Evolution of Chemotherapy with Platinum Compounds*

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ABSTRACT

Cancer is a major disease entity and cause of death in the human population. The discovery of cisplatin has revolutionized the chemotherapy of human cancer. The full therapeutic potential of cisplatin has not been realized due to the serious side effects and emergence of cisplatin-resistant tumor cells associated with its usage. Protective methods such as extensive hydration, improved schedules of administration, alternate routes of administration, and use of protective agents against specific side effects have allowed the use of higher doses of cisplatin against cisplatin-resistant tumors and has extended the list of tumor systems responsive to cisplatin chemotherapy. Incorporation of cisplatin into a number of cisplatin-based anti-cancer drug combinations has enhanced its effectiveness and allowed the use of lower doses of cisplatin, thus reducing its toxic side effects. Finally, the availability of cisplatin analogues, such as carboplatin and others with reduced toxicity, but increased effectiveness against cisplatin-resistant tumors, has expanded the potential scope and therapeutic promise of the platinum anti-cancer agents. The evolution of chemotherapy with the platinum antitumor compounds is ongoing.

Introduction

In a study designed to assess the effects of electric fields on the growth of bacteria, Rosenberg noted that cells of Escherichia coli grew up to 300-fold their normal length when subjected in a liquid medium to the amplified output from an oscillator delivered at 1000 H at 2 A. Additional experiments revealed that this growth pattern was not due to the electric field per se, but to a long-lived chemical form of platinum released from the presumed inert platinum electrodes, which were immersed in the chemically defined growth medium containing ammonium and chloride ions. The principal chemical species involved was the classic square planar Peyrone's chloride, or cis-dichlorodiammineplatinum (II), which has subsequently been given the generic name cisplatin.

In initial assays, cisplatin (cis isomer) suppressed the extent of development of many rodent and other animal tumors. The corresponding trans isomer was devoid of any appreciable action on tumors. These extremely impressive findings of cisplatin against the animal tumors led to its clinical evaluation against numerous human tumor systems.
Routes of Administration

Cisplatin is not absorbed appreciably when given orally and is most frequently given by the intravenous route. In routine use cisplatin is given as a slow intravenous infusion over a period of hours, as a continuous infusion over a period of several days, or in some protocols by intra-arterial infusion. Intra-arterial administration of 100 mg/m² of cisplatin every seven to 14 days is reported to have produced an 82% response rate in patients with advanced head and neck cancer, one-third of which were complete responses.

Absorption and Distribution

Three hours after a bolus injection into rats, the highest platinum concentrations were detected in kidneys, liver, adrenals, bone, tendon, skin, small intestines, and spleen, while the lowest concentration was found in brain. This preferential uptake of the metal into organs of excretion is altogether compatible with the gastrointestinal and renal toxic actions of the drug.

Plasma platinum levels were measured in patients after a mean cisplatin dose of 95 mg/m² (range 40–150). Peak levels in plasma were attained soon after the end of the 6-hour infusion, and the mean level was 11.6 μmol/L (range 2.4–21.9).

Metabolism

Conversion of cisplatin to its pharmacologically active adducts is strictly nonenzymatic and occurs in the intracellular environment in the presence of low chloride concentrations. The aquated platinum species can react with a number of nucleophilic groups in both the intracellular and extracellular compartments. Important interactions are the bifunctional linkages to the nitrogen-7 (N7) and oxygen-6 (O6) positions of guanine; this is considered to be a critical biochemical action involved in expression of the antineoplastic drug action. No high degree of specificity should be inferred, however, as platinated adducts with other purines and pyrimidines have been identified. Aquated adducts of the trans isomer do not possess the requisite intramolecular dimensions to effect this bifunctional link, which may largely explain the lack of antitumor action of this isomer.

Excretion

The principal route of excretion of cisplatin and its metabolites is through the kidneys, with about 90% of an administered dose excreted in the urine within five days after injection. Little or no excretion occurs via the fecal route. Synthetic adducts of cisplatin with specific DNA components also appear in urine after systemic administration. Urine from 16 patients receiving therapeutic infusions of cisplatin contained a mean platinum concentration of 71.3 nmol/L (range 13.1–133.3) when measured 6–24 h, post-infusion.

