Recent Developments of Platinum-based Antitumor Drugs

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Abstract— Even after cisplatin was approved four decades ago, platinum-based medications continue to have a leading position in cancer treatment plans. The efficacy of these medications in treating many tumour types has been proven, however their ability to treat cancers is still restricted due to the onset of severe side effects and rising drug resistance. The development of platinum (IV) prodrugs with various inhibitors has resulted from our understanding of the mechanisms of action of platinum compounds in cancer treatment. These prodrugs are being studied for their potential to reverse the effects of platinum compounds through alternative biological pathways, such as immune stimulatory mechanisms. Pt-based anti-cancer medications have advanced significantly in cancer therapy in recent years thanks to developments in chemical synthesis and nanotechnology. Numerous tactics were based on the cisplatin-like anti-cancer mechanism, and they were somewhat successful by changing existing platinum drugs. Platinum-based nano-drugs, such platinum nanoclusters, have demonstrated encouraging outcomes in clinical application and offer unique anti-cancer mechanisms. They also have significant potential in tumor-targeted therapy. This study summarises the development of Pt-based anti-cancer drug application in cancer therapy, with a focus on how to modify the drugs to increase the anti-tumor efficacy.

Keywords: Anti-cancer, Drugs, Platinum complex, Therapy

I. INTRODUCTION

The development of chemotherapeutic procedures for the treatment of tumors has advanced significantly since Rosenberg's discovery [1] of the anticancer effects of platinum compounds. The Food and Drug Administration (FDA) approved cisplatin, a platinum medication, in 1978 for the treatment of various types of cancer. Crucially, cisplatin-based chemotherapy for testicular cancer is thought to be nearly curative [2]. Worldwide clinical approval has been granted to the platinum compounds cisplatin, carboplatin, and oxaliplatin [3], which are used in almost half of all cancer therapy chemotherapeutic treatments. Unfortunately, the emergence of resistance and serious side effects, including as myelosuppression (carboplatin), peripheral neurotoxicity (oxaliplatin), nephrotoxicity (cisplatin), and ototoxicity (cisplatin), restrict the efficacy of platinum-containing anticancer therapy [4]. For cancer survivors, these toxicities significantly lower quality of life and are dose-limiting. Therefore, alternative platinum compounds and application tactics have been created, and are currently being developed, to prevent the development of resistance and harmful, undesired effects.

II. WHY PLATINUM COMPLEXES

The ligand-exchange kinetics of platinum coordination compounds plays an important role for Pt-compounds to be used as drugs. Platinum-ligand bond plays an important role in the mechanistic pathway of the compounds. Pt-compounds have high kinetic stability, so the ligand exchange occurs slowly. Platinum-ligand bonds are moderately stable. Thus Platinum is rapidly bound by soft nucleophiles which are typically sulphur containing residues in human peptides and proteins; this includes the amino acids methionine and cysteine. kinetic *trans* effect is also responsible for the ligand-exchange reactions [5,6].

III. PLATINUM (II) COMPLEXES

Generally neutral square-planar Pt(II) compounds used as used as anti-cancer with general formula is $[PtA_2X_2]$ [7,8]. Schematic diagram of Platinum(II) compounds shown in Figure 1.

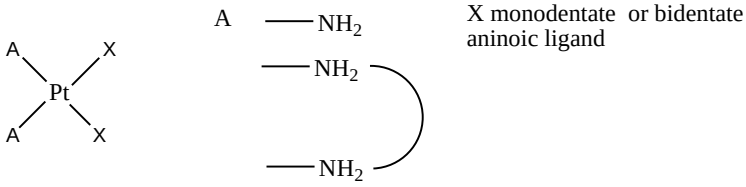

Figure 1: Structure of Platinum (II) compounds.

Generally, anti-cancer compounds of platinum (II) have this type of structures. Cisplatin, *cis*-diamminedichloroplatinum (II), is a well-known example of such a compound [9]. Cisplatin has been used in clinical practice worldwide. The use of the cisplatin

as anti-cancer drugs has encouraged the advancement of modern therapeutic inorganic chemistry [10]. Second- and third-generation platinum (II) complexes have been developed by altering the cisplatin structure to include coordinated bond(s) with different features, such as basicity and electronic steric effects [11, 12]. Different generation of Platinum complex are given in Figure 2. These changes allow the complexes to interact with DNA *via* coordinate bonds.

