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RECENT DEVELOPMENTS IN THE FIELD OF ANTICANCER METALLOPHARMACEUTICALS

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ABSTRACT: Metallopharmaceuticals play an important role in contemporary society as therapeutic and diagnostic agents. Many metallopharmaceuticals have been developed to treat/cure a variety of cancers. Besides platinum compounds- cisplatin, carboplatin, oxaliplatin, tetraplatin, satraplatin etc., non-platinum compounds viz. NAMI-A, KP1019, KP46, auranofin and As_2O_3 etc. have shown promising results and many of them are in different phases of clinical trials. Traces of metals are essential for the proper functioning of enzymes in our body and also for the activity of many drugs of organic nature. Chelation in many cases causes drastic change in biological properties of ligands as well as metal moiety. Metal complexes are supposed to exert their effect by intercalation/cleavage of DNA/RNA, arrest of cell cycle and alteration of cell membrane functions. Recently, different strategies to overcome resistance against metal-based anticancer drugs and targeted drug delivery to cancerous cells have been described. These include the encapsulation, conjugation and prodrug formation with different polymer/macromolecules. The review includes the recent developments in anticancer metallopharmaceuticals being developed as therapeutic agents during the recent past.
Keywords: Metal-based drugs, Chelation, Resistance, Encapsulation, Prodrug.

INTRODUCTION

Metal-based drugs have been used as therapeutic agents since ages [1]. They are being used for the treatment of a variety of ailments viz. cancer, diabetes, rheumatoid arthritis, inflammatory and cardiovascular diseases as well as diagnostic agents [2-4]. Many organic compounds used in medicine do not have a purely organic mode of action and require traces of metal ions directly or indirectly for activation or biotransformation. Our health, aging, physiological disorders and diseases are related to the state of the metal ions and their complexes with biomolecules in the body. Traces of metals are essential for the biological processes as about 30-40 % of all known proteins including metalloenzymes require metal cofactors (e.g., Fe, Cu, Zn, Ni, Mn) for their proper folding into an active three dimensional (3-D) structure [5-7]. The iron porphyrin complex of hemoglobin in red blood cells (RBCs) for oxygen transportation and storage, the magnesium porphyrin complex of chlorophyll in green plants for photosynthesis, and cobalt in the coenzyme B_{12} for the transfer of alkyl groups from one molecule to another molecule, are some of the examples of the role of metal ions in biological systems. The amount of metals present in the human body is approximately 0.03% of the body weight. Low metal ion concentrations may be harmful for the body. It has been reported that in cancerous parts of the kidney, the concentrations of Cd, Cr, Ti, V, Cu, Se, and Zn were found to be at a lower level than in the non-cancerous parts [8]. Ligands having electron donor atoms like N, O, S, and P etc. may form coordination bond with metal ion in specific conditions. Chelation causes drastic changes in biological properties of ligands as well as metal moiety and in many cases it causes synergistic effect of metal ion and ligand both [9-10]. A few well known metallopharmaceuticals include platinum(Pt) anticancer agents: cisplatin, carboplatin and oxaliplatin; arsenic(As) anticancer agent arsenic trioxide and gold(Au) anticancer agent auranofin [11-13]. Various mechanisms have been proposed for their action including intercalation with DNA/RNA, cleavage of DNA strands and alteration of cell membrane functions. In classical chemotherapy, anticancer agents target DNA directly in a number of ways and in most cases it is non-covalent bonding, which involves intercalation of planar aromatic molecules between the base pairs of DNA helix, which ultimately trigger cell death. Recently, many chemotherapeutic agents have been prepared which taget extranuclear cell components. A wide variety of coordination spheres, oxidation states, and redox potentials of coordination and

organometallic complexes give kinetic and thermodynamic properties of complexes towards biological receptors.

METAL COMPLEXES AS ANTICANCER AGENTS

The clinical success of cisplatin and related platinum based drugs as anti-cancer agents constitute the most impressive contribution to the use of metals in medicine. The metal compounds containing ruthenium, arsenic, titanium, copper, gold, silver, tin and rhodium etc. with promising chemotherapeutic potential and having similar or different mechanism of action than the platinum based drugs have also been reported.

