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FROM BENCH TO BESIDES: TRANSLATING INSIGHTS INTO CISPLATIN NEPHROTOXICITY MANAGEMENT

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ABSTRACT

Although cisplatin is a commonly used chemotherapeutic agent that has been demonstrated to be effective against a range of solid tumors, its therapeutic efficiency is typically limited by its nephrotoxic side effects. Renal tubular damage, oxidative stress, inflammation, and apoptotic cell death are known outcomes of cisplatin nephrotoxicity, however the exact processes underlying the toxicity are still unknown despite decades of investigation. With a focus on the molecular mechanisms underlying cisplatin-induced nephrotoxicity, such as oxidative stress, inflammation, and mitochondrial dysfunction **[1]**. The nephrotoxicity of cisplatin can be reduced and avoided in a number of ways. These include novel therapeutic approaches including stem cell therapy and reno protective medications, as well as pharmaceutical medicines that specifically target specific pathways.

Keywords: Cisplatin Nephrotoxicity Management, Anti-neoplastic medications, CDDP (cis-diamminedichloroplatinum (II)

INTRODUCTION:

Anti-neoplastic medications are used in the treatment of several solid organ cancers, such as those of the ovary, testis, breast, head, and neck. One such medication is cisplatin, sometimes referred to as CDDP (cis-diamminedichloroplatinum (II).

Among the risks are myelosuppression, ototoxicity, autotoxicity, and allergic responses. Nephrotoxicity is one cisplatin adverse effect for which there is a dose limit. Cisplatin has been known to be nephrotoxic since it was first made available more than 25 years ago. However, cisplatin is still often recommended despite significant efforts over the next decades to develop less hazardous but similarly effective alternatives **[2]**.

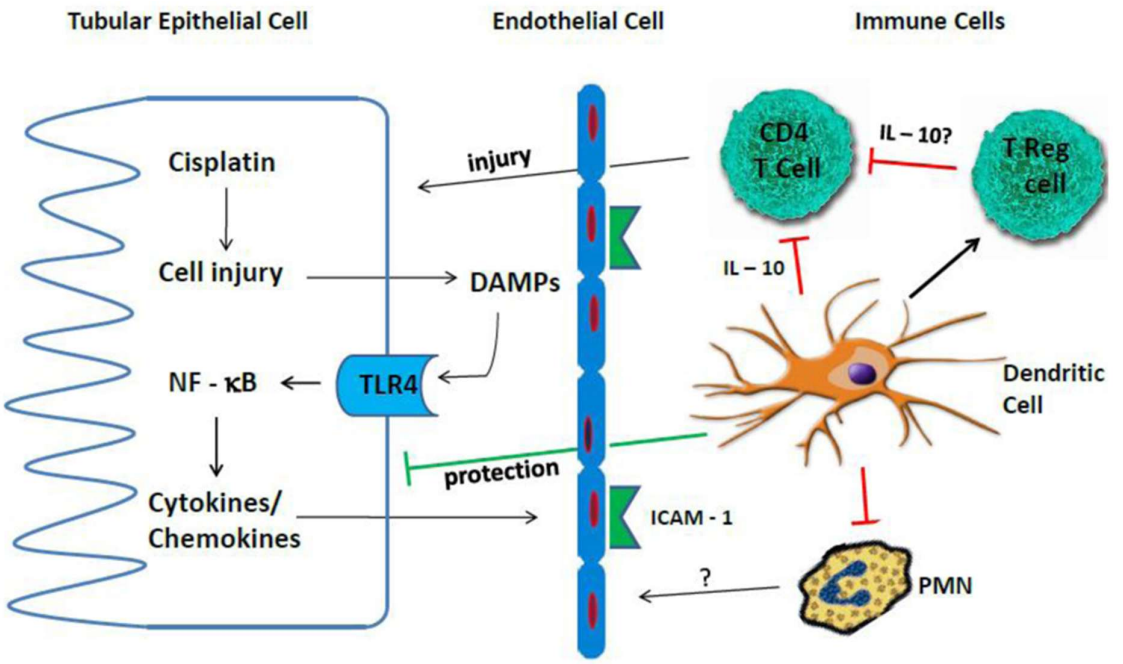
Treatment regimens for testicular, lung, ovarian, cervical, small-cell and non-small-cell bladder cancers, as well as other cancers, still frequently include it. Since cisplatin is a generic medication in the US, it is challenging to monitor sales and usage. The best anticancer drug for cancers of the testicles, bladder, ovaries, lungs, and head and neck area is cisplatin. When cisplatin is used with drugs such as vinblastine, bleomycin, cyclophosphamide, fluorouracil, and doxorubicin, there is a higher chance of secondary morbidity; however, the effectiveness of treating different malignancies has also increased. Even though cisplatin was developed in 1845, its harmful effects were not completely recognized until 1965.

