

# Scientific Symposium on Paraplatin

## AN IMPROVED PLATINUM ANTI-CANCER DRUG

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The commercial launch of the second generation Cisplatin analogue "Paraplatin" (Carboplatin) on 7 April marked the culmination of a twelve-year development programme pioneered by Johnson Matthey and the Institute of Cancer Research. Though Carboplatin was first synthesised in 1971, it was not until the launch of Cisplatin in 1978/79 (1) that real impetus was given to the analogue studies, as the need to develop a drug less toxic than Cisplatin became evident. The search was taken up on a worldwide basis, the enormous interest and commitment to this study being evidenced by four international symposia, the most recent of these being reviewed in this journal in 1984 (2). That symposium highlighted the clinical trials then being undertaken with several platinum compounds, though it was apparent at that stage that Carboplatin was the leading candidate for commercialisation. Prior to entry into clinical trials, Carboplatin was the subject of a major development programme at Johnson Matthey to define its structure and stability, and the quality assurance procedures necessary for the manufacture of the bulk compound to the exacting standards required of pharmaceutical products. Throughout this period close contact with the Institute of Cancer Research and Bristol-Myers ensured that the necessary pre-clinical biological screening data for anti-tumour activity, drug distribution and toxicity were also obtained.

The launch at Imperial College, London was accompanied by a scientific symposium with presentations by those most influential in the development of this new drug to an audience of leading cancer specialists and the medical and scientific press. The symposium was opened by Britain's eminent inorganic chemist, Nobel laureate Professor Sir Geoffrey Wilkinson.

Appropriately, the opening talk was presented by one of Professor Wilkinson's former students, Dr. M. J. Cleare (Johnson Matthey PLC) who was the first to synthesise Carboplatin in Professor Rosenberg's laboratory at Michigan State University. His talk on the structure-activity relationships for platinum compounds and the chemistry of Carboplatin highlighted the stability of the new drug, the structure-activity relationships for platinum ligand instead of the chloride ligands of Cisplatin and results in greatly reduced toxicity compared with the parent compound, while retaining equivalent anti-tumour activity. In particular, animal tests showed minimal kidney toxicity and reduced nausea, with bone marrow toxicity being the dose limiting effect.

### Preclinical and Clinical Studies

Professor K. R. Harrap of the Institute of Cancer Research described the preclinical evaluation of a number of platinum analogues, conducted in collaboration with Johnson Matthey, which led his group to recommend Carboplatin as the compound of choice for clinical trials from some 350 compounds tested. Of particular importance in this selection was the narrow spectrum of toxicity of the compound, as indicated above, and its activity in a lung tumour model. Carboplatin was the only compound out of eight final candidates which would cure mice bearing this tumour using a non-toxic dose. His group conducted pharmacokinetic studies in mice which indicated higher platinum levels in the ovary for Carboplatin compared with an equitoxic dose of Cisplatin, suggesting that Carboplatin might have potential for ovarian cancer treatment.

Presentations on clinical studies with Carboplatin were dominated by speakers from the

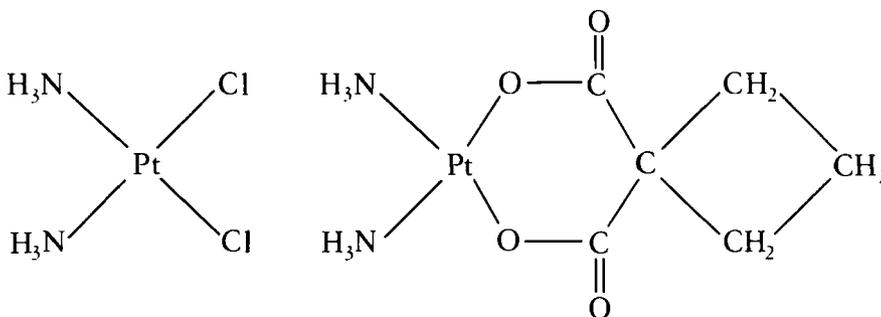
The active agent of the new anti-cancer drug, "Paraplatin", is currently prepared at the Johnson Matthey Technology Centre, Sonning Common. This compound was originally codenamed JM-8, being the eighth compound submitted by Johnson Matthey for evaluation by Bristol-Myers. It is produced in a clean room facility to meet the high standards of purity required of a pharmaceutical intermediate. The drug has been licensed in the U.K. for the treatment of ovarian and small cell lung cancer and has the major advantage of reduced toxicity, cutting down the adverse side effects which were the unfortunate results of its predecessor, Cisplatin



