RESEARCH PAPER

A Study on Different Metals Useful: Cancer Therapy

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ABSTRACT:

The Metals are essential for 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, either as drugs or prodrugs, become very attractive probes as potential anticancer agents. This has serious consequences for normal cells and become responsible for the development of various disorders. Several strategies for delivering the cytotoxic drugs to cancerous sites that limit systemic toxicity and other adverse effects have recently been evolved. Among them, biomolecule-conjugated metal complexes-based cancer targeting strategies have shown tremendous advantages in cancer therapy. 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.

Keywords: Cancer, metal, zinc, copper, platinum, metal complex, DNA, proteasome etc.

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.**INTRODUCTION**:

Many metal-containing compounds have been utilized throughout history to treat a wide variety of disorders [1]. In medicinal chemistry — traditionally dominated by organic chemistry— metal complexes have gained favour as diagnostic tools and anticancer agents [2]. Research in anticancer agents was stimulated by the accidental discovery of cisplatin, *cis*-[$Pt^{II}(NH_3)_2Cl_2$]. However, its clinical use is restricted due to dose-dependent toxicity and resistance coupled with a narrow spectrum of activity [3, 4]. These limitations have triggered a search for platinum-based compounds that show lower toxicity, higher selectivity, and a broader spectrum of activity [5, 6]. The complexes known as carboplatin and oxaliplatin, among others seen in Fig. **1** arose from this search. Nevertheless, in addition to numerous platinum analogs, other metal complexes containing metal ions such as zinc(II), copper(II), gold, and copper chelating agents have received considerable attention as potential anticancer agents [7-8]. Additionally, the investigation of ruthenium-containing compounds in clinical trials attests to the rich potential of utilizing non-platinum metal-based compounds in the treatment of cancer [9-10]. Furthermore, metals that take advantage of their unique physiochemical properties have been utilized as powerful tools in cancer diagnosis [11]. This review discusses the role of selected metals in biological processes in cells as they pertain to malignancy and to highlight the medicinal applications of the metals and their complexes in the design and development of metal drugs for the treatment of cancer. Metal-based anticancer agents are among the most successful therapeutic agents, as evidenced by their frequent prescription to patients since their discovery. In fact, there is a plethora of reports in recent years on the transition metal complexes proving highly efficient as anticancer agents. Among other metal-based anticancer compounds, Cu(II) complexes recommended themselves as promising cytostatic agents due to Cu(II) plays a crucial role in cell growth and metabolism. Although there is a variety of mechanisms underlying the Cu-based drugs' anticancer effect, generally, it is based on the interplay between the metal and the organic ligand. For example, these agents act as Chelators, displace other ions from the enzyme binding sites, trigger intracellular copper accumulation, cytotoxicity, and activate apoptosis inhibitor factor (XIAP). Some of them are known to inhibit proteasome and interfere with DNA through binding along with the major or the minor DNA grooves and intercalation.(12-15).

Scope of metal complexes in the treatment of cancer

Therapeutic potential of metal complexes in cancer therapy has attracted a lot of interest mainly because metals exhibit unique characteristics, such as redox activity, variable coordination modes and reactivity toward the organic substrate.(16) These properties become an attractive probe in the design

of metal complexes[8] that selectively bind to the biomolecular target with a resultant alteration in the cellular mechanism of proliferation. Several metal-based compounds have been synthesized with promising anticancer properties, some of which are already in use in clinical practice for diagnosis and treatment while some are undergoing clinical trials.(17) Metal-based compounds synthesized recently are products of drug design targeted at achieving specific objectives that the original compound could not achieve and such compounds exhibit a different spectrum of cytotoxicity. Compounds in this group include the following.

Anticancer properties of copper complexes

Copper complexes exhibit cytotoxic properties with the mechanism of action different from that of the clinically used platinum compound cisplatin.(18) A spectrum of activities varies among these compounds, depending on the type of ligand attached to the simple copper complex. Cytotoxic effects of copper-based complexes have been investigated based on the assumption that endogenous copper may be less toxic for normal cells relative to cancer cells.(19) The situation is entirely different; copper can undergo redox activity and competitively bind to the site that could otherwise be occupied by other metals.(19) Copper is an essential cellular element necessary for many biological pathways. It is also a cofactor in enzyme catalytic processes.(19) The role of copper in angiogenesis has been a subject of controversy; generally, the role of metals in this process is still under scrutiny.(19) However, copper complexes are known to mimic superoxide dismutase (SOD),(20) an important antioxidant enzyme that protects cells from harmful radical superoxide through its dismutation to nontoxic molecules.(20).

Silver complexes in cancer therapy

Silver complexes have been known for a long time for their antimicrobial activities[63] and are widely used in the treatment of infected wounds and burn cases.(21) In the past, silver complexes did not receive much attention compared to other metals,(22) although silver complexes also demonstrated good cytotoxic activity against many cancer cell lines.(22)Recently, cytotoxic properties of silver(I) complexes have attracted a great deal of interest, this is because most silver(I) complexes have been found to exhibit a greater cytotoxic activity than cisplatin(22)with relatively low toxicity and greater selectivity toward cancer cells.(23).

