Effectiveness of Platinum Metal Complex in Cancer and Tumor Therapy: A Review of Existing Literature

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Abstract

Metals are important cellular materials selected by many biochemical processes in living organisms. Metals are invested with astonishing characteristics such as redox activity, different coordination modes, and sensitivity towards organic groups or compounds. Including the upper properties of metal, they are regulated in normal conditions, and excursive metal ion concentration is combined with lots of pathological disorders in cancer. The coordination complex of metal used as a drug or prodrug may be a very fascinating probe as a cancer recovery drug. The improvement of metal complexes with anticancer properties has had plenty of influence on cancer chemotherapy. The discovery of the cisplatin complex is considered a landmark, and a new era is beginning in cancer treatment. Cisplatin has acquired meaningful clinical advantages for several types of solid tumors, but its impact has been hampered by its toxic side effects and the occurrence of secondary malignancies and tumor resistance. Other platinum complexes develop the cancer therapy system through their improved activity, among them carboplatin, oxaliplatin, and satraplatin, which are the most promising. This review gives a concise idea of various platinum metal complexes and metal-chelating compounds, shows their potential impact on molecular targets in tumor cells, their advantageous use in cancer therapy, and gives a concise overview of their side effects on cells and limitations.

Keywords: *Cancer, DNA adduct, proteosome inhibitors, apoptosis, cross link*

Introduction

Metal complexes, especially transition metals, have unique medicinal properties. They are, like other fields of treatment, effective in therapies. This article

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discusses the therapeutic properties of metallic complex compounds that examine the effectiveness of Pt metal compounds, like Hg, Pt, Bi, and Au organometallic compounds, that are being used as therapeutic agents in cancer and tumor-like diseases. Metal ions are essential for many living organisms and are largely important for diagnostic and therapeutic purposes to study and treat a variety of human diseases [1]. Metal complexes have surprising medicinal properties. Metal-based drugs are essential for the treatment of lots of ailments like diabetes, rheumatoid arthritis, inflammatory and cardiovascular diseases, as well as for diagnosis purposes.

The earliest study on the therapeutic use of transition metal complexes in cancer and leukemia began in the sixteenth century. In 1960, the anti-tumor activity of the inorganic metal complex cis-diamine-dichloroplatinum (II) (cisplatin) was invented. Cisplatin is one of the most frequently used and most active cytostatic drugs for the treatment of solid carcinomas. Other metals, viz., gallium, germanium, tin, bismuth, titanium, ruthenium, rhodium, iridium, molybdenum, copper, and gold, showed activity against cancer [2]. Nowadays, radiation-related cancer therapy is very important for us. Proton therapy is one of them and can be used to lessen tumors instead of surgical intervention [3]. In modern times, in the field of medicine, the progress of metal- and metal-based complexes is increasing day by day. Scientists emphasize transition metal complexes for drug delivery, therapeutic agents, anti-tumor agents, and anti-diabetic agents.

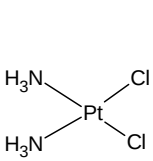
Feature of metal ions and metal based complex

The sector of inorganic medicinal fields is not limited; metal ions may disperse from biological systems for purposes of therapy and diagnostic use [4]. Metal has the common property that it contains positively charged ions in solution that may be fixed by the negatively charged biomolecule. The binding ability depends on the coordination environment therein and the nature of the species, which may be cationic, anionic, or neutral [5,6]. High-proclivity metal ions with significantly polarized groups are coordinated with the metal ions by the hydrolysis reaction pathway [7]. In the early days, the development of the anticancer properties of metal complexes gained remarkable importance in the medicinal inorganic chemistry field [7,8]. In pathological disorder treatment, metal has been used in human history; it reached a landmark in the 1960s with the invention of the cisplatin complex. It has been used for the treatment of cancer. Many other metal-complex drugs achieve an optimal therapeutic response [9,10]. By studying properties, chemists found that conventional carbon-based compounds have some limitations compared to metal-based compounds in the development of new medicinal fields. We want to say in this review that metal complexes are more advantageous than carbon-based compounds like organometallic compounds. Advantageous because their coordinate ligand configuration three-dimensionally permits the

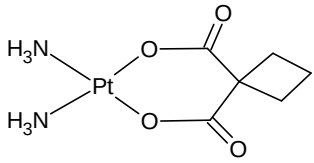
functionalization of groups that may bind to definite molecular targets [11]. Complexes of metal-based compounds customize a wealthy environment to constitute a different molecular structure that refers to a broad spectrum of coordination numbers and geometries with kinetic properties that can never be seen with traditional carbon-based compounds [12, 13]. The anticancer property of metal is due to having partially filled d orbitals in transition metal [14]. Designing coordination compounds for participation in biological redox reactions that play a vital role in the minimal doses and bioavailability of the agent oxidation state of metal is a major consideration [15]. When designing radiopharmaceuticals, the most noticeable point is the metal radioactive properties that are generally used for cancer diagnosis and other medicinal purposes [9].

