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Clinical Oncology Update

Clinical Development of Platinum Complexes in Cancer Therapy: an Historical Perspective and an Update

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The vast amount of basic research on platinum coordination complexes has produced, over the past 25 years, several thousand new molecules for preclinical screening and 28 compounds which have entered clinical development. The goals of these research activities have been to identify compounds with superior efficacy, reduced toxicity, lack of cross-resistance or improved pharmacological characteristics as compared with the parent compound, cisplatin. After the remarkable therapeutic effects of cisplatin had been established, only a few other platinum compounds succeeded in reaching general availability. Whereas carboplatin is an analogue with an improved therapeutic index (mostly driven by reduced organ toxicity) over that of cisplatin, new compounds clearly more active than or non-cross-resistant with cisplatin have not yet been identified. The platinum analogues that remain under investigation are focusing on expanding the utilisation of platinum therapy to tumour types not usually treated with, or responsive to, cisplatin or carboplatin. In addition, novel routes of administration constitute another avenue of research. The clinical development of platinum coordination complexes, with emphasis on those compounds still under active development, is reviewed. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: platinum coordination complexes, cancer therapy, clinical development, historical perspective, update
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INTRODUCTION

PLATINUM-CONTAINING coordination complexes have been used in the therapy of cancer for more than 25 years. The parent compound of this class of antitumour agents, cis-dichloro-diammine-platinum (II), or cisplatin, was first administered to a cancer patient in 1971 and became available for general oncology practice in 1978 (Platinol®, Bristol-Myers Squibb), first in Canada and shortly thereafter in the United States, followed eventually by the rest of the world. Because of the high level and broad spectrum of antitumour activity of the parent compound, extensive research has continued in this area. At the last count, some 28 platinum complexes have entered clinical trials as anticancer agents. Of these, four are currently approved (cisplatin and carboplatin, world-wide; oxaliplatin, in a few countries only; nedaplatin, in Japan only) and a few more remain under clinical investigation.

For the purpose of this review, we have, somewhat arbitrarily, grouped the platinum complexes into four categories. These categories reflect both a chemical class and the general rationale for their development, as follows:

(1) Cisplatin analogues, generally developed with the intent of increasing the efficacy over that of the parent compound.
(2) Carboplatin analogues, generally developed with the intent of reducing the toxicity of the parent compound.
(3) Diaminocyclohexane (DACH) compounds, generally developed with the intent of achieving lack of cross-resistance with the parent compound.
(4) Platinum IV coordination compounds, developed in order to explore different pharmacological properties conferred by different ligands and leaving groups.

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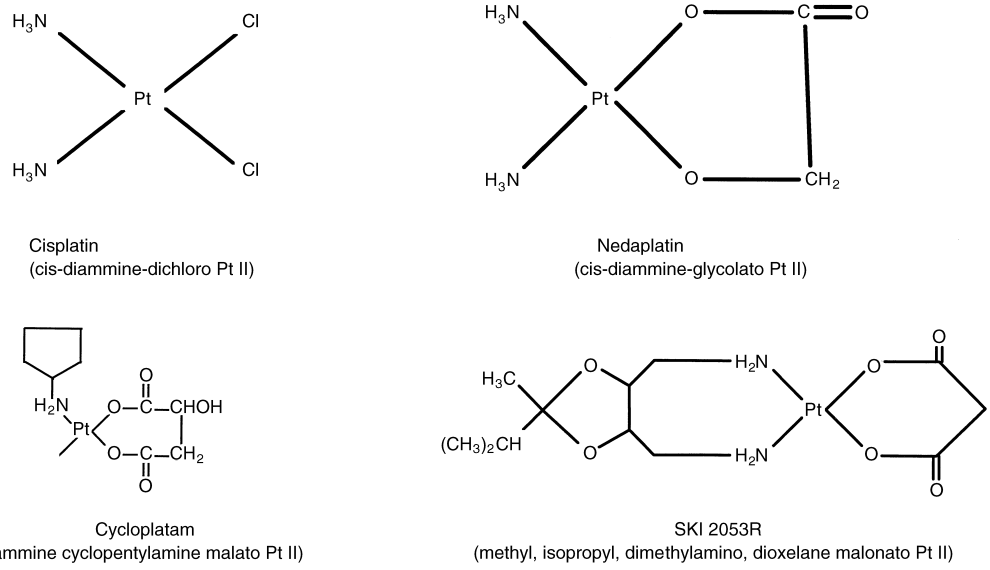


Figure 1. Cisplatin and analogues.

Table 1. *Cisplatin and analogues*

Compound	Phase II dose (mg/m^2)	Limiting toxicity	Development status
Cisplatin	60–120	Nephrotoxicity Neurotoxicity	Approved (1978) worldwide: germ cell, ovary (phase III) bladder and other indications outside the US, including head and neck, lung NSC, oesophageal, cervix, gastric, prostate cancer and neuroblastoma
Nedaplatin	87.5–100	Myelosuppression	Approved (1995) in Japan only: lung NSC (phase III) testis, head and neck, lung SC, bladder, ovary, oesophagus and cervix cancer
Cycloplatam	80–100	Myelosuppression	Phase II (ovary, breast) in former Soviet Union
SKI 2053R	360	Liver toxicity	Phase II (stomach) in Korea

NSC, non small cell; SC, small cell.

CISPLATIN AND ANALOGUES

Cisplatin

The antiproliferative properties of platinum coordination complexes were first observed in 1965 by Barnett Rosenberg at Michigan State University, in East Lansing, Michigan [1]. Whereas the credit for this discovery appropriately goes to the Rosenberg group, it is not widely known that the molecule of cisplatin was first synthesised in 1844 in Turin by Michele Peyrone, a young chemist who was pursuing research in the area of medical chemistry. The compound was known as the 'Peyrone's chloride' and it was not until 1892 that, in Zurich, Alfred Werner elucidated the sterical configuration of the molecule [2].

