New Platinum and Ruthenium Complexes - the Latest Class of Potential Chemotherapeutic Drugs - a Review of Recent Developments in the Field

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Abstract: New Platinum and Ruthenium complexes display antitumour and antimetastatic potentials and lower host toxicities. This mini-review examines some the more recent developments in this field, and explores their interactions with biologically-relevant species. The article also refers to more recent work in the area of molybdenum and copper(II) chemistry.

Keywords: Cisplatin, BBR3464, picoplatin, satraplatin, lipoplatin, NAMI-A, KP1019, RAPTA, cancer, chemotherapeutics, apoptosis.

INTRODUCTION

In recent years, the worldwide success of the anticancer drug, cisplatin has caused a veritable explosion of research in medicinal bioinorganic chemistry [1]. The discovery of cisplatin serves as a prime example of a scientific accident. In 1964, American biophysicist Barnett Rosenberg and his colleagues at Michigan State University, East Lansing, USA, examined the effect of an electrical field on the growth of bacteria. They suspended a bacterial culture between two Platinum electrodes, and after applying an electric field for one hour, discovered that the bacterial cells stopped dividing. The inhibition of cell division involved some kind of Platinum-based complex derived from the electrodes. This led Rosenburg to discover a Platinum-based anticancer drug, namely, cisplatin (Fig. (**1**)), or *cis*-diamminedichloroplatinum(II), which has the formula, $[Pt(NH_3)_2Cl_2]$. This complex can exist in three potential isomers, two geometrical isomers, *cis*-diamminedichloroplatinum(II), *trans*-diamminedichloroplatinum(II) (Fig. (**1**)), and a third form; a dimeric polymerization-type isomer called Magnus' Green Salt (Fig. (**1**)), $[Pt(NH_3)_4][PtCl_4]_n$, which is used as a semi-conductor.

Once cisplatin enters cells, it undergoes aquation. Each chloride ligand is replaced with a molecule of water, which generates a positively-charged species. The reaction scheme is shown below:

Outside the cell: $Pt(NH_3)_2Cl_2$

Inside the cell: $Pt(NH_3)_2Cl_2 + H_2O \rightarrow [Pt(NH_3)_2Cl(H_2O)]^+ + Cl^-$

$[Pt(NH_3)_2Cl(H_2O)]^+ + H_2O \rightarrow [Pt(NH_3)_2(H_2O)_2]^{2+} + Cl^-$

This reaction occurs within the cell because the intracellular chloride ion concentration is relatively low inside the cell (~3-20 mM) [2]. Aquation does not occur in solution because cisplatin is typically given in a saline solution with a much higher chloride ion concentration (~100 mM).

Cisplatin kills cancer cells by forming covalent adducts with DNA (deoxyribonucleic acid) [3]. Early *in vitro* studies with salmon sperm DNA showed that cisplatin binds to the N7 position of the imidazole ring of the purine bases of DNA. X-ray crystallographic [4] and nuclear magnetic resonance studies [5] have confirmed the structure of this adduct. The purine base guanine is the usual target, but the other purine base, adenine, is a lesser target. If only one chlorine atom leaves, Platinum can form a monofunctional adduct, but if both chlorines leave as a result of aquation, a bifunctional adduct results [6]. The vast majority of adducts form on the same DNA strand and involve bases adjacent to one another. Such adducts are called intrastrand adducts or cross-links. Sixty-to-sixty-five percent of all cisplatin-induced adducts occur between adjacent guanine bases on the same strand and are called 1,2-d(GpG) intrastrand adducts (Fig. (**2AI**)); twenty-to-twenty-five percent are 1,2-d(ApG) intrastrand adducts (Fig. (**2AII**)). Other less frequently produced intrastrand adducts consist of 1,3-d(GpXpG) intrastrand cross-links (2%), where another base lies between the two platinated guanines (Fig. (**2AIII**)), and monofunctional adducts on guanines (~2%, Fig. (**2B**)). Some two percent of adducts involve platination of guanines on opposite strands (Fig. (**2C**)) and are termed G–G interstrand cross-links [7]. DNA-cisplatin-protein adducts form infrequently (Fig. (**2D**)) [8].

There are several different theories as to why cisplatin kills cells, but the majority view is that 1,2-intrastrand cross-links are the cytotoxic lesion. This explains why the *trans* isomer of cisplatin, *trans*-diamminedichloroplatinum(II), which is unable to form 1,2-intrastrand cross-links, is not an effective antitumor agent [9]. Such cross-links, however, are not the only reason cisplatin is so toxic to cancer cells. The

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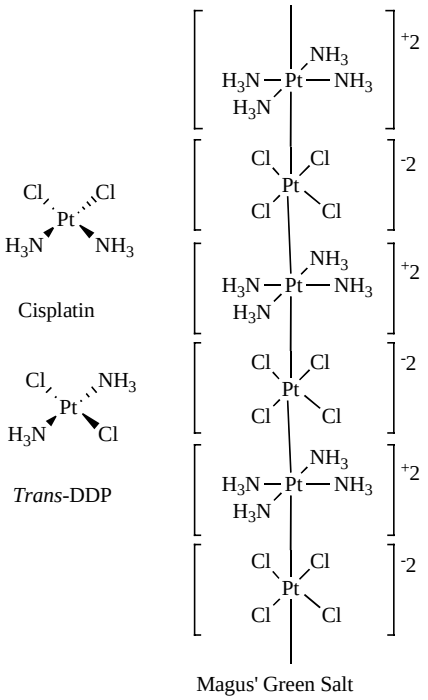

Fig. (1). Cisplatin and its isomers.

DNA repair machinery can repair a variety of lesions, but the kind of lesion induced by cisplatin seems to confound this repair machinery and induce cell death.

A primary component of cisplatin-induced cell death is the high mobility group (HMG) proteins. These proteins are closely associated with the curvature of chromatin. HMG domains are about eighty amino acids long, and consist of three rather basic α-helices. The presence of HMG proteins seems to correlate with cisplatin/carboplatin sensitivity. The testis, for example, is exquisitely sensitive to cisplatin, and expresses several HMG domain proteins. In particular, members of the HMGB family bind to those 1,2-d(GpG) cross-links induced by cisplatin, but not to DNA cross-links generated by *trans*-diamminedichloroplatinum(II). Upon association with 1,2-d(GpG) cross-links, they prevent replicative bypass (translesion synthesis) [10]. Other HMGB proteins (SRY, UBF, and LEF-1) have been shown to block nucleotide excision repair (NER) (see [11] for a review), transcription, and DNA replication. This might explain how cisplatin kills cells, since this block in cellular processes probably relays DNA damage signals that initiate apoptosis [12]. Support for this theory comes from the work of He, *et al.*, who found that exposure of MCF-7 breast cancer cells to estrogen caused overexpression of HMGB1 and sensitization to cisplatin killing [13].

