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Understanding and Improving Platinum Anticancer Drugs – Phenanthriplatin

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Abstract

Approximately half of all patients who receive anticancer chemotherapy are treated with a platinum drug. Despite the widespread use of these drugs, the only cure that can be claimed is that of testicular cancer following cisplatin treatment. This article reviews some of our recent work on phenanthriplatin, a cisplatin derivative in which a chloride ion is replaced by phenanthridine, and one of its analogues, the previously reported pyriplatin. These cationic complexes form monofunctional adducts on DNA that do not significantly distort the duplex yet efficiently block transcription. Cell-based assays reveal altered cellular uptake properties and a cancer cell-killing profile different from those of established platinum drugs. Mechanistic work, including a crystal structure analysis of platinum-modified DNA in the active site of RNA polymerase II, is discussed.

Keywords

cytotoxicity; transcription; RNA polymerase II; X-ray structure; monofunctional platinum; pyriplatin; review

Platinum-based drugs have become a mainstay of cancer therapy; approximately half of all patients undergoing chemotherapeutic treatment receive a platinum drug (1). The widespread use of platinum agents in the treatment of cancer began with the discovery of the antineoplastic activity of cisplatin by Barnett Rosenberg in the 1960s (2). Despite the pervasiveness of platinum drugs in cancer treatment regimens, a number of attendant disadvantages exist (3). For instance, no single agent is equally effective against all cancer types and some types appear to be inherently resistant to treatment with any of the currently approved platinum agents. In addition to such resistance, populations of cancer cells can acquire resistance over time by a process of somatic evolution (4). Moreover, a number of side-effects, ranging from minor to dose-limiting in toxicity, accompany treatment with platinum agents (5). In an attempt to circumvent these problems, a large number of platinum complexes have been prepared and tested for anticancer activity. One strategy that has been used by chemists has been to devise target compounds that differ significantly from those prescribed by the traditional structure–activity relationships (SARs) established in the 1970s (6). Such ‘non-classical’ platinum complexes include Pt(IV) prodrugs, complexes with *trans* stereochemistry, polyplatinum compounds, platinum-tethered intercalators, and

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Conflicts of Interest

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monofunctional complexes. Compounds in the latter category are distinguished from the classical platinum drugs in that they form monofunctional adducts as opposed to bifunctional cross-links. Recently we described the potent anticancer activity of the monofunctional complex $cis\text{-[Pt(NH}_3)_2\text{Cl(phenanthridine)]}^+$, or phenanthriplatin (7). This review summarizes some of our recent results derived from investigations of the biological properties of phenanthriplatin. We begin with a brief overview of the discovery of the anticancer activity of cisplatin and how subsequent work led to the formulation of SARs. The success of these SARs in guiding researchers to the discovery of carboplatin and oxaliplatin is described, together with recent efforts to move away from these traditional SARs. Our work leading to the discovery of phenanthriplatin is then discussed, along with recent results that may help to shed light on the potency of this monofunctional compound. Structures of key platinum complexes discussed in this review are depicted in Figure 1.

Cisplatin and the Structure–Activity Relationships

The preparation of a coordination complex with the simple formula $cis\text{-[Pt(NH}_3)_2\text{Cl}_2]$ was first described by Peyrone in the mid-19th century and, as was often the custom at the time, the compound came to bear his name as Peyrone's chloride (8). The discovery of the antineoplastic properties of this complex by Barnett Rosenberg is a great example of the role that serendipity can play in science (9). During the course of investigating the effect of electric fields on bacterial cell division, platinum electrodes that had been chosen for their inertness began to leach platinum ions into the ammonia-containing growth medium. The bacteria incubated in this growth medium continued to grow but did not divide. Rigorous control experiments revealed that the most potent agent to recapitulate this effect in bacteria was Peyrone's chloride. In a deductive leap, Rosenberg proposed that if this platinum complex could inhibit bacterial cell division then it might be able to stop the uncontrolled cell growth that characterizes cancer. In 1969, Rosenberg published the results of a study showing that $cis\text{-[Pt(NH}_3)_2\text{Cl}_2]$ was effective in treating sarcoma 180 and leukemia L1210 in mice (2). In 1978, only nine years after the initial publication describing its anticancer activity, this compound, which came to be known as cisplatin (Figure 1), was approved by the US Food and Drug Administration (FDA) for clinical treatment of genitourinary tumors (10). The rapid approval resulted from a combination of a dire need for new chemotherapeutic drugs at the time and the diligent persistence of Rosenberg (11).

