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Inorganic Coordination Chemistry: Where We Stand in Cancer Treatment?

Pedro Pedrosa, Andreia Carvalho,
Pedro V. Baptista and Alexandra R. Fernandes

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http://dx.doi.org/10.5772/intechopen.80233

Abstract

Metals have unique characteristics such as variable coordination modes, redox activity, and reactivity being indispensable for several biochemical processes in cells. Due to their reactivity, their concentration is tightly regulated inside the cells, and abnormal concentrations are associated with many disorders, such as cancer. As such metal complexes turned out to be very attractive as potential anticancer agents. The discovery of cisplatin was a crucial moment, which prompted the interest in Pt(II) and other metal complexes as potential anticancer agents. This chapter highlights the state of the art on metal complexes in cancer therapy, highlighting their uptake mechanisms, biological targets, toxicity, and drug resistance. Finally, based on the importance of selective target of cancer cells, drug delivery systems will also be discussed.

Keywords: cancer therapy, metal complexes, mechanism of action, clinical trials, platinum, ruthenium, copper

1. Introduction

Metal compounds are of undeniable importance to medicine, either for their toxicity or for their effectiveness in disease treatment. In ancient Egypt, copper was used to reduce inflammation and iron to treat anemia [1]. In modern medicine, noticeable discoveries of metal-based compounds marked the last centuries such as $K[Au(CN)_2]$, by Robert Koch, at around 1890, to treat tuberculosis; arsphenamine developed in the 1910s to cure syphilis; and Cisplatin discovered by Barnett Rosenberg in the late 1960s as an anticancer agent [2]. The latter marked a milestone in drug discovery for inorganic complexes, revolutionizing cancer

treatment and shifting focus to rational design to improve metal-based drugs, where other coordination compounds (e.g., gold, ruthenium, titanium, and copper) were also explored with some reports of (pre)clinical and clinical candidates [3, 4].

Transition metals, such as zinc, iron, and copper, are involved in several biological processes, from electron transfer to enzyme cofactors meaning that their intracellular concentration is tightly regulated, otherwise it can lead to the development of various pathological disorders such as Menkes and Wilson diseases associated with copper impairment and accumulation, respectively [4]. A common characteristic of these metals is their ability to form reactive oxygen species (ROS), which are a part of cellular redox balance and fundamental in cell metabolism, signal transduction for proliferation, differentiation, and cell death, among others [3]. Redox homeostasis is controlled by compartmentalizing reactions in the cell in subcellular units such as mitochondria and peroxisomes [3]. It is therefore understandable the great impact that metal complexes can have on such redox balance. Disturbing the oxidant-antioxidant balance promotes an oxidizing environment leading to oxidative stress. When ROS are formed inside the cells, they can induce the lipid peroxidation of cell membranes, disrupt the mitochondrial membrane potential promoting membrane depolarization, induce DNA single-strand breaks, and oxidize the cysteine residues resulting in protein structural changes [3]. Cancer cells are known to have a different redox metabolism from normal cells, with augmented levels of intracellular ROS, mostly due to increased metabolic activity and hypoxia, especially in the core of solid tumors [4]. Metal complexes, due to their redox properties, have been shown to disturb cellular redox homeostasis resulting in enhanced levels of oxidative stress prompting cancer cell death [4–8].

DNA is the main intracellular target for a high number of anticancer metal complexes (e.g., cisplatin, carboplatin, and oxaliplatin); however, several other targets are known (**Figure 1**) [4].
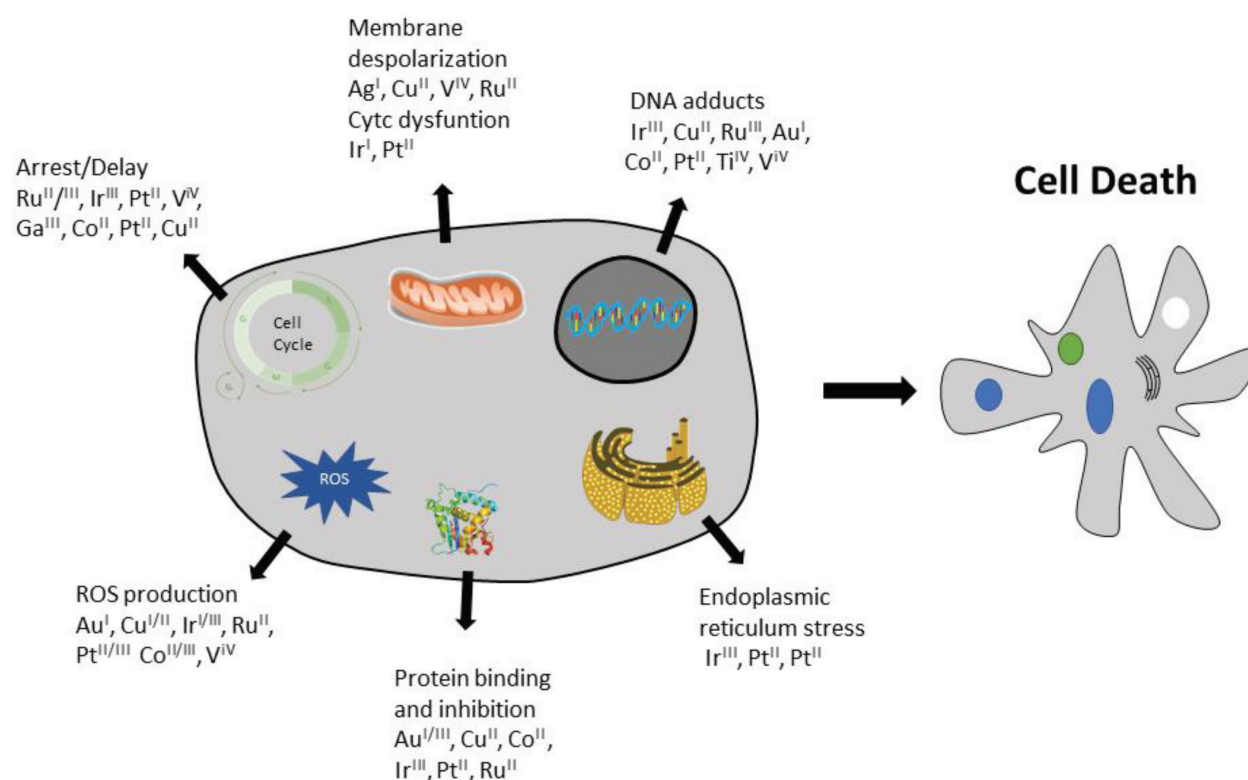

Figure 1. Schematics of metal complex mechanisms of action that promotes cell death.

