

Platinum Co-ordination Complexes in Cancer Chemotherapy

A REVIEW OF THE FOURTH INTERNATIONAL SYMPOSIUM

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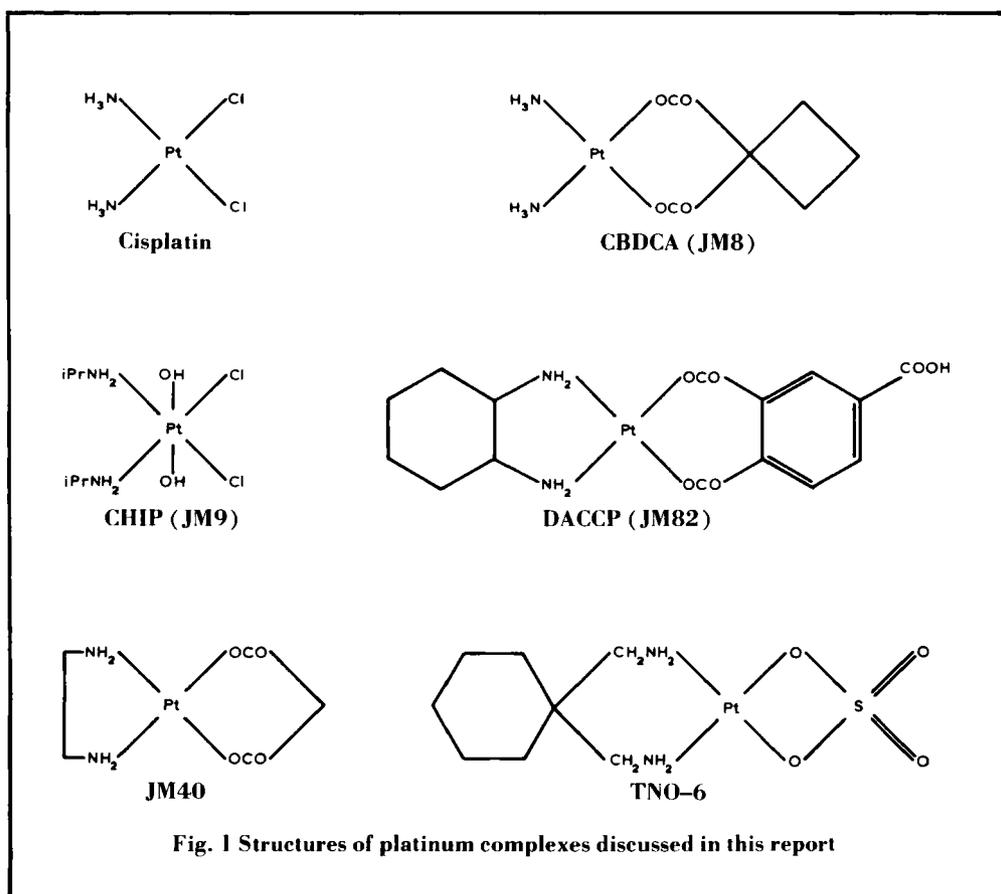
Following its widespread adoption into clinical practice in the early 1970s the drug cisplatin (*cis*-diamminedichloroplatinum(II), *cis*-[PtCl₂(NH₃)₂]) has improved substantially the response rates in a number of malignant conditions, particularly testicular and ovarian cancer. However, the clinical utility of the drug is limited by its toxic side effects. The most significant of these is kidney toxicity (nephrotoxicity), though in addition cisplatin produces severe nausea and vomiting, high frequency hearing loss and neurotoxicity. In the past decade immense efforts have been devoted to elucidating the molecular mechanism of the action of cisplatin, and its biochemistry and pharmacology, both in animals and man. Because of the toxic restrictions of the drug much attention has been devoted also to identifying analogues which retain cisplatin's useful anti-tumour properties, but which are so far as possible devoid of its toxic limitations. The international meeting held at the University of Vermont, Burlington, U.S.A. during June 1983 provided a timely opportunity, not only to review current knowledge on the molecular mechanisms of action of platinum complexes and their pharmacological properties, but also to compare data emerging from studies of those derivatives which are undergoing clinical evaluation. Inevitably, limitations of space and the scientific predilections of this reviewer may conspire to create an unintentional imbalance in the report of what proved to be an excellently conceived and highly successful meeting. If this be so, then apologies must be accorded in advance to those scientists whose work may seem to have been overlooked.