Cisplatin also significantly affects signal transduction pathways inside cells, ultimately inducing apoptosis [14-18]. It also activates the endoplasmic reticulum (ER) stress pathway, which is characterized by the unfolded protein response (UPR) [19, 20]. The UPR can culminate in the activation of caspase-12, which induces apoptosis [21, 22].

Clinically, cisplatin is the principal treatment for ovarian, testicular, and bladder cancers. [23, 24]. When combined with other anti-cancer drugs, cisplatin is also used to treat cancers of the lung, head-and-neck, esophagus, stomach, colon, bladder, cervix, uterus. It also serves as a second-line treatment for advanced cancers of the breast, pancreas, liver, kidney, prostate, and against glioblastomas, metastatic melanomas, and peritoneal or pleural mesotheliomas [reviewed in 25, 26]. Despite its wide use, cisplatin can cause serious side effects, such as chronic damage to the kidneys, persistent peripheral neuropathy, ototoxicity (resulting in permanent hearing loss), gastrointestinal toxicity (emetogenesis) and asthenia [27]. Cisplatin can also cause testicular damage and induce sterility [28]. Furthermore it is inactive against some secondary cancers.

Limited solubility in aqueous solutions is one of the disadvantages of cisplatin, which is crucial for intravenous administration [29]. Additionally, acquired Platinum drug resistance effectively restricts the widespread use of cisplatin. Several mechanisms contribute to this drug resistance, including altered drug accumulation [30-32], reduced interaction with its intracellular targets, enhanced DNA repair [33, 34], and increased detoxification [35, 36]. Reduced susceptibility to apoptosis has also been proposed as a mechanism of resistance to a variety of antitumor drugs, including Platinum compounds [37-39]. Moreover, alterations in signal transduction pathways can affect cellular response to cytotoxic drugs [40-42].

This mini-review examines some of the more recent developments in Platinum and Ruthenium-based complexes, and surveys their synthesis, structure, and biological activity. Additionally, some recent, novel Molybdenum and Copper complexes with potential anti-cancer activity are explored.

NEWER PLATINUM-BASED ANTICANCER DRUGS

Given the limitations of cisplatin, researchers have devoted considerable energy to discovering similar anticancer drugs that do not share its severe side effects. It has been over forty years since the first publication that outlined the biological activity of cisplatin. Out of the thousands of synthesized and evaluated Pt(II) complexes, only three compounds, cisplatin, carboplatin (Fig. (**3**)), and oxaliplatin (Fig. (**3**)) have been approved for worldwide clinical practice (in 1978, 1993, and 2002, respectively) [43-50]. In addition, Nedaplatin (Fig. (**3**)) has been approved in Japan for the treatment of head-and-neck, testicular, lung, ovarian, cervical, and non-small-cell lung cancers [51, 52]. Lobaplatin (Fig. (**3**)) is registered in China for the treatment of chronic myelogenous leukemia, inoperable metastatic breast and small cell lung cancer [53-55]. Heptaplatin (Fig. (**3**)) has been approved in South Korea for gastric cancer [56-61].

In clinical practice, Platinum drugs are administered intravenously. However, Platinum drugs that could be effectively administered orally are strongly desirable in order to increase their potential clinical uses in outpatient settings. In recent times, several new Platinum complexes have entered clinical trials. The focus of most of this research has been on devising new methods of synthesis for such complexes and developing a greater understanding of their properties such as cellular uptake, the potential side-effects, tumor specificity, biodistribution, *etc* [62-65].

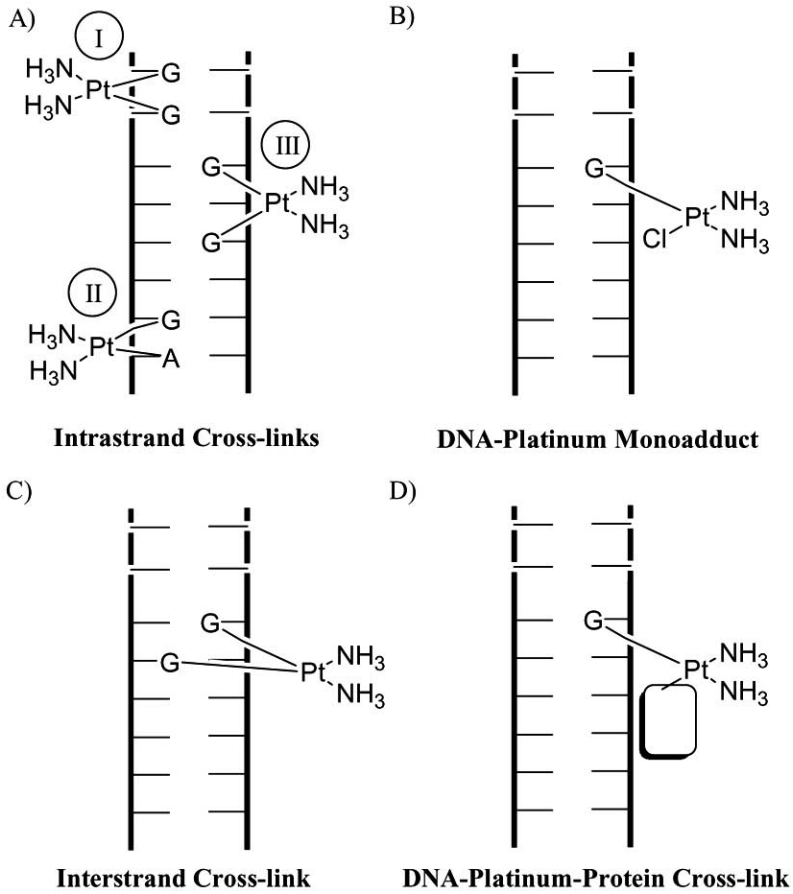

Fig. (2). The types of DNA adducts formed by cisplatin. A) Intrastrand cross-links formed by cisplatin with DNA. I) 1,2-d(GpG) intrastrand cisplatin cross-links. These are the majority adduct formed by the reaction of cisplatin with DNA. II) 1,2-d(GpA) intrastrand cisplatin cross-links, which are the second-most heavily formed adducts. III) 1,3-d(GpXpG) intrastrand cisplatin cross-links, which are only formed about two percent of the time. B) Monoadducts formed with DNA. These are probably formed if cisplatin is incompletely aquated. C) d(G-G)-interstrand cisplatin crosslinks. D) DNA-cisplatin-protein adducts. Figure adapted from [194].

