Platinum Coordination Complexes in Cancer Chemotherapy

A REVIEW OF THE SECOND INTERNATIONAL SYMPOSIUM

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Effective anti-cancer agents are sometimes found by large-scale testing against animal tumours and sometimes by the rational design of chemicals. More often than not, however, they originate from a chance observation made in another area of research. Such was the discovery of the platinum compounds with anti-cancer activity which arose from the now famous observation of Professor Rosenberg and his colleagues that electrolysis products from platinum electrodes could inhibit the growth of bacteria. Observations of this sort remain a scientific curiosity unless followed up by skilful research. Rosenberg's publication on "Platinum Compounds; A New Class of Anti-tumour Agent", which identified the inhibitory compound, was soon followed by a series of papers showing that *cis*-dichlorodiammine platinum (II) (commonly referred to nowadays as cis Pt II) was an inhibitor of many different types of animal tumour.

The cancer clinician has relatively few drugs available for treatment of inoperable cancer. None is highly selective for cancer cells and their use is almost always associated with serious toxicity to the patient. Furthermore, there are still many types of cancer, particularly the solid carcinomas of the lung and digestive tract, which do not respond well to any form of treatment. Naturally, a new class of agent with high activity in animal tests will arouse great interest, since a novel structure may indicate a novel mechanism of action against those human cancers which do not respond at present to chemotherapy.

The growing interest in the platinum compounds was evident from work presented at the first International Symposium on the bacterial, viral and anti-tumour activities of platinum compounds held at Michigan State University in 1970 and later at a special session of the VII International Congress on Chemotherapy in Prague in 1971. Both meetings were, however, preliminary inasmuch as clinical studies of the platinum compounds were only just beginning. The Second International Symposium on Platinum Coordination Complexes in Cancer Chemotherapy, held at Wadham College, Oxford in April, devoted one day to the results of the first clinical trials of cis Pt II, and so for the first time enabled a preliminary assessment of the likely usefulness of platinum complexes in the clinic. Besides the session on clinical trials there were four half-day sessions on the chemistry of the platinum compounds, their reactions with biomacromolecules and their biological effects in *in vitro* systems and in whole animals. From this material an attempt can now be made to answer the three questions that must be asked of any new class of anti-cancer agent.

What is the mechanism of action of the agent and does it act quite differently from known anti-cancer agents?

How effective is the agent in the clinic when used either alone or in combination, and is it useful in the treatment of cancers which do not respond to known agents?

Is it possible to design analogues of the compound with less side effects and more potent anti-cancer action?

A review of the chemistry of the coordination complexes delivered by Dr R. J. P. Williams, of the University of Oxford, made it quite clear that other types of complex could be synthesised with properties similar to

cis Pt II. This was confirmed by Dr M. J. Cleare, of Johnson Matthey, who summarised the data of various authors on rhodium, iridium and palladium complexes, some of which have anti-tumour activity in experimental systems. Rhodium compounds are known to inhibit cell division in *E. coli*, but, unfortunately, no correlation was observed between this property and anti-tumour effect, so what might have become a rapid and simple test system for new anti-tumour metal complexes is not practicable. Among the most interesting new types of anti-tumour agent described were the platinum "blues" already referred to by Dr Rosenberg in his introductory talk. These complexes of platinum containing uracil and thymine ligands are of particular interest because of their extreme solubility in water; some of the new derivatives of cis Pt II have high selectivity against animal tumours, but are virtually insoluble in water.

In the second session, a review by Dr A. J. Thomson (University of East Anglia) and a report on a number of papers by Dr A. B. Robins (Institute of Cancer Research) provided convincing evidence of the importance of purines as a cellular target for the platinum compounds. Using a variety of nucleosides, the N(7) atoms of adenosine and guanosine were shown to be susceptible to attack by cis Pt II as well as the $6NH_2$ of adenosine and the N(3) of the pyrimidine nucleoside cytidine. Using different polynucleotides, it was shown that Poly A was particularly reactive to $PtEn^{C14}Cl_2$. A number of reaction products were identified, indicating that besides monofunctional reaction, bidentate chelation involving one base or cross linking of two bases could also occur. Examination of molecular models of DNA revealed a number of sites where cross-linking would take place, especially where there was a sequence of adenine-thymine and thymine-adenine base pairs. In such a situation the two adenosine residues lay above one another about 3 Å apart and therefore were ideally situated for bidentate cis-isomer linking. Direct evidence for cross-linking of DNA was obtained from thermal melting studies where, at high platinum diamminedichloride concentration, complete renaturation of thermally melted DNA was observed.