After Rosenberg's observation, cisplatin was one of the four compounds initially tested, and found to be active, in the murine sarcoma 180 model [3]. The antitumor activity of cisplatin was independently confirmed by other laboratories and in other tumor models, in the U.S.A. and in the U.K. Following the completion of toxicology studies in rodents, dogs and monkeys, the first cancer patient received cisplatin treatment in April 1971 at the Wadley Institute of Molecular Medicine in Dallas, Texas [4, 5]. The US National Cancer Institute (NCI) also became interested in cisplatin and sponsored the clinical development of the compound, beginning with a phase I trial initiated in June 1971 by the Southwest Cancer Chemotherapy Study Group at Henry Ford Hospital in Detroit, Michigan and MD Anderson Hospital in Houston, Texas, U.S.A. [6]. The first evidence of substantial single-agent antitumour effect became available in 1974, both in testicular [7] and in ovarian cancer [8], with reports of objective responses in 3/7 and 7/19 patients, respectively. The excitement of these results, however, was tempered by the observation of high incidence of organ toxicity, renal in particular. Only in 1976 did investigators from Memorial Sloan-Kettering in New York [9] and from Roswell Park Memorial Institute in Buffalo, New York [10] report on the possibility to circumvent the nephrotoxicity of cisplatin via high-volume fluid hydration and forced diuresis, thus allowing the safe administration of high doses of the drug (1–3 mg/kg).

The following years witnessed the continuation of intense clinical research on cisplatin, which became the first platinum compound to be approved for cancer therapy. The relative lack of myelosuppression of the compound has favoured its incorporation in combination regimens. Cisplatin-containing combinations are curative in germ-cell tumours [11]. Several randomised trials and two extensive meta-analyses, have suggested that the use of cisplatin significantly prolongs survival in ovarian cancer [12] and in non-small cell lung cancer (NSCLC) [13]. In addition, cisplatin has become a mainstay of the treatment of bladder, cervix, head and neck, oesophageal and small cell lung cancer, among others, as well as of some paediatric malignancies [14].

Because of the important antitumour activity of the compound, research has continued even after the initial regulatory approvals. Of note, two avenues of research have been pursued. The first consisted of attempts to ameliorate the side-effect profile of cisplatin. Various protective compounds have been studied, with variable success, ranging from the early attempts with penicillamine and other substances for renal toxicity, to amifostine for neurotoxicity and to the 5HT3 antagonists for emesis. The second direction in research was more specifically focused on the development of cisplatin analogues.

Nedaplatin

Nedaplatin (cis-diammine-glycolato-0,0′platinum II, 254-S, CDGP) is a compound developed by the Shionogi Pharmaceutical Company of Osaka, Japan. The selection of this drug was based upon antitumour effects considered to be superior to those of cisplatin in rodent models (P388 leukaemia, B16 melanoma, Lewis lung carcinoma) and in xenografted human tumours (MX-1 breast carcinoma, Daudi lymphoma). However, nedaplatin was cross-resistant with cisplatin in the L1210/CDDP leukaemia model. The drug had reduced nephrotoxicity, but increased myelosuppression in animal models [15]. Nedaplatin, unlike cisplatin, had low affinity for protein binding.

The entire clinical development of the compound has been conducted in Japan. Two schedules, 60 min and 120 h infusion, were studied in phase I. The recommended phase II dosage was similar, 100 and 87.5 mg/m^2, for both regimens [16, 17]. Dose-limiting toxicity was myelosuppression, with late nadirs (week 4–5) and late recovery (week 6) observed with the continuous infusion schedule. Minor abnormalities of renal function tests were observed and the short infusion regimen, accompanied by modest hydration and diuretics, was selected for further development. Single-agent efficacy, with response rates of 25% or more, was observed in phase II trials in head and neck, testicular, lung (small and non-small cell), oesophageal, bladder, ovarian, and cervical cancer, the indications of nedaplatin currently approved in Japan. Lower response rates were obtained in gastrointestinal, prostate and breast cancer [18]. Only one, relatively small, randomised clinical trial of cisplatin versus nedaplatin (both in combination with vindesine) in the treatment of non-small cell lung cancer has been reported [19]. In this trial, both platinum drugs were administered at 90 mg/m^2 (and vindesine at 3 mg/m^2 on day 1 and 8) every 4 weeks. The 57 patients given cisplatin required hydration with 2,500–4,500 ml of fluids, the 64 patients given nedaplatin required a smaller volume of 1,000–2,000 ml. Only partial responses were observed in this trial, 9 (16%) with cisplatin/vindesine, and 8 (13%) with nedaplatin/vindesine. Overall survival was also comparable. The cisplatin arm showed more toxicity in terms of grade III–IV leucopenia (50 versus 27%), nephrotoxicity and gastrointestinal toxicity (more frequent and severe). The nedaplatin arm presented more frequent thrombocytopenia. No mention of neurotoxicity or ototoxicity was made. Data from other clinical trials, including combination chemotherapy regimens, are very limited.

Cycloplatam

Cycloplatam (ammine cyclopentylamine malato platinum II) is a racemate synthesised by the Kurnakow Institute of General and Inorganic Chemistry, Russian Academy of Science, Moscow, Russia. The compound was studied at the Cancer Research Centre of the Russian Academy of Medical Science in Moscow and selected for development based upon antitumour effects considered to be superior to those of cisplatin in murine tumour models (P388 leukaemia, MOPC plasmacytoma, hepatoma 22a). In addition, nephrotoxicity appeared to be reduced compared with cisplatin [20].

The clinical development of the compound is currently being pursued in countries of the former Soviet Union. A phase I trial has been conducted in Moscow, using a daily×5 schedule. The recommended dose for phase II trials was 80–100 mg/m^2/day×5 and myelosuppression was considered to be dose-limiting. Emesis and nephrotoxicity (the latter in 1 patient) were observed during this study [20]. Only two phase II reports have appeared in the literature, both in abstract form. A trial performed in ovarian cancer reported a response rate of 59%, with a median response duration in excess of 5 months. However, of the 18 patients analysed, 6 were previously untreated and, of the pretreated, only 4 had received prior platinum-containing therapy. Myelosuppression was the most important side-effect, but no nephrotoxicity or neurotoxicity was observed [21]. Another trial, performed in breast cancer, reported a response rate of 70%. However, all the objective responses were observed in 14/20 previously untreated patients and no activity was seen in patients previously given combination chemotherapy. The incidence of emesis was very high and a few cases of hypertension were observed. No nephrotoxicity was reported [22]. At the present time, no direct comparative clinical trials exist for cycloplatam versus any other platinum agent. The New Drug Development Office (NDDO) of the European Organization for the Research and Treatment of Cancer (EORTC) has evaluated cycloplatam and found it to be inferior to cisplatin in murine and xenografted tumour models. However, a different spectrum of activity was observed in one lung cancer xenograft model [23]. The EORTC will perform additional preclinical studies with the compound.