NEW GENERATIONS OF ANTI-CANCER DRUGS OF PLATINUM

Among the newer Platinum compounds, the polynuclear Platinum complexes are among the most promising. A systematic evaluation of these bifunctional DNA-binding agents revealed that a drug designated as BBR3464 (Fig. **(4)**; $[\{trans\text{-}PtCl(NH_3)_2\}_2\mu\text{-}\{trans\text{-}Pt(NH_3)_2(H_2N(CH_2)_6NH_2)_2\}]^{4+}$) shows no cross resistance with cisplatin in a panel of human tumor xenografts, and *in vitro*-selected cisplatin-resistant cell lines, including leukemia, osteosarcoma, and ovarian carcinoma cells [66-74].

Like cisplatin, BBR3464 forms cross-linked adducts with DNA that probably induce cell death. The high positive charge on BBR3464 facilitates its rapid binding to DNA. This preassociation with DNA significantly affects the kinetics of adduct formation [75]. The half-life of BBR3464 DNA binding is 40 minutes, which is significantly faster than the neutral cisplatin [76]. When bound to supercoiled DNA circles, BBR3464 tends to unwind the DNA and preferentially forms interstrand rather than intrastrand DNA cross-links [77, 78]. BBR3464-induced interstrand cross-links are typically between guanine residues separated by two bases in either the 3′→3′ or 5′→5′ direction.

Detailed studies of DNA adducts formed by BBR3464 with linear DNA octamers have further elucidated how this drug interacts with its target. BBR3464 forms 1,4-interstrand cross-linked adducts with the self-complementary DNA octamer 5′-d(ATGTACAT)$_2$-3′. Specifically, the two Platinum atoms form bonds with the N7 positions of two guanines in the major groove that are located four base pairs on opposite DNA strands. [79, 80]. Structural analyses of these adducts by nuclear magnetic resonance (NMR), mass spectroscopy (MS), and other means showed that these BBR3464-induced adducts lack the kinking of the DNA double helix and unwinding that is so characteristic of those formed by cisplatin. HMG proteins [81], which bind to cisplatin intrastrand cross-links, do not recognize these 1,4-interstrand cross-links. Additionally, BBR3464-induced 1,4-interstrand cross-links are not removed by nucleotide excision repair and probably persist for a longer time than those formed by cisplatin [82]. Interestingly, when a binuclear Platinum-based antitumor drug, BBR3005 ($[\{trans\text{-}PtCl(NH_3)_2\}_2\ (H_2N(CH_2)_6NH_2)]^{2+}$), was subjected to the same analyses, the adducts it formed with DNA were structurally similar to those formed by the trinuclear BBR3464. [79]. Thus the mechanism by which these polynuclear Platinum complexes kill cancer cells

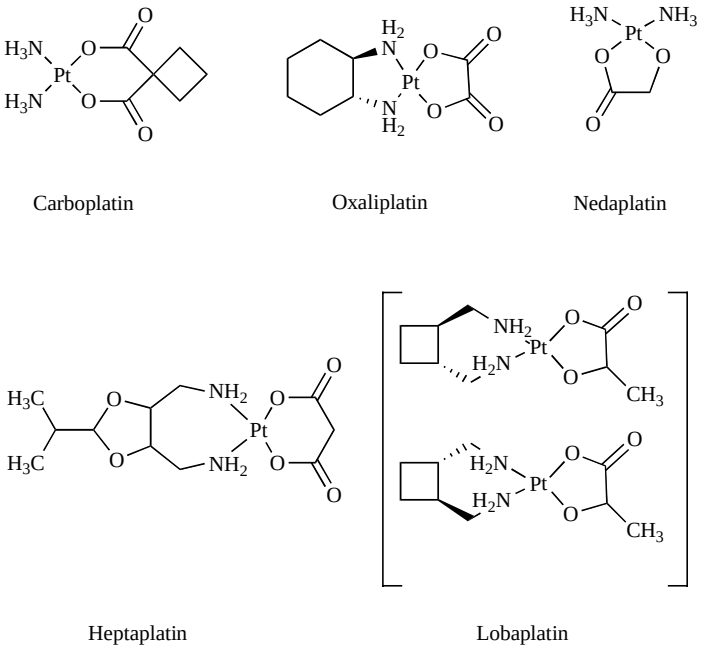

Fig. (3). Newer platinum-based anticancer drugs. Lobaplatin is a mixture of two diasteriomers.

