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AN INSIGHT INTO METAL BASED ANTI-CANCER DRUGS

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ABSTRACT

Metal complexes play critical role in the treatment of cancer. Cis-platin which is model anti-cancer drug has been used in the treatment of various types of cancer. But due to its side effects and resistance phenomenon efforts have been made to explore the possibility of synthesizing novel non-platinum based anti-cancer drugs. In addition to platinum based drugs, complexes of other transition metals like titanium, ruthenium, palladium and gold etc. also show pronounced anti-cancer activity. The Complexes with titanium and ruthenium have already been evaluated in phase I and phase II clinical trials. Some transition metal complexes show good anticancer activity against cis-platin resistant cell lines. This review will provide an insight into various platinum as well as non-platinum based anti-cancer drugs.

Key words: Transition metal, cis-platin, Nucleic acid, protein, platinum, titanium, ruthenium, palladium, gold, anti-cancer, drug, amines, biological activity.

INTRODUCTION

Metals play an important role in our daily life due to their incorporation in our diet in varying quantities[1,2]. Due to potential pharmacological applications of transition metal based complexes such as anti-diabetic, anti-neurological, anti-bacterial, anti-fungal, anti-cancer agents, metal complexes have been used in medicinal chemistry since sixteenth century. Transition metals have tendency to form variety of complexes due to the presence of vacant *d*-orbitals in their valence shell. They can take part in various biological processes which show their interaction with electron rich biological components like proteins and nucleic acid because metal centers are positively charged and favored to attack on negatively charged biomolecules[3-6]. Various transition metals such as platinum(Pt), titanium(Ti), ruthenium(Ru), rhodium(Rh), iridium(Ir), molybdenum(Mo), copper(Cu) and gold(Au) in their complex form are effective against solid tumors in animals and human beings. The first metal complex discovered to exhibit anti-cancer activity was cis-platin (cis-diaminedichloroplatinum(II)). This drug is considered best for treatment of certain types of cancers but due to its toxicity, its utilization has been limited at broad range[7-9]. In coming era, interest has been growing in developing non-platinum based anti-cancer drugs due to their less toxicity.

Also, non-platinum compounds may provide different oxidation states, coordination geometries, and affinities for certain types of biological ligands[10]. It has been established that ligands having O, N, S in their stem showed increased biological activity due to increase in coordination capacity[11,12]. It has been reported in literature that due to the symmetry of ligand(s) uptake of drug by cancerous cells has been increased[13]. The necessary conditions for a complex to have anti cancer activities are as i) Complex should be neutral so that it can diffuse through the hydrophobic cell membrane. ii) Complex should have square planer structure i.e. leaving group should be at cis-position. iii) Leaving groups should be labile, so that they can be easily substituted. iv) Groups which are not substituted should have low trans effect like NH_3, heterocyclic amines or diamines[14]. Amine ligands influence the anti-cancer property, because non leaving amine ligands are the reason for anti-cancer property[15]. Recently, some non metallocene titanium complexes having oxygen based ligands have been synthesized and it has been established that ligand lability is not essential to show anti-tumor activity[16].

Platinum Complexes as anti cancer agents:

The first metal based anticancer drug discovered was *Cis*-diaminedichloroplatinum(II) (cis-platin) by Rosenberg et al[8,9].Cis-platin acts by interacting with DNA (Deoxy ribo nucleic acid) via cross linking with two adjacent guanine molecules, followed by the replacement of two chloride groups by water molecules and form aquated cis-platin which stops the replication of DNA and obstruct the cell growth which is the ultimate aim of anti- cancer drugs[14]. Cis-platin has been used in the treatment of various types of cancers such as testicular, ovarian, lung, neck, and head cancers. This metal complex used in the treatment of various cancerous malignancies and is one of the best-selling anti-cancer drug all over the world. Cis-platin has several disadvantages some of which may include that by treating the cells with cis-platin, necrotic and apoptic cell death occur simultanesly. Also, it has limited solubility in water hence it is given intravenously to reduce the harm to the kidney. Other side effects of using cis-platin are emesis, nausea, vomiting, nephrotoxicity, neurotoxicity, myelosuppression, oto-toxicity[14]. Also only a limited number of tumors can be treated with platinum based drugs. In addition to cis-platin many other platinum based drugs (Carboplatin, Oxaliplatin, nedaplatin and lobaplatin) passed for current tumor therapy[1]. The new platinum complexes of the formula [Pt(2,2'-bipyridine)amino acid]$^{n+}$ where n =1-2 and amino acid is an anion of L-histidine, L-Lysine, L-asparagine, L-tryptophan, or L-tyrosine, had been prepared by interaction of [Pt(2,2'-bipyridine)Cl_2] and an appropriate amino acid (sodium salt) in water or water-methanol mixture which are highly negatively charged molecules. In case of Histidine the Platinum atom binds with $–NH_2$ group of Histidine and in case of other amino acids Platinum binds by NH_2 and COO^- groups and these complexes were used against P-388 Lymphocytic leukemic cells[18]. An octahedral complex of Platinum(IV) with adamantylamine of composition bis(acetato)(1-adamantylamine)amminedichloro platinum(IV) had been prepared and showed resistance factor 2.84 fold lower than cis-platin because adamantylamine is a bulky hydrophobic ligand and the use increase the uptake of compound by the cancerous cells and able to overcome the

