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Review Paper

Overcoming Cisplatin's Challenges: A Promising Future in Cancer Care; A Comprehensive Review

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ABSTRACT

Background: Cisplatin's common use as an anti-neoplastic drug poses significant challenges due to its adverse effects, including renal disorders, neuropathies, hearing impairment, and gastrointestinal issues.

Methods: A comprehensive search was done across major bibliographic databases, including PubMed, Embase, Web of Science, Google Scholar, and Scopus on cisplatin's application in various cancer treatments. A manual examination of article reference lists was conducted, collecting data from 1990 to October 2023 for up-to-date research analysis.

Results: Cisplatin primarily acts by binding to DNA in the cell nucleus and disrupting DNA transcription and replication, leading to cytotoxicity and malignant cell destruction. Mechanisms of resistance included altered drug absorption, increased efflux and detoxification, modified targets, and increased DNA repair. Interactions with matrix proteins, pH changes, and food affect cisplatin effectiveness. Cisplatin-induced DNA damage mainly forms DNA adducts, causing intra- and inter-strand cross-links. Despite its therapeutic benefits, inevitable adverse effects, like nephrotoxicity, ototoxicity, gastrointestinal diseases, hepatotoxicity, cardiovascular issues, and neuropathy exist. Strategies to mitigate these include hydration therapy, thiol-containing agents, antioxidants, and modulators. Combination therapy enhances cisplatin efficacy.

Conclusion: Cisplatin is a potent anticancer tool marked by challenges from adverse effects and emerging resistance. Ongoing research focuses on combined therapeutic approaches and supports interventions to enhance efficacy and reduce adverse effects, fostering optimism for better cancer treatments.

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1. Introduction

Cancer has significantly affected numerous individuals for an extended period, ranking as the world's second most prevalent cause of mortality, following closely behind heart disease [1]. This ailment is intricately linked to genetics, epigenetics, and environmental influences, leading to a wide spectrum of variations at the levels of tissues, tumors, and individual cells [2, 3]. In the context of cancer, the usual sequence of cellular processes and signaling pathways is disrupted [4]. Regulations governing cell division are frequently overlooked, and cancer cells function autonomously, almost as if they were orchestrating their unique symphony [5].

The treatment of cancer varies depending on the cancer type and its stage. Patients receive a combination of conventional and therapeutic approaches, including surgery, chemotherapy, radiation therapy, immunotherapy, gene therapy, hormone therapy, and photodynamic therapy, as well as combined therapies [6–8]. Cisplatin is a potent and invaluable chemotherapy agent employed in the treatment of a wide spectrum of malignancies, including bladder, cervix, head and neck, ovary, non-small cell lung, prostate, esophagus, and metastatic breast cancers [9–13]. Cisplatin stands as one of the most frequently utilized anticancer medications, often employed either alone or in combination with other chemotherapy drugs to address conditions, such as head, ovarian, and lung cancers [10, 14]. This medication interacts with nitrogen atoms found in adenine and guanine within the DNA molecule, instigating damage to the DNA of cancerous cells and inhibiting their replication, ultimately resulting in cellular demise [15]. Resistance to cisplatin in cancer cases often presents a substantial impediment to successful chemotherapy [14, 16].

In mammals, cisplatin can permeate cell membranes either via diffusion through a copper transporter or simple diffusion mediated by its receptors [17]. Upon entering the cell cytoplasm, cisplatin undergoes hydrolysis and transforms into a potent electrophile, which subsequently reacts with intracellular nuclei. This compound primarily forms interactions with the purine bases present in nucleic acids, leading to the formation of DNA-DNA or DNA-protein cross-links [15, 18]. The consequences of these alterations include disruptions in DNA structure, activation of repair mechanisms, and the subsequent induction of apoptosis [18]. Cisplatin is believed to play a constructive role in generating oxidative stress, activating intrinsic and extrinsic apoptosis pathways, promoting P53 expression, and suppressing proto-oncogenes [14, 19, 20].

Using cisplatin for cancer treatment comes with some real challenges. It can lead to harsh side effects, like kidney problems, nerve damage, hearing issues, and gastrointestinal disorders, like nausea and vomiting [21–25]. It is challenging when cancer becomes resistant to cisplatin [26]. This resistance can happen from the beginning or develop over time and is influenced by various factors [27]. Even though cisplatin is used a lot for different types of cancer, it often does not work well for patients with advanced cancer that has spread [28].

2. Materials and Methods

Search method and eligibility criteria

A comprehensive search was conducted among major electronic databases, including PubMed, Embase, Web of Science, Scopus, and Google Scholar to identify studies investigating the mechanisms of cisplatin in the treatment of various types of cancer, along with its associated adverse effects on the human body. Data were collected from 1990 to 2023 (October 2023) using specific keywords, such as “cisplatin”, “cancer”, “adverse effects”, “combination” and “mechanism of action” using all equivalents and similar phrases. After the initial search, relevant articles were selected based on the evaluation of their titles and abstract content, and duplicate and irrelevant articles were removed to align with our research objectives. This review included a wide range of articles, including experimental and observational studies, case reports, reviews, and commentaries, focusing on the efficacy of cisplatin in treating diverse types of cancers, as well as its associated side effects and the impact of various compounds on mitigating these effects. Additionally, we assessed the advantages of combining cisplatin with other agents. The search was limited to articles published in the English language.

