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Brief Overview About Cisplatin Toxicity and The Potential Protective Role of Ferulic Acid

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Abstract: Cisplatin is an effective anti-neoplastic agent, that could be used against many types of cancers. Even high dosages of cisplatin are more effective, there is a concern due to their toxic side effects especially on renal tissue. The harmful effects of cisplatin were resulted in oxidative stress, apoptosis and also DNA damage. Ferulic acid (FA), is a plant phenolic acid that turns out to be a potential antioxidant phenoxy radical. Phenolic compounds are known for their roles on neurodegenerative diseases, cancer, diabetes, coronary heart diseases, inflammation states and idleness as potential therapeutic agents. It has been already reported that FA with its antioxidant properties is able to neutralize nitric oxide and hydroxy-radical groups that lead to DNA damage.

Keywords: Cisplatin, Toxicity, Ferulic Acid.

CISPLATIN

CHEMISTRY:

The chemotherapeutic agent; cisplatin is a drug which has broad efficacy in variable types of cancers as brain, breast, ovarian, bladder, lung, head and neck, testicular, cervical and esophageal cancers. Cisplatin is neutral and DNA destroying agent. Its chemical name is cis-di-ammine-di-chloro-platinum (II) **(1).** Cisplatin molecular structure is a central platinum atom with two chlorine atoms surrounding and two ammonia groups in a *cis* configuration. The bond angles for the platinum core are fixed, resulting in DNA bending to accommodate the structure of the drug **(2)**.

PHARMACOKINETICS

It was well known most cisplatin is found in the cytosol and is not protein bound **(3)**.

Previous experiments found that cisplatin clearance was biphasic in nature, with a rapid phase half-life of 22 min and a slow phase half-life of 5 days with significant amounts of platinum are still detectable in plasma 12 days after intravenous injection **(4)**.

Previous experiments on dogs detected rapid increase in those urinary levels of platinum following administration, with about 60% from the dose detected in the urine during the first 4 hours while about 76% from the administered dose detected within 48 h after administration. On the other hand, minimal percentage of platinum was excreted in bile. It is thought that secretion involves active accumulation of secreted substances in the renal cells and passive transport into the tubule of the lumen. The most active site of secretion is the pars recta of the proximal renal tubules, and it is also the most injured site of the kidney from cisplatin nephrotoxicity. Therefore, concurrent treatment with medications that are beleived to be excreted by this route may significantly decrease renal cisplatin uptake **(1).**

In the previous studies, it was reported that cisplatin is distributed to all tissues; while, in the 1st hour, it tends to accumulate in the kidney, liver, skin and muscle with high renal tissue concentrations present as long as 12 days after treatment **(5).**

MECHANISM OF ACTION:

The mechanism of action of cisplatin is mediated by the interaction of cisplatin with DNA in order to for DNA adducts. The principle mechanism of action is exertion of cytotoxicity on tumour cells by the formation of DNA adducts that include mono-, inter, and intrastrand cisplatin DNA crosslinks which arrest the cell cycle at S, G1 or G2-M and so induces apoptosis **(6)**. This is due to the arresting of cells at G2, S or G1-phases induced by cisplatin of the cell cycle in an effort to correct the injury. The primary DNA adducts is the intrastrand crosslink adducts which is responsible for apoptosis activation. This induces the failure of the adequate repair that induces aberrant mitosis of the cells followed by apoptosis **(7)**.

The resulting impairment of the DNA replication is responsible for the death of fastest proliferating cancer cells. Therefore, apoptosis embraces various pathways that converge on a single non-reversible phase in which nucleases and proteases digest the doomed cell **(8).**

Evidence from past researches on apoptosis have reported variable cellular factors that determine the cell survival. As reported by Zhu *et al*, these factors are p53-tumor suppressor, Bcl-2 family of proteins and intracellular signal-transduction pathways that are often facilitated by phosphatidylinositol 3-kinase and protein kinases **(9).**

As mentioned in the above mechanism, cisplatin actions can be improved by preventing arrest of the cell cycle or through inhibition of protein kinase**.**

According to previous researches, when the cisplatin was given, displacement of one or two chloride atoms occured immediatly; this gave an aqua-complex known as aquation. The condition within the cell encouraged the dissociation of chloride because the lower intracellular concentration of chloride **(8).**

According to previous researches, proof had shown that the most notable changes to the DNA that resulted into its death as a result of cisplatin administration was 1, 2-intrastrand cross-link purine bases. This represents approximately 90% of DNA adducts. However as stated by Yoshikawa *et al* other adducts such as inter-strand, 1, 3-intrastrand adducts and other nonfunctional adducts have been closely linked to toxicity of the drug **(10).**

At the molecular levels, apoptosis is complemented through caspases which are groups of intracellular cysteine proteases that slit substrates to aspartic acid residues. Once activation of caspases occur, they target and invade both the nuclear and the cytoplasmic factors that are responsible for the maintenance of cellular architecture and engage in DNA repair, replication and transcription. This process is also boosted by the fact that regulation of apoptotic pathways is enhanced in the presence of anti-apoptotic as well as apoptotic proteins **(5)**.

SIDE EFFECTS:

Anemia was reported with cisplatin administration can be due to diminished erythroid stem cells or erythropoietin **(11).** Cisplatin has been found to induce red blood cells sensitization and hemolytic anemia **(12).**

Electrolyte disturbances: hypokalemia, hypocalcemia, and hypomagnesemia are common with cisplatin use. Hyponatremia and hypophosphatemia were found in many patients treated with cisplatin combination regimens **(11).**

Emetogenic effects: Within the 1st 6 hours after administration of cisplatin, acute nausea and vomiting may happen. It usually lasts for 24 hours and may continue for up to 5-10 days and can be prevented by pre-treatment with a 5-HT3 antagonist (e.g., ondansetron) and corticosteroid **(13).** On the other hand, 24 hours or more following cisplatin therapy, **delayed** nausea and vomiting appear. The progression and intensity of cisplatin-induced emetogenic effect occur more in combinations with other emetogenic drugs, young ages, females, rapid infusion and in high doses. Corticosteroids are the main line of treatment of delayed emetogenic effect, while other combinations can be used **(14)**.