Mechanism of Action

Cisplatin is a neutral, square planar molecule containing two chloride leaving groups oriented in a cis-configuration. After parenteral administration, the presence of high extracellular chloride ion concentrations (about 100 meq of Cl⁻/L) suppresses the aquation reactions of cisplatin. The inert cisplatin molecules permeate the cell membranes into cells by substantially a passive manner in the intact unreacted form, where they encounter low intracellular chloride concentrations, much lower than in the extracellular fluid, a condition which favors the aquation reactions.

At lower intracellular chloride concentrations cisplatin loses its chlorine atoms and is converted into aquated, reactive electrophiles that can bind covalently to a variety of cellular macromolecules, including DNA. Thus, this series of nonenzymatic reactions provides the only known activation processes necessary for ultimate interaction of the drug with critical intracellular molecules.

Cisplatin usually reacts readily with the N7 and O6 positions of guanine and also to the
adenine and cytosine bases of DNA to form a variety of monofunctional and bifunctional DNA adducts. Intrastrand cross-linking may occur by the binding of cisplatin to adjacent guanines or interstrand cross-linking can ensue following attachment to nucleophilic sites on two different strands of DNA or DNA and protein. The predominant bidentate lesions appear to be d(GpG)Pt (60%), d(ApG)Pt (15%), and d(CpNpG)Pt (20%) of the total interstrand cross-linked DNA adducts. These 1,2-intrastrand adducts produce a local kinking and unwinding of duplex DNA. Less frequently observed platinum-DNA adducts include monoadducts and d(G)₂Pt interstrand crosslinks (less than 5%). These interstrand crosslinks impede the DNA replication and transcription processes.

The fact that the activated form of cisplatin can also react with non-DNA nucleophilic sites, such as the thiol groups of proteins or other intracellular nucleophiles, may help explain some of the toxic effects associated with cisplatin.

Tumors Responsive to Cisplatin or Cisplatin-Based Combinations

The discovery of cisplatin has revolutionized cancer chemotherapy. Hundreds of clinical studies over the past 25 years have now firmly established cisplatin (Platinol®, Bristol Company) as a major antineoplastic agent for use in chemotherapy of metastatic testicular tumors, metastatic ovarian tumors, and advanced cancer of the urinary bladder. In combination with selected other antineoplastic agents, cisplatin is also of some benefit in the treatment of certain brain tumors and squamous cell carcinoma of the head and neck.

Some of the tumors responsive to cisplatin or cisplatin combinations are listed below. Recent advances in reducing cisplatin-induced nephrotoxicity have allowed the use of higher doses of the drug in treating cancer patients. These increased doses have enhanced the response rates in patients bearing cisplatin-sensitive cancers, such as testicular and ovarian cancer, with prolongation of survival. The use of high-dose cisplatin (up to 200 mg/m² per cycle) has improved cisplatin efficacy against tumors moderately sensitive to cisplatin and has begun to produce promising results with tumors resistant to the lower doses of cisplatin. The use of high-dose cisplatin has increased its value in cisplatin-based combinations of anticancer drugs and has lengthened the list of cisplatin-responsive tumors.

Cisplatin has induced clinical responses in at least 40 different tumor systems including: adrenocortical tumors, aerodigestive tract cancers, anal cancers, bladder cancers, bone sarcomas, breast adenocarcinomas (including metastatic), certain lymphomas, cervical carcinomas, childhood germ cell tumors, endometrial carcinomas, gastrointestinal cancers (esophageal, gastric, pancreatic, gallbladder and biliary tract, colonic, rectal, retroperitoneal sarcoma), germ cell tumors of all types (testicular and ovarian, including disseminated), head and neck cancers, hepatobiliary cancers, laryngeal cancer, leiomyosarcomas, lung cancer, mediastinal childhood tumors, malignant lymphomas, malignant melanoma, nasopharyngeal cancers, ovarian cancers, pancreatic cancers, paranasal sinus cancers, penile cancer, pleural mesotheliomas, prostate cancers, salivary gland cancers, seminomas, soft tissue sarcomas, stomach cancers, testicular cancers, thymomas, urothelial tract cancers (renal pelvis, ureter, urinary bladder, urethra, prostatic ducts), vaginal cancers, and vulvar cancers. Cisplatin is effective when used alone against these tumor systems, but often is even more effective when used in a number of chemotherapeutic regimens consisting of two or more anticancer drugs.