3. Results

The mechanism of action of cisplatin

The primary mechanism of cisplatin is widely recognized as its binding to DNA within the cell nucleus, subsequently disrupting normal transcription and DNA replication processes [20, 29]. These disruptions can instigate cytotoxic processes that ultimately lead to the death of cancer cells [30]. Following intravenous administration, cisplatin rapidly disperses in the tissues and exhibits a strong binding affinity, binding up to 95% to plasma proteins [31, 32]. This binding is primarily attributed to platinum’s high reactivity with thiol group sulfur [33]. Recent research indicates that the copper transport-

er protein CTR1 also plays a role in cisplatin attraction [15] cisplatinum, or cis-diamminedichloroplatinum (II). Cisplatin tends to reduce the concentration of CTR1, which in turn, reduces the accumulation of cisplatin within cancer cells. Cells with higher CTR1 expression may accumulate more cisplatin, rendering them more sensitive to its effects [15] cisplatinum, or cis-diamminedichloroplatinum (II).

Drug accumulation

Cisplatin is typically administered intravenously, allowing it to circulate throughout the bloodstream [20]. High blood serum chloride concentrations can affect cisplatin by substituting chloride groups, hindering its interaction with water molecules. Therefore, cisplatin reaches the outer surface of cancer cells primarily as a neutral molecule [34]. While the precise biochemical mechanisms underlying cisplatin uptake into cells are not fully understood, passive diffusion is believed to be the primary method of absorption. However, certain facilitated or active transport mechanisms may also contribute to cisplatin intracellular accumulation [34]. While cisplatin absorption is not saturable or inhibited by structural analogs, its degree of absorption relies on energy and can be modulated by pharmacological agents, such as the Na^+/K^+-ATPase inhibitor ouabain [35].

Within cells, chloride concentrations typically range between 2 and 30 mM. The formation of aqueous species from cisplatin occurs as one or both chloride-leaving groups are substituted by water molecules, resulting in the formation of $[Pt(H_2O)Cl(NH_3)_2]+$ and $[Pt(H_2O)_2(NH_3)_2]+$cations. These mono and diaquated forms of cisplatin exhibit high reactivity toward the nucleophilic centers of biomolecules, with water (H_2O) serving as a superior leaving group compared to chloride (Cl) [36].

Binding to non-DNA targets

Before accumulating in the cell cytoplasm, cisplatin has the potential to bind to cell membrane phospholipids and phosphatidylserine [37]. Additionally, within the cytoplasm of many cells, cisplatin can react with various components containing nucleophilic sites, including the cytoskeleton's microfilaments, thiol-containing proteins, and peptides, as well as RNA [37, 38]. As a result, it is estimated that over 1% of cisplatin molecules entering the cell bind to nuclear DNA, while the majority ultimately bind to proteins and other biomolecules [39]. Due to the strong reactivity of platinum compounds with soft nucleophiles, like sulfur donor biomolecules, glutathione tripeptide (GSH) is believed to be one of the primary non-DNA targets of cisplatin [40]. GSH is abundantly present in cells at concentrations of around 0.5 to 10 mM [41]. Both glutathione and other thiol-containing molecules, like metallothioneins, rapidly bind to platinum, forming inactivated platinum-GSH adducts that are subsequently expelled from the cell through non-specific glutathione conjugate pumps [42] (Figure 1).