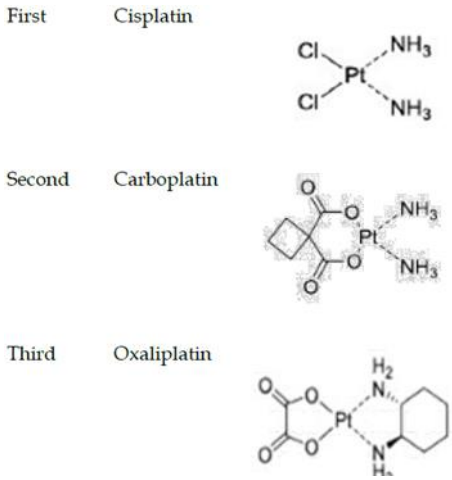

Figure 2: Different generation of Platinum complex

IV. MECHANISM OF ACTION OF PLATINUM-BASED DRUGS

When Cisplatin, is administered intravenously, due to the relatively high (about 100 mM) concentration of chloride ion in the bloodstream it remains neutral and unchanged [13]. Then cisplatin can bind with plasma protein within 24 h of administration because cisplatin can bind with plasma proteins albumin, cysteine, transferring etc. resulting deactivation of larger amount of applied cisplatin. Through passive diffusion and transport proteins, such as copper-transporter 1 (CTR1) and organic cation transporter OCT1-3 (organic cation transporter 1–3), the remaining active platinum compounds penetrate tumor cells [14, 15]. Then the platinum compounds get hydrated and subsequently forms $[PtCl(NH_3)_2(H_2O)]^+$ and $[Pt(NH_3)_2(H_2O)_2]^{2+}$ respectively [16]. These species finally enter into nucleus and binds to DNA via intra or inter crosslinks causing DNA damage [17]. Simultaneously, in this process excessive reactive oxygen species (ROS) get produced and onset of apoptosis occurs. Similar mechanism of cytotoxicity also occurs in case of other platinum compounds like carboplatin, oxaliplatin, nedaplatin etc. Binding of Platinum (II) complex with DNA shown in Figure 3.

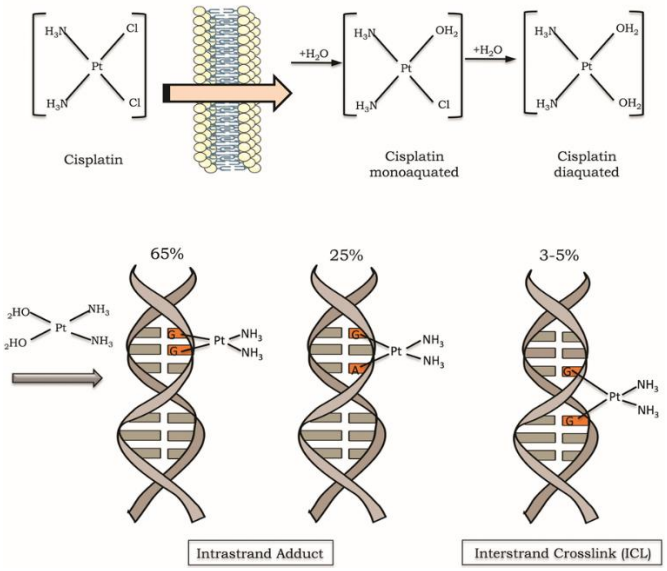

Figure 3: Binding of Platinum (II) complex with DNA

V. FUNCTIONALIZATION OF PLATINUM (II) COMPLEXES

Over the last few decades, researchers have become increasingly interested in attaching platinum-based medications to various functional molecules or nanoparticles, both with and without targeting functions [18,19]. The functionalization of platinum-based drugs has a number of potential benefits, including (i) increased drug concentration specifically within the target area [20]; (ii) increased bioactivity, which can enable theranostic applications [21]; and (iii) the possibility of unified pharmacokinetics across diverse functional molecules [22]. Pharmaceuticals based on functionalised platinum so offer a potential way to overcome the limitations of Pt-based drugs, enhance the effectiveness of diagnostic agents, and eventually enable more accurate and thorough diagnostic capabilities. Functionalised platinum-based medications can also be used as magnetic resonance imaging (MRI) contrast agents or fluorescent probes [23].