Clinical studies for cisplatin started in or around 1971. Despite being a potent anticancer drug, its clinical use has been restricted because of several side effects, the most serious of which is nephrotoxicity **[3]**. The primary reason for the dose-limiting nephrotoxic effect of cisplatin is its immediate cytotoxic impact on the proximal and distal tubules of the loop of Henle.

Decreases in creatinine clearance and electrolyte abnormalities, especially hypomagnesemia, are characteristics of this impact. Seizures may occur from a severe magnesium shortage after cisplatin treatment. The increased magnesium and potassium lost in the urine as a result of cisplatin may be partially restored with supplements. Moreover, studies on both humans and animals have shown that hydration and the use of diuretics can greatly reduce cisplatin-associated nephrotoxicity. Nephrotoxicity resulting from cisplatin may present with several manifestations. However, the most serious Nephrotoxicity caused by cisplatin can manifest itself in different ways. On the other hand, acute kidney injury (AKI), one of the most prevalent presentations, affects 20–30% of individuals.

PATHOGENESIS:

Inside the renal cells: - The organic transporter route is the primary mechanism for cisplatin absorption. Compared to other organs, the kidney accumulates cisplatin more than any other organ, making it the major organ for its excretion. The concentration of cisplatin in serum is approximately five times lower in proximal tubular epithelial cells. The overabundance of cisplatin in kidney tissue is one of the factors causing cisplatin-induced nephrotoxicity. In rats, excretion of cisplatin is primarily accomplished via glomerular filtration; secretion is a secondary mechanism. There does not seem to be tubular reabsorption. Both the proximal and distal nephrons absorb cisplatin through the peritubular route. The highest concentration of cisplatin is absorbed by the distal collecting tubule, the S1 section of the proximal tubule, and the S3 segment of the proximal tubule. Six transporters also have a role in the entry of cisplatin into the cell, in addition to passive diffusion **[4]**. Different regions may contribute differently through active absorption by a transport mechanism and passive diffusion across the cellular membrane. Transporter-mediated absorption is most likely the primary pathway in renal cells. The organic cation transporter (OCT 2) is necessary for the absorption of cisplatin into the proximal tubules of both animal and human tissues. These membrane proteins mediate polyspecific, voltage-dependent, bidirectional, pH-independent, electrogenic, and Na-independent transport. In humans, three different OCT isoforms have been found. While OCT1 is the predominant isoform found in the liver and OCT2 is the primary OCT found in the kidney, OCT3 is extensively expressed, especially in the placenta. One could contend that a deficiency in cisplatin is the reason behind the organ-specific toxicity of human OCT1. the less harmful varieties of oxaliplatin and carboplatin **[5]**. Cimetidine is an organic cation competitor for the transport at human OCT2, which reduces the amount of cisplatin-induced proximal tubule cell death. OCT isotype gene and protein expression, as well as cisplatin toxicity resistance, are reduced in nine diabetic rats. It's unclear if these transporters facilitate cisplatin's penetration of cancerous cells. A novel study has shown that in human ovarian cancer cells, the absorption of cisplatin is regulated by the distinct transporter system called copper transport protein 1.



