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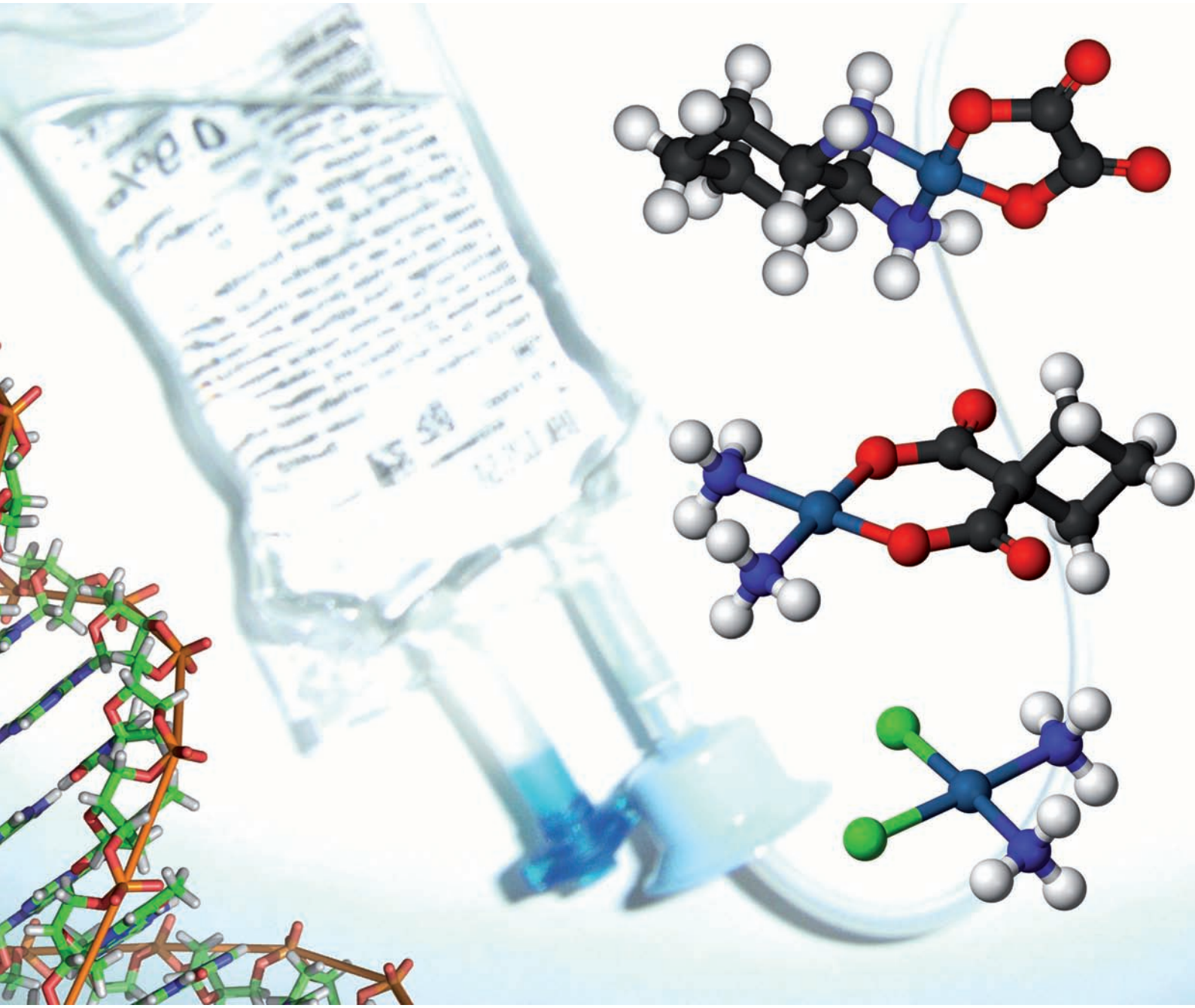

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The status of platinum anticancer drugs in the clinic and in clinical trials

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Since its approval in 1979 cisplatin has become an important component in chemotherapy regimes for the treatment of ovarian, testicular, lung and bladder cancers, as well as lymphomas, myelomas and melanoma. Unfortunately its continued use is greatly limited by severe dose limiting side effects and intrinsic or acquired drug resistance. Over the last 30 years, 23 other platinum-based drugs have entered clinical trials with only two (carboplatin and oxaliplatin) of these gaining international marketing approval, and another three (nedaplatin, lobaplatin and heptaplatin) gaining approval in individual nations. During this time there have been more failures than successes with the development of 14 drugs being halted during clinical trials. Currently there are four drugs in the various phases of clinical trial (satraplatin, picoplatin, Lipoplatin™ and ProLindac™). No new small molecule platinum drug has entered clinical trials since 1999 which is representative of a shift in focus away from drug design and towards drug delivery in the last decade. In this perspective article we update the status of platinum anticancer drugs currently approved for use, those undergoing clinical trials and those discontinued during clinical trials, and discuss the results in the context of where we believe the field will develop over the next decade.

Introduction

Since the discovery of the therapeutic potential of *cis*-diamminedichloridoplatinum(II), or cisplatin, by Barnett Rosenberg (1926–2009)[1] it has become one of the major drugs in cancer chemotherapy. Today it is used in 32 of 78 treatment regimes listed in Martindale[2] in combination with a wide range of other drugs including: topoisomerase II inhibitors (doxorubicin, etoposide, mytomycin, bleomycin and epirubicin), mustards (cyclophosphamide, melphalan and ifosfamide), antimetabolites (gemcitabine, 5-fluorouracil (5-FU) and methotrexate), vinca alkaloids (vinblastine and vinorelbine) and taxols (paclitaxel).[2] Cisplatin is currently used to treat testicular cancer (for which it has a 90% cure rate), ovarian, bladder, melanoma, non-small cell lung cancer (NSCLC), small cell lung cancer (SCLC), lymphomas and myelomas.[2,3]

In the blood stream where the chloride concentration is relatively high (100 mM) the chloride ligands stay attached to the drug although binding to serum proteins, such as human serum albumin, does occur (Fig. 1).[4] When it reaches the tumour, cisplatin is thought to be taken up into the cells by three possible mechanisms: passive diffusion, copper transporter proteins (*e.g.* CTR1) and/or organic cation transporters.[5] Once inside the cell, the lower chloride concentration (4–20 mM) results in drug

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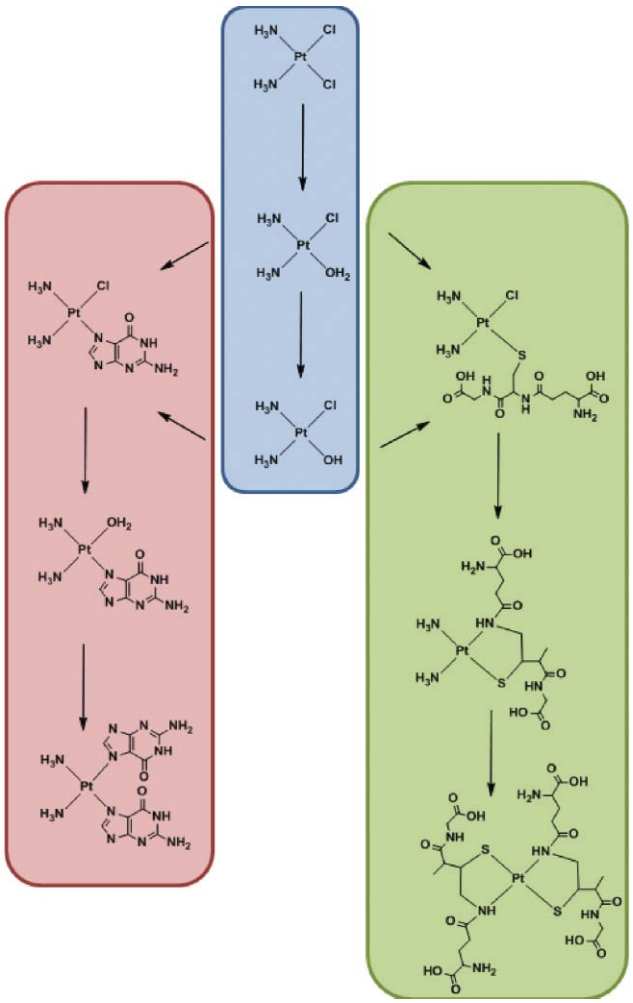

Fig. 1 Simplified biological processing of cisplatin inside cells showing (blue) drug aquation, (red) DNA binding through the N7 of guanine and (green) deactivation and degradation by the tripeptide L-glutathione. Charges have been omitted for charity.

aquation with the loss of one or both of the chloride ligands.[4] When aquated, cisplatin can go on to bind to its target, DNA. Cisplatin will bind at the N7 position of guanine, and to a lesser extent adenine, through the formation of a covalent coordinate bond with the lone pair of the nitrogen atom.[4] Ring closure through the formation of a second DNA bond forms a range of adducts, particularly 1,2-GpG intrastrand adducts that bend the DNA (between 30 and 60° towards the major groove) and unwinds the helix (up to 23 °).[6] This DNA distortion prevents replication and transcription, which ultimately leads to cellular apoptosis.[4] Cisplatin is also known to bind to RNA and interfere with cellular RNA processing, which may assist in the action of the drug.[7]

Unfortunately, the use of cisplatin is restricted because of severe dose-limiting side effects which arise from the indiscriminate uptake of the drug into all rapidly dividing cells (tumours, but also for example bone marrow) and the body's attempt to excrete the drug through the kidneys. These side effects include: nephrotoxicity (reduced kidney function and damage), neurotoxicity (nervous system damage), ototoxicity (hearing loss), and myelosuppression (reduction in bone marrow activity). To some degree the nephrotoxicity of cisplatin can be reduced through the use of saline hyperhydration before and after treatment.[8] As a single agent, cisplatin does not cause alopecia (hair loss).

The severe side effects of cisplatin mean that the dose delivered to patients can be sub-lethal to tumours, particularly ovarian cancers, which means they are then able to develop resistance to further drug treatment. There are three main mechanisms of drug resistance:[9]

- Reduced drug uptake and/or increased drug efflux.
- Degradation and deactivation by intracellular thiols. In particular this may be due to raised glutathione levels which can be as high as 10 mM inside resistant cells.
- Improved repair or tolerance of DNA–cisplatin adducts.

The toxicity of, and cellular resistance to, cisplatin have driven the development of improved platinum-based anticancer drugs that display fewer or more tolerable side effects and/or are able to overcome one or more resistance mechanisms. In the 30 years since cisplatin's first approval for human use, 23 other platinum-based drugs have entered clinical trials with only two

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Ruby completed a BSc (Hons) in Medical Biochemistry at the University of Glasgow then attended Napier University, Edinburgh and graduated with an MSc in Drug Design and Biomedical Science (with distinction). Ruby's PhD project is split between the University of Strathclyde and the Beatson Institute for Cancer Research, University of Glasgow through a studentship from the Scottish Universities Life Science Alliance. She has an interest in photography, enjoys travelling, cooking, reading and swimming.

