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Role of Platinum Metal as an Anticancer Drug

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ABSTRACT

Metals are essential cellular components selected by nature to function in several indispensable biochemical processes for living organisms. Metals are endowed with unique characteristics that include redox activity, variable coordination modes, and reactivity towards organic substrates. Due to their reactivity, metals are tightly regulated under normal conditions and aberrant metal ion concentrations are associated with various pathological disorders, including cancer. For these reasons, coordination complexes, drugs become very attractive probes as potential anticancer agents. The use of metals and their salts for medicinal purposes, from iatrochemistry to modern day, has been present throughout human history. The discovery of cisplatin, cis-[PtII(NH3)2Cl2], was a defining moment which triggered the interest in platinum(II)- and other metal-containing complexes as potential novel anticancer drugs. Other interests in this field address concerns for uptake, toxicity, and resistance to metallodrugs. This review article highlights selected metals that have gained considerable interest in both the development and the treatment of cancer. For example, copper is enriched in various human cancer tissues and is a co-factor essential for tumour angiogenesis processes. However the use of copper-binding ligands to target tumour copper could provide a novel strategy for cancer selective treatment. The use of nonessential metals as probes to target molecular pathways as anticancer agents is also emphasized. Finally, based on the interface between molecular biology and bioinorganic chemistry the design of coordination complexes for cancer treatment is reviewed and design strategies and mechanisms of action are discussed.

I. INTRODUCTION

The medicinal uses and applications of metals and metal complexes are of increasing clinical and commercial importance. Monographs and major reviews, as well as dedicated volumes, testify to the growing importance of the discipline. Relevant reviews are to be found throughout annual series, for example Metal Ions in Biological Systems and Coordination Chemistry Reviews. The field of inorganic chemistry in medicine may usefully be divided into two main categories: firstly, ligands as drugs which target metal ions in some form, whether free or protein-bound; and secondly, metal-based drugs and imaging agents where the central metal

ion is usually the keyfeature of the mechanism of action.This latter class may also be conveniently expanded toinclude those radionuclide's used in radioimmunoimaging and radio immunotherapy. A reasonable estimate of the commercial importance is approaching US$5 billion annuallyfor the whole field. A list of clinically used chelating agents may be found in most pharmacopoeias,While new chelating agents continue to be sought. The use of chelating agents in the treatmentof Wilson's disease is a good example of how medical problems due to free metal ion (Cu-II)toxicity may be ameliorated by chelating agents. The extensive work on matrix metalloproteinase'slikewise represents a case study in design of small organic ligands as drugs to inactivate ametalloenzyme. Over expression of these zinc-containing enzymes is associated with severalDiseases including arthritis and cancer, so inhibition of the zinc active site is a reasonable drugdevelopment strategy. Indeed, enzymatic zinc is an attractive target because of the diversity of itsstructural and catalytic roles in enzymes.This chapter is restricted to the uses of well-definedinorganic compounds as drugs and chemotherapeutic agents. Current uses and prospective uses, aswell as those of essentially historical relevance, are covered. An important distinction to be made isbetween drugs as chemotherapeutic agents, whose function is to kill cells and drugs acting by apharmacodynamic mechanism—whose action must be essentially reversible and or short-lived.

Anticancer Platinum complex

Platinum (II) complexes has been used as anti cancer drugs since long, among them cisplatin has proven to be a highly effective chemotherapeutic agent for treating various types of cancers. This prototypical anticancer drug remains one of the most effective chemotherapeutic agents in clinical use. Cisplatin, (cis-[PtCl2 (NH3)2], also known as cis-DDP), (**Fig. 1**) is perhaps the best known example of a small molecule metal-containing drug. Cisplatin enters cells by passive diffusion and also, as recently discovered, by active transport mediated by the copper transporter in yeast and mammals. The cytotoxicity of cisplatin originates from its binding to DNA and the formation of covalent cross-links. Binding of cisplatin to DNA causes significant distortion of helical structure and results in inhibition of DNA replication and transcription. Inside the cell it interacts with a number of other negatively charged biomolecules besides DNA such as proteins, sulphur-containing compounds like metallothioneins and glutathione that sequester heavy metals like Pt and remove it from the cell.DNA damage and subsequent induction of apoptosis may be the primary cytotoxic mechanism of cisplatin and other DNA-binding antitumor drugs.Cisplatin is used for the treatment of testicular cancer, epithelial ovarian cancer, gestational trophoblastic tumours, and small cell lung cancer as well as for cervical, nasopharyngeal, oesophageal, and head and neck cancers. Despite this success, the clinical use of cisplatin against this and other malignancies is severely limited by dose-limiting side-effects such as n hepatic- and nephrotoxicity. In addition to the high systemic toxicity, inherent or acquired resistance is a second problem often associated with platinum-based drugs, which further limits their clinical use. In an effort to address these shortcomings, 2nd and 3rd generation platinum analogs, namely carboplatin and oxaliplatin (**Fig. 1**)have been designed and clinically approved to maintain a more manageable toxicity profile.