Cisplatin Medication: - Cisplatin must change into nephrotoxic substances in the proximal tubule cells in order to cause damage to cells; it cannot directly harm cells. The tissues with the highest concentration of cisplatin are the microsomes, mitochondria, cytoplasm, and nuclei. Glutamyl transpeptidase and cysteine S-conjugate lyase-dependent mechanisms metabolize the molecule produced when glutathione and cisplatin conjugate. This specific thiol seriously damages the kidneys **[7]**. While glutamyl transpeptidase is present on the surface of cells, cysteine-S-conjugate-lyase is an inside enzyme. Inhibiting these two enzymes reduces nephrotoxicity but has no effect on the kidneys' ability to absorb cisplatin. However, the anticancer properties of cisplatin are lessened when -glutamyl transpeptidase activity falls. It is unknown how cysteine S-conjugate-lyase inhibition might affect cisplatin's anticancer properties. There has only been one study on cysteine S conjugate lyase activity in tumor cells, and the results indicate that the enzyme is unusually low in specific human renal cell carcinomas **[6]**. With hydrolytic processes that result in monohydrate molecules, ciprofloxacin can be helpful. Despite not being kidney-specific, the monohydrated molecule is more harmful to renal cells than cisplatin. Its production is aided by the typically low intracellular chloride concentrations. Reconstituted cisplatin in hypertonic saline can reduce the amount of monohydrated complex produced. While nephrotoxicity is decreased, there may be a small anticancer effect as well.

Biochemical change in the renal cells:

Cisplatin causes some genes to change. Drug resistance (MDR1, P-gp), cytoskeleton structure and function (Vim, Tubb5, Tmsb10, Tmsb4x, Anxa2), cell adhesion (Spp1, Col1a1, CLU, Lgals3), apoptosis (cytochrome c oxidase subunit I, BAR, heat-shock protein 70-like protein, Bax), tissue remodelling (clustering, IGFBP-1, TIMP-1), and detoxification (Gstm2, Gstp2) are among the genes that are upregulated after cisplatin-induced injury. Numerous genes are inhibited by cisplatin, including those that encode growth factors or their binding proteins (Egf, Ngfg, Igfbp3, Ghr), localize to the proximal tubules (Odc1, Oat, G6pc, Kap), and control intracellular calcium homeostasis (SMP-30). These gene alterations are linked to tissue remodelling. cisplatin-induced proximal tubule regeneration and destruction. The intracellular signalling pathways of mitogen-activated protein kinase (MAPK) mediate the nephrotoxicity of cisplatin. Different chemical and physical stimuli can simultaneously activate the serine/threonine kinase cascades that make up the MAPK region sequence. They control the capacity of a cell to multiply, divide, and endure. Extracellular regulated kinase (ERK), p38, and Jun N-terminal kinase/stress-activated protein kinase (JNK/SAPK) are the terminal proteins of the three main MAPK pathways. While the precise involvement of the ERK pathway in proximal tubule damage is yet understood, certain events in the distal nephron may cause localized proximal tubule damage through autocrine and paracrine pathways **[8]**. The mediating factor in proximal tubule cell damage is P38 activation. The process of p38 activation is mediated by hydroxyl radicals generated by cisplatin. In cisplatin-induced nephrotoxicity, the JNK/SAPK pathway has not been given much attention in the literature.

Cellular Events that Injure Renal Tissue:

The nephrotoxicity associated with cisplatin is produced by a complicated network of in vivo events that include oxidative stress, apoptosis, inflammation, and fibrogenesis. High dosages of cisplatin induce necrosis in proximal tubule cells, while lower amounts induce apoptosis through a caspase-9-dependent mechanism. the primary cisplatin-mediated mechanisms of acute tubular cell injury. The JNK/SAPK pathway in cisplatin-induced nephrotoxicity has not received significant attention in the literature **[9]**.

Events Within the Cell that Harm Renal Tissue:

Numerous complex in vivo mechanisms, including oxidative stress, apoptosis, inflammation, and fibrogenesis, are associated with cisplatin nephrotoxicity. Higher doses of cisplatin result in necrosis, but smaller doses cause proximal tubule cell