Table 1 Platinum-based anticancer drugs which have achieved marketing approval for human use in at least one nation state

Drug	Other names/brand names/formulation names		CAS number	Development company/Marketer	DLT	Country
Cisplatin	Platinol® Platidiam Platinex® Platistin Platosin Cisplatyl Platiblastin®	Briplatin Abiplatin® Lederplatin Neoplatin Platibastin Peyrone's chloride	15663-27-1	Generic	Nephrotoxicity	Global
Carboplatin	Paraplatin® Paraplatine Carbomedac® Carbosin	JM 8 Cycloplatin CBDCA Ribocarbo	41575-94-4	Generic	Myelosuppression	Global
Oxaliplatin	Eloxatin® Dacotin®	Dacplat® Elplat®	61825-94-3	Sanofi-Aventis	Neurotoxicity	Global
Nedaplatin	Aqupla®	254-S NSC375101D	95734-82-0	Shionogi Pharmaceuticals	Myelosupression	Japan
Lobaplatin	—	—	135558-11-1	Asta-Medica	Thrombocytopenia	China
Heptaplatin	Sunpla	SKI 2053R Eptaplatin NSC-644591 NSC-D-644591	146665-77-2	SK Chemicals Life Sciences	Nephrotoxicity/ Intra-abdominal bleeding	Korea

gaining global approval and another three gaining marketing approval in individual nations. In this perspective we appraise the current status of platinum drugs in the clinic and those currently undergoing clinical trials. We also examine those drugs whose development was halted during clinical trials and discuss the future of platinum drug development.

Clinically approved drugs

A list of platinum-based anticancer drugs which have achieved marketing approval for human use in at least one nation state is given in Table 1.

Carboplatin (approved world-wide)

The toxicity of platinum-based drugs is directly related to the ease with which the leaving groups are aquated. Platinum complexes with highly labile ligands, such as water or nitrate, are very toxic whereas ligands such as bis-carboxylates, which aquates very slowly, are significantly less toxic. Diammine[1,1-cyclobutanedicarboxylato(2–)-*O*,*O*′]platinum(II) was designed specifically to reduce the side effects associated with cisplatin treatment (Fig. 2). This is achieved through the replacement of the dichloride ligands with 1,1-cyclobutanedicarboxylate, which aquates with a rate constant of 10^{-8} s^{-1}, compared with 10^{-5} s^{-1} for cisplatin.[10,11]

Because of its lower reactivity, carboplatin can be administered in much higher doses (300–450 mg m^{-2}) than cisplatin (20–120 mg m^{-2}), depending on the administration schedule.[2] The side effects of carboplatin are also different with leukopenia, neutropenia and thrombocytopenia as the dose limiting toxicities (DLTs). Once aquated carboplatin yields the same active component as cisplatin and forms the same DNA adducts, and is therefore only clinically

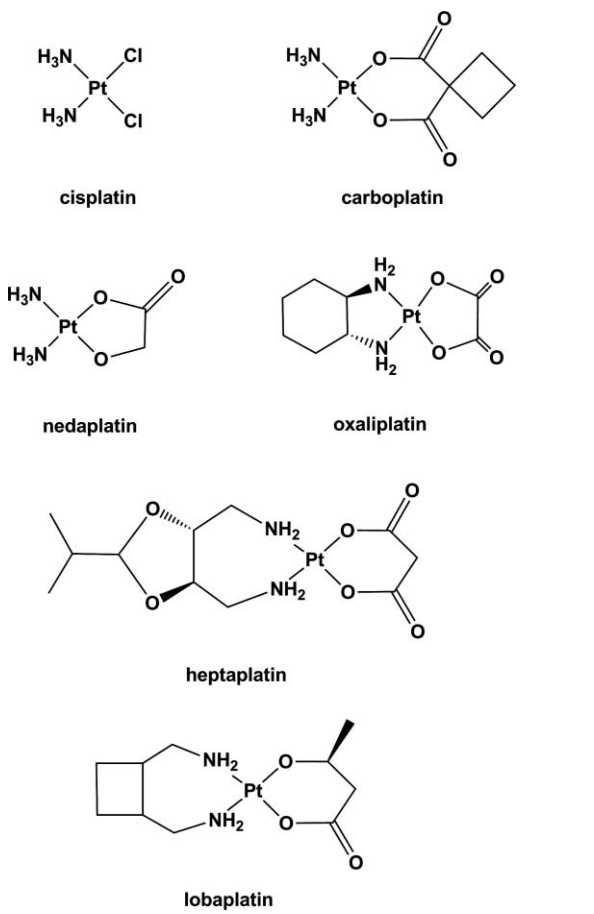

Fig. 2 The platinum-based anticancer drugs which have gained marketing approval for human use in at least one nation state.

useful for treating the same cancer types. Carboplatin is now the drug of choice for ovarian cancer, in preference to cisplatin, and has recently undergone additional Phase II and III trials for the treatment of salivary gland cancer[12] and advanced mullerian cancer[13] to further expand its clinical application.

Oxaliplatin (approved world-wide)

[Oxalate(2–)-*O*,*O*′][1*R*,2*R*-cyclohexanediamine-*N*,*N*′]platinum-(II) was the first drug approved that was capable of overcoming cisplatin resistance. In oxaliplatin the two ammine ligands have been replaced by a single bidentate ligand, (1*R*,2*R*)-cyclohexane-1,2-diamine (*R*,*R*-dach).[4] Oxaliplatin is thought to overcome cisplatin resistance through the different adducts it forms with DNA.[14] Whilst it predominantly forms GpG intrastrand adducts, the bulky hydrophobic dach ligand points into the DNA major groove which prevents binding of DNA repair proteins.[15] The oxalate ligand also greatly reduces the severity of the side effects of the drug compared with cisplatin.[14]

Oxaliplatin was first approved in France in 1996, the USA in 2002 and Japan in 2005. The drug was developed and marketed throughout the world by Sanofi-Aventis and whilst the Food and Drug Administration in the USA (the biggest pharmaceutical market in the world) approved generic formulations of the drug in August 2009, deals between Sanofi-Aventis and six generics manufactures means all will stop selling alternative versions of oxaliplatin by 30 June 2010 until 09 August 2012. Until then sales were worth more than US$1.3 billion per year. Oxaliplatin currently has wide approval for the treatment of adjuvant and metastatic colorectal cancers when used in combination with 5-FU and folinic acid.[2] Recent clinical trials have tried to extend its spectrum of activity to include the treatment of metastatic gastric and oesophagogastric adenocarcinoma,[16] and improve its effectiveness against colorectal cancers through its administration with different drugs such as irinotecan and capecitabine.[17] Ongoing clinical trials as of April 2010 include examination for efficacy in gastric, fallopian tube and ovarian, breast, NSCLC, pancreatic cancers, acute myeloid leukaemia, indolent lymphoma, and heptoma.

Nedaplatin (approved in Japan)

Diammine[hydroxyacetato(2–)-*O*,*O*′]platinum(II) is a second-generation platinum analogue that is ten times more water soluble than cisplatin, and is significantly less nephrotoxic than both cisplatin and carboplatin.[18,19] Preclinical and clinical studies demonstrated that nedaplatin has anticancer activity superior to that of carboplatin and equivalent to that of cisplatin.[19,20] Since its approval in 1995, it has been used in the treatment of NSCLC, SCLC, oesophageal cancer and head and neck cancers.[19,21] The MTD of nedaplatin is 90 mg m^{-2} and the DLTs are thrombocytopenia and neutropenia.[22]

Recently, several Phase I and Phase II studies have shown promising results when nedaplatin is used in combination therapies. For the treatment of oral squamous cell carcinoma, a nedaplatin and docetaxel regime gave a partial response (PR) rate of 33%.[23] Nedaplatin with paclitaxel in the treatment of metastatic oesophageal carcinoma gave a complete response (CR) rate of 3% and a PR rate of 41%,[24] and nedaplatin with irinotecan followed by gefitnib in the treatment of NSCLC had an overall response (OR) rate of 43%.[25]

Two further clinical trials have been conducted to investigate the effect of replacing cisplatin with nedaplatin in patients normally treated with a regime of cisplatin and 5-FU for oesophageal squamous cell carcinoma,[18,26] and locoregionally advanced nasopharyngeal carcinoma.[27] Both studies found no difference in the overall survival rates. It was concluded, however, that replacing cisplatin with nedaplatin may prove useful when treating cancer patients that also present with renal impairment.[18,26]

Lobaplatin (approved in China)

[2-Hydroxypropanoato(2–)-*O*1,*O*2][1,2-cyclobutanedimethanamine-*N*,*N*′]platinum(II) is a third-generation platinum anticancer drug delivered as a diastereomeric mixture of *S*,*S* and *R*,*R* configurations of the carrier ligand. The drug does not induce alopecia,[28] renal, neuro- or ototoxic side effects after either IV bolus injection or infusion.[29-33] Anaemia and leukopenia are common,[28,29,34] as are nausea and vomiting, although the latter two can be well-controlled with antiemetics.[28,29,34] The common DLT is thrombocytopenia.[28,30,32–37] Lobaplatin is currently approved for the treatment of chronic myelogenous leukaemia (CML), inoperable metastatic breast cancer and SCLC.[38] In 2003 Ainan Tianwang International Pharmaceutical signed a US$4.3 million deal for manufacturing and marketing rights in China.[39]

Recently, lobaplatin has been trialled in combination with vinorelbine in the treatment of late-stage NSCLC but it demonstrated no significant improvement in efficacy compared with a vinorelbine/cisplatin regime.[40] A similar lobaplatin/vinorelbine regime did however produce a 37% PR rate in patients treated for advanced breast cancer with modest and recoverable non-haematological toxicities.[36] Lobaplatin with 5-FU and leucovorin is currently undergoing Phase III trials for the treatment of recurrent or metastatic oesophageal carcinoma.[41]

Heptaplatin (approved in the Republic of Korea)

[Propanedioato(2–)-*O*,*O*′][2-(1-methylethyl)-1,3-dioxolane-4,5-dimethanamine-*N*,*N*′]platinum(II) was selected for clinical trials because its *in vitro* and *in vivo* cytotoxicity was equal, or superior, to cisplatin in various cell lines.[42,43,44] It also displayed high stability in solution,[42] no remarkable toxicity[42,43,44] and potent anticancer activity towards cisplatin-resistant cells.[42,44] The MTD of heptaplatin is 480 mg m^{-2} with DLTs of hepatotoxicity, nephrotoxicity and myelosuppression. It is currently used in the treatment of gastric cancer.[45,46]

Since obtaining marketing approval the drug has been further evaluated in a Phase II trial where it demonstrated an increased response rate in combination with 5-FU and leucovorin of 38%,[47] compared with 17% as a single agent.[48] Previous studies have shown that patients experience lower nephrotoxicity with heptaplatin (360 or 400 mg m^{-2}) when compared to cisplatin (60 mg m^{-2}),[47–50] however, one randomised Phase III study highlighted that nephrotoxicity was more severe with heptaplatin.[51]

The most recent Phase III trial comparing a heptaplatin (400 mg m^{-2})/5-FU regime with a cisplatin (60 mg m^{-2})/5-FU regime demonstrates the survival and response rates to be comparable, 7.3 months *vs*. 7.9 months and 34% *vs*. 36%, respectively.[52] The

Table 2 Platinum(II)-based drugs which entered human clinical trials but which have not been given marketing approval