In the following sections, we will summarize the current knowledge on Pt, Au, Ru, Ti, Pd, Ir Cu, V, Co, Ga, and Os complexes, highlighting their uptake mechanisms, biological targets, toxicity, and drug resistance mechanisms and elucidating how far they are from translation to the clinics in cancer therapy.

1.1. Platinum

Platinum-containing complexes revolutionized cancer treatment since the introduction of cisplatin. Synthesized in 1844, it was used for the first time, more than 100 years later to treat patients with testicular cancer with survival rates over 90% [9]. Since then, more than 3000 platinum derivatives were synthesized and tested for antiproliferative potential against cancer cells. Today, there are six platinum drugs approved in cancer treatment, three of them—cisplatin, carboplatin, and oxaliplatin—by Food and Drug Administration (FDA) and used worldwide and the other three approved in specific countries—nedaplatin in Japan, lobaplatin in Korea, and heptaplatin in China [10]. Platins are the first-line therapeutics in several cancers either alone, in combination with radiotherapy, or with other antitumor or antiangiogenic drugs [9, 11, 12]. Their cellular effects result from four main steps: (i) internalization, (ii) aquation, (iii) formation of DNA adducts, and (iv) cell response (either survival or apoptosis) [13]. Once inside the cells, the ligands (chloride in cisplatin, dicarboxylate in carboplatin, and oxalate in oxaliplatin) are substituted by water molecules that interact with nucleophilic centers on purine bases of DNA, promoting not only cross-linking of the N7 sites of adjacent guanine nucleobases, but also interstrand crosslinks, inducing severe structural distortion of the double helix. This stalls DNA transcription and arrests the cell cycle at the G2/M transition. DNA repair machinery is recruited, and if unable to repair, cells trigger apoptotic cell death [13]. However, some cells enhance their DNA repair activity becoming resistant to cisplatin that have been associated with patient's relapse [14, 15]. Other DNA damage-independent processes have been proposed such as destabilization of redox homeostasis by increasing the intracellular levels of ROS. Cisplatin metabolism is in part performed by glutathione leading to its decrease, affecting NADPH pools, resulting in dysfunctional mitochondrial redox status, and causing ROS [16]. For all FDA approved platins, the mechanism of action is believed to be very similar, with incremental variations [17, 18]. Carboplatin has less toxicity than cisplatin because 1,1-cyclobutanedicarboxylate is a poorer leaving group than chloride lowering its potency being primarily used for ovarian cancer treatment [19]. Oxaliplatin was the latest approved platinum drug and is a part of the first-line treatment for colorectal cancer. In contrast to cisplatin and carboplatin, oxaliplatin features a quelating nonleaving group, 1,2-diaminocyclohexane (DACH) in place of the two monodentate amine ligands. It also features a bidentate chelating oxalate leaving group ligand [19]. Oxaliplatin does not form adducts as efficient as cisplatin, but the hydrophobicity and size of the DACH group make it more efficient in inhibiting DNA polymerization and repair [3]. Oxaliplatin cellular uptake is active and through copper transporters 1 and 2 and organic cation transporters (OCTs) 1 and 2; the latter explains its efficacy against colorectal cancer (with OCTs overexpression) [9]. Nedaplatin features *cis* ammine nonleaving group ligand (glycolate), associated with its greater water solubility. It has less toxicity than cisplatin and less nephrotoxic and is mainly used in combination therapy to manage urological tumors [20].

Heptaplatin features malonate as a chelating leaving group ligand and a chelating 2-(1-methylethyl)-1,3-dioxolane-4,5-dimethanamine nonleaving group ligand, which forms a seven-membered chelate ring. It is used for gastric cancer, but its advantage over cisplatin

has controversial results in clinical trials [11]. Lobaplatin, a derivative of heptaplatin, fuses a cyclobutene ring to the seven-membered chelate ring instead of a dioxolane with an S-lactate as a leaving group ligand. It was originally approved to manage patients with chronic myelogenous leukemia, small-cell lung cancer, and metastatic cancer showing noncross-resistance to cisplatin [21]. Phase I clinical trial is undergoing to expand its use in combination therapy in solid tumors [22].

Currently, there are other platinum drugs in clinical trials: satraplatin, picoplatin, and two polymer/liposomal-based platinum drugs—ProLindac and Lipoplatin. Satraplatin, bis-(acetato)-ammine-dichloro-(cyclohexylamine) platinum(IV), was enrolled in several Phase I, II and III clinical trials mainly in conjunction with other drugs (e.g., docetaxel, paclitaxel, and capecitabine), but all have been recently terminated or concluded. Satraplatin was administered orally, absorbed by the gastrointestinal mucosa, and reduced in the bloodstream into more than six different Pt(II) complexes of which cis ammine dichloride(cyclohexylamine)-platinum(II) is the most important and showed anticancer activity against platinum sensitive and resistant cell lines. One of the most relevant Phase III trials evaluated a combination of satraplatin and prednisone against hormone refractory prostate cancer who had progressed after initial chemotherapy. In this study, 40% of patients had reduced risk of prostate cancer progression [23].

Picoplatin, cis-ammine-dichloride(2-methylpyridine) platinum(II), has a pyridine ring nearly perpendicular to the platinum plane, thus positioning the ligand's methylpyridine in a position that protects the metal center from nucleophilic attacks, specially by thiols. It has shown ability to overcome platinum drug resistance [23]. In Phase I clinical trials, picoplatin showed some side effects such as neutropenia, thrombocytopenia, nausea, and vomiting; however, no neuro- or nephrotoxicity was observed, and in three different Phase II clinical trials, it showed reduced efficacy as first- and second-line therapy. It is currently undergoing Phase I and Phase II studies as a combination therapy for colorectal cancer [24, 25].