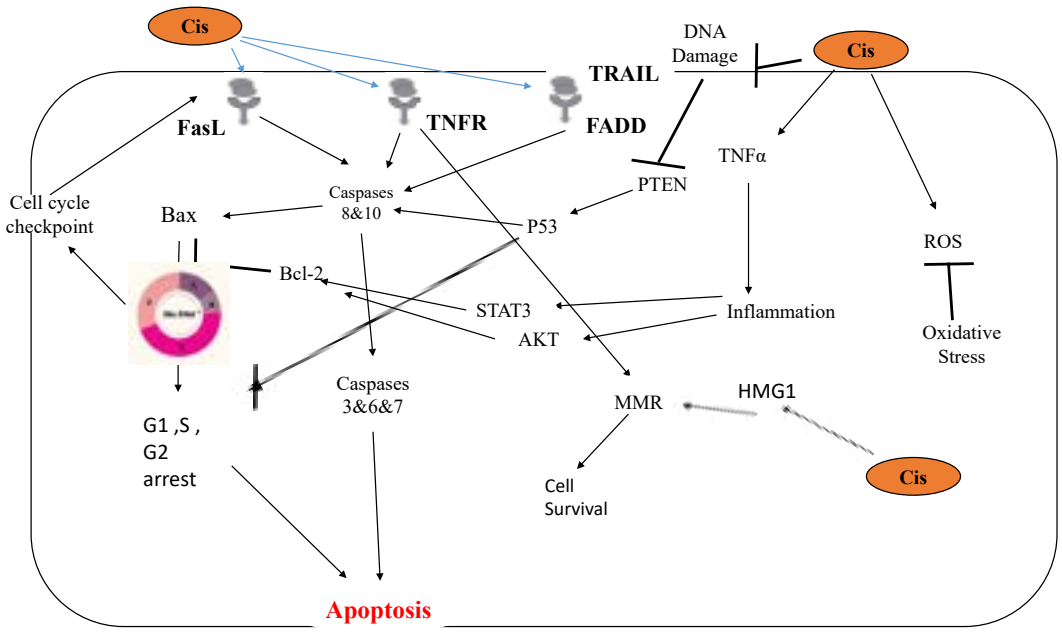

Figure 1. Mechanism of action underlying the anticancer effects of cisplatin

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The interaction with non-DNA targets is thought to contribute to the mechanism of cisplatin's cytotoxicity in cancer cells [29]. It is known that cisplatin's reaction with cellular components can disrupt the function of crucial proteins. For example, cisplatin can inhibit Hsp90 (heat shock protein 90) by binding to its C-terminal ATP-binding site [43]. Hsp90 is vital for signal transduction and cell cycle regulation [44].

Binding to DNA

Cisplatin is known for its high nucleophilicity, making it particularly reactive with the N7 atoms of guanine and adenine in the major groove of DNA [45]. This reactivity leads to the formation of various DNA adducts with distinct structures upon reaction with cisplatin [15, 46] cisplatinum, or cis-diamminedichloroplatinum (II). Initially, monofunctional DNA adducts are formed, but a majority of them exhibit higher reactivity, resulting in the creation of inter- or intra-strand cross-links. It has been observed that over 55% of cisplatin adducts consist of intra-strand crosslinks, specifically 1,2-d (GpG) and around 20-25% are d(ApG) intra-strand crosslinks. Minor adducts include 1,3 intra-strand cross-links and inter-strand cross-links. Additionally, DNA-protein cross-links have been reported for cisplatin [47]. The 1,2 inter-strand DNA adducts, although not definitively proven, are believed to play a crucial role in cisplatin's anticancer activity, especially with certain high mobility group proteins (HMG1) recognizing these platinum-DNA 1,2 adducts. Notably, trans-platinum compounds, which do not form 1,2-adducts, are inactive for anticancer activity due to their high reactivity [48, 49] (Figure 1).

Furthermore, the efficiency of DNA repair systems, such as nucleotide excision repair (NER), varies for different types of adducts [50]. TNER is more efficient at repairing 1,3 inter-strand adducts compared to 1,2 intra-strand adducts, while 1,2 adducts, such as d(GpG), are less effectively repaired [51]. The cytotoxic mechanism of cisplatin may involve not only 1,2 inter-strand cross-links but also other adducts, such as inter-strand cross-links, making it important to consider the broader spectrum of adducts in understanding cisplatin's anticancer activity. Additionally, certain DNA repair enzymes are more efficient at removing 1,3 intra-strand adducts than 1,2 intra-strand adducts, highlighting the complexity of cisplatin's interactions with DNA [52] (Figure 1).

Cisplatin resistance

Cisplatin treatment encounters a significant challenge in the form of resistance exhibited by cancer cells [14]. It is important to note that the nature of cisplatin resistance varies among different types of cancer. Some cancers, such as ovarian, testicular, small cell lung, and head and neck cancers, exhibit sensitivity to cisplatin [53]. Conversely, colorectal cancer and non-small cell lung cancer tend to be highly resistant to this drug [53]. There are two primary categories of cisplatin drug resistance: Intrinsic resistance and acquired resistance. Intrinsic resistance represents the initial resistance observed when starting cisplatin treatment, while acquired cisplatin resistance is initially responsive but eventually loses its effectiveness over time [54]. Several factors contribute to cisplatin resistance. These include reduced cellular uptake of the drug, increased drug efflux from cells, detoxification of the drug by cellular thiols, alterations in drug targets, and enhanced DNA repair mechanisms [55, 56].

Understanding the mechanisms behind cisplatin resistance is crucial for developing strategies to overcome this obstacle and improve the efficacy of cisplatin-based cancer treatments.

Circulation and drug delivery

The delivery of chemotherapy drugs to tumor sites via blood circulation and oxygenation differs significantly from regular blood flow [57]. While hypoxia can negatively impact the efficacy of various drugs, its influence on cisplatin remains relatively limited [58]. Interestingly, cisplatin exhibits substantial variability in its concentration when found in different types of human tumors, with notably higher levels detected in necrotic cells compared to viable ones [15] cisplatinum, or cis-diamminedichloroplatinum (II). It is worth noting that the concentration of cisplatin in human autopsy tissues does not consistently correspond to the blood flow velocity in the respective organs [59].