Drug	Other names	CAS Number	Development companies	Reason
JM-11	—	38780-38-0	Johnson Matthey	Blood/urine clearance not better than cisplatin
NSC 170898	PAD	38780-36-8	Wadley Institute	Poor water solubility
Ormaplatin	Tetraplatin NSC 363812	62816-98-2	NCI (USA)/UpJohn	Severe and unpredictable cumulative neurotoxicity
Sebriplatin	CI-973, NK121	110172-45-7	Parke-Davis, Nihon Kayaku	No activity in Phase II
Enloplatin	CL 287,110	111523-41-2	American Cyanamid	No activity in Phase II
Zeniplatin	CL 286,558	111490-36-9	American Cyanamid	Serious nephrotoxicity
Spiroplatin	TNO-6	74790-08-2	Bristol Myers	Unpredictable renal failure
Cycloplatam	—	109837-67-4	N.S. Kurnakov Institute of General and Inorganic Chemistry	Unknown
Miboplatin	DWA2114R	103775-75-3	Chugai Pharmaceuticals	Activity not better than cisplatin
Iproplatin	JM-9 CHIP	62928-11-4	Johnson Matthey/Bristol Myers	Activity not better than cisplatin or carboplatin
TRK-710	—	173903-27-0		Unknown
SPI-77	STEALTH® liposomal cisplatin, SPI-077	SPI-077	Alza Pharmaceuticals/Johnson & Johnson	No activity in Phase II
Aroplatin	L-NDDP NDDP	114488-24-3	Antigenics/Aronex Pharmaceuticals	Economic
BBR3464	Triplatin	172903-00-3	Novuspharma/Boehringer Mannheim Italia/Roche	No activity in Phase II

advantage of the heptaplatin treatment was that the toxic side effects of neutropenia and emesis were less severe and proteinuria levels were lower.[52] A supporting Phase III trial demonstrated that the two heptaplatin/5-FU regimes (34 and 36% response rate) were comparable with a cisplatin/5-FU regime (response rate 34%).[53]

Discontinued drugs

In order to develop drugs that are more cytotoxic to cancers and have fewer and/or less severe side effects, it is important to know what drugs have previously undergone clinical trials but subsequently failed either due to a lack of activity or because of their toxicity (Table 2). In some instances drugs may also be discontinued in clinical trials simply for economic reasons. To date, 14 platinum-based drugs (Fig. 3) have completed at least one Phase I trial with only a few reaching Phase III.

JM 11

Dichloridobis(isopropylamine)platinum(II) was one of the first cisplatin-derivatives tested as a potential drug candidate. *In vivo* trials demonstrated a therapeutic index superior to cisplatin in ADJ/PC6 tumour xenografts (JM 11: 25, cisplatin: 8.1) and a similar increase in life span for mice with L1210 leukaemia (70 and 95%, respectively).[54–56] JM 11 underwent a single Phase I trial, not to evaluate drug DLT or MTD but to examine pharmacokinetics in comparison to cisplatin. At a single dose of 27 mg, it was found that the blood and renal clearances were not significantly different from cisplatin with no evidence of tumour uptake. As such, drug development was abandoned.[57,58]

NSC 170898

Dichloridobis(cyclopentylamine)platinum(II) is a simple derivative of cisplatin where the ammines of cisplatin have been functionalised with cyclopentylamine ligands.[56] Despite its very poor water solubility, *in vivo* testing showed that the drug was less toxic than cisplatin and had a much better therapeutic index (200–235) compared with cisplatin (8.1) in PC6 tumour bearing mice.[54,56] NSC170898, however, was less effective than cisplatin in treating L1210 with an increase in life span of only 41% compared with 95% for cisplatin.[56] This drug underwent a single Phase I trial but was not further developed because of its poor solubility.[59,60]

Ormaplatin

Tetrachlorido(1,2-cyclohexanediamine-*N*,*N*′)platinum(IV) is a prodrug that undergoes reduction by proteins with sulfhydryls groups ($t_{1/2}$: 5–15 min) in tissue and blood plasma to dichlorido-(D,L-*trans*-1,2-diaminocyclohexane)platinum(II).[61] Upon aquation inside the cell, it yields a similar active component to oxaliplatin, although in ormaplatin the carrier ligand is a mix of the Δ- and λ-isomers of the diaminocyclohexane ligand. Ormaplatin was chosen from a family of 28 similar complexes[62,63] because of its *in vitro* and *in vivo* activity in L1210 leukaemia,[64] A2780/CP70 ovarian,[65] B16 melanoma, myeloma and mammary cancers.[64,66]

Six Phase I clinical trials were conducted under the sponsorship of the National Cancer Institute (USA) examining single monthly, weekly × 2 (a single weekly dose given for two consecutive weeks), daily × 5 (a single daily dose given for five consecutive days) and intraperitoneal administration regimes of ormaplatin.[66–68] In the regular multiple dosing trials cumulative severe neurotoxicity (at total doses greater than 200 mg m^{-2}) was the DLT and in two trials a safe MTD could not be determined.[66,68] As a single monthly IV infusion, a safe dose of 98 mg m^{-2} was recommended for Phase II trials, with myelosuppression (thrombocytopenia and granulocytopenia) the DLT.[67] As with the multiple dosing trials, cumulative neurotoxicity was also observed. In total more than 118 patients have been treated with ormaplatin. No Phase II trials of ormaplatin have been reported in the literature.

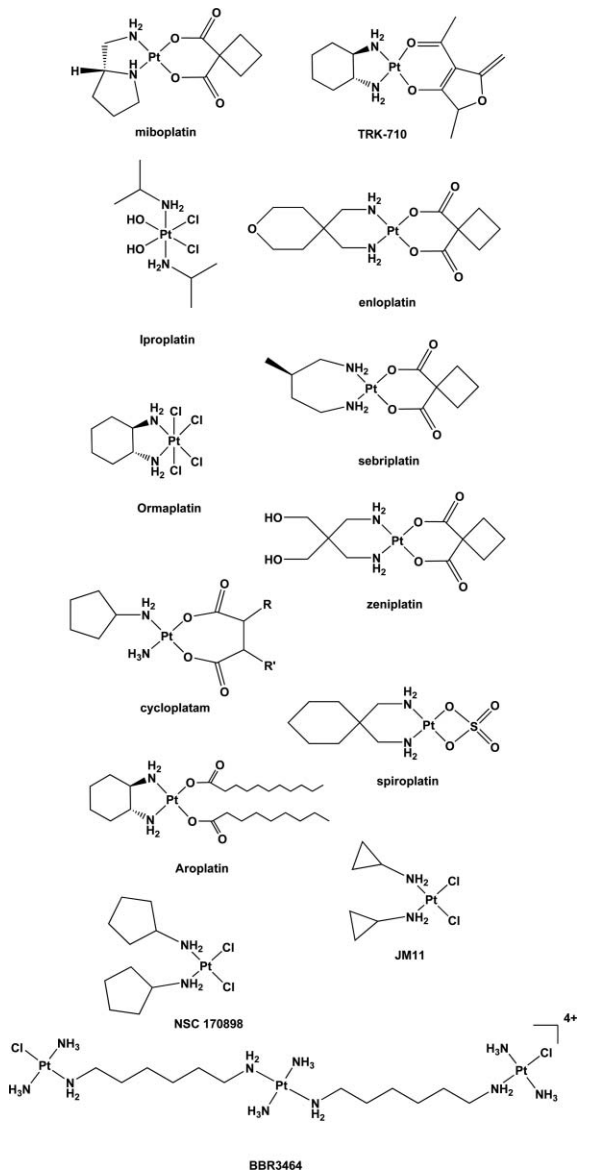

Fig. 3 The platinum-based anticancer drugs which entered human clinical trials, but their development was not continued because of severe/unpredictable side effects from Phase I, because of a lack of activity in Phase II/III trials, or for economic reasons. Cycloplatam: where R = OH, R′ = H and where R = H, R′ = OH.

Sebriplatin

[1,1-Cyclobutanedicarboxylato(2–)-*O*,*O*′](2-methyl-1,4-butanediamine-*N*,*N*′)platinum(II) which contains the same leaving group as carboplatin, displayed better cytotoxicity than cisplatin in 24 of 37 cisplatin sensitive and resistant cancer cell lines tested.[69] In particular the drug demonstrated some potential in overcoming cisplatin resistance in ovarian cancer and considerable potential as a treatment for leukaemia;[69–72] a cancer in which platinum drugs have never showed efficacy in humans. Sebriplatin also demonstrated synergies when co-administered with hyperthermia.[73,74]

Two Phase I trials were completed with sebriplatin as a daily × 5 and a once monthly IV infusion.[75,76] In the multiple dosing trial neutropenia was the DLT, but was rapidly recoverable, with mild/infrequent vomiting and nausea.[75] The MTD was determined to be 40–50 mg m^{-2} from which a Phase II dose of 30 mg m^{-2} day^{-1} for 5 days was recommended.[75] In the once monthly trial a MTD of 290 mg m^{-2} was determined with granulocytopenia as the DLT for patients previously untreated with platinum, radiation or stem cell toxin therapy, and a MTD of 230 mg m^{-2} for those who had previously been treated with at least one of these regimes.[76] Doses of 230 and 190 mg m^{-2} were recommended for Phase II trials in these groups of patients.

A single Phase II study has been reported for metastatic breast cancer, treated with 230 mg m^{-2} of sebriplatin once every 21 days.[77] Two partial responses were observed and several minor responses. Whilst the results indicated that further examination of that dose and schedule were not warranted, the authors hypothesised that the drug may be more efficacious at higher doses if colony-stimulating factors were also used.[77] No other Phase II trial results have been reported in the literature.

Enloplatin

[1,1-Cyclobutanedicarboxylato(2–)-*O*,*O*′][tetrahydro-4*H*-pyran-4,4-dimethylamine-*N*,*N*′]platinum(II) is a water-soluble drug (450 mg mL^{-1})[78] with the same leaving group as carboplatin and a carrier ligand similar to zeniplatin (see below). Preclinical trials indicated cytotoxicity in breast,[78] ovarian, cisplatin resistant SCLC and embryonal carcinoma cancers.[78,79] *In vivo* trials of enloplatin also displayed low renal toxicity, good physical stability and a lack of cross-resistance with cisplatin.[78,79]

Initial Phase I studies indicated that nephrotoxicity was the DLT,[80] although in a later Phase II trial it was found that the nephrotoxicity was manageable and neutropenia was dose limiting.[81] In the only reported Phase II trial in the literature, 18 patients with platinum resistant ovarian cancer were treated with single IV dose every 21 days, without prehydration, from which only one PR was observed.[81]

Zeniplatin

[1,1-Cyclobutanedicarboxylato(2–)-*O*,*O*′][2,2-bis(aminomethyl)-1,3-propanediol-*N*,*N*′]platinum(II) was selected for development from a family of 20 structurally related complexes.[78] Whilst the drug was less active than cisplatin and carboplatin in P388, L1210 and L1210 CPR cells *in vivo*, it showed comparable activity in MX-1 breast and H207 tumour xenografts and higher cytotoxicity in B-16 melanoma and M5076 reticulum sarcoma cells.[78] In addition, it is significantly more water soluble (7 mg mL^{-1}) than cisplatin (2 mg mL^{-1}) and has less severe side effects.[78]

Phase I results showed that zeniplatin had a MTD of 145 mg m^{-2}, with leukopenia and neutropenia the DLTs.[82] In total, zeniplatin was tested in 308 Phase II patients with advanced ovarian,[83,84] breast,[85] advanced malignant and metastatic melanomas,[86,87] advanced renal,[86] and advanced NSCLC.[88] The response rates were generally poor with a PR rate of 10–14%. Only two patients were reported to have achieved a CR (with lymph-node metastasised melanoma).[86] Clinical development of the drug was halted due to serious nephrotoxicity, even with prehydration, which was not seen previously in clinical trials or in animals.[86] In another study, 16% of patients also experienced a fever of unknown origin.[84]

Spiroplatin

[Sulfato(2–)-*O*,*O*′][1,1-cyclohexanedimethylamine-*N*,*N*′]platinum(II) was discovered and developed in the Netherlands. This drug is unique in that it is the only one to have reached clinical trials with a sulfato ligand as the leaving group which binds to the platinum through the oxygen atoms.