Lipoplatin is a liposomal nanoparticle formulation of cisplatin with dipalmitoyl phosphatidyl glycerol (DPPG), soy phosphatidyl choline (SPC-3), cholesterol, and methoxy polyethylene glycol (mPEG2000)-distearoyl phosphatidylethanolamine (DSPE). The PEG allows cisplatin to evade the immune system increasing the circulation time. Lipoplatin fuses with cancer cells through DPPG, a fusogenic lipid embedded in the lipid bilayer allowing the release of cisplatin inside the cytoplasm of tumor cells [26]. It has successfully finished Phase III clinical trials showing superior effects when in combination with paclitaxel compared to cisplatin. Due to enhanced permeability and retention (EPR) effect, the nanoparticles are concentrated inside the tumor with 40- to 200-fold higher platinum concentration than healthy tissues [26].

ProLindac is a nanopolymer composed of [Pt(R,R-dach)], the active group of oxaliplatin, bound to an hydrophilic biocompatible polymer [hydroxypropylmethacrylamide (HPMA)] to better increase tumor targeting by EPR. The polymer segments are connected by amidomalonate chelating group and a triglycine spacer. The amidomalonate-platinum chelate bond breaks at low pH for releasing platinum complex in the hypoxic tumor microenvironment. ProLindac showed activity against cisplatin resistant cell lines [27]. Clinical trials showed no acute significant adverse effects. ProLindac has currently finished Phase II in combination with paclitaxel in the second-line treatment of pretreated advanced ovarian cancer with 66% of all patients achieving disease stabilization [27].

Despite all advances, platinum complexes still suffer from severe side effects as well as intrinsic or acquired multidrug drug resistance (MDR), limiting its applications. To surpass this, novel strategies are being explored. Some examples include the "rule-breaking" platinum compounds: complexes with glucose ligands, complexes that display trans geometries [28], positively charged molecules, Pt(IV) prodrugs that become reduced to Pt(II) inside the cells, and photo-active molecules, among others [6, 29]. Of those we will highlight three approaches, first the tentative to vectorize Pt(II) to cancer cells through glucose as a ligand. Cancer cells overexpress glucose transporters making them an ideal target for active therapy [29]. Patra and coworkers showed that this is a viable conjugation with increased accumulation of platinum in tumor cells and comparable efficacy *in vivo* with oxaliplatin [29]. Later, Lippard et al. described a Pt(IV)-(D)-1methyltryptophan conjugate coupled with an indoleamine-2,3-dioxygenase (IDO) ligand. IDO is an inhibitory immune checkpoint target that enhances antitumor immune response, thus increasing the efficacy of common chemotherapeutics and radiotherapy. This prodrug killed hormone-dependent, cisplatin resistant, and human ovarian cancer cells, by deregulating the autocrine-signaling loop IDO-AHR-IL6 and paving the way to new platinum immune-chemotherapy [30]. A photoactive platinum(IV) anticancer complex trans-$[Pt(N_3)_2(OH)_2(Py)_2]$ was used in photodynamic therapy. Upon irradiation with blue light, it binds to amino acid residues of thioredoxin, a multifunctional enzyme that regulates gene transcription, redox signaling, and cell growth, inhibiting cell apoptosis, overexpressed in several cancers, leading to an increase oxidative stress persistent for more than 48 h *in vitro*, with a potent antiproliferative activity. The complex might be suitable for treatment of peripheral cancers such as bladder and esophageal [10, 31].

1.2. Ruthenium

Ruthenium complexes are already recognized as an effective alternative to platinum complexes, providing different mechanisms of action, different spectrum of activities, and potential to overcome platinum associated MDR [32]. Ruthenium has numerous properties: (i) they can exist in multiple oxidation states (II, III, and IV), all accessible under physiologic conditions, an advantage in the reducing environment of cancer tissues; (ii) they have the ability to coordinate ligands that can modulate their activity and have the same kinetics of ligand substitution in aqueous medium as that of Pt(II) complexes [33]; (iii) they have the possibility of occupying a large number of spatial positions due to its octahedral coordination geometry allowing to explore more and different ligands compared to platinum complexes; (iv) they reduced toxicity compared to platinum compounds and attributed to their ability to mimic iron binding to serum transferrin [34, 35] with higher selectivity for their targets due to selective uptake by the tumor compared with healthy tissues [36].

In the last year, several ruthenium compounds have been synthetized, and their antiproliferative activities and mechanism of action against several tumors characterized [8, 37–39], where cell membrane changes, cell death due to intrinsic apoptosis pathway and/or autophagic pathway, ROS induction, inhibition of topoisomerase I and II might be the cause of their cytotoxicity/antiproliferative activities [8, 39–44]. KP1019, trans-$[Ru(In)_2Cl_4]$ [InH] (In = indazole), is known to bind transferrin and causes apoptosis through the mitochondrial pathway promoting the formation of ROS [45]. $[Ru(bpy)(phpy)(dppz)]^+$ has found to be very cytotoxic against cancer cell line, the high affinity that presents for DNA leads to damages in the transcription

factor NF-κB [46]. DW1/2 inhibits PI3K and GSK3-β, which leads to apoptosis mediated by the mitochondrial and p53 pathways [34]. Several Ru(II) complexes demonstrate high-binding affinity to DNA [47–49]. Some of these complexes appear to act by intercalation in the tumor cells, although in some cases it has been demonstrated that they can operate by DNA photocleavage [50–52]. Ruthenium complexes with polypyridine ligands such as 2,2-bipyridine (bpy), 1,10-phenanthroline (phen), and 2,2':6,2"-terpyridine (terpy) ligands have been largely explored as molecular DNA probes due to their photophysical properties and the ability of polypyridyl ligands to intercalate with DNA [35, 38, 53–55]. This type of ligands stabilizes the ruthenium metal ion in the oxidation state (II), resulting in solution-stable complexes of aqueous solution. Polypyridine ligands can confer photoluminescent properties to Ru(II) complexes, through a charge transfer between the metal and the ligand [56].

