisplatin-DNA adduct formation through covalent binding has been observed at the N7 positions of the imidazole ring of two adjacent guanines.[11] Inter and intrastrand crosslinks and nonfunctional adducts have been reported to contribute to cisplatin's toxicity.[12,13] As shown in Figures 1 and 2, research conducted in our laboratory has demonstrated that cisplatin inhibits cell growth, induces DNA adducts and causes cytotoxic effects in leukemia cells in a concentration-dependent manner.[14]

Cisplatin-Induced Oxidative Stress
Cancer cells exhibit high metabolism, demanding elevated reactive ROS concentrations to facilitate their propagation. ROS affect key signaling proteins that are involved in biochemical pathways for cell proliferation. Tumor development and progression are regulated by ROS production by modulating biological pathways such as activation of extracellular-regulated kinase 1/2 (ERK1/2) and ligand-independent Receptor Tyrosine Kinases (RTK), evasion of apoptosis or anoikis through activation of Src, nuclear factor kappa-light-chain-enhancer of activated B cells (NF-ƙ) and phosphatidylinositol-3 kinase (PI3K), secretion

of metalloproteinase into the extracellular matrix, Met overexpression, and Rho–Rac interaction for tissue invasion, metastasis and angiogenesis by releasing vascular endothelial growth factor and angiopoietin.[15]

Cisplatin has shown to generate ROS directly or indirectly through mitochondria.[16,17] Cisplatin cytotoxicity was related to lipid peroxidation, confirming the role of oxygen free radicals.[18] This release of lipid peroxidation by-products such as malondialdehyde (MDA) increases carbonylation of proteins, inducing oxidative damage of cell membranes, and eventually triggering apoptosis.[19] Similar to other published reports, we have previously demonstrated that cisplatin strongly induces oxidative stress leading to lipid peroxidation, increased MDA production, reduced GSH activity, and DNA damage in acute promyelocytic leukemia (APL) cells (Figure 3).[14]

Cisplatin Modulation of Calcium Signaling
Biological processes like gene regulation, cell proliferation, migration, death, etc., are influenced by intracellular calcium levels. However, intracellular Ca^{2+} homeostasis is altered in cancer cells to enhance cell proliferation, increase cell motility and invasion, fight cell death, and avoid immune-attack.[20] Tumorigenic pathways are associated with altered expression level or abnormal activation of Ca^{2+} channels, transporters or Ca^{2+} ATPases.[21]

A recent study has shown that calcium efflux from the Endoplasmic Reticulum (ER) regulates cisplatin-induced apoptosis in human cervical cancer cells.[22] Endoplasmic reticulum is a cytosolic target of cisplatin via caspase-3 activation in cytoplasts since they require calcium and the activity of the calcium-dependent protease calpain. Cisplatin treatment has been reported to increase the expression of 78-kDa glucose-regulated protein (Grp78/BiP), biomarker of ER stress.[23] A dose-dependent increase of Ca^{2+} was observed in cisplatin-treated MCF-7 cells, suggesting the fact that the specific pathway responsible for cell death depends on the cell type and the treatment conditions.

Cisplatin-Induced Cell Apoptosis
Induction of apoptosis in cancer cells through intrinsic and extrinsic pathways, involves regulation of caspase-dependent proteolysis of several cellular proteins, membrane blebbing and endonucleolytic cleavage of chromosomal DNA.[24] In response to various apoptotic stimuli, initiator caspases such as caspase-2, −8, −9, or −10 are activated, in turn activating zymogenic forms of executioner caspases (caspase-3 or −7). These cascades of events result in