Phase I trial results gave a MTD from a single IV infusion of 35–40 mg m^{-2} or from a daily × 5 infusion of 8–9 mg m^{-2}.[89,90] The DLTs were myelosuppression (leukopenia and thrombocytopenia) in both trials.[89,90] A CR was seen in one patient with lung metastased breast cancer and one PR for a patient with adenocarcinoma of the lung.[89]

Phase II trials evaluated spiroplatin in a range of cancer types including renal cell carcinoma, ovarian and malignant melanoma.[91,90] In the first trial patients with advanced ovarian carcinoma were given a once monthly IV infusion of 30 mg m^{-2} but none of the patients displayed cancer remission.[91] In the second trial patients were given a 30 mg m^{-2} infusion every three weeks. Of the 64 people treated only three patients showed a response.[92] The lack of drug activity and subsequent unpredictable severe renal toxicity (renal toxicity was observed in Phase I trials but it was not severe) meant the drug did not move into Phase III trials.[91,92]

Cycloplatam

[Hydroxybutanedioato(2–)-*O*1,*O*4][ammine(cyclopentanamine)]-platinum(II) was discovered and developed in Russia by the N.S. Kurnakov Institute of General and Inorganic Chemistry. Cycloplatam was used in two different chiral forms, with the hydroxyl on the leaving group in either the *cis* or *trans* position in relation to the cyclopentane ring of the carrier ligand.[93] Preclinical trials indicated drug activity *in vitro* in a range of cancer cell lines (mainly ovarian cancer cell lines), with some ability to overcome cisplatin-resistance, and *in vivo* activity in human tumour xenografts (particularly lung cancer).[93] All publications dealing with the clinical trials of cycloplatam have been published only in Russian, but it is known that cycloplatam was examined in Phase II trials as a treatment for urinary bladder, cervical carcinoma, prostate and pleural mesothelioma.[94]

Miboplatin

[1,1-Cyclobutanedicarboxylato(2–)-*O*,*O*′][(*R*)-2-aminomethylpyrrolidine-*N*,*N*′]platinum(II) contains an unsymmetric alicyclic diamine as the carrier ligand and was selected for further clinical studies due to its good water solubility,[95,96] lower nephrotoxicity and potent anticancer activity in prostate, breast, colon, ovarian, oesophageal and pancreatic cancer. In contrast to cisplatin, *in vitro* studies have shown that the anticancer effect of miboplatin is time dependent.[97] It is more potent when administered at multiple low doses compared with a high single bolus injection.[97,98] An *in vivo* study investigating the increase in survival time of leukaemia bearing mice demonstrated synergism when miboplatin was administered with adriamycin or vindesine, whereas cisplatin showed sub-additive cytotoxicity with the same drugs.[95]

In Phase I clinical trials the DLTs of miboplatin were gastrointestinal toxicity and neutrocytopenia at a MTD of 1200 mg m^{-2} day^{-1}.[98] The recommended dose for Phase II trials was 800 mg m^{-2} as a 1 h IV infusion repeated every three to four weeks.[98] In Phase II clinical trials, miboplatin achieved an OR rate of 44% in the treatment of ovarian cancer and 21%, with one CR, in the treatment of breast cancer.[99]

In Phase III trials the effectiveness of miboplatin was compared with cisplatin against ovarian cancer. A response rate of 39% was achieved with miboplatin and 47% with cisplatin.[100] In a separate Phase III clinical trial miboplatin at 800 mg m^{-2} was compared to cisplatin at 50 mg m^{-2} (both in combination with cyclophosphamide and doxorubicin), where the cisplatin regime displayed superior cytotoxicity.[95] The lower effectiveness of miboplatin compared with cisplatin in both trials meant drug development was abandoned.[96]

Iproplatin

cis,*trans*,*cis*-Dichloridodihydroxidobis(isopropylamine)platinum-(IV) is an octahedral-based drug similar to ormaplatin, in that it is reduced *in vivo* to a platinum(II) species that then undergoes aquation and DNA binding.[101] Of all the platinum-based drugs to enter human clinical trials but which failed to achieve marketing approval, iproplatin is by far the most studied, with five Phase I, 22 Phase II and a single Phase III trial, involving more than 1000 individual patients, reported in the literature.

Phase I trials demonstrated that myelosuppression, particularly cumulative thrombocytopenia,[102] was the DLT at a MTD of 350 mg m^{-2} as a single IV infusion every three weeks, but with a recommended dose of 300 mg m^{-2} for Phase II trials. Patients treated on a daily × 5 schedule every three weeks had a recommended Phase II dose of 45–65 mg m^{-2};[103] or 95 mg m^{-2} when administered weekly × 4 with a two week break before the next course.[104]

Drug activity was examined in a variety of cancer types in Phase II, including: ovarian,[105] urothelial,[106] malignant pleural mesothelioma,[107] breast,[108–111] squamous cell carcinoma, paediatric disseminated neuroblastoma and other pediatric malignant solid tumours,[112–114] germ cell carcinomas,[115,116] adenocarcinoma of the upper gastro-intestinal tract,[117] colorectal,[118–120] cervical,[121,122] SCLC and NSCLC,[123,124] squamous cell carcinoma of the head and neck,[125] and testicular cancers.[126] Patients included those previously untreated and treated with other chemotherapeutics, including platinums. Iproplatin was largely inactive in the majority of these tumour types and in many cases where it was active,[121] it was found to be less effective than either cisplatin or carboplatin (the latter of which was undergoing Phase II trials at the same time).[114,117,122] Advancement of the drug was also hindered by occasional toxic deaths and dose reductions due to cumulative thrombocytopenia.[108,119,126] Only one Phase III trial of iproplatin has been reported, for ovarian cancer, where it was administered in combination with cyclophosphamide and compared to similar regimes using cisplatin or carboplatin from this trial.[127] It was concluded that the iproplatin response rate was not different from cisplatin.[127]

TRK-710

[3-Acetyl-5-methyl-2,4(3*H*,5*H*)-furandionato-*O*3,*O*4][1,2-cyclohexanediamine-*N*,*N*′]platinum(II) demonstrated activity in endometrial and NSCLC with similar efficacy to cisplatin at equimolar concentrations.[16,128] Furthermore, it displayed activity

in cisplatin resistant cell lines associated with a higher uptake rate compared to cisplatin.[16,128] A Phase I trial showed that TRK-710 displayed lower nephrotoxicity and myelosuppression compared with cisplatin.[129] No other Phase I or II results have been reported.

SPI-077

This drug is a liposomal formulation of cisplatin which utilises steric stabilisation to avoid rapid clearance by macrophages.[130] Encouraging preclinical activity was accredited to prolonged circulation time and enhanced tumour uptake in a variety of tumour models with minimal and reversible toxicities.[131–134]

Treatment in Phase I and II clinical trials was generally well tolerated with little or no haematological, renal, hepatic, gastro-intestinal or neurological toxicities and no requirement for routine hydration.[130,135–139] Dose escalation studies with single agent SPI-077 up to 420 mg m^{-2} did not reach a MTD but were instead limited by infusion volume, which was increased to control infusion reactions.[139–141] A lack of clinical activity despite the administration of large doses, coupled with an apparent absence of cisplatin related toxicities raised concerns over the bioavailability of cisplatin from the liposomes.[130,138,142–144] A pharmacokinetic study revealed platinum–DNA adduct levels in white blood cells were more than ten-fold lower than after comparable doses of non-liposomal cisplatin.[139] *In vitro* studies confirmed negligible (< 10%) release from the liposomes, with extremely slow release kinetics.[131,135] Reformulation was recommended in order to achieve liposomes which were more permeable to cisplatin once exposed to the hypoxic and acidic tumour environment.[130,135,138,139,144]

More recently, low frequency ultrasound (LFUS) has been shown to facilitate the release of cisplatin from the liposomes.[145] Such use of LFUS may improve therapeutic efficacy of liposomal formulations but is likely to be practicable only for superficial tumours.[146]

Aroplatin™

Also known as L-NDDP consists of a lipophilic cisplatin analogue, *cis*-bis-neodecanaota-*trans*-(1*R*,2*R*-diaminocyclohexane)platinum(II), liposomally encapsulated in a 7:3 ratio of dimyristoyl phosphatidylcholine (DMPC) and dimyristol phosphatidylglycerol (DMPG) with a drug to lipid ratio of 1 : 15.[147] Preclinical studies have demonstrated that the bioavailability of NDDP is dependent on liposomal encapsulation.[147,148] The DMPG component is important for moderating stability and anticancer activity[148–151] as it enhances the acidic environment of the liposomal suspension and hence increases the conversion of the NDDP prodrug to the active moiety.[152]

L-NDDP exerted equal cytotoxicity in cells lines both sensitive and resistant to cisplatin (human ovarian[151] and colon carcinoma[153]) and displayed increased activity compared to cisplatin in liver metastases,[148] no nephrotoxicity in dogs[154] and no cross resistance with cisplatin both *in vitro* and *in vivo*.[150,151,153] It has been proposed that the most likely mechanism for cellular uptake is a direct cell membrane to liposome interaction with rapid exchange of NDDP.[148] Anticancer activity is exerted *via* chemical activation by forming one or more active intermediates *in situ* by intercalating between phospholipid molecules of the bilayer.[150,152]

A Phase I trial on patients with metastatic tumours examining delivery by single IV injection every four weeks determined the MTD to be 312 mg m^{-2} and the DLT as myelosuppression.[155] A Phase II trial of this regime was undertaken in patients with therapy-refractory advanced colorectal cancer.[156] Treatment was generally well tolerated with 45% of patients receiving a dose escalation and the response rate was comparable to single agent oxaliplatin.[156,157]

A second Phase I trial looking at intrapleural administration of Aroplatin for 30 minutes every 21 days in patients with malignant pleural effusions determined a MTD of 450 mg m^{-2} (50% higher than IV administration) with chemical pleuritis as the DLT.[158] Again no nephrotoxicity was observed and, in contrast to IV administration, there was an absence of myelosuppression.[158] A subsequent Phase II trial using intrapleural administration achieved a 42% response rate with significant but manageable toxicity, however, efficacy was limited to areas in direct contact with the pleural space.[159]

Intraperitoneal administration was also investigated in patients with peritoneal carcinomatosis or sarcomatosis.[160] This delivery method allows for prolonged drug exposure to the abdominal cavity and low systemic absorption thus allowing increased drug doses and reduced systemic toxicity.[160] The MTD was 400 mg m^{-2} every 28 days and the DLTs were fatigue and abdominal pain.[160]

Until recently Aroplatin had been undergoing various Phase I and Phase I/II trials as a single agent and in combination therapies treating resistant pancreatic and advanced colorectal cancers, advanced solid malignancies and malignant pleural mesothelioma. For economic reasons, however, development of Aroplatin has now been halted.