SKI 2053 R

SKI 2053 R (methyl, isopropyl, dimethylamino, dioxelane malonato platinum II) has been developed by the Sunkyong Industry Research Center, Seoul, Korea. The decision to pursue clinical development with this compound was based on superior *in vitro* effects, compared with cisplatin, including cisplatin-resistant cell lines. Animal toxicology has suggested reduced nephrotoxicity, compared with cisplatin, and bone marrow toxicity as the main side-effect [24].

Clinical development is ongoing in Korea. A phase I trial began in 1993 and the compound was administered over 1 h infusion every 4 weeks. The recommended dosage for phase II trials was 360 mg/m^2. At higher doses, 2/3 patients developed grade IV liver toxicity, severe myelosuppression and renal toxicity. At the recommended dosage, emesis was the most significant toxicity [24]. Only one phase II trial has so far been reported, in gastric cancer. Previously untreated patients were treated and in 6/35 patients (17%) responses were seen, with a median duration of 5.5 months. Median overall survival was 8.5 months. Only grade I or II myelosuppression was observed. Moreover, grade I or II proteinuria was seen in 47% of the patients and liver function test elevation occurred in 10% of the patients. These side-effects were reversible. No neurotoxicity was observed [25].

Cisplatin analogues abandoned

Two compounds studied in the late 1970s at the Wadley Institute, did not proceed past phase I clinical trials. The cyclopentylamine platinum II (PAD) was administered to only 8 patients and then abandoned because of lack of solubility [26]. Platinum uracil blue (PUB) was also administered to 13 patients and then abandoned because of cardiac toxicity [27].

Cyclopropylamine platinum II (CP, JM-11), labelled with a radioactive isotope, was administered to only 4 patients at the Christie Hospital and Holt Radium Institute in Manchester, U.K. [28, 29]. The experiment was carried out in an attempt to identify less nephrotoxic agents by analysing their disposition. The compound presented a low urinary clearance and was abandoned.

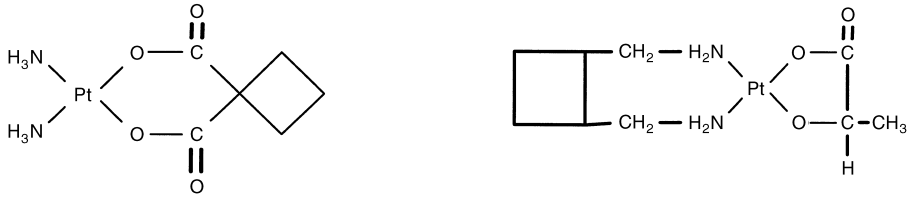
Finally, the ethylenediamino malonate platinum II (JM-40) was brought to the clinic at the Free University Hospital and The Netherlands Cancer Institute of Amsterdam, the Netherlands, under the auspices of the EORTC/NDDO [30]. A total of 22 patients were treated, with doses up to 1–1.2 g/m^2. Nephrotoxicity and emesis were dose-limiting, an observation which, coupled with the low potency of the compound, discouraged further development.

CARBOPLATINS AND ANALOGUES

Carboplatin

Carboplatin (cis-diammine- 1,1′-cyclobutane dicarboxylate platinum II, CBDCA, JM-8) has been developed by the Bristol-Myers Squibb Company, Princeton, New Jersey, in collaboration with the Institute of Cancer Research, Sutton, U.K. and the Johnson-Matthey Company, Reading, U.K. [31, 32]. It is the only cisplatin derivative currently available worldwide for the treatment of cancer. The selection of carboplatin for clinical development was supported by several features. First, the cyclobutane ring offered a more stable ligand than the chloride groups in the cisplatin molecule. It was thought that the resulting reduced reactivity would lessen the nephrotoxic potential of the molecule. Second, a systematic biological evaluation was conducted, which compared head-to-head compounds with different configurations. This evaluation encompassed not only the antitumour characteristics of the molecules tested, but also their toxicological properties. The animal models taken into consideration and sometimes specifically developed for that purpose, addressed nephrotoxicity, myelosuppression, emesis and neurotoxicity. At the end of this extensive preclinical evaluation, carboplatin was the compound with the least non-haematological toxicity compared with cisplatin. Its *in vivo* antitumour effects were comparable to those of cisplatin in several tumour models, both of murine and human origin and carboplatin was found to be cross-resistant with the parent compound in the L1210, P388 and M5076 murine models.

Phase I clinical trials of carboplatin began in 1980 at the Royal Marsden Hospital in London, U.K. [33]. The drug was initially administered in 300 ml of fluids, over 1 h of infusion, every 4 weeks. The first phase I trial confirmed the preclinical prediction of reduced organ toxicity. The recommended dose for phase II was 300–400 mg/m^2 and dosing was limited by myelosuppression, chiefly thrombocytopenia. Importantly, evidence of significant antitumour activity was obtained during the first clinical trial of carboplatin, in particular in ovarian cancer patients. The interest in carboplatin was very high at the time. Both the EORTC Early Clinical Trials Group and the US NCI initiated phase I trials with the compound. Indeed, a large number of schedules and regimens of administration were studied in the early years of carboplatin development [34]. These included, besides the single intermittent bolus tested initially, daily×5, weekly, and 24 h continuous infusions. These studies were rapidly followed by special phase I studies in paediatric and in leukaemic patients, as well as by studies utilising the intraperitoneal route of administration. Finally, the toxicological profile of carboplatin made it appealing to pursue high-dose studies with bone marrow support, which enabled



Carboplatin
(diammine cyclobutane dicarboxylato Pt II)

Lobaplatin
(diamminomethyl cyclobutane lactate Pt II)

Figure 2. Carboplatin and analogues.