Platinum compounds

The platinum antitumor drugs cisplatin (*cis*-$Pt(NH_3)_2Cl_2$), carboplatin and oxaliplatin (Fig.**1**) have wide applications in modern cancer chemotherapy. Cisplatin, the first coordination compound developed for cancer treatment, approved by the U.S. Food and Drug Administration in 1979, is still one of the most effective drugs to treat testicular, ovarian, bladder, and head and neck cancer [14-15]. Cisplatin as a principal component of combination regimens, is the most suitable agent for the treatment of ovarian and bladder cancers (dose 20 mg/m^2 -100 mg/m^2, usually for up to 5 consecutive days) but having disadvantage of onset of clinical resistance after treatment including side effects of nephrotoxicity, neurotoxicity, ototoxicity, and emetogenesis. DNA is accepted to be the cellular target of cisplatin. It damages the DNA by stimulating apoptosis via a p53 dependent pathway. Although in some cancer cell lines or tumor types, p53–independent pathways have been observed [16-17]. Carboplatin shows a reduced toxicological profile compared to cisplatin and maintaining similar spectrum of activity. In contrast, oxaliplatin has shown activity against cisplatin-resistant cell lines and showed improved response in combination therapy for metastatic colorectal cancer as compared to oxaliplatin monotherapy. In addition to the well known platinum compounds, some little known compounds viz. nedaplatin and lobaplatin have shown promising anticancer activity and approved for use in Japan and China, respectively. Other platinum complexes viz. tetraplatin, satraplatin (bis(acetato)amminedichloro(cyclohexylamine)platinum(IV) or JM-216 and iproplatin are in different stages of clinical trials. One of the metabolites of satraplatin, [*cis*-amminedichloro(cyclohexylamine)platinum(II)] or JM118 is believed to be responsible for the anticancer activity [18-19]. Recently, satraplatin in combination with prednisolone has been considered for approval by the FDA for the treatment of hormone-refractory prostate cancer. In contrast to satraplatin, picoplatin (*cis*-ammine(2-methylpyridine)dichloroplatinum(II)/AMD473/ZD0473 was especially designed to overcome resistance against cisplatin [20]. A trinuclear platinum complex BBR-3464 with altered DNA-binding characteristics as compared to cisplatin has shown some promising results in phase II of clinical trials. BBR-3464 binds to DNA more rapidly than cisplatin and forms longer interstrand crosslinks [21]. In several studies, BBR-3464 showed activity in cisplatin-sensitive and -resistant, as well as p53-mutated tumor models [22-23] but in phase II study, a poor response rate was observed in patients with gastric and gastro-oesophageal adenocarcinoma [24] and found ineffective against sensitive or refractory small cell lung cancer [25] and consequently the clinical development of BBR-3464 has been suspended. Therefore, much attention has been given on designing new platinum compounds with improved pharmacological properties and a broad range of antitumor activity. The strategies include the incorporation of carrier groups that can target tumor cells with high specificity. Drug delievery system that can target only tumor cell and prevent binding to non-pharmacological target may be effective in reducing adverse drug effects and resistance.

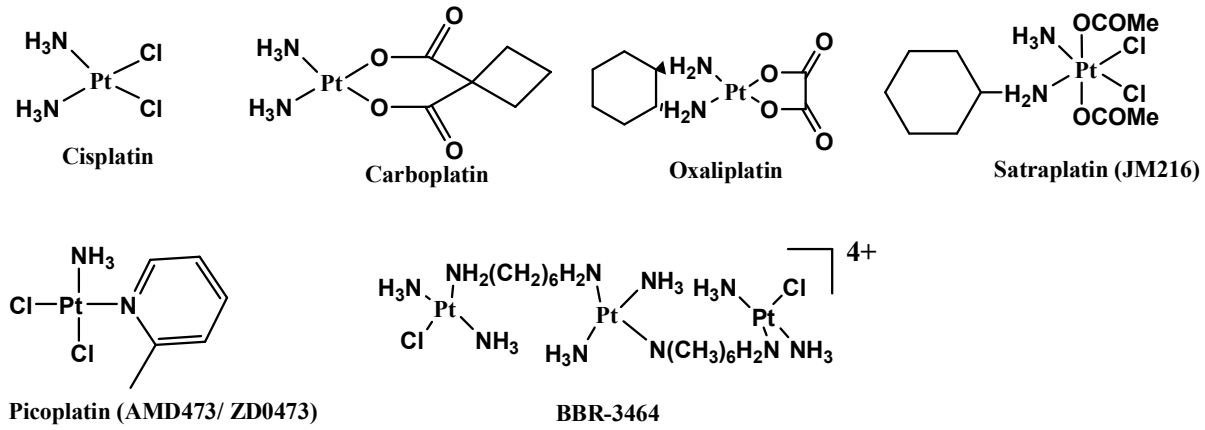

Fig. 1. Structures of some platinum anticancer drugs

In classical chemotherapy, anticancer agents target DNA directly which ultimately trigger cell death. Much effort has been given towards combating the high systemic toxicity of traditional platinum anticancer agents by designing drug delivery systems capable of delivering platinum to tumor cells only. The encapsulation of cisplatin and carboplatin in the hollow protein cage of ferritin (the iron storage protein) showed cytotoxic activity against the rat pheochromocytoma cell line (PC12) which preferably internalized by some tumour tissues [26]. In a different approach, minicells, bacterially–derived 400 nm anucleate particles, have been packed with chemotherapeutics such as cisplatin and labelled with bispecific antibodies. This resulted in endocytosis and ultimately drug release in cancer cells [27]. In another approach, Pt(IV) prodrugs have been designed to overcome cisplatin and its analogues' toxicity [28].