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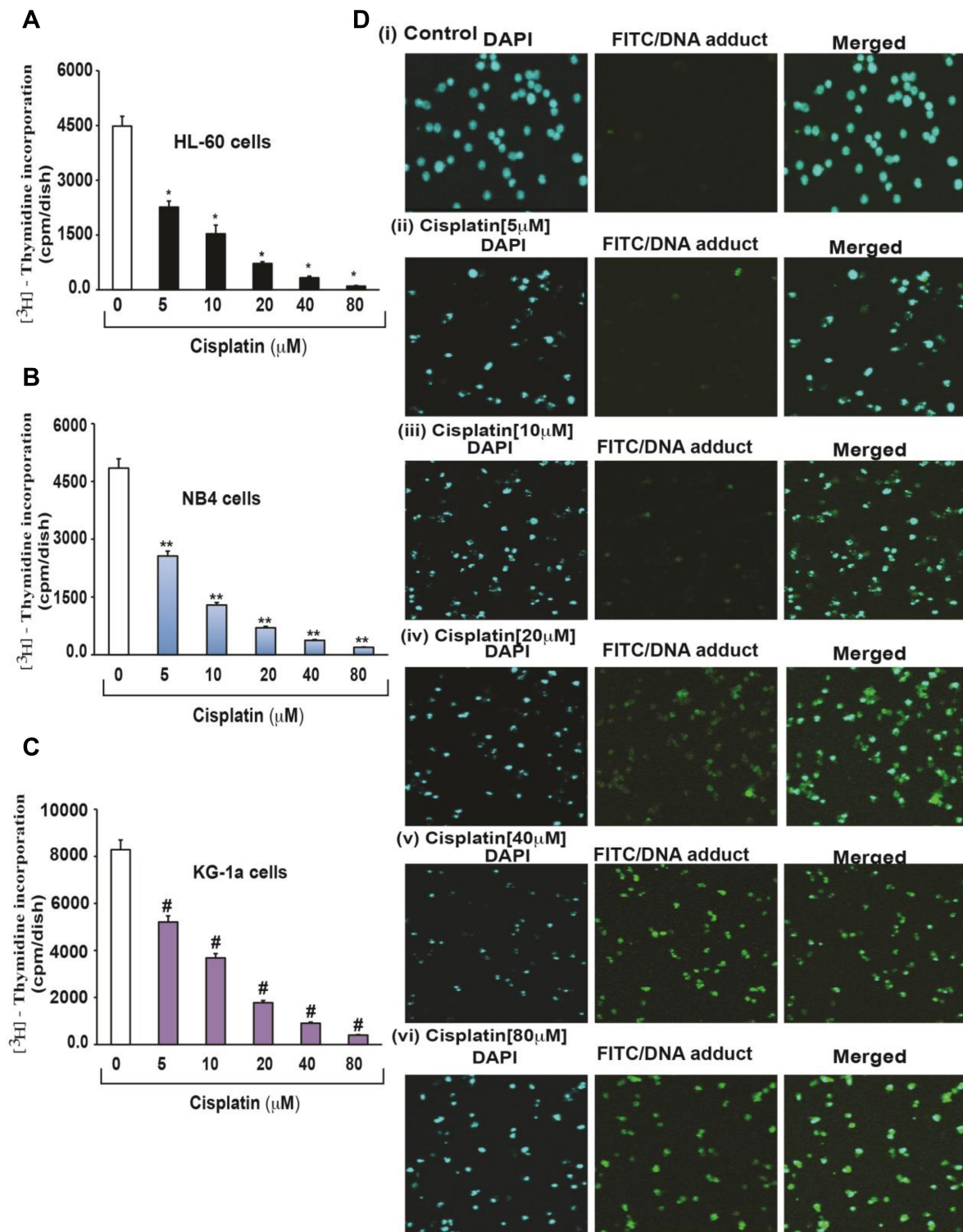
Figure 1 Cisplatin-induced growth inhibition and formation of DNA-adduct in APL cells.[14] APL cells (HL-60, NB4 and KG-1a) were exposed to various concentrations (0, 5, 10, 20, 40, and 80 μM) of cisplatin for 24 hours and further incubated for 24 hours with tritium labeled thymidine. After incubation, cells were harvested by centrifugation and counted using liquid scintillation analyzer. 3H-methyl thymidine incorporation was expressed as cpm/dish. Data represent the means of three independent experiments ± SDs. Highly statistically significant decreases (p < 0.01) in cell proliferation were observed in all cisplatin-treated APL cells including HL-60 (**A**), NB4 (**B**) and Kg-1a (**C**) cells. Cisplatin–induced formation of DNA adduct was assessed by immunocytochemistry and confocal microscopy analysis. APL cells were treated with various concentrations of cisplatin for 48 hours and immunocytochemistry as well as confocal microscopy using FITC filter were performed to confirm DNA adduct formation. The results showed that cisplatin caused a significant concentration-dependent increase in DNA-adduct formation in APL cells [**D** (i–vi)]. Multiple symbol indicators (*, **, #) indicate highly significant reductions (p<0.01) in growth between control and cisplatin-treated cells, respectively, for HL-60, NB4, and KG1a cells. Reproduced from Kumar S, Tchounwou PB. Molecular mechanisms of cisplatin cytotoxicity in acute promyelocytic leukemia cells. Oncotarget. 2015;6(38):40734–40746. Creative Commons license and disclaimer available from: http://creativecommons.org/licenses/by/4.0/legalcode.[14]
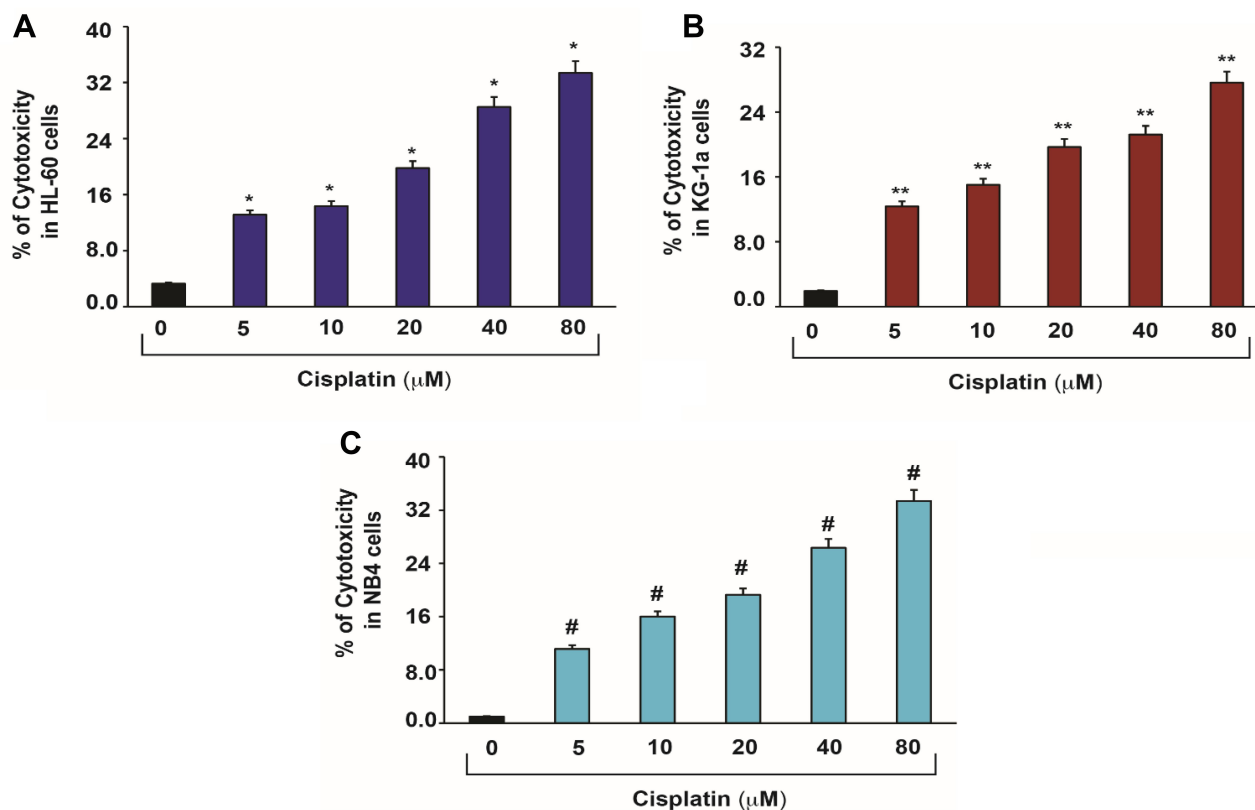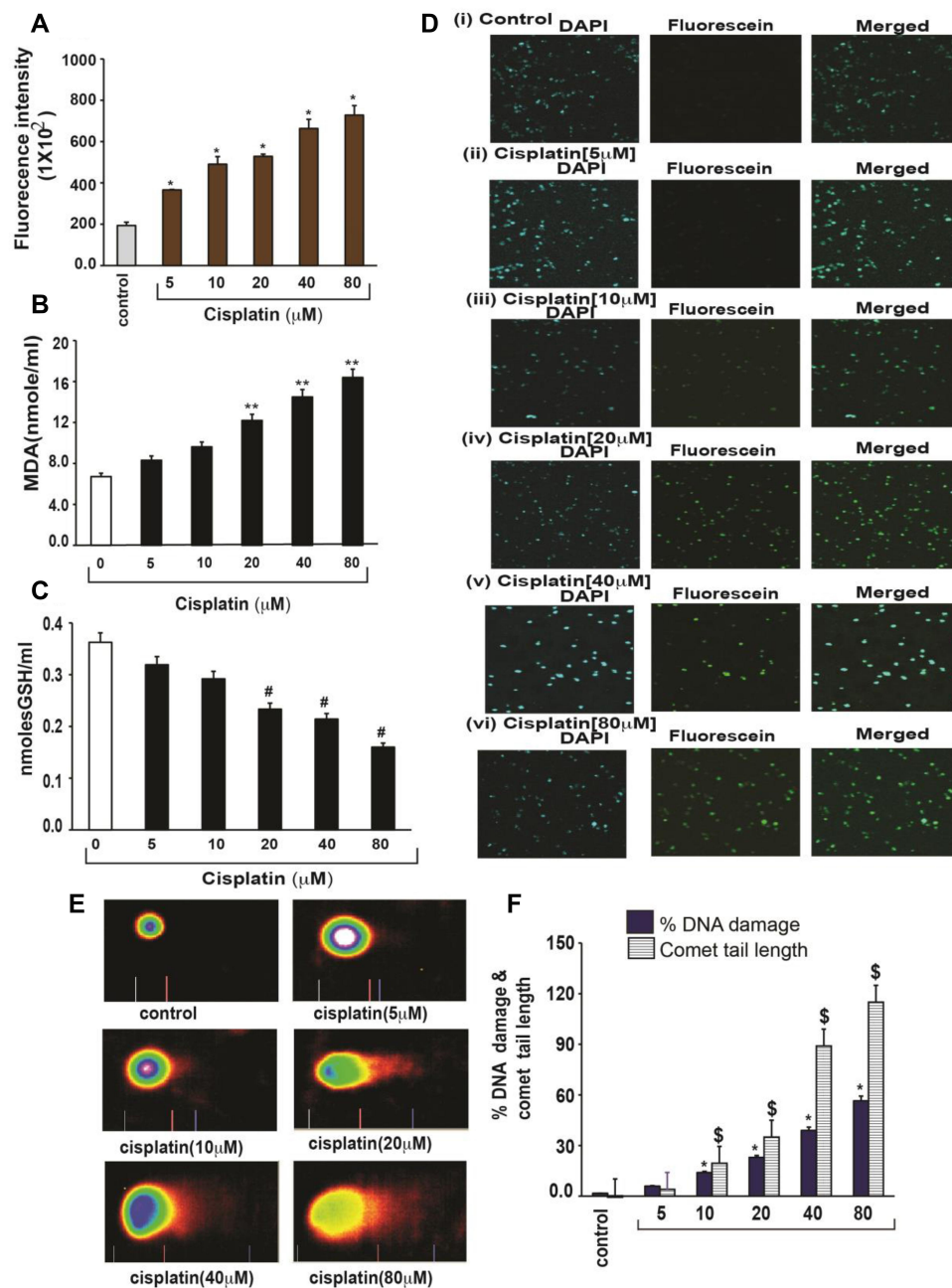
Figure 2 Cisplatin-induced cytotoxic effects in APL cells.[14] APL cells were exposed to various concentrations (0, 5, 10, 20, 40 and 80 μM) of cisplatin for 48 hours and LDH released in medium was measured using Promega non-radioactive cytotoxicity assay technical bulletin protocol. Then, % cytotoxicity was calculated by dividing the levels of released LDH in treated cells over the total LDH released from control cells. Highly statistically significant increases (p < 0.01) in cytotoxicity were observed in all cisplatin-treated APL cells including HL-60 (**A**), KG-1a (**B**) and NB4 (**C**) cells in a concentration-dependent fashion. Multiple symbol indicators (*, **, #) indicate highly significant increases (p<0.01) in cytotoxicity between control and cisplatin-treated cells, respectively, for HL-60, NB4, and KG1a cells. Reproduced from Kumar S, Tchounwou PB. Molecular mechanisms of cisplatin cytotoxicity in acute promyelocytic leukemia cells. Oncotarget. 2015;6(38):40734–40746. Creative Commons license and disclaimer available from: http://creativecommons.org/licenses/by/4.0/legalcode.[14]

proteolytic cleavage of explicit cellular substrates and, therefore, lead to cell death.[25] Apoptosis can be executed through either extrinsic or intrinsic pathway. In the extrinsic pathway, initiator caspases are activated via death-inducing signal complex (DISC) concerning the engagement of extracellular ligands like Fas or Tumor necrosis factor (TNF). In the intrinsic pathway of apoptosis, mitochondrial outer membrane permeabilization leads to activation of certain pro-apoptotic proteins like cytochrome c and mitochondria-derived activator of caspases. In the cytoplasm, binding of cytochrome c to the adaptor protein Apoptotic Protease Activating Factor-1 (APAF-1) forms apoptosome.[25] Since the balance between pro- and anti-apoptotic B-Cell Lymphoma 2 (BCL-2) family proteins is a fundamental determinant for the initiation of mitochondrial outer membrane permeabilization, cancer cells may escape apoptosis by modulating the apoptotic

pathways transcriptionally, translationally, and post-translationally.[25]

The apoptotic mechanism via cisplatin therapy varies by cell type. The molecular mechanism of cisplatin-induced apoptosis involves activation of tumor protein 53 (p53), phosphorylation of activator protein (AP-1) component leading to cell cycle arrest through stimulation of p21 and downregulation of cyclins and cyclin-dependent kinases.[14] Studies have been done to show that cisplatin induces cell death by mechanisms mediated by p53, p38 mitogen-activated protein kinase (p38 MAPKs) and/or the c-jun N-terminal kinases (JNK) activation suggesting activation of the intrinsic pathway of apoptosis through alteration of the mitochondrial membrane potential, release of cytochrome C, and up-regulation of caspase 3 activity.[26–28] However, research studies suggest that cisplatin-induced cell death not only relies on the event of apoptosis but also on necrosis[29] or autophagy.[30]