Table 2. Carboplatin and analogues

Compound	Phase II dose (mg/m^2)	Limiting toxicity	Development status
Carboplatin	300–400 AUC 6–8	Thrombocytopenia	Approved (1985) worldwide: ovary, first- and second-line (phase III) and other indications outside the U.S.A.,
	800–1200 AUC 10–12 (with bone marrow support)	Neurotoxicity	including head and neck, lung SC, testicular, bladder, cervix cancer and lymphoma
Lobaplatin	50–70	Thrombocytopenia	Phase III (oesophagus) in Europe

SC, small cell.

the delivery of doses two or three times higher than the standard recommended dose [34]. The single intermittent bolus schedule remained the regimen of choice, because of its practicality, but also because the other regimens studied did not appear to provide any meaningful advantage. Moreover, early in the development of the compound, H. Calvert and collaborators were able to uncover the fact that carboplatin is cleared almost exclusively by glomerular filtration, thus directly correlating renal clearance and myelosuppression [3]. Eventually, M. Egorin and collaborators correlated these two factors with antitumour activity in ovarian cancer [35]. These characteristics of carboplatin generated further research on dosing formulas devised to optimise the delivery of the compound [36–38]. As a result, in today's practice it is appropriate to prescribe the dosage of carboplatin according to the desired area under the time concentration curve (AUC).

The spectrum of antitumor activity of carboplatin is very wide and the single agent effects of the compound have been studied in more than 90 single agent phase II trials [34]. In general, efficacy has been observed in tumour types known to be responsive to the parent compound. In ovarian cancer, where the largest database on single agent carboplatin has been accumulated, cross-resistance with cisplatin was evident, but the favourable characteristics of carboplatin allowed treatment continuation and dose intensification, in several patients who were not able to continue receiving cisplatin [34]. These data prompted the initial approval of carboplatin (Paraplatin®, Bristol-Myers Squibb) for the treatment of ovarian cancer, which occurred in 1985 in the U.K. and in Canada. Approval in the U.S.A. ensued in 1988, on the basis of two prospectively randomised trials comparing carboplatin versus continuous infusion fluorouracil or intravenous (i.v.) etoposide, in patients not suitable for further cisplatin therapy [39].

Carboplatin is the compound for which the largest number of randomised clinical trials versus the parent compound is available. These comparisons have allowed us to define the role of carboplatin in cancer therapy, as well as to verify the reliability of predictions made by the preclinical models. In previously untreated ovarian cancer, a meta-analysis of 11 trials with more than 2,000 patients has not been able to detect any difference in survival between cisplatin and carboplatin treated patients, alone or in combination [12]. In consideration of the equivalence of the efficacy results, but also of the significantly reduced non-haematological toxicity (emesis, nephrotoxicity, neurotoxicity and ototoxicity) observed in patients receiving carboplatin, the drug was also approved for the primary treatment of ovarian cancer. The rationale dosing of carboplatin, based upon the desired AUC, has allowed the development of novel active combinations. Among them, the combination of carboplatin and paclitaxel is being increasingly utilised, not only in ovarian cancer but also in NSCLC, head and neck, bladder cancer and other tumour types. Besides the potential for reduced neurotoxicity, this combination seems to offer the possibility to reduce the carboplatin-induced thrombocytopenia by pharmacodynamic modulation [40, 41].

Carboplatin is used today in a variety of combination chemotherapy regimens, including many high-dose programmes delivered with peripheral blood stem cell or autologous bone marrow transplantation. Its clinical success has stimulated further interest in this class of platinum coordination compounds.

Lobaplatin

Lobaplatin (diamminomethyl cyclobutane lactate platinum II, D-19466) is being developed by Asta Medica AG, Frankfurt, Germany. The experimental data indicated higher or similar antitumor effects compared with cisplatin or carboplatin, both *in vitro* and *in vivo* and a preclinical toxicity profile similar to that of carboplatin. In addition, lack of cross-resistance with cisplatin was observed *in vitro* and *in vivo* in a human embryonal cell line and in the P388 murine leukaemia, respectively [42].

Three phase I trials have been completed in Europe, exploring the single intermittent bolus [42], the daily×5 [43] and the 72 h continuous infusion schedules [44]. The dose-limiting toxicity was thrombocytopenia in all trials, and the recommended phase II dose was 50–70 mg/m^2 (the latter with the daily×5 regimen). Correlations between creatinine clearance and maximum tolerated dose were made during one of these trials [43]. No significant organ toxicity was reported, although emesis was constantly observed at doses above 20 mg/m^2.

In consideration of the fact that phlebitis was fairly frequent with the prolonged infusion, phase II trials were conducted with the single intermittent bolus schedule, at 4-week intervals. A trial in ovarian cancer performed in Europe has reported positive results (5/22 responses, or 23%) in which the population included two-thirds of patients with platinum resistance [45]. However, a study performed in the U.S.A. failed to confirm these results, with no objective responses in 17 resistant patients [46]. Efficacy was low in head and neck (3/43 or 7%) [47] and in lung cancer (0% in small cell, 5% in non-small cell) [48] and in bladder cancer (2/17 or 12%) [49], with objective responses seen mostly in platinum-unpretreated patients. With the exception of the results of studies performed in China and mostly in previously untreated patients [48], the only positive phase II results of lobaplatin have so far been achieved in oesophageal cancer [50]. Five partial responses were obtained in 14 untreated patients (36%), whereas no response was obtained in 4 pretreated patients. Currently, a randomised trial of the combination of lobaplatin and fluorouracil (with chronomodulation) is ongoing in oesophageal cancer [51].

Carboplatin analogues abandoned

Several compounds containing the cyclobutane ring were developed in the late 1980s, in the hope of improving upon the carboplatin characteristics. Of interest, all of them completed phase I evaluation and were abandoned at a later stage of development. Two of these compounds, enloplatin and zeniplatin, were developed by the American Cyanamid/Lederle Company [52].

Enloplatin (cyclobutane dicarboxylato (2-)0′,0′ tetrahydro-4H pyran-4,4-dimethyl amine-N,N′ platinum II, CL 287, 110) was evaluated only in one phase I study with a single intermittent bolus regimen, and produced both myelosuppression and nephrotoxicity as dose-limiting toxicities [53]. A single phase II was performed at doses of 700 mg/m^2 in ovarian cancer, with negligible efficacy [54]. The compound was abandoned because of nephrotoxicity and low activity.

Zeniplatin (2,2-bis amino methyl-1,3-propanediol-N-N′ 1,1-cyclobutane dicarboxylate 2-0,0′ platinum II, CL 286, 558) was also evaluated in a single phase I trial using the intermittent schedule [55]. Dose-limiting toxicity was myelosuppression and a number of phase II trials were conducted

at doses of 120–145 mg/m^2. Although antitumour effects were seen in ovarian, NSCLC, head and neck, breast cancer and melanoma, high-volume fluid hydration had to be introduced during the course of the phase II programme, due to the emergence of nephrotoxicity [56]. Unfortunately, even the introduction of prophylactic hydration did not succeed in averting renal toxicity [57] and compound development was abandoned [58].