The concentration of cisplatin within human tumors is subject to variability, influenced by factors, such as blood pressure, heart rate, tumor type, and metastatic location [60]. Tumors, due to their impaired self-regulation of blood flow, are more susceptible to fluctuations in blood pressure compared to normal tissues [60]. Moreover, various factors, including alterations in blood pressure, can selectively affect blood flow within tumors, consequently affecting the targeted delivery of drugs to the tumor site [60]. Factors, such as elevated fibrinogen levels and alterations in red blood cell shape have the potential to diminish tumor blood flow and increase blood viscosity. Conversely, agents that reduce blood viscosity can enhance tumor blood flow, ultimately leading to improved drug delivery [60].

Influx or efflux of drug

Cisplatin-induced apoptosis is subject to various influences within the tumor microenvironment [61]. Extracellular matrix proteins, such as laminin, collagen type IV, and fibronectin, as well as extracellular gamma-glutamyltransferase (GGT), can modulate cisplatin's effectiveness by binding to tumor cells and rendering the drug inactive through thiol groups [62]. The typically acidic extracellular pH in tumors can affect cisplatin uptake, with lower extracellular pH levels enhancing drug absorption [60]. Dietary factors, like glucose and bicarbonate, have the potential to alter tumor extracellular pH, consequently affecting cisplatin's efficacy [63]. Additionally, certain elements, like mannitol, NaCl, $CaCl_2$, and KCl can influence cisplatin absorption and cytotoxicity in vitro [63].

Resistance mechanisms encompass increased efflux of cisplatin from cells, including efflux from the cell nucleus [64]. Copper-transporting P-type adenosine triphosphatases ATP7A and ATP7B are involved in platinum efflux and resistance [65]. The binding of platinum to proteins, where it becomes less cytotoxic, can contribute to resistance. Several pumps, including MRP1, MRP2, p-glycoprotein, and MVP/LRP, may participate in cisplatin resistance, although their clinical relevance varies [15] cisplatinum, or cis-diamminedichloroplatinum (II). Furthermore, abnormal sorting of cisplatin transporters and lysosomal proteins, along with the sequestration of the drug within intracellular organelles, such as melanosomes, can influence resistance. Intracellular pH levels can also affect cisplatin efflux and subsequently, its cytotoxicity [52]. The clinical significance of these resistance mechanisms remains uncertain, and further research is essential to gain a comprehensive understanding of their implications.

DNA repair

Cisplatin-induced damage to DNA, particularly in actively transcribed regions, is primarily managed by the nucleotide excision repair (NER) system, encompassing genes, such as ERCC1, ERCC1/XPF, XPA, and BRCA1 [54]. Elevated ERCC1 expression has been linked to diminished effectiveness of platinum-based treatments in ovarian cancer and NSCLC [66]. Polymorphisms in XPD, a crucial component of NER transcriptional repair, can influence the sensitivity to platinum-based therapies [54].

Cisplatin resistance may also be attributed to various factors, including the up-regulation of XPA, activation of the Fanconi anemia/BRCA pathway, and the overexpression of DNA polymerase-ε, which plays a role in translesion synthesis across platinated cross-links [67]. DNA polymerase-η and DNA polymerase-ζ are involved in a potentially mutagenic bypass mechanism for replication-blocking DNA adducts, which could contribute to resistance [68]. Additionally, mechanisms, like topoisomerase-II and homologous recombination repair may enhance the repair of platinum-induced DNA damage, while non-homologous end-joining repair could increase platinum's efficacy [69]. While clinical evidence supports the involvement of the NER pathway in platinum resistance, further research is necessary to fully understand the role of other DNA repair systems.

Reduced DNA mismatch repair

The process of DNA post-replication mismatch repair (MMR) plays an essential role in the response to platinum-induced DNA damage, leading to apoptosis and increased sensitivity to platinum-based therapies [70]. Interestingly, cells lacking MMR or with reduced nuclear levels of MMR proteins, such as hMLH1 and hMLH2, often show high resistance to cisplatin and reduced propensity for apoptosis [70]. An intact p73 and c-Abl system is essential for MMR to effectively induce apoptosis. Cells lacking p73 expression may be resistant to cisplatin-induced DNA damage [56]. Furthermore, concomitant loss of p53 function increases resistance. In clinical scenarios, frequent methylation and down-regulation of the hMLH1 gene are observed in germ cell tumors after treatment, implying the potential clinical relevance of DNA mismatch repair deficiency in the context of platinum resistance [71].

Nrf2 signaling pathway

Nuclear factor erythroid-related factor 2 (Nrf2), functioning as a transcription factor, holds a pivotal role in safeguarding cellular integrity against oxidative harm [72, 73]. Elevated levels of ROS stimulate Nrf2 signaling, thereby augmenting the activity of crucial antioxidant enzymes, like catalase, superoxide dismutase, and glutathione peroxidase, which are paramount in mitigating oxidative stress. Intriguingly, the activation of Nrf2 in cancer cells paradoxically engenders resistance to chemotherapy by diminishing ROS levels, consequently curtailing oxidative stress-induced cell demise [74]. Furthermore, cisplatin treatment exacerbates mitochondrial dysfunction, heightens ROS levels, and begets drug resistance [14]. While Nrf2 promptly responds to oxidative stress by activating genes responsible for antioxidant defenses, it can also contribute to cisplatin resistance [75]. Natural compounds, such as melatonin and phytochemicals exhibit the capability to trigger Nrf2 and confer cellular protection [76, 77]. Conversely, Nrf2 deficiency

culminates in a reduction of total glutathione (GSH) levels, exacerbating cisplatin resistance [75]. Exploring the regulation of Nrf2 through microRNAs emerges as a promising avenue to reestablish cisplatin sensitivity in cancer cells and counteract drug resistance.