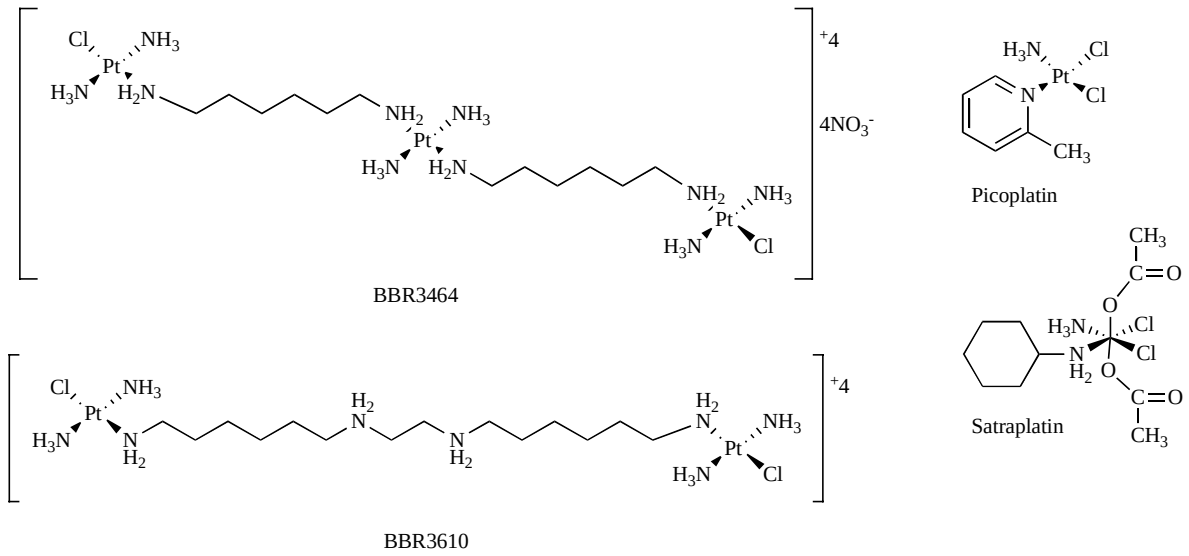

Fig. (4). Experimental Platinum anticancer drugs.

seems to be similar, and is distinct from the mechanism used by cisplatin.

The entrance of polynuclear Platinum complexes into cells relies on passive and active uptake. Biophysical analyses of interactions between membrane phospholipids and BBR3464 or a related compound, BBR3571 ([{*trans*-$PtCl(NH_3)_2\}_2(H_2N(CH_2)_3NH_2(CH_2)_4NH_2)]^{3+}$) established electrostatic, hydrogen and covalent interactions between these drugs and negatively-charged phospholipids like 1,2-dipalmitoyl-*sn*-glycero-3-phosphatidic acid, 1,2-dipalmitoyl-*sn*-glycero-3-phosphatidyl-serine, and 1,2-dipalmitoyl-*sn*-glycero-3-phosphatidyl-glycerol. Entropic and enthalpic changes in liposomes strongly suggested that both drugs are not only able to interact with the negatively-charged head groups of the phospholipids, but are also able in insert into the liposome bilayer. Thus a type of "phosphate shuttle" that makes and breaks low-energy associations between the charged membrane phospholipids and these drugs could facilitate their passive entrance into cells [83].

Passive transport is not the only way Platinum-based compounds can enter cells. Both cisplatin and BBR3464 can enter cells by means of the Copper transporter, hCTR1, and, to a lesser extent, ATP7B. Copper increases the uptake of cisplatin and BBR3464 in ovarian and colorectal carcinoma cell lines, but decreases cisplatin-induced apoptosis in cancer

cells lines. On the other hand, Copper increases BBR3464-induced apoptosis [84].

The molecular mechanisms by which BBR3464 overcomes cisplatin resistance are largely unknown. However, its ability to induce long-distance intra- and inter-strand cross-links [75, 76], which are not produced by conventional mononuclear Platinum compounds, suggests that BBR3464 may escape the classical mechanisms of cisplatin resistance related to DNA damage recognition and repair. Moreover, due to its ability to modify DNA in a manner that is different from that of cisplatin, BBR3464 could evoke distinct pathways of cellular response to DNA damage (e.g., triggering the apoptotic pathway), the nature of which depends on the genetic background of the tumor. In fact, unlike cisplatin, which is generally less active against tumor models carrying a mutated *p53* gene [85], BBR3464 displays high activity against human tumor cell lines and xenografts characterized by mutant *p53* [86], probably as a consequence of its ability to induce p53-independent programmed cell death [87, 88]. Since over 50% of all human cancers show mutational inactivation of *p53* [89], the potential activity of BBR3464 against cisplatin-resistant or *p53*-mutated tumors makes it an exciting candidate for clinical evaluation.

Preclinical studies with BBR3464 showed that this drug could overcome cisplatin and carboplatin resistance in cancer cell lines. In a neuroblastoma xenograft, BBR3464 showed a minimal therapeutic dose (MTD) of 0.35 mg/kg, compared to 4 mg/kg for cisplatin. It also showed superior activity against *p53*-mutant tumors [68, 86, 87]. Phase I trials showed significant dose-limiting side effects, that included myelosuppression, and diarrhea, but there were indications that BBR3464 was active against melanoma, pancreatic, lung and ovarian cancers. Phase I clinical trials have been completed [90] and phase II studies have begun. Unfortunately, in phase II studies, BBR3464 was not an effective treatment for either small cell lung cancer [91], or gastric-esophageal adenocarcinoma [92]. Concerns exist that BBR3464 is bound by serum proteins and degraded before it can accumulate inside cancer cells. Therefore, new ways of administering this drug (see below) could give it a new chance as an anti-cancer agent [25].

Another multinuclear Platinum compound, BBR3610 (Fig. (**4**)), promotes cell killing by activation of caspase-8-dependent mechanisms, which is enhanced by ERBB1/PI3K inhibitors and the activation of BAX and caspase-9 [93]. BBR3610 is extremely potent and displays an IC_{90} dose that is 250 times less than that of cisplatin against LNZ308 and LN443 glioma cells. Thus BBR3610 may serve as a chemotherapeutic agent for gliomas.

Besides the polynuclear Platinum complexes, newly evaluated mononuclear Platinum complexes show promise. Picoplatin (Fig. (**4**); *cis*-amminedichloro(2-methylpyridine) Platinum(II)), which is also known as ZD0473, AMD473, and JM473, resulted from a fruitful collaboration between an academic institution, the Institute of Cancer, and a commercial pharmaceutical company, Johnson Matthey/AnorMed [94]. Because cisplatin is detoxified by the tripeptide glutathione [7, 95], these researchers decided to insert a bulky 2-methylpyridine at the Platinum center to sterically hinder the reaction with glutathione, while preserving the ability of the drug to form adducts with DNA [96]. Like cisplatin, picoplatin causes intrastrand adducts that introduce a local bend into DNA.

Pre-clinical studies with a panel of ovarian carcinoma cell lines revealed that picoplatin has an antitumor activity between that of cisplatin and carboplatin. However, in a cell line in which thiol substitution was the main mechanism of resistance to cisplatin and carboplatin, picoplatin activity was essentially unaltered. Picoplatin also showed activity against other cell lines in which resistance resulted from decreased drug transport, or increased DNA repair/increased tolerance to Platinum-DNA adducts [97]. Picoplatin also showed synergistic activity with paclitaxel against cisplatin-resistant and cisplatin-non-resistant cancer cell lines [98, 99].