NK-121/CI-973 (1,1-cyclobutane dicarboxylato (2-)2 methyl 1-1,4-butane-diamine-N,N′ platinum II) is another carboplatin analogue developed initially by the Nippon-Kayaku Company in Japan and by Parke-Davis Pharmaceutical, Warner-Lambert Company in the U.S.A. [59]. Phase I evaluation was performed both in Japan (one trial, single intermittent bolus) [60] and in the U.S.A. (two trials, single intermittent bolus and daily×5 schedule) [61, 62]. Of interest, although there was consensus on the dose-limiting toxicity (neutropenia and leucopenia), the Japanese investigators recommended, for phase II, a higher dose (300 mg/m^2) than the U.S.A. investigators (190–230 mg/m^2 daily×1, 30 mg/m^2 daily×5). Although several phase II trials have been performed, only one in ovarian cancer has been reported [63] and the compound has been abandoned due to modest antitumour activity [64].

Miboplatin (R-2-amino methyl pyrrolidine 1,1-cyclobutane dicarboxylate platinum II, DWA 2114R) was developed by Chugai Pharmaceutical Co. Ltd, Gotemba, Shizuoka, Japan [65]. The clinical development was carried out exclusively in Japan. In phase I, both a short, 20 min and a long, 24 h intermittent infusion were studied. Dose-limiting toxicity was neutropenia, and the phase II recommended dose was 800–1000 mg/m^2 [66]. Although the spectrum of activity did not differ from that of cisplatin, efficacy was observed in several tumour types, especially in ovarian cancer [67]. Thus, miboplatin was compared at 800 mg/m^2 with cisplatin 50 mg/m^2 (both in combination with cyclophosphamide and doxorubicin) in a phase III trial in this indication [68]. Response rates were 47% in 30 patients in the cisplatin arm and 39% in 31 patients in the miboplatin arm. Thrombocytopenia was higher in the cisplatin arm, but anaemia and nephrotoxicity were higher in the miboplatin arm [67]. The compound was abandoned after the completion of this study.

DIAMINOCYCLOHEXANE (DACH) COMPOUNDS

Oxaliplatin

Oxaliplatin (trans-L-diaminocyclohexane oxalate platinum II, L-OHP) is a compound first synthesised by Y. Kidani at Nagoya City University, Nagoya, Japan and eventually developed in Europe, primarily in France [69]. The rationale for development was based upon the observation of antitumour effects superior to those of cisplatin in murine leukaemias and of reduced toxicity in animal models. Moreover,

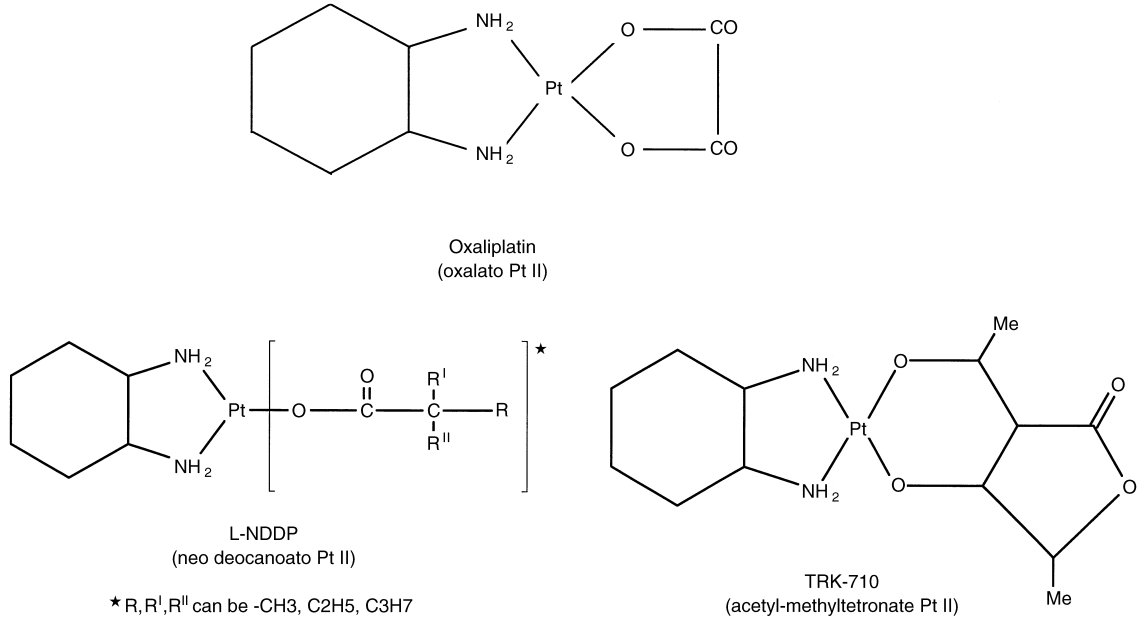


Figure 3. DACH compounds.

Table 3. DACH compounds

Compound	Phase II dose (mg/m^2)	Limiting toxicity	Development status
Oxaliplatin	100–130	Neurotoxicity	Approved (1996) in France (and elsewhere): second-line colorectal cancer (phase II)
L-NDDP	300 (i.v.)	Myelosuppression	Phase I (loco-regional routes) in the U.S.A.
	400 (i.a.)	Chemical hepatitis	
	450 (i.p.)	Chemical pleuritis	
TRK-710	Not reached	Not reached	Phase I (intermittent bolus) in Japan

the compound behaved differently than other platinum complexes in *in vitro* cytotoxicity testing, including lack of cross-resistance in one cisplatin-resistant colon cancer line [70].

Phase I clinical trials were, initially, supported in Europe by the Roger Bellon Laboratories, Neuilly, France, and then by Debiopharm, Lausanne, Switzerland. Their findings were somewhat contradictory. The first study reported severe emesis to be dose-limiting, at 45 mg/m^2 given intermittently [71]. However, subsequent studies which adopted the same regimen reported cumulative, sensory neuropathy to be dose-limiting at 130–135 mg/m^2 [72, 73]. Finally, a phase I trial of a chronomodulated 120 h continuous infusion regimen recommended a dose of 35 mg/m^2/daily×5 (175 mg/m^2 total), with neutropenia and emesis as the most relevant toxicities [74].