The reader is referred to Figure 1 for the structures of platinum complexes discussed and to the end of the article for a list of background references supporting this report. The proceedings of this conference are published by Martinus Nijhoff and full acknowledgement of the contributing authors, which is omitted from this review, can be found therein.

Molecular Mechanisms of Action

The reactions generally believed to be responsible for the anti-cancer activity of platinum co-ordinating complexes are the combination of the platinum complex with two donor groups of the bases of DNA, illustrated in Figure 2, producing links within one strand (intrastrand) or between the two strands (interstrand) of the double helix. There is much consensus that the initial binding of cisplatin to DNA occurs via the N7 nitrogen atom of a guanine base. However, the availability of a second co-ordination site in cisplatin facilitates further reaction with other components of DNA. Favoured binding sites are the N7 atom of another guanine molecule, the N1 and N7 of adenine and the N3 of cytidine. Intrastrand binding of cisplatin to guanine-guanine, guanine-adenine-guanine, and guanine-cytidine-guanine fragments has been reported. Interstrand guanine-guanine crosslinks are also produced but are detected in substantially lower quantities than are the intrastrand products.

The role of the interstrand link in the action of cisplatin was also questioned since this lesion is apparently formed and removed at the same rates in cells sensitive to cisplatin and in those that are resistant to it.



The effect of other drugs, such as bleomycin, on the interaction of cisplatin with DNA has been studied and correlated with the utility of these drugs in combination therapies for cancer treatment.

Some reservations were expressed concerning the theory that DNA is the primary intracellular binding site for platinum. The potential existence of other sites which might be associated with their action was implied by data which demonstrated the cross-linking of proteins in the cell nucleus to DNA by cisplatin. Significantly these proteins (non-histone nuclear proteins) are important in maintaining the fidelity of DNA replication.

Before concluding this account on molecular mechanisms it is important to acknowledge the recent development of sensitive

immunochemical techniques which have facilitated the accurate measurement of platinum-induced DNA crosslinks and their removal in mammalian cells. In general terms these techniques exploit the recognition of selective platinum-nucleotide sequences by an anti-serum raised against a cisplatin-DNA complex.

Pharmacology of Platinum Co-ordination Complexes

The major presentations under this heading revolved around discussions of the pharmacokinetics of cisplatin in relation to those of other platinum complexes currently undergoing clinical evaluation. The comparative pharmacokinetics of cisplatin in rat and man underlined the high chemical reactivity of this

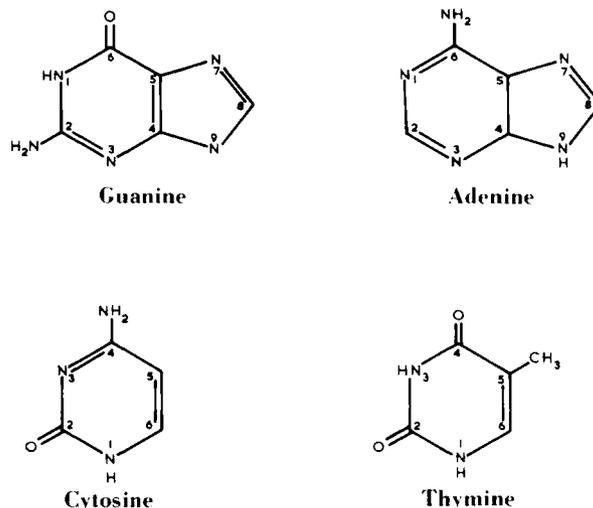


Fig. 2 Structures of the DNA bases

compound, its rapid binding to plasma proteins following its intravenous administration and its incomplete elimination in the urine; for example, patients excreted only 20 per cent of an administered dose in the first hours following administration. The decay of plasma levels of total platinum in patients receiving cisplatin can be explained in terms of three phases with a final phase half life considerably in excess of 24 hours. These data are confirmatory of many previous studies to which the reader has been referred in the first, background, section above.