Cellular uptake of ruthenium complexes may occur through two mechanisms, energy dependent (endocytosis and active transport) and energy independent (facilitated diffusion and passive diffusion) [40]. For example, the complex $[Ru(phen)_2(mitatp)]^{2+}$ exhibited significant antitumor activity against several tumor cells, and flow cytometry experiments showed that the ruthenium compounds penetrate the cell membrane and accumulate in the nucleus, leading to cell cycle arrest and apoptosis [57]. The ruthenium compound $[Ru(DIP)_2(dppz)]^{2+}$ showed cellular uptake through an energy-independent process [58]. Transferrin is used to transport iron centers into the cell, where the cancer cells have a high number of transferrin receptors compared to healthy cells [59]. Ruthenium complexes are transported by transferrin into cells by binding to two ruthenium centers. Upon entry into cells, the complex is released at acidic pH. For example, KP1019 can use iron transport systems to locate itself inside the cell, binding to the DNA with a preference shown for G and A residues [36].

Several other ruthenium(II) metal complexes have been described in the literature that offers the possibility of designing molecules suitable for binding to specific biological targets, due to the fact that they exhibit a wide range of coordination numbers and possible geometries that allow the spatial organization of the different anions and organic ligands (for a review, See [60–64]). Examples with *in vitro* and *in vivo* antitumor activities are ruthenium(II) (η^6-arene) complexes, such as [Ru (η^6-C_6H_6) (dien)] Cl (dien = ethylenediamine), and RAPTA, ruthenium(II)-arene complexes with the monodent ligand PTA (PTA = 1,3,5-triaza-7-phosphoadamantene) [46–48]. Stable bidentate chelating ligands (e.g., dien), more hydrophobic arene ligand (tetrahydroanthracene), and chloride ligand were associated with complexes with increased activity [65]. The RAPTA family comprises a monodent ligand PTA and the η6-arene ligand. Recently, the RAPTA-C complex has been shown to reduce the growth of primary tumors in preclinical models in ovarian and colorectal carcinomas through an antiangiogenic mechanism [66]. RAPTA-C binds selectively to the nucleus of the histone protein in the chromatin, resulting in the chloride binding of the ligands, and the inhibition of moderate growth in primary tumors *in vivo* is translated [67]. Sadler and coworkers studied ruthenium complexes (II)-arene with dien ligands ([Ru (n-6-arene) Cl (dien)] and demonstrated to be stable and soluble in water, exhibiting anticancer activity both *in vitro* and *in vivo*, including activity against cisplatin-resistant cancer cells. The dien ligand was used because of the similarities presented with the ammonium ligands in cisplatin, which are thought to contribute for cytotoxicity, forming a hydrogen bond with the DNA [68].

Of the numerous ruthenium complexes with antitumor action studied, only five Ru(III) complexes have entered clinical trials: trans-[RuCl$_4$ (DMSO) (Im)] [ImH] (NAMI-A, Im = imidazole), KP1019, NKP-1339 (KP1019 sodium salt), KP1339, and Ru(II)-based therapeutic TLD1433 [35, 69]. NAMI-A is an antimetastatic compound that reduces the metastases and prevents the spread of secondary tumors [70, 71], whereas KP1019 is a cytotoxic compound effective against primary tumors [72]. NAMI-A and KP1019 are prodrugs that are activated *in vivo* by reduction to Ru(II) and well tolerated in clinical applications. The exact mode of action of both complexes is not clear, but it is known that they interact with DNA. NAMI-A and KP1019 successfully completed Phase I clinical trials; however, NAMI-A was recently withdrawn after Phase II due to its poor efficacy [69, 73]. In addition, the combination of gemcitabine with NAMI-A allows entry into a new Phase II [70], but the combination was not well tolerated by patients and did not continue to Phase III [73]. KP1019 demonstrated low solubility that limited further development. NKP-1339 is a GRP78-targeted ruthenium-based anticancer compound and administered intravenously with promising results in solid tumors, such as colorectal carcinoma and neuroendocrine tumors [74]. The results obtained so far in clinical trials with some of these Ru(III) drug candidates fostered the increased interest in Ru(II) candidates for cancer therapy [40]. Recently, TLD1433, a mixed ligand Ru(II)-polypyridyl compound, entered Phase I of clinical trials for nonmuscle invasive bladder cancer treatment with photodynamic therapy (PDT) [75].

The interaction between the compounds and the plasma proteins is recognized as a crucial step in the access to bioavailability of metal complexes [32, 76, 77]. Serum albumin is the major protein in blood plasma acting as the carrier and distributor of many drugs because of its ability to bind reversibly to a variety of exogenous compounds [78, 79]. Their binding may increase solubility and prolong the *in vivo* half-life of the compounds, with a specific drug release at the target [77, 79, 80]. The interaction between compounds and proteins is usually analyzed by electronic absorption and fluorescence quenching. As various drugs bind to proteins in plasma, there has been an increasing investigation in the field of plasma protein binding (PPB). Ru(II) compounds bind preferentially to human serum albumin (HSA) and serum transferrin (Tf). These binding affinities showed that HSA appears to be the better partner [81]. KP1019 is known to strongly bind to serum proteins and hamper P-glycoprotein-mediated efflux, making this ruthenium therapeutic attractive for multidrug-resistant tumor therapy [82]. RAPTA-C has shown a binding affinity to thioredoxin reductase and cathepsin B [83].

More recently, nanotechnology has provided numerous nanoplatforms that may act as vehicles for the active and more specific deliver of ruthenium(II) complexes toward cancer cells, namely Ru(II)—selenium nanoparticles, Ru(II)—gold nanomaterials, and Ru(II)—silica composite [39, 78–80]. Recently, Ru(II)-polypyridyl/thiol-selenium nanoparticles were found to be a powerful theranostic system, acting simultaneously as an imaging agent while fostering cancer cell death [84]. Chen and collaborators described a nanoparticle/Ru(II) polypyridyl system that is able to release a DNA-binding agent [Ru(bpy)$_2$(H2O)$_2$]$^{2+}$ upon laser irradiation [85]. In this sight, this nanosystem might improve ruthenium complex stability, distribution, and delivery specifically toward cancer cells providing a new avenue as a future therapeutic strategy [86].

