Platinum Anti-Cancer Agents

TWENTY YEARS OF CONTINUING DEVELOPMENT

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It is now 20 years since the publication of the anti-tumour activity of platinum compounds by Barnett Rosenberg and his colleagues. During this time platinum-based drugs have made a major contribution to cancer therapy with significant benefits for many patients. This article summarises the history of platinum agents in this field and indicates the current and possible future directions of research.

It was in 1962 that an apparently unrelated experiment in cell division provided the stimulus for the investigation of the potential of platinum complexes as anti-tumour agents. Barnett Rosenberg, the then recently appointed Professor of Biophysics at Michigan State University, U.S.A., was investigating the effect of electromagnetic fields on the division process for cells of higher organisms (eukaryotic cells). However, while testing his apparatus on the less organised cells of the bacterium Escherichia Coli (prokaryotic cells) he noted the formation of giant filaments containing undivided bacterial cells. It was not until three years later that he was able to publish his results, having finally concluded that the effect was due to dissolution of tiny amounts of platinum from the electrodes, followed by reaction with chloride and ammonium ions in the growth medium to generate compounds which could inhibit cell division. The relationship between this effect and potential anti-cancer activity was not appreciated immediately, and it was a further four years later, in 1969, that the initial anti-tumour screening results were published in the journal *Nature*. This work identified *cis*-dichlorodiammineplatinum(II), *cis*-$[PtCl_2(NH_3)_2]$, and *cis*-tetrachlorodiammineplatinum(IV), *cis*-$[PtCl_4(NH_3)_2]$, as highly potent agents in murine tumour screens. Further anti-tumour screening was provided by the National Cancer Institute of America leading to the selection of the platinum(II) compound (cisplatin, NSC 119875, as shown in Figure 1 opposite) for preclinical evaluation. Despite evidence of a broad range of toxic effects clinical trials were initiated in 1971. During this period cisplatin was also evaluated by the Institute of Cancer Research in the U.K. leading to clinical trials at the Royal Marsden Hospital in London.

Clinical trials of Cisplatin

The early trials confirmed that cisplatin therapy was associated with a number of side effects. The most significant were kidney toxicity and severe nausea and vomiting. Additionally, neuropathy and hearing loss were observed in some patients. Importantly, the kidney toxicity was found to be cumulative when multiple doses were given as a course of treatment. Thus, while encouraging responses were noted in patients with some tumour types, particularly those of genito-urinary origin, the toxicity of the treatment discouraged doctors from conducting clinical trials, and in 1973 doubts were expressed as to whether cisplatin would find a place in cancer therapy. However, some spectacular results on testicular cancer, when cisplatin was used in combination with other drugs, kept interest alive.

Between 1973 and 1977, in the majority of clinical trials cisplatin was used in low doses (20–30 mg/m^2, milligrams of drug per square metre of body surface area), either as a single agent or in combination therapy, to minimise kidney toxicity. A major breakthrough occurred in 1977 with the development of the

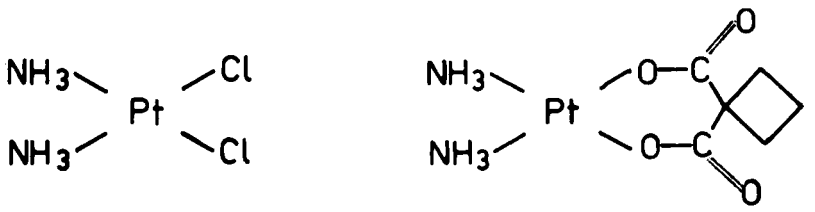

Fig. 1 Licensed platinum drugs; the structure on the left is that of Cisplatin, NSC 119875, while that on the right is the second generation analogue Carboplatin

technique of giving cisplatin with pre- and post-hydration and mannitol-induced diuresis. This minimised the concentration of cisplatin in the kidneys and allowed doses up to 120 mg/m^2 to be given with tolerable kidney toxicity. The significant therapeutic benefits of cisplatin could then be more fully realised. For testicular cancer, prior to the use of cisplatin, complete remission rates had been increased to 36 per cent by the use of combination chemotherapy. With the inclusion of cisplatin response rates were increased to essentially 100 per cent, with approximately 70 per cent complete remissions, and today over 90 per cent long term remissions are achieved. Cisplatin therapy also achieved major improvements in response rates for ovarian cancer and recurrent or metastatic head and neck tumours. In both these latter cases, however, remissions are often of limited duration.