The phase II programme was carried out using mostly a dosage of 130 mg/m^2, administered over 2–3 h every 3 weeks. Objective responses to single agent oxaliplatin have been reported in non-Hodgkin's lymphoma (9/22 or 41%) [75] breast cancer (3/14 or 21%) [76], malignant melanoma (3/15 or 20%) [77], NSCLC (3/20 or 15%) [78], glioblastoma (1/9 or 11%) [77] and head and neck cancer (4/42 or 10%) [79]. A negative study was reported in 10 patients with astrocytoma [80]. The most favourable results of oxaliplatin have been published in ovarian cancer, with two studies reporting objective responses in 4/12 (33%) [77] and in 9/31 (29%) [81] of the patients, including some who had developed clinical resistance to cisplatin or carboplatin. Finally, oxaliplatin has shown activity in a series of three single-agent phase II trials in fluorouracil-pretreated patients with colorectal cancer [82]. In these studies, objective response rates have been observed in 10, 11 and 10% of the patients, respectively. No responses have been seen in a subsequent small series (13 patients) with similar characteristics [83]. However, a multicentre phase II trial in previously untreated patients reported a response rate of 24% [84]. These results have formed the basis for approval of oxaliplatin for the secondary treatment of metastatic colorectal cancer in France and in a few other countries, where it is marketed by the Sanofi Company. They also provided the rationale for combining oxaliplatin with fluoropyrimidines [82].

Results from two randomised trials of this combination have been reported. The first one compared a chronomodulated versus a constant-rate delivery of the combination (oxaliplatin 20 mg/m^2/daily×5 and 5-fluorouracil (5-FU) 600 mg/m^2 daily×5, with leucovorin) [85]. 92 patients were randomised, and the chronomodulated regimen provided significantly superior response rates (53 versus 32%) and survival (19 versus 14.9 months). Emesis and peripheral sensitive neuropathy were more frequent with the chronomodulated regimen, stomatitis was more frequent with the constant-rate regimen. A second, more traditionally designed trial, is comparing the combination of oxaliplatin and fluorouracil versus 5-FU alone. In 200 patients, a significantly superior response rate (53 versus 16%) and time to progression (7.7 versus 4.6 months) has been reported. Peripheral neurotoxicity, diarrhoea, mucositis and emesis were significantly more frequent with the combination [86]. Another randomised trial of oxaliplatin 130 mg/m^2, this time versus cisplatin 100 mg/m^2 (both drugs are combined with cyclophosphamide 1,000 mg/m^2) is ongoing in ovarian cancer. Preliminary results in 182 patients have indicated similar response rates (52 versus 65%), time to progression (20.9 versus 26.2 months) and survival (11.9 versus 13.2 months) for the oxaliplatin versus the cisplatin regimen. Toxicity was more intense in the cisplatin arm, in terms of myelosuppression and nephrotoxicity. Neuropathy was more frequent with oxaliplatin [87].

L-NDDP

L-NDDP (cis-bis-neodecanoato-trans-R,R-1,2-diaminocyclohexane platinum II) is the first formulation in liposomes of a platinum analogue to be studied in the clinic. It was developed at the MD Anderson Cancer Center, Houston, Texas, U.S.A. with the support of The Liposome Company, Princeton, New Jersey, U.S.A. [88]. The rationale for developing the compound was reduced nephrotoxicity and lack of cross-resistance with cisplatin in murine leukaemias. The liposomal delivery system was adopted because of lack of solubility.

The entire clinical development of the compound has been performed, so far, at MD Anderson. A phase I trial of the i.v. administration of L-NDDP was undertaken there [89] and the dose-limiting toxicity was myelosuppression, at doses of 312.5 mg/m^2. Fever and transient liver dysfunction were attributed to liposomes. No phase II trials of the compound have been reported. However, attempts at local-regional delivery have been made by using the hepatic intra-arterial [90] and the intrapleural [91] routes of administration. Chemical hepatitis was present with the former, chemical pleuritis with the latter approach, although somewhat higher-doses of L-NDDP could be administered.

TRK-710

TRK-710 (1-1,2-diaminocyclohexane-alpha-acetyl-gamma-methyltetronate platinum II) is an analogue of carboplatin synthesised by Toray Industries, Kamakura, Kanagawa, Japan. The compound was selected for clinical development because of lack of cross-resistance with cisplatin in *in vitro* and *in vivo* models, in particular in the L1210/CDDP model, as well as of reduced renal and bone marrow toxicity [92]. A difference in mechanism of action from that of cisplatin, based upon different cell-cycle effects, has been proposed [93]. Phase I clinical trials have started in Japan, with initial doses of 20 mg/m^2 administered over 1 h.

DACH analogues abandoned

Four DACH compounds were developed at the Wadley Institute. The bis monobromo acetato trans 1,2-diaminocyclohexane platinum II (MBA) was abandoned after 9 patients had been treated in phase I because of moderate thrombocytopenia and the occurrence of a severe hypersensitivity reaction [27]. Bis-pyruvato 1,2-diaminocyclohexane platinum II (PYP) also entered phase I clinical trials in late 1982 and 16 patients were treated. The maximum tolerated dose was 18 mg/kg. Nephrotoxicity, hypomagnesiumaemia, SGOT elevation, emesis, diarrhoea and myelosuppression were observed. Despite evidence of antitumour effect in 2 patients with leukaemia, the compound was abandoned [94].

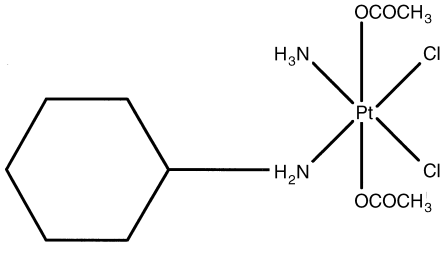
Two other compounds entered clinical trials at the Wadley Institute, both in the racemic and in the isomeric (neo-) form [26, 27]. Sulphato 1,2 diaminocyclohexane platinum II (SHP, neo-SHP, JM-20) was abandoned in phase I after 22 patients were treated because of moderate myelosuppression and the occurrence of severe allergic reactions. Malonato 1,2 diaminocyclohexane platinum II (PHM,

neo-PHM, JM-74) was studied in more than 100 patients in phase I and II studies performed not only at the Wadley Institute, but also at the Institut Gustave Roussy in Paris, France. Some activity was observed in patients with chronic leukaemias treated in Texas and in cisplatin-pretreated patients with testicular cancer treated in France. Low levels of antitumour activity and renal toxicity, requiring high-volume hydration and forced diuresis, prompted the discontinuation of clinical development.