BBR3464

[*trans*-Diamminechloridoplatinum(II)][(μ-*trans*-diamminedihexanediamine-*N*,*N*′)platinum(II)] nitrate is a multinuclear platinum(II) drug chosen as the lead agent from a family of di- and trinuclear complexes.[161] Whilst BBR3464 displays higher and faster uptake into cisplatin sensitive and resistant cells,[162,163] and faster DNA binding with more DNA adducts formed compared with cisplatin,[164–166] it is the formation of a range of unique DNA adducts that are thought to be the mechanism by which it derives its potent cytotoxicity. Whereas cisplatin forms rigid, short-range intrastrand adducts, the adducts of BBR3464 are more commonly defined as flexible and long range, with a high degree of interstrand cross-links.[167–174] It is also able to induce B to Z and B to A transitions in DNA conformation upon binding.[175,176] More recently it has been shown to be able to form phosphate clamps with the backbone of DNA[177] and have possible interactions with membrane phospholipids.[178]

In preclinical *in vitro* and *in vivo* trials, BBR3464 displayed cytotoxicity at concentrations up to 1000-fold lower than cisplatin in sensitive cell lines and a significant ability to overcome cisplatin resistance in glioma, ovarian, neuroblastoma, astrocytoma, osteosarcoma, melanoma, cervical, SCLC, NSCLC and prostatic cells.[179–186] Preclinical trials also indicated that it displayed severe systemic toxicity, which was confirmed in Phase I.[186] The BBR3464 MTD of 0.17 mg m^{-2} day^{-1} on a daily × 5 administration produced DLTs of neutropenia and gastro-intestinal toxicity.[187] Delivery of BBR3464 in a separate Phase I trial as a single dose every 28 days

Table 3 Platinum-based anticancer drugs which are currently undergoing clinical trials in humans

Drug	Other names	CAS number	Development companies
Satraplatin	JM216 BMS 182751 BMY 45594 POplat Orplatna®	129580-63-8	Spectrum Pharmaceuticals and Agennix AG (previously known as GPC Biotech AG) Johnson Matthey (previous) Bristol-Myers Squibb (previous)
Picoplatin	JM473 NX473 ZD0473 AMD0473	181630-15-9	Pionard (current) NeoRex (previous) Anormed (previous) Johnson Matthey (previous)
ProLindac™	AP 5346	674289-90-8	Access Pharmaceuticals
Lipoplatin™	Nanoplatin™ Oncoplatin	Listed under the same number as cisplatin	Regulon Nanocarrier (licensee)

gave an alternative MTD of 0.9 mg m^{-2}.[188] Subsequent Phase II trials found the MTD was increased to as high as 1.1 mg m^{-2} but in several studies the side effects experienced by some patients resulted in a dose reduction back to 0.9 mg m^{-2}.[189]

Four Phase II trials have been reported in the literature for ovarian, SCLC, NSCLC and gastric and gastro-oesophageal adenocarcinoma.[189–192] The lack of activity observed in the gastric and SCLC did not warrant further evaluation for these cancer types,[189,190] and although positive results were observed for some patients in the NSCLC (two objective responses and 11 PR from 33 patients) and ovarian (five PR from 46 patients) the drug has not moved into Phase III trials. The results of another Phase II study of BBR3464 in locally advanced or metastatic pancreatic cancer which started in 2001 under contract to Theradex® and the National Cancer Institute (USA) has yet to be reported.

Drugs currently in clinical trials

There are currently four drugs (Table 3) in various stages of clinical trials, with two of these being close to gaining marketing approval (satraplatin and picoplatin). Both of these drugs have demonstrated efficacy in Phase III trials and both are active when administered orally. Two other drugs (ProLindac™ and Lipoplatin™) will become the first polymer/liposomal-based platinum drugs if approved.

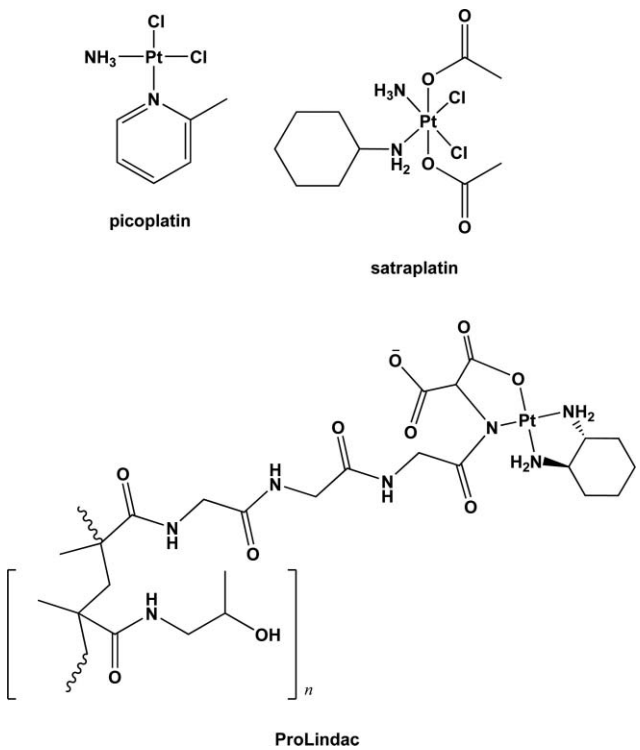

Fig. 4 The platinum-based anticancer drugs which are currently undergoing clinical trials for human use. Not shown: Lipoplatin.

Satraplatin

Bis(acetato-*O*)amminedichlorido(cyclohexylamine)platinum(IV) is an orally active platinum drug that has shown anticancer activity against several platinum sensitive and resistant cell lines including human lung, ovary, cervix and prostate (Fig. 4).[193–195] Satraplatin is readily absorbed by the gastrointestinal mucosa and once in the blood stream is reduced to yield at least six different platinum(II) complexes with *cis*-amminedichlorido(cyclohexylamine)platinum(II) being the most active and abundant.[194–197]

Satraplatin was first studied in humans on a single intermittent schedule which was abandoned because of non-linear pharmacokinetics with saturable absorption and dose limiting vomiting and nausea.[195] To improve absorption and tolerability, satraplatin was administered on a daily × 5 schedule. The MTD was determined to be 45–50 mg m^{-2} day^{-1} with DLTs of myelosuppression and nausea.[195] Daily doses of 40–45 and 120 mg m^{-2} were recommended for Phase II studies for previously treated and untreated patients, respectively.[195] In another Phase I trial, seven of eight patients with squamous cell carcinoma of the head and neck achieved a CR when given 20–30 mg of satraplatin three times a week concurrently with radiotherapy.[195,197] Satraplatin as a single agent in a Phase II trial achieved a PR rate of 38% when given 120–140 mg m^{-2} day^{-1} for five days (repeated every three weeks) for the treatment of SCLC.[195] In a separate Phase II trial satraplatin at 120 mg m^{-2} day^{-1} for five days every four weeks for the treatment of hormone refractory prostate cancer achieved a 31% PR rate.[195]

A Phase III trial evaluated satraplatin and prednisone against refractory cancer (SPARC) *versus* placebo plus prednisone in 950

patients with hormone refractory prostate cancer who had progressed after initial chemotherapy. It was reported that satraplatin reduced the risk of prostate cancer progression by 40% and had achieved a progression free survival rate of 11.1 weeks compared to 9.7 weeks in the placebo group. As a result of these positive results GPC biotech filed for accelerated approval of satraplatin.[198] This was rejected by the FDA on the basis that satraplatin failed to show a convincing benefit in terms of overall survival and concerns were raised that only 51% of patients in the trial had received prior docetaxel.[198,199]

Currently satraplatin is undergoing a variety of Phase I, II and III clinical trials in conjunction with various drugs such as docetaxel in the treatment of prostate cancer, paclitaxel in the treatment of NSCLC and capecitabine to treat advanced solid tumours.[200]

Picoplatin

cis-Amminedichlorido(2-methylpyridine)platinum(II) was designed primarily to circumvent glutathione-mediated drug resistance.[201–203] The pyridine ring sits nearly perpendicular to the plane of the platinum atom, thus positioning the ligand's methyl group directly over the metal centre.[204] This provides steric hindrance to the attack of the drug by nucleophiles, particularly thiols. *In vitro* studies demonstrated picoplatin's ability to overcome platinum drug resistance, showing anticancer activity in cisplatin, carboplatin and oxaliplatin resistant cell lines.[205,206] Furthermore, an *in vivo* study found the use of picoplatin resulted in greater growth delays of human ovarian tumour xenografts in mice by 34 days compared with cisplatin (10.4 days) and carboplatin (6.4 days).[205,207]

Picoplatin entered clinical trials in November 1997 and from Phase I trials determined a MTD of 150 mg m^{-2} with the DLTs being neutropenia, thrombocytopenia, nausea and vomiting.[202,208] A single dose of 120 mg m^{-2} every 21 days was recommended for Phase II trials.[202,209] Picoplatin side-effects have also been examined in combination with the taxanes: docetaxel and paclitaxel, with docetaxel and prednisone, and with 5-FU and leuvorin. When administered with 5-FU and leucovorin (FOLPI regime) every four weeks the MTD remains 150 mg m^{-2}, but when administered once every two weeks the MTD drops to 85 mg m^{-2}. Intravenous picoplatin administered once every three weeks with docetaxel (75 mg m^{-2}) and prednisone (5 mg) as first line treatment for patients with metastatic refractory prostate cancer found that picoplatin increased the overall median survival rate from 18.9 months in patients that did not receive picoplatin to 21.4 months, with the most common side effect being neutropenia.

Although picoplatin is well tolerated with no neuro- or nephrotoxicity, it was withdrawn from three different clinical Phase II trials in which its efficacy was tested as first and second line therapy in advanced NSCLC and as second line in SCLC. This was due to continued disease progression which occurred in 82% of first-line NSCLC patients and 82 and 77% of second-line NSCLC and SCLC patients, respectively.[209] Picoplatin is currently undergoing various Phase I and Phase II studies as a treatment for colorectal cancer in combination with 5-FU and leucovorin, in combination with docetaxel for prostate cancer and as a treatment for patients with progressive or relapsed NSCLC.[200]

ProLindac™

This drug is a nanopolymer consisting of [Pt(*R*,*R*-dach)], the active moiety of oxaliplatin, bound to a hydrophilic biocompatible polymer (hydroxypropylmethacrylamide, HPMA) so as to better target solid cancers through the enhanced permeability and retention effect.[210–213] The two polymer segments are connected *via* an amidomalonato chelating group and a triglycine spacer.[214] The amidomalonate–platinum chelate, attached to the platinum centre through the nitrogen and oxygen atoms, is stable at physiological pH[210] but the low pH found in the extracellular space of hypoxic tumours enables the sustained release of the active platinum complex[215] *via* breakage of these bonds.[206] Investigation into the *in vitro* effects of ProLindac showed that there were 20 times more platinum–DNA adducts at pH 3 than pH 7.4, presumably due to better drug release from the polymer at the lower pH.[214]

The anticancer activity of ProLindac has been assessed in mice with B16 melanomas and ovarian carcinomas. It demonstrated superior growth inhibition, reduced toxicity towards normal cells, increased and more sustained plasma platinum levels, increased delivery of [Pt(*R*,*R*-dach)] to the tumour and prolonged elevation of platinum levels, compared with oxaliplatin.[215] In a study comparing cytotoxicity in a panel of cancer lines (including: breast, ovarian, lung and prostate) ProLindac displayed time- and concentration-dependent cytotoxicity of similar efficacy to oxaliplatin and was active against several cisplatin resistant cell lines.[214]

In a Phase I trial, patients with advanced solid tumours were treated with a one hour IV infusion administered on days 1, 8 and 15 of a 28-day cycle.[216] The treatment was well tolerated with no neutropenia or significant hematologic toxicity and a MTD of 640 mg m^{-2}. Vomiting and nausea were controllable with antiemetics.[216] The DLT of this regime was renal insufficiency.[216] ProLindac also showed anticancer activity in some metastatic melanoma and advanced ovarian cancer patients.[216]

A Phase I/II trial evaluated the anticancer activity of ProLindac as a single agent in the treatment of advanced ovarian cancer, where patients had previously been treated with platinums (except oxaliplatin) at least twice.[217] In this trial, weekly doses were considered unsuitable due to the prolonged half life of ProLindac, so patients were administered with a two hour IV infusion every two or three weeks.[217,218] Treatment was again well tolerated and clinically-meaningful disease stabilisation was achieved in 42% of all patients and 66% of patients who received the highest dose (560 mg m^{-2} $week^{-1}$ over three weeks or 1100 mg m^{-2} $week^{-1}$ over two weeks).[218] This result was comparable to single agent oxaliplatin trialled in a less heavily pre-treated population.[217] All patients experienced at least one side effect although most were mild at grade 1–2, and there were no signs of acute neurotoxicity.[217] Also trialled was a new ProLindac formulation made by an improved scalable process, which the company intends to use for future clinical trials. Access Pharmaceuticals claim that no patient experienced any acute significant adverse events from the new formulation, while treatment had the same beneficial sustained biomarker decrease and disease stabilisation as seen previously.