Cisplatin combinations with 5-fluorouracil (5-FU) and doxorubicin appear to be successful in treating non-hormone-producing metastatic adrenal cortical carcinoma. Tumor Cellular Resistance to Cisplatin

A problem with successful treatment of tumors with platinum compounds is the emergence of drug-resistant tumor cells. Mechanisms that may limit the formation of lethal
platinum-DNA adducts include altered drug transport, drug inactivation, and mechanisms that enable a cell to repair or tolerate platinum-DNA damage once it occurs. Development of cellular resistance to cisplatin may involve at least five different mechanisms: (a) decreased cellular uptake of cisplatin, (b) diminished intracellular formation of DNA-platinum adducts, (c) enhanced repair of DNA-platinum adducts or lesions, (d) cellular tolerance to DNA-platinum adducts, and (e) alterations or defects in cisplatin-induced programmed cell death (apoptosis).

Cisplatin appears to enter cells both by passive diffusion and also by energy requiring carrier-mediated transport. Interruption of the above prevents cellular intake and intracellular accumulation of cisplatin (cisplatin accumulation defect). This treatment problem may be solved by using another platinum compound in cisplatin-resistant tumor cells. Diminished platinum adduct formation may result from cellular inactivation of cisplatin through binding to sulfhydryl-rich intracellular metallothionein (MT) proteins which may sequester up to 10 molecules of cisplatin per molecule of MT. Cisplatin may also be inactivated by intracellular conjugation with glutathione (GSH) in a 1:2 GSH-platinum ratio. Up-regulation of GSH synthesis may occur in cisplatin-resistant tumor cells. Enhanced repair of DNA-platinum adducts or lesions by nucleotide excision repair (NER), XPE, and other DNA repair proteins may help produce cisplatin-resistant tumor cell lines through enhanced DNA repair.

Cellular tolerance to DNA-platinum adducts may result from an enhanced replication by-pass ability in which tumor cells are able to continue DNA synthesis past a DNA-cisplatin adduct or lesion to successfully complete DNA synthesis to reach the G2 phase and arrest. The post-replication repair process is therefore able to correct DNA damage before cellular mitosis.

Alterations or defects in programmed cell death (apoptosis) may prevent normally lethal intracellular levels of cisplatin from killing cisplatin-resistant tumor cells. This may involve the alteration or deactivation of signaling pathways or components which activate apoptosis. Factors which inhibit the activity of signal transduction pathways may reduce cellular sensitivity to cisplatin. Wild-type p53 tumor protein is required for proper G1 cellular arrest and induction of apoptosis following DNA damage. Mutations in tumor p53 protein may be associated with decreased cellular sensitivity to cisplatin and prevention of apoptosis.

**Toxicities Associated With High-Dose Cisplatin**

High-dose cisplatin-induced toxicities are listed in Table I.

Early cisplatin treatments were hampered by a dose-limiting nephrotoxicity comprised chiefly of a dose-related, cumulative impairment of renal tubular function. Recent developments such as intensive patient hydration, the use of furosemide or other diuretic agents, and the administration of cisplatin in hypertonic saline solutions have markedly reduced the problems of nephrotoxicity and allowed the use of high-dose cisplatin therapy. At one major cancer center, thiosulfate protected against clinically significant cisplatin-induced nephrotoxicity in 131 patients. Chloruresis with high chloride concentrations stabilizes urinary cisplatin with the production of less cytotoxic and nephrotoxic aquated species in the renal tubules. The intense hydration and diuretic action of furosemide produce high volumes of glomerular filtrate which dilute cisplatin and its aquated species and reduce resorption into cells of the proximal tubules. Unfortunately, the use of high dose cisplatin has increased the clinical significance of other cisplatin-induced adverse effects. Nausea and vomiting have become more severe and protracted. Peripheral neuropathy has replaced nephrotoxicity as the dose-limiting toxicity. Ototoxicity with tinnitus and high-frequency hearing loss (4000–8000 Hz) occurs in most patients maintained on long-term, high-dose cisplatin. Myelo-suppression is more severe in high-dose than
### TABLE I