1.3. Copper

Copper is an essential element in the organism, important for the function of enzymes and pro-teins involved in energy metabolism, respiration, and DNA synthesis [87]. This metal acts as a catalytic cofactor in several enzymes and is involved in hemoglobin formation, xenobiotics, catecholamines biosynthesis, collagen crosslinking, and oxidation-reduction reactions in which it reacts with molecular oxygen for the production of free radicals [87]. Copper-dependent enzymes, such as cytochrome C oxidase, superoxide dismutase, ferroxidases, monoamine oxidase, and dopamine b-monooxygenase, are involved in ROS neutralization. In addition, efflux of anticancer drugs such as cisplatin employs specific copper efflux transporters ATP7A and ATP7B, together with multidrug efflux pumps belonging to the ABC superfamily [e.g., P-glycoprotein (Pgp, ABCB1) and multidrug resistance protein 2 (MRP2, ABCC2)] [88, 89].

Copper complexes are the most studied transition metal complexes for their antitumor proper-ties because endogenous metal ions may lead to less systemic toxicity. The properties of the copper complexes are determined by the nature of their ligands, which themselves may exhibit antiproliferative activity [87]. Several Cu(II) complexes with a variety of ligands containing N, S, or O have been developed, demonstrating different mechanisms for their antitumor activity [6, 90, 91]. The ligands neutralize the electrical charge of the copper ion and facilitate the transport of the complex through the cell membrane, interacting noncovalently with proteins or intercalating into the DNA molecule [92]. Copper complexes are capable of inducing DNA breaks through hydrolytic or oxidative cleavages [93–97]. Recently, a copper(II) complex $[Cu(C_{20}H_{22}NO_3)_2]\cdot H_2O$ was synthesized, and its mechanism of action evaluated by spectroscopic methods, showing that the complex binds to calf-thymus DNA through a partial intercalation and presents a static quenching process as binding mechanism. The cytotoxicity evaluation in cancer cell lines showed an enhanced cytotoxicity compared with the Schiff base ligand; thus, a positive synergetic effect may be occurring [98]. Horman et al. developed functionalized Cu(II) cyclen complexes with three (2-anthraquinonyl)methyl substituents that efficiently inhibited DNA and RNA syntheses resulting in high cytotoxicity accompanied by DNA condensation/aggregation phenomena [99]. Sigman et al. reported the first set of copper complexes with phen ligand with good cytotoxic activities [100]. The complex with two phen ligands is capable of cleaving the DNA by binding to the deoxyribose units, acting as a chemical nuclease [101]. Trejo-Solis et al. synthesized a class of Cu(II) complexes having the general formula [Cu (NN) (AA)] NO_3, wherein NN is phen or bipy, and AA is a nitrogen-oxygen donor or oxygen-oxygen donor ligand that is capable of inducing autophagy and programmed cell death cells by activation of ROS and JNK in glioma cells [102]. Another study demonstrated the antitumor properties of phen Cu(II) complexes with different alkyl chains. One of them showed a promising anticancer activity as well as antimetastatic and antiangiogenic potential, evidencing the versatility of Cu(II) complexes for cancer therapy [103].

A complex of Topo-I inhibitors, [Cu (N) L] Cl (N = phen, bipy or 5,50-dimethyl-2,20-bipyridine; L = doubly 5-triphenylphosphonium-methyl)-salicylaldehyde deprotonated hyde-benzoyl hydrazone, exhibits good cytotoxic activity against human lung and prostate adenocarci-noma cell lines [104], with the most active compound of this family being the one containing the fen motif.

Proteasome inhibition is another mechanism by which copper complexes exercise their antitu-mor activity. For example, Cu(II) complexes containing phen, 8-hydroxyquinolinate, pyrrolidine

dithiocarbamate, or (pyridine-2-ylmethylamino)-methylphenolate have been shown to induce apoptosis by proteasome inhibition [105].

Copper complexes with thiosemicarbazone ligands have antitumor activity by inhibiting enzymatic activity and inducing cell apoptosis [106]. A Cu pro-drug derived from thiosemi-carbazone based on the His146 residue in the IB subdomain of palmitic acid (PA)-modified human serum albumin (HSA-PA) was able to kill cancer cell by targeting DNA and proteins. Also, the efficient delivery of the Cu pro-drug was improved when the leaving group was replaced with His146 and coordinated with Cu^{2+} to form the HSA − PA complex. The HSA-PA complex showed better tolerance and a higher drug accumulation in the tumor, a stronger capacity for inhibiting tumor growth, and a lower toxicity in other tissues [107].

Casiopeína IIgly, one of the most promising drugs, shows a strong inhibition of cell proliferation against a glioma C6 cell line, *in vivo* as well as *in vitro*. This drug promotes cell death by an increase of ROS, with the consequence mitochondria damage followed by apoptosis caused through, caspase dependent and caspase independent pathways. Cas IIgly prevents malignant cells to continue with their life cycle, by inhibiting estrogen-mediated G1/S cell cycle progression [108, 109]. Currently, Cas IIIia is in Phase I clinical trials in Mexico, and experimental evidences demonstrated that the main mechanism of action is related to generation of ROS and DNA damage, through intercalation process [110].

Copper complexes are normally water insoluble. Therefore, the use of polymers/nanoparticles with suitable size can increase cellular internalization, distribution, and targeting of tumor cells with reduced toxicity in healthy cells. Intramolecular copper containing amphiphilic hyperbranched polytriazoles (mPEGhb-S-S-PTAs) was synthesized via Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC) reaction, forming copper-triazole coordination polyprodrugs that were used to delivery copper and for label-free cellular bioimaging, a novel theranostic (diagnostic and therapy simultaneously) application toward cancer therapy [111].

1.4. Vanadium

The major molecular targets for anticancer effects of vanadium compounds are the breakdown of cellular metabolism through the generation of ROS, GSH depletion, changes in cellular organelles, some pathways of signal transduction, and caspases, which can lead to cell cycle arrest and cell death. Pombeiro et al. synthesized two water-soluble heterometallic potassium-dioxidovanadium(V) complexes, with an antiproliferative potential toward human colorectal carcinoma, lung, and breast adenocarcinoma cell lines. They demonstrate that the complex has a very high cytotoxic potential in the HCT116 cell line, a positive trait for future *in vivo* studies [112].

