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TRANSITION METAL COMPLEXES AS POTENTIAL THERAPEUTIC AGENTS

Surendra Singh, Ph. D.

M.Sc., M.Phil., Ph.D., Associate Professor, Dept of Chemistry, Govt. Degree College, Mant, Mathura (U.P.)

Abstract

Transition metals have an important place within medicinal biochemistry. Research has shown significant progress in utilization of transition metal complexes as drugs to treat several human diseases like carcinomas, lymphomas, infection control, anti-inflammatory, diabetes, and neurological disorders. Transition metals exhibit different oxidation states and can interact with a number of negatively charged molecules. This activity of transition metals has started the development of metal-based drugs with promising pharmacological application and may offer unique therapeutic opportunities. To provide an update on recent advances in the medicinal use of transition metals, a Medline search was undertaken to identify the recent relevant literature.

Key words: *Transition metals, metal complexes, anticancer drugs, metal therapeutics.*

Introduction

Metals have an esteemed place in medicinal chemistry. Transition metals represent the d block element which includes groups 3 - 12 on the periodic table. Their d shells are in process of filling. This property of transition metals resulted in the foundation of coordination complexes. Metal complex or coordination compound is a structure consisting of a central metal atom, bonded to a surrounding array of molecules or anions. Sophus Jorgensen in Denmark synthesized metal conjugates for the first time in the mid 1870's. In 1893 the major break-through in this field was occurred when Alfred Werner investigated a series of compounds, which contained cobalt, chlorine and ammonia. He was awarded the Noble Prize in 1913 for his work.

The earliest reports on the therapeutic use of transition metal complexes in cancer and leukemia date from the sixteenth century. In 1960 the anti-tumor activity of an inorganic complex cis-diammine-dichloroplatinum (II) (cisplatin) was discovered. Cisplatin has developed into one of the most frequently used and most effective cytostatic drug for treatment of solid carcinomas. Other metal like gallium, germanium, tin, bismuth, titanium, ruthenium, rhodium, iridium, molybdenum, copper, gold were shown effective against tumors in man and animals.

TRANSITION METAL COMPLEXES AS ANTICANCER AGENTS

Platinum based anticancer drugs 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 (Jamieson 1999). Cisplatin moves into the cell through diffusion and active transport.

Inside the cell it causes platination of DNA, which involves interstrand and intrastrand cross-linking as well as formation of adducts, usually through guanine, as it is the most electron rich site and hence, easily oxidized.

Formation of cisplatin DNA adducts causes distortion and results in inhibition of DNA replication (Lee, 2002).

Cisplatin DNA adducts also serve as binding site for cellular proteins such as repair enzymes, histones, transcription factors and HMG-domain proteins (Louie 1999; Volkter 1999; Cohen et al. 2001). The binding of HMG-protein to cisplatin-DNA adduct has been suggested to enhance anticancer effect of the drug (He 2000; Wong 2002). Beside the effectiveness of cisplatin against cancer, it has encountered many side effects.

Drugs like cisplatin does not specifically affect cancer cells but it also effect the rapidly dividing cells of certain normal tissues, such as those found in hair follicles, bone marrow, and the lining of the gastrointestinal tract. Inside the cell it interacts with a number of other negatively charged bio molecules besides DNA such as proteins, sulphur-containing compounds like metallothioneins and glutathiones that sequester heavy metals like Pt and remove it from the cell. Pt (II) and Pt (IV) complexes are photo reactive. Irradiation of cis-platin modified DNA with

UV light can induce cross-links with the protein HMG, which can inhibits RNA transcription (Bartkowiak 2009; Qutob 2004; McKay 2001).