Figure 3 Cisplatin-induced oxidative stress and DNA damage in APL cells.[14] APL cells were exposed to various concentrations (0, 5, 10, 20, 40, and 80 μM) of cisplatin for 48 hours. ROS release was assessed by spectrofluorometry based on DCF fluorescence intensity after 30 min incubation with dichlorofluorescein diacetate (DCFDA). After incubation, ROS release was measured through measuring DCF fluorescence intensity by spectrofluorometry. Malondialdehyde (MDA) and GSH concentration levels were also measured by spectro-photometry. DNA damage was analyzed by both TUNEL and alkaline gel electrophoresis (Comet) assays. (**A**) ROS concentrations; (**B**) MDA concentrations; (**C**) GSH concentrations; (**D**) TUNEL assay images of DNA damage; (**E**) Comet assay images of DNA damage; (**F**) Percentages of DNA damage, and Comet tail lengths. Multiple symbol indicators (*, **, #, $) indicate highly significant increases ($p<0.01$) in ROS (*), MDA (**), DNA damage (*) and Comet tail length ($), and highly significant decreases ($p<0.01$) in GSH ($) between control and cisplatin-treated cells. Reproduced from Kumar S, Tchounwou PB. Molecular mechanisms of cisplatin cytotoxicity in acute promyelocytic leukemia cells. Oncotarget. 2015;6(38):40734–40746. Creative Commons license and disclaimer available from: http://creativecommons.org/licenses/by/4.0/legalcode.[14]

Cisplatin and Protein Kinase C

Protein kinase C (PKC) is a family of lipid-dependent serine/threonine kinases that have been subdivided into 3 groups such as conventional (α, β1, βII andγ), novel (δ, ε, η and θ), and atypical (ζ, 1/λ).[31,32] PKC shows a fundamental role in signal transduction involved in the regulation of cell proliferation, differentiation and apoptosis. Mitochondrial dysfunction via depolarization of the mitochondrial inner membrane (decreases the active Na^+ transport) leads to cisplatin-induced apoptosis and these events are mediated by

activation of caspase-3 by acting downstream of cytochrome c release from mitochondria.[33–35]

Cisplatin and Mitogen-Activated Protein Kinase (MAPK)

Mitogen-activated protein kinases (MAPK) are a family of structurally related serine/threonine kinases regulating cell proliferation, differentiation, and cell survival.[36–38] The MAPK subfamilies consist of the extracellular signal-regulated kinases (ERK), the c-jun N-terminal kinases (JNK)/ stress-activated protein kinases (SAPK), and the p38 MAP kinases.[39] Studies have been conducted showing that cisplatin-induced DNA damage results in the activation of ERK1/2 via PKCδ.[40] ERK is activated via a signaling pathway involving Ras, Raf, MEK, and ERK, transducing signals from the plasma membrane to the cell nucleus.[36]

Cisplatin and Jun Amino-Terminal Kinase (JNK)

The c-Jun NH_2-terminal kinases (JNKs) are an evolutionarily conserved sub-group of mitogen-activated protein (MAP) kinases. Phosphorylation of c-Jun activates activator protein-1 (AP-1) transcription factor which is a major target for JNK signaling pathway.[41,42] c-Jun N-terminal kinase regulates numerous essential cellular functions like cell proliferation, differentiation, survival and apoptosis while activating and inhibiting substrates for phosphorylation transcription factors consequently inducing expression of pro-apoptosis and pro-survival factors. Studies establish that the JNK/c-Jun pathway is activated by cisplatin-induced DNA damage in a dose-dependent manner.[43–45] Therefore, it is proposed that JNK signal pathway is very crucial in cisplatin treatment, regulating pro-apoptosis factor and improving resistance to cisplatin-based chemotherapy.[46]

Cisplatin and p38 Mitogen-Activated Protein Kinase (MAPK)

p38 MAPK is a member of mitogen-activated protein kinases regulating migration and proliferation of tumor cells, epithelial-mesenchymal transition, cell intravasation, and colonization of distant sites signaling.[47] Previous studies reported that inhibition of p38 induced apoptosis mediated by ROS and JNK in cells resistant to cisplatin, irinotecan and 5-fluorouracil.[48] Hence, p38 MAPK inhibition results in ROS upregulation, which in turn activates the JNK pathway via inactivation of phosphatases, sensitizing tumor cells to cisplatin-induced apoptosis.[49] High p38 MAPK phosphorylation has been correlated with poor life expectancy in patients with HER-2 negative breast cancer.[50]

Cisplatin and AKT

AKT is one of the major downstream effectors of Phosphoinositide 3-kinases (PI3K).[51] Upon PI3K activation, AKT is translocated to the inner membrane, where it is phosphorylated by PDK1.[52] This AKT modification activates the mammalian target of rapamycin complex 1 (mTORC1). Studies reveal that complete AKT activation leads to additional substrate-specific phosphorylation events in both cytoplasm and nucleus, like inhibitory phosphorylation of the pro-apoptotic forkhead box transcription factors (FOXO) proteins.[53]

Akt/mTOR survival pathway plays an important role in cisplatin treatment in human cancer cells. Cisplatin activates Akt in lung cancer cells mediated by Epidermal Growth Factor (EGFR), Src and PI3-kinase and reduces apoptosis by survivin upregulation, the inhibitor of apoptosis protein that is overexpressed in many tumors but is absent in most normal adult tissues.[54] However, cisplatin treatment reduces survivin expression, thereby inhibiting Akt in few cancer cells.[55]

Cisplatin and Signaling for DNA Damage

DNA is considered as the primary target of cisplatin.[56,57] Studies show that covalent bonding of cisplatin with the N7 position of purine bases to form 1, 2- or 1, 3-intrastrand and interstrand crosslinks interferes with DNA replication and transcription.[58] Since nucleotide excision repair (NER) system plays major role in DNA repair, low levels of XP complementation group A (XPA) and excision repair cross-complementation group I (ERCCI) have been noticed.[59,60] On the other hand, mismatch repair (MMR) system proteins (MSH2 and MLH1) have been reported to uncouple from their function to restore lost genetic information.[61–63]

p53 and DNA Damage Response to Cisplatin Treatment

p53 is a sequence-specific transcriptional activator, playing a vital role in apoptosis, inhibition of cell cycle progression, senescence, differentiation and acceleration of DNA repair.[64] If a cell undergoes stress to become cancerous, p53 is triggered to either repair the DNA damage (eg, Growth Arrest and DNA Damage-inducible 45 (GADD45)) or induce programmed cell death through

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(Bcl-2-associated X protein) Bax activation.[65] However, most of the cancer signaling pathways inactivate p53 for its protective tumor-suppressor ability, and hence its activation paves a way for novel chemotherapy.

Recognition of DNA adducts induced by cisplatin is the first step towards triggering apoptosis. Molecular mechanisms of cisplatin-induced cell death via p53 include activation of FADD-like interleukin-1β converting enzyme (FLICE)-like inhibitory protein ubiquitination.[66,67] The intra-strand lesions generated by cisplatin-induced DNA crosslinks activate the MMR system and in turn trigger tyrosine kinase c-Abl, leading to apoptosis.[68] So, studies show that cisplatin-induced ERK activation is an upstream regulator of the p53 response to DNA damage caused by cisplatin.[69] Though p53 plays a vital role in cisplatin-induced DNA damage response, p53-negative cells also respond, proposing alternate pathways.[58] Increased accumulation of p53 has been found in cisplatin-resistant cell lines with dysfunctional p53.[70]

Cyclobutanedicarboxylate (c-Abl) and DNA Damage Response to Cisplatin Treatment

c-Abl is a non-receptor tyrosine kinase localized in the nucleus and cytoplasm involved in the regulation of cell growth, survival and morphogenesis. C-Abl is activated in response to cisplatin activating JNK/stress-activated protein kinase (SAPK).[71] Activation of c-Abl in response to cisplatin led to phosphorylation and stabilization of p73, a member of the p53 family, to trigger apoptosis.[72]

In addition, studies demonstrate that c-Abl can activate the p38 MAPK signaling pathway not only via tyrosine kinase mechanism but also through MKK6 in cisplatin-based therapy. This serves as an interesting evidence of a novel signaling mechanism that fails to inhibit the p38 MAPK pathway alone or in combination with cisplatin.[73]