In phase I clinical trials, picoplatin was well tolerated, with myelosuppression presenting as the dose-limiting toxicity. Side effects included neutropenia, thrombocytopenia, nausea, anorexia, mild alopecia and a metallic taste. There were no signs of the nephrotoxicity, neurotoxicity and ototoxicity so commonly caused by cisplatin. Picoplatin also showed some efficacy against ovarian and nonsmall cell lung cancers, and mesotheliomas and melanomas that had proven refractory to other treatments [100]. Further phase I studies that combined picoplatin with paclitaxel [101], gemcitabine [102], and vinorelbine [103, 104] established the safety of these drug combinations.

In Phase II clinical studies, picoplatin showed activity against Platinum-pretreated ovarian cancers [105, 106], and cisplatin-resistant small cell lung cancers [107]. Other phase II trials are underway. The sponsoring company, Poniard, has initiated phase III clinical tests, and this drug is being developed as a second-line treatment for small cell lung cancers after cisplatin or carboplatin treatment has failed. Combinations of picoplatin, and other antitumor drugs (5-Fluorocytosine and Leucovorin) are being developed as a first-line treatment for metastatic colorectal cancer.

Satraplatin (Fig. (**4**); JM216; bis(aceto)amminedichloro-(cyclohexylamine) Platinum(IV)), is the only oral platinating agent that has been tested in clinical studies. When administered orally to mice with human ovarian carcinoma xenografts, satraplatin showed antitumor activities equal to those of intravenously administered cisplatin, or carboplatin [108]. It also displayed activity against human cancer cells that had acquired cisplatin resistance due to reduced Platinum transport [109]. Satraplatin undergoes *in vivo* biotransformation into six products, of which JM118 is the major one [110]. JM118 maintains activity against mouse embryo cells that have lost the copper-influx transporter CTR1 [111]. Both satraplatin and JM118 have antitumor activity against human prostate cancer and other tumor types, including several cell lines resistant to cisplatin, docetaxel and mitoxantrone. JM 118 is sixteen times more potent than satraplatin against prostate cancer cell lines [112, 113].

In phase I studies, satraplatin showed similar toxicities to carboplatin when given orally [114], but most side effects were manageable. Two small phase II studies that examined the antitumor activity of satraplatin against prostate cancer

showed promise [115, 116]. A phase III study called the Satraplatin and Prednisone Against Refractory Cancer (SPARC) trial examined 950 prostate cancer patients. Patients who received Satraplatin showed decreased disease progression, but the overall length of survival was the same for both the control and Satraplatin groups [117]. The failure of satraplatin in this portion of its Phase II/III clinical studies has proven to be a major setback for this drug. GPC Biotech, the manufacturers of satraplatin, has withdrawn its new drug application with the Food and Drug Administration in the U.S., and the future of this drug is uncertain [118]. Satraplatin might have other uses as a cancer treatment if combined with radiation therapy [119].

Another new innovation that has breathed new life into cisplatin utilizes a novel way to deliver the drug. Lipoplatin nanoparticles are liposomes made from 1,2-dipalmitoyl-*sn*-glycero-3-phosphatidyl-glycerol (DPPG) with cisplatin molecules in the center. The negatively-charged DPPG lipids increase the ability of these liposomes to fuse with cancer cells. The liposome exterior is coated with polyethylene glycol molecules to provide a hydrophilic surface that escapes surveillance by the immune system. These tiny particles (100 nm) also easily pass through blood vessels (extravasation) to tumors [120]. The accumulation of the drug inside the tumor is up to 200-times that found in normal tissues [121]. Therefore Lipoplatin can treat tumors with fewer side effects.

Clinical studies have confirmed the efficacy of Lipoplatin. A phase I clinical study on twenty-seven patients failed to show any neurotoxicity, ototoxicity, nephrotoxicity, or alopecia [122]. In phase II clinical studies, patients with non-small cell lung cancer or pancreatic cancer were given either Lipoplatin alone or a combination of Lipoplatin and some other drug, and showed a response rate and stable disease of over 70% [123]. Because Lipoplatin can cross the blood-brain barrier, it can potentially be used to treat brain tumors as well [124]. Lipoplatin is currently undergoing phase III studies.

Liposomal preparations of oxaliplatin (Lipoxal), are also undergoing clinical evaluation. Phase I clinical studies show that Lipoxal is a well tolerated agent that decreased the other side-effects of oxaliplatin, especially myelosuppression and gastrointestinal tract toxicities [125]. Lipoxal was used to treat patients with tumors that are highly insensitive to chemotherapy, and showed activity against cancers that have metastasized to the bones. Phase II studies are still ongoing, and phase III studies have begun. Combinations of Lipoxal with other anticancer drugs are also undergoing phase II clinical evaluations [126-128]. Also in phase II studies is L-NDDP (Aroplatin), a liposomal formulation of a structural analog of oxaliplatin (*cis*-bis-neodecanoato-*trans*-R,R-1,2-diaminocyclohexane platinum (II)), in patients with therapy-refractory advanced colorectal cancer [129]. This new preparation is another way to extend the efficacy of an already heavily used anticancer drug.

NEW GENERATION OF RUTHENIUM BASED ANTICANCER DRUGS

Ruthenium complexes are regarded as promising alternatives to Platinum complexes. The initial discovery in the 1970s that Ruthenium red possesses antitumor properties [130] motivated Clarke and his collaborators to develop and systematically examine *fac*-$[RuCl_3(NH_3)_3]$ and *cis*-$[RuCl_2(NH_3)_4]Cl$ as anticancer agents. Unfortunately, these compounds were too insoluble to serve as competitive anticancer agents [131].

The chemistry of Ruthenium complexes is well understood and offers many approaches to innovative metallopharmaceuticals. Ruthenium complexes have a tendency to adopt octahedral coordination geometries instead of the square-planar geometries of Platinum complexes. The appeal of organoruthenium complexes lies in their stability, both in the solid state and in solution. They exhibit slow rates of ligand dissociation, which allows for a more controlled release of the active form of the drug [132]. Ligand stability is crucial in drug design because fast ligand dissociation deactivates the drug before it reaches its target. An additional advantage of the octahedral coordination geometry of ruthenium(II) complexes is the possible tuning of ligand affinities, substitution rates, and redox potentials.