All the papers discussing the comparative pharmacokinetics of CBDCA [diammine(1,1-cyclobutanedicarboxylato)platinum(II), JM8] in animals and man stressed its lower chemical reactivity compared with cisplatin, its more complete urinary excretion, its lower rate and extent of binding to plasma proteins and its lack of nephrotoxicity. All the reports argued that plasma clearance of CBDCA was multi-phase with a distribution phase half life in the range of three to 13 minutes for rabbit, rat and man, and a terminal elimination phase half life in the region of four to seven hours in the same

species. The main route of excretion is in the urine, 70 to 95 per cent of the total platinum administered being eliminated in 24 hours for rabbits, rodents and humans, the major part as unchanged drug. The concentrations of platinum detectable at 24 hours in the mouse kidney following treatment with equitoxic doses of either cisplatin or CBDCA are comparable, yet the former is nephrotoxic while the latter is not. Clearly the more stable molecular configuration of CBDCA underlies this difference. In addition CBDCA concentrates in mouse ovary while cisplatin does not. In a study of the pharmacokinetics of CBDCA in patients with impaired kidney function the terminal half life for total platinum was in excess of 24 hours, causing a potentially greater toxic risk in such patients due to their longer exposure to the drug. However, appropriate dose reduction allows control of CBDCA toxicity in these patients.

Broadly similar pharmacokinetic observations were encountered with CHIP [*cis*-dichloro-*trans*-dihydroxybis(isopropylamine)platinum(IV), JM9]. ¹⁹³Pt labelled CHIP was

used to study its pharmacokinetics and tissue distribution in the rat. In most tissues CHIP concentrations were approximately twice those achieved following the administration of an equitoxic dose of cisplatin. However, CHIP concentrations in ovary and brain were substantially lower than for cisplatin, which may be a disadvantage. CHIP elimination from rat tissues, measured as loss of ^{195}Pt occurred with an approximate half life of eight hours. The plasma decay of platinum species following the administration of CHIP in man occurs in two phases with a median elimination phase half life of 69 hours. Several urinary metabolites have been detected, one of which, *cis*-dichloro-bis(isopropylamine)platinum(II), corresponds to the reduced form of the parent drug. Total platinum urinary excretion in patients over 24 hours ranged from 15 to 61 per cent of the total drug administered.

Also reported were the results of an extremely careful comparative assessment of the pharmacokinetics in the dog of cisplatin and four analogues; CBDCA, CHIP, 1,1-di(aminomethyl)cyclohexane(sulphato)platinum(II) (TNO-6), and ethylenediamine(malonato)platinum(II) (JM40). The four analogues are all currently undergoing clinical study and it will be of interest to see how predictive is the dog model of human pharmacokinetics for platinum analogues.

Clinical Studies with Platinum Co-ordination Complexes

The Complex DACCP, JM82

Results of a phase I study of 4-carboxy-phthalato(1,2-diaminocyclohexane)platinum(II) (DACCP, JM82) were reported in which 46 heavily pretreated patients received JM82 by rapid intravenous infusion every 3/4 weeks in the dose range 40 to 800mg/m². The units mg/m², that is milligrams of drug used per square metre of patient surface, are used as a more reliable indication of drug tolerance than mg drug/kg patient weight. The major dose limiting toxicity was thrombocytopenia (reduction in blood platelets), the nadir occurring on day 11 after treatment. At 640mg/m²

some evidence of nephrotoxicity was observed. One treatment-related death occurred due to renal failure, though this patient also received aminoglycoside antibiotics which can impair renal function. Many patients experienced nausea and vomiting, though this seemed quantitatively less than that induced by cisplatin. Some 15 per cent of patients experienced fevers, 30 per cent diarrhoea and 10 per cent allergic reactions. Two partial responses were seen, these being in head and neck, and in cervical cancer, while two minor responses were observed for one gastric and one non small cell lung cancer.