ProLindac is currently in Phase II,[217] and in early 2010 the initiation of a combination study was announced with paclitaxel in the second-line treatment of pre-treated advanced ovarian cancer based upon good results of the oxaliplatin/paclitaxel regime.[219]

Synergistic effects have been observed previously with 5-FU, gemcitabine, docetaxel and SN-38.[214]

Lipoplatin™

Lipoplatin is a liposomally encapsulated form of cisplatin developed in an effort to reduce cisplatin's systemic toxicity profile and allow administration of greater doses whilst improving targeting to primary tumours and metastases.[220–222]

The nanoparticulate liposomes are reverse-miscelles,[222] composed of dipalmitoyl phosphatidyl glycerol (DPPG), soy phosphatidyl choline (SPC-3), cholesterol and methoxy-polyethylene glycol-distearoyl phosphatidylethanolamine (mPEG2000-DSPE).[222,223] Lipoplatin crosses cell membranes more easily than native cisplatin due to the fusogenic nature of the DPPG lipids.[222] In addition, the presence of a PEG coating prevents detection by immunogenic entities.[222] Enhanced circulation time in body fluid and small particle size (90–130 nm) mean the liposomes preferentially extravasate to tumours through their leaky and/or compromised vasculature.[222–224]

Phase I trials in pancreatic cancer[225] and NSCLC[226] patients in combination with 1000 mg m^{-2} gemcitabine found MTDs of 100 and 120 mg m^{-2}, respectively.[215,216] These regimes produced almost negligible nephrotoxicity, ototoxicity and neurotoxicity following IV infusion.[227] Accumulation in malignant tissues was observed, with platinum levels on average 10–50 times greater in tumours than adjacent normal tissues, and up to 200 times greater in colon cancers.[227] Gastric tumours displayed the highest levels of total platinum (up to 260 μg/g tissue) suggesting Lipoplatin as a candidate for gastric tumours.[227]

Phase II trials have examined the effectiveness of Lipoplatin against NSCLC. One such study did not recommend progression to Phase III studies, with only a 5% PR rate and 16% stable disease rate out of 19 pretreated patients.[228] Improved activity was shown when combining 120 mg m^{-2} Lipoplatin on days 1, 8 and 15 with gemcitabine 1000 mg m^{-2} on days 1 and 8 of a three-week cycle (LipoGem). This regime showed a disease control rate (DCR) of 71%.[229] This was compared to a 32% DCR in a cisplatin/gemcitabine (CisGem) control study.[229] The LipoGem regime continued to show slight superior activity over CisGem in Phase III across a variety of histological NSCLC subtypes, excluding squamous cell carcinomas.[230] A safety profile more favourable than cisplatin was also observed, with particular regard to nephrotoxicity, neurotoxicity and asthenia.[230] Lipoplatin has also been studied with gemcitabine for malignant pleural mesothelioma, where a response was observed in one patient.[231]

Phase III trials in squamous cell carcinoma of the head and neck (SCCHN) compared Lipoplatin 100 mg m^{-2}/d (days 1, 8, 15) and 1000 mg m^{-2}/d 5-FU (days 1–5) to a cisplatin/5-FU regime.[232,233] Lipoplatin/5-FU was associated with reduced renal and haematological toxicity compared with cisplatin/5-FU[232,233] and reduced occurrence of ototoxicity.[232] Lipoplatin regimes also displayed reduced nephrotoxicity,[229,230] vomiting and/or nausea and asthenia compared with cisplatin controls.[219,220]

Concurrent Lipoplatin, 5-FU and radiotherapy has been studied recently in Phase I/II trials for the treatment of locally advanced gastric cancer.[234] Twelve patients were treated with Lipoplatin at a dose of 120 mg m^{-2} $week^{-1}$, 5-FU at 400 mg m^{-2} $week^{-1}$ (day 1), and radiotherapy was given through 3.5-Gy fractions on days 2, 3, and 4.[234] Minimal nephrotoxicity and neutropenia were reported.[234] Response rates reached 80% tumour disappearance in patients receiving five cycles, supporting further studies of Lipoplatin in adjuvant postoperative or preoperative radio-chemotherapy regimes for the treatment of gastric cancer.[234]

Conclusions

The design and synthesis of platinum anticancer drugs is very much a mature field. In the 40 years since the discovery of cisplatin only six drugs have gained marketing approval whereas 14 were discontinued during clinical trials. All of these drugs demonstrate severe side effects which greatly limit the dose which can be administered, thereby reducing the effectiveness of the drugs. This is because the basic chemical structure of all platinum drugs is the same; amine carrier ligands with chlorido, sulfato or dicarboxylato leaving groups. In addition, of those drugs that are close to gaining approval (satraplatin and picoplatin) the leap from Phase III to marketing is getting harder and longer because of more stringent requirements to demonstrate not just improved quality of life for the patient but also improved survival rates. Whilst there will always be a need for new platinum drugs, no new small molecule platinum drug has entered clinical trials since 1999 (BBR3464). Instead, the last decade has witnessed a shift in focus towards the use of delivery vehicles, and three of these types of "drugs" (Aroplatin, Lipoplatin and ProLindac) entered clinical trials during this time. As can be seen in our perspective, these generally demonstrate far fewer and less severe side effects than the native drugs whilst also maintaining their cancer killing ability.

The development of new and better delivery vehicles for platinum drugs will rely almost entirely on inorganic and physical chemists, rather than pharmacists or medical researchers as the issues are almost entirely chemical. Clever design of delivery vehicles for platinum drugs will require chemists to develop systems that are able to: ensure the resultant drug-delivery vehicle complexes are soluble in and biocompatible with physiological media, control the overall size and shape of the drug-delivery vehicle complexes, ensure the platinum drugs are released intact from the delivery vehicle and without changing the drug active component after aquation, control the rate and location of drug release, and finally ensure they are stable against degradation in storage and *in vivo*.

References

1 J. D. Hoeschele, *Dalton Trans.*, 2009, 10648–10650.
2 *Martindale: The complete drug reference*, ed. S. C. Sweetman, Pharmaceutical Press, London, 35th edn, 2007.
3 M. Watson, A. Barrett, R. Spence and C. Twelves, *Oncology*, Oxford University Press, Oxford, 2nd edn, 2006.
4 L. Kelland, *Nat. Rev. Cancer*, 2007, **7**, 573–584.
5 C. A. Puckett, R. J. Ernst and J. K. Barton, *Dalton Trans.*, 2010, **39**, 1159–1170.
6 E. R. Jamieson and S. J. Lippard, *Chem. Rev.*, 1999, **99**, 2467–2498.
7 E. G. Chapman and V. J. DeRose, *J. Am. Chem. Soc.*, 2010, **132**, 1946–1952.
8 M. J. Piccart, H. Lamb and J. B. Vermorken, *Ann. Oncol.*, 2001, **12**, 1195–1203.
9 K. Kehe and L. Szinicz, *Toxicology*, 2005, **214**, 198–209.
10 S. Neidle, I. M. Ismail and P. J. Sadler, *J. Inorg. Biochem.*, 1980, **13**, 205–212.