**Toxicities Associated with Cisplatin**

<table>
<thead>
<tr>
<th>Nephrotoxicity</th>
<th>Transient and reversible in 25% of patients. Frequency of dose-limiting severity is declining because of current protective measures.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal toxicity</td>
<td>Severe, protracted nausea and vomiting. Damage to small intestine (crypt cells).</td>
</tr>
<tr>
<td>Ototoxicity</td>
<td>Tinnitus or high-frequency hearing loss. May be dose-limiting in cases of long term cisplatin administration or multiple treatment cycles.</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>Peripheral neuropathy may be dose-limiting. Loss of taste sensation. Ataxia. Seizures.</td>
</tr>
<tr>
<td>Myelosuppression</td>
<td>Leukopenia. Thrombocytopenia</td>
</tr>
<tr>
<td>Allergic</td>
<td>Occasional anaphylactoid-like reaction.</td>
</tr>
</tbody>
</table>

This is consistent with the increased severity of ototoxicity in patients receiving cycles of high-dose cisplatin.

Some schedules of high-dose cisplatin administration may be associated with less cisplatin-induced toxicity than others. Using alternate routes of cisplatin administration other than intravenous may offer therapeutic advantages. Intraarterial delivery of cisplatin directly to tumor sites tends to expose the tumor to higher levels of drug without concurrently increasing toxicity. Intratumoral chemotherapy may offer the same advantages. Intrapertitoneal injections of cisplatin can produce much higher peritoneal levels of cisplatin than can result from intravenous injections. This can be important in preventing recurrence of gastrointestinal cancers at resection.

### Methods That Decrease Cisplatin-Induced Toxicity

Several methods are currently being evaluated for the reduction of high-dose cisplatin-induced toxicity (Table II). The use of hypertonic saline and vigorous hydration effectively reduces nephrotoxicity but does not protect against cisplatin-induced ototoxicity. In the guinea pig, the degree of hearing loss and cochlear hair-cell loss demonstrates a highly positive correlation with the dosage of cisplatin administered and with animal weight loss, but less positively with serum levels of cisplatin.

<table>
<thead>
<tr>
<th>Methods Used to Decrease Cisplatin-Induced Toxicity</th>
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<tbody>
<tr>
<td>Extensive hydration—increased urine volume</td>
</tr>
<tr>
<td>Administration of cisplatin in hypertonic saline.</td>
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<tr>
<td>Administration of excess fluids during cycles of treatment.</td>
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<tr>
<td>Use of diuretic agents.</td>
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<tr>
<td>Improved schedules of administration</td>
</tr>
<tr>
<td>Alternate routes of administration (other than IV)</td>
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<tr>
<td>Intra—arterial administration.</td>
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<tr>
<td>Intratumor administration.</td>
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<tr>
<td>Use of protective agents</td>
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<tr>
<td>Diethyldithiocarbamate (DDTC).</td>
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<tr>
<td>WR 2721.</td>
</tr>
<tr>
<td>Sodium thiosulfate.</td>
</tr>
<tr>
<td>Granulocyte—macrophage colony—stimulating factors (GmCSF) and other lymphokines.</td>
</tr>
<tr>
<td>Use of analogs such as carboplatin that exhibit decreases in nephrotoxicity, gastrointestinal toxicity, neurotoxicity, and ototoxicity</td>
</tr>
<tr>
<td>Carboplatin usage is associated with increased myelosuppression especially of platelet production.</td>
</tr>
<tr>
<td>Use of cisplatin—based drug combinations in chemotherapy (additive of synergistic anti-tumor actions may allow the use of lower doses of cisplatin)</td>
</tr>
</tbody>
</table>
sites by killing tumor cells disrupted and spilled into the operative field. The higher concentrations of cisplatin in the peritoneal cavity may persist and not be associated with increased toxicity. Improvement of differential toxicity between tumor and normal tissues may be improved by intratumor injection of a matrix system that allows slow release of cisplatin.

The use of protective agents against cisplatin-induced toxicity has enjoyed success. Diethyldithiocarbamate (DDTC) is a chelating agent that has demonstrated protective effects against cisplatin-induced toxicity without altering its antitumor effects in preclinical cancer models and it is being evaluated clinically. WR 2721 appears to protect against high-dose cisplatin-induced toxicities, especially neurotoxicity, and allows higher doses of cisplatin to be administered without abrogation of its antitumor effects. Sodium thiosulfate protects against cisplatin-induced toxicities, possibly by directly reacting with cisplatin, but the antitumor activity is reduced. However, the increased doses of cisplatin, allowed by the reduced toxicity conferred by sodium thiosulfate, increases the antitumor effect. Granulocyte colony stimulating factor is a potent stimulator of neutrophil production and has been shown to reduce the hematopoietic toxicity conferred by cisplatin.