GROUP

PERIOD	IIIB	IVB	VB	VIB	VIIB	VIIIB			IB	IIB
	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn
	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd
	La	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg
	Ac	Unq	Unp	Unh						

Figure 1. Transition metals series

Like many other anticancer drugs, cisplatin (Figure 1) also faces the same problem called "Drug Resistance". It is major complication in cancer chemotherapy (Piulats 2009; Pill 1997), because of decreased intercellular accumulation of cisplatin, it cannot form adduct with DNA (Chu 1994; Stryer 1995). Organometallic compound like Iron (III)-salophene with selective cytotoxic and anti-proliferative properties have been used in platinum-resistant ovarian cancer cells (Lange et al., 2008).

Different strategies have been used to improve efficacy of cisplatin like use of nanotechnology to specify the effect of the drug in the target cells (Liang 2010). Pt (II) complexes have been conjugated to molecules like porphyrin ring. The porphyrin enhances the tumor tissue specificity of the Pt (II) complexes. Porphyrins are used as photodynamic therapeutic agents and can offer additional antitumor activity by photo-induced mechanism (Lottner, 2002).

The clinical use of cisplatin is limited because of the toxicity to the normal cells and drug resistance, therefore, new platinum based anticancer drugs has also been synthesized such as carboplatin, oxaplatin, nedaplatin etc. Other drugs are being developed that have slower hydrolysis rate than cisplatin, are longer acting and require more infrequent doses. One such drug is 2-pincoline Pt complex, which is active by injection and oral administration.

Platinum complexes with distinctively different DNA binding modes from cisplatin may provide higher antitumor activity against cisplatin resistant cells. The trans isomer of diamminedichloro Pt (II) has also been studied, trans DDP offers a different attachment mode with DNA and is used as anticancer drug for cisplatin resistant cancer cells. A series of trans piperazine compounds were reported to have significant cytotoxicity against cisplatin resistant cells (Albertella, 2004; Najajreh, 2002). Pt (II) complexes with thiourea have showed anti-cancer activity against leukemia cell lines (Martins, 2001; Brow, 2002). Pt (II) has also been complexes with estrogen hormone and used as anticancer agent for the treatment of hormone dependent cancer like breast cancer (Jackson, 2001).

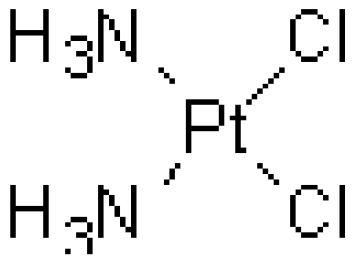

Figure 2. Cisplatin.

Non-platinum anticancer agents

Platinum is not the only transition metal used in the treatment of cancer, various other transition metals (Figure 2) have been used in anticancer drugs (Chen et al., 2009). Titanium complexes such as Titanocene dichloride had been recognized as active anticancer drug against breast and gastrointestinal carcinomas (Colley et al., 1991).

Gold complexes also show anti-cancer activity, these complexes act through a different mechanism as compared to cisplatin (Au et al., 2008). The target site of Au complexes is mitochondria not DNA. Certain gold complexes with aromatic bipyridyl ligands have shown cytotoxicity against cancer cells (Marcon et al., 2002).

The 2-[(dimethylamino) methyl] phenyl gold (III) complex has also proven to be anti tumor agent against human cancers. (Messori et al., 2000). Gold nanoparticles when used in combination with radio therapy or chemotherapy enhance DNA damage and make the treatment target specific (Zheng et al., 2009). Lanthanum has also been used to treat various forms of cancer (Kapoor, 2009). Ansari et al. in 2009 studied some complexes of Mn (III) induce tumor selective apoptosis of human cells.

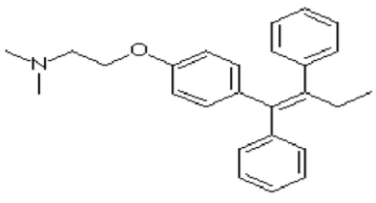

Figure 3. Tamoxifen.

Many ruthenium complexes were studied which showed anti-proliferative effects in human ovarian cancers. Ruthenium complexes with oxidation state +2 or +3 show antitumor activity against metastasis cancers. Ruthenocene derivatives act as anti estrogen (Pascal et al. 2005).