Platinum and analogous metal complex

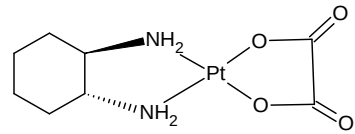
Structure of some Pt metal complex



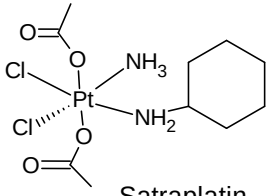
Cisplatin



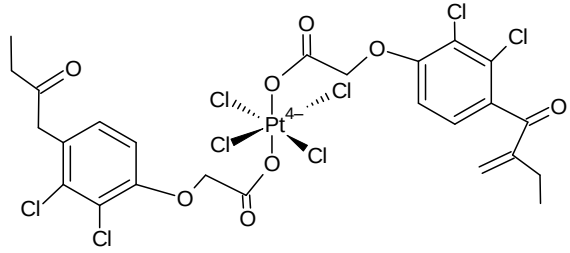
Carboplatin



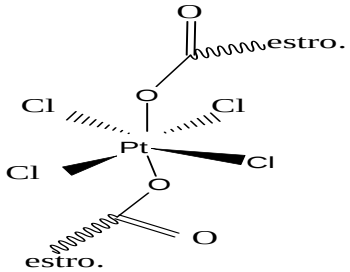
Oxaliplatin



Satraplatin



ethacraplatin



Estrogen-Pt(IV) complex

Cis complex Trans complex

Platinum diazide complexes

Fig. (1). Chemical structures of platinum (II) complexes, cisplatin, carboplatin, and Oxaliplatin. The platinum (IV) complex satraplatin has been used to overcome concerns of low bioavailability. Platinum (IV) complexes have been designed with appended moieties (estrogen and the GHT inhibitor ethacraplatin) to optimize the anticancer effects of cisplatin. Platinum (IV) diazide complexes have been designed that are activated upon irradiation.

Mode of action against tumor and cancer

Cisplatin and its platinum (Pt) (II) derivatives play a vital role in the fight against various human cancers, such as testicular, ovarian, head-neck, and lung tumors. However, their importance in clinics is small due to dose-dependent toxicities and acquired drug resistances, which require lots of research effort toward the improvement of a more effective Pt (II) delivery method [16]. Around three thousand platinum and its derivatives have been produced, and the work undergoes clinical trials; half are rejected [17]. The most popular metal complex that is used in the medication of lots of cancerous malignancies is the platinum metal cisplatin, which is in modern times one of the best-used anti-cancer drugs in the world medicine field [18]. Because of increased toxicity, its extensive clinical use has been hampered, as has the presence of intrinsic and acquired barriers [19, 20]. 2nd and 3rd generation platinum analogs are an effort to address a shortcoming commonly known as carboplatin and oxaliplatin, which have been approved to maintain toxicity profiles [21]. Carboplatin is reactive in the conduct of lung, ovarian, head, and neck cancer therapy [22]. In colorectal cancer therapy, oxaliplatin is clinically proven, but cisplatin is resistant [23]. Platinum-based compounds' ligand exchange kinetics are liable to show antitumor activity [24]. Platinum metal complexes show steady ligand exchange behavior; for this reason, complexes have stable kinetics of ligand exchange that permits slow ligand exchange [24,25]. In between the trans and cis-platinum complexes, the transposition is easily substituted for the cis position [26]. Cisplatin showed its anticancer activity by reacting with DNA and forming an adduct that interrupts DNA transcription and replication and halts programmed cell death (Fig. 27). The widely studied matter of the interaction of cisplatin with DNA makes it obvious that the platinum-GG intrastrand cross-link is the troublesome lesion liable for its cytotoxicity [28]. Metal centers are mainly responsible for biological activity; interactions with DNA metal complexes show biological and medicinal activity [29]. Cells take up the

cisplatin complex either through passive or active transport [30, 31]; water molecules are replaced by chloride ions before reacting with DNA to form a coordination bond with the nitrogen atom of DNA, specifically by cross-linking [30, 32]. The cause of cisplatin stability towards hydrolysis is the high concentration of chloride ions in blood plasma (100 mM). Rapid hydrolysis undergoes a higher rate for lower chloride ion concentration as the activated cationic species bind with DNA [33-35]. On the other hand, carboplatin complexes have a helpful pharmacokinetic profile, which first seems to be a slower rate of conversion towards active species [36]. Several-fold higher doses of carboplatin are essential compared to cisplatin, and a ten-fold slower adduct formation rate was shown [36,37]. In the cisplatin complex, the chloride group is replaced by the cyclobutane dicarboxylate ligand. The carboplatin group has good aqueous solubility and higher stability because of its six-membered ring with platinum metal [38]. The diminishing side effect is achieved while retaining a similar level of clinical activity and cross-resistance to cisplatin [39]. Through the binding of platinum-based complexes, various signal transduction pathways are activated that interfere with various cellular processes, such as DNA replication and transcription, triggering apoptotic cell death [40]. Cisplatin and carboplatin show antitumor activity through the formation of identical 1,2-intrastand DNA cross-links [41,42]. In the last few decades, the platinum drug investigation has been dominated by the clinical use of cisplatin, carboplatin, and most recently, oxaliplatin [43]. Because of persistent problems like toxicity and resistance, researchers have taken innovative strategies to develop modern platinum drugs [44,45]. Rather than cisplatin and carboplatin in oxaliplatin, the bulky diaminocyclohexane (DACH) carrier ligand undergoes less cross-resistance and has a more friendly toxic profile [39]. Because of the character of 1,2 intrastrain cross-link mismatch repair (MMR) recognition proteins, it is not possible to form oxaliplatin-induced DNA adducts that were obtained by a molecular standpoint study [37]. The above statement gives an idea about a critical determination in its holding of antitumor property through cisplatin-resistant cells [46,47]. In 2002, the FDA accepted the oxaliplatin complex for the treatment of advanced colon cancer in combination with chemotherapy [23]. The advanced knowledge acquired by the study of the platinum (II) complex, which includes cellular processing and resistance mechanisms, coupled with a further understanding of the mechanisms of action, may collaborate with the modern generation of analogs for clinical purposes [48]. Two important features of clinically approved platinum-based complexes are poor solubility and low bioavailability, which denotes the search for novel platinum-based complexes with importance for oral administration [49]. Platinum (II) complexes show ligand exchange behavior; platinum (IV) complexes are octahedral complexes that present two extra ligand sites, show kinetic inertness, and have lower activity; for that reason, they minimize the target effect [50]. The change of platinum (IV) complexes to platinum (II) is responsible for its activation and can be used as a pro-drug [51,52]. Among octahedral platinum (IV) complexes,