Following the initial reports of the anticancer activity of cisplatin, inorganic chemists began preparing a variety of platinum complexes with different ligands and testing their antineoplastic effects. The collective result of these many separate studies was the emergence of a set of rules governing molecular structure that appeared to be required in order for a platinum complex to have activity (12). These SARs specified that the platinum complex have square-planar geometry, be charge neutral, contain two *cis* am(m)ine ligands, and have two *cis* anionic ligands. The anionic ligands could not bind the platinum too tightly, or activity would be reduced. If these ligands were too labile, however, the compounds exhibited prohibitively high levels of toxicity. Moreover, the two am(m)ine ligands or two anionic ligands could be replaced by a chelating diamine or chelating dicarboxylate, respectively. Extensive drug discovery programs were initiated that relied on systematic variation of ligands according to these rules. As a result of these programs, two other platinum agents, *cis*-diamminecyclobutane-dicarboxylatoplatinum(II) and *R,R*-cyclohexane-1,2-diamineoxalatoplatinum(II) were approved by the FDA for clinical use in the United States (13). The former is commonly referred to as carboplatin and the latter as oxaliplatin (Figure 1). These two compounds obey the classical SARs and were thought to operate by a mechanism of action similar to that of cisplatin.

Mechanism of Action of Classical Platinum Agents

In years following the initial clinical implementation of cisplatin, much research by laboratories worldwide was conducted to determine the mechanism by which this drug carries out its anticancer action. As a result, a relatively clear picture has emerged of the steps involved in this process (14). Although some details continue to be refined, the four main steps in the mechanism of action are (i) cellular uptake, (ii) aquation/activation, (iii) DNA platination, and (iv) cellular processing of Pt–DNA lesions, leading to cell survival or apoptosis.

Passive diffusion was initially thought to play a significant role in the uptake of cisplatin (15). The importance of passive diffusion was embedded in the SARs through the requirement of charge neutrality. In recent years, however, active transport *via* the copper transporters CTR1 and CTR2 has been implicated as a major route of platinum access into the cell (16). The matter has not been unambiguously resolved, however, and new iconoclastic data continue to surface (17). Studies of overexpression of the organic cation transporters (OCTs) 1 and 2 revealed that these proteins help facilitate entry of oxaliplatin into cells, and the propensity of colorectal cancer cells to overexpress these transporters may explain the efficacy of this drug in the treatment of this particular malignancy (18). As discussed below, a study of the ability of these OCTs to transport cationic monofunctional platinum compounds ultimately led to the discovery of phenanthriplatin.

Once cisplatin has entered the cell, a lower chloride ion concentration of approximately 3–20 mM, as compared to ≈ 100 mM in the extracellular fluid, favors the substitution of the chloride ligands for water molecules (19). The chelating dicarboxylate of carboplatin exchanges for water much more slowly and it has been proposed that activation by carbonate may be important in permitting this compound to bind to DNA (20). This mechanism, however, does not occur with cisplatin (21). The cellular target of the three FDA-approved platinum drugs, as well as many related compounds that have been investigated, is nuclear DNA. The aquated/activated platinum complexes can react with nucleophilic centers on purine bases of DNA, particularly the N7 positions of guanosine and adenosine residues. The two labile coordination sites on the platinum center permit cross-linking of adjacent guanine bases. To a lesser extent, the platinum center can coordinate to guanine bases from different DNA strands to form interstrand cross-links. The major intrastrand dGpG cross-link induces a significant distortion in the DNA double helix (22). The DNA lesion is then recognized by cellular machinery that either repairs the lesion, bypasses it, or initiates apoptosis. The most significant mechanism by which classical platinum complexes are believed to induce apoptotic cell death is inhibition of transcription. When RNA polymerases transcribe DNA, they stall at the platinum cross-link and recruit the transcription-coupled repair machinery. If this machinery is unable to repair the lesion, then the cell evokes a programmed cell death pathway.