Cisplatin Modulation of Gene Expression

It has been reported that several genes are modulated and work collectively to induce apoptosis/autophagy of cancer cells upon cisplatin treatment. Genes related to drug transportation (CTR1, ATP7A, ATP7B, GSH, Metallothioneins), DNA repair system (ERCC1, MLHI, MSH2, POLH, REV3, BRCA1, BRCA2, VDAC) and pro-apoptotic and apoptotic proteins (Bax, BCl-2, surviving, caspases, MAP Kinases, TP53) have shown altered expression.[74] Genome-wide studies through Affymetrix Gene Chip Human Exon 1.0
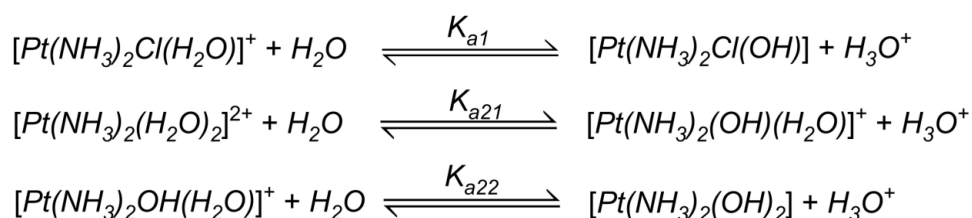
Sequence Tag Array have identified six, two, and nine representative SNPs that contribute to cisplatin-induced cytotoxicity through their effects on 8, 2, and 16 gene expressions. These genetic variants contribute to 27%, 29%, and 45% of the overall variation, respectively, in cell sensitivity to cisplatin.[75] cDNA microarray analysis of gene expression profiles showed overexpression of GST-pi mRNA, DNA repair associated genes ((X-ray repair complementing defective repair in Chinese hamster cells) XRCC5, XRCC6, ERCC5, MutL homolog 1 (hMLH1)), apoptosis inhibitors (Insulin-Like Growth Factor (IGFR) type I and II), while apoptosis inducer (caspase 3 and Bcl-2 homologous antagonist killer (BAK)) were underexpressed.[76]

Computational Studies with Cisplatin

The anticancer activity of cisplatin has led to several experimental and theoretical studies to further understand its structural and spectroscopic properties. Various computational tools are used to study molecular mechanisms in cancer biology. Genome-scale metabolic model (GSMM) has been used to understand the accurate prediction of numerous metabolic phenotypes, including growth rates, nutrient uptake rates, gene essentiality, etc.,[77] Another model called embedded multiscale method has been used to analyze hyperthermic treatment of cancer based on systemically injected vascular magnetic nanoconstructs carrying super-paramagnetic iron oxide nanoparticles.[78]

Solvation is the critical step in activating cisplatin to its active forms, $[Pt(NH_3)_2(OH_2)Cl]^-$ and $[Pt(NH_3)_2(OH_2)_2]_2^+$, wherein chloride ions are displaced by water molecules.[79] The thermodynamic and kinetic aspects of hydration reactions of cisplatin were studied using polarizable continuum model revealing the fact that all the hydration reactions are slightly endothermic while the Gibbs energies of cisplatin hydration amount to 7.0 for the chloride and 14.2 kcal/mol for ammonium replacement.[80] The equilibrium constants of individual pKa have been shown by many laboratories to be $pK_{a1} = 5.5$, $pK_{a21} = 7.3$ and $pK_{a22} = 6.6$ (Figure 4).

Cisplatin undergoes substitution reactions by an associative mechanism in the case of Pt (II), a common mechanism for the transition metals.[81] Rate constants for dechlorination for the first and second steps and both cis- and trans-conformers at T = 318.2 K, p^H 2.8–3.4 and 0.1 M $NaClO_4$ solution were also determined. The concentration of Cl^- anions, when passing from blood is about 100 mM, and to cellular environment is about 10–80 mM.[80] Cisplatin is studied to be very hydrophilic, with an octanol–water partition

$$[Pt(NH_3)_2Cl(H_2O)]^+ + H_2O \xrightleftharpoons{K_{a1}} [Pt(NH_3)_2Cl(OH)] + H_3O^+$$

$$[Pt(NH_3)_2(H_2O)_2]^{2+} + H_2O \xrightleftharpoons{K_{a21}} [Pt(NH_3)_2(OH)(H_2O)]^+ + H_3O^+$$

$$[Pt(NH_3)_2OH(H_2O)]^+ + H_2O \xrightleftharpoons{K_{a22}} [Pt(NH_3)_2(OH)_2] + H_3O^+$$

Figure 4 Chemical reactions showing hydrolysis of cisplatin. Reproduced with permission from Burda JV, Zeizinger M, Leszczynski J. Hydration process as an activation of trans- and cisplatin complexes in anticancer treatment. DFT and Ab initio computational study of thermodynamic and kinetic parameters. *J Comput Chem*. 2005;26(9):907–914. Copyright © 2005 Wiley Periodicals, Inc.[81]

coefficient (log P_{oct}) of less than −2.0.[82] This leads to poor intestinal absorption of cisplatin, and therefore, intravenous administration is suggested.

The high ligand binding affinity of activated cisplatin with biomolecules in the cellular environment, like guanines in DNA, forms an intrastrand 1,2- d(GpG) complex, peptides (glutathione), or peptides with sulphur-containing amino acids, cysteine, and methionine, or RNAs, introduce the prospect of their use in chemopreventive application. The preference of cisplatin's affinity towards guanine at the N7-position is established experimentally explaining formation of weak hydrogen bond between the chloride ligand of cisplatin and the H_2N−C6 group of adenine and stronger molecular orbital interaction for guanine compared to adenine.[83] Free energy reactions of cisplatin derivatives with cysteine showed strong thermodynamic stability and exhibited clear constant preferences in the whole pH range.[84] Further studies were conducted to describe the physicochemical properties of cisplatin through a model capable of quantitatively describing and interpreting the structural and vibrational properties.[85]

Taken together, cisplatin-induced cancer cell death is mediated through a series of biochemical effects and molecular mechanisms that include the formation of DNA adducts, induction of reactive oxygen species, genotoxic damage, p53 activation, MAPK and JNK signaling, overexpression of p38, p21 and cell cycle arrest, activation of apoptotic genes/proteins, and down-regulation of proto-oncogenes and related proteins. Figure 5 presents the specific molecular mechanisms of action of cisplatin resulting from experimental studies conducted in molecular pharmacology laboratories including ours.[14]

Toxicological Effects of Cisplatin
Overview
Modulation of intracellular changes controlling the regulation of few signaling pathways and depletion of bioavailable Cu pool leads to sensitization of cisplatin transport and triggers apoptosis.[86] Toxic effects of cisplatin are varied and have been an area of concern for many oncologists, practitioners and researchers. Cisplatin is a potent chemotherapeutic drug associated with several side effects such as myelotoxicity, gastrointestinal toxicity, neurotoxicity, ototoxicity, cardiotoxicity and nephrotoxicity.[87] Common side effects of cisplatin include nausea and vomiting.[88] Therapeutic strategies such as cell cycle inhibitors,[89] heavy metal chelating agents,[90] bioflavonoids,[91] algae,[92] and natural products[93,94] have been documented to manage the toxicological implications without compromising oncolytic action.
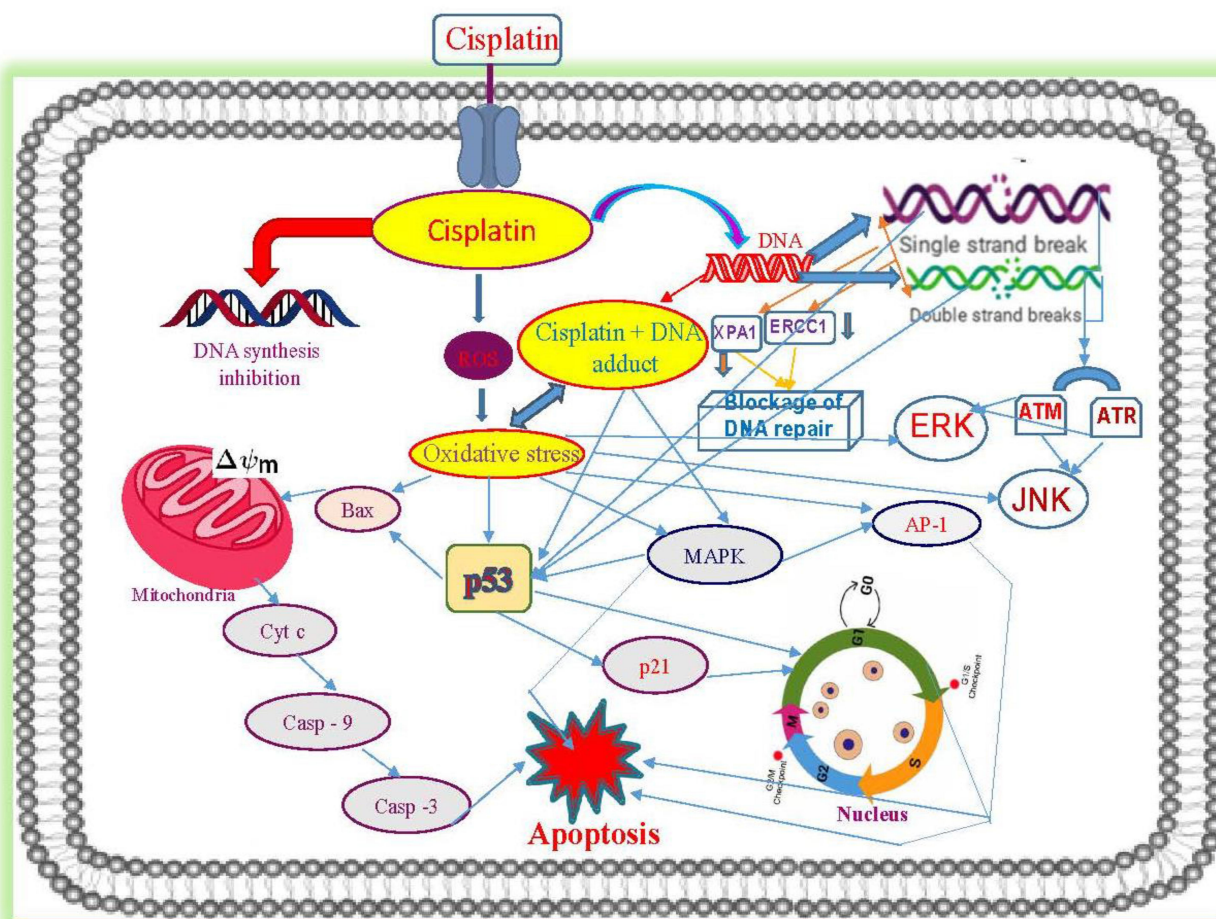
Hepatotoxicity
Clinical studies have shown cisplatin-induced liver damage either alone or in combination with other drugs.[95] Oxidative stress played an important role in cisplatin-induced hepatotoxicity.[96] Cisplatin-induced hepatotoxicity resulted in elevated expression of cytochrome P450 leading to reduction of cell viability, through reduced GSH, and higher ROS production.[97] Clinical manifestations of liver damage from a histopathology standpoint include high levels of serum alanine transaminase (ALT) and Aminotransferase (AST), liver caspase-3 activity, and increased positive staining in Terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) assay.[98]