When compared to Platinum-containing drugs, Ruthenium-based anticancer drugs exhibit a low general toxicity [133], and specifically accumulate inside cancer cells [134]. Ruthenium has the ability to mimic iron when binding to certain biomolecules, including serum transferrin and albumin [135], which are responsible for solubilization, transport, and detoxification of iron in mammals. Rapidly-growing cancer cells have a greater requirement for iron, which leads to an overexpression of transferrin receptors on their surfaces and permits Ruthenium compounds to accumulate inside them.

One series of Ruthenium compounds that have been extensively studied for anticancer activity are the Ruthenium arene complexes, that contain a 1,3,5-triaza-7-phosphatricyclo[3.3.1.1]decane (PTA) group for increased water solubility. These "RAPTA" (Ruthenium-arene PTA) compounds have an arene-capped Ruthenium(II) center [136-139]. RAPTA compounds are highly active against cancer cell lines [140, 141], and, *in vivo*, they effectively reduce lung metastases in mice without significantly affecting the primary tumor [142].

RAPTA complexes can interact with DNA, but do so in a pH-dependent manner. In studies with plasmid DNA, RAPTA-C [(Fig. (**5**)); Ru (η^6-p-cymene)Cl_2(PTA)] caused almost no DNA damage at pH > 7, but at pH < 7, caused widespread DNA damage [143]. However, it is doubtful that DNA is the primary target of RAPTA complexes. Detailed analyses of the binding of several different RAPTA derivatives to DNA showed no direct correlation between oligonucleotide binding and cytotoxicity [144, 145]. Likewise, the induction of DNA damage in Ehrlich ascites carcinoma (EAC) cells by RAPTA-C seems to result from the induction of apoptosis rather than causing it. EAC cells from RAPTA-C-treated mice showed induction of *JNK*, *p53*, and *BAX*, all of which are pro-apoptosis genes. RAPTA-C also caused down-regulation of *cyclin E*, which is required to drive cells toward M phase, and the antiapoptosis gene *Bcl-2*. RAPTA-C treatment also caused Cytochrome c release from mito-

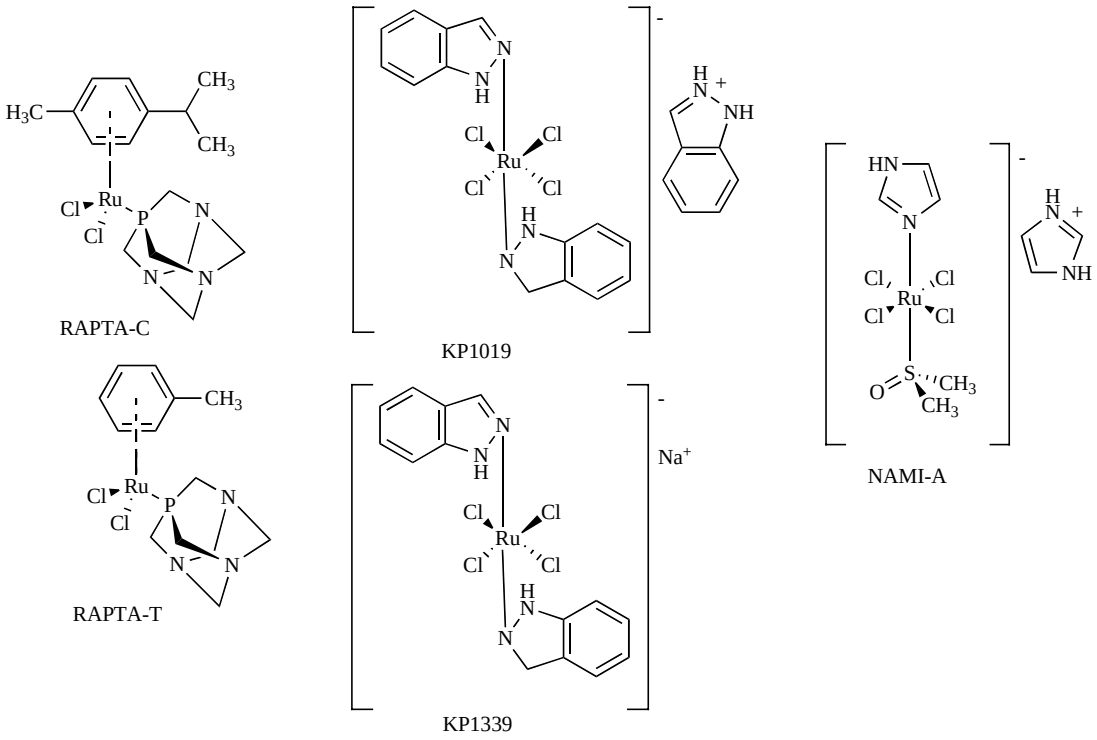

Fig. (5). Ruthenium anticancer compounds.

chondria and subsequent activation of caspase-9, which drives cells to apoptosis [146].

The anti-metastasis activity of RAPTA derivatives might result from their enzymatic inhibition capacities. When RAPTA derivatives were tested against two enzymes that are crucial for metastasis, thioredoxin reductase (E.C. 1.8.1.9) and cathepsin B (E.C. 3.4.22.1), several complexes inhibited these enzymes. In particular, three derivatives were potent inhibitors of cathepsin B (IC_{50} 1.5-2.5 μM) [147]. Since cathepsin B probably plays important roles in tumor metastasis [148], this activity might be a prevalent part of the biological activity of RAPTA. Likewise, another RAPTA derivative, RAPTA-T [Fig. (**5**); Ru(η^6-toluene)Cl_2(PTA)], reduced metastatic processes *in vitro* like migration, invasion, and re-attachment to a new growth substrate. Thus it seems that RAPTA primarily targets cell surface molecules and not DNA [141].