Unconventional Platinum Anticancer Agents

Despite the clinical success that has been enjoyed by cisplatin, carboplatin, and oxaliplatin, treatment with these compounds inflicts a number of deleterious side-effects (23). Among those affecting patient quality of life are nephrotoxicity, fatigue, emesis, alopecia, ototoxicity, peripheral neuropathy, and myelosuppression (24, 25). In many treatment regimens, one or more of these side-effects will often be dose-limiting. Another serious limitation of current platinum-based therapies is that some types of cancer are inherently resistant to treatment and many others develop resistance with time (26). In an effort to circumvent the mechanisms that give rise to such inherent or acquired resistance, and to mitigate other side-effects, platinum compounds deviating in structure from the prescripts of

the traditional SARs have been investigated. The hypothesis is that a difference in structure will result in an altered mechanism of action and, consequently, a different spectrum of anticancer activity.

Several structural motifs have been explored (6). Some of the more commonly investigated categories include *trans* diam(m)ine complexes (27), polyplatinum compounds (28), photoactivatable azide complexes (29), intercalator-linked species (30), and monofunctional compounds (31). Pt(IV) complexes have also been studied and are believed to act primarily as prodrugs that release active Pt(II) species following their intracellular reduction (32). Our current re-investigation of these compounds stems from the discovery that *cis*-[Pt(NH₃)₂(pyridine)Cl]⁺ is much more successful at killing cancer cells that overexpress OCT1 than those that do not (33). The *cis*-[Pt(NH₃)₂(pyridine)Cl]⁺ cation, which came to be called pyriplatin (Figure 1), contains only a single labile chloride ligand and thus, unlike cisplatin, can only form a monofunctional adduct on DNA; that is, only a single bond can be formed to between the platinum center and a donor atom on DNA. The nature of this adduct was revealed by an X-ray crystallographic analysis of a dodecamer of site-specifically pyriplatin-platinated duplex DNA (34). In contrast to the structure of DNA bearing a cisplatin 1,2-intrastrand cross-link, pyriplatin induced little distortion of the DNA double helix upon binding.

This difference in DNA lesion structure produces different spectra of activity for pyriplatin and cisplatin in a panel of human cancer cell lines (35). Lesions formed by cisplatin inhibit RNA polymerase II, the enzyme that is responsible for transcription of mRNA precursors that ultimately form proteins in humans (36). If the polymerase becomes stalled at the platinum adduct, additional proteins are recruited to repair the damage. If the damage cannot be repaired then the cell will initiate an apoptotic pathway.

The evaluation of transcription inhibition and DNA repair can be carried out in live human cells using techniques developed in our laboratory over the past five years that employ platinated mammalian expression vectors (37, 38). The platination of the expression vector can be either global or site-specific. When studied using these techniques, the site-specific monofunctional pyriplatin lesion was found to inhibit transcription in cells as readily as the site-specific bifunctional cisplatin lesion (39). The inhibition of RNA polymerase II from a site-specifically platinated DNA plasmid was subsequently investigated using an *in vitro* transcription assay. The polymerase was unable to extend the RNA transcript past the pyriplatin lesion. In order to further explore the interaction of the pyriplatin lesion with RNA polymerase II, the crystal structure of the enzyme stalled at the lesion was solved and analyzed (40). We found that the growing RNA strand terminated at the post-translocation step of transcription. This result stands in contrast to similar stalling induced by cisplatin and UV cross-links, which block RNA polymerase II procession at the translocation step (41). Detailed analysis of the crystal structure indicated the steric bulk of the pyridine ligand to be instrumental in blocking subsequent translocation.

Phenanthriplatin – A Potent Monofunctional Compound

Pyriplatin displayed a spectrum of activity that differed from that of any of the clinically approved platinum drugs (35). The overall potency of pyriplatin, however, was much less than that of cisplatin in all cell lines tested. The structural studies with RNA polymerase II indicated the importance of the steric hindrance to enzyme action by the pyridine ligand. In an effort to improve efficacy, the *N*-heterocyclic Am of *cis*-[Pt(NH₃)₂(Am)Cl]⁺ was systematically varied with an emphasis on increasing steric bulk (7). The most potent compound discovered in this search was that for which Am was phenanthridine. This compound, termed phenanthriplatin, was 7–40 times more active than cisplatin in an initial

screen of human cancer cells from a variety of organs. In the more extensive NCI60 panel of cell lines (42), phenanthriplatin showed a spectrum of activity that differed significantly from that of any other platinum anticancer agent in the NCI database.