Metallothionein induction has been reported to prevent toxic side effects of cisplatin and Adriamycin used in combination.

Methods that appear to enhance cisplatin antitumor efficacy include the coadministration of nifedipine, the use of cisplatin with isolated limb or whole body hyperthermia, synergistic combinations with other anticancer agents, or combinations of cisplatin with radiation therapy.

Coadministration of diethyldithiocarbamate (DDTC) with cisplatin reduces the toxicity of cisplatin in animals with no reduction of its anti-tumor action. Limited clinical trials have also been reported. Co-administration of DDTC with cisplatin to rats increases 5-hour biliary excretion of platinum about 18-fold. The relationship of this increase in biliary platinum excretion to reduced renal toxicity remains to be clarified.

Further increases of cisplatin doses would be expected to produce even better therapeutic benefits. This will be possible only if pharmacological techniques are found to combat other cisplatin-induced toxicities such as dose-limiting neurotoxicity, frequent ototoxicity and the increased degree of myelosuppression associated with high-dose cisplatin, especially when used with other myelosuppressive anticancer agents.

**Cisplatin Analogues**

In dealing with platinum compounds the term leaving group has been applied to the chlorine atoms or moieties that replace chlorine and are displaced under physiologic conditions. In general, the toxicity and pharmacokinetic behavior of platinum compounds appears to be greatly determined by the structure and characteristics of the leaving group. Agents with less easily displaced groups (e.g., cyclobutanedicarboxylates) have lower plasma protein binding, longer plasma half-lives, and greater renal excretion with less nephrotoxicity. Carrier ligands are the amino groups or similar substituents not displaced in physiologic environments. Interaction with DNA is believed to occur after cisplatin loses its chlorine atoms or leaving groups through aquation to yield a reactive electrophile. Cisplatin exhibits a bad toxicity profile. Modification of the drug to contain less labile leaving groups was investigated for alteration of this toxic feature. The search for a less toxic agent was pursued at the Institute for Cancer Research in the United Kingdom and led to the development of carboplatin.

Structural manipulation of the leaving group appears to influence tissue and intracellular distribution of the platinum coordination complexes while the stable carrier amine groups determine the structures and types of the DNA-platinum adducts. An interesting feature is that cisplatin and carboplatin are effec-
tive but not often curative and resistant tumors may arise. Use of another platinum compound which produces a different spectrum of DNA lesions may be effective against the cisplatin- or carboplatin-resistant tumors.\textsuperscript{18}

Some cisplatin analogues are discussed below:

1. Carboplatin: Carboplatin was developed at the Institute for Cancer Research in the United Kingdom.\textsuperscript{60} Nephrotoxicity studies in mice revealed that substitution of more stable ligands for the chloride leaving groups, as in cisplatin, reduced nephrotoxicity without sacrificing antitumor activity.\textsuperscript{61} In carboplatin the leaving group is a cyclobutanodicarboxylato ligand. Based on the superior therapeutic index, the greater ease of administration and more predictable individualized dosing has caused carboplatin to replace cisplatin in the treatment of many but not all platinum-sensitive tumors. The leaving group of carboplatin is a cyclobutanodicarboxylato ligand which undergoes a slower rate of aquation than the chlorides of cisplatin. Carboplatin is usually administered by rapid IV infusion. Carboplatin forms a similar spectrum of DNA lesions and cisplatin, but 100-fold higher concentrations to obtain equivalent DNA platination levels. Carboplatin exhibits a slower rate of aquation than cisplatin. The relative frequency of the individual lesions produced by carboplatin differ from those of cisplatin. These are \( \text{d(GpNpG)} \text{Pt}(40\%), \text{d(GpG)} \text{Pt}(30\%), \text{and d(ApG)} \text{Pt}(15\%).\textsuperscript{62} \) As with cisplatin, carboplatin produces relatively few monoadducts and interstrand cross-links.

Carboplatin is metabolized and excreted more efficiently through the kidneys than cisplatin. These characteristics help explain the reduced incidence and severity of nausea and vomiting, nephrotoxicity, and neurotoxicity of carboplatin when compared to cisplatin. Hydration may further reduce nephrotoxicity at higher carboplatin doses. Carboplatin is associated with a dose-limiting myelosuppression, especially of marrow platelet production which produces thrombocytopenia.\textsuperscript{18} Alopecia may occur, especially in the use of carboplatin-based combination chemotherapy.