acquired cis-platin resistance[13]. Pt(IV) complex with adamantylamine penetrate as a whole complex inside the cell membrane. It may be due to hydrophobicity of ligand. The symmetry of hydrophobic adamntylamine ligand lightens the penetration of whole complex inside the cell membrane. The penetration of Pt(IV) complex with adamantylamine had been improved and facilitates transport across cell membrane. This hydrophobic ligand enhances accumulation inside cancer cell and trigger rapid cell death in both cis-platin sensitive and cis-platin resistant cell lines[15]. The Pt(II) Complexes bearing pyridine carboxyldimines containing bulky aromatic groups examined for their potential cytotoxicites against human ovarian carcinoma and cis-platin resistant cell line[19]. A series of *trans*-platinum(IV) complexes with functionalized aromatic carboxylate ligands *cis, cis, trans*-$Pt(NH_3)_2Cl_2(CO_2C_6H_4R)_2$ where R may be H, *p*-vinyl, *p*-methoxy, *p*-iodo, *p*-cyano, *p*-carboxyl had been synthesized and due to presence of aryl groups uptake of drugs had been improved and facilitate transport across cell membrane. These complexes were evaluated for cellular uptake and inhibition of cell proliferation against a panel of lung, colon and breast carcinoma cell lines[20].

Gold Compounds having anti-cancer activities:

The interaction of cytotoxic gold(III) compounds with DNA is weak than that of platinum analogues but gold(III) complexes have good interaction with model proteins and target proteins. The mode of action of gold(III) compounds is significantly different than that of cis-platin. Some compounds like $[Au(en_2)]Cl_3$ (en=ethylene diamine), $[Au(dien)Cl]Cl_2$ (dien=diethylene diamine), $[Au(cyclam)](ClO_4)$ 2Cl, $[Au(terpy)Cl]Cl_2$ (terpy=terpyridine), and $[Au(phen)Cl_2]Cl$ (phen=phenanthroline) were characterized in solid state and in solution. These compounds of gold were tested on human ovarian cell line A2780,which were either sensitive or resistance to cis-platin[21]. A new compound Chloro-glycylhistidinate gold(III) (GHAu) had good biological property and tested for cytotoxic properties in *vitro* against MOLT-4 (human leukemia) and C2C12 (mouse tumor) cell lines[22,23]. Nowadays, gold(III) compounds are good cytotoxic agents. Plenty of gold(III) compounds were characterized and synthesized in the last fifteen years[24]. Gold complexes containing bipyridine ligands of general formula $[Au(N\Lambda N)Cl_2]PF_6$ where (NΛN) = 2,2'-bipyridine, 4,4'-dimethyl bipyridine, 4,4'-dimethoxy-2,2'-bipyridine, 4,4'-diamino-2,2'-bipyridine showed moderate to good cytotoxicity in *vitro* towards human ovarian carcinoma cell line and cis-platin resistance variant[25].

RUTHENIUM COMPLEXES:

Ruthenium complexes have attracted much attention as building blocks for new transition metal based anti-tumor agents. Ruthenium compounds offer the potential over anti-tumor platinum(II) complexes currently used in the clinic because of reduced toxicity, a novel mechanism of action and the prospect of non cross resistance[26-29]. Organo ruthenium complexes due to presence of lipophilic arene can interact better than that of cis-platin inside the cell, by causing chlorine dissociation which is an important factor for cell death. Ruthenium(III) complexes of general formula $[Ru(\eta^6\text{-arene})Cl_2(NC_5H_4OOC\text{-}C_5H_4\ FeC_5H_5)]$ where arene may be C_6H_6, C_6H_5Me, *p*-PrC_6H_4Me, and C_6Me_6 and of formula $[Ru(\eta^6\text{-arene})Cl_2]_2$ $(NC_5H_4OOC\text{-}$