The relative binding of ruthenocene derivatives were very high and even better than hydroxyl tamoxifen (Figure 3) which is novel antagonist for estrogen (Clarke, 2003).

Ruthenocene complexes with aromatic ligands represent a relatively new group of compounds with antitumor activity. Ru (III) imidazole and Ru (III) indazole exhibit anti cancer properties (Morris et al., 2001).

Galanski and his co-workers studied the anticancer properties of Ru (III) arene complexes (Galanski et al., 2003). Ruthenocene-cymene complexes have shown to damage DNA by forming monofunctional adducts selectively with guanine bases (Allardyce et al., 2001).

Ruthenocene complexes show antiproliferative effect on the MCF-7 (ER-positive) breast cancer cell lines. Many of Ru complexes exhibit anti-estrogen properties similar to that observed for novel anti-estrogen Tamoxifen (Anne, 2005).

Complexes of transition metal like Iron have shown remarkable anti-proliferative properties (Lange et al., 2008; Ray et al., 2007; Sun et al., 2007). Ferrocifenes exhibit anticancer activity against hormone dependent and hormone independent breast cancers (Top et al., 2003). The ferrocene derivatives having hydroxyl group in phenyl ring and have high affinity for estrogen receptor.

Many organometallic analogues of tamoxifen used as a vehicle for introducing other cytotoxic agents to the cancer cells (Kiat et al., 2006).

Normally, cancers are diagnosed at a stage of the disease when some anatomical changes occur in the body in the form of well defined tumors. These masses can be removed by surgery however this therapy is not suitable for treatment of small or hidden tumors. Nano-technology offers potential solutions to this problem for the treatment of various types of cancers. Hirsch et al. (2003) used silica gold nanoshells technology for thermal ablative therapy of cancer. Metal nanoshells are a class of nanoparticles with tunable optical resonances that has highly favorable optical and chemical properties for biomedical imaging and therapeutic applications.

Nanoshells absorb light in the near infrared which can be used to deliver a therapeutic dose of heat by using moderately low exposures of extra corporeally applied near-infrared (NIR)

light. It has been reported by Asharani et al (2009) silver nanoparticles exhibit anti proliferative activity.

Loo et al. 2004 described several examples of nanoshell-based diagnostic and therapeutic approaches including the development of nanoshell bioconjugates for molecular imaging. Mercaptopurines are well known ant leukemic drugs but their use has been hampered by their short half life. This problem has been overcome by the use of gold nanoparticles in combination with mercapto-purines.

Conjugation therapy of 6-mercaptopurine with gold nano-particles not only enhanced its anti-leukemic and anti-inflammatory activity but also reduces the quantity of dose and side effects of the drug (Podsiadlo et al., 2008).

TRANSITION METAL COMPLEXES AS ANTI-INFECTIVE AGENTS

Transition metals like silver have been used for years as anti microbial agents. Silver has low toxicity as compared to other transition metals. Silver nitrate is still given to the infants to prevent the development of opthalmia neonato-rum. One of the most commonly used compounds of silver is silver (I) sulfazine; it is used to treat severe burns to prevent them from bacterial infections (Clarke et al. 1975). Chlorohexidine- Silver Sulfadiazine is an anti infective metal complex against catheter infections in vivo (Bassetti et al., 2001). Organometallic complexes of Pt, Rh, Ir, Pd, and Os with active organic molecules have been reported to exhibit trypanocidal activity (Lorisean et al., 1992). An increasing amount of data showing the beneficial use of zinc (Zn) in treating diarrhea continues to emerge from epidemiological and clinical trials (Hoque et al., 2009). Fukushima and collegues also studied the role of zinc in maintenance hemodialysis patients (2009).

Nitrogen containing macrocyclic complexes of Manganese (II) have shown anti microbial activity. An octahedral geometry for these complexes has been confirmed by spectroscopic analysis. Many manganese complexes have been screened against a number of pathogenic fungi and bacteria to evaluate their growth and potential (Singh and Chaudhary, 2004).