RAPTA compounds are generally well tolerated *in vivo*, but are prone to hydrolysis, and must be administered in saline to suppress the cleavage of chloride ligands [149]. Because hydrolysis products can confound pharmacokinetics studies and jeopardize clinical evaluation trials, it is preferable to use hydrolysis-resistant RAPTA derivatives. To this end, Ang and co-workers replaced the labile chloride ligands with bidentate ligands. They synthesized these molecules by reacting dimers of [(η^6-cymene)RuCl(μ-Cl)]$_2$ with either an excess of silver oxalate or silver 1,1-cyclobutanedicarboxylate in a polar solvent (acetonitrile), followed by treatment with stoichiometric amounts of PTA. Bidentate carboxylate ligands have been used to make cisplatin derivatives that are used routinely in clinical practice, like carboplatin and oxaliplatin, more water soluble and hydrolysis resistant [56-61]. These new, bidentate RAPTA complexes, Ru(η^6-cymene)(PTA)(C_2O_4) and Ru(η^6-cymene)(PTA)($C_6H_6O_4$), resisted hydrolysis in water, and displayed much lower lower pK_a values and greater kinetic stability than RAPTA derivatives with two chloride ligands in place of the carboxylate ligands. When assayed *in vitro* against cultured cancer cell lines, they displayed approximately the same anticancer activity as RAPTA-C. In oligonucleotide binding assays, measured by matrix-assisted laser desorption ionization mass spectrometry, the bidentate RAPTA derivatives once again exhibited characteristics similar to RAPTA-C. Thus, these novel RAPTA derivatives with bidentate carboxylate ligands possess biological properties similar to other RAPTA derivatives, and highly desirable chemical properties [150]. This strategy might represent an ingenious way to develop new, stable and highly water-soluble RAPTA adducts.

A prominent Ruthenium(III) complex with anticancer activity is indazolium [*trans*-tetrachlorobis(1*H*-indazole)ruthenate(III)], otherwise known as KP1019 or FFC14a (Fig. (**5**)). KP1019 is made by refluxing ruthenium(III) chloride ($RuCl_3$) with ethanol and hydrochloric acid, and then treating this solution with excess indazole. The result is a red-brown powder [151]. The sodium salt (sodium *trans*-[tetrachlorobis(1H-indazole)ruthenate(III)] has been designated KP1339 (Fig. (**5**)), and is made from the indazolium salt by using a methathesis reaction with ammonium salts. KP1339 is thirty-five times more water soluble than KP1019.

KP1019 is quite stable both as a solid and in aqueous solution [152]. An examination of KP1019 hydrolysis over time with electrospray ionization-mass spectroscopy (ESI-MS) showed that chloride ions are exchanged for water or

hydroxyl groups. Capillary electrophoresis (CE) and high-performance liquid chromatography (HPLC) experiments showed that temperature and pH influence the kinetics of hydrolysis, but only a small fraction of KP1019 (~2%) was hydrolyzed within one hour [153].

In the blood stream, KP1019 can react with serum proteins like albumin and transferrin within minutes [154]. Many studies of the interactions of Ru(III) with plasma proteins support the hypothesis that transferrin transports KP1019 throughout the body [155, 156]. KP1019 binds specifically binds to transferrin. Circular dichroism spectroscopy and ESI-MS showed that two Ru molecules are bound to each transferrin protein [157]. KP1019 also binds human serum albumin. In fact, the majority of Ru species (80-90%) in the blood stream is bound to albumin [157, 158]. Transport of KP1019 into cells is transferrin-mediated [159]. KP1019 can bind nucleotides, and competitive binding studies show that it preferentially binds guanine monophosphate over other bases [160]. However, KP1019 induced fifteen-fold fewer interstrand DNA cross-links than cisplatin in cancer cells [161]. KP1019-induced DNA adducts possess a low capacity to terminate transcription [162].

KP1019 induces apoptosis in tumor cells by the intrinsic mitochondrial pathway [163]. Caspase-3 is activated some four hours after administration of the drug. Sensitivity of cells to KP1019 depends on the expression of Bcl-2 [164]. KP1019-induced apoptosis is not dependent on p53, which suggests that DNA-strand breaks are not the main mechanism of cell killing [165].

In preclinical studies, KP1019 displayed a significant ability to inhibit the growth of human colon carcinoma cell lines [166]. *In vitro* studies in mice made use of tumors induced by intrarectal application of acetoxymethylnitrosamine [167] Such tumors showed exquisite sensitivity to KP1019, even though they were resistant to cisplatin and other chemotherapeutic agents [168]. KP1019 caused a 70-90% average reduction of tumor growth without causing any toxic side effects [169]. The drug is also active against other tumor types as well [167-171].

In phase I clinical studies, KP1019 showed no adverse effects when administered twice a week at doses ranging from 25-600 mg [153, 166]. Since KP1019 uses different means to kill tumor cells than Platinum-based drugs, it shows promise as a treatment for tumors that may develop cisplatin resistance [153, 166, 169, 172-173]. The low general toxicity of KP1019 at effective doses also makes it an attractive chemotherapeutic agent.

Perhaps the most notable Ruthenium anticancer drugs developed so far are the Ru(III) complexes NAMI {Na[*trans*-$RuCl_4$] (DMSO)(imida)]}, and its more stable imidazolium analogue NAMI-A, {H_2Im[*trans*-$RuCl_4$(DMSO)HIm[imidH] or imidazolium-*trans*-DMSO-imidazole-tetrachlororuthenate} (Fig. (**5**)). NAMI-A is an innovative metal-based compound suitable for the pharmacologic treatment of tumors [174] that shows high selectivity for solid tumor metastases, and low toxicity at pharmacologically active doses. This drug has successfully completed phase I clinical trials [175].

Since NAMI-A binds collagen very effectively [176], it exerts its greatest biological response in tissues that possess large quantities of collagen, like the lungs. Indeed NAMI-A reduces metastasis and growth of several different types of solid metastasizing lung cancers in animal models [177-179]. Despite the structural similarities between KP1019 and NAMI-A, they utilize distinct anticancer mechanisms. Specifically, NAMI-A affects the interaction of tumor cells with the extracellular matrix (ECM). It increases actin-dependent cell adhesion [180, 181], inhibits ECM degradation by decreasing the production of metalloproteases [182], inhibits angiogenesis [183], and reduces malignancy by decreasing cell invasiveness and migration. NAMI-A prevents tumor cells from invading matrigel without causing extensive cytotoxicity or permanently affecting progression through the cell cycle [184].