Marketing Approval Granted

Cisplatin was licensed from Research Corporation, representing Michigan State University, by Bristol-Myers, and in 1978 marketing approval was obtained in the U.S.A. for its sale under the tradename Platinol, followed closely by approval in the U.K. in March 1979. Licences in numerous other countries followed and Platinol sales are now in excess of $100 million per year. Further clinical trials over the past 10 years have extended its use, such that it is now probably the most widely used anti-cancer drug. In addition to genito-urinary disease (testicular, ovarian, cervix, bladder) and head and neck cancer for which cisplatin was originally licensed, it is now one of the drugs used in the chemotherapy of lung cancers, both small cell and non-small cell types; 75 and 25 per cent, respectively, of patients receiving some chemotherapy. Regrettably, responses to chemotherapy are often of short duration for these tumours. Recent reports of clinical trials using single agent cisplatin in the treatment of metastatic breast cancer suggest that it may also in the future achieve a role in the management of this disease.

In vitro and in vivo studies have suggested a significant dose-response relationship for cisplatin, encouraging clinicians to seek means of safely administering higher doses. Administration in hypertonic (3 per cent) saline has been used to deliver 200 mg/m^2 cisplatin (as 40 mg/m^2 each day for five days) with tolerable kidney toxicity, but under these circumstances the neurotoxicity is not relieved, reducing the benefit of this approach. Protective or rescue therapy involving the administration of sulphur-containing compounds, for example diethyldithiocarbamate (DDTC) or thiosulphate, to counter cisplatin toxicities is also being investigated. Trials in this area are complicated by the need to establish both the appropriate dose and the scheduling of the counter-agent relative to cisplatin in order to obtain protective action, while not diminishing the anti-tumour activity. This approach has been most successful when cisplatin has been given intra-arterially or intraperitoneally to achieve locally high concentrations, with the counter-agent being delivered intravenously.

Another factor limiting patient compliance with high dose cisplatin is the severe gastrointestinal disturbance that is commonly

experienced. Anti-emetic drugs such as metoclopramide have been used to moderate this effect with limited success. Recently, however, a number of new anti-emetic drugs (5-HT_3 antagonists) have entered clinical trials and seem to offer the prospect of enhanced anti-emetic effects with reduced side effects compared with metoclopramide.

Structure-Activity Studies of Platinum Compounds

The evaluation of other platinum complexes as anti-tumour agents has taken place since 1970. Early work at Michigan State University established the range of compounds possessing anti-tumour activity. More detailed work on structure-activity correlations was carried out in the U.K. with support from Johnson Matthey and Rustenburg Platinum Mines, principally involving synthetic chemists at University College, London, and the screening facilities of the Institute of Cancer Research. The major achievement of this programme was to define a structure toxicity relationship based on the leaving ability of the anionic ligands, rather than identifying improved activity relative to cisplatin. More stable compounds, for example those containing bidentate malonate ligands, are less toxic than reactive compounds, such as those containing nitrate or sulphate ligands. Prior to the licensing of cisplatin to Bristol-Myers a number of other platinum complexes were unsuccessfully tested by clinics and academic institutes in attempts to select an alternative compound with similar activity but reduced toxicity. Following the launch of cisplatin, Bristol-Myers in conjunction with Johnson Matthey and the Institute of Cancer Research took up this challenge. Using the experience gained during the structure-activity studies in the early 1970s, in combination with the results of Bristol-Myers in-house screening, diammine(1,1-cyclobutanedicarboxylato)platinum(II) (JM-8, carboplatin, as shown in Figure 1 on previous page) was selected as a promising candidate. The activity of this compound against a human lung tumour implanted in immune-deprived mice (a xenograft) was a key feature in the decision of the Institute of Cancer Research to propose its evaluation in clinical trials. These trials, supported by Bristol-Myers, were initiated in 1981 at the Royal Marsden Hospital. The results, in agreement with the preclinical evaluation, showed carboplatin to have little kidney toxicity and neurotoxicity, with reduced nausea and vomiting when compared with cisplatin. The dose limiting factor was toxicity to the bone marrow, causing a reduction in the number of platelets (thrombocytopoenia) and white blood cells (leucopoenia). This was a reversible effect with cell levels recovering over 4 to 6 weeks. These results were later confirmed in many other hospitals in trials evaluating a variety of dose schedules.