Carboplatin is second generation drug which have lesser side effect. Carboplatin is effective in the treatment of ovarian carcinoma, lung, and head and neck cancers, while oxaliplatin is clinically approved for the

treatment of colorectal cancer, which is resistant to cisplatin. Picoplatin (cis-PtCl2(NH3)(2-pic), previously AMD473; **Figure 1**) is a new generationSterically hindered platinum cytotoxic compound that provides a differentiated spectrum of activity against a wide range of human tumour cell lines and an improved safety profile. It is designed to overcome acquired resistance to cisplatin in vitro and in human tumour xenografts L-NDDP (Aroplatin; **Figure 1**) is a liposomal formulation of cis-bis-neodecanoato-trans R, R-1,2-diaminocyclohexane platinum (II), a structural analogue of oxaliplatin.

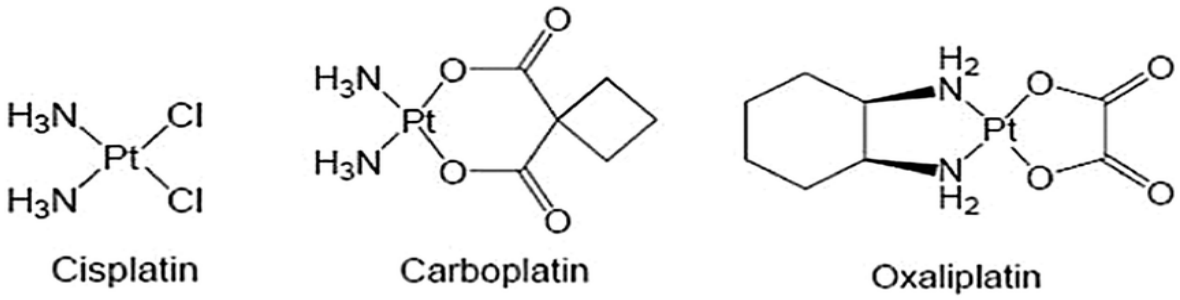

Figure 1: Platinum Containing Drug

Copper as an Anticancer drug.

One of the transition metal, whose complexes are extensively tested for antitumor application, is copper. Copper is a trace element essential for human life. It is a building element of several important enzymes (e.g. superoxide dismutase, cytochrome oxidase, tyrosine's) and it regulates the intracellular redox potential, while its complexes possess antibacterial, antifungal, antiviral, anti-inflammatory and anticancer properties. As potential anticancer Drugs, there are currently extensively studied mainly complexes of copper (II). There are only few complexes of copper (I) in the literature, whereas they also show a very strong cytotoxic activity against tumour cells in vitro.

Anticancer Activity of Copper

Anticancer activity of copper Over 95% of copper (both Cu(II) and Cu(I)) that is present in serum is bound to ceruloplasmin (peroxidise). However, it is not responsible for transporting copper inside the cell. Before they enter the cell, copper(II) ions are reduced to copper(I) by metalo-reducatases located on the cell's surface. Cu+ions are transported into the cell mainly by a specific copper transporter . The independent system of entering the cell, enables biologically active copper compounds to penetrate the cell surface without binding to other agents as opposite to coordination compounds of other metals. Anticancer activity of copper (I) compounds may be a result of different mechanisms. They are described in the following paragraphs of this review. Anticancer activity of copper complex compounds is related to their ability to produce reactive oxygen species (ROS). Copper(I) ions can reduce hydrogen peroxide to hydroxyl radical. Copper (II) ions may in turn be reduced to Cu(I) by superoxide anion(O2•-),or glutathione. Therefore, it can be concluded that the production of reactive oxygen species such as OH•are driven by the copper, regardless of the form in which it is initially introduced into the body – Cu+, or Cu2+[2, 5].Superoxide anion (O2•-) is the product of reduction of the molecular oxygen that occurs in many biological processes. It is converted into hydrogen peroxide