death via a caspase-9-dependent mechanism. the main mechanisms by which tubular cells suffer acute damage from cisplatin. The primary mechanism by which cisplatin induces acute kidney impairment is oxidative stress injury. Direct interactions between reactive oxygen species (ROS) and proteins, lipids, and DNA result in structural damage **[10]**. The xanthine-xanthine oxidase system, mitochondria, and a cell-resident NADPH oxidase are the sources of reactive oxygen species (ROS). All of these pathways are linked to cisplatin-induced acute kidney damage, and these systems all produce reactive oxygen species (ROS) in presence of cisplatin. Cisplatin causes an increase in free radical production and a decrease in the synthesis of antioxidants due to its activation of hexokinase and glucose-6-phosphate dehydrogenase. The result of these free radicals denature of proteins and peroxidation of the lipid components of the cell membrane is enzymatic inactivation. Mitochondrial dysfunction could potentially be caused by free radicals. Cisplatin dramatically reduces the renal activity of glutathione peroxidase, catalase, and superoxide dismutase and suppresses antioxidant enzymes. It has been demonstrated that antioxidants such melatonin, vitamin C26, and vitamin E31 guard against cisplatin-induced acute nephrotoxicity. It is unclear how nephrotoxicity and antioxidant-antioxidant systems relate to one another. Research has also been done on the nephrotoxicity caused by reactive nitrogen species and cisplatin. Peroxynitrite lowers cellular defenses and causes chemical DNA breakage, lipid peroxidation, altered protein structure and function, and thiol pool oxidation **[11]**. Through peroxynitrite metabolism, the soluble complex FeTPPS treatment lessens nitrosative stress and nephrotoxicity brought on by cisplatin. These results suggest that peroxynitrite may be involved in the nephrotoxicity and protein nitration caused by cisplatin.

It is still uncertain if nitric oxide has a negative impact on renal damage. Hypoxia and mitochondrial damage are associated with renal impairment caused by shifter in. In cisplatin-induced nephrotoxicity, pathological alterations mostly affect the S3 segment of the proximal tubule in the outer stripe of the outer medulla **[12]**. This kidney segment is more vulnerable to ischemia insult and suffers damage in a number of toxic acute renal failures.

34 hypoxic tubules make up the outer medulla of cisplatin-induced nephrotoxicity, as seen by imidazole staining. One important factor contributing to cisplatin-induced nephrotoxicity is hypoxia, which is mostly caused by the decreased renal blood seen early in the drug's toxicity. Conversely, hypoxia inducible factor 1 (HIF-1) in the S3

area of the proximal tubules is activated by in vivo cisplatin damage **[13]**. The primarily adverse processes of angiogenesis, erythropoiesis, and glycolytic adaptation that take place in cells in response to hypoxia are mediated by the transcription factor HIF-1. The apoptotic damage induced by cisplatin, associated with increased caspase 9 activity, cytochrome c release, and loss of mitochondrial membrane potential, is more likely to occur in animals lacking the HIF-1 component **[14]**.

Therefore, the ultimate impact of hypoxia on cisplatin-induced kidney injury remains unclear. It is now understood that both aberrant and normal cell death require apoptosis. Caspases 1, 8, and 9 activate caspase 3, the main executioner caspase responsible for renal tubule apoptosis. Either an internal mitochondrial pathway or an exterior surface receptor pathway can be activated to achieve this. DNA fragments and oxidative stresses in mitochondria activate the caspase 9.36 pathway. Caspases 8 become active upon binding of extracellular tumor necrosis factor (TNF-) to a cell surface receptor **[15]**. If kidney impairment is caused by cisplatin, then both routes can be involved. Moreover, in the lack of Fas ligand, cisplatin can quickly cluster Fas into membrane lipid rafts, starting an apoptotic cascade. There is evidence linking this route to the cytotoxicity of cancer cells. The possibility of nephrotoxic consequences is unknown. In the cisplatin-induced kidney injury model, caspases 1 and 3 immediately begin to activate. Furthermore, caspase 1 increases the kidney's inflammatory response to cisplatin therapy and raises interleukin 1_ (IL-1_) levels. Mice deficient in caspase-1 have decreased levels of ATN and apoptosis caused by cisplatin. Mice deficient in caspase-1 have decreased levels of ATN and apoptosis caused by cisplatin. Deoxyribonuclease I, an incredibly active endonuclease I those accounts for more than 80% of the kidney's total endonuclease activity, is necessary for DNA fragmentation linked to cisplatin-induced nephrotoxicity. Animals with deoxyribonuclease I mutations have primary renal tubular epithelial cells that are resistant to cisplatin injury in vitro. Changes in inflammation brought on by cisplatin do very little harm to the kidneys. Recent research indicates that inflammation plays a significant role in the pathogenesis of kidney damage brought on by cisplatin **[16]**. TNF- expression rises in the kidney as a result of these mechanisms. Other cytokines that are elevated in the kidneys by cisplatin include hemeoxygenase-1, intercellular adhesion molecule (ICAM), transcription growth factor (TGF), monocyte chemoattractant protein-1 (MCP-1), and TNF receptor 1 (TNFR1). Reduction of kidney damage is one of 41 TNF's main functions.