Cardiotoxicity
Several experimental and clinical studies support the fact that increased oxidative stress and apoptosis have been involved in the cisplatin-mediated cardiotoxicity.[99] Acute cardiovascular toxicity by cisplatin has been observed by direct damage of the vascular endothelium because of an increase of von Willebrand factor released by endothelial cells during chemotherapy.[100] Cisplatin-induced vascular toxicity is becoming an increasing

Figure 5 Molecular mechanisms of cisplatin-induced cytotoxicity in APL cells. Reproduced from Kumar S, Tchounwou PB. Molecular mechanisms of cisplatin cytotoxicity in acute promyelocytic leukemia cells. Oncotarget. 2015;6(38):40734–40746. Creative Commons license and disclaimer available from: http://creativecommons.org/licenses/by/4.0/legalcode.[14]

concern affecting up to 12% of the patients.[101] Clinical manifestations of cardiotoxicity due to cisplatin chemotherapy include heart failure, angina, acute myocardial infarction, thromboembolic events, autonomic cardiovascular dysfunction, both hypertension and hypotension, myocarditis, pericarditis, and severe congestive cardiomyopathy, supraventricular tachycardia, ventricular arrhythmias, atrial fibrillation, occasional sinus bradycardia and occasional complete atrioventricular block reported in the literature.[102]

Nephrotoxicity

The concentration of cisplatin in proximal tubular epithelial cells of kidney is roughly 5 times the serum concentration leading to cisplatin-induced nephrotoxicity.[91] Clinical and experimental literature on cisplatin nephrotoxicity states that unbound cisplatin is freely filtered at the glomerulus and transported into renal tubular cells of kidney.[103] Clinical manifestations include tubular damage and dysfunction leading to decrease in glomerular filtration, segmental degeneration, necrosis, and desquamation of the epithelial cells in the pars convoluta and pars recta of the proximal tubules and the distal tubules.[104] Long-term cisplatin treatment and injury may cause cyst formation and interstitial fibrosis.[105] Mechanisms of cisplatin nephrotoxicity include high expression of calcitonin receptor (Ctr1) and its localization to the basolateral membrane of the proximal tubule, suggesting that Ctr1 is an important cisplatin uptake mechanism in these cells.[106] Another investigation showed knockout of the Octamer-binding protein 2 (OCT2) gene significantly reduced urinary cisplatin excretion and nephrotoxicity.[107] Low concentrations of cisplatin resulted in apoptotic cell death while at higher concentrations necrosis has been reported.[17,108]

Other Organ Toxicity

Neurotoxicity is the third and most serious cisplatin toxicity.[109] Cisplatin treatment caused high levels of Pt–DNA binding and apoptosis of dorsal root ganglion neurons. Studies report changes in the circulation of nerve growth factor could be responsible to the dorsal root ganglia sensory neuron damage induced by cisplatin and return to normal levels after recovery from the neurotoxic damage.[110]

Cisplatin-induced ototoxicity affects up to 93% of the patients receiving cisplatin chemotherapy. Clinical symptoms include progressive and irreversible sensorineural hearing loss.[111] It is hypothesized that transporters interfere in cisplatin influx, leading to cisplatin-induced ototoxicity. Several transporters like copper transporters, organic cation transporters, the transient receptor potential channel family, calcium channels, multidrug resistance-associated proteins, mechanotransduction channels and chloride channels have been studied to understand the pathophysiology of cisplatin-induced ototoxicity.[112]

Testicular toxicity has been linked to cisplatin treatment with damaging effects on spermatogenesis and testicular endocrine function.[113] Histopathological studies have shown spermatogenic damage, germ cell apoptosis, Leydig cell dysfunction and testicular steroidogenic disorder.[114,115]

Retinal toxicity has also been observed after high-dose cisplatin treatment.[116] Clinical manifestations such as secondary glaucoma, internal ophthalmoplegia, retinopathy, cavernous sinus syndrome have been observed after administration of cisplatin.[117]

Cisplatin Resistance
Overview of Mechanisms of Resistance

Molecular mechanisms of cisplatin resistance leading to therapeutic failure include abnormal gene expression, reduced intracellular drug accumulation, enhanced DNA damage repair, efficient drug efflux, altered cell regulatory pathways, abnormal formation of blood and lymphatic vasculature promoting tumor growth, progression, and metastasis, etc.[74] Here below, we discuss several events occurring either before or after cisplatin interacts with the target leading to drug resistance.

Drug Uptake and Efflux for Cisplatin

Reduced uptake and increased efflux are characteristic features of cells exhibiting cisplatin resistance. While CTR1 plays a major role in reduced uptake, ATP7A/ATP7B and MRP2 regulate increased efflux of the drug and metallothioneins may bind and inactivate cisplatin.[118]

Reduced Uptake

The uptake of cisplatin by a cell is a major contributing factor for its resistance. It is estimated that about 50% of cisplatin uptake is regulated by CTRs while other half is transported via passive diffusion or by other transporters.[119] Several studies have been conducted to confirm the roles of copper transporters (CTR) in cancer resistance to cisplatin.[120] In vitro studies in leukemia proved that resistant cells had 36–60% reduction in uptake compared to sensitive cells.[121] Copper, the main CTR1 substrate, homeostasis regulates the up-take of cisplatin.[122,123] CTR1 is happened to be a major protein leading cisplatin uptake.[9] Cisplatin uptake is mediated by the copper transporter 1, distributed to various intracellular compartments by the copper chaperones, and exported from tumor cells with the help of ATP7A and ATP7B.[124] Cisplatin binds to the metal-binding domain of ATPase in a similar way to that in the Atox1, such copper-induced interaction between Atox1 and ATPase is the basis of the copper transportation in cells.[125] Hence, the link between Ctr1 and cisplatin transport may clarify cisplatin resistance to some extent in humans and suggests ways of regulating sensitivity and toxicity to cisplatin.

Increased Efflux

Previous studies conducted on gene expression of Multi-Drug Resistance (MDR) proteins found that MRP2 (MDR protein 2) as the major ATPase responsible for an increased efflux of cisplatin in resistant cells.[126] P-glycoprotein, MRP1 (Multi-Drug Protein 1) and MRP2 (Multi-Drug Protein 2) belong to ATP-binding cassette (ABC) transporter proteins leading to multi-drug resistance via reduced cellular drug accumulation.[127]

P-Glycoprotein (P-gp) is usually overexpressed in most of the cancer types contributing towards chemoresistance.[128] Structurally, P-gp consists of 12 transmembrane regions and two ATP-binding sites resulting in efflux of every effective drug. P-gp is an ABCB1 member of the ABC (ATP binding Cassette) drug transporter family.[129] Knockdown of P-gp or using P-gp inhibitors (Dofequidar fumarate) have sensitized the cells towards cisplatin resistance further confirming their role in effective chemotherapy.[130] Even though cisplatin is not a substrate for P-gp, studies show that P-gp depresses cisplatin-induced caspase-3 activation, reduces cisplatin-

induced Bcl-2 suppression and substitutes cisplatin-induced apoptosis progression, thereby, modulating changes in cell regulatory pathways leading to loss of cisplatin sensitivity.[131] A study conducted on cisplatin-resistant cells showed that upregulation of miR130a might be associated with MDR1/P-glycoprotein-mediated drug resistance. Their results from real-time qRT-PCR for miR-130a expression level and Western blot analysis for comparison of P-gp expression in both cisplatin-resistant and parent cells validated the contribution of P-gp in cisplatin responsiveness. Therefore, miR130a might modulate the expression levels of MDR1 mRNA and P-gp.[132] Using natural products like Asiatic acid, Hesperetin, etc., as inhibitors for P-gp has proved to be effective by modulating NF-kB and MAPK–ERK pathways leading to apoptosis, thereby sensitizing cells for cisplatin therapy.[133,134]

Increased Inactivation
Upon cisplatin administration, the platinum atom binds to endogenous thiols glutathione (GSH) and metallothioneins (MTs) forming complex that is effluxed from the cell in an ATP-dependent fashion by the glutathione transporter family.[135] Moreover, prolonged exposure to cisplatin leads to overexpression of MT, GSH, and other cellular thiols, leading to cell's resistance to cisplatin.[136] Additionally, their reactivity seems to be faster than that of glutathione.[137]

Role of Metallothioneins
Several studies have been conducted to establish the relationship between metallothionein and cisplatin resistance in variety of cancers. Poor outcome of cisplatin chemotherapy has been linked to regulation of metallothionein gene expression.[138–141] Gene regulation studies via RNA interference targeting expression of MT inhibited cisplatin resistance.[142] Translocation of metallothionein from cytoplasm to nucleus seems to be the possible event leading to cisplatin resistance by protecting DNA from cytotoxic effect.[143] Hence, MTs have been shown to play an important role in carcinogenesis since they regulate the supply of zinc for proteins and the activity of zinc-dependent transcription factors to modulate tumor cell growth and proliferation. Therefore, chemotherapy targeting metallothionein can be a novel proposal to increase the efficacy of cisplatin treatment.