In Vitro Effects

The session on *in vitro* effects was elegantly reviewed by Dr J. J. Roberts, of the Chester Beatty Institute, with Dr H. C. Harder, of the George Washington University as rapporteur. Cis Pt II has a variety of effects on viruses and bacterial and mammalian cells in culture. The underlying theme of both talks was that despite the diversity of biological effects observed almost all could be ascribed to a primary attack on DNA. Cis Pt II was particularly effective in preventing the transforming ability or infectivity of a number of viruses if they were of the double-stranded DNA type, but not if they were of the single-stranded RNA type. RNA viruses such as Rous sarcoma virus, which were inhibited by cis Pt II, were known to require a DNA intermediate for replication. Many of the experiments that had previously been used to show the importance of DNA as a target site for the alkylating agents have now been extended to studies with the platinum complexes. Thus, like many alkylating agents, cis Pt II induces prophage either directly or indirectly in virus infected cells and the importance of DNA repair mechanisms in determining sensitivity was evident from studies on mutant bacteria which have lost the ability to repair particular types of DNA damage. Effects on DNA were shown to be largely irreversible and a number of papers showed unequivocally that at dose levels of cis Pt II just causing cell kill, there was a considerable effect on DNA synthesis but no effect at least over the first few hours on RNA or protein synthesis. Using synchronous cells in culture, it was found that the agents were not acting specifically on any phase of the cell cycle, only small differences in sensitivity occurring if the agent was added during different phases of the cycle. The most

debated point in the subsequent discussion was the nature of the cytotoxic DNA reaction. While cross-linking of either the inter- or the intra-strand type can occur, studies using cis- and trans-Pt II and Pt IV derivatives did not clearly point to any particular type of DNA reaction as being the most cytotoxic.

Animal Trials

A review of the data obtained in whole animals was presented by Dr T. A. Connors. The rapporteur of the session, Dr P. B. Conran (University of Connecticut), had the hardest task of the meeting in being asked to report on no less than 15 papers dealing with recent research in this field, but this he did with remarkable clarity. Cis Pt II is clearly one of the most active agents in experimental chemotherapy, having effects ranging from good inhibition to complete cures in animals transplanted with a variety of tumour lines. Not only transplanted tumours are inhibited but also some virally and chemically induced tumours which are generally less amenable to chemotherapy. It did, however, resemble the best alkylating agent cyclophosphamide in its spectrum of action and in a number of other properties including its inability to inhibit tumours with acquired resistance to alkylating agents. However, there are also sufficient differences to hope that cis Pt II or its analogues may be active against tumours not responding to alkylating agents. Many analogues of cis Pt II have now been synthesised and tested and some appear to be superior in having a much higher safety margin due to a lower toxicity. The general cytotoxic properties of cis Pt II was evident from papers presented on its immunosuppressive action and on its ability to suppress adjuvant-induced arthritis. Encouraging results were obtained on the use of cis Pt II in combination with other anti-tumour agents. Combination chemotherapy has been responsible for some of the big advances made in recent years, especially in the treatment of malignancies such as acute lymphoid and myeloid leukaemia and Hodgkin's disease, and cis Pt II was found to be particularly effective in its anti-tumour effects when used in combination with a number of clinically useful agents. It was also effective in combination with γ-irradiation. Some experiments were described which indicated that, against certain tumours, the host's immunological response combined with the action of the platinum complex in causing tumour regression. Stimulation of the host's immune response potentiated the effect of cis Pt II although timing was important since the complex itself suppresses the immune response. This finding is of clinical importance since recent work has demonstrated that clinical responses may be greatly improved by immunostimulation after chemotherapy.