The crystal structure of phenanthriplatin revealed the phenanthridine ligand, which is oriented perpendicular to the platinum coordination plane, to be positioned such that one of the aromatic C–H groups blocks an open face of the platinum center. This steric hindrance is similar to that in picoplatin, *cis*-[Pt(NH₃)(α -picoline)Cl₂], which is proposed to protect it from deactivation by off-target biological nucleophiles such as thiols (43). Similarly, phenanthriplatin reacts with *N*-acetyl cysteine more slowly than pyriplatin, which lacks the axial steric protection. Both phenanthriplatin and pyriplatin, however, react at similar rates with guanosine monophosphate, indicating that the protection that the former enjoys from thiols does not hamper its ability to bind to the DNA nucleobases.

Given the large, planar structure of the aromatic phenanthridine ligand, it is possible that it could interact with DNA by an intercalative mechanism. In order to assess whether the binding of phenanthriplatin to DNA is intercalative, covalent, or some mixture of the two, fluorescent Scatchard plots of the binding of ethidium bromide to calf-thymus DNA in the presence of phenanthriplatin were prepared. The influence of the concentration of the platinum complex on the displacement of ethidium from DNA, in conjunction with an analysis of the change over time, indicates with which of these modes the platinum complex binds DNA (44). The results proved that phenanthriplatin binds to DNA in a purely covalent manner, like cisplatin.

Transcription inhibition assays analogous to those described above for pyriplatin were carried out with site-specifically phenanthriplatin platinated GLuc expression vectors. Again, the monofunctional adduct significantly inhibited transcription in a variety of cell lines. The cells recovered their ability to transcribe the vector over time, indicating that the platinum lesion can be repaired. The repair occurred at different rates in different cell lines. If transcription inhibition by monofunctional adducts is the cause of apoptotic cell death, then an increased capacity to transcribe the platinated vector over time indicates that a cell should be more resistant to treatment with the platinum complex. We observed a negative correlation between the capacity of cells to repair the phenanthriplatin lesion and cytotoxicity.

Concluding Remarks

The development of platinum-based anticancer compounds has long been focused on the synthesis and evaluation of complexes that obey the SARs set forth in the 1970s. These pursuits have produced carboplatin and oxaliplatin, two widely employed anticancer drugs. The prevalence of inherent and acquired resistance to platinum treatment, however, requires the development of new complexes that operate *via* different mechanisms. Although initially thought to be ineffective, the recent discovery of phenanthriplatin has revealed that monofunctional compounds can indeed be potent anticancer agents. They distort DNA significantly less than cisplatin, but their efficacy tracks with transcription inhibition, corroborating the fact that DNA is their major target. The spectrum of activity of these compounds is highly differentiated from that of classical platinum complexes, giving rise to the hope that they might form a class of clinically relevant drug candidates. In a more general sense, these results also validate the exploration of other metal complexes that can only interact with DNA in a monofunctional manner as anticancer drug candidates.

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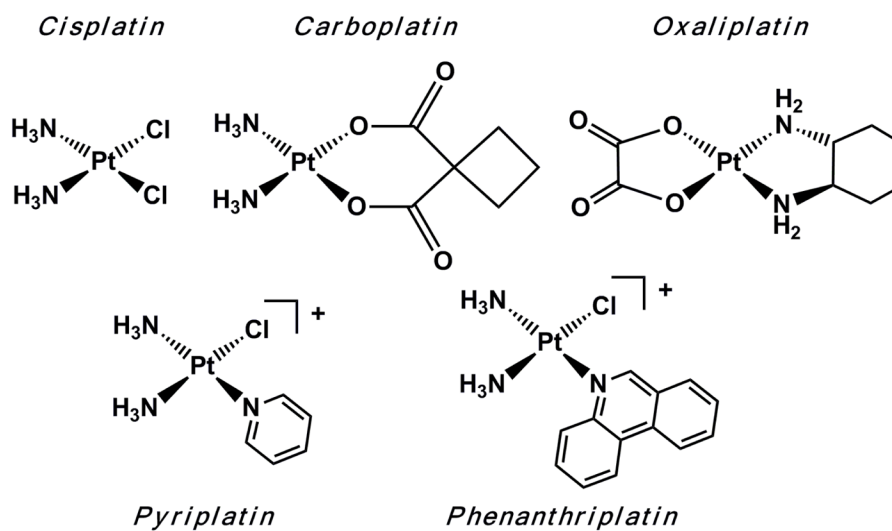


Figure 1.
Platinum anticancer agents discussed in this review.