Metal complexes of Pt (II) and Ru (II) with o-vanillin- (4-methyl thiosemicarbazone), and o-vinillin- (4-phenyl thiosemicarbazone) have been prepared, characterized by chemical methods and studied for antibacterial, anti-fungal, and antiamoebidal activity and have been proven more efficient anti infective agents (Offing et al., 1996).

Transition metals have also been proved useful in the treatment of malaria. One strain plasmodium falciparum has become resistant to major antimalarial drugs such as quinolines.

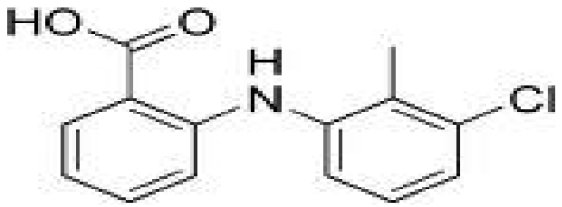

Figure 4. Tolfenamic acid.

Metal complexes of Ga (III), Al (III), and Fe (III) were found to be active against malaria. Metal complexes of o-vanillin- (4-methyl thiosemicarbazone), and o-vanillin- (4-phenylthiosemicarbazone) exhibit anti-malarial activity in mice infected with plasmodium berghei indicating that cures were attainable at dose levels upto 60 mg/kg but with toxic death prevalence at higher doses (Singh and Chaudhary, 2004).

TRANSITION METAL COMPLEXES AS ANTI-INFLAMMATORY AGENTS AND FREE RADICAL QUENCHERS

Transition metals have also been used as anti-inflammatory and anti-arthritic agents (Arayne et al., 2009).

Several inject able transition gold complexes like sodium aurothiomalate, aurothioglucose and sodium aurothiopropanol are used clinically in the treatment of severe cases of rheumatoid arthritis. Gold and silver nanoparticles conjugated with heparin derivative possess anti-angiogenesis properties (Kemp et al., 2009). Silver nanoparticles are used in the development of an antimicrobial gel formulation for topical use (Jain et al., 2009). Gold has been used in the treatment of peripheral psoriatic arthropathy (Nash and Clegg, 2005). As a product of oxygen metabolism, superoxide anion can trigger oxidative injury to tissues. This activity has been suggested to be associated with riper fusion and inflammatory diseases as well as neurological disorders such as Parkinson's disease and Alzheimer's disease.

In living systems, a natural defense system against superoxide mediated oxidative damages involves SODs, enzymes that catalysis the conversion of superoxide into oxygen and hydrogen peroxide. Metallic gold treatment reduces proliferation of inflammatory cells in brain injury (Pedersen et al., 2009). There are some side effects of anti-arthritic therapy using Au (I), mostly when it is oxidized to Au (III) by some of the potentially strong oxidants such as H2O2 available in inflammatory situations. Excessive use of gold complexes for the

treatment of juvenile rheumatoid arthritis and osteoarthritis causes pain and fever. Among cutaneous symptoms intolerance was measured at low frequency, wider use of gold salts like gold salicylates and gold pyrazolone derivatives cause urticaria and angioedema (Rethy et al., 2004).

Tolfenamic acid (Figure 4) and its metal complexes has been studied as anti-inflammatory, anti proliferative, and radical-scavenging agents by (Kovala et al., 2009).

Among transition metals complexes of Cu and Fe are capable of catalyzing dismutation of the superoxide anion. In addition, Mn complexes dose not bind to NO and react slowly with H2O2, demonstrating specificity towards superoxide anion. Interaction of SOD mimics with NO and H2O2 levels, both of which can cause high blood pressure and weaken the immune system. NO are an excellent ligand for transition metal ions and these metal nitrosyls having therapeutic values. Sodium nitropruside is used clinically to treat cardiovascular diseases by releasing NO but CN- toxicity limited its application, however, discovery of new ruthenium nitrosyl complexes offer promising biological applications (Cameron et al., 2003). Over production of NO contributes to various diseases like sepsis, arthiritis, diabetes and epilepsy.