Clinical Trials and Marketing Approval of Carboplatin

Clinical trials at the Royal Marsden Hospital continued in the early 1980s, with a comparison of the effectiveness of carboplatin and cisplatin in the treatment of ovarian cancer. The response rate and long term survival rates indicated equivalence in activity between the two drugs, with carboplatin offering a reduced spectrum of toxicity. Carboplatin was also found to be a highly active drug for the treatment of small cell lung cancer, though as noted above for cisplatin-containing chemotherapy, the responses were of short duration. These results, confirmed by other trials in Europe and the U.S.A., prompted Bristol-Myers to seek approvals for the marketing of carboplatin. A product licence was granted in the U.K. in March 1986, in the majority of other European countries in the period 1986–88, and most recently in the U.S.A.

As for cisplatin, evidence of a dose-response relationship was obtained in clinical trials encouraging investigations of high dose schedules. In these studies employing doses up to 1600 mg/m^2, four times greater than the "normal" dose, the range of toxic effects was little changed from that previously observed, with severe haematological toxicity being countered by platelet transfusions and

autologous bone marrow transplantation when necessary. The majority of these trials involved treatment of tumours refractory to other drugs, often including cisplatin, and though response rates were not high, the results for ovarian cancer and acute leukaemia were sufficiently encouraging for these trials to continue. Improved techniques for mitigating the haematological toxicity of high dose chemotherapy are being developed, and one of the most promising is the administration, with or without autologous bone marrow transplantation, of growth factors for bone marrow cells, stimulating the production of certain white blood cells. These growth factors are now more widely available through recombinant DNA production techniques, and the results of clinical trials in combination with carboplatin are awaited with interest.

Clinical Trials of Carboplatin

Type of tumour	Number of trials	Response, per cent
Lymphoma	3	27
Breast	4	10
Melanoma	3	10
Stomach	5	6
Esophagus	2	4
Colon/rectum	3	2
Paediatric—brain	2	22
Paediatric—other solid tumours	2	6

The activity of carboplatin has been found to be similar to that of cisplatin in a number of other tumour types, for example testicular, head and neck, non-small cell lung and bladder cancer, with probably somewhat less activity in cervical cancer. The results of trials on a number of other tumours are given in the Table. Response rates for lymphomas and breast cancers are significantly higher for patients who have not received prior chemotherapy.

When compared with cisplatin therapy, the reduced emesis associated with carboplatin and the avoidance of hydration techniques provides a significant improvement in the quality of life for patients undergoing treatment. While cost advantages may lead to the continued use of cisplatin in the first line treatment of testicular and ovarian cancer, the greater ease with which carboplatin can be used in high dose schedules suggests that it will substitute for cisplatin in the treatment of advanced or refractory disease. Also the absence of kidney and neurotoxic complications makes carboplatin a suitable agent for use in the palliative treatment of cancer, for example lung tumours.