The high kinetic inertness and the two extra sites for ligands attachment of Pt(IV) complexes relative to their Pt(II) analogues give drug stability and offer many possibilities for modification of pharmacokinetic properties. Hypoxic condition in tumor cells favors intracellular reduction of Pt(IV) to Pt(II) which is essential for cytotoxicity and hence provide better ways of delivering cisplatin (or its analogues) to the target tumour cells. Also, the specially designed polymer coated micelles protect platinum from binding to intracellular thiols and prolong time in bloodstream leading to accumulation of drugs in tumour tissue and enhance delievery of drug to tumor sites. Recently, Poly ethylene glycol (PEG) micelle containing poly aspartic acid has been employed to circumvent drug distribution and thus display prolonged circulation time in the bloodstream and higher accumulation in target tumor cells [29]. A series of platinum-polymer conjugates with *trans*-1,2-diaminocyclohexane have been investigated which showed more cytotoxicity against multidrug resistant cell line Colo320 DM cells [30]. Similarly, the platinum-polymer conjugates with attached galactose exhibited cell specific cytotoxic activity against human hepatic cells [31]. The estrogen tethered platinum(IV) complex exhibited cell specific cytotoxic activity against breast cancer cells which is activated by intracellular reduction and thus releasing cisplatin and estradiol. It induces high mobility group (HMG)-domain protein HMGB1 leading to protection of cisplatin-DNA lesions from repair mechanism [32]. In the similar way to overcome drug resistance, platinum(IV) complex ethacraplatin when reduced in tumor cells, releases ethacrynic acid and cisplatin. Ethacrynic acid inhibits glutathione-*S*-transferase (GST) which is involved in cellular defence mechanism against xenobiotics [33]. Platinum-intercalator conjugate, for example, a series of *cis*-ethylenediamineplatinum(II) complexes with tethered 9-aminoacridine-4-carboxamides are able to overcome drug resistance in human ovarian carcinoma cell lines *in vitro* [34]. Platinum(IV) prodrug conjugated with single-walled carbon nanotubes (SWNT) has shown promising results when compared to the untethered complex and cisplatin [35]. In other strategies, photochemical activation of platinum(IV) drugs to release active antitumor agent rather than intracellular reduction has been applied. The *trans*-dihydroxyplatinum(IV) prodrug after irradiation has shown growth inhibition of human bladder cancer cells and cytotoxicity towards human skin cells (HaCaT keratinocytes) [36]. Recently, the photochemical activation of platinum-porphyrin conjugate has shown improved and tumour specific cytotoxic activity on irradiation [37].

Non-platinum compounds

Besides platinum antitumour compounds, ruthenium compounds have shown very promising anticancer activity. They have shown activity on tumors which developed resistance to cisplatin or in which cisplatin is inactive. They showed less toxicity than platinum complexes [38]. Ruthenium compound, NAMI-A (imidazolium *trans*-[tetrachloro(DMSO)(imidazole)ruthenate(III)]), as an antimetastatic drug and KP1019 (indazolium trans-[tetrachlorobis(1H indazole) ruthenate(III)]) (Fig. **2**) as an anticancer drug against colon carcinomas and their metastases have entered clinical trials so far. Both compounds showed relatively little side-effects and better tolerance in clinical phase I trials. Ruthenium compounds with anticancer activity appear to penetrate tumors through a transferrin-mediated process and bind to cellular DNA following intracellular activation by reduction. In addition to ruthenium(III) compounds, ruthenium(II)-arene and osmium(II)-arene complexes have shown promising results in preclinical evaluation [39-41]. Although, most ruthenium compounds target DNA but their induced damage seems to be different from platinum-based drugs, suggesting additional cellular targets. In case of NAMI-A, DNA is thought to be a less important target, and anti-angiogenic activity based on the NO metabolism has been described. NAMI-A interaction with the microenvironment involving integrin activation that results in reduced cell invasiveness and migration has been proposed and this may be the reasons for the activity of ruthenium compounds against cisplatin-resistant tumors.