VI. PLATINUM (IV) PRODRUGS

Various strategies have been employed to limit the side effects, including modifications of platinum drugs [24], using prodrugs [25], carriers such as heparin [26], antibodies [27], pH-, temperature-, and ultrasound-responsive hydrogels [28], silk [29], functionalized and self-assembled nanoparticles [30], liposomes, multilamellar liposomes [31], engineered exosomes [32], peptides [33], and dendrimers [34]. Despite these strategies, cancer cells often display increased resistance to platinum-based drugs [35]. To overcome these challenges, Pt(IV) prodrugs have been developed, which have many advantages over Pt(II) drugs [36]. Due to inertness and slower ligand exchange of Pt(IV) prodrugs off-target reactions get reduced and thus the concentration of the active drugs increases. Pt(IV) prodrugs are less reactive with biomolecule than the Pt(II) compounds. In cancer cells under appropriate conditions Pt(IV) prodrugs are reduced to Pt(II) compounds, which then binds to DNA [37]. During this reduction process Platinum losses ligand from the coordination sphere and coordination no changes from 6 to 4, which may have additional pharmacological effects [38]. In this Pt(IV) prodrugs to Pt(II) conversion bioreductants plays vital role. This six-coordinate octahedral molecular geometry in Pt(IV) offers improved kinetic stability as well as many pharmacological activities such as lipophilicity, redox stability, tumor selectivity, and improved bioactivity [39]. However, the exact mechanism of Pt(IV) prodrugs is not clear [40]. Because Pt(II) reduction is thought to be necessary before these can interact with their intended biological targets, they are referred to as prodrugs. Clinical trials have assessed a number of cisplatin analogues that have been converted into Pt(IV) complexes. According to these findings, Pt(IV) complexes have several advantages over cisplatin, including oral availability and less adverse effects [41, 42].

VII. FUNCTIONALIZATION OF PLATINUM (IV) COMPLEXES

Hydroxido, chlorido, and acetato are often utilized as axial ligands in clinical studies to change the pharmacokinetics of Pt(IV) prodrugs [43]. To block various enzymes and processes involved in cancer cell growth, bioactive ligands have been included into Pt(IV)-ligand conjugates [44]. This strategy also has the advantage of having a unified pharmacokinetic effect to increase the possibility that the bioactive ligand and cytotoxic Pt(II) cargo will work together to improve chemotherapy efficacy.

VIII. NANOMATERIALS AS DRUG CARRIERS

Nanocarrier-based platinum drug delivery systems offer a viable alternative to conventional platinum medicines [45]. Gold nano clusters (GNCs) have gained popularity as drug transport carriers in recent years due to their strong photostability [46], water solubility, and biocompatibility [47]. Compared to ordinary nanoparticles, GNCs typically have a particle size of less than 2 nm and a longer blood circulation period. Pt medicines can be efficiently loaded in GNCs and accumulate in tumor tissues because to the enhanced permeability and retention (EPR) effect, resulting in greater therapeutic efficacy and less systemic toxicity. Furthermore, ultrasmall GNCs are typically eliminated from the body due to ineffective renal clearance, showing good metabolism and biocompatibility. Superparamagnetic iron oxide nanoparticles (SPIONs) as drug carriers are very important due to their advantages of low toxicity, biocompatibility, biodegradability, and well water dispersion. [48]. Other important nanomaterials as drug carriers are Mesoporous silica nanoparticles (MSNs) [49,50], organic polymeric nanoparticles etc. Pt drugs encapsulated in polymeric nanoparticles reduce the side effects without affecting drug efficacy.

IX. PT NANOCLUSTERS (PT NCS) AS A NEW PT DRUG FOR CANCER THERAPY

Pt NCs have received a lot of attention in bioanalysis and biomedicine due to their unique physicochemical properties, including as ultra-small size, exact structure, photoluminescence, X-ray absorption, minimal cytotoxicity, and high biocompatibility [51,52]. Pt NCs, in particular, offer promising anti-cancer applications due to their unusual molecular composition and high biological safety profile. These very surface-active Pt NCs are impacted by internal acidic organelles such as endosomes and lysosomes, and they rapidly disintegrate to generate oxidative Pt states that can adhere to and alter DNA structure, resulting in cancer cell death. Furthermore, ultra small Pt NCs can bind to the grooves of the DNA double helix, causing further DNA damage. Thus, eliminating cancer cells using Pt NC-based nano-drugs appears to have a synergistic impact of both Pt NCs and Pt ions that cause DNA damage.

X. FUTURE PERSPECTIVES AND CONCLUSION

Pt-based anti-cancer medicines serve an important role in clinical cancer therapy, with satisfactory efficacy. Cisplatin and other first-line clinical platinum anti-cancer medications are relatively ancient pharmaceuticals with a known molecular mechanism for treating malignancies. The side effects severely limit the use of platinum anticancer medicines. As a result, researchers have looked into improved Pt-based medicines that could boost anti-cancer efficacy while reducing systemic toxicity. Pt NC-based nano-drugs have received a lot of interest due to their intrinsic longer blood circulation duration, EPR effect, and ease of surface functionalization. Continued research into the cellular and molecular pathways involved will provide insights into new therapeutic targets and strategies for the development of more effective and targeted platinum-based therapies.

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