It triggers the production of reactive oxygen species, starts apoptosis, and orchestrates the activation of the kidney's vast chemokine and cytokine repertoire. TNF-neutralizing antibodies and TNF-production inhibitors (GM6001 and pentoxifylline) lower serum and kidney TNF-protein levels from 30% to over 100% **[17]**. They reduce the cisplatin-induced elevations in mRNA for TGF-_, RANTES, MIP-2, and MCP-1. TNF-inhibitors also reduce structural damage and increase the renal impairment caused by cisplatin by 50%. Mice lacking in TNF have a significant resistance to the nephrotoxic effects of cisplatin. In addition, cisplatin may cause fibrosis around the afflicted tubules and an invasion of macrophages and lymphocytes. Following weekly injections of 2 mg/kg body weight cisplatin, the corticomedullary junction showed the peak of fibrotic lesions in week 7. Over the course of a 19-week observation period, all kidney damage was healed after stopping cisplatin treatment because of the replacement of regenerated renal tubules and a decrease in fibrotic tissues. BUN and creatinine levels dropped as the healing process progressed. After multiple sessions of cisplatin therapy, significant renal tubulointerstitial fibrosis has been found in a patient45 and other large animals **[18]**. Under specific conditions, myofibroblast cells create extracellular matrices. In conclusion, cisplatin directly harms tubules in a number of ways. BUN and creatinine levels dropped as the healing process went on. After multiple sessions of cisplatin therapy, significant renal tubulointerstitial fibrosis has been found in a patient45 and other large animals. Renal interstitial fibrosis is significantly impacted by TGF-1 and TNF, two fibro genic factors secreted by macrophages. Under some circumstances, myofibroblast cells generate extracellular matrices. In conclusion, cisplatin directly harms tubules in a number of ways. During this damage, there may be significant interactions between these several pathways. For instance, cellular damage is caused by the production of ROS, TNF-induced apoptosis, and the interaction of several cytokine actions **[19]**. Nevertheless, it also increases HIF-1 activity, promotes nitric oxide generation, and produces inducible nitric oxide synthase in nonmonic renal tubule cells—all of which may reduce negative effects.

Pathophysiological Impact of Injury from Cisplatin: -

The glomerulus filters remove 80% of a dose in a single day by releasing bound cisplatin to the extent that each pathway and its combinations contribute. Three hours after cisplatin infusion, there may be a decrease in renal blood flow, which lowers the glomerular filtration rate (GFR). Calcium channel blockers or angiotensin converting enzyme inhibitors are unable to

stop the reduction in renal blood flow and GFR caused by cisplatin-induced ARF. What mediators caused this reduction is unknown at this time. Given the greater salt chloride supply in the macula densa, the variations in renal blood flow and GFR are most likely an indication of higher renal vascular resistance brought on by enhanced tubular-glomerular feedback.

No, intratubular obstruction is not the main cause of cisplatin-induced nephrotoxicity. Most cisplatin-treated patients exhibited stable renal function. One to two weeks following treatment, 25% of patients experience reversible azotaemia. On the other hand, a considerable portion of the population has a progressive decrease of renal function. Large doses and frequent administration may harm the kidneys permanently. Alcohol use, age, and kidney radiation all increase toxicity **[20]**. Prior to the proximal tubular failure observed in cisplatin nephrotoxicity, there are changes in renal hemodynamic. 48–72 hours after cisplatin treatment, vascular resistance increases, and proximal and distal tubular reabsorption are both hampered. Acute poisoning alters solute transport, cell cation concentration, ATPase activity, In the pars convolute and pars recta of the proximal and distal tubules, there is segmental degeneration, necrosis, and desquamation of the epithelial cells. Patients with acute renal failure most commonly have acute necrosis, which is usually seen in the proximal convoluted tubules **[21]**. Exposure time, concentration, and dosage all affect the severity of necrosis. There isn't interstitial nephritis. Focal acute tubular necrosis is more likely to occur when nephrotoxicity persists. The flattened epithelium lining cystic dilated tubules and aberrant mitotic patterns with hyaline casts and unique nuclei are indicative of this condition. Interstitial fibrosis and cyst development may arise from long-term exposure to and damage from cisplatin. Criteria for Assessing Cisplatin Damage The harm that cisplatin causes to the kidneys is unique diagnostic features.