Vanadocene is a metallocene with a metal ion sandwiched between two cyclopentadienyl rings. Vanadocene dichloride, $[VCp_2Cl_2]$, was the first vanadocene that showed interesting results in preclinical studies [113]. This complex showed a strong activity *in vitro* against several tumor cells. In addition, *in vivo* studies demonstrated antitumor properties with vanadocene dichloride [114]. Some vanadocene derivatives present cytotoxic effect against T-lymphocytic leukemia cells, where the mechanism used evolves the DNA damage and p53 activation [115]. On the other hand, vanadocenes are effective agents against human testicular

cell lines [36]. Vanadocenes containing fen ligands are promising anticancer agents, due to their high anticancer activity, solubility, and stability [37]. Currently, there are two complexes under preclinical trial [VCp_2Cl_2] and Metvan, bis(4,7-dimethyl-1,10-phenanthroline) sulfatooxovanadium(IV). Metvan induces cell damage through apoptosis in several cell lines, with a special cytotoxic in ovarian and testicular cancer cell resistant to cisplatin. *In vivo* models, Metvan shows a promising anticancer activity on glioblastoma and breast cancer [116]. Cortizo et al. developed a delivery system of vanadium(IV) with aspirin (VOAspi) functionalized with poly(beta-propiolactone) (PbetaPL) films. VOAspi-PbetaPL film inhibited cell proliferation of UMR106 osteosarcoma cells in a dose-response manner [117].

1.5. Iridium

Iridium complexes are emerging as a class of anticancer agents. Novohradsky et al. studied the mechanisms of new cytotoxic iridium(III) complex in cancer cells. A half-sandwich cyclometallated Ir(III) complex [(η^5-Cp*)(Ir)(7,8-benzoquinoline)Cl] bearing a C^N chelating ligand was designed and studied its uptake in ovarian cancer cells [118]. The temperature dependence and the coincubation with different substrates (such as ouabain, 2-deoxy-D-glucose and oligomycin, verapamil, reversan, and buthionine sulfoximine) indicate that an energy-independent passive diffusion and an energy-dependent transport play a partial role in the complex accumulation. Moreover, the competition experiments with $CuCl_2$ suggested an involvement of Ctr1 pathway in the compound's uptake. The authors highlighted the importance of ATP-dependent processes and transport proteins, such as Na/K-ATPase for accumulation of Ir complexes. The iridium complexes may exert anticancer efficacy through various mechanisms including modulation of cellular redox reactions and inhibition of protein kinases. Recently, the cyclometalated iridium(III) complexes have gained increasing attention in bioimaging and biosensing applications due to their luminescence properties, for example, large Stokes shifts, long-lived luminescence, high quantum yields, and cell permeability [119].

1.6. Titanium

Since the 1970s, when the first titanium complex arises, a series of complexes containing titanium, Ti, as a metal center have been synthesized and characterized, and some of them were shown to possess a wide spectrum of antitumor properties. Indeed, titanium complexes such as titanocene dichloride and octahedral species budotitane are promising anticancer results being translated to (pre)- and clinical trials. Preclinical trials had shown efficacy in a broad of tumors [113, 120]. Budotitane was investigated in Phase I trial, and pharmacokinetic study administered as i.v. infusion twice weekly with a starting dose of 100 mg/m^2. However, no response was observed, but 17 of 18 patients have been resistant as they had received prior chemotherapy [121]. Titanocene dichloride showed promising results in Phase I trials with patients suffering from various cancer types. In one study, 40 patients with refractory solid malignancies the titanocene dichloride revealed a two minor responses (in bladder carcinoma and in nonsmall cell lung cancer), with dose-limiting toxicity side effect was nephrotoxicity [122]. Phase II trials were conducted at 270 mg/m^2 every 3 weeks with 14 patients suffering from metastatic renal-cell carcinoma [123]. However, no significant response was noted, and the effectiveness of the treatment was limited in both cases. The instability under physiological

condition and low solubility in aqueous media were the reasons of low activity in Phase II trials [124]. On the other hand, it was found that titanocene dichloride binds to DNA through the phosphate backbone, inhibiting DNA synthesis and leading to cell death [125]. The binding studies allowed to conclude that the cellular uptake of titanocene dichloride can be mediated by the iron transferrin transporter protein [126].

1.7. Gallium

The biological activity of gallium(III) arises from chemical similarity with iron(III). They have similar ionic radius, ionization potential, and electronic affinity [127]. However, the principal difference is that Ga(III) is nonreducible, whereas Fe(III) is reduced to Fe(II) under physiological condition [63].

Clinical Phase I and Phase II studies were performed on gallium nitrate, gallium chloride, and gallium maltolate. The first-generation gallium nitrate demonstrated, in several clinical trials, efficacy against bladder cancer and urothelium carcinoma, but these studies were discontinued due to ocular toxicity. The most promising results, come from the combination with vinblastine and ifosfamide, in a Phase II trial GA were effective in metastatic urothelial carcinomas at a dose of 300 mg/m^2/24 h for 5 consecutive days. However, the duration of the responses was short at 20 weeks. This was associated with a high toxicity, and 11 of 27 patients had anemia and renal function alteration [128]. Oral gallium chloride seems to potentiate the action of cisplatin and etoposide. Oral gallium maltolate demonstrated higher bioavailability than gallium chloride. Preclinical studies have demonstrated synergy between Ga and paclitaxel [129]/gemcitabine [130]. Currently, two compounds are in clinical trials, gallium tris-8-quinolinolate (KP46) and gallium tris-maltolate. KP46 contains the metal chelating agent 8-hydroxyquinoline and has an inhibitory effect in cell growth proliferation *in vitro* and *in vivo* superior to gallium salt. An oral formulation of KP46 demonstrates a pattern of cytotoxicity with synergism across a broad range of antitumor agents targeting the endoplasmic reticulum in multiple tumor types [131, 132]. Gallium maltolate, (3-hydroxy-2-methyl-4H-pyran-4-onato) gallium, is an oral formulation for therapeutic use. This compound entry in Phase I demonstrated an oral bioavailability of about 27–47%. At doses as high as 3500 mg/day for 28-day cycles, no dose-limiting toxicity or drug-related adverse effects were observed [133]. However, this study was discontinued, and no new results were published. The mechanism of action of gallium(III) has been studied, and Ga^{3+} ions normally compete with Fe^{3+} for binding transferrin. Analyzing the biological pathways of gallium(III), it seems that its mechanism of action is associated with the inhibition of ribonucleotide reductase (RR). The enzyme RR produces during the transition from G1 to S phase of the cell cycle and catalyzes the conversion of ribonucleotides to deoxyribonucleotides [63].