Adverse effects of cisplatin

Nephrotoxicity

Renal excretion is the major pathway of cisplatin elimination; thus, cisplatin can be concentrated in renal tubules and leads to dose-limiting renal toxicity [78]. Cisplatin-induced nephrotoxicity involves acute kidney disease (AKD) and chronic kidney disease (CKD), excessive urination or polyuria, renal magnesium loss and hypomagnesemia, Fanconi-like syndrome and anemia, and cases treated with cisplatin-based chemotherapy regimens constantly lose 15% to 35% of their normal renal system function [78]. The nephropathy caused by cisplatin can be classified into 1) tubular epithelial cell damage (primarily proximal tubules), 2) small blood vessels injury, 3) glomerular damage, 4) interstitial inflammation (nephritis), and 5) secretion of pro-inflammatory cytokines (e.g. TNF-α, IL-6, and IL-1-β) [78]. The initial effects of cisplatin are reduction of renal blood flow (RBF), decrease of glomerular filtration rate (GFR), and polyuria that are coincident with elevated electrolyte elimination, decreased creatinine clearance and increased levels of blood urea nitrogen (BUN) [31, 78]. The anti-tumor and possibly the nephrotoxic properties of cisplatin may result from its cellular uptake by Ctr1 transporter and then cytosolic biotransformation of cysteine conjugate of cisplatin by β-lyase to more potent reactive electrophilic metabolites (diaquo-diammineplatinum or mono-chloro-mono-aquodiammineplatinum), which are able to bind to DNA and alkylating purine and pyrimidine nitrogenous bases [78]. These reactive metabolites can also depict cytotoxic activity by the development of oxidative stress and causing damage to macromolecules, such as proteins and lipids, likely leading to normal cell death [52, 78]. These findings proposed that cisplatin may contribute to acute renal failure through its capacity to inhibit DNA synthesis as well as transport functions [79].

Ototoxicity

The occurrence of cisplatin-associated ototoxicity varies from 10 to 90% of patients receiving cisplatin-based regimens and children and older adult patients are more susceptible to this effect of cisplatin [80]. Cisplatin primarily influences the cochlea (so-called the organ of Corti), particularly the outer hair cells (OHCs) in the inner ear [81]. Considering the restricted regenerative capability of the sensory hair cells and other supporting cells, serious cellular damage, such as inflammation, excessive ROS production, and necrosis induced by cisplatin will result in irreversible toxicity and high-frequency permanent hearing loss [81]. Concomitant use of drugs, such as loop diuretics (furosemide and bumetanide) and aminoglycoside antibiotics (kanamycin and amikacin) may exacerbate cisplatin-induced ototoxicity and nephrotoxicity [81]. Several therapeutic options have been proposed to relieve cisplatin-related ototoxicity, among which the administration of systematic or local and anti-inflammatory drugs and antioxidants medications are very crucial [23].

Gastrointestinal toxicities

Nausea and vomiting are major symptoms that develop 1-4 h after starting treatment with cisplatin and may last up to 24 hours after chemotherapy [82]. Cisplatin causes remarkable nausea and emesis by triggering the release of 5-hydroxytryptamine (5-HT; serotonin) from enterochromaffin cells (ECs) of the intestinal mucosa, which stimulates the 5-HT_3 receptors located in the adjacent vagal afferent neurons (VANs), thereby leading to the vomiting reflex activation [83, 84]. Noticeable nausea and emesis appear approximately in all patients and commonly can be managed by 5HT_3 receptor antagonists (ondansetron and granisetron), substance P receptor [neurokinin 1 (NK1)] antagonists (aprepitant, rolapitant, and fosaprepitant), and administration of high-dose (4–8 mg daily) corticosteroids (e.g. dexamethasone and methylprednisolone) [83]. Other gastrointestinal toxicities that have been observed and reported by cisplatin include diarrhea, pancreatitis, mucositis, dysgeusia or sense of metallic taste, intestinal barrier disruption, etc. [85].

Hepatotoxicity

In aggressive treatment protocols where high doses of cisplatin are used for tumor growth inhibition, therapy-related hepatotoxicity also appears [86]. However, cisplatin-associated hepatotoxicity has received less attention and available information about the underlying mechanisms of this damage is not enough [87]. It has been reported that oxidative stress through the over-production of ROS, reduction of the antioxidant defense system (reduced glutathione and glutathione reductase levels and increased glutathione peroxidase, catalase, and gamma-glutamyl transpeptidase levels), elevated bilirubin levels, increased expression of CYP2E1, and disturbance in the mitochondrial integrity and function plays an essential role in cispl-

atin-related liver injury [88]. Administration of high doses of selenium, vitamin E, N-acetyl-cysteine, and proven formulations containing liver-supportive ingredients, such as silimarin can reduce cisplatin-induced hepatotoxicity [89].