$C_5H_4FeC_5H_4$-$COOC_5H_4N$), where arene=*p*-PrC_6H_4Me and C_6Me_6 were cytotoxic against A2780 and cis-platin resistant human ovarian carcinoma cell lines[30]. It had been studied that the interaction of [(η^6-*p*-cymene)Ru(ATSC)Cl)]PF_6 complex (where ATSC=9-Anthraldehyde thiosemicarbazone) with human serum albumin protein can result into anti-cancer activity as biological activity is not always related to their DNA binding ability. So, protein could be the biological target of these compounds[31]. The four cationic ruthenium(II) complexes with formula [Ru(η^5-C_5H_5)(pph_3)$_2$]$^+$ with L=5-phenyl-1-H-tetrazole (TzH), imidazole (ImH) , benzo [1,2-b;4,3-b'] dithio-phen-2-carbonitrile (Bzt), and [5-(2-thio phen-2-yl)-vinyl] thiophene-2-carbonitrile] (Tvt) were evaluated as anti-tumor agents. Out of these the first three compounds show much higher toxicity than cis-platin against human leukemic cancer cells (HL-60 cells)[32]. The advantages in using ions of transition metals other than platinum include the availability of additional coordination sites in octahedral complexes and altered shape of the complex, changes in ligand affinity and substitution kinetics, change in oxidation state, and photodynamic approaches to therapy[33].

Palladium Complexes:

The marginal anti-tumor activities of the palladium complexes were explained on the basis of fast reactivities of leaving groups as the reactivity of palladium(II) complexes is much higher as compared to platinum(II) complexes e.g. the reactivity of palladium(II) complexes having 1,2-Diaminocyclohexne and dicarboxylate ligands was 10^5 times more than that of platinum(II) complexes having similar ligands[34]. The Pd(II) complexes of the form trans-$PdCl_2L_2$(where L=3-hydroxypyridine, 2-hydroxypyridine, 4-hydroxypyridine) had been synthesized and it had been found that the Solubility, reactivity, electronic and steric properties can be modified by varying the geometry and ligands around the metal center. Out of these the compound of 2-Hydroxy pyridine was found to be most active against A2780, $A2780^{cisR}$ and $A2780^{ZD0473R}$ ovarian cancer cell lines. It had been found that both metal and ligand take part in biological activity of the complex but due to the rapid hydrolysis of palladium complexes (10^5 faster that Platinum analogues), they dissociate easily before reaching their pharmacological target[35]. The platinum(II) and palladium(II) complexes of 2,2'-bipyridine (bipy) with ethyl dithio carbamate (Et-dtc) in which the di thio carbamate ligand coordinate with pt(II) or pd(II) center as bidentate with two sulphur atoms were water soluble and were tested for their in *vitro* anti-tumor activity against chronic myllogenous leukemia cell line K562. But these complexes show cytotoxic concentration (Cc_{50}) values lower than that of cis-platin. The mode of interaction of these complexes were investigated by circular-dichromism, ultraviolet difference and flouroscence spectroscopy. The interaction of Pd(II) complex with DNA and its anti- tumor activity against K562 is more than that of its Pt(II) analog[36]. The series of palladium complexes with Salicyldamine thio semicarbazone having formula [pd(salt scR)PPh_3], {H_2Salt scR = Salicyldehyde thio semicarbazone R=H, 3-tert butyl, 3-methoxy, 5-chloro} were prepared by reaction of appropriate salicyldamine thiosemicarbazone with $Pd(PPh_3)_2$ in which thiosemicarbazone coordinate to the palladium in a tridentate manner that is through phenolic oxygen, imine nitrogen and thionate sulphur forming five or six

membered chelate rings with in the structure and the fourth coordination site is occupied by PPh_3. The biological activity of thiosemicarbazone ligand and palladium complexes were investigated towards WHC01 oesophageal cancer cell line and against two strains of malarial parasite plasmodium Falciparum W2 (Chloroquinone resistant)[37]. Another palladium(II) compound with 5-methyl uracil of the general formula PdL_2Cl_2 where L= 5-methyl uracil was prepared by Anshu Srivastava et. al. and it had been found that this light brown compound was hygroscopic and had thermal stability up to 260˚C with anti-tumor activity[38].