Carboplatin exhibits an antitumor spectrum including the following: aerodigestive tract, cervical, childhood retinoblastoma, endometrial, esophageal, melanoma, ovarian, pleural mesotheliomas, soft tissue sarcomas, testicular cancers, and most other tumors sensitive to cisplatin.

Carboplatin, an analog of cisplatin, is being compared clinically to cisplatin. Carboplatin and cisplatin both undergo aquation hydrolysis to produce identical cytotoxic species and both form the same DNA adducts. Carboplatin does not exhibit the dose-limiting neurotoxicity associated with cisplatin. However, high-dose carboplatin is more myelosuppressive than high-dose cisplatin.\textsuperscript{16}

Currently cisplatin and its analog cis-diammine-cyclobutanedicarboxylato-platinum (II) (carboplatin) have been approved for use in the United States by the Food and Drug Administration. Clinical studies comparing the anticancer profiles of these two agents are ongoing.

2. DACH (1,2-diaminocyclohexane)-derivatives and analogues: The most promising of these is DACH-(oxalato)platinum-(II) known as oxaliplatin which forms chiefly intrastrand cross-links more rapidly than those produced by cisplatin.\textsuperscript{63} In addition, some unique cross-links form with oxaliplatin.\textsuperscript{64} In this compound the oxalato moiety is the leaving group and DACH the stable carrier group. Oxaliplatin is active against a range of cisplatin-resistant tumor cell lines.\textsuperscript{65} Oxaliplatin has a more slowly reacting leaving group than with cisplatin which explains its decreased nephrotoxicity. Oxaliplatin is associated with a dose-limiting sensory neuropathy which presents in two forms: (a) dysesthesia of the extremities which may even involve the perioral region but which is not of long duration or
cumulative with repeated doses, and (b) cisplatin-like which affects the extremities and is cumulative with repeated doses.\textsuperscript{18} Oxaliplatin-induced nausea and vomiting are mild and generally respond to 5HT3 antagonists.

DACH-ligand-containing platinum compounds differ from cisplatin in tissue specificity and apparently are non cross-resistant.\textsuperscript{66,67} Some cisplatin-resistant tumor cells can replicate DNA past cisplatin-induced DNA adducts but not past DACH-induced platinum adducts.\textsuperscript{68} This is another example in which structural alterations of carrier ligands may modify the spectrum of antitumor activity and overcome resistance to cisplatin or carboplatin.

Certain other DACH compounds have not been clinically accepted. DACH-(malonato)platinum is insoluble in aqueous solutions.\textsuperscript{69} DACH-(4-carboxyphthalato)-platinum(II) is too inactive against tumors,\textsuperscript{70} and tetraplatin (ormaplatin) is too nephrotoxic.\textsuperscript{71} Tetraplatin has four chlорide atoms as leaving groups and DACH as the stable carrier group. CI-973 (NK-121) exhibits myelosuppression and inactivity against tumor cells.\textsuperscript{72}

3. Platinum(IV) compounds: Platinum(II) structures are planar molecules while platinum(IV) compounds have an octahedral configuration.\textsuperscript{18} Iproplatin(IV) lacks antitumor activity,\textsuperscript{18} Ormaplatin(IV) is not stable under physiological conditions,\textsuperscript{72} and JM-16 produces myelosuppression affecting leucocytes and platelets about equally\textsuperscript{73} and undergoes rapid metabolic inactivation.\textsuperscript{60} Mild to moderate nausea and vomiting are common and respond best to metoclopramide or ondansetron orally in combination with dexamethasone. Nephrotoxicity and neurotoxicity are unusual.\textsuperscript{18} Whereas most platinum compounds are designed for IV usage, members of this group such as JM-16 are being designed to be orally bioavailable.\textsuperscript{60}

4. Bis-Platinum derivatives: These compounds utilize the “incorporation of two platinum molecules, each capable of adduct formation, together with a variable linker region.”\textsuperscript{18} The formation of interstrand cross-links is more common than that of intrastrand cross-links with use of these compounds. Therefore, DNA repair may be less efficient and repair proteins inactivated by these compounds.\textsuperscript{74} These compounds exhibit in vivo activity against a variety of cisplatin-resistant tumor cells.