Other adverse outcomes

In some cases, mainly overdose and combined regimens with other drugs, cisplatin is also able to induce other toxicities in different systems, including cardiovascular toxicity (bradycardia, ischemic vascular events, myocardial ischemia/ infarction, coronary artery vasospasm, etc.), neurotoxicity (peripheral neuropathy manifested mainly by sensory disturbance such as paresthesia and loss of proprioception), retinopathy and vision problems, mild-to-moderate myelosuppression and hematological disorders (anemia, transient thrombocytopenia, and leukopenia), and electrolyte abnormalities, including hypomagnesemia, hypocalcemia, hypophosphatemia, and hypokalemia [15, 85, 90] cisplatinum, or cis-diamminedichloroplatinum (II).

Alleviation of cisplatin-induced toxicities

Up to now, various supportive and therapeutic strategies, including aggressive volume expansion by intravenous (IV) fluid therapy, administration of thiol-containing adjuvants by IV infusion, antiemetic drugs, etc. have been used clinically to alleviate cisplatin-induced toxicities in different body organs [85, 91]. Unfortunately, to date, no specific antidote has been introduced for the treatment of cisplatin poisoning [85, 91]. Although a number of other medicinal agents (e.g. allopurinol, Colestipol, ditiocarb sodium, ORG 2766, etc.) or natural-occurring agents (curcumin, silimarin, resveratrol, etc.) have been evaluated to reduce the various toxicities caused by cisplatin, none of them had a proven efficacy and more clinical studies are required to prove their potentially beneficial effects [20, 92, 93].

Alleviation of nephrotoxicity

Fluid therapy

The standard and recommended protocol in all guidelines for the prevention of cisplatin-induced nephrotoxicity is to use lower doses of cisplatin and the administration of high volumes (4-6 L/day) of isotonic saline solutions [94]. Sodium chloride saline solutions enhance the anionic (ionized) state of cisplatin and decrease urine platinum concentrations to limit renal toxicity [94]. Hydration therapy with 0.9% sodium chloride and mannitol as an osmotic diuretic agent is required to achieve a urinary output of 1-3 mL/kg/h for 6-24 hours [94]. Given the urine flow-dependent and creatinine clearance-independent manner of cisplatin renal clearance, it is essential to manage urinary output and fluid intake in the targeted and balanced state without electrolyte imbalances [78, 94]. Hemodialysis is not effective in patients suffering from cisplatin overdoses, likely as a consequence of the high protein binding property of this anti-neoplastic drug [94]. However, in renal failure cases, hemodialysis may be helpful. Plasmapheresis was noted as a valuable approach, which binds a major part of cisplatin to plasma proteins and thereby reduces its concentration in blood circulation significantly [94].

Amifostine

Amifostine is a thiol-containing agent that has been clinically used to regulate cisplatin-induced nephrotoxicity. Amifostine is an organic thiophosphate cytoprotective adjuvant and is a prodrug that is dephosphorylated by alkaline phosphatase in tissues to a pharmacologically active free thiol metabolite and is responsible for the reduction of the cisplatin-induced oxidative stress and cumulative nephrotoxicity [95, 96]. It is most effective when administered prior to cisplatin, and may offer additional beneficial effects by limiting myelosuppression, mucositis, and neurotoxicity. Non-cancerous and normal cells are preferentially protected, as amifostine and its metabolites accumulate in normal host cells at concentrations 100 times higher than in cancer cells. Administration of amifostine can give rise to hypotension; thus, the patient receiving this drug must be hydrated adequately and intermittent blood pressure monitoring during therapy is needed [94–96].

Sodium thiosulfate

Sodium thiosulfate or thiosulfuric acid is an inorganic sulfur donor agent that acts by binding to extracellular protein-unbound platinum species, which limits the cisplatin accumulation and deposition in the renal tubules to develop insult [97]. Thiosulfate may limit neurotoxicity, nephrotoxicity, and ototoxicity from cisplatin [98]. Like amifostine, several mechanisms are proposed, by which this agent evokes its cytoprotective activity, including binding to reactive cisplatin intermediates, scavenging free radicals, or regenerating intracellular glutathione [98]. Thiosulfate needs to be administered as soon as possible after cisplatin exposure to achieve maximum efficacy, and as an intravenous infusion because of its short plasma half-life (approximately 20 minutes) [94]. When thiosulfate was administered as an IV bolus of 4 g/m^2 and continued as an infusion of 12 g/m^2 over 6 hours, it limited renal toxicity in patients receiving cisplatin at a dose as high as 270 mg/m^2 [94].

