

9.5: Platinum Anticancer Drugs- A Case Study

History of the Discovery⁴⁷

cis-[Pt(NH₃)₂Cl₂], a molecule known since the mid-19th century, has been a subject of considerable importance in the of inorganic stereochemistry and substitution reaction kinetics.⁴⁸ Its biological was discovered by accident. In the mid-1960s, biophysicist Barnett Rosenberg, at Michigan State University, was studying the effects of electric fields on the growth of *Escherichia coli* cells in culture. They had hypothesized that, during cell division, the orientation of the mitotic be affected by local electric which they hoped to perturb. Instead, they observed growth without cell division, the result being elongated, spaghetti-like bacterial filaments approaching 1 cm in length. After much detective work, they realized that small amounts of platinum from the electrodes used to apply the electric fields had reacted with NH₄Cl in their buffer to produce various platinum ammine halide compounds. Two of these, *cis*-[Pt(NH₃)₂Cl₂] and *cis*-[Pt(NH₃)₂Cl₄], were capable of inducing filamentous growth in the absence of any electric field. Since chemicals that produce filamentation in bacteria had been known to exhibit antitumor activity, Rosenberg was eager to have his platinum compounds tested. Unable to convince existing agencies like the National Cancer Institute (who to their credit later spearheaded the development of cisplatin) that a heavy-metal complex could actually be beneficial to animals, the Michigan State group set up their own animal-tumor screens. The results were nothing short of spectacular. Injection of *cis*-DDP directly into the abdominal cavity of mice into which a solid Sarcoma-180 tumor had been implanted led within a few days to a blackening (necrosis), reduction in size, and eventual disappearance of the tumor (Figure 9.5). The cured mouse enjoyed a normal lifespan. From these and other animal studies, physicians became convinced that administering platinum compounds to cancer patients might be worthwhile, and a new field involving bioinorganic chemistry and cancer chemotherapy was born. The drug, marketed as Platinol with the generic name cisplatin, received FDA approval in 1979 and is today one of the leading anticancer agents.

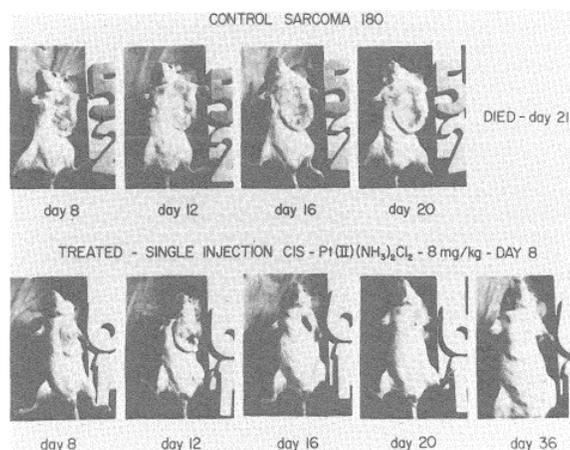


Figure 9.5 - Photographic demonstration of the dramatic ability of cisplatin to cure a Sarcoma-180 murine tumor (reproduced by permission from Reference 47).

Principles that Underlie Drug Development

1. Strategic Considerations

There are two general routes to the development of inorganic complexes, and indeed most chemical compounds, as drugs. One, illustrated by cisplatin, arises from an empirical observation of biological activity followed by attempts to optimize the efficacy through investigations of structure-activity relationships (SAR). The goals are to minimize toxicity, to develop cell culture and animal screens for testing related compounds, and ultimately to elucidate the molecular mechanism. Knowledge of the molecular mechanism might even lead to a rational strategy for designing better drugs.