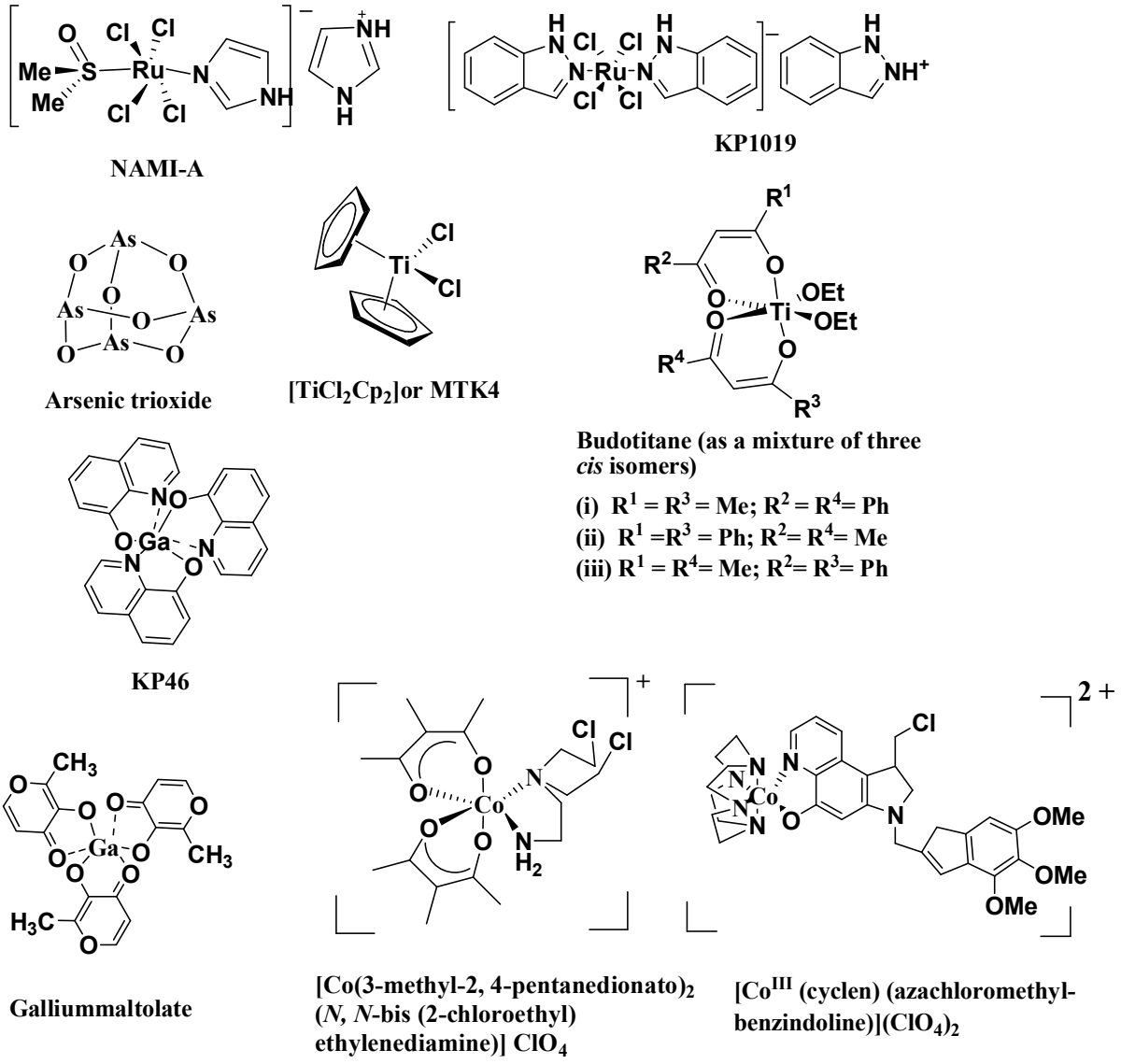

Fig. 2. Structures of some non-platinum anticancer drugs

Arsenic and arsenic compounds have been used as therapeutic agents for the treatment of chronic myelogenous leukemia [42-43]. Arsenic trioxide (As_2O_3), the most widely used arsenical-based cancer drug, was approved in 2000 for the treatment of relapsed/ refractory acute promyelocytic leukemia (APL) and currently evaluated for the treatment of other cancers including multiple myeloma and neuroblastoma [44-49]. As_2O_3 affects numerous intracellular signal transduction pathways and alters cellular functions. It inhibits tumour growth by inactivating oncogenic PML-RARα fusion protein leading to cell differentiation [46]. Arsenic induced apoptosis is suggested to be due to oxidative stress leading to generation of ROS by depletion of intracellular glutathione (GSH) [50], cleavage of DNA strand, accumulation of Ca^{++}, upregulation of caspase-3, down regulation of Bcl-2, suppression of p53 etc. [51]. As_2O_3 induced accumulation of Ca^{++} ions causes mitochondrial depolarization by opening of mitochondrial permeability transition pore (MPTP) that facilitate the release of cytochrome-c [52]. Recently, thioredoxin reductase, which is associated with many cellular processes such as antioxidant defence and redox homeostasis, has been suggested to be an important target for As_2O_3 [53]. Combination therapy of As_2O_3 and radiation has shown very promising results in murine models of the disease. It showed enhanced response to cervical cancers and malignant gliomas treated with As_2O_3 in phase I of clinical trials. Enhanced response of combination therapy is supposed to be due to inhibition of proliferation, arrest of G1 and/or G2-M phase of cell cycle and induction of apoptosis by caspase activation, suppression of p53 & Bcl-2 etc. In vitro studies showed synergistic effect of As_2O_3 in combination with interferon/ascorbic acid against various lymphoma cells [46]. Other immune-mediated and anti-angiogenic effects of As_2O_3 on multiple myeloma tumors have also been proposed.

Many gallium compounds have shown anticancer property because of gallium accumulation in lymphoma

and various other tumor cells. Gallium nitrate [$Ga(NO_3)_3$] has shown promising anticancer activity in phase I/II of clinical trials and later approved for the treatment of hypercalcemia of malignancies by reducing the elevated Ca^{2+} in blood [54]. Hypercalcemia is often associated with bone cancers in which rapid bone loss leads to elevated Ca^{2+} in blood. Gallium reduces the rate of bone loss by inhibition of the action of osteoclasts, which produce acid onto the bone surface dissolving mineral and protein components.

Anticancer activities of gallium nitrate against malignancies, especially non-Hodgkin's lymphoma, non-squamous cell carcinoma of the cervix, and bladder cancer have been reported. Gallium maltolate, (tris(3-hydroxy-2-methyl-4H-pyran-4-onato)gallium(III) and KP46 (tris(8-quinolinolato)gallium(III)) are currently in clinical evaluation. Only in a few reports, gallium maltolate has shown activity against refractory prostate cancer and multiple myeloma whereas the anticancer activity of KP46 against several refractory tumors in a phase I trial has shown promising results. Gallium complexes of ligands such as 8-hydroxyquinoline [55], thiosemicarbazones [56] and pyridoxal isonicotinoyl hydrazone [57] have also been known for their promising results. Gallium compounds may be designed to deliver the Ga^{3+} ion more effectively and selectively to the target site. Gallium in combination with bisphophonates has been prepared to improve oral availability of gallium.