Ruthinium polyaminocarboxylate complexes are efficient NO scavengers (Mosi et al., 2002; Spasojevic et al., 2003; Clark et al., 2003).

Many human diseases are associated with the over-production of oxygen free radicals that inflict cell damage. A manganese (II) complex with bis (cyclohexylpyridine)-substituted macrocyclic ligand has designed as a functional mimic of the superoxide dismutase (SOD) enzymes that normally remove these radicals (Li et al., 2002). Mangnese complexes have also been used to treat cell and tissue oxidative injuries by acting as superoxide anion scavenger (Failli et al., 2009).

Magnesium is used for the treatment of asthema in children (Bichara and Goldman, 2009). Some Cu complexes are also active against inflammation but their use is limited (Angelusiu et al., 2009). Cu (II) complexes tend to dissociate and bind to natural ligands such as albumins (Halova et al., 2006; Ward et al., 2005). Zinc has been proved to be involved in the inhibition of pro inflammatory cytokines (Haddad, 2009).

TRANSITION METALS AS ANTI-DIABETIC AGENTS

More than 2 - 8% of world's population is suffering from diabetes (Wild et al., 2004). It is a condition in which body do not produce a hormone called insulin which is necessary for the

absorption of glucose in cells (Rother, 2007). Scientists are looking for alternative approaches for the treatment of diabetes (Nahas et al., 2009). Control of the glucose level in the blood plasma has been achieved by administration of vanadium and zinc in form of inorganic salts. It has been shown that elements are poorly absorbed in their inorganic forms and required high doses, which have been associated with undesirable side effects.

Vanadium complexes with organic ligands have proved to be less toxic, with improved solubility and lipophilicity.

There are a number of vanadium complexes that have been developed, all of which have insulin-mimetic properties [Badmaey et al., 1999]. The molecular mechanism responsible for the insulin-like effects of vanadium compounds have been shown to involve the activation of several key components of insulin-signaling pathways.

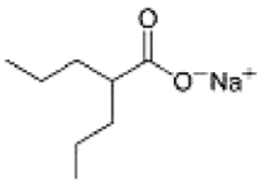

Figure 5. Sodium Valproate.

It is interesting that the vanadium effect on these signaling systems is independent of insulin receptor protein tyro-sine kinase activity, but it is associated with enhanced tyrosine phosphorylation of insulin receptor substrate (Mehdi et al., 2006). Chromium supplementation significantly improved glycemia among patients with diabetes but do not show any significant effect on glucose metabolism in healthy individuals (Balk et al., 2007). Higher zinc intake has also been associated with a slightly lower risk of type 2 diabetes in women (Sun et al., 2009).

TRANSITION METAL AS NEUROLOGICAL DRUGS

Transition metal complexes are also used in the treatment of neurological disorders (Hashimoto et al., 2003).

One example of this is lithium. Lithium has been used to cure many neurological disorders like Huntington's chorea, tardive dyskinesia, spasmodic torticollis, Tourette's syndrome, L-dopa induced hyperkinesias, Parkinsonism, organic brain disorders, drug induced delusional

disorders, migraine and cluster headache, periodic hyper-somnolence, epilepsy, meniere's disease and periodic hypokalemic paralysis.

The mechanism of action involves Li inhibiting the scavenging pathway for capturing inositol in the resynthesis of polyphosphoinositides in the brain (Camins, 2009). Valproate treatment in combination with lithium delays disease onset, reduces neurological deficits and prolongs survival in an amyotrophic lateral sclerosis mouse model (Feng, 2008) (Figure 5). Other transition metals like zinc are involved as a transmitter in the neuronal signaling pathways. Neuronal Zn (II) serves as an important, highly regulated signaling component responsible for the initiation of a neuroprotective pathway (Aras, 2009).