5. Trans-Platinum(II) Analogue

Trans-isomers of cisplatin form structurally different DNA-platinum adducts than cis-isomers and exhibit less antitumor activity but are kinetically more reactive.\textsuperscript{18} A series of platinum compounds bearing the trans configuration have been developed and are under clinical investigation.\textsuperscript{75,76}

A platinum(IV) series which are metabolized to trans-platinum(II) compounds show promising preclinical activity and DNA-binding properties different from those of cisplatin.\textsuperscript{18,77,78}

6. Mixed Amine Platinum Compounds

A series of mixed amine platinum derivatives (platinum(II) and platinum(IV)) have been synthesized and are planned for clinical evaluation.\textsuperscript{18,60}

**Analytical Methods for Detecting Platinum Levels in Biological Samples**

Platinum has an atomic number of 78 and atomic mass of 195.08, with a valence of 2 or 4, and a melting point of about 1769°C. Its abundance is about 2 times 10⁻⁵% of the earth’s crust.\textsuperscript{79}

Some of the analytical methods used to determine cisplatin (Pt) levels in biological tissues and fluids include:\textsuperscript{80,81} (a) flame or electrothermal (flameless) atomic absorption spectrophotometry,\textsuperscript{82,83} (b) high-performance liquid chromatography (HPLC),\textsuperscript{84,85,86,87,88} (c) flame atomic emission spectroscopy (FAES),\textsuperscript{89} (d) inductively coupled plasma emission spectrometry (ICP-AES),\textsuperscript{90,91} (e) instrumental neutron activation analysis (INAA),\textsuperscript{80,81} (f) mass spectrometry (MS), (g) gas chromatography mass spectrometry (GC/MS) and com-
bined gas chromatography-mass spectrometry (GC/MS), including derivative spectroscopy,\(^{80,81}\) (h) colorimetric techniques,\(^{80,81}\) (i) x-ray fluorescence spectrometry (XRF),\(^{92}\) and (j) electrochemical techniques.\(^{80,81,93,94}\)

Many of these potential methods are too insensitive to measure the concentrations of platinum seen in clinical samples, or they possess other problems, making them impractical. Measurement of cisplatin in biological fluids has been virtually restricted to radioactive studies, flame (FAAS) or electrothermal atomic absorption spectrophotometry (EAAS) techniques, X-ray fluorescence, and HPLC methods.\(^{84,95}\) FAAS and EAAS techniques are probably the methods of choice in the measurement of platinum concentrations in biological samples.

Inductively coupled plasma atomic emission spectrometry (ICP-AES) is rapidly gaining importance in trace element analysis. Advantages over EAAS include its capability for simultaneous analysis of more than one element (quantometer design) and linear calibration curves over a wider range of values (five orders of magnitude or more) than EAAS. Disadvantages when compared to EAAS include poorer detection limits for most metals, expensive instrumentation, and the need for highly trained spectroscopists.\(^{91}\)

Colorimetric methods lack specificity for platinum but may react with a number of transition metals to form colored complexes.

Mass spectrometry (MS) and combined gas chromatography mass spectrometry (GC/MS) techniques have been used to measure chromium levels and to a lesser extent to measure concentrations of lead and selenium. The possible applications of these techniques to the measurement of other metals, such as Pt, have received little attention probably because these techniques are complex, require great operator expertise or skill, require expensive equipment and supplies, and require special air-conditioned environments and therefore are impractical for most clinical laboratories.

Another laboratory method to quantitate DNA-adduct formation involves enzymelinked immunosorption assays (ELISA) using monoclonal antibodies to detect major intrastrand DNA adducts.\(^{83}\) Alkaline elution methods and gel electrophoresis assays of purified DNA are available.\(^{83}\)

**Summary**

Cisplatin and its platinum antitumor analogues have revolutionized the field of human cancer chemotherapy. Improved protective methods allow better control of associated toxic side effects and the use of higher doses of platinum agents against emerging resistant tumors. New therapeutic applications and increased effectiveness of old therapeutic applications are realized and developed frequently. The expanding co-usage of the platinum antitumor agents with other classes of anti-cancer drugs, other platinum agents with different characteristic mechanisms of action, surgery, radiation treatments, immunotherapy, and other approaches to anti-cancer therapy show great promise, and are a part of the ongoing evolution and enhancement of cancer chemotherapy with platinum compounds.

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