Uptake of Cells: -

Second- and third-generation platinum drugs, carboplatin and oxiplatin, have been licensed for use in medical operations due to their lesser nephrotoxicity. Their entry into renal tubular cells is restricted by their inability to interact with human OTC2. Clinical trials demonstrate that carboplatin is equally effective as cisplatin in treating ovarian cancer and demonstrates quantitatively comparable anticancer activity in vitro. **[22]**.

This drug may be given in combination to other nephrotoxic treatments if the patient has a history of renal impairment or is unable to obtain cisplatin. Even though dose-dependent nephrotoxicity has been demonstrated, it is not as bad as cisplatin's.

The only adverse impact that 400 mg/m2 of carboplatin generates is subclinical tube damage. When the dosage approaches800mg/m2, overt nephrotoxicity occurs **[23]**. To reduce the risk of renal failure, high dosages of carboplatin are administered in combination with diuretics and aggressive saline-based hydration. Even in patients receiving repeated dosages or experiencing renal insufficiency, oxaliplatin has not been demonstrated to adversely affect renal function. Oxaliplatin treatment for advanced colorectal cancer is now approved. Studies are being conducted to see if it can replace carboplatin or cisplatin in the treatment of specific cancer types **[24]**. In diabetic animal models, cisplatin reduces rib degeneration. Rats with diabetes mellitus exhibit normal cisplatin pharmacokinetics; nevertheless, their kidneys' organic cation transport system is disrupted because streptozotocin-induced diabetes damages the kidneys. All four molecules share the same structural characteristic, R-CH(NH2)-[CH2]1 2-S-R, which may be crucial in blocking the transportation of cisplatin and may also have future therapeutic applications **[25]**.

Intracellular Distribution: -

Procainamide shields the kidneys from the nephrotoxic effects of cisplatin while retaining its anticancer properties. Rats may be more resistant to cisplatin-induced damage if procainamide and cisplatin mix to generate a less lethal molecule after accumulation in the kidney.

Antioxidant Drugs: Combining allopurinol and ebselen reduces the nephrotoxicity and ototoxicity that cisplatin causes in a rat model. Allopurinol is a xanthine oxidase inhibitor that may reduce the generation of reactive oxidation species. It has been shown that a variety of sulfur-containing compounds reduce the nephrotoxicity of cisplatin without affecting its anticancer efficacy in patients with non-small-cell lung cancer, metastatic colon, breast, and ovarian malignancies. By giving a thiol group, amifostine, an organic thiophosphate, can very selectively protect healthy tissue from cancerous tissue. This characteristic might lessen the toxicity that cisplatin causes.

The organic thiophosphate amifostine can particularly prevent malignant tissue from coming into contact with healthy tissue by introducing a thiol group. This property may reduce the toxicity that cisplatin produces **[26]**. The only medication approved by the FDA that can lessen patients' cumulative renal impairment is amifostine.

receiving cisplatin for advanced ovarian cancer and non-small-cell lung cancer experience. Through the absorption of free radicals, this medicine lowers toxicity. It may also bind and detoxify platinum molecules by reducing the synthesis of platinum-DNA adducts. However, because

of its drawbacks and cost, this medication's use is limited **[27]**. Furthermore, cisplatin should only be used in clinical studies related to malignancies due to concerns about possible disruptions to its anticancer effect.

Signal Transduction-

The thymus secretes serum thymic factor, a nonapeptide thymic hormone that aids in T cell activation and proliferation. Serum thymic factor increases heat shock protein levels and significantly decreases prolonged ERK activation to protect kidneys from cisplatin-induced damage in the rat model. Stronger selective MAPK/ERK inhibitors have also been shown to reduce inflammation and apoptosis, which lowers the kidney damage that cisplatin produces. However, as MAPK/ERK activation mediates cisplatin-induced death in human tumor cells, blocking this pathway may reduce cisplatin's anti-tumor actions **[28]**.