The second general approach to drug design begins with known biochemistry. For example, ribonucleotide reductase is required in the first committed step in the biosynthesis of DNA, the conversion of ribo- to deoxyribonucleoside dir)hclspat.es. The mammalian enzyme contains a binuclear non-heme iron center required for activity. Compounds that would selectively inhibit this enzyme by destroying this center are potentially useful as antiviral or antitumor agents. Another example is the enzyme reverse transcriptase, encoded by the HIV (AIDS) virus and required for its integration into the genome of the host cell. Compounds like 3'-azidothymidine (AZT) are accepted by the enzyme as substrates but, when added to the growing DNA chain, cannot be linked to the next nucleotide. Chain termination therefore occurs and the replication process becomes permanently interrupted. Attempts to

find organic molecules or inorganic complexes that are more effective chain terminators than AZT constitute a rational strategy for developing new anti-AIDS drugs.

In the remainder of this chapter we describe research that has evolved following the discovery of biological activity for cisplatin. Although the initial breakthrough was serendipitous, subsequent studies have revealed many aspects of the molecular mechanism. From this known biochemistry we may one day be in a position to design more effective anticancer drugs and therapies based upon the fundamental bioinorganic chemistry of cisplatin.

2. Pre-clinical and Clinical Trials⁴⁹

Predicting the chemotherapeutic potential of an inorganic compound such as *cis*-DDP prior to its introduction into human cancer patients is an important objective. Compounds are most easily tested for their cytotoxic effects on bacterial or mammalian cells in culture. Shown in Figure 9.6 are results for the survival of cultured L1210 cells in the presence of increasing amounts of *cis*- or *trans*-DDP.^{50,51} The data reveal the markedly greater toxicity of the *cis* isomer, which is a much better anticancer agent than its stereoisomer. Unfortunately, no single assay has yet been found that can predict the chemotherapeutic potential of platinum compounds in humans. The best that can be obtained are results relative to those for *cis*-DDP, in which case toxicity at low dose is usually scored positive.

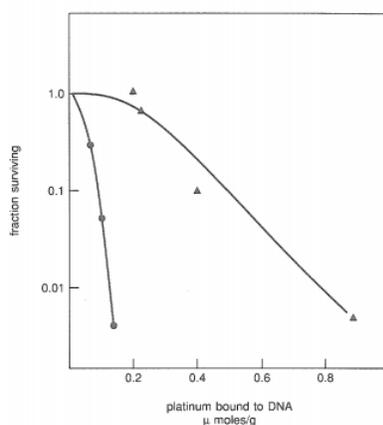


Figure 9.6 - Differential toxicity of *cis*- (●) and *trans*-DDP (▲) on HeLa cells growing in culture (reproduced by permission from Reference 51).

The next level of testing, often employed directly without first examining cell-culture results, involves animal (usually mammals, excluding human) screens.⁴⁹ Among the most popular measures of the chemotherapeutic activity of platinum compounds has been their ability to prolong the survival of mice bearing the L1210 or P388 leukemia. A suspension of cells is inoculated intraperitoneally (i.p., in the abdominal cavity), producing a leukemia that eventually progresses to the generalized disease. In one commonly used protocol, platinum compounds are dissolved in physiological saline (0.85 percent NaCl) or sterile H₂O and injected i.p. 24 h, 5, 9, and 13 days after inoculation of the leukemia cells. Several indices of antitumor activity and toxicity have been defined. The percent I.L.S., or increased lifespan measures the mean survival of treated versus control animals that were given no platinum drug. A related index is the median survival, percent T/C (Test/Control), which is 100 + percent I.L.S. The LD₅₀ value measures toxicity as mean lethal dose, the amount of drug (usually in mg/kg body weight) required to kill half the animals. Potency is defined by ID₉₀, the inhibiting dose at which 90 percent of the tumor cells are killed. From these values, a therapeutic index (TI) = LD₅₀/ID₉₀ is sometimes defined, which should be substantially greater than one. Typical values for *cis*-DDP are 85 percent I.L.S. at 8 mg/kg for the L1210 tumor, 13.0 mg/kg LD₅₀, and 1.6 mg/kg ID₉₀ resulting in a TI of 8.1.