Among the metallocene dihalide complexes MX_2Cp_2 (where M=Ti, V, Mo, Nb etc., X= halide and Cp = η^5-cyclopentadienide), titanocene, $TiCl_2Cp_2$ or MTK4 is the most successful anticancer agent as shown in phase I/II clinical trials. Previously DNA was supposed to be the target of $[TiCl_2Cp_2]$ in a manner similar to cisplatin due to the similarity in Cl---Cl distances. Later, the aquous chemistry of $[TiCl_2Cp_2]$ showed that DNA is not the site of action for this drug. The anticancer activity of $TiCl_2Cp_2$ is due to inhibition of collagenase type IV activity, which is involved in regulation of cellular proliferation, protein kinase C and DNA topoisomerase II activities. Titanium may also replace iron in transferrin and facilitate cellular uptake into tumor cells [58]. The titanocene dichloride is believed to be accumulated via the transferrin–dependent pathways. Dose limiting toxicities of titanium compounds include nephrotoxicity and elevation of creatinine and bilirubin levels [59-60].

Budotitane, *cis*-$[(CH_3CH_2O)_2(bzac)_2Ti^{IV}]$, where bzac=1-phenylbutane-1,3-diketonate (exists as a mixture of three *cis* isomers) (Fig. **2**), was the first non-platinum transition-metal anticancer agent to be tested in clinical trials [61-62]. It is effective against a number of tumors in animals and is well tolerated. *In vitro* and *in vivo* experiments with budotitane showed no significant DNA damage. The dose-limiting side effects include cardiac arrhythmia, hepatotoxicity, renal toxicity and a reversible loss of taste.

Other titanium compounds such as Ti(IV) citrate, Ti(IV) dehydroascorbate and Ti(IV) oxalate are known. The promising results of Ti(IV) citrate on tumors in rats [63], Ti(IV) dehydroascorbate to treat tumors in humans [64] and the reduction in incidence of spontaneous tumors in mice by Ti(IV) oxalate [65] lead to development of many Ti(IV) anticancer drugs. Ti(IV) compounds are known to inhibit proteases and telomerases [66-67]. Inhibition of proteases in rapidly growing tumor cells may block the growth of tumor cells. Inhibition of telomerase may control all protein synthesis. Duffy and McCure found the inhibitory activity of hydrolyzed $Ti(SO_4)_2$ by binding Ti(IV) with free carboxyl group of Asp-189 of trypsin [68]. In telomerases, the terminal DNA sequence TTAGGG which is repaired in chromosomes [69], is homologous with the critical target proposed for cisplatin [70]. Kohlstaedt et al. [71] have identified carboxylic groups on two amino acids (Asp) in the active site of telomerases which bind metal ions and are highly conserved.

Gold compounds, well known for their clinical anti-arthritic properties, have also been reported to possess antitumor activity [72]. Au(I) phosphine compounds such as auranofin, a linear tetraacetylthioglucose gold(I) phosphine complex, triethylphosphine gold(I) chloride(Et_3PAuCl), bis[1,2-bis(diphenylphosphino) ethane] gold(I) chloride $[Au(dppe)_2]Cl$, Au(I) *N*-heterocycyclic carbine complexes of the type $[(R_2Im)_2Au]^+$ (where R= alkyl substituents and Im= imidazole) and Au(III) compounds such as $[Au(en)_2]Cl_3$, $[Au(dien)Cl]Cl_2$ and the cyclometallated complex $[Au(bipy^{dmb}\text{-}H)(OH)]PF_6$ ($bipy^{dmb}$= 6-(1,1-dimethylbenzyl)-2,2′-bipyridine) are known to exhibit promising antitumor properties [73-77]. Auranofin has been found cytotoxic to p388 leukaemia cells and inhibited DNA polymerases. Triethylphosphine gold(I) chloride inhibited tumor colony formation in vitro, interacted with DNA, and inhibited oxidative phosphorylation, ATP production and the viability of isolated rat hepatocytes.

Bis[1,2-bis(diphenylphosphino)ethane]gold(I)chloride $[Au(dppe)_2]Cl$ had shown significant antitumor activity in a number of murine tumor models in vivo. $[Au(dppe)_2]Cl$ also inhibited tumor colony formation in vitro, interacted DNA strand, induced DNA-protein cross links and showed antimitochondrial effects on P388 leukemia cells and isolated hepatocytes. Tetrahedral Au(I) complexes of bidentate pyridyl phosphines have shown promising in vitro and in vivo antitumor properties based on their lipophilicity. But the difficulty with most Au(III) compounds is their stability, because they readily reduced to Au(I) under physiological conditions. Some Au(III) complexes have been investigated which have significant antitumour properties and in which the Au(III) oxidation state is stabilized by appropriate ligands. The antitumour Au(III) dithiocarbamate complexes have been recently reported by Fregona and co-workers. The complexes $[Au(DMDT)X_2]$ and $[Au(ESDT)X_2]$ (where DMDT= N,N-dimethyldithiocarbamate and ESDT = ethylsarcosinedithiocarbamate; X= Cl, Br) are more cytotoxic in vitro than cisplatin including in human