Of twenty-eight evaluable non small cell lung cancer patients entered into a phase II study only one partial remission was observed. In a similar phase II study of colon cancer, almost completed, no responses have been seen. The authors conclude that this drug is unquestionably less active than cisplatin, though it is certainly less toxic. Other difficulties with this drug include its purity, stability and formulation.

The Complex TNO-6

A phase I study of 1,1-di(aminomethyl)cyclohexane(sulphato)platinum(II) (TNO-6) was reported involving 53 patients, 44 of whom had received prior treatment with cisplatin, in the dose range 5 to 35mg/m² by infusion over three to six hours. The maximum tolerated dose was 35mg/m², toxicity being due to leucopenia (reduction in white blood cells) and thrombocytopenia, the nadir occurring on day 14 after treatment. However, there was also a variety of evidence of nephrotoxicity. In particular, proteinuria, indicative of kidney damage, becomes apparent at 25mg/m² and is cumulative following repeat treatments, for example 5g at day 3 to 7 on the third cycle of treatment. Significantly TNO-6 induced massive proteinuria in the dog, though none of the other platinum analogues in clinical study produced this effect. This agent appeared not to be substantially less emetic than cisplatin. Responses seen: one complete remission in a lung metastasis of breast cancer, one partial

response in non small cell lung cancer, two minor responses (one ovary, one small cell lung cancer), one fall in circulating tumour markers in a patient with testicular teratoma. It seems likely that the severe toxic side effects of TNO-6 may prohibit its further clinical study, particularly since other non-nephrotoxic and active analogues are available.

The Complex CBDCA, JM8

The results of a phase I study of diammine (1,1-cyclobutanedicarboxylato) platinum (II) (CBDCA, JM8) were reported in which 60 patients had been entered at doses between 20 and 520mg/m² given by 1 hour infusion at four weekly intervals. Many of these patients had received prior treatment with cisplatin. Thrombocytopenia was the dose-limiting toxicity, the platelet nadir occurring at 21 days after treatment. Vomiting was seen in most patients treated at doses above 200mg/m², though this side effect was less severe than with cisplatin. No renal toxicity or hearing loss was observed and only minimal and infrequent signs of neurotoxicity were seen. Recommended dose for phase II evaluation is 400mg/m². Responses were seen in ovarian cancer and mesothelioma. Two phase II studies in ovarian cancer were also reported. The first was of 33 patients who had been treated previously with cisplatin. One complete (CR) and six partial (PR) responses were seen. This included one complete and four partial responses in the subgroup of 19 patients definitely resistant to cisplatin.

In the second study of 36 ovarian cancer patients who had not previously received cisplatin a response rate comparable to that which would be expected with cisplatin was observed (8 CR, 11 PR), though with much reduced side effects. In a second phase II study of 18 patients with small cell carcinoma of the bronchus, a response rate of 34 per cent was seen, while two of eleven patients with non small cell carcinoma also responded.

It was generally concluded that CBDCA is a much less toxic drug than cisplatin, possessing at least comparable activity which merits further clinical evaluation. In addition, there

is some evidence that it exhibits activity against cisplatin resistant disease.

The Complex CHIP, JM9

Two repeat dose phase I investigations of *cis*-dichloro-*trans*-dihydroxybis (isopropylamine) platinum(IV) (CHIP, JM9) were reported. One, using a schedule of five daily doses repeated every four weeks in the dose range 20 to 65mg/m²/day, included 34 patients where the dose limiting toxicity was thrombocytopenia. The maximum tolerated dose in patients who had received previous chemotherapy with other drugs was 45mg/m²/day. Partial responses were observed in one patient with adenocarcinoma of the lung and in another patient with colon carcinoma metastatic to the lung.

