



Effects of Cisplatin Intoxication on Serum Liver, A Short Review

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Abstract: Cisplatin is a widely used and effective drug for the treatment of solid tumors ranging from ovarian, lung, bladder, breast, head and neck, and testicular cancers. However, its clinical use was rapidly limited due to unexpected and very severe renal toxicity and effective cancer chemotherapy with this agent has been further complicated by the lack of information concerning the mode of action and the species responsible for eliciting the anticancer activity. In this regard, Dose limiting side effects, such as ototoxicity, neurotoxicity, and nephrotoxicity, are generally encountered with a majority of patients treated with cisplatin-based chemotherapy. The present review includes a brief discussion of the nature and underlying mechanism of Effects of cisplatin intoxication on liver.

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1. Introduction

The kidneys and the liver are two of the organs where cisplatin accumulates, frequently leading to nephrotoxicity and hepatotoxicity. Moreover, the toxicity profile of cisplatin significantly reduces patient survival and quality of life (2). Presently, the specific mechanisms of cisplatin-induced nephrotoxicity and hepatotoxicity are not fully understood. An increase in inflammatory cytokines and the initiation of inflammatory responses have been reported as key factors in cisplatin-induced toxicity, though these exact mechanistic targets remain elusive (1-3).

Cisplatin is an antineoplastic agent developed by Rosenberg et al. They were studying the effects of electrolysis products from a platinum electrode on growing cells (1-10). Rosenberg et al. resulted that certain electrolysis products of platinum mesh electrodes were capable of inhibiting cell division in *Escherichia coli* and this created much interest in the possible use of these products in cancer. Since the identification of cis-dichloro diammine platinum (cisplatin) as the agent responsible for this activity, much interest has been created in the use of coordination complexes of platinum, palladium, and other noble metals in the treatment of cancer disease (1, 11-13).

Hill et al. tested cisplatin. In spite of its suitable antineoplastic activity against ovarian, lung, bladder, breast, head and neck, and testicular cancer, its clinical use was rapidly limited due to unexpected and very

severe renal toxicity. In the animal studies, treatment with LEM significantly reduced the effects of cisplatin intoxication on serum liver biomarkers and serum renal biomarkers. Meanwhile, LEM diminishes significantly the effect of cisplatin on the level of lipid peroxidation in liver and kidney tissues. The activities of the antioxidant enzymes (reduced glutathione, glutathione peroxidase, superoxide dismutase, and catalase) were increased in groups pretreated with LEM and quercetin. Additionally, the normal histological structures of the liver and kidney were restored after treatment with LEM (4).

Reactive oxygen species (ROS) are free radicals such as the hydroxyl radical (OH) and the superoxide anion or molecules like hydrogen peroxide. The production of ROS is a normal physiological event in various organs, including liver and kidney tissues. However, the overproduction of ROS causes structural damage of biological macromolecules including nucleic acids, proteins and lipids that results in the formation of cytotoxic secondary products such as malondialdehyde (MDA). The administration of some antioxidants such as vitamin E, vitamin C, selenium and carotenoids before or after treatment with cisplatin could protect or ameliorate against nephrotoxicity and hepatotoxicity (5).

Cisplatin has been used for many years in hepatic arterial infusion. Cisplatin had no clear effect on number of size of FAH, cell proliferation (mitosis) or cell loss (TUNEL positive). Sorafenib enhanced the development of FAH. Morphometric quantification

revealed a sorafenib-induced 2–3-fold increase in number (FAH per cm² and FAH per cm³), size and volume fraction of FAH. This unexpected finding was confirmed in two experiments. The effect was driven by an increased cell proliferation in the FAH, resulting in an increased, 5.4-fold growth advantage of FAH versus the surrounding liver in sorafenib-treated FTL (6).

Pregnancy and fetal age have an impact on cisplatin protein binding because of lower albumin levels. The resulting higher levels of free drug in the mother and fetus may increase the risk of toxicity in both. Good outcomes are possible. Long-term follow-up studies reveal normal fertility in women previously treated with cisplatin. Cisplatin causes severe mitochondrial toxicity in the maternal rat kidney. Side effects include nephrotoxicity, ototoxicity, neuropathy, optic neuritis, papilledema, seizures, anemia, hypokalemia, hypoglycemia, blurred vision, paresthesia, ataxia, elevated hepatic enzymes, rash, urticaria, muscle weakness, and loss of taste (7).

The most common measures used to prevent cisplatin-induced nephrotoxicity are hydration with electrolyte replacement, forced diuresis, and antiemetic therapy; severe myelosuppression often requires the administration of granulocyte colony-stimulating factors. There is no specific chelation therapy for cisplatin intoxication. Amifostine, an organic thiophosphate, may diminish cisplatin-induced toxicity by donating a protective thiol group (8).

In 1999, Itoh and coworkers reported that cisplatin inhibits Hsp90 chaperone activity. Affinity purification and protein fingerprinting studies were used to demonstrate that cisplatin binds to the Hsp90 C-terminal domain. Subsequently, Csermely and coworkers demonstrated that cisplatin is a C-terminal inhibitor that binds near the previously identified C-terminal nucleotide-binding site. Studies by Rosenhagen and colleagues indicated that the administration of cisplatin to neuroblastoma cells resulted in the degradation of steroid hormone receptors (androgen and glucocorticoid receptors), but no other Hsp90-dependent clients, such as Raf-1, Ick, and c-rac. Moreover, by use of a heat-shock factor (HSF)-dependent luciferase reporter assay, they showed that cisplatin does not induce the heat-shock response (9).

2. Conclusions

The results suggest that unlike compounds that bind Hsp90, cisplatin selectively inhibits some Hsp90 functions and thus, could provide insights into novel ways to modulate its chaperone activity. Recently, it was shown that LA-12, an optimized derivative of cisplatin, exhibits higher affinity for Hsp90 than cisplatin and moreover, induces the degradation of

additional Hsp90 client proteins, such as mutant p53, Cyclin D1, and estrogen receptors. In addition, LA-12 exhibits a more favorable pharmacokinetic profile as compared to cisplatin and demonstrates enhanced cytotoxicity against multiple cancer cell lines, including those that are cisplatin resistant (10).

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