tumour cells lines intrinsically resistant to cisplatin. Au(III) antitumour complexes recently reported by Che and co-workers are a series of Au(III) porphyrins that exhibit potent in vitro and in vivo anticancer properties toward hepatocellular carcinoma and nasopharyngeal carcinoma. The mode of action has been demonstrated that mitochondria are the major cellular target. Although, the exact intracellular targets responsible for their antitumor activity are unclear, mitochondrial thioredoxin reductase (TrxR) has been suggested as potential targets involved in the antitumor and cytotoxic activities of gold(I) and gold(III) complexes. The molecules having thiolate group such as albumin, glutathione show high affinity with gold(I) for thiolate sulphur and are supposed to be possible target sites for gold(I). The mechanism of action is supposed to be due to thiolate exchange reactions. $[Au(CN)_2]^-$ which is the main metabolite in gold metabolism, is supposed to play an important role in antitumour and cytotoxic activities. Au(III) porphyrin 1a induces apoptosis though both caspase-dependent and caspase-independent mitochondrial pathways. [Au $(dppe)_2$]Cl in combination with cisplatin provided greater activity compared with either agent given alone [78]. Other gold compounds such as gold(I) thiocyanate and tertiary phosphine complexes of AuSCN have been investigated for their antitumor activity [79-80].

More recently, a hydrophilic tetrakis(tris(hydroxymethyl)phosphino)gold(I) complex (Fig. 3) has been reported with promising cytotoxic activity against several tumor cell lines. The cell cycle studies with HCT-15 cells derived from human colon carcinoma revealed that inhibition of cell growth may result from elongation of the G1 phase of cell cycle [81]. Gold(I) and (III) complexes have also been reported to bind to DNA in vitro and can cleave DNA in cell culture [82]. Au(III) complexes with their metal centers being isoelectronic and isostructural to Pt(II) are thus promising candidate as anticancer agents. Recent reports indicate that gold compounds exhibit cytotoxic properties towards several tumor cell lines and they are also effective on cells resistant to cisplatin [83-86]. For example, triethylphosphine gold(I) chloride binds with DNA and inhibits oxidative phosphorylation. $[Au(dpype)_2]Cl$ shows promising in vitro and in vivo antitumor properties against B16 melanomia and p388 leukemia cells [87]. Gold(III) complexes such as $(C_2H_5)_3P$-$AuBr_3$ [88], $[Au(PPh_3)L]$ (L = imidazole) [89], $[AuCl_2(dmamp)]$, (dmamp=2-(dimethylaminomethyl) phenyl) [75], RAu(III)L (L= thiosalicylate) [90] and a number of amine–and aminoquinoline-gold(III) complexes [91] are known to exhibit antitumor and cytotoxic activities against melanoma and lung tumor cells [92] and found to possess DNA binding properties. Gold(III) - tetraaryl porphyrins are known to exert high potency than cisplatin in destroying human cancer cells including drug resistant variants [93].

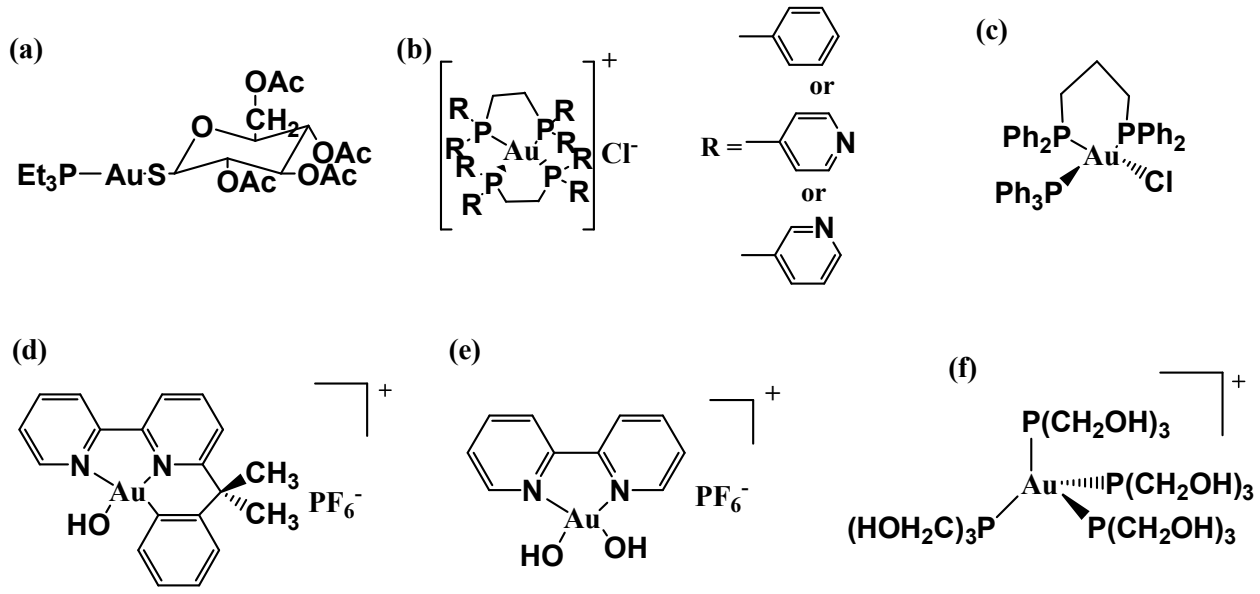

Fig. 3. Structures of some important gold anticancer drugs (a) Auranofin (b) Au(I) complex with 1,2-bis(diphenylphosphino)ethane and 1,2-bis (dipyridylphosphino)ethane (c) Tetrakis(tris(hydroxymethyl)phosphino)gold(I) complex (d) $[Au(bipy)(CH_3)_2(OH)]PF_6$ (e) $[Au(bipy)(OH)_2]PF_6$ (f) Chlorotriphenylphophine-1,3-bis(diphenylphosphino) propanegold(I) complex