11 U. Frey, J. D. Ranford and P. J. Sadler, *Inorg. Chem.*, 1993, **32**, 1333–1340.
12 S. A. Laurie, L. L. Siu, E. Winquist, A. Maksymiuk, E. L. Harnett, W. Walsh, D. Tu and W. R. Parkulekar, *Cancer*, 2010, **116**, 362–368.
13 R. T. Penson, D. S. Dizon, S. A. Cannistra, M. R. Roche, C. N. Krasner, S. T. Berlin, N. S. Horowitz, P. A. Di Silvestro, U. A. Matulonis, H. Lee, M. King and S. M. Campos, *J. Clin. Oncol.*, 2010, **28**, 154–159.
14 T. Boulikas and M. Vougiouka, *Oncol. Rep.*, 2003, **10**, 1663–1682.
15 J. Kasparkova, M. Vojtiskova, G. Natile and V. Brabec, *Chem.–Eur. J.*, 2008, **14**, 1330–1341.
16 F. Lordick, B. Luber, S. Lorenzen, S. Hegewisch-Becker, G. Folprecht, E. Woll, T. Decker, E. Endlicher, N. Rothling, T. Schuster, G. Keller, F. Fend and C. Peschel, *Br. J. Cancer*, 2010, **102**, 500–505.
17 R. Zarate, J. Rodriguez, E. Bandres, A. Patino-Garcia, M. Ponz-Sarvise, A. Viudez, N. Ramirez, N. Bitarte, A. Chopitea and J. Gacia-Foncillas, *Br. J. Cancer*, 2010, **102**, 987–994.
18 A. Kuwahara, M. Yamamori, K. Nishiguchi, T. Okuno, N. Chayahara, I. Miki, T. Tamura, T. Inokuma, Y. Takemoto, T. Nakamura, K. Kataoka and T. Sakaeda, *Int. J. Med. Sci.*, 2009, **6**, 305–311.
19 E. M. Alberto, M. F. A. Lucas, M. Pavelka and N. Russo, *J. Phys. Chem. B*, 2009, **113**, 14473.
20 Y. Kawai, S. Taniuchi, S. Okahara, M. Nakamura and M. Gemba, *Biol. Pharm. Bull.*, 2005, **28**, 1385–1388.
21 T. Boulikas, A. Pantos, E. Bellis and P. Christofis, *Cancer Ther.*, 2007, **5**, 537–583.
22 T. Kodaira, F. Nobukazu, H. Tachibana and S. Hidano, *Anticancer Res.*, 2006, **26**, 2265–2268.
23 H. Kurita, E. Yamamato, S. Nozaki, S. Wada, I. Furuta, M. Miyata and K. Kurashina, *Cancer Chemother. Pharmacol.*, 2010, **65**, 503–508.
24 Y. Gong, L. Ren, L. Zhou, J. Zhu, M. Huang, X. Zhou, J. Wang, Y. Lu, M. Hou and Y. Wei, *Cancer Chemother. Pharmacol.*, 2009, **64**, 327–333.
25 F. Oshita, K. Yamada, H. Saito, K. Noda, N. Hamanaka and M. Ikehara, *J. Exp. Ther. Oncol.*, 2004, **4**, 343–348.
26 H. Yamashita, H. Nakagawa, M. Tago, H. Igaka, N. Nakamua, M. Shiraishi, N. Sasano and K. Ohtomo, *Dis. Esophagus.*, 2006, **19**, 15–24.
27 J. Zheng, G. Wang, G. Y. Yang, D. Wang, X. Luo, C. Chen, Z. Zhang, Q. Li, W. Xu, Z. Li and D. Wang, *Jpn. J. Clin. Oncol.*, 2010, **40**, 425–431.
28 K. Mross, F. Meyberg, H. H. Fieberg, K. Hamm, U. Hieber, P. Aulenbacher and D. K. Hossfeld, *Onkologie*, 1992, **15**, 139–146.
29 J. A. Gietema, H.-J. Guchelaar, E. G. E. de Vries, P. Alenbacher, D. Th. Seifer and N. H. Mulder, *Anti-Cancer Drugs*, 1993, **4**, 51–55.
30 J. A. Gietema, G.-J. Veldhuis, H.-J. Guchelaar, P. H. B. Willemse, D. R. A. Uges, A. Cats, H. Boonstra, W. T. A. Van Der Graaf, D. T. Sleijfer, E. G. E. de Vries and N. H. Mulder, *Br. J. Cancer*, 1995, **71**, 1302–1307.
31 J. J. Kavanagh, C. L. Edwards, R. S. Freedman, M. B. Finnegan, O. Balat, D. Tresukosol, K. Bunk, S. Loechner, M. Hord, J. L. Franklin and A. P. Kudelka, *Gynecol. Oncol.*, 1995, **58**, 106–109.
32 M. Degardin, J. P. Armand, B. Chevallier, P. Cappeleare, M.-A. Lentz, M. David and H. Roche, *Invest. New Drugs*, 1995, **13**, 253–255.
33 J. Welink, E. Boven, J. B. Vermorken, H. E. Gall and W. J. F. v. d. Vijgh, *Clin. Cancer Res.*, 1999, **5**, 2349–2358.
34 J. A. Gietema, E. G. E. d. Vries, D. T. Sleijfer, P. H. B. Willemse, H.-J. Guchelaar, D. R. A. Uges, P. Aulenbacher, R. Voegeli and N. H. Mulder, *Br. J. Cancer*, 1993, **67**, 396–401.
35 C. Manegold, P. Drings, U. Gatzemeier, J. v. Pawal, H. H. Fiebig, W. Queisser and L. Edler, *Onkologie*, 1996, **19**, 248–251.
36 W.-j. Ma, Q.-y. Zhang, W.-h. Zhao and S. Zhao, *Linchuang Zhongliuxue Zazhi*, 2009, **14**, 816–817.
37 C. N. Sternberg, P. de Mulder, S. Fossa, S. Kaye, T. Roberts, A. Pawinsky and S. Daamen, *Ann. Oncol.*, 1997, **8**, 695–696.
38 A. I. Limited, *Drugs R&D*, 2003, **4**, 369–372.
39 http://www.aeternazentaris.com/en/page.php?p=60&q=24, accessed 5th February 2010.
40 J. Shi, *Xiandai Zhongxiyi Jiehe Zazhi*, 2008, **17**, 5105–5107.
41 M. S. Shchepinov, M. F. Denissenko, K. J. Smylie, R. J. Worl, A. L. Leppin, C. R. Cantor and C. P. Rodi, *Nucleic Acids Res.*, 2001, **29**, 3864–3872.
42 D.-K. Kim, G. Kim, J. Gam, Y.-B. Cho, H.-T. Kim, J.-H. Tai, K. H. Kim, W.-S. Hong and J.-G. Park, *J. Med. Chem.*, 1994, **37**, 1471–1485.
43 D.-K. Kim, H.-T. Kim, J.-H. Tai, Y.-B. Cho, T.-S. Kim, K. H. Kim, J.-G. Park and W.-S. Hong, *Cancer Chemother. Pharmacol.*, 1995, **37**, 1–6.
44 D.-K. Kim, H.-T. Kim, Y.-B. Cho, J.-H. Tai, J. S. Ahn, T.-S. Kim and K. H. Kim, *Cancer Chemother. Pharmacol.*, 1995, **35**, 441–445.
45 J.-W. Lee, J.-K. Park, S.-H. Lee, S.-Y. Kim, Y.-B. Cho and H.-J. Kuh, *Anti-Cancer Drugs*, 2006, **17**, 377–384.
46 N. K. Kim, T.-S. Kim, S.-G. Shin, Y. L. Park, J. A. Lee, Y.-B. Cho, K. H. Kim, D. S. Heo and Y.-J. Bang, *Cancer*, 2001, **91**, 1549–1556.
47 W. S. Lee, G.-W. Lee, H. W. Kim, O.-J. Lee, Y.-J. Lee, G. H. Ko, J.-S. Lee, J. S. Jang and W. S. Ha, *Cancer Res. Treat.*, 2005, **37**, 208–211.
48 S. C. Oh, S. Y. Yoon, J. H. Seo, C. W. Choi, B. Y. S. Kim, S.-G. Shin, Y. H. Kim, S.-Y. Kim, H. J. Yoon, K. S. Cho and J. S. Kim, *Cancer Res. Treat.*, 2003, **35**, 117–122.
49 N. K. Kim, S.-A. Im, D.-K. Kim, M. H. Lee, C. W. Jung, E. K. Cho, J. T. Lee, J. S. Ahn, D. S. Heo and Y.-J. Bang, *Cancer*, 1999, **86**, 1109–1115.
50 Y. J. Min, S.-J. Bang, J. W. Shin, D. H. Kim, J. H. Park, G. Y. Kim, B. K. Ko, D. H. Choi and H. R. Cho, *J. Korean Med. Sci.*, 2004, **19**, 369–373.
51 J.-H. Ahn, Y.-K. Kang, T.-W. Kim, H. Bahng, H.-M. Chang, W.-C. Kang, W.-K. Kim, J.-S. Lee and J.-S. Park, *Cancer Chemother. Pharmacol.*, 2002, **50**, 104–110.
52 K. H. Lee, M. S. Hyun, H.-K. Kim, H. M. Jin, J. Yang, H. S. Song, Y. R. Do, H. M. Ryoo, J. S. Chung, D. Y. Zang, H.-Y. Lim, J. Y. Jin, C. Y. Yim, H. S. Park, J. S. Kim, C. H. Sohn and S. N. Lee, *Cancer Res. Treat.*, 2009, **41**, 12–18.
53 A. Ohstu, Y. Shimada, K. Shirao, N. Boku, I. Hyodo, H. Saito, N. Yamamichi, Y. Miyata, N. Ikeda, S. Yamamoto, H. Fukuda and S. Yoshida, *J. Clin. Oncol.*, 2003, **21**, 54–59.
54 P. D. Braddock, T. A. Connors, M. Jones, A. R. Khokhar, D. H. Melzack and M. L. Tobe, *Chem.-Biol. Interact.*, 1975, **11**, 145–161.
55 T. A. Connors, M. Jones, C. J. Ross, P. D. Braddock, A. R. Khokhar and M. L. Tobe, *Chem.-Biol. Interact.*, 1972, **5**, 415–424.
56 T. A. Connors, *FEBS Lett.*, 1975, **57**, 223–233.
57 S. E. Owens, N. Thatcher, H. Sharma, N. Adam, R. Harrison, A. Smith, A. Zaki, J. C. Baer, C. A. McAuliffe, D. Crowther and B. W. Fox, *Cancer Chemother. Pharmacol.*, 1985, **14**, 253–257.
58 N. Thatcher, H. Sharma, R. Harrison, A. Smith, A. Zaki, C. A. McAuliffe, D. Crowther and B. W. Fox, *Cancer Chemother. Pharmacol.*, 1982, **9**, 13–16.
59 J. M. Hill and R. J. Speer, *Anticancer Res.*, 1982, **2**, 173–186.
60 T. Boulikas, A. Pantos, E. Bellis and P. Christofis, *Cancer Ther.*, 2007, **5**, 537–583.
61 G. R. Gibbons, S. Wyrick and S. G. Chaney, *Cancer Res.*, 1989, **49**, 1402–1407.
62 W. K. Anderson, D. A. Quagliato, R. D. Haugwitz, V. L. Narayanan and M. K. Wolpert-DeGilippes, *Cancer Treat. Rep.*, 1986, **70**, 997–1002.
63 W. C. Rose, J. E. Schuring, J. B. Huftalen and W. T. Bradner, *Cancer Treat. Rep.*, 1982, **66**, 135–146.
64 A. Rahman, J. K. Roh, M. K. Wolpert-DeFilippes, A. Goldin, J. M. Venditti and P. V. Woolley, *Cancer Res.*, 1988, **48**, 1745–1752.
65 R. J. Parker, J. A. Vionnet, F. Bostick-Bruton and E. Reed, *Cancer Res.*, 1993, **53**, 242–247.
66 R. J. Schilder, F. P. LaCreta, R. P. Perez, S. W. Johnson, J. M. Brennan, A. Rogatko, S. Nash, C. McAleer, T. C. Hamilton, D. Roby, Y. R. C., R. F. Ozols and P. J. O'Dwyer, *Cancer Res.*, 1994, **54**, 709–717.
67 K. D. Tutsch, R. Z. Arzoomanian, D. Alberti, M. B. Tombes, C. Feierbend, H. I. Robins, D. R. Spriggs and G. Wilding, *Invest. New Drugs*, 1999, **17**, 63–72.
68 T. J. O'Rourke, G. R. Weiss, P. New, H. A. Burris, G. Rodriguez, J. Eckhardt, J. Hardy, J. G. Kuhn, S. Fields, G. M. Clark and D. D. Von Hoff, *Anti-Cancer Drugs*, 1994, **5**, 520–526.
69 S. O'Brien, H. Kantarjian, E. Freireich, D. Johnston, K. Nguyen and M. Beran, *Cancer Res.*, 1992, **52**, 4130–4134.
70 H. Kobayahi, Y. Takemura, H. Miyachi and T. Ogawa, *Invest. New Drugs*, 1991, **9**, 313–319.
71 W. L. Elliott, B. J. Roberts, C. T. Howard and W. R. Leopold, *Cancer Res.*, 1994, **54**, 4412–4418.
72 R. P. Perez, P. J. O'Dwyer, L. M. Handel, R. F. Ozols and T. C. Hamilton, *Int. J. Cancer*, 1991, **48**, 265–269.
73 I. Takahashi, Y. Maehara, H. Kusumoto, S. Kohnoe and K. Sugimachi, *Cancer Chemother. Pharmacol.*, 1993, **33**, 31–35.