Role of GSH
Studies have been conducted to identify the role of glutathione transferase (GST) P1-1 that is often overexpressed in drug-resistant tumors, as a cis-DDP-binding protein.[144] The control mechanism involves GST P1-1 binding to the c-Jun N-terminal kinase (JNK) to inhibit JNK phosphorylation, triggering downstream apoptosis signaling. In addition, other studies have reported that GST P1-1 knockout mice are sensitive to cisplatin treatment than their wild-type counterparts.[145]

Increase in Repair of DNA Damage
Formation of DNA adducts leading to cell death signaling pathway is often impaired in cisplatin-resistant cells. Not only DNA damage repair system is improved but also translesion synthesis mediates cisplatin responsiveness.

Nucleotide Excision Repair (NER) System
Usually, NER protects DNA integrity by chopping damaged nucleotides followed by DNA synthesis. ERCC1-XPF endonuclease is essential for NER of DNA lesions performing interstrand crosslink repair.[146] However, early reports suggest that sensitivity to cisplatin treatment has been identified with low expression of NER proteins, like Xeroderma Pigmentosum group A (XPA) and Excision repair cross-complementing-1 (ERCC1), lacking NER repair mechanism in several cancers.[60] Overexpression of human ERCC-1 may inhibit a pathway specific to the repair leading to cisplatin sensitivity.[147] Hence, ERCC1 expression is considered as a biomarker for the prediction of cisplatin resistance.

Mismatch Repair (MMR) System
Genomic stability is maintained by MMR system involves the correction of mismatched nucleotides in the complementary DNA strands via insertions or deletions, arising from DNA replication errors. hMLH1 is the human homologue of the yeast mismatch repair gene MLH1.[148] Loss of expression of the hMLH1 and hPMS2 of MMR complex after administration of cisplatin has been observed in cisplatin resistance types.[149] Such loss of hMLH1 protein has been linked to methylation of the hMLH1 promoter.[148]

Translesion Synthesis
Translesion synthesis (TLS) is a DNA damage tolerance process by which DNA replicates past DNA lesions. Cisplatin adduct resulting in a delayed replication complex will trigger DNA polymerases including POLH, POLI, POLK, REV1, REV3 and REV7.[150] This will result in bypass of the lesion by translesion synthesis so that replication can resume. In addition, defects in

MLH1 and MSH6 (the MMR proteins) are associated with increased level of translesion synthesis, the phenomenon whereby DNA synthesis is not blocked but proceeds beyond cisplatin adducts.[151] Increased translesion synthesis occurs in cisplatin-resistant cells due to overexpression of Human Homolog of the *Saccharomyces cerevisiae* 3 (REV3).[152] REV3 is the catalytic subunit of TLS polymerase ζ, plays an important role in DNA damage response induced by cisplatin. Combined knockdown of REV3 and Ataxia Telangiectasia and Rad3-related protein (ATR) enhanced cytotoxicity in cisplatin-sensitive and -resistant cell line.[153]

Homologous Recombinational Repair
Homologous recombination system repairs breaks in the double-stranded DNA. Cisplatin adducts are usually recognized in the S Phase of cell cycle and treated by HRR. However, HR-deficient cells (mutated BRCA1/2) are more sensitive to cisplatin treatment establishing the role of BRCA1 and BRCA2 to cisplatin resistance.[154] Moreover, it has been reported that cisplatin resistance develops in sensitive tumors because of secondary mutations that compensate for BRCA1/2 deficiency.[155]

Cytoplasmic Proteins
Studies show that cytoplasmic proteins like voltage-dependent anion channel (VDAC) are found to be responsible for the cisplatin-resistant phenotype.[156] VDAC is a mitochondrial protein with vital and lethal functions. Cisplatin binds to mitochondrial DNA as well leading to cell death possible direct effect of cisplatin on mitochondria independent of nuclear DNA interaction.[157]

Control Mechanisms for Cisplatin Resistance
Although clinical data show high initial response to platinum-based chemotherapy, over time neoplasms become refractory, increasing mortality due to chemoresistance. Cisplatin resistance has been studied extensively for better understanding in drug designing and treatment. Previous studies showed the evidence of different mechanisms responsible for resistance to cisplatin treatment.

Nrf2 Signaling
Cisplatin decreases mitochondrial membrane potential reducing ATP content with an increase in ROS.[158] Another study introduced HIF-independent, CD133-mediated mechanism

of cisplatin resistance.[159] CD133 is a biomarker for glioblastoma (GBM). The molecular mechanism of CD133-dependent resistance could be upregulation of CD133 under hypoxic conditions that may lead to activation of the anti-apoptotic Akt pathway, resulting in drug resistance.[160] Further molecular studies have revealed the role of nuclear factor erythroid 2-related factor 2 (Nrf2) as the sensor of oxidative stress, and has been shown to be involved in cisplatin resistance and chemoprotection.[161–164] Under normal physiological conditions, Kelch-like ECH-associated protein 1 (Keap1)-Nrf2 blocks Nrf2 in the cytoplasm, however, oxidative stress activates Nrf2 through the PI3K/Akt signaling pathway and translocate into the nucleus activating the small musculoaponeurotic fibrosarcoma oncogene homologue (sMAF) heterodimerization.[165,166] This leads to the activation of the genes containing the antioxidant response element (ARE), activating the transcription of antioxidant enzymes.[167] It has been shown that natural products such as melatonin and berberine have cytoprotective effect from oxidant injuries through activation of the Nrf2 pathway.[161–163] Studies show a regression in cisplatin-mediated cytotoxicity in Nrf2-deficient cells via reduction in total GSH levels leading to cisplatin resistance.[168] A recent study has been conducted on micro RNAs (lncRNAs, circRNAs, NF-κB, SOX2 and TRIM65) and their regulation in cisplatin chemotherapy of lung cancer via targeting various pathways such as Wnt/β-catenin, Rab6, CASP2, PTEN, and Apaf-1 and STAT3 to suppress cisplatin resistance.[169] Further investigations indicated that microRNA-mediated regulation of Nrf2 signaling pathway restoring cisplatin sensitivity in human cancer cells is considered as a novel therapy.[170]

Epithelial–Mesenchymal Transition (EMT)
EMT is a physiological process necessary for embryonic development. However, cancer cells apply this mechanism significantly contributing to chemoresistance. The mechanism involves converting the immobile epithelial cells into mobile mesenchymal cells and therefore regulating cell–cell adhesion and cellular extracellular matrix.[171] This cascade of events leads to tumor cell invasion. Cisplatin stimulates macrophages to secrete chemokine ligand 20 (CCL20) for recruiting T helper cells to maintain the immunosuppressive tumor microenvironment facilitating cancer cell progression and chemokine receptor 6 (CCR6) enhancing tumor cell migration and induces the EMT mechanism, causing EMT-mediated drug resistance.[172–176]

Autophagy

Autophagy is a "self-eating" mechanism that is important for balancing out energy demands during growth and also stress. Therefore, autophagy serves as a survival mechanism, where toxic and aged organelles and macromolecules are degraded. Studies have shown that prolonged exposure to cisplatin impedes autophagy leading to cisplatin resistance.[177] A recent study has demonstrated that under hypoxia, cisplatin-induced apoptosis is significantly reduced suggesting autophagy-mediated cisplatin resistance.[178] Recent studies have also pointed out that hypoxia-inducible factor (HIF)-1α and histone deacetylases 4 (HDAC4) facilitate the interaction between p53 and rat sarcoma (RAS) signaling in cisplatin-resistant cell lines through dysregulation of apoptosis and autophagy.[179] GAS5 downregulation is linked to cisplatin resistance by inhibiting autophagy resulting in cisplatin sensitivity in Non-small cell lung carcinoma (NSCLC) cells.[180] Reports show that cisplatin-treated ovarian cancer cells showed decreased putative serine/threonine protein phosphatase (PRPA1)-medicated autophagy.[181] In addition, autophagy is studied as a cytoprotective process during cisplatin-induced injury.[182,183]

Combination Therapy of Cisplatin with Other Cancer Drugs
Overview

Drug resistance has been observed in many patients who have relapsed from cisplatin treatment due to its cellular uptake and efflux of cisplatin, increased biotransformation and detoxification in the liver, and increase in DNA repair and anti-apoptotic mechanisms. To overcome drug resistance, cisplatin has been commonly used in combination with some other drugs in treating a wide variety of cancers.