Titanium based anti-cancer drugs:

In the last few years there has been growing interest in developing non-platinum based anti-cancer agents due to their pronounced biological activity[39-51]. After the discovery of cis-platin, the first non-platinum anti-cancer drugs were budotitane and titanocene dichloride which are titanium based anti cancer drugs. Since titanium is second most abundant transition metal and ninth of all the elements on earth and pure titanium and titanium alloy are widely used for orthopedic and dental implants. Titanium is present in many biomaterials such as food in the form of whitening pigment. So it may incorporated in drugs and in to living systems with low toxicity[10]. Also Ti(IV) is an oxophillic metal and form strong bond with acidic DNA as well as other biological molecules. Titanium as a metal posseses a wide spectrum of anti-tumor properties. Titanium based compounds i.e. bis (β-diketonato)titanium(IV) [Budotitane] and titanocene derivatives offer an alterative for cancer chemotherapy. The anti-tumor activity of budotitane was reported in 1982.This was first non-platinum complex tested in clinical trials and used against ascites and solid tumor. This drug had maximum tolerable dose of 230 mg on two week schedule with side effects of cardiac arrhythmia. It had been reported that doses higher than maximum tolerable result in liver and kidney toxicity[52]. Erich Dubler had synthesized and crystallized di-chloro derivatives of budotitane and found that anti-tumor activity appear due to unsubstituted phenyl rings, if phenyl rings get replaced by methyl groups, activity totally disappears[53]. The first metallocene i.e. titanocene dichloride show anti-tumor activity against colon, lung and breast cancer although the mechanism of cytotoxicity is not clear yet. This complex also exhibits antiproliferative activity against solid ascite tumor. Titanocene dichloride show anti-tumor activity against doxorubicin and cis-platin resistant ovarian carcinoma cells and also less toxic effect than cis-platin. The advantage of this complex is that no evidence of nephrotoxicity or myolotoxicity had been reported. It has been found in literature that studies on chemistry of titanium as anti tumor agent are more limited[52]. Titanocene dichloride are proved to be superior compounds of its derivatives since in addition to anti-tumor properties titanocene dichloride exhibits anti-viral[54], anti-arithmetic, and anti-inflammatory activities[55]. This compound exhibits higher toxicity than cis-platin, doxorubicin, mitoxantrone and vinblastine in human renal cell carcinoma. The other halides or pseudohalides of Cp_2TiX_2 (where X=F, Br, I, NCS, N_3) were tested for ehrlich ascite tumor in mice and show anti proliferative activity similar to Cp_2TiCl_2. Budotitane and titanocene dichloride possess same limitation that they have low hydrolytic stability at physiological pH[52]. In this respect titanium(IV) complexes offer a new outlook for chemotherapy. The

novel titanocene compounds are better than cis-platin for apoptic effect in vitro and they can induce more apoptosis than cis-platin. TitanoceneY (bis-[(p-methoxybenzyl) cyclopentadienyl titanium dichloride) had better effect in prostate, pancreas, breast and ovarian cell lines and in uterine and renal cancer cells[56]. Michael shavit et al studied Ti(IV) complexes of oxygen-based ligands. They had prepared the homoleptic complex of hydroxyamino 1,3,5 triazine ligands. These triazine ligands possess mild reactivity despite having no labile groups. This complex was effective against colon and ovarian cancer cells[16]. Since titanocene dichloride is active against colorectal, lung and breast carcinomas, new derivatives may have anti-tumor activity profile. These complexes have advantage that they do not show common side effects such as emesis, alopecia, or bone marrow impairment[52]. These features make titanium compounds interesting for combined therapy and further study[16]. The novel achiral titanocene (Titanocene C and Titanocene Y) anti-cancer drug are almost ten times less toxic than cis-platin. The antiproliferative activity of titanocene Y had been studied in 36 human tumor cell lines and in explanted human tumors and albumin was the carrier protein to take titanocene at the target place inside the cell. Prostate, cervix and renal cell cancer were prime target of these titanocene[57]. Titanocene dichloride react with trimethyl tin fluoride giving a new class of cytotoxic active substance in which Ti-F bond is 75 Kcal/mol more stable than Ti-Cl bond and due to fluorides ions product were not cytotoxic at concentration below

10^{-3}M. But the drawback of this complex was that they show instability in water solution[58]. Also titanocenyl amide complex having triflouromethoxy group on para position show more cytotoxicity than titanocene dichloride due to $–OCF_3$ group on Para position and more stability in aqueous solution. Different compounds were synthesized by replacing $–OCF_3$ by another groups and these were found active against breast cancer cell line MCF-7[59]. In addition to these, titanium alkoxide complex show toxicity in breast, colon and pancreatic cancer cell lines but molecular mechanism yet to be elucidated[60].

SUMMARY

Cis-Platin is the model drug used against mainly testicular and ovarian cancer cell lines but many other non-platinum based drugs have been synthesized which are the alternatives of cis-platin. Other transition metal complexes of titanium, ruthenium, palladium and gold etc. have also been used for the chemotherapy. Due to less side effects of titanium metal complexes, they can be used for the synthesis of new metal based anti-cancer drug. Specifically amine based ligands which are highly charged have been used for the treatment of cancer whose ultimate target is DNA.

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