Sensory **peripheral neuropathies** are the common impacts on the nervous system in the form of lower and/or upper limb paresthesia especially in geriatric patients. Motor affection can also present in the form of gait difficulties with diminished or even absent deep tendon reflexes **(11)**.

Another side effect is **otic impact** which can be presented with tinnitus with or without deafness. This results from inner ear damage which is irreversible and cumulative. Ototoxicity appears to be dose related. These impacts may be more severe in children than in adults **(15)**.

Nephrotoxicity is considered a serious problem with cisplatin administration. It can be presented as electrolyte disturbances as hypomagnesemia or hypokalemia and even renal insufficiency. The risk for these adverse effects is in direct relation with the dose and duration of cisplatin. It may be reduced through adequate hydration. increased risk can also occur in old ages **(16).**

Shiraishi *et al.,* (17) stated that dose-dependent cumulative nephrotoxicity was considered the main cisplatin toxic effect, where about one-third of the cases developed nephrotoxicity after cisplatin single dose (50–100 mg/m2). This could be attributed to the low molecular weight and uncharged character of cisplatin that allowed free unbound cisplatin in the plasma to be filtered by the glomerulus, which further caused trapping of cisplatin in the renal cortex **(18)**.

***Antioxidant agents for prevention of cisplatin-induced toxicity:**

Liberation of reactive oxygen species and vasoconstriction in the microvasculature is responsible for the cisplatin-induced injury.. There had been many studies that interestingly stated, reactive nitrogen species had also been encompassed in cisplatin-induced toxicity. Cisplatin heightened the release of peroxynitrite and nitric oxide in tissues. Peroxynitrite induced functional and structural changes of lipid peroxidation, reduction in cellular defenses and chemical cleavage of DNA and proteins by oxidation of thiol pools **(19).**

Medicinal plants were a good origin for multiple natural antioxidants, and they were utilized worldwide for the treatment of diseases. Recently, researchers have shown a raised concern in getting natural antioxidants from plant origins for treatment or prevention of multiple diseases **20).**

It was demonstrated that antioxidant agents; vitamin E and selenium and were effective in diminishing oxidative stress induced toxicity of cisplatin **(21)**.

another research on rats stated that the conjunction of ebselen and allopurinol, xanthine oxidase inhibitor with the potential to diminish ROS generation, diminished cisplatin induced nephrotoxicity. Ebselen as a glutathione peroxidase imitator, was a great scavenger of peroxynitrite **(22).**

Several pharmacologic agents including N-acetylcysteine, theophylline had also been studied to prevent and or diminish toxicity of this anticancer drug. Theophylline which is a known nonselective adenosine receptor antagonist was proposed for prevention of CIN **(23, 24).**

Properties of Ferulic Acid

Ferulic acid, like p-coumaric, synapine, caffeic, syryte and vanillin acids is the most common cinnamic acid derivative. Ferulic acid is most commonly present in parsley, rhubarb, spinach, grapes, whole grains and cereal seeds, mainly oats, wheat, rye, and barley. One of the most vital roles of phenolic acids, especially cinnamic acid derivatives, is their antioxidant impacts, that depends mainly on the number of methoxy and hydroxyl groups attached to the phenyl ring **(25, 26).**

It was studied that ferulic acid had minimal toxicity and had variable beneficial physiological functions as antimicrobial, anti-inflammatory, antithrombotic, anti-arrhythmic and anticancer activity (for instance lung, breast, colon and skin cancer). It reduced injury of nerve cells and helped to repair injured cells. Furthermore, it was used as a sport supplement as it alleviated muscle fatigue by neutralizing free radicals in muscle tissues. It had been widely applied in food and pharmaceutics. **(27, 28)**.

Antioxidative Activity of Ferulic Acid

Its antioxidant features were basically related to free radicals scavenging effect, binding transition metals such as copper and iron, and inhibition of lipid peroxidation. The mechanism of antioxidative activity of ferulic acid was the ability to form stable phenoxyl radicals, by the interaction of the molecule of antioxidant with the radical molecule. This made it difficult to initiate a complex reaction cascade resulting in the liberation of free radicals. This compound could also act as hydrogen donor, giving atoms directly to the radicals. This is specifically vital for the cell membrane lipids protection from undesired processes of autoxidation. As an antioxidant, ferulic acid and its related compounds could bind transition metals such as iron and copper **(29).** This inhibited the formation of toxic hydroxyl radicals, that induced peroxidation of the cell membrane **(30).**

Literature data stated rising efficacy of ferulic acid and its related compounds in minimizing cyclooxygenase and xanthine oxidase activity. It was therefore supposed that ferulic acid diminished the amount of ROS generated by the enzyme-catalyzed transformation **(31).**

Mahmoud et al. (32) suggested that pre-treatment with FA in methotrexate induced nephrotoxicity in rats resulted in diminished ROS production and enhanced antioxidant defense mechanisms. Pre-treatment with FA inhibited apoptosis of methotrexate through its double antioxidant and anti-inflammatory impacts. FA down-regulated cytochrome c, caspase-3 and Bax and boosted Bcl-2 in the renal tissues of methotrexate-intoxicated rats, showing a potent anti-apoptotic effect.

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