Anti-inflammatory Drugs: -

Many inflammatory disorders are treated with salicylates. It is thought that their reduced prostaglandin synthesis and cyclooxygenase activity are what give them their anti-inflammatory properties. On the other hand, in mice poisoned with cisplatin, high doses of salicylate can stabilize IB and decrease NF-B transcription activity, which lowers renal inflammation and TNF production **[29]**. Salicylates have no effect on cisplatin's anti-neoplastic properties. The rate of tumor removal is consistent when cisplatin and sodium salicylate are given simultaneously. The discovery that TNFR1 mediates TNF's anti-tumor activity and TNFR2 mediates cisplatin's nephrotoxicity may help to explain this **[30]**. Furthermore, salicylate's suppression of the cell survival factor NF-B may boost the efficacy of chemotherapy. In animal models, IL-10 and Melanocyte Stimulating Hormone (MSH) reduce TNF production, hence mitigating the kidney damage caused by cisplatin. By blocking the release of cytochrome c from mitochondria and restricting the transfer of Bax proteins from the mitochondria, fibrines reduce the generation of free fatty acids and apoptosis in vitro models **[31]**. In an animal investigation, fibrers were found to reduce cisplatin-induced nephrotoxicity. Human study is required to determine whether these drugs can stop cisplatin nephrotoxicity.

Mechanisms of Cisplatin Nephrotoxicity: -

Accumulation of Cisplatin in Kidney Cells: -

The kidney eliminates cisplatin through glomerular filtration in addition to tubular secretion. Higher levels of cisplatin in the kidney than in the blood may be a sign that renal parenchymal cells are actively absorbing the drug. Previous studies have used renal slices, cultured renal epithelial cells, and isolated perfused proximal tubule segments to show how cisplatin changes

from a basolateral to an apical orientation. Recent research indicates that the entry of cisplatin into cells may be mediated by two different membrane transporters, Ctr1 and OCT2 **[32]**. Additionally, it has been shown that the uptake of cisplatin into mammalian cells, such as ovarian cancer cells, is mediated by the copper transporter Ctr1.

Ctr1 is a protein that is only found in the basolateral membrane of the proximal tubule and is highly expressed in adult kidneys **[33]**. Ctr1 expression was downregulated in vitro, which decreased cytotoxicity and cisplatin uptake and suggested that Ctr1 was involved in the cisplatin absorption mechanisms of these cells. The role that Ctr1 plays in cisplatin nephrotoxicity in vivo has not been studied **[34]**. Moreover, the organic cation transporter OCT2 (SLC22A2) is responsible for the transportation of cisplatin. The hypothesis that these substrates share a transport pathway is supported by the observation that cisplatin inhibits the absorption of extra OCT2 substrates. The OCT2 substrate cimetidine also reduced the cytotoxicity and nephrotoxicity of cisplatin in both in vitro and in vivo settings. Two recent finding have suggest they may be Major role in mediating. First, cisplatin nephrotoxicity and urine excretion were considerably reduced by OCT2 gene deletion; second, a nonsynonymous single-nucleotide polymorphism (rs316019) in the OCT2 gene was found to be related with a lower incidence of cisplatin-induced nephrotoxicity in humans.

Early Diagnosis of nephrotoxicity: -

The use of cisplatin increases the sensitivity of tests for tubular enzymes produced during injury, such as leucine amino peptidase, alanine aminopeptidase, and N-acetyl beta-glucosaminidase. Serum creatinine is probably the least accurate biomarker of GFR in the early stages of renal impairment, despite the fact that it has been shown that individuals with abnormally low serum creatinine concentrations may see a noticeable decline in GFR before reaching the upper normal threshold." It has been found that inulin and cisplatin remain relatively stable during the whole spectrum of GFRS. In the future, these could serve as sensitive indicators of cisplatin nephrotoxicity. Research has also been done on the excretion of albumin, amino acids, and beta-macroglobulin through the urine. Dynamic magnetic resonance imaging (MRI) enhanced by Frank and associates