Of relevance to the use of carboplatin in refractory tumours is the degree of cross-resistance with cisplatin. Clinically this has been found to be high, though occasionally responses are seen to carboplatin for disease resistant to cisplatin. This is believed to result from pharmacokinetic differences since studies indicate the same mechanism of action for the two drugs. This mechanism is thought to involve platinum binding to DNA. Analysis of

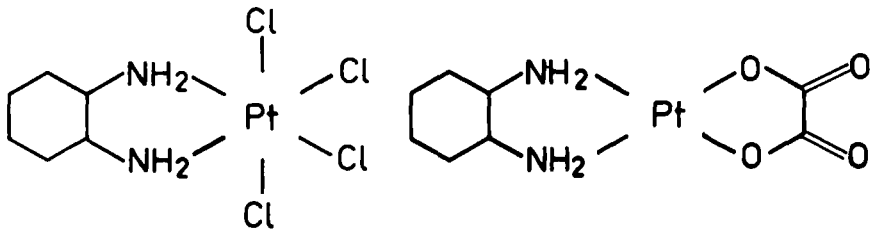

Fig. 2 Platinum complexes containing the ligand 1,2-diaminocyclohexane, currently in clinical development; Tetraplatin (Upjohn) is shown on the left and Oxaliplatin (Rhone-Poulenc) is shown on the right