In addition to being tested in mice, cisplatin and related compounds have been screened in other mammals, specifically dogs and monkeys, mainly to look for possible dose-limiting side effects. Severe vomiting, once thought to be an insurmountable obstacle, was monitored by using ferrets. None of the animal screens can substitute for the ultimate test, however, which is human clinical trials. In 1972, such trials were initiated using terminally ill cancer patients. It was determined that intravenous (i.v.) injection, rather than i.p. or oral administration, was the preferred method for giving the drug. Further details of the clinical development of cisplatin are discussed in a later section.

From the animal screens emerged the set of structure-activity relationships enumerated earlier (Section IV.E.1). Both cisplatin and carboplatin conform to these rules, and to date no compounds with demonstrably better antitumor activity have been tested in

humans. The decision to move an experimental drug into the clinic is a difficult one, however, and it may be that molecules such as cis- $[\text{Pt}(\text{NH}_3)_2(4\text{-Br-py})\text{Cl}]\text{Cl}$ (see Section V.D.7.c) would be effective for tumors that are refractive to cisplatin chemotherapy. In any case, the foregoing chain of events, from studying the effects of a compound on cells in culture through animal screens and eventually to humans, constitutes the principal route for introducing a new anticancer drug. The process can take more than a decade.

3. Mechanism of Action Studies

Once a class of compounds has been identified as biologically active, studies to elucidate the molecular mechanism of action can be undertaken. A first step is to identify the major cellular target or targets responsible for the chemotherapeutic properties of the drug. These investigations must also focus on chemical transformations that might take place in the solutions being administered and in the biological fluids that transport the drug to its ultimate target site. The next major step is to characterize the adduct or family of adducts made with the biological target molecule. The structure and kinetic lifetime of these adducts need to be investigated. Once this information is in hand, the effect of the adducts on the structure, stability, and function of the biological target molecule must be studied. Here many powerful new methodologies of modern molecular biology, genetics, and immunology can be brought to bear on the problem. The ultimate goals are to translate the molecular events elucidated into a realistic mechanism for how the drug molecule brings about its toxic effects selectively at the sites responsible for the disease and to use this information to design even better drugs.

Having progressed this far, we next need to bridge the gap between fundamental knowledge gained in studies of the mechanism of action and the SAR gleaned through pre-clinical and clinical trials. Whether such a happy situation can be reached for cisplatin remains to be seen, but there are encouraging signs, as we hope to demonstrate in the following discussion.

Clinical Picture for Cisplatin and Carboplatin^{49,52}

1. Responsive Tumors and Combination Chemotherapy

It was an early observation that the best responses to cisplatin occurred in patients with genitourinary tumors. For testicular cancer, once a leading cause of death for males of age 20-40, cisplatin cures nearly all patients with stage A (testes alone) or B (metastasis or retroperitoneal lymph nodes) carcinomas. Platinum is usually given in combination with other drugs, commonly vinblastine and bleomycin for testicular cancer. This combination chemotherapy, as it is known, has several objectives. Some tumors have a natural or acquired resistance to one class of drugs and, by applying several, it is hoped that an effective reduction in tumor mass can be achieved. In addition, various drugs are known to affect different phases of the cell cycle, so several are applied simultaneously to allow for this possibility. Finally, synergism, where the response is greater than expected from simple additive effects, can occur, although it is rare. In addition to testicular cancer, platinum chemotherapy has produced responses in patients with ovarian carcinomas (>90 percent), head and neck cancers, non-small-cell lung cancer, and cervical cancer. Cisplatin is also effective when combined with radiation therapy.

2. Dose-limiting Problems; Toxicology

An early and quite worrisome adverse side effect of cisplatin was kidney toxicity. This problem, not commonly encountered with the older cancer drugs, nearly prevented its widespread use and eventual FDA approval. The major breakthrough here was made by E. Cvitkovic, who, while working at Sloan-Kettering Memorial Hospital in New York, administered large quantities of water by intravenous injection to patients, together with an osmotic diuretic agent such as D-mannitol. The rationale was that such hydration could ameliorate kidney toxicity by flushing out the heavy-metal complex. This simple idea worked, and the dose of the platinum compound could be increased threefold without accompanying nephrotoxicity. Hydration therapy is now commonly employed when cisplatin is administered. Among the other toxic effects encountered in cisplatin chemotherapy are nausea and vomiting, but this problem has also been controlled by use of antiemetic agents. Patients have also been known to experience bone-marrow suppression, a ringing in the ears, and occasional allergic reactions.