NAMI-A also influences EMC-dependent cell signaling. The mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway controls cell proliferation and differentiation, and plays a central role in tumor cell invasion and migration [185, 186]. Incubation of cultured endothelial cells with serum or phorbol 12-myristate 13-acetate (PMA) activates the MAPK/ERK pathway, but co-incubation of cells with serum or PMA and NAMI-A inhibits ERK-induced autophosphorylation, protein kinase C-mediated phosphorylation of MEK-1 and -2, and expression of *c-myc*, which is a downstream target of the MAPK/ERK signaling pathway [187].

NAMI-A also activates apoptosis in endothelial cells by inducing the release of Cytochrome c from mitochondria. Free Cytochrome c initiates apoptosis by forming a complex with Apaf-1 that then activates caspase-9 [188]. Normally, the heat shock protein HSP27 binds to released Cytochrome c and prevents it from complexing with Apaf-1 [189]. However, NAMI-A also causes down-regulation of *hsp27* in endothelial cells, which results in caspase activation, and, eventually, apoptosis [190]. Endothelial cells play a crucial role in angiogenesis [191], and inhibition of the MAPK/ERK signaling pathway in endothelial cells prevents angiogenesis [192, 193]. Since angiogenesis is crucial for tumor metastasis, the antimetastatic capability of NAMI-A might stem primarily from its tendency to inhibit MAPK/ERK signaling. NAMI-A, however, does not seem to simply target one particular signal transduction pathway. Instead this drug seems to exploit the growth and differentiation abnormalities in tumor cells to hasten their death, or drive those cells with the greatest metastatic potential towards more normal phenotypes.

FUTURE STRATEGIES

Cisplatin's stability, aqueous solubility, and slow kinetics of ligand substitution have prompted extensive studies on new Platinum(II) and Platinum(IV) drugs. However, the emergence of resistance and limited progress in the development of such complexes have led to the development of non-Platinum(II) metal complexes that have unique mechanisms of action. Molybdenum- and copper-containing complexes are particularly interesting.

Certain Copper(II) complexes show anticancer activity. Schiff base derivatives of 3-formylchromone 3-6 that hold

Cu(II) ions in a bent square-planar geometry stabilize Cu^{2+}/Cu^{+} redox forms. Molecular modeling studies showed that these complexes could interact with portions of the major signaling molecule Protein Kinase B (PKB or Akt). *In vitro* evaluation of these complexes against hormone-independent and metastatic breast (BT20), prostate (PC-3), and *K-ras* mutant (COLO 357) and *K-ras* wild-type (BxPC-3) pancreatic cancer cells showed that one particular molecule (complex seven), which displayed the tightest binding to PKB, also had the greatest anticancer activity [195]. The same research group also made Schiff base copper complexes of quinoline-2-carboxaldehyde that demonstrated dose-dependent activity against two prostate cancer cell lines. One of these complexes (FPA-137; quinoline thiosemicarbazone) had an IC_{50} of 3.2-4 μM, compared to the IC_{50} of clioquinol (10 μM) and pyrrolidine dithiocarbamate (20 μM) [196].

The ability of other Cu(II) complexes to induce apoptosis in cancer cells results from proteasome inhibition. The proteasome hydrolyzes, unfolded, damaged, unneeded, or marked proteins, and it is essential for cell division, growth, and differentiation [197]. Inhibition of the proteasome in prostate cancer cells sensitizes them to apoptosis [198]. Complexes of dithiocarbamate derivatives with copper and other metals inhibit the 26S proteasome and induce apoptosis in breast cancer cells [199, 200]. Schiff bases of copper with L-glutamate also inhibit the proteasome and induce apoptosis in human breast cancer and leukemia cells [201]. Two other compounds, 8-hydroxyquinoline-copper(II) and 5,7,-dichloro-8-hydroxyquinoline-copper(II) inhibit the proteasome and induce apoptosis in breast cancer cells [202]. Other Cu(II) complexes like Isatin-Schiff base Copper(II) complexes [203], and a novel complex, *bis*(phenanthroline)-4-methylcoumarin-6,7-dioxacetatocopper(II) [204], induce apoptosis in cancer cells in yet uncharacterized ways. Copper-adenine complexes attack several different intracellular targets and also possess potential anticancer activity [205].

Several Molybdenum complexes display excellent anticancer potentials. In particular the polyoxomolybdates show activity against tumors that have previously resisted chemotherapy [206, 207]. Another drug, tetrathiomolybdate, has an uncanny ability to chelate copper ions. Copper ions are essential for migration and proliferation of endothelial cells, and tumor angiogenesis [208]. Tetrathiomolybdate depletes the body of copper ions, inhibits angiogenesis, and starves tumors to death. Phase I clinical trials have been successfully completed [209], and phase II trials have confirmed that tetrathiomolybdate is effective against advanced kidney cancer, and after surgical resection of mesothelioma [210, 211]. Such compounds or their derivatives might provide excellent alternatives to cisplatin treatment in the future.

In a recent review, Paul Dyson (Swiss Federal Institute of Technology, Lausanne, Switzerland) and Gianni Sava (University of Trieste, Italy) note that the discovery of new metal-based antitumour drugs has heavily relied on cell viability assays that generate IC_{50} values [62]. Even though many thousands of new compounds have been synthesized, very few have entered into the clinical trial stage. Furthermore, some drugs that failed the initial cell-viability tests have been shown to possess palmary antitumour activity. For example, NAMI-A and RAPTA derivatives failed the original National Cancer Institute (NCI) screens and would have been discarded as potential anticancer drugs were they not "rescued" by intrepid researchers who continued to work on them. This leaves us with the uncomfortable conclusion that many potentially useful anticancer drugs are falling through the cracks created by the present methods of screening potential drugs. To solve this problem, Dyson and Sava suggest that the development of new assays that use cell lines that contain the appropriate drug targets are far more important for future drug discovery programs than the discovery of new DNA-binding drugs. Parallel developments should focus on assays that rapidly identify potential drug targets and interactions with particular molecules. Conversely, they argue that such research should rely less on cell viability assays and the derivation of IC_{50} values, since sole dependence on these experiments can potentially disqualify drugs with great antitumor potential.

In summary, although the original research in the area of metal-based anticancer agents largely involved Pt(II) complexes, considerable focus on this area still exists. Ru complexes possess great potential and more recent work on Mo and Cu(II) complexes, albeit while still in the formative stages, holds some promise in the fight against cancer.

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