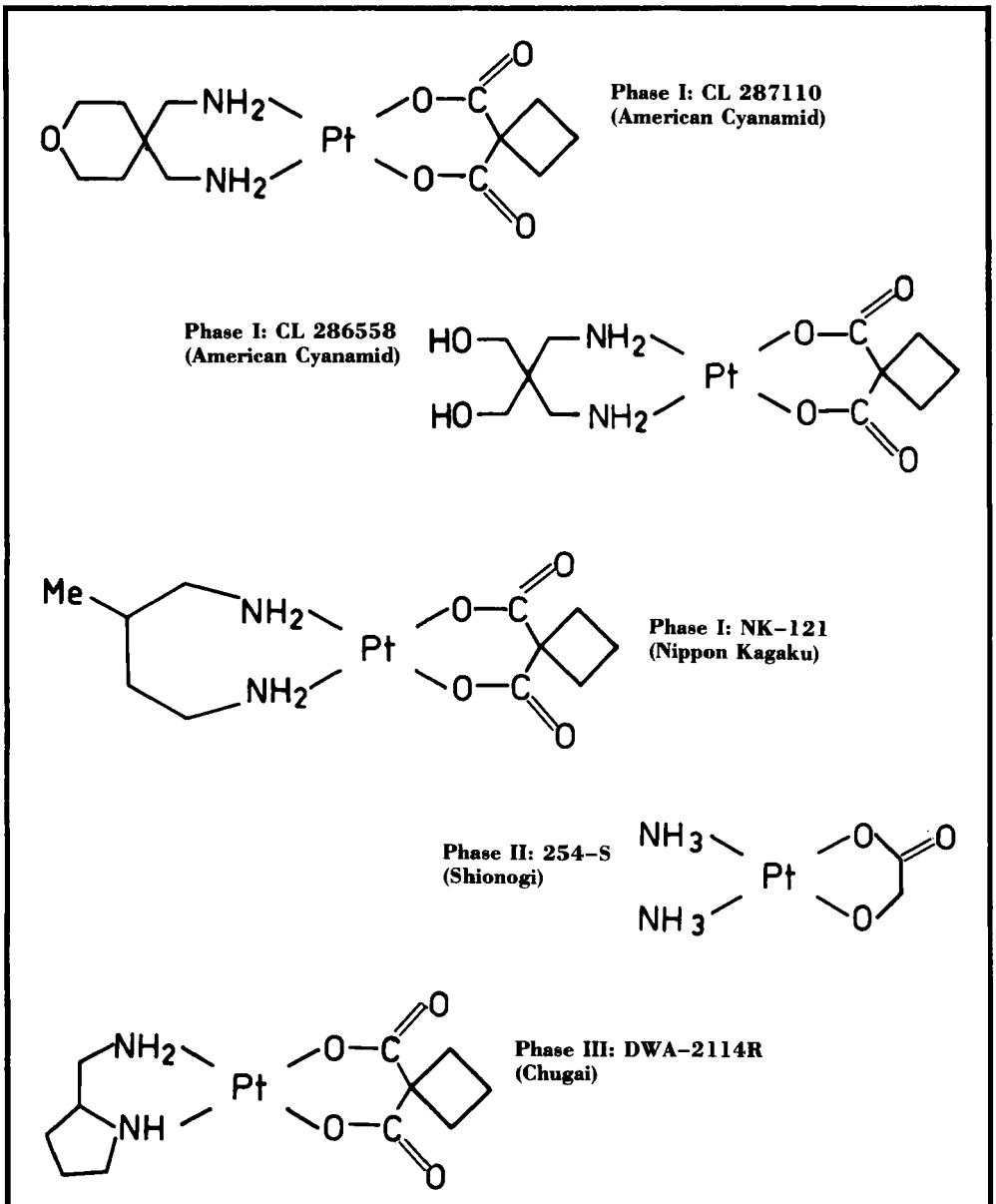

Fig. 3 Platinum complexes used in clinical trials

the products of in vitro and in vivo reactions of cisplatin with DNA has shown that binding to two neighbouring or next neighbouring guanine residues is the preferentially formed adduct. Detailed NMR spectroscopy and X-ray crystallography studies on various cisplatin-guanine adducts have been carried out to define the structure and effect of this binding to DNA. Interestingly, the role of the 5′-phosphate in hydrogen bonding to one ammine group of cisplatin may explain the results of early structure-activity studies, which showed

that complexes containing primary amines were more active than those of secondary amines, while tertiary amine complexes were inert.

Other investigators of the mechanism of the action of platinum drugs have attempted to define the difference between sensitive and resistant strains of a particular cell line. Evidence has been found of differences in the level of deactivating sulphur donor ligands (for example metallothionein or glutathione) within the cell, differences in the permeability of the cell membrane, and variations in platinum concentration within the cell which may account for the differences in sensitivity. It is likely that different mechanisms are displayed by different cell types, and possible that resistance arises from a combination of mechanisms.

The Continuing Development of Platinum Compounds

Attempts to identify platinum compounds which will not be cross-resistant with cisplatin have formed a key part of many efforts to develop alternative complexes for clinical evaluation. As early as 1977, complexes containing the 1,2-diaminocyclohexane ligand were known to be effective agents against the L1210 leukaemia cell line resistant to cisplatin. Numerous complexes containing this ligand have been evaluated in clinical trials, with the latest compounds in clinical development being oxaliplatin and tetraplatin, these being shown in Figure 2. Due to toxicity and little evidence of activity, none of these complexes has received widespread evaluation to date, so a lack of cross-resistance in the clinic has not been proven.

Many of the other complexes currently in clinical trials also contain diamine ligands for the same reason. Another common feature of these platinum complexes is the 1,1-cyclobutanedicarboxylate group which assists in providing adequate aqueous solubility for formulation while reducing toxicity compared with cisplatin, see Figure 3. It remains to be seen whether any of these compounds will have advantages over carboplatin. However, it is certain that researchers seeking new complexes for development will continue to see a lack of cross-resistance to cisplatin as a major goal. It is hoped that improvements in screening techniques through the use of human tumour xenografts will provide a better basis for assessing cross-resistance in a clinically relevant manner.

Other therapeutic goals for the further development of platinum based chemotherapy include oral delivery, a different spectrum of anti-tumour activity and improved targeting of the drugs. Targeting studies using hormonal recognition or linking to monoclonal antibodies have been carried out, and, while these programmes require many years of research, drugs with greatly improved selectivity will undoubtedly be developed.

The Future Outlook for Platinum Anti-Cancer Drugs

The early development of platinum drugs relied heavily on U.S. government support with little interest from pharmaceutical companies in a metal-based drug. The number of companies developing platinum drugs today clearly indicates that this is no longer the case. We may therefore look forward to significant advances during the next 20 years, to fulfil the potential of these agents for the benefit of cancer patients worldwide.

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