Cisplatin and Paclitaxel

Paclitaxel (Taxol®) chemically synthesized from bark of western yew acts as an effective treatment for various cancers especially ovarian and breast cancer.[184] However, because of its low therapeutic index, an improved delivery system is deemed necessary. Therefore, a combination therapy of intravenous paclitaxel plus intraperitoneal cisplatin has been employed to improve the survival of ovarian cancer patients.[185] Numerous clinical studies have been conducted to test the efficacy of this combination in various cancers.[186,187] The literature search disclosed that there exists an inverse relationship between platinum and taxane with about 26 genes responsible for this effect.[188]

Cisplatin and Tegafur-Uracil (UFT)

Tegafur-uracil (UFT) is an oral fluorouracil (FU) composed of tegafur and uracil. Antitumor effects of UFT are low in most malignant tumors.[189] But UFT is widely used in Japan as a postoperative adjuvant chemotherapy because of its mild toxicity characteristics.[190] Few studies have reported that the combination of cisplatin with UFT has a significant effect in patients.[191–194] While other research groups have pointed out that fluorouracil alone is a better regimen than in combination with cisplatin.[195]

Cisplatin and Doxorubicin

In 1960, doxorubicin (DOX) was isolated from *Streptomyces peucetius*. DOX is widely used antineoplastic drugs alone or in combination due to its cytotoxic activity.[196] The combination effect studied to be an effective therapy with modest antitumor activity with tolerable adverse effects in patients.[197,198] Chemotherapy with cisplatin-doxorubicin significantly enhanced overall survival for endometrial cancer patients.[199] However, compared with cisplatin plus doxorubicin, cisplatin monotherapy yielded similar survival among children with standard-risk of hepatoblastoma.[200]

Cisplatin and Gemcitabine

Gemcitabine [2'- deoxy- 2', 2'- difluorocytidine monohydrochloride (β isomer); dFdC] is a novel nucleoside analogue with antiviral effects and efficient for anticancer therapy with mild toxicity profile.[201] Its mode of action associated with the incorporation of gemcitabine diphosphate (dFdCTP) into DNA is most likely considered as being the major mechanism by which gemcitabine causes cell death.[202] Clinical studies have shown that cisplatin plus gemcitabine has a significant survival advantage without the addition of substantial toxicity.[203,204]

Cisplatin and Vitamin D

Not only as a steroid hormone playing critical role in mineral homeostasis and bone metabolism, but Vitamin D [1α, 25-dihydroxycholecalciferol] also had broad-spectrum anti-tumor activities.[205] Calcitriol acts through both genomic and non-genomic mechanisms.[206] Vitamin D

compounds are found to be effective against colorectal, breast, prostate, ovarian, bladder, lung, skin cancers and leukemia.[207] The molecular mechanisms behind their cytotoxicity involve inhibition of cancer cell proliferation and invasiveness, induction of differentiation and apoptosis, and promotion of angiogenesis.[205] Combination therapy of Vitamin D with cisplatin or carboplatin inhibited cell proliferation in breast cancer cell lines.[208] Studies on SCC showed synergy between cisplatin and Vitamin D via regulating Lipocalin-2 (LCN2)-modulated NF-κB pathway.[209] Furthermore, Glutathione Peroxidase 1 (GPX1) expression has been studied to be crucial in cisplatin-resistance but can be reduced by vitamin D.[210] The combination therapy with calcitriol offers evidence and support for the further study of calcitriol and its implications in cancer chemotherapy.

Other Possible Drug Combinations

Scientific evidence shows that combination therapies of cisplatin with other drugs have been tested in cancer cell lines for more efficacy. Some have shown additive while few other responses have been found to be synergistic. Table 1 presents the different drug combinations used to treat various cancers in combination with cisplatin.

Natural Products

Chemoresistance has become a serious challenge in the cancer management. However, natural products, in the form of chemo sensitizers have attracted the attention of researchers. Natural products for cancer therapy have been very promising after thorough clinical and pre-clinical investigations. The bioactive components derived from these natural products have been tested for anti-cancer activity. These compounds work either alone or in combination with conventional chemotherapeutic drugs to alleviate the side effects of the drug administered and also protecting healthy cells in vicinity. The molecular target for individual product varies, but leading to dose and time-dependent cytotoxicity. The majority of natural products effectively target cancer cells specific ROS-sensing signaling pathways, thus attacking tumor development and progression. We have compiled the updated literature available on natural products in a tabular form below, describing the role of natural products in overcoming cisplatin chemo-resistance (Table 2).

Table 1 Other Potential Cancer Drug Combinations with Cisplatin

Drug	Cancer	Reference
Cyclophosphamide	Advanced carcinomas of salivary gland	[233,234]
Mitomycin & Vindesine	Non–small-cell lung cancer	[235]
Etoposide	Non–small-cell lung cancer	[235,236]
Hydroxyurea	Cervical cancer	[237]
Docetaxel	Gastric cancer	[238]
Bevacizumab	Non–small-cell lung cancer	[239]
Irinotecan	Neuroendocrine carcinoma Gastric cancer Esophageal cancer	[240–242]
Methotrexate	Squamous cell carcinoma cancer	[243]
Dacarbazine, Tamoxifen	Melanoma	[244]
Ifosfamide	Non–small-cell lung cancer	[245]
Mitomycin	Non–small-cell lung cancer	[246]
Capecitabine	Gastric cancer	[247]
Bleomycin	Ovarian cancer	[248]
Epirubicin	Hepatocellular carcinoma	[249]
Adriamycin	Uterine stromal sarcoma	[250]
S-1 DCS	Gastric cancer	[251]

Nanotechnologic Formulations

Effective drug delivery and tumor targeting are of paramount importance in clinical oncology. However, the pharmacokinetics of chemotherapy drugs is often affected by factors like poor solubility, loss of bioactive structure, inadequate cellular uptake, short plasma half-lives due to rapid excretion from kidneys or enzymatic degradation, drug resistance, and side effects due to non-specific binding.[211] Several nanoparticle formulations have been developed to address the problems encountered by conventional chemotherapy. More than a few nanoparticle platforms are designed with polymers and targeting agents enhancing colloidal stability and successful delivery of the bioactive compound in cancer cells. Clinically relevant therapeutic and diagnostic nanoparticles include two categories, Organic (liposomes, protein-based, polymeric/micelle) and inorganic (iron oxide, silica, and gold).

Table 2 Natural Products Used in Reducing Cisplatin Toxicity and Suppressing Its Resistance

Natural Compound	Organism	Category	Signaling Pathway	Year	Reference
Melatonin	*Homo sapiens*	Hormone	Nrf2	2020	[161]
Resveratrol	Several plants	Polyphenol	Nrf2	2020	[162]
Berberine	*Berberis aristata*	Isoquinoline Alkaloid	Nrf2	2019	[163]
Luteolin	*Reseda luteola*	Flavonoid	Sox2	2016	[252]
Cryptotanshinone	*Salvia miltiorrhiza Bunge*	Quinoid	Nrf2	2015	[253]
Licorice	*Glycyrrhiza glabra*	Hydroalcohol	CYP1B1	2017	[254]
Novobiocin	*Streptomyces niveus*	Antibiotic	HSP90	2008	[255]
Tangeretin	Citrus Fruits	Flavonoid	PI3K/Akt	2009	[256]
Shikonin	*Lithospermum erythrorhizon*	Napthoquinones	Pyruvate Kinase M2	2017	[257]
Diallyl trisulfide	*Allium sativum*	Organosulfide	Nrf2	2017	[258]
Curcumin	*Curcumin longa*	Polyphenol	BRCA	2014	[259]
Vitamin C	N/A	Ascorbic Acid	P53	2016	[260]
Celastrol	*Tripterygium wilfordii*	Triterpenoid	ERK1/2 and p38 MAPK	2019	[261]
Chinese Bayberry Leaves	*Myrica rubra*	Proanthocyanidins	HIF-1α and VEGF	2018	[262]
Oleuropein	*Olea europaea*	Monoterpenoids	Matrix metalloproteinase	2018	[263]
Terrein	*Aspergillus terreus*	Cyclopentanone	ERK	2017	[264]

Inorganic NPs are mainly used for cancer imaging applications along with thermal ablation of tumors while organic NPs are approved for vaccination, hemostasis, drug delivery systems, and topical dermal delivery.[212]

Nanocarriers

Clinical manifestations of a typical tumor site include leaky blood vessels and poor lymphatic drainage.[213] Hence, multiple drug resistance occurs because of lack of control on drug delivery in conventional chemotherapy.[129] In spite of non-specific diffusion, a nanocarrier can escape into the tumor tissue through leaky vasculature via EPR effect offering many advantages over free drugs. Studies have shown that nanoparticle diameter size <200 nm is more effective for successful drug delivery.[214,215] Not only nanocarriers protect the drug from premature degradation, they also enhance absorption of the drugs into a selected tissue and improve intracellular penetration.[216] Targeted drug delivery is possible through nanocarriers by conjugating a ligand molecule that binds to specific receptors on cell surface.[217] A recent study has shown that cisplatin-loaded human epidermal growth factor receptor 2

