Molecular Mechanisms and Immunomodulatory Effects of Platinum Analogs on Some Genes and as Anticancer Drugs: Review Article
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Abstract

Platinum analogs includes cisplatin, oxaliplatin and carboplatin. Cisplatin is a chemotherapeutic drug with excellent success in the management of human malignancies. Molecular mechanism of action related to its capacity to crosslink of DNA purine bases; also, by interfere with DNA repair, leading to DNA break, and consequently lead to apoptosis in cancer cells. Cisplatin also found to have immunomodulatory properties besides its cytotoxic effect.

Keywords: Cisplatin, Cancer, Molecular and Immunomodulatory effects, Genes repair

Platinum Analogs

Platinum analogs includes cisplatin, carboplatin, and oxaliplatin. Cisplatin is an inorganic metal. Numerous platinum analogs have been consequently synthesized. Cisplatin has main antitumor action in numerous solid tumors, cisplatin and the other platinum analogs are extremely cleared via the kidneys through the urine, so, dose adjustment is necessary in the case of renal dysfunction. Platinum analogs have the same clinical pharmacological action, cytotoxic effect and mechanisms of resistance as cisplatin [1].

Cisplatin as effective anticancer drug

Cisplatin is broadly used drugs for treatment of different human cancers and greatly valuable [3,4]. Cisplatin has antitumor action in a diversity of malignancies like ovarian cancer, lung, breast, brain, renal, testicular tumors and head and neck malignancies. Drug resistance and extensive adverse effects lead to give it with additional cancer drugs as original therapeutic strategies for numerous malignancies [2]

Cisplatin cellular uptake

Cisplatin is activated by entrance the cell and its chloride atoms in the cytoplasm are substituted with H2O molecules and the resulting powerful electrophile product be capable of act in response with every nucleophile, like proteins’ (-SH groups) and nitrogen donor atoms of nucleic acids. It binds to N7 reactive center on purine residues and this led to DNA damage in cancer cells and death of apoptotic cells [5,6,7,8,9].
Cisplatin reactivity

Cisplatin is a neutral inorganic complex which interact with DNA, that terminate in repair of the damage of DNA or start of the irreversible apoptotic program. Cisplatin need to be activated via equation reactions [10]. The monosaturated structure is known as an extremely reactive type, however its creation considers as the limiting step to reaction with numerous endogenous nucleophiles. Therefore, as cisplatin enters cells, it becomes susceptible to cytoplasmic inactivation via the intracellular components [11].

Cisplatin molecular mechanisms of action

Oxidative Stress induction

Cancer cells have more reactive oxygen species (ROS) than normal cells, as a result of oncogenic stimulation, bigger metabolic action and impair mitochondrial function. [12]

In some situations, a thiol group possibly will form of the radicals which sequentially may interact with molecular oxygen, then production of reactive oxygen species can be produced [13]. During cisplatin therapy, a significant decrease in plasma amount and activity of different antioxidants like glutathione might happen [14,15]. Lipid peroxidation, as a result of extreme ROS production reflects oxidative stress, and related to cisplatin-induced renal toxicity [16,17,18,19]. Oxidative stress is the major means related to cisplatin-induced cardiac toxicity [20, 21,22,23].

Modulation of Calcium Signaling

Ca2+ is necessary for normal biological functions [24]. Three main groups of membrane -associated proteins directly occupied in Ca2+ regulation. First group is channels, second one is ATPases and third one is exchangers [25].

Cisplatin causes disturbance of calcium homeostasis which leads to lipid peroxidation and inhibit enzymatic activity. Then damage the cells via mitochondrial injure, decrease mitochondrial activity, reduction of adenosine triphosphate (ATP) and other cofactors. These events most likely cause apoptosis and tissue necrosis. So, enhancement of calcium concentrations, through calcium supplementation, can perform cytoprotecting effect, via contending for with its binding sites and stop different toxicities related to it [2]. In previous study, cisplatin enhances Ca2+ in tumor cell lines which cause activation of apoptosis and cell death [26].