1.8. Osmium

Osmium(II) complexes are the heavier congeners of ruthenium, exhibit slower kinetic than ruthenium, and are substitution-inert (Os(II) and Os(III) complexes). In addition, they offer a more complex interaction with double-helical DNA. However, the reactivity of the Os(II)-arene complexes can be adjusted by the chemistry of the aqueous solution. Sadler et al. synthesized

and developed osmium(II) arene complexes and proved their anticancer properties by systematically varying the chelating ligand in kinetics and thermodynamic reaction of the complexes [134, 135]. These series of N,O-chelates ligands are important choices in the stability and cancer toxicity [134, 136]. DNA-binding studies on a series of complexes of the type osmium(II)-arene have shown that these complexes bind to polymeric DNA, where some coordinate with guanine and others undergo quantitative reaction with DNA [137].

Recent work from Sadler and coworkers showed the distribution of osmium in cancer cells treated with relevant doses of Os^{II} arene azopyridine complex by using X-ray fluorescence nanoprobe. This analysis shows localization of Os in mitochondria and not in nucleus and mobilization of calcium from endoplasmic reticulum [138]. Osmium compounds have been extensively exploited because they are capable to induce the formation of ROS, targeting mitochondria, and oxidize NADH to NAD^+ that lead to interference in the redox signaling pathways in cancer cells and are capable to interfere with cell cycle [69, 139]. In the last year, osmium analogs of the ruthenium anticancer agents, such as RAPTA-C, NAMI-A, and KP1019, have been developed. Therefore, osmium complexes demonstrated a good stability and inertness toward hydrolysis or ligand substitution. These are promising results for a future understanding of the mechanism of action of osmium compounds [134].

1.9. Gold

Gold in its elemental form is stable in an extensive range of conditions. Gold oxidation states range from −1 to +5, but I and III are the most relevant. The coordination geometry of gold(I) complexes is not only generally linear accepting two ligands, but it can also coordinate three (trigonal) or four (tetragonal) ligands. Au(I) prefers to bind with thiolates, cyanides, phosphines, and soft halides [140]. Mainly due to the success of platinum compounds, and that gold(III) is isoelectronic with platinum(II) and forms similar square-planar complexes, a large number of gold(I) and gold(III) compounds have been studied for their anticancer activity [6]. Till now, auranofin [tetra-O-acetyl-b-D-(glucopyranosyl)thio](triethylphosphine) is the only gold compound ever approved. Used since 1985 as oral drug for the treatment of rheumatoid arthritis, its side effects, and restricted efficacy, it is only used for severe cases [141]. Some studies proposed its use as anticancer drug, and it is currently under several Phase I and II clinical trials to treat chronic lymphocytic leukemia (NCT01419691), lung cancer (NCT01737502), and glioblastoma (Glioblastoma).

The mode of action of auranofin is still not clear, and it is thought to be related with inhibition of thioredoxin reductase (TrxR). As gold has a high affinity for thiol and selenol groups, it tends to bind to amino acid residues, forming stable, irreversible adducts. TrxR is an essential enzyme in many cellular processes, mainly in balancing the redox homeostasis, controlling the level of ROS, and preventing DNA damage. As cancer cells tend to overexpress redox enzymes, they are mostly affected by auranofin. Selenoproteins, such as TrxR, when inhibited by auranofin compromise the mitochondria, leading to production of ROS that cause cellular oxidative stress and ultimately intrinsic apoptosis [141]. Several reports show the effect of auranofin against several tumors *in vitro*, including cisplatin resistant tumors [141]. Aurothiomalate is another gold compound, which is currently investigated in Phase I clinical trials to treat patients with advanced nonsmall cell lung cancer (NCT00575393). Its mechanism of action seems to be linked with protein kinase Ciota, which is overexpressed in

nonsmall cell lung cancer, ovarian, and pancreatic cancers, playing a critical role in oncogenesis. Aurothiomalate has been shown to inhibit PKCiota signaling having potent antitumor activity in preclinical studies [142, 143]. Using the same mechanism, aurothioglucose also showed antitumor efficacy *in vitro* against nonsmall cell lung cancer cells [144]. For the cellular uptake, it was proposed that Au(I) enters the cell through albumin bond or through other thiol metabolites [144]. A recent study by Mármol proposes an alkynyl gold(I) complex [Au(C ≡ C-2-NC$_5$H$_4$)(PTA)] to treat colorectal carcinoma. In their study, using Caco-2 cells, gold complex enters the mitochondria and disrupts its normal function, triggering the necroptosis. Necrose-inducing compounds are mainly interesting as they are an alternative chemotherapy for apoptosis resistance tumors [145].

1.10. Other complexes

Cobalt complexes have normally two accessible oxidation states. Co(III) is kinetically inert, whereas Co(II) is labile. Some studies demonstrated that Co(III) complexes can act as carriers for selective delivery of drugs [69]. However, when Co(III) is reduced to Co(II), the molecule is released in its active form and can kill cancer cells [146]. Hexacarbonyl dicobalt and alkynes exhibit a promising activity of antitumor activity [147]. The activity is most pronounced when the alkyne is the propargyl ester of aspirin (CoASS), which inhibits the cyclooxygenase enzymes COX-1 and COX-2 [147, 148]. It was shown that CoASS itself inhibits COX-1 and COX-2 more strongly than ASA alone and enhanced the cytotoxicity against breast cancer cell line [148]. The development of new complexes bearing different types of pyrazole-based ligands demonstrated the potential use of these complexes as antiproliferative agents [149].

A new compound CoCl(H$_2$O)(phendione)$_2$][BF$_4$] (phendione = 1,10-phenanthroline-5,6-dione) (TS265) was demonstrated to induce cell cycle arrest in S phase with a subsequent cell death by apoptosis and high cytotoxicity against colorectal carcinoma cell [76]. Fernandes et al. evaluated the efficiency of two metal compounds [Zn(DION)$_2$]Cl (TS262, DION = 1,10-phenanthroline-5,6-dione) and TS265 and the application of AuNPs as a drug delivery system to improve the anticancer efficacy of these compounds in a new canine mammary tumor (FR37-CMT) [150]. The same group formulated a multifunctional nanovectorization system using gold nanoparticles to enhance cytotoxic of TS265. This nanoformulation efficient delivered the cytotoxic cargo in a controlled selective manner [151]. Two mononuclear Ni^{II} and Mn^{II} compounds with a "scorpionate" type precursor demonstrated to induce damage in ovarian cancer cells through ROS accumulation. In addition, the mononuclear Ni^{II} compound induced mitochondria dysfunction and autophagy cell death [5].