Isocitrato 1,2-diaminocyclohexane platinum II (PHIC) was developed in France by the Sanofi Company [95]. After two phase I trials (single intermittent bolus and daily×5) were completed, showing thrombocytopenia and CNS neurotoxicity at 1200–1500 mg/m^2, the drug was abandoned because of difficulties in the synthesis of the compound [96].

4-Carboxyphtalato 1,2-diaminocyclohexane platinum II (DACCP, JM-82) was studied at Memorial Sloan-Kettering Cancer Center, New York, New York, U.S.A. [97]. The compound was developed because of its lack of cross-resistance with cisplatin in murine leukaemia models, an observation made first for this class of compounds by J. Burchenal at that institution [98]. Johnson-Matthey and Bristol-Myers Squibb supported early clinical trials performed at Memorial. The phase I trial showed thrombocytopenia to be dose-limiting at 640 mg/m^2. Limited phase II studies reported low levels of activity in the two tumour types adequately studied (colorectal and NSCLC) and the compound was abandoned, also because of chemical instability.

Two other compounds similar to the DACH series have also been abandoned: the bis-monobromoacetato trans 1,2-diaminocyclooctane platinum II (DACO, BOP) was administered to 5 patients at the Wadley Institute and abandoned due to the nephrotoxicity related to its insolubility [27]. Spiroplatin, the 1,1 diaminomethyl cyclohexane sulphate platinum II (TNO 6, SPAC) was developed by the TNO Institute, Utrecht, The Netherlands and by Bristol-Myers Squibb, because of its lack of cross-resistance with cisplatin and reduced nephrotoxicity in animal models [99]. Phases I and II were completed in Europe in more than 300 patients, but minimal activity was seen in platinum-pretreated patients. In addition, acute renal failure occurred in a few patients and it was not prevented by the introduction of pre- and post-hydration [100]. The compound development was, therefore, abandoned.



JM-216
(bisacetato-dichloro-cyclohexylamine Pt IV)

Figure 4. Platinum IV compounds.

PLATINUM IV COORDINATION COMPOUNDS

JM-216

JM-216 (bis-acetato-ammine-dichloro-cyclohexylamine platinum IV, BMS-182751) is not the first platinum IV coordination compound brought to clinical development, but it is the first platinum-containing anticancer agent expressly developed for oral administration. The compound has been developed by the Bristol-Myers Squibb Company in collaboration with the Johnson-Matthey Company and the Institute of Cancer Research [101, 102]. The compound exerted, when administered orally, comparable antitumour effects to those of parenterally administered cisplatin or carboplatin. *In vivo* evaluation encompassed murine plasmocytoma (ADJ/PCS) [101] and reticulosarcoma (M5076) [102] as well as several human ovarian carcinoma xenografts [101, 102]. Of interest, lack of cross-resistance of JM-216 with cisplatin, observed *in vitro* in several human cancer cell lines, and ascribed to increased intracellular accumulation, has not been confirmed *in vivo* [103]. The existence of a true synergistic effect between orally administered JM-216 and etoposide, similar to that observed in the past with parenterally administered cisplatin (or carboplatin) and etoposide, has been reported *in vivo* in a murine leukaemia model (P388) [104]. Animal toxicity testing indicated that orally administered JM-216 was devoid of nephrotoxicity and neurotoxicity in rodents, was less emetogenic than cisplatin (and similar to carboplatin) in ferrets and was dose-limited by myelosuppression, presenting a similar profile to parenterally administered carboplatin in dogs [103]. Oral bioavailability ranged in rodents between 41 and 84% for JM-216, whereas it was 37% for cisplatin and 22% for carboplatin [103].

The first phase I trial of JM-216, which utilised an intermittent schedule, began in 1992 in the U.K. [105]. Doses ranging from 60 to 700 mg/m^2 were studied, but pharmacological evaluation revealed saturable absorption of doses of 200 mg/m^2 and above. Thus, this schedule was abandoned. Of note, emesis (mostly prevented by oral anti-emetic premedication) and myelosuppression were observed, as well as diarrhoea. 1 patient with ovarian carcinoma, who had previously received cisplatin, showed a fall in her CA125 tumour marker levels of more than 50% for more than 4 months. She was treated with 120 mg/m^2 of JM-216. Three subsequent phase I trials, in Europe [106], the U.S.A. [107] and Japan [108] have explored the daily×5 regimen, reaching very similar conclusions. Dose-limiting toxicity, after oral administration to fasting patients who did not receive hydration, was myelosuppression, at 100–120 mg/m^2/daily×5 (the lower-dose was recommended for previously treated patients). Retreatment was possible every 4–5 weeks (every 3 weeks in good risk patients). Other toxicities consisted of emesis, with generally

Table 4. *Platinum IV compounds*

Compound	Phase II dose (mg/m^2)	Limiting toxicity	Development status
JM-216	100–120 daily×5 35–45 daily×14	Myelosuppression Delayed myelosuppression	Phase II (prostate, lung SC, lung NSC, ovary, gastric, colon, breast, cervix), world-wide

SC, small cell; NSC, non small cell.

mild intensity, median duration of vomiting for 1 day and of nausea for 5 days. Diarrhoea and stomatitis were also observed, but no clear evidence of neurotoxicity, nephrotoxicity or ototoxicity occurred. Linear pharmacokinetics were observed for both total and ultrafilterable platinum, with this schedule. Another phase I trial explored a 14-day schedule [109]. With this regimen, myelosuppression was still dose-limiting, but late nadirs (week 4–5) occurred for neutropenia and thrombocytopenia, with recovery by week 6–7. Emesis and diarrhoea were minimal and the maximum tolerated dose was 35–45 mg/m^2/daily×14. Finally, a phase I study of the combination of JM-216 and radiation therapy is close to completion [110]. This approach is appealing because of the radiosensitising properties of platinum compounds as well as the convenience of oral administration. In this trial, myelosuppression and oesophagitis were dose-limiting in patients receiving 60 mg/m^2/daily×5 of JM-216, concomitantly to daily doses of 200 cGy for 6–7 weeks (total dose: 60–70 Gy). Courses of JM-216 were repeated on day 21.