(HER2) targeted poly(lactic-co-glycolic) nano platform system increases the therapeutic efficacy by taking advantage of overexpressed (HER2) receptors, using them as docks for targeted chemotherapy.[218] Such specific-binding leads to receptor-mediated internalization, a requisite for drug release inside the cell. A successful liposomal formulation of encapsulated into liposome has been clinically investigated as lipoplatin.[219] The therapeutic efficacy of lipoplatin is attributed to its primary action targeting tumors and hence, causing a greater damage to tumor tissues compared to normal tissues.[220] In addition, preclinical studies with lipoplatin have shown less nephrotoxicity compared to cisplatin, contributing cytoprotective function to adjacent cells.[221,222] Also, for the first time, lipid-coated cisplatin nanoparticles administered through microneedle in a mice xenograft model significantly induced cytotoxicity and apoptosis (apoptotic index of 58.6%). This cisplatin-nanoparticle microneedle system did not elicit other organ toxicity in the animal model, indicating that it is bio-safe.[223] Another study on human melanoma tumor cells treated with cisplatin nanoparticle showed significant cytotoxicity through the "neighboring

Table 3 Cisplatin-Nanoparticle Combinations Under Clinical Trials

Name (Company)	Formulation	ClinicalTrials.gov Identifier	Status	Cancer Type
Lipoplatin (Regulon, Inc)	PEG- liposome-based	NCT02702700	Phase I	Pleural Malignancies
SPI-77 (ALZA Pharmaceuticals)	PEG- liposome-based	NCT00004083	Phase II Pilot	Ovarian Cancer
		NCT00102531	Phase Ib/IIa	Osteosarcoma Metastatic to the Lung
		NCT00004033	Phase II	Malignant Pleural Mesothelioma
		NCT01861496	Phase I/II	Advanced or Refractory Tumours
NC-6004 Nanoplatin (NanoCarrier Co., Ltd)	Polymeric -Micelles	NCT00910741	Phase I/II	Pancreatic Cancer
AroplatinTM (Aronex Pharmaceuticals)	Liposomes	NCT00316511	Phase I	B-Cell Lymphoma
		NCT00081536	Phase I/II	Colorectal Cancer
		NCT00081549	Phase I/II	Metastatic Pancreatic Cancer
		NCT00043199	Phase II	Colorectal Cancer
		NCT00057395	Phase I/II	Solid Malignancies
		NCT00004033	Phase II	Malignant Pleural Mesothelioma
LiPlaCis (LiPlasome Pharma)	Liposome Based	NCT01861496	Phase I/II	Advanced or Refractory Tumours

effect" upon administration of 1 mg/kg dosage.[224] We reviewed recent clinical investigations of cisplatin nanoparticle formulations in a tabular form showing their importance as a disruptive technology for effective chemotherapy (Table 3).

Combination Chemotherapy with Nanoparticles

The combination of drugs with nanoparticles is advantageous over single drug administration. Those benefits include absolute delivery of a correct ratio of each drug, synergistic therapeutic effects, suppressed drug resistance, and the ability to control drug exposure temporally.[225] Combination therapy of doxycycline and cisplatin-loaded polysaccharide-based nanovehicles was found to be synergistic for breast cancer treatment.[226] This nanoparticle-based drug delivery was made possible from HER2 antibody-decorated nanoparticles assembled from aldehyde hyaluronic acid and hydroxyethyl chitosan with spherical shape, having an average size of ~160 nm and a zeta potential of −28 mV, and showing a pH-responsive surface charge reversal and drug release with significant enhancement on the cellular uptake.[226] Another interesting study has shown the delivery of doxorubicin and

cisplatin via a single polymer-caged nanobin prepared with doxorubicin-encapsulated liposomal core protected by a pH-responsive cisplatin prodrug-loaded polymer shell.[227] The cytotoxicity of each drug at low doses exhibits higher synergy than combinations of either the free drugs or separately nano-packaged drugs. A synergistic cytotoxic effect of doxorubicin and cisplatin has been accomplished by designing polymeric nanogels of about <100 nm in size based on polyacrylic acid. The experimental results have shown efficacy for the multidrug-resistant MCF-7/ADR tumor with reduced side effects.[228] Furthermore, systemic co-delivery of cisplatin and doxorubicin through hyaluronic acid-modified amine-terminated fourth-generation polyamidoamine dendrimer nanoparticles was shown to be effective treatment for breast cancer treatment.[229]

Combination of cisplatin and a protein phosphatase 2A inhibitor (4-(3-carboxy-7-oxa-bicyclo[2.2.1]heptane-2-carbonyl)piperazine-1-carboxylic acid tert-butyl ester) using PEG-b-PLGA micelles has facilitated to overcome tumor resistance to cisplatin.[230] This combination has shown to prolong drug residence in the blood while minimizing the side effects. In vitro studies with mesoporous silica

nanoparticles loaded with cisplatin and phthalocyanine has been evaluated for its potential treatment efficacy in HeLa cells as nanocarriers.[231] The confocal microscopy experiments presented that the silica nanomaterials can be effectively internalized in HeLa cells. The in vitro and in vivo studies with oligonucleotides assembled Au nanorod for combination remote-controlled drug delivery of doxorubicin and cisplatin have reported significant cell toxicity and controlled solid tumor growth, respectively. The design included a complementary DNA (cDNA) with the 5′ amine functional group assisted to chain cisplatin-Dox with amide bond.[232] We discussed updated literature on nanoparticle formulations, in combination with cisplatin in Table 4.

Table 4 Nanoparticles Used in Combination with Cisplatin

Cancer Type	NP Platform	Year	Reference
Breast Cancer	Doxorubicin- liposomal core cisplatin- polymer shell	2010	[227]
Lung	ScFvEGFR-Heparin-Cisplatin NP	2011	[265]
Melanoma	Lipid Coated NP	2013	[224]
Prostate Cancer	PLGA-mPEG NP	2007	[266]
Hepatocellular Carcinoma	Lipid-coated Cisplatin NPs Co-loaded with miRNA-375	2016	[267]
Mice Xenograft	Lipid Coated Cisplatin NP	2018	[223]
Bladder Carcinoma	Gemcitabine Monophosphate NPs and Cisplatin NP	2014	[268]
Non–Muscle-Invasive Bladder Cancer	Cisplatin loaded poly L-aspartic acid sodium salt NP	2017	[269]
Human Ileocecal Adenocarcinoma	Fucoidan-Cisplatin nanoparticles	2017	[270]
Breast Cancer	poly(γ,l-glutamic acid)-Cisplatin NP	2019	[271]
Brain Cancer	Cisplatin-Loaded Poly (Butylcyanoacrylate) NP	2019	[272]
Melanoma	Losartan microspheres and (PLG-g-mPEG)-cisplatin NP	2019	[273]
Renal Adenocarcinoma	Cisplatin-Loaded Polybutylcyanoacrylate NP	2020	[274]
Ovarian Carcinoma	Cisplatin-loaded lipid-chitosan hybrid NP	2019	[275]
Colorectal Cancer	Alginate nanogel co-loaded with cisplatin and gold NP	2019	[276]
Glioblastoma	Cisplatin-loaded NPs with Polyethylene glycol matrix	2017	[277]
Ovarian Carcinoma	Cisplatin loaded cysteine-based poly-(disulfide amide) NP	2017	[278]
Breast Cancer	Cisplatin loaded Solid Lipid NPs	2020	[279]
Colon Adenocarcinoma	Cisplatin and Gold NPs co-loaded into alginate hydrogel	2019	[280]
Glioblastoma	Folate/Cisplatin-si-GPX4 in Iron Oxide NP	2020	[281]
Ovarian Carcinoma	Cisplatin-loaded PLGA NP	2019	[218]
Hepatocellular Carcinoma	Cisplatin-oleanolic acid co-loaded calcium carbonate NP	2019	[282]
Head and Neck Cancer	Gold NP coated with glucose and cisplatin	2018	[283]
Human Cervical Cancer	Pegylated liposomes loaded with cisplatin and magnetic NP	2018	[284]
Ovarian Carcinoma	AS1411 - PEGylated poly(lactic-co-glycolic acid) NP	2018	[285]
Lung Carcinoma	EGFR-targeted lipid polymeric NP co-loaded with cisplatin and doxorubicin	2019	[286]

Conclusions

Cisplatin is a commonly used metal coordination compound that was approved for clinical treatment of various cancers. Its molecular mechanism of action primarily involves formation of DNA adducts leading to onset of programmed cell death through initiation of major signaling pathways. Production of free radicals from ruptured cell membrane due to disruption of calcium homeostasis, lipid peroxidation, DNA damage, p53 activation, overexpression of p38, MAPK and JNK signaling pathways, caspase 3 and caspase 9 activation, and down-regulation of oncogenes, collectively trigger apoptosis of cancer cells. These molecular mechanisms of toxic action constitute that hallmarks of cisplatin bio-activity. However, its clinical utilization for cancer treatment has also raised safety concerns associated with a number of side effects including hepatotoxicity, cardiotoxicity, neurotoxicity, retinal toxicity and other systemic effects. Another cause for concern is related to drug resistance associated with the alterations in cisplatin uptake and efflux processes; increased drug biotransformation and excretion, and enhanced DNA repair mechanisms to reduce cisplatin toxicity to cancer cells. Both drug resistance and safety issues in cancer monotherapy with cisplatin have led to the development and implementation of novel therapeutic strategies that include combination treatments with other cancer drugs such as doxorubicin, gemcitabine, paclitaxel, vitamin D, and tegafur-uracil, as well as the application of nanotechnology-based formulations to enhance cisplatin drug delivery to cancer patients.

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Disclosure

All authors have declared that they do not have any competing and/or financial interests for this work.

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