More recently, attempts have been made to extend cisplatin treatment to other broad classes of tumors by raising the dose above the ~5 mg/kg body weight levels given by i.v. injection every few weeks. Direct injection into the peritoneal cavity has been employed for refractory ovarian tumors. These more aggressive therapeutic protocols have been frustrated by drug resistance, a phenomenon by which cells learn to tolerate a toxic agent and for which many mechanisms exist, and by the return of the usual cisplatin side effects, most notably kidney toxicity and neurotoxicity. In order to combat toxic effects to the kidneys, chemoprotector drugs have been introduced. Based on the known affinity of platinum(II) complexes for sulfur-donor ligands, sodium diethyldithiocarbamate (DDTC) has been given both to experimental animals and to humans by i.v. infusion over about an hour following cisplatin

administration.⁵³ DDTC inhibits many of the toxic side effects, particularly to the kidneys and bone marrow, without itself producing long-term side effects or apparently inhibiting the antitumor properties of *cis*-DDP. Similar efforts have been made to reduce the toxic effects of cisplatin with other sulfur-containing compounds including thiosulfate and the naturally occurring biomolecules glutathione, cysteine, and methionine. The relative amounts of the latter three molecules can be controlled by drugs that affect their normal cellular concentrations.

Another approach to reducing cisplatin toxicity is to develop new classes of platinum drugs or different routes of their administration. Carboplatin (Figure 9.4) is one result of these efforts. The bidentate chelating dicarboxylate leaving group in carboplatin presumably retards the rates of reactions leading to toxicity, but does not adversely interfere with the chemistry required for antitumor activity. Recently, promising platinum compounds for oral administration have been developed.⁵⁴ In Pt(IV) complexes of the kind *cis, trans, cis*-[Pt(NH₃)(C₆H₁₁NH₂)•(O₂CCH₃)₂Cl₂], where C₆H₁₁NH₂ is cyclohexylamine, have been found to be effective in preclinical screens. The greater kinetic inertness of these complexes apparently renders them sufficiently stable to the chemically harsh environment of the gastrointestinal tract. Once absorbed into the bloodstream, these compounds are metabolized to the Pt(II) analogues, *cis*-[Pt(NH₃)(C₆H₁₁NH₂)Cl₂], which are presumed to be the active form of the drug. The Pt(IV) compound has recently entered clinical trials.

Although impressive inroads have been made in the management of human tumors by platinum chemotherapy, the fact remains that, apart from testicular and to a lesser extent ovarian cancer, the median survival times are measured in months. Clearly, there is much room for improvement.

3. Pharmacology^{49,52}

Solutions of cisplatin are usually given in physiological saline (NaCl), since hydrolysis reactions occur that can modify the nature of the compound and its reactions *in vivo* (see below). Cisplatin is rapidly cleared from the plasma after injection, 70-90 percent of the platinum being removed within the first 15 minutes. It has been found that more than half the platinum binds to serum proteins and is excreted. Most of the platinum exits the body via the urine within a few days. These results account for the use of multiple-dose chemotherapy at intervals of several weeks. Animal studies employing *cis*-DDP labeled with ^{195m}Pt, a 99 keV γ -emitter with a 4.1-day half-life, reveal retention half-times in various tissues of 8.4 (kidney), 6.0 (ileum), 4.1 (liver), 2.8 (tumor), and 1.9 (serum) days following a single dose. Platinum distributes widely to all tissue, with kidney, uterus, liver, and skin having the most, and muscles, testes, and brain the least amount of the compound. There is no evidence for selective uptake into normal versus tumor cells.

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