The phase II trials so far reported have all utilised the daily×5 schedule. Positive results have been observed in small cell lung cancer, in patients with no prior chemotherapy, who received initially JM-216 at 120 mg/m^2/daily×5 every 3 weeks [111]. However, about half the courses administered had to be delayed due to myelosuppression. A total of 27 patients were treated (the majority with extensive disease) and partial responses were observed in 12 of the 23 evaluable patients (52%). No severe emesis and no nephrotoxicity or neurotoxicity were observed [11]. A negative phase II trial has been reported in NSCLC [112]. No objective responses were seen in 13 evaluable patients (1 achieved a partial response which was not confirmed a month later). These previously untreated patients appeared to tolerate doses of 120 mg/m^2/daily×5 every 3 weeks. Severe gastrointestinal toxicity occurred in a few patients and 5HT3 antagonists were administered prophylactically in slightly more than half the patients. A second phase II study in NSCLC, randomised versus cisplatin 100 mg/m^2, is ongoing. Perhaps the most interesting phase II results of JM-216 have been reported in hormone-refractory prostate cancer [113]. Patients received JM-216 at 120 mg/m^2/daily×5 every 4 weeks. The dose had to be reduced to 100 mg/m^2/daily×5 in most patients and most required dosing delays due to late nadirs. Updated results indicated that prostate specific antigen (PSA) level reductions occurred in 8/24 (33%) evaluable patients, out of 34 enrolled. Tumour shrinkage and significant pain reduction was also observed in this trial. These results compare favourably with recently published results in the treatment of hormone-refractory disease as well as with the only report of PSA responses with a platinum agent (carboplatin) [114] and warrant further investigations. Phase II studies of JM-216 are ongoing in ovarian cancer, in cervix cancer, in gastrointestinal malignancies and in breast cancer. Combination studies with other orally administered anticancer agents, such as etoposide and UFT, an oral fluoropyrimidine, are also ongoing.

Platinum IV compounds abandoned

Ormaplatin (tetrachloro-d,L-trans-1,2 diaminecyclohexane platinum IV, tetraplatin) is a molecule which combined the platinum IV configuration with the DACH ring. It was developed by the Pharmacia-Upjohn Company, Kalamazoo, Michigan, U.S.A., in collaboration with the NCI. The rationale for clinical development involved substantial evidence of lack of cross-resistance with cisplatin, not only in murine but also in human tumour models [115]. Moreover, the compound was less nephrotoxic than cisplatin in animals. A fairly large phase I clinical trial programme was launched by the NCI, which encompassed several different regimens of administration, including intermittent bolus (two studies), daily×5 (two studies), days 1 and 8 and finally, a trial of the intraperitoneal route. Altogether, more than 150 patients received the drug in phase I. However, development of ormaplatin was interrupted because of severe, cumulative, often unpredictable peripheral neurotoxicity observed on all schedules tested [116]. Unfortunately, this neurotoxicity continued to increase for a while after drug discontinuation and tended to recover very slowly. The acute dose-limiting toxicity was myelosuppression and emesis was almost universal, but controlled by 5HT3 antagonists. Severe abdominal pain limited the intraperitoneal administration of ormaplatin.

Iproplatin (cis-dichloro-trans-dihydroxy-bis-isopropylamino platinum IV, CHIP, JM-9) is the most extensively studied, among the platinum compounds which have been abandoned. The drug was developed by Bristol-Myers Squibb, in collaboration with Johnson-Matthey and the Institute of Cancer Research [117, 118]. The US NCI eventually joined in the development of the compound [119]. Its selection for clinical development was prompted by its structure (at the time, it was the first platinum IV to be brought to the clinic), its broad spectrum of activity in murine tumour models and its reduced nephrotoxicity as compared with cisplatin. Phase I clinical trials were performed with intermittent bolus infusion (two studies), daily×5 (two studies) and weekly schedules. In addition, a paediatric phase I study was conducted with the single intermittent regimen. In all studies myelosuppression was dose-limiting, emesis was present and nephrotoxicity and neurotoxicity were minimal. Because of the early observation of clinical efficacy in ovarian cancer, three additional phase I trials adopted the intraperitoneal route of administration. At the completion of the phase I programme, which began in late 1980 at Roswell Park Cancer Institute [120], Buffalo, New York, more than 100 patients had been treated. An extensive programme of single agent phase II trials was performed, involving more than 1,000 patients, enrolled in more than 35 studies. The majority of the trials adopted doses of 270–300 mg/m^2, administered every 4 weeks and a few utilised 45–75 mg/m^2/daily×5. The best single agent activity was reported in ovarian cancer, with objective response rates of 46, 35 and 14% observed in three large independent trials [121–123]. Activity was seen in subsets of patients resistant to previous cisplatin treatment. Initial phase II response rates in excess of 20% in small cell lung cancer [124], head and neck [125], cervix [126] and bladder cancer [127] were not subsequently confirmed in patients with poorer pretreatment characteristics [128, 129].

Several of the phase II studies of iproplatin were randomised versus carboplatin. This study design allowed a comparison of their respective safety profiles, across tumour types [130]. This analysis indicated that iproplatin induced more thrombocytopenia, more vomiting and more diarrhoea than carboplatin.

Phase III trials provided a comparative assessment of iproplatin efficacy. They were performed in previously untreated, advanced ovarian cancer. A single agent comparison of iproplatin 300 mg/m^2 versus carboplatin 400 mg/m^2

reported significantly inferior response rates, time to progression and overall survival for iproplatin [131]. A second, smaller trial which compared iproplatin with carboplatin and with cisplatin, all in combination with cyclophosphamide, yielded very similar results, which did not reach statistical significance because of sample size [132]. Thus, iproplatin was finally abandoned.

CONCLUSIONS

A quarter of a century of clinical research on platinum coordination compounds has yielded remarkable anticancer agents. Cisplatin, the parent compound of the whole class, has exerted a broad spectrum of antitumour activity in solid tumours, and curative effects in germ cell cancer. Carboplatin has successfully been developed as a second generation compound with reduced organ toxicity and, when dosed appropriately, produces antitumour efficacy comparable to cisplatin. The search for a platinum agent with increased activity still remains an elusive goal. It is hoped that progress will be brought about by new agents which might expand upon the utilisation of the platinum compounds in new tumour types (such as oesophageal, colorectal, or prostate cancer) or through innovative approaches (such as radiosensitisation, loco-regional, or oral administration) to their utilisation.

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