Selected targets in anticancer drug design

Platinum complexes are widely used anticancer agents. Their use is primarily based on the pharmacological properties of cisplatin,(24) which acts as a model for the design of other metal-based compounds for use in cancer therapy.(24) Since all clinically utilized platinum compounds share the same mechanism of action, (24) many researchers are now seeking to make increasingly drastic measures to the general molecular framework shared by these compounds to achieve a novel mechanism of cell death.(24) Most of the research in this field is tailored toward ligand substitution method. This way, platinum-based compounds with different rates of substitution reactions at the central atom in the biological system can be developed.(25)

Steroids are important delivery vectors that can be used to target overexpressed oestrogen receptors (ER) cancer cells, such as those of breast, ovarian, colon and prostate tumours. The bioconjugation of oestrogen derivatives with the biocompatible copper metal centre has been studied by Erxleben and colleagues with the aim of understanding the interaction of phenanthroline ligands with DNA. The oestradiol–copper complexes 55a–d are more effective than cisplatin against A431, MCF-7, 2008, A2780 ER+ and HCT-15 ER-cancer cells. The low and sub-micromolar activity has been confirmed even in 3D spheroids models, increasing with the lipophilicity of the phenanthroline ligands.(26).

New plantinum complexes as a product of drug design:

Recently, more platinum complexes are being synthesized, and their anticancer activities against tumour cell lines are being evaluated. This involves remodelling of the parent compound (platinum) by conjugating it with the different ligand to achieve the desired outcome. In most cases, pharmacokinetic parameters, spectrum of activity and toxicity profile are improved to circumvent those challenges inherent from the parent compound. (27)

Ruthenium complexes in cancer therapy and drug design:

For the past few decades, the use of metal–bases complexes in the treatment of cancer has been dominated by a spectrum of challenges emanating from the use of platinum complexes and platinum-derived drugs in clinical practice. While it is virtually impossible to deny the success of platinum drugs in chemotherapy,(28) it is however important to note its limitation such as drug resistance, limited spectrum of activity and worsening side effects.(28) To surmount these challenges, efforts have been made to critically consider other metal-based complexes with cytotoxic properties, such as ruthenium, gold and iron complexes. Ruthenium compounds developed for this purpose are known to cause fewer and less severe side effects.(28) Ruthenium can form octahedral complexes that give opportunity for exploring more ligands compared to platinum (II) complexes that only form square planar complexes.(28)

Nanoparticles in cancer therapy:

Nanotechnology has greatly enhanced drug delivery system (29) and to a large extent provides a means of direct drug delivery to the active site, thereby reducing the unwanted effects by limiting the drug effect to specific site and leaving other tissues untouched. In cancer medicine, nanoparticles (NPs) provide an advanced bioavailability, in vivo stability, intestinal absorption, solubility, sustained and targeted delivery and therapeutic effectiveness of several anticancer drugs.(29) Most potent chemotherapeutic agents used in the treatment of cancer have a narrow therapeutic index and have been used in several tumour types;(30) however, their cytotoxic effects affect both normal and cancerous cells.(30)This created a big challenge in the dosing of metal-based complexes in cancer therapy. Therefore, the opportunity provided by NPs to selectively target cancer cells and leave behind healthy cells untouched has gained interest in the design of metal-based cytotoxic drugs.(31).

Cell membranes for cancer therapy:

These components facilitate no covalent interactions with other biomolecules including proteins and lipids, which help to shape cellular and organelle membranes. Membranes' lipid composition and distribution are not uniform. Lipid asymmetry between the inner and outer membrane leaflets is caused by phospholipid enrichment with amine or serine moieties in the inner leaflet, whereas choline and sphingomyelins (SMs) predominate on the exterior. In addition, recent research has focused on the development of metal compounds capable of targeting DNA noncanonical configurations, even though DNA is generally found as a duplex structure. Target specific sequences using tailored compounds to target certain structural features allows metal complexes to attach to nucleic acids [32,33]. Ruthenium (II) complexes that can bind to extended DNA; iron(II) that binds to DNA in three-way junctions; and various metal-containing polycyclic planar aromatic compounds that bind to G-quadruplex DNAs, such as metal-salphen and platinum(II) terpyridine complexes, were reported [34-37]. All of these noncanonical structures are found to be potential targets for structure- and shape-specific binders. Moreover, RNA has even more noncanonical structural components than DNA, but it has been less investigated as a metal complex target. RNA is an important molecule: in recent decades, messenger ribosomal and transfer RNA have been discovered, permitting the passage of genetic material from DNA to proteins in enormous quantities of noncoding RNAs [38-41].

Conclusion:

The higher concentrations of copper is a common trademark of many human tumours, targeting tumour cellular copper with copper chelating agents *via* inhibition of cancer cell proteasome has emerged as an exciting new avenue in cancer therapy. Along this line, metals including gallium (III), Zinc(II), and copper(II) when combined with asymmetric tridentate appended ligands represent an innovative new class of proteasome inhibitors. 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 by building on the underlying knowledge gained from medicinal inorganic chemistry.

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