DNA Damage

Cisplatin can kill cancer cells via its harmful effect on DNA, mostly through forming Pt-d(GpG), Pt-d(ApGaran), Pt-d(GpXpG) intrastrain diadduct and minor one, Pt-G-G interstrand cross-links [33,34]. Mutations which related to number of signals linked with stress. Activation of cell cycle check points happens after the damage of DNA, so the delay of cell cycle chain lead to restore or to lastingly get rid of the cells by cell fatality [35].
Tumor suppressor gene p53 and Cell Apoptosis

Cisplatin mainly induces a controlled figure of cell fatality called apoptosis. Apoptosis has extrinsic and intrinsic pathways. Extrinsic way is started as ligands bind to the tumor necrosis factor-α (TNFα) receptor, after that; oligomerization and recruitment of procaspase-8 through adaptor molecules to produce the death-inducing signaling complex (DISC), while the intrinsic way is began via stress of cells, like DNA break, ensuing production of cytochrome-c of the mitochondria leading to activation of procaspase-9 via the interaction with apoptosis promoting activating factor-1 (APAF-1) and production of an active apopozole complex, figure 1.[27,28].

P53 is involved in the initiation of apoptosis in cisplatin-induced toxicity of kidney, where DNA destruction caused through causes phosphorylation and consequent activation of p53 [29,30]. Apoptosis resulted from cisplatin in renal tubular cells could as well engage the endoplasmic reticulum pathway [31,32].

![Diagram](image)

**Figure 1.**

The pathways included in mediating cisplatin-induced cellular effects [11].
DNA Repair genes and platinum-based chemotherapy

Tumor cells may produce drug resistance through repair mechanisms which offset the DNA damage caused by chemotherapy. DNA repair enzymes are rising targets for original anticancer methods of treatment [36,37]. Platinum’s molecular mechanism of resistance is complex [38]. Platinum-DNA monoadducts and intrastrain crosslinks may be repaired via nucleotide excision repair. Interstrand crosslinks (ICL) may be repaired via activation of ICL repair, that includes numerous repair systems [39]. Every one of excision repair cross-complementing (ERCC) members has distinctive effects in DNA repair development, and its expression level. In a prospective research, Sullivan et al. analyzed the SNPs in eight DNA-repair linked genes and establish that after the management of platinum-based chemotherapy, the response of patients with stages III considerably connected with SNPs in ERCC1 and ERCC3 genes, whereas the response of patients with stage IV related to genetic variant in the ERCC4 gene [40]. Iraqi study established that patients with low expression ERCC1 had chemo-sensitive response as comparison with those with elevated expression. Therefore, these results recommend that overexpression of ERCC1 is connected with platinum drug resistance in Iraqi breast cancer patients. The patients with low levels of ERCC1 expression have advantage from platinum-based chemotherapy [41].

Cisplatin and immune system

Numerous anticancer drugs are established to exert antitumor activities through tumor cell killing and via stimulating an immune-promoting inflammatory reply [42,43]. The immune-promoting actions include initiation of immunogenic cell death (ICD). The ICD procedure include discharge, liberate or exposure of damage-associated molecular patterns (DAMPs) [44,45] that begin an efficient priming of an immune reaction against antigens liberated from dying cells [46]. The anticancer action of cisplatin found to be related to its capability to cross-link DNA and slow down mitosis and as well to its effects on immune system. These special effects can be very vital for fighting tumors. Cisplatin-induced antitumor immunomodulation happened at a moment while rising antineoplastic strategies are ever more including the immune system frankly. Current developments in oncology occupy synergizing like novel immunotherapies with conventional chemotherapeutics as doxorubicin and cisplatin-based managements [47]. A research found that cisplatin induction of tolerogenic dendritic cells (DCs) so as to showed obviously enhanced level of IL-10 creation by stimulate activation of the p38 MAPK and NF-κB signaling pathways devoid of any modify on TNF-α and IL12p70 levels. IL-10-forming CD3+CD4+LAG-3+CD49b+CD25-Foxp3- Tr1 cells, which was considerably enhanced with no changing the Foxp3+ regulatory T cell population. These tolerogenic DCs as an outcome make possible the forming and differentiation of T-helper 2 and T-reg 1 cells as well to IL-10-producing which induced inflammatory situation, this connection can give cancer cells with an chance to evade the immune system[48].
Conclusions

Cisplatin is one of cytotoxic drugs and it destroy cancer cells by damaging DNA, and by inhibiting its synthesis and mitosis, and enhance apoptotic cell death. Cisplatin also has immunomodulatory effects by induce Th 2, T-reg, IL-10 producing besides its cytotoxic effect.

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References