N-acetyl cysteine (NAC)

In some animal and clinical studies, N-acetyl cysteine (NAC) was used to hinder cisplatin-associated renal toxicity and showed paradoxical outcomes. However, this agent may be useful in high-risk patients for nephrotoxicity [99]. N-acetyl cysteine is a thiol group-rich supplement derived from L-cysteine amino acid, which prevents cisplatin from depleting cellular GSH content or raising the peroxide and malondialdehyde (MDA) levels [99]. It directly decreases the amount of ROS, prevents mitochondrial-mediated apoptosis induced by cisplatin, and protects against renal injury. Its optimum protective effect is observed when administered during or two hours after chemotherapy [99].

Theophylline

It is hypothesized that the contraction caused by cisplatin in small vessels is mediated by the adenosine receptor and therefore, its inhibition by theophylline (adenosine receptor blocker) can prevent this event. There are a few studies claiming that theophylline can be effective in improving the glomerular filtration rate (GFR) that is impaired by cisplatin. However, more clinical trials are needed to prove its potentially beneficial effects [100].

Glycine

In limited experimental studies, it has been mentioned that the administration of glycine amino acid can reduce the kidney damage caused by cisplatin. For example, a study has shown that the injection of glycine was able to reduce the platinum uptake by the renal tubular cells [101]. Alleviation of neurotoxicity

BNP7787

BNP7787 is a disulfide of MESNA (sodium 2-mercaptoethane sulfonate) and is being investigated as another thiol-containing detoxifying agent for cisplatin toxicity. In controlled animal trials, BNP7787 was shown to limit cisplatin-induced nephrotoxicity, neurotoxicity, and myelosuppression [94].

Vitamin E

Vitamin E is a fat-soluble vitamin that is found in various foods and natural supplements. Several studies have shown that vitamin E-rich dieting as well as vitamin E supplementation (400 IU daily) is beneficial in mitigating the symptoms of peripheral neuropathy in cisplatin-treated patients [102].

Fosfomycin

Fosfomycin is a broad-spectrum antibiotic used to treat uncomplicated urinary tract infections and cystitis [103]. In addition to antimicrobial activity, fosfomycin acts as a free-radical scavenger and anti-inflammatory agent if administered 2-3 days prior to cisplatin, thereby leading to the alleviation of cisplatin-related neurotoxicity, nephrotoxicity, and ototoxicity [104].

Cisplatin-based combination therapy

While cisplatin has demonstrated efficacy in the treatment of various human cancers, it is accompanied by several challenges, including chemotherapy resistance, tumor recurrence, significant side effects, unfavorable prognosis, and numerous adverse reactions in patients [14, 105–107]. In order to address these complexities associated with cisplatin therapy, combination therapy has emerged as a valuable strategy [14]. Combination therapy involves the concurrent use of two or more drugs, radiotherapeutic agents, natural bioactive compounds, etc. each possessing distinct mechanisms of action [14, 108, 109]. Table 1 presents a comprehensive compilation of diverse combination therapies involving cisplatin.

The utilization of combination therapy holds significant promise in mitigating the limitations associated with cisplatin treatment [105, 110]. By integrating drugs with complementary procedures, we increase treatment results minimize the above-mentioned issues and ultimately improve the overall prognosis for cancer patients [111–113].

The combination of metformin with cisplatin leads to a substantial increase in the apoptosis index, surpassing the effects observed in both monotherapy and control groups. Notably, this synergistic effect closely resembles the impact achieved by the mTOR inhibitor rapamycin and consistently manifests across various cancer types, including lung, breast, colon, gastric, and ovarian cancers. Furthermore, the co-administration of metformin and cisplatin results in a reduction in tumor volume compared to monotherapy [14].

The mTOR/Akt signaling pathway assumes a pivotal role in sensitizing cancer cells and enhancing the efficacy of cisplatin, particularly in cases characterized by high resistance to cisplatin [123]. The combination of metformin and cisplatin induces a substantial increase in anti-proliferative effects and a higher percentage of apoptotic cells compared to cisplatin monotherapy, in addition to inhibiting migration and invasion. While cisplatin exhibits a dose- and time-dependent inhibition of cell proliferation, metformin expe-

Table 1. Illustration of various combination treatments with cisplatin

Drug	Combined Drug	Type of Cancer	Ref
Cisplatin	Metformin	Lung-ovarian, breast, colorectal, nasopharyngeal, meningioma, and endometrial cancer	Jafarzadeh et al. (2022) [14]
Cisplatin	Fluorouracil	Head and neck squamous cell carcinoma	Jacobs et al. (1992) [114]
Cisplatin	Mitomycin C	Colorectal cancer,	Pinto et al. (2016) [115]
Cisplatin	5-fluorouracil	Bladder cancer, and gastric cancer	Hussain et al. (2001) [116]
Cisplatin	Vinblastine+bleomycin	Cervical carcinoma	Friedlander et al. (1983) [117]
Cisplatin	Thymoquinone	Lung cancer	Jafri et al. (2010) [118]
Cisplatin	Phenoxodiol	Prostate cancer	McPherson et al. (2009) [119]
Cisplatin	Trastuzumab	Breast cancer	Pegram et al. (1999) [120]
Cisplatin	Cyclophosphamide and paclitaxel	Ovarian cancer	McGuire et al. (1996) [121] Cai et al. (2015) [122]

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dites the cytotoxic effects of chemotherapy and enhances cell sensitivity to cisplatin [14].