satraplatin showed astonishing properties when administered orally, and in the treatment of hormone-refractory prostate cancer, it reaches an advanced clinical stage [53]. Platinum (iv) complexes show greater stability and are bio-reductive; for this reason, they show advantageous medicinal properties to reach biological targets. A pivotal role is played by the two axial acetate groups, increasing the lipophilic character and providing a more bioactive agent [49,54]. Purposes of metabolic action: satraplatin is structurally similar to cisplatin but different in the replacement of one of its amine groups by a cyclohexylamine group [54]. Satraplatin has antitumor properties similar to those of cisplatin, which were proved by cross-linking with DNA intra- and inter-stand [49,55]. These complexes offer many opportunities to modify bioactive ligands as tumor-targeting moieties to better facilitate the delivery of platinum to its active site by reduction and intracellular modification]56]. Based on the observation that cisplatin sensitized estrogen and treated breast cancer cells [57], Barnes et al. formulated a Pt (IV) estrogen compound to sensitize ER (+)-breast cancer cells and overcome cisplatin resistance [58]. The intracellular reduction of the compound led to the release of one equivalent of cisplatin and two equivalents of estradiol. The high mobility group protein is entailed in upregulation by its mechanism; platinum-DNA adduct repair is blocked by the protein, which is very important [56,58]. Ethacrynic acid is a modified alternative method that is familiar for glutathione S-transferase inhibitors [59]. Photoactivation of the platinum (iv) complex is better than the usual intracellular reduction mode; it is another strategy [60,61]. At the site of the tumor elicited by the action of the complex, which shows selectivity in tumors, it is advantageous; the collateral damage to the normal tissue is potentially mitigated [35]. The transposition of the platinum (iv) complex was structured as dihydroxy and bonded with two azide ligands (Fig. 1) [60,61]. Under the dark state, these prodrugs are nontoxic, but when irradiation starts, it results in growth inhibition of the bladder cells of humans. At this time, toxicity is avoided by human skin cells. The noticeable fact is that the cis azide complex is not able to exhibit cross-resistance to cisplatin, and the cause of cytotoxicity is a different platinum-DNA adduct formation [56, 60, 61]. Astonishing developments have been made in the field of platinum analog agents, and their pharmacological effects may come to light in the medicinal field concerning design strategies and mechanistic properties. Current development depends on the platinum coordination complex, including the structure-activity relationship and tumor resistance mechanism, which can help facilitate 1816 Current Pharmaceutical Design, 2010, Vol. 16, No. 16. Frezza et al., the clinical introduction of the next generation of platinum-based anticancer agents [48].

Conclusion

The cisplatin complex showed a significant clinical response for solid tumors, but for some toxic drug resistance development, its applicability has been limited. The history of drug development gives us knowledge that heavy metal

complexes have an important property in chemotherapy. At the time of the development of novel metals based on anticancer drugs, at least two questions have been raised. The first question is that even essential metals can be moderately toxic when the amount of metal is large. For safe and significant use, the meta-based drug dosage is critical. This could be denoted by selectively optimal concentrations that are toxic to cancer cells and normal cells viable. To reach this achievement is difficult. Cisplatin has demonstrated that its clinical impact is not surprising. Another question to be answered by scientists that is included in this article is how metal-based drugs, especially platin, work and what mechanism is followed. In the early days, researchers focused on the use of different metals and their metal complexes as tumor-specific apoptosis inhibitors and proteasome inhibitors. The meaningful preclinical effect fills a significant niche in the development of metal-based anticancer drugs by clarifying how molecular targets differ from those of platinum-based complexes. The future development of anticancer drugs and therapies depends on their molecular targets, uptake, bioavailability, and structural refinement of metal complexes.

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