Although the intensive study of transition metals is focused on a specific biomolecular target, some complexes are developed for other purposes. For example, palladium-porphyrin complex (TOOKAD-soluble) acts as a photosensitizer and has progressed to Phase III clinical trial for the photodynamic treatment of prostate cancer (NCT01875393). Phase II clinical trials were evaluated the efficacy and safety of a single dose of the drug and light dosage combination of TOOKAD® Soluble in the focal treatment of patients with localized prostate cancer, 6 months after treatment. Positive results obtained at 6-month negative biopsies were acquire. This complex has a dual role; that is, it provides the ideal photophysical properties to the porphyrin and is inert enough not to be displaced during therapy (**Table 1**) [152].

Name	Description	Target cancer	Approved/clinical trial	Refs.
Platinol	Cisplatin	Metastatic testicular, ovarian and bladder cancers	FDA approval	[153]
Paraplatin	Carboplatin	Advanced ovarian cancer	FDA approval	[153]
Eloxatin	Oxaliplatin	Advanced colorectal cancer in combination with 5-FU and leucovorin	FDA approval	[153]
Aqupla	Nedaplatin	Urological tumors	Approved in Japan	[153]
Lobaplatin	1,2-Diammino-l-methylcyclobutane-platinum(II)-lactate	Inoperable metastatic breast and small cell lung cancer	Approved in China	[153]
Heptaplatin	Cisplatin analogs	Gastric cancer	Approved in Korea	[154]
Picoplatin	2-Methylpyridine analog of cisplatin	Colorectal cancer in combination with 5-FU and leucovorin	Phase II	[11]
Satraplatin	Bis-(acetate)-ammine dichloro-(cyclohexylamine) platinum(IV)	Colorectal cancer in combination with 5-FU and leucovorin/prostate cancer in combination with docetaxel	Phase II/III	[153]
Lipoplatin	Liposomal form of cisplatin	Locally advanced gastric cancer/squamous cell carcinoma of head and neck	Phase II/III	[155]
ProLindac	Oxaliplatin with hydrophilic polymer	Ovarian cancer/head and neck cancer	Phase II/III	[153]
NAMIA-A	$RuCl_4$ (DMSO) (Im)	Metastatic tumor (lung, colorectal, melanoma, ovarian, and pancreatic) in combination with gemcitabine	Phase II	[156]
KP1019	Trans-$[Ru(In)_2 Cl_4]$ [InH]	Advanced colorectal cancer	Phase I	[157]
NKP-1339	KP1019 sodium salt	Colorectal carcinoma and neuroendocrine tumors	Phase I	[74]
TLD1433	Ru(II)-polypyridyl compound	Nonmuscle invasive bladder cancer treatment with photodynamic therapy (PDT)	Phase I	[75]
Aurothiomalate	Gold compound	Advanced nonsmall cell lung cancer	Phase I	[158]
Auranofin	TetraO-acetyl-b-D-(glucopyranosyl)thio] (triethylphosphine)	Chronic lymphocytic leukemia, lung cancer, and glioblastoma	Phase I/II	[141]
CasII-gly	Casiopeína	Cervical cancer cell	Phase I in Mexico	[159]
KP46	Gallium tris-8-quinolinolate	Solid tumors	Phase I	[132]

Name	Description	Target cancer	Approved/clinical trial	Refs.
TOOKAD® Soluble	Palladium-porphyrin complex	palladium-porphyrin complex	Phase III	[152]
Gallium tris-maltolate	(3-Hydroxy-2-methyl-4H-pyran-4-onato) gallium	Hepatocellular carcinoma	Phase I	[160]

Table 1. Clinical approved/undergoing clinical trials and metal compounds for anticancer therapeutic application.

2. Conclusion

Since the discovery of cisplatin, coordination complexes have been widely used in cancer therapy. Thirty years after its approval as a chemotherapeutic agent by the FDA, cisplatin remains to be one of the best-selling anticancer agents. Thousands of metal compounds have been described since then with only a few passing for clinical trials and even less getting approval. Both the high costs translating a promising drug to the clinic and the focus of pharma to go for new targeted therapies with minimum side effects instead of new cytotoxic agents can explain the current stall in the discovery of novel metal anticancer drugs. Despite the significant efforts in cancer treatment to increase efficacy without promoting side effects and/or resistance by cancer cells, cancer remains one of the major causes of death worldwide. To overcome this fatality, the identification of unique cellular and biochemical features of each tumor and the knowledge of the molecular mechanisms and biological targets of anticancer agents have, together, brought up the necessity for both synthesis and evaluation of new compounds with more promising antiproliferative potential with specific intracellular targets in cancer cells. The success of clinical treatment sparked interest in platinum compounds and other complexes (Ru, Cu, Au, and Co) containing metal ions to be used as anticancer agents. Well-established *in vitro* and *in vivo* studies, such as those shown in this chapter, are extremely important because the interest of a better quality of treatment is increasingly demanded. In addition to the development of more effective drugs, novel nanoscale drug delivery systems showing improved pharmacokinetic and pharmacodynamic properties, such as increased bioavailability, have emerged in the last decade as promising solutions for the required therapeutic efficacy. Combination of new metal complexes with known chemotherapeutic agents already in the market targeting different cellular pathways in a nanostructure may provide a new avenue and the future for cancer therapy.

Acknowledgements

Conflict of interest

Authors declare no conflict of interests.

Author details

Pedro Pedrosa†, Andreia Carvalho†, Pedro V. Baptista and Alexandra R. Fernandes*

*Address all correspondence to: ma.fernandes@fct.unl.pt

UCIBIO, Department of Life Sciences, Faculty of Science and Technology, NOVA University of Lisbon, Caparica, Portugal

† Both authors contributed equally

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