Modulation of Cisplatin Induced Nephrotoxicity: -

Because of cisplatin's serious adverse effects, which include nephrotoxicity, its usefulness as an antitumor agent is frequently restricted. One-third of patients often experience variable degrees of cisplatin-related side effects after standard-dose regimens. Countless investigations on

both humans and animals have been conducted in an effort to comprehend the mechanism underlying cisplatin-associated nephrotoxicity and, consequently, reduce its adverse effects. A number of tactics have been investigated to lessen the negative effects of cisplatin therapy, such as using less intense care and substituting the less toxic analogue of cisplatin, carboplatin, with the more toxic one, which is nephrotoxic and neurotoxic. Compared to cisplatin, carboplatin produces a reactive species far more slowly.

Moreover, carboplatin's plasma half-life is much times longer than cisplatin's. It goes without saying that carboplatin causes unjustified side effects such as bone marrow malfunction, tiredness, and infertility. To lessen nephrotoxicity brought on by cisplatin, aggressive hydration with saline has been employed, frequently in conjugation with mannitol. To reduce kidney damage following cisplatin treatment, two litres of 5% dextrose in 0.5 N saline given over the course of 12–24 hours before treatment and at least 24 hours of intravenous fluid afterward are beneficial. An organic thiophosphate molecule with cytoprotective potential is amifostine, also known as ethanol. The active free thiol metabolite may bind to free radicals produced in the kidney to lessen the harmful effects of cisplatin on the kidney tissues.

Compared to patients treated with cisplatin alone, patients treated with amifostine prior to cisplatin therapy were observed to have decreased renal impairment. Proadministration of a zinc-histidine complex has been found to mitigate kidney damage generated by cisplatin in experimental animals, potentially through the prevention of peroxidative damage. It has recently been demonstrated that the 32-kDa microsomal enzyme heme oxygenase-1 (HO-1) reduces the necrosis and apoptosis caused by cisplatin. It has been demonstrated that cisplatin therapy increased kidney damage in homozygous mice with a targeted deletion of the HO-1 gene (HO-1) in comparison to wild-type mice (HO-1) **[35]**.

Methods to Reduce Nephrotoxicity: -

Time-tested strategies to lessen cisplatin nephrotoxicity include aggressive hydration and avoiding other nephrotoxic substances like aminoglycosides. Studies both experimental animals and humans indicate that a range of therapies can be used to modify abnormalities in renal function that occur after cisplatin therapy. It appears that the key events happen practically immediately following cisplatin delivery, even though it takes a few days for the severe abnormalities in renal function to fully emerge; consequently, precautions should be taken prior to, during, or shortly after cisplatin infusion **[31]**. The most

popular treatment technique for preventing cisplatin-induced nephrotoxicity is infusion of mannitol with either furosemide or Nacl Solution through randomised research AI-Sarraf et al. demonstrated that mannitol added to a cisplatin-plus-hydration regimen has a protective impact on kidney function. The difference between changes in NaCI excretion in the urine and urine flow rate suggests that salt loading matters more than hydration level." Ozols et al. introduced hypertonic saline (NaCI 3%), which is now used in clinics **[32]**. They administered divided doses of cisplatin in 250 mL of 3% NaCI, however they observed neither a decrease in CI nor an increase in serum creatinine. However, in one trial, hypertonic saline was unable to prevent nephrotoxicity when cisplatin was given without fractionation (50–60 mg/m2/d for two days in a row) **[36, 37]**.

CONCLUSION: -

One major and dose-limiting cisplatin hazard is nephrotoxicity. The combination of cisplatin's entry into renal epithelial cells, damage to nuclear and mitochondrial DNA, activation of several pathways leading to both cell death and survival, and start of a strong inflammatory response result in cisplatin nephrotoxicity. Despite the wide range of potential treatment targets presented by this system, individual therapies in animal models have typically only offered partial protection. Furthermore, not enough research has been done to determine how various treatments affect cisplatin's effectiveness as a chemotherapy drug. Moving forward, combinatorial strategies which target multiple mechanisms, such as reducing cisplatin uptake and reducing inflammation, may offer the best chance for clinically meaningful prevention.

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