Royal Marsden Hospital, which participated in the first clinical trials of the drug in 1981, and which has maintained a leading role in its clinical development since that time. The Phase I studies aimed at confirming the toxicity profile of the new drug were described by Dr. H. Calvert. As anticipated, bone marrow toxicity proved to be dose limiting with a reduction in blood platelets being the most severe effect. Other toxicities normally associated with Cisplatin (kidney toxicity, peripheral nerve damage, hearing loss) were almost totally absent. Also the nausea and vomiting following administration of the drug was significantly less for Carboplatin than for Cisplatin. One ongoing development of this trial is an attempt to improve the accuracy of dosing for patients of different kidney function. Since clearance of the drug from the body is dependent on kidney function, patients with poor kidney performance are exposed to higher levels of the

drug over a longer period for the same dose than those with good kidney function. By monitoring drug excretion and kidney function in a number of patients a formula has been derived which allows prediction of the dose required to achieve any desired concentration  $\times$  time value, once the patient's kidney function has been measured by standard tests. This work is still in progress and at present a standard dose of  $400 \text{ mg/m}^2$  (or slightly less for heavily pre-treated patients) is recommended.

Dr. Eve Wiltshaw described the Phase II/Phase III studies for the treatment of ovarian cancer at the Royal Marsden Hospital. These trials formed the basis of the licence application for the use of Carboplatin for ovarian cancer (which affects 4000 to 5000 women in the United Kingdom each year) which was granted to Bristol-Myers on 25th March. In Stage III disease (metastatic cancer limited to the lower abdomen) Carboplatin showed equivalent



The structure on the left is that of Cisplatin, cis-diamminedichloroplatinum(II) the anti-cancer platinum drug launched in 1978/79, while that shown on the right is the second generation analogue Carboplatin, diammine(1,1-cyclobutanedicarboxylato)platinum(II). This second generation drug combines similar activity with reduced toxicity

activity to Cisplatin with a similar long term survival rate of about 30 per cent, but producing markedly less toxicity. There was some evidence of a lack of cross-resistance between the two drugs suggesting that failure of one of them to halt the disease should not be taken as a reason not to attempt the use of the other. For Stage IV patients (metastatic disease spreading beyond the lower abdomen) long term survival with current regimens is low (about 10 per cent) and a trial is in progress to evaluate a high-dose therapy with Carboplatin. Doses up to 1000 mg/m<sup>2</sup> are given with careful monitoring of the patient's blood counts; blood transfusions and bone marrow transplants being given when required. A response rate of 60 per cent has been achieved initially, with half of these being complete remissions. This trial will therefore be continued to allow better definition of the dosing regime and to confirm these promising results.

Data on the treatment of small cell lung cancer (S.C.L.C.), which is the other indication for which the use of Carboplatin has been approved, was presented by Dr. I. Smith. S.C.L.C. represents about 20 per cent of the lung cancer cases in the U.K. (7000 to 8000 patients) and is the most chemo-sensitive form of lung cancer. Responses, when achieved, are often of short duration and thus drugs of low toxicity are necessary when considering pallia-

tive therapy for patients with advanced disease. The low toxicity of Carboplatin makes it an acceptable candidate in this area. Initial evaluation as a single agent in previously untreated patients indicated a good response rate, 60 per cent, higher than seen for any other single agent to date. Responses were, however, of very short duration (mean 4.5 months) and trials are now in progress to evaluate combination regimens which may lead to more enduring remission. High-dose Carboplatin is also being evaluated in patients with all types of lung cancer at a less advanced stage, where there is the possibility of achieving complete remissions. Doses up to 1600 mg/m<sup>2</sup> have been used at which level the bone marrow toxicity, though severe, is still manageable. Other toxicities including some hair loss, diarrhoea and general malaise occur at this dose but these are not sufficiently severe to prevent continuation of therapy. Too few patients have been treated to date to evaluate the benefit of this treatment but the initial results are sufficiently promising to warrant continuation of the trial.