Other metal compounds including cobalt complexes such as [Co(3-methyl-2,4-pentanedionato)$_2$(*N,N*-bis(2-chloroethyl)ethylenediamine)]ClO_4, [Co^{III}(cyclen)(azachloromethylbenzindoline)]$(ClO_4)_2$ [94], organotin complexes, rhodium complex (rhodium carboxylate) [95], nickel complex of thiosemicarbazones [96-97], lithium salt of γ–linolenic acid (LiGLA) and vanadium compounds such as vanadyl sulfate and sodium orthovanadate etc. have also been reported to possess promising anticancer activities. The *N,N′*-donor ligands such as 1,10-phenanthroline (phen), 1,10-phenanthroline-5,6-dione (phendione) and a range of their Cu(II), Mn(II) and Ag(I) carboxylate complexes have shown promising results even better than cisplatin against selected cancer cell lines [98-101].

RESISTANCE MECHANISM AND STRATEGIES TO OVERCOME RESISTANCE AGAINST METAL-BASED ANTICANCER DRUGS

Reduced intracellular drug concentrations

Metal-based drugs are suggested to be transported into tumor cells via transferrin-dependent or/and transferring-independent pathways. Transporters, especially Ctr1, which are involved in the cellular uptake of cisplatin play an important role in chemotherapy. Inhibition of Ctr1 in murine embryonic fibroblasts has shown reduced uptake of cisplatin, carboplatin and oxaliplatin [102]. Another mechanism involved in drug resistance is the enhanced drug efflux before reaching their intracellular targets mainly by overexpression of ATP-driven transmembrane pumps involving P-type ATPases, ATP7A and ATP7B that lead to altered distribution [103]. ABC-transporter-mediated resistance is one of the most prominent mechanisms involving members of ABC-transporter family ABCB1, ABCC (MRPs), ABCC2 and ABCG2 (BCRP) leading to reduced intracellular drug concentration but this hypothesis is not valid to all platinum anticancer drugs [104-108]. ABCC1 expression has shown to confer GSH-dependent As_2O_3 resistance in several cell models [109-114]. One way to overcome ABC-transporter-mediated drug resistance is to develop drugs containing ABC-transporter modulating ligands in combination with cytotoxic metal drugs. Several Ru(II)-arene complexes conjugated with modified phenoxazine- and anthracene- based ligands have been made for this purpose [115]. A lanthanum compound, [tris(1,10-phenanthroline)lanthanum(III)]trithiocyanate (KP772/FFC24), showed promising anticancer properties in ABC transporter- overexpressing cells by cell cycle arrest and induction of apoptosis along with complete loss of ABCB1 gene expression in a MDR cell line [116].

Drug binding and metabolization

The binding of metal ions with endogenous thiols such as glutathione (GSH) and metallothionein (MT) is one of the main mechanisms of detoxification. Overexpression of these cysteine-rich molecules is thought to have an important role in the development of resistance of tumor cells to various metal-based drugs. In satraplatin resistant M1/JM216R cells, enhanced GSH level was found and GSH is thought to be responsible for drug detoxification [117]. In contrast, increased levels of MT but not GSH were found in BBR-3464-resistant A2780 cells [118]. New Pt(IV) compound, LA-12 which is active against cisplatin-resistant A2780cisR cells has displayed elevated GSH levels [119-120]. The arsenic compounds have also shown interaction with cellular thiols. As_2O_3 treatment has shown enhanced MT expression in several myeloma cell lines and human leukemic cells rapidly developed resistance due to elevation of cellular GSH *in vitro* [110, 121-122]. Based on the understanding of mechanism of action, the decreased GSH levels render cancer cells more sensitive to As_2O_3 [123-125]. Ascorbic acid, which is known to deplete cellular GSH pools, has been used in combination with As_2O_3 to obtain better therapeutic results.

In contrast to platinum and arsenic drugs, the anticancer activity of ruthenium compounds is independent to cellular GSH levels and the thioredoxin system has been also identified to play an important role in the cellular redox metabolism and antioxidant defense mechanism [126]. Many tumor cells with elevated level of the thioredoxin reductases (TrxR) have been reported to be chemotherapy-resistant [127]. Several redox-reactive chemotherapeutics, including metallodrugs like cisplatin, As_2O_3 and the gold compound auranofin have been described to inhibit TrxR [127, 128-129]. Moreover, the recognition of TrxR as potent target for chemotherapy led to the development of several platinum and gold-containing drugs such as TrxR inhibitors [127, 130].

To circumvent resistance mediated by enhanced GSH levels, the strategies are adopted to design molecules with bulky group to confer steric hindrance with the platinum center. The most successful candidate in these molecules is picoplatin, which was designed to exert a reduced reactivity with thiols. A bulky methylpyridine ring was introduced into the molecule to confer steric hindrance with the platinum center. Consequently, picoplatin has been shown to be less conjugated to GSH and MT than cisplatin [131-132]. Also GSH-mediated resistance to cisplatin and arsenic compounds are accompanied by over expression of GST. To overcome GST-mediated resistance, ethacrynic acid, a known GST inhibitor, was linked to the platinum center to form ethacraplatin, shown to be a potent inhibitor of GST [133]. Recently, Ru(II)-arene complexes were described [134] to overcome GSH-mediated resistance. A new copper complex, copper *N*-(2-hydroxy acetophenone) glycinate (CuNG) has been recently reported to reduce cellular GSH *in vivo* and showed more potency than ethacrynic acid [135]. It is supposed that CuNG depletes cellular GSH at non-toxic concentrations through conjugation [136].