Combination therapy has proven effective in reducing tumor growth and volume in animal studies, promoting cancer cell apoptosis, significantly reducing colony formation and spherogenesis, and mitigating side effects [110]. This synergy achieved by combining metformin with cisplatin significantly impedes the growth of cancer cells through multifaceted anticancer mechanisms, encompassing pathways involving AMPK/mTOR, E-cadherinw, and MMP-9. These findings underscore the potential of metformin-cisplatin combination therapy to enhance the efficacy of cancer treatment [14].

Clinical, in vivo, and in vivo studies of this combination therapy include 4 mg of cisplatin and 200 mg/kg of metformin administered orally daily across various cancer types, such as advanced non-small cell lung, ovarian, breast, and colon cancers, etc. Consistent results have demonstrated that this combined approach elevates apoptosis and induces tumor cell death while sensitizing cisplatin-resistant cells to treatment. These compelling findings underscore the clinical relevance and effectiveness of metformin-cisplatin combination therapy in cancer management [14]. Additionally, other combination therapies have shown promise in various cancer types. For instance, the combined treatment of cisplatin and fluorouracil has proven effective for head and neck squamous cell carcinoma [114]. When the combination of mitomycin C and cisplatin is employed, positive outcomes are observed in the treatment of colorectal cancer [115]. Patients with bladder and stomach cancer have benefited from the combination of cisplatin and 5-fluorouracil, which has been a successful treatment option [116]. Combining cisplatin with vinblastine and bleomycin has yielded acceptable results in the treatment of uterine cancer and enhanced sensitivity in resistant cells [117]. Moreover, cisplatin in conjunction with thymoquinone has demonstrated efficacy in lung cancer [118]. Additionally, cisplatin combined with fenoxodiol has shown promise in prostate cancer cell lines [119]. Furthermore, combination therapy involving trastuzumab and cisplatin plays a crucial role in breast cancer treatment [120]. Finally, the combination of cisplatin with cyclophosphamide and paclitaxel is a favorable choice for ovarian cancer, as it has been reported to enhance the effectiveness of cisplatin against cisplatin-resistant ovarian tumor cells compared to cisplatin monotherapy [121, 122].

4. Conclusion

In conclusion, cisplatin stands as a widely utilized chemotherapeutic agent, primarily exerting its mechanism of action through DNA binding, which leads to disruptions in transcription and DNA replication, ultimately culminating in the demise of cancer cells. It also engages with various non-DNA targets, thereby contributing to its cytotoxicity. Nevertheless, the application of cisplatin in clinical settings often encounters multifaceted chal-

lenges, encompassing resistance development, adverse effects, and constraints in drug delivery.

The emergence of cisplatin resistance can be attributed to multiple factors, including diminished drug uptake, augmented efflux, cellular thiol-mediated detoxification, modifications in drug targets, and enhanced DNA repair mechanisms. Effectively surmounting these resistance mechanisms stands as a pivotal endeavor to enhance the efficacy of cisplatin-based cancer therapies. The effective delivery of cisplatin to tumor sites via the circulatory system, in conjunction with adequate oxygenation, is contingent upon a myriad of factors, encompassing tumor type, metastatic localization, and alterations in blood pressure regulation. An in-depth comprehension of these factors remains imperative for the optimization of drug delivery to tumor regions.

Cisplatin-induced toxicities, spanning nephrotoxicity, ototoxicity, gastrointestinal adversities, hepatotoxicity, etc. can significantly impede the quality of life of patients. Numerous strategies have been explored to alleviate these toxicities, encompassing fluid therapy, the use of thiol-containing agents, like amifostine and sodium thiosulfate, antioxidants, such as N-acetyl cysteine and vitamin E, as well as adenosine receptor blockers, like theophylline. The advent of combination therapy involving cisplatin has surfaced as a valuable approach to augment treatment outcomes and ameliorate the limitations associated with cisplatin monotherapy. Various combination therapies have exhibited promise in the treatment of diverse cancer types, including head and neck squamous cell carcinoma, and lung, ovarian, breast, colon, colorectal, bladder, stomach, uterine, and prostate cancers.

Overall, cisplatin maintains its essential place in cancer treatment, and ongoing research efforts are directed towards increasing its efficacy while reducing adverse effects and overcoming the challenges of resistance through the application of combination therapies and novel approaches.

Ethical Considerations

Compliance with ethical guidelines

This research was approved by the Research Ethics Committee of Shahid Beheshti University of Medical Sciences (Code: IR.SBMU.LASER.REC.1402.024).

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Authors' contributions

Conceptualization and supervision: Jaber Zafari; Data curation and original draft preparation: Najmeh Abedini Nazari, Behnam Omidi Sarajar and Seyedeh Zohreh Azarshin; Review & editing: Fatemeh Javani Jouni and Jaber Zafari; Final approval: All authors.

Conflict of interest

The authors declared no conflicts of interest.

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