Clinical Testing

The all-day session on clinical trials began with Dr S. Carter (National Cancer Institute), who outlined the world-wide clinical programme of the American National Cancer Institute. Because there are so many different types of cancer at various stages of growth at time of diagnosis, and since response can be measured subjectively or objectively ranging from slight tumour regression to complete remission, the results of clinical trials are notoriously variable unless strictly controlled. The National Cancer Institute programme conducts its clinical trials in three phases, according to a strictly controlled protocol. It was encouraging to note that most of the clinical papers presented data using this protocol. Phase I of the trial is simply a means of determining the maximum dose level of the new agent tolerated by patients and the optimum schedule of administration. It is also an important preliminary step to determine whether any form of toxicity occurs that was not predicted from animal studies. Since the patients entering this phase of the trial have advanced cancer, good responses are not necessarily expected. The second phase of the trial serves to indicate whether the compound has any useful anti-tumour effect when used under the

optimum conditions determined from Phase I studies. For this purpose, at least nine out of ten classes of cancer are used with adequate numbers of patients in each group; the groups being strictly controlled with respect to status of the patient and the disease, dosage schedule, measurement of response and statistical evaluation of the results. In the case of cancer where drugs of choice are already quite effective, such as in Hodgkin's disease, the new agent may be used after failure of the chosen treatment in comparison with another agent. Finally, a new agent enters Phase III if it passes the criteria of Phase II. In this final phase, the agent is compared in a trial, with the drugs of choice and in combination with them and with other forms of treatment that may be used.

At present only one Phase II trial of cis Pt II is under way, against advanced carcinoma of the large bowel. Of twelve patients so far evaluated, no responses were obtained, which is disappointing, in contrast with the drug of choice 5-fluorouracil. It was questioned, however, as to whether the dose schedule of cis Pt II used in this trial was optimal.

Phase I studies had confirmed, in man, the toxicity predicted from dogs and monkeys, of bone marrow depletion and toxicity to the intestinal mucosa and kidney, but not the predicted liver damage. Many patients also suffered from deafness which was not predicted from animal studies.

Most of the work presented dealt primarily with Phase I studies and were, therefore, accounts of toxicity in man. The limiting toxicity to the kidney had obviously made clinicians a little cautious in extending their trials to Phase II. It was pointed out, however, that kidney toxicity need not prevent the use of a drug if it proved to be highly effective, since a number of antibiotics used in "life or death" situations also cause severe kidney damage. Furthermore, this toxicity could be minimised by hydration of the patient prior to, and during infusion of cis Pt II.

A number of authors had observed good responses in Phase I studies, including Dr J. M. Hill (Wadley Institute), who found some good remissions in squamous cell carcinoma. Two papers were worthy of special mention: Dr H. J. Wallace (Roswell Park), reporting on a preliminary trial on patients with tumours of the genitourinary tract, observed particularly good responses with testicular tumours and a Phase II clinical trial is planned. Dr Eve Wiltshaw (Chester Beatty) in a trial of 25 patients with adenocarcinoma of the ovary, obtained seven good responses. This was of particular importance since cis Pt II was only given after conventional surgery and treatment with the agent of choice, the alkylating agent chlorambucil. Once resistance to chlorambucil had developed, patients had, in some cases, been shown to be cross-resistant to other alkylating agents even at high doses. To obtain remissions with cis Pt II at this stage implies that the compound certainly differs from the alkylating agents in some aspects of its action. Although the remissions obtained both with testicular and ovarian tumours were usually only for a few months, such work must be followed up.

The general opinion of the clinicians was that although the kidney toxicity of cis Pt II might prove limiting and certainly made one cautious in using it in a Phase II clinical trial, it was a compound with interesting properties. They looked forward to the availability for clinical trial of the new derivatives reported on earlier in the symposium. Such compounds might retain the useful anti-tumour properties of cis Pt II, but not have the unwanted kidney toxicity.

Sir Alexander Haddow, the former Director of the Chester Beatty Research Institute, in his concluding speech, was optimistic about the clinical future of the platinum compounds. Although they obviously had some similarities to known agents, they were sufficiently different in some properties to hope that the results presented were just the beginning of the story of the use of platinum compounds in cancer chemotherapy.