through dismutation. Both of these forms of ROS lead to the formation of another type of reactive oxygen species – the hydroxyl radical (OH•). It occurs in a reaction catalyzed by copper (or iron) ions. This radicals believed to be the main factor causing DNA damage in cells under oxidative stress Copper compounds are also thought to have nuclease activity. The ability of copper to cut a DNA helix has been proved in studies conducted with the use of Cu(I) complexes with two molecules of 1,10-phenanthroline (phen). [Cu(phen)2]+was initially noncovalently bound to DNA. In this form, it was oxidized to a copper (II) compound in the presence of hydrogen peroxide. The final result of those processes was cutting DNA or RNA strands into fragments. The postulated factor directly responsible for cutting the DNA was an adduct in which [Cu(phen)2]2+was coordinated with the hydroxyl radical OH•and linked by non-covalent interactions with DNA .Copper compounds coordinated to phenanthroline skeleton ligands (see Fig. 1), such as [Cu(dmp)2]+, are thought to have the ability of intercalation. Furthermore, it was indicated that the [Cu(dmp)2]+(dmp=2,9-dimethyl-1,10-phenanthroline) can be an inhibitor of the process of DNA transcription [9]. The [Cu(bcp)2]+(bcp=2,9-dimethyl-4,7-diphenyl-1,10-phenanthroline) is in turn believed to possess the ability of forming bridges between double-stranded fragment of DNA and another fragment of such a type

Mononuclear compounds

In 1987 Berners-Price and co-workers [11] presented copper(I) complexes with molecular formula [Cu(P-P)]Cl, where central Cu+ion was coordinated with two molecules of bidentate phosphine. The structures of these complexes are presented in Figure 1

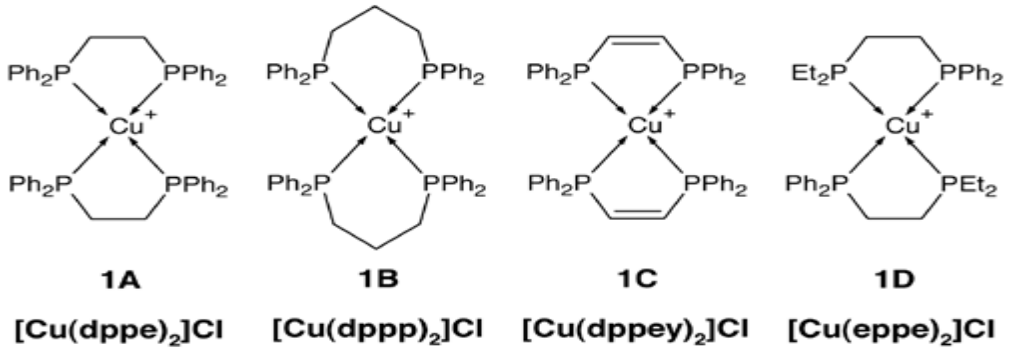

Fig. 1. The structures of copper(I) complexes with bidentate phosphine

II. CONCLUSION

Recent advances in medicinal inorganic chemistry gives significant prospects for the utilization of metal complexes in the development anticancer drugs. Platinum complexes cisplatin has proven to be a highly effective chemotherapeutic agent for treating various types of cancers. Besides the established use to treat arthritis, gold complexes exhibit anticancer property. Since higher concentrations of copper is a common trademark of many human tumours, targeting tumour cellular copper with copper chelating agents emerged as an exciting new approach in cancer therapy Antiproli-ferative activity for cervical cancer cells was proved

for copper complexes. Ruthenium complexes with antitumor activity are also emerging rapidly. Since metals are endowed with unique properties that are absent in conventional carbon-based drugs, the positive trend in anticancer drug discovery can be continued for the design of new metal based drugs.

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