Professor M. Peckham described the use of Carboplatin in testicular cancer. As a consequence of the high cure rate now possible for this disease using Cisplatin-containing combination therapy, the evaluation of Carboplatin has been restricted to patients who could not receive Cisplatin due to complications from its

toxicity or to patients with very advanced disease for whom the prognosis was not very favourable. The accrual of patients into the study has thus been slow, but results to date indicate that Carboplatin retains the pronounced activity of Cisplatin against testicular tumours and that its use in combination with other drugs such as Etoposide and Bleomycin can produce a high percentage of disease-free patients even for very advanced tumours.

Two other speakers, Dr. B. Leyland-Jones of the National Cancer Institute and Dr. C. Franks of Bristol-Myers Co. Ltd., provided a broader view of the trials involving Carboplatin in the U.S.A. and Europe, respectively. The drug is being evaluated in Phase II trials for a wide spectrum of tumours, and where activity is seen Phase III trials will be initiated to define whether Carboplatin can offer any benefit over the best existing therapies. In a number of these trials Carboplatin is being compared with Iproplatin (JM-9).

### Continuing Developments

The proceedings were concluded by Bristol-Myers', Senior Vice-President for anti-cancer research, Dr. S. Carter. He reviewed the day's presentations, acknowledging the contribution made by Professor Harrap's team at the Institute of Cancer Research and the clinicians of the Royal Marsden Hospital to the development of Carboplatin, enabling its launch as "Paraplatin" only five years after the initiation of clinical trials. He outlined the Bristol-Myers'

strategy for the development of "Paraplatin" through continuing clinical trials which will involve its inclusion in combination drug therapies and in combined treatments with irradiation (3) and/or surgery. In addition, high-dose therapies and the use of alternative routes of administration will continue to be explored. Finally, he indicated that Bristol-Myers remains active in the further development of platinum drugs, in collaboration with Johnson Matthey, with particular attention being paid to improvements in selectivity by targeting with monoclonal antibodies.

The symposium clearly highlighted the role of Carboplatin as an analogue of Cisplatin. The new drug possesses similar activity, and probably a similar spectrum of activity, but has a very much narrower and more manageable range of toxicities. In view of the number and the promise of ongoing trials it is anticipated that the use of Carboplatin will be extended beyond the ovarian and small cell lung cancers for which it has been approved initially.

### Acknowledgement

"Paraplatin" is a trade mark for Carboplatin, JM-8, and is owned by Bristol-Myers Co. Limited. Applications for the registration of "Paraplatin" as a trade mark are pending.

### References

- 1 E. Wiltshaw, *Platinum Metals Rev.*, 1979, **23**, (3), 90
- 2 K. R. Harrap, *Platinum Metals Rev.*, 1984, **28**, (1), 14
- 3 E. B. Douple, *Platinum Metals Rev.*, 1985, **29**, (3), 118

## The Chemistry of the Platinum Group Metals

Following the successful meetings held in Bristol in 1981 and Edinburgh in 1984, a third international conference on this topic is to be held in Sheffield from 12th-17th July 1987, organised by the Dalton Division of the Royal Society of Chemistry. Among the topics to be discussed are homogeneous and heterogeneous catalysis, organic synthesis, bio-inorganic chemistry, chemotherapy, fuel cells, metal surface structure, and organometallic, coordination and hydride chemistry.

Professor P. M. Maitlis will deliver his Dalton Division Presidential Address at this

conference and the T. A. Stephenson Memorial Lecture will be given by Professor E. A. V. Ebsworth. Distinguished overseas scientists who have already agreed to give talks include Prof. G. P. Chiusoli, Prof. R. H. Crabtree, Dr. D. B. Dombek, Prof. M. Ichikawa, Prof. H. D. Kaesz, Dr. D. Milstein, Prof. I. I. Moiseev and Prof. A. Yamamoto.

Anyone wishing to contribute to the poster sessions, or to receive further information, should contact Dr. J. F. Gibson, Secretary (Scientific), Royal Society of Chemistry, Burlington House, London W1V 0BN, England.