Preliminary results from the other continuing comparison study were reported where 16 heavily pretreated patients received CHIP as a single intravenous infusion once weekly for four weeks in the dose range 40 to 95mg/m². Treatment was repeated following a two week observation period. Thrombocytopenia was the dose limiting toxicity, the maximum tolerated dose being 95mg/m² per week for four weeks. No nephrotoxicity was observed, though all patients experienced mild to moderate nausea and vomiting.

Conclusions

Unquestionably this was a productive and exciting meeting. The molecular pharmacology of platinum complexes is moving away from the somewhat restrictive area of nuclear DNA to embrace reactions with nuclear proteins which may be of more significance. Possibly by the next international meeting these latter studies may provide an answer to some of the enigmas shrouding the mechanisms underlying the selective cytotoxicity of platinum complexes.

At the clinical level a range of platinum complexes, each demonstrably less toxic in animal models than cisplatin, have undergone evaluation. CBDCA (JM8) would appear to be a viable alternative to cisplatin, though CHIP (JM9) also exhibits substantially less toxicity than cisplatin. Phase II/III results on JM9 are

awaited and upon their completion it could be developed further. Of the remaining compounds, JM82 and TNO-6 would appear not to merit further study, while JM40 is still at an early stage of its phase I evaluation. Interest-

ingly, although JM82 and TNO-6 exhibit activity against experimental cisplatin-resistant tumours, no evidence has accrued to suggest that these compounds would possess comparable activity in the clinic.

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The United States National Fuel Cell Seminar

Progress on fuel cells was discussed at the meeting held at Orlando, Florida during November 1983. The most notable developments were the test programmes organised by gas and electricity supply utilities, and also the intense efforts by Japanese industry.

Overall, the conference presented an impressive picture of fuel cell commitment. In the United States alone, expenditure on research and development, and demonstration programmes amount to \$78 million, of which \$55 million is devoted to phosphoric acid cells using platinum catalysts. Japanese competition is likely to lend added impetus to rapidly commercialise these new energy generators.

The on-site/integrated energy system programme is proceeding well, with 45 fuel cells being installed by 30 gas utilities in the U.S.A. and Japan. Surveys carried out by gas companies indicate a substantial market for combined heat and power devices in a variety of applications including nursing homes and hotels. The present manufacturers (United Technologies Corporation) were said to be increasing module size from 40kW to between 200kW and 400kW, while Engelhard Corporation are constructing 100kW generators.

Two 4.5MW power stations have been built by United Technologies Corporation and installed in New York and Tokyo for operation by Consolidated Edison and Tokyo Electric Power, respectively. The New York unit has

been plagued by legislative and technical problems and it is now hoped to start operation early in 1984. The Tokyo plant was started up in April 1983, site preparation, installation and commissioning having taken less than 3 years. To date, the plant has produced 177,000kWh of power at an overall efficiency of 38.6 per cent.

The efforts of Japanese industry were reflected in the number of delegates attending, 55 out of 315, and in the numerous papers presented. The Ministry of International Trade and Industry are funding two major groups to develop 1MW phosphoric acid fuel cells by 1986. Mitsubishi and Fuji Electric Company are studying atmospheric pressure technology, operating at 190°C, with a current density of 200mA/cm² at 0.7 volt per cell and a platinum loading of 0.9mg/cm². They have made a 50kW unit and are designing a 200 to 300kW module.

In addition, Hitachi and Toshiba are collaborating to develop high pressure technology, operating at 7 atmospheres and 205°C, the cells giving 220mA/cm² at 0.72 volts, with a platinum utilisation of 6.5g/kW.

Each of the Japanese companies are developing systems independently, Toshiba having built a 50kW unit and Fuji having had a 30kW generator on trial at a power station in Kansai province. Sanyo reported progress on their 50kW combined heat and power unit, developed using technology licensed from Energy Research Corporation. D.S.C.