TRANSITION METALS AS DELIVERY PROBES AND DIAGNOSTIC TOOLS

Metal complexes may be used as research probes of biological function and as potential diagnostic and therapeutic agents (Khan et al. 2009). Unique properties of transition metals like redox activity, lewis acidity, electrophilicity, valency, geometry magnetic spectroscopic and radiochemical properties can be used to measure cellular functions.(Ali et al. 1999; Wenyu et al. 2004; Radha et al., 2004).

Success of selective drug therapies depends on the drug's depot time in the target to treat. Depot time is currently being prolonged, using drug-eluting beads or microspheres for selective internal radiation therapy. The use of transition metals as a tool for radiopharmaceutical tracking of particles injected into tumors is increasing day by day (Luboldt et al., 2009). The use of gold nanorods for photoacoustic molecular imaging with simultaneous multiple targeting is reported.

The potential in improving cancer diagnosis is demonstrated. Gold nanoparticles have been synthesized inside ethosomes, vesicles composed of phospholipids, ethanol, and water, which could be very efficient not only in delivery probes to the skin but also as diagnostic and therapeutic multimodal agents (De la Presa et al., 2009).

Being a stable transition metal makes them less reactive and less toxic. Their easy circulated and distribution in the body makes them vehicle of choice for drug delivery (Terentyuk et al., 2009). The nanoparticles injected into the tumor cells increases their ability to absorb radiation of specific wavelength. This property has been used in Lymphotropic nanoparticle-enhanced magnetic resonance imaging of prostate cancer (Ross et al., 2009).

Antibody-conjugated gold nanoparticles have been used to deliver immune-globulins to the retina in the rabbit eye and also for the in vivo photoacoustic molecular imaging (Li et al., 2008; Hayashi et al., 2009). Ultrasmall particles of iron oxide exhibits super-paramagnetic properties and are used as negative contrast agent in magnetic resonance imaging (MRI) which significantly improved the sensitivity of detection of inflamed tissues (Radermacher et al., 2009).

CONCLUSION

With the advancement in the field of inorganic chemistry the role of transition metal complexes as therapeutic compounds is becoming increasingly important. Recent advances in inorganic chemistry have made possible formation of number of transition metal complexes with organic ligand of interest, which can be used as therapeutic agent. Significant progress in the synthesis of platinum based anti-cancer drugs like cisplatin has been made. Although, these drugs have proven to be highly effective chemotherapeutic agent for treating various types of cancers, they have encountered the same drawbacks like other anti-cancer drugs are:

(i) Resistance to these drugs occurs when cells once destroyed by a particular drug no longer respond to the treatment with the same drug. When cells become resistant to drug, doses must be increased, a large dose escalation can lead to severe multi-organ toxicities, such as failure of kidney and bone marrow.

(ii) Drug toxicity is not limited; these drugs not specifically destroy cancer cells but also destroy rapidly and dividing normal cells like hair follicles.

Several new derivatives of cisplatin such as carboplatin, nedaplatin, oxaplatin have been made which are less toxic and more effective than cisplatin. Other transition metals like Ru, Ti, Os, Au, Fe, Co, etc have also been used as anticancer therapeutics.

The use of transition metal complexes as therapeutic compounds has become more and more pronounced.

These complexes offer a great diversity in their action; they do not only have anti-cancer properties but have also been used as anti-inflammatory, anti-infective and anti diabetic compounds. Development of transition metal complexes as drugs is not an easy task; considerable effort is required to get a compound of interest. Beside all these limitations and side effects transition metal complexes are still the most widely used chemotherapeutic

agents and make a large contribution to medicinal therapeutics in a way that is, unimaginable in few years back.

Future direction

Therapeutic applications of transition metal complexes is an under developed area of research and is full of opportunities for further progress. Basic principles to guide the synthesis and development of transition metal based pharmaceuticals are lacking. Development of new methodologies such as combinatorial chemistry will be helpful in the synthesis of inorganic compounds as therapeutic agents. Similarly, the action of metal complexes in the whole living organisms are expected to differ in general from the action of non-metal containing agents and may offer unique research, diagnostic, or therapeutic opportunities.

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