Enhanced repair mechanisms and increased DNA damage tolerance

Enhanced DNA repair is another factor that may cause cisplatin resistance [137]. Most platinum drugs including satraplatin and picoplatin bind to DNA in a similar way as cisplatin [138]. DNA platination is primarily repaired by the nucleotide excision repair (NER) system. The expression of the excision repair cross complementation group 1 (ERCC1) protein, an important part of NER system, has been associated with development of resistance against platinum drugs [139].

Besides increased DNA repair mechanism, the increased tolerance to DNA damage plays an important role in platinum drug resistance [140-141]. The mismatch repair (MMR) pathway is also involved in resistance mechanism and loss of this pathway has shown to confer low-level resistance to cisplatin and carboplatin due to failure of repair mechanism leading to cleavage of DNA strand and thus apoptosis [142-144]. Cisplatin and carboplatin adducts are recognized by MMR proteins with higher efficacy than those of other platinum drugs including oxaliplatin and satraplatin [143, 145]. Based on these data the role of the MMR system on the anticancer activity of metal drugs seems to be variable and complex.

Another tolerance mechanism to platinum drugs involves enhanced replicative bypass, also called translesion synthesis, especially by DNA polymerases β and η [144]. It was found that satraplatin-DNA adduct was more efficient in blocking polymerase-mediated translesion synthesis than cisplatin and oxaliplatin [142]. But in case of BBR-3464, upregulation of DNA polymerase β showed no effect on the anticancer activity [146].

Modification of survival pathways

Mutation of the tumor suppressor p53 and over expression of anti-apoptotic bcl-2 and bcl-xL lead to impaired apoptosis and are associated with cellular protection against the clinically used platinum drugs [147-148]. A significant enhancement of As_2O_3 sensitivity against leukemic cells was observed after inhibition of anti-apoptotic bcl-2 [149].

The JAK (Janus family of tyrosine kinases) and STAT (signal transducers and activators of transcription) pathway have been shown to play distinct roles in several cellular processes ranging from apoptosis and differentiation, to proliferation and survival [150-151]. STAT family members especially STAT3, STAT5a, and STAT5b regulate many oncogenes and/or genes with prosurvival functions like cyclinD1, bcl-xL and c-myc [150-151]. Recent study revealed a significant association of the JAK/STAT signalling pathway with sensitivity to cisplatin and picoplatin but not carboplatin and oxaliplatin in ovarian cancer cells [152]. STAT1 and STAT3 were suggested to be involved in resistance against cisplatin and satraplatin [153]. Several platinum(IV) complexes (CPA-1, CPA-7, and $Pt(IV)Cl_4$) were recently reported to inhibit STAT3 [154-155]. As_2O_3 has also shown inhibiting property of the JAK/STAT pathway [156].

NFκB

The transcription factor NF-κB plays an important role in cancer chemotherapy and regulation/activation of this pathway has been associated with resistance against chemotherapy [157]. Anticancer activity of cisplatin is also influenced by activation of NF-κB [148]. On contrary, constitutive activation of NF-κB does not render cells resistant to As_2O_3 and NF-κB seems to be one of the important cellular targets for As_2O_3-induced apoptosis. It is based on the binding to the activation loop of the IκB kinase (IKK) catalytic subunits [158-159].

Metal-responsive transcription factor

In cell signalling pathway, the role of metal-responsive transcription factor, MTF1 (a zinc finger protein), and the metal-response element (MRE) to control expression of metallothionin (MT) and other components such as zinc (ZnT1) and copper (Ctr1) transporters in metal homeostasis has been recognized [160-161]. Although induction of MT and ZnT1 expression via MTF1 was shown to protect cells against zinc toxicity [162]. Recently, microarray studies revealed that gallium nitrate-resistant lymphoma cells displayed a marked increase in MTF-1, MT-2A and ZnT-1 and this indicates that the MTF-1 might be involved in acquired resistance against metallodrugs [163].

CONCLUSIONS

It is apparent that opportunities exist to explore inorganic chemistry for the discovery and development of anticancer metallopharmaceuticals. The encouraging results of preclinical and clinical studies of metal compounds form the basis for further investigation towards the development of metallopharmaceuticals for better healthcare. The unique properties of metals provide an advantage in the further development of metallotherapeuticals and may have activity against refractory and relapsed diseases. Further, understanding the mechanism of actions, cellular target etc. and the properly designed metal compounds will increase the selectivity and specificity of the compounds. The traditional organic drugs alone may not be complete without a parallel exploration of metal pharmacology as many organic drugs require interactions with metals for activity. It is clear that metal compounds offer new properties that cannot be found amongst purely organic agents. The therapeutic application of metal complexes is still an unexplored area of research and may be useful to develop novel therapeutic agents. A wide variety of coordination spheres, ligands design, oxidation states and redox potential can systematically alter the kinetic and thermodynamic properties of the complexes towards biological receptors. Therefore, they offer opportunities for the design of novel agents for the treatment of a variety of diseases and conditions including cancers.

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