74 I. Takahashi, Y. Maehara, H. Kusumoto, T. Kusumoto, H. Baba, S. Kohnoe and K. Sugimachi, *Oncology*, 1996, **53**, 68–72.
75 P. J. O'Dwyer, G. R. Hudes, J. Walczak, R. Schilder, F. LaCreta, B. Rogers, I. Cohen, C. Kowal, L. Whitfield and R. A. Boyd, *Cancer Res.*, 1992, **52**, 6746–6753.
76 R. L. Theriault, I. A. Cohen, L. Esparza, C. Kowal and M. N. Raber, *Cancer Chemother. Pharmacol.*, 1993, **31**, 333–337.
77 R. L. Theriault, R. S. Walters, F. A. Holmes, L. Esparza-Guerra, C. Kowal and G. N. Hortobagyi, *Cancer Chemother. Pharmacol.*, 1996, **38**, 289–291.
78 P. Bitha, S. G. Carajal, R. V. Citarella, R. G. Child, E. F. Delos Santos, T. S. Dunne, F. E. Durr, J. J. Hlavka, S. A. Lang, H. L. Lindsay, G. O. Morton, J. P. Thomas, R. E. Wallace, Y.-i. Lin, R. C. Haltiwanger and C. Pierpont, *J. Med. Chem.*, 1989, **32**, 2015–2020.
79 C. Meijer, N. H. Mulder, H. Timmer-Bosscha, W. J. Sluiter, G. J. Meersma and E. G. E. de Vries, *Cancer Res.*, 1992, **52**, 6885–6889.
80 L. R. Kelland, S. J. Clarke and M. J. McKeage, *Plat. Met. Rev.*, 1992, **36**, 178–184.
81 A. Kudelka, Z. H. Siddik, D. Tresukosol, C. L. Edwards, R. S. Freedman, T. L. Madden, R. Rastogi, M. Hord, E. E. Kim, C. Tornos, R. Mante and J. J. Kavanagh, *Anti-Cancer Drugs*, 1997, **8**, 649–656.
82 P. F. Dodion, D. de Valeriola, N. Crespeigne, J. D. Kantrowitz, M. Piccart, F. Wery, J. Kerger, M. J. Egorin, A. Forrest, N. R. Bachur, P. Alaerts, A. Carver, R. Rastogi, L. Hammershaimb and S. Saletan, *Ann. Oncol.*, 1991, **2**, 589–596.
83 P. H. B. Willemse, J. A. Gietema, D. T. Sleijfer, N. H. Mulder, E. G. E. de Vries, F. de Halleux, R. B. Rastogi and M. Birkhofer, *Proc. Am. Assoc. Clin. Oncol.*, 1991, **10**, 191.
84 M. Markman, L. C. DeMarco, m. Birkofer, D. Budman, T. Hakes, B. Reichman, S. Rubin, W. Jones, R. Barakat, J. Curtin, J. L. Lewis, L. Almadrones, A. Hoffman, R. Rastogi and W. Hoskins, *J. Cancer Res. Clin. Oncol.*, 1993, **119**, 234–236.
85 M. Piccart, J. Kerger, E. Tueni, E. Van Der Schueren, C. Kennes, S. Bartholomeus, K. Vantongelen, R. Rastogi and M. Birkhofer, *Proc. Am. Assoc. Cancer Res.*, 1991, **32**, 1222.
86 S. Aamdal, U. Bruntsch, J. Kerger, J. Verweij, W. ten Bokkel Huinink, J. Wanders, R. Rastogi, H. R. Franklin and S. B. Kaye, *Cancer Chemother. Pharmacol.*, 1997, **40**, 439–443.
87 I. Olver, M. Green, W. Peters, A. Zimet, G. Toner, J. Bishop, W. Ketelbey, R. Rastogi and M. Birkhofer, *Am. J. Clin. Oncol.*, 1995, **18**, 56–58.
88 A. L. Jones and I. E. Smith, *Br. J. Cancer*, 1991, **63**(Suppl 13), 7.
89 B. C. Tanis, J. B. Vermorken, W. W. Bokkel Ten Huinink, I. Klein, H. Gall, A. T. Van Oosterom, G. Simonetti, J. G. McVie, W. J. F. Van Der Vijgh and H. M. Pinedo, *Eur. J. Cancer Clin. Oncol.*, 1991, **27**, 268–273.
90 J. B. Sørensen, S. Groth, S. W. Hansen, M. H. Nissen, M. Rørth and H. H. Hansen, *Cancer Chemother. Pharmacol.*, 1985, **15**, 97–100.
91 N. Colombo, E. Sartori, F. Landoni, G. Favalli, L. Vassena, L. Zotti, E. Materman, C. R. Franks, S. Pecorelli and C. Mangioni, *Cancer Treat. Rep.*, 1986, **70**, 793–794.
92 B. C. Tanis, J. B. Vermorken, W. W. ten Bokkel Huinink, A. T. van Oosterom, T. A. Splinter, K. J. Vendrik, D. T. Sleijfer, M. E. Van Der burg, E. Van Der Putten and H. M. Pinedo, *Oncology*, 1992, **49**, 99–103.
93 M. Drees, W. M. Dengler, H. R. Hendriks, L. R. Kelland and H. H. Fiebig, *Eur. J. Cancer*, 1995, **31**, 356–361.
94 S. G. Bagrova and N. N. Blokhin, *Voprosy Onkologii*, 2001, **47**, 752–756.
95 K. Akamatsu, K. Endo, T. Matsumoto, K. Kamisango, K. Morikawa, M. Koizumi and K. Koizumi, *Br. J. Cancer*, 1992, **66**, 827–832.
96 D. Lebwohl and R. Canetta, *Eur. J. Cancer*, 1998, **34**, 1522–1534.
97 H. Kobayashi, Y. Takemura, H. Miyachi and T. Ogawa, *Invest. New Drugs*, 1991, **9**, 313–319.
98 K. Tamura, S. Makino and Y. Araki, *Cancer*, 1990, **66**, 2059–2063.
99 H. Aoyama, K. Kubo, J. Uchino, H. Hayasaka, K. Asaishi, M. Izuo, M. Ogawa, H. Majima, M. Yasutomi and T. Wada, *et al*., *Cancer Chemother.*, 1992, **19**, 1033–1039.
100 T. Kato, M. Yakushiji, H. Nishimura, Y. Terashima, H. Sasaki, T. Yamabe, A. Yajima, S. Fujimoto, M. Hashimoto and I. Nishiya, *Cancer Chemother.*, 1992, **19**, 1285–1293.
101 L. Pendyala, J. W. Cowens, G. Chheda, S. P. Dutta and P. J. Creavne, *Cancer Res*, 1988, **48**, 3533–3536.
102 V. H. C. Bramwell, D. Crowther, S. O'Malley, R. Swindell, R. Johnson, E. H. Cooper, N. Thatcher and A. Howell, *Cancer Treat. Rep.*, 1985, **69**, 409–416.
103 F. P. Paolozzi, R. Gaver, B. J. Poiesz, A. Louie, S. DiFino, R. L. Comis, N. Newman and S. Ginsberg, *Invest. New Drugs*, 1988, **6**, 199–206.
104 S. P. Chawla, B.-S. Yap, D. M. Tenney, G. P. Bodey and R. S. Benjamin, *Invest. New Drugs*, 1988, **6**, 311–317.
105 C. Sessa, J. Vermorken, J. Renard, S. Kaye, D. Smith, W. ten Bokkel Huinink, F. Cavalli and H. Pinedo, *J. Clin. Oncol.*, 1988, **6**, 98–105.
106 R. de Wit, M. Tesselaar, T. C. Kok, C. Seynaeve, C. J. Rodenburg, J. Verweij, P. A. Helle and G. Stoter, *Eur. J. Cancer Clin. Oncol.*, 1991, **27**, 1383–1385.
107 B. M. J. Cantwell, C. R. Franks and A. L. Harris, *Cancer Chemother. Pharmacol.*, 1986, **18**, 286–288.
108 G. N. Hortobagyi, D. Frye, F. A. Holmes, V. Hug, G. Fraschini and A. U. Buzdar, *Cancer Treat. Rep.*, 1987, **71**, 1193–1196.
109 J. B. Vermorken, S. Gundersen, M. Clavel, J. F. Smyth, P. Dodion, J. Renard and S. B. Kaye, *Ann. Oncol.*, 1993, **4**, 303–306.
110 E. S. Casper, T. C. Smart, T. B. Hakes, M. Ochoa and R. J. Kaufman, *Invest. New Drugs*, 1988, **6**, 87–91.
111 D. J. Meisner, S. Ginsberg, A. Ditch, A. Louie, N. Newman, R. Comis and B. Poiesz, *Am. J. Clin. Oncol.*, 1989, **12**, 129–131.
112 R. Nitschke, C. Pratt, M. Harris, J. Krischer, T. J. Vietti, H. Grier, W. Kamps and S. Toledano, *Invest. New Drugs*, 1992, **10**, 93–96.
113 R. P. Castleberry, A. B. Cantor, A. A. Green, V. Joshi, R. L. Berkow, G. R. Buchanan, B. Leventhal, D. H. Mahoney, E. I. Smith and F. A. Hayes, *J. Clin. Oncol.*, 1994, **12**, 1616–1620.
114 H. S. Friedman, J. P. Krischer, P. Burger, W. J. Oakes, B. Hockenberger, M. D. Weiner, J. M. Falletta, D. Norris, A. H. Ragab and D. H. Mahoney, *J. Clin. Oncol.*, 1992, **10**, 249–256.
115 R. E. Drasga, S. D. Williams, L. H. Einhorn and R. Birch, *Cancer Treat. Rep.*, 1987, **71**, 863–864.
116 B. A. Murphy, R. J. Motzer and G. J. Bosl, *Invest. New Drugs*, 1992, **10**, 327–330.
117 A. S. Goldenberg, D. Kelsen, J. Dougherty and G. Magill, *Invest. NewDrugs*, 1990, **8**, 71–75.
118 N. J. Petrelli, P. J. Creaven, L. Herrera and A. Mittelman, *Cancer Chemother. Pharmacol.*, 1989, **23**, 61–62.
119 R. Asbury, A. Kramer, M. Green, R. Qazi, R. Skeel and D. G. Haller, *Am. J. Clin. Oncol.*, 1989, **12**, 416–419.
120 J. B. Blitzer, N. Newman, S. Ginsberg, A. Louie, A. Scalzo and B. Poiesz, *Am. J. Clin. Oncol.*, 1988, **11**, 650–651.
121 W. P. McGuire, J. A. Blessing, K. Hatch and P. J. DiSaia, *Invest. New Drugs*, 1986, **4**, 181–186.
122 V. Lira-Peurto, A. Silva, M. Morris, R. Martinez, S. Groshen, F. Morales-Canfield, F. Tenorio and F. Muggia, *Cancer Chemother. Pharmacol.*, 1991, **28**, 391–396.
123 B. Kramer, R. Birch, A. Greco, K. Prestridge, P. DeSimone and G. Omura, *Am. J. Clin. Oncol.*, 1988, **11**, 643–645.
124 J. Granfortuna, N. Newman, S. Ginsberg, A. Louie, L. Robert, J. J. Gullo and B. J. Poiesz, *Am. J. Clin. Oncol.*, 1989, **12**, 355–357.
125 R. Abele, M. Clavel, S. Monfardini, U. Bruntsch, J. Renard, M. Van Glabbeke and H. M. Pinedo, *Eur. J. Cancer Clin. Oncol.*, 1987, **23**, 387–389.
126 M. Clavel, S. Monfardini, S. Gundersen, S. Kaye, P. Siegenthaler, J. Renard, M. Van Glabbeke and H. M. Pinedo, *Eur. J. Cancer Clin. Oncol.*, 1988, **24**, 1345–1348.
127 H. Anderson, J. Wagstaff, D. Crowther, R. Swindell, M. J. Lind, J. McGregor, M. S. Timms, D. Brown and P. Palmer, *Eur. J. Cancer Clin. Oncol.*, 1988, **24**, 1471–1479.
128 *Platinum and other metal coordination compounds in cancer chemotherapy 2*, ed. H. M. Pinedo and H. H. Schornagel, Plenum Press, New York, 1996.
129 T. Saito, Y. Manabe and H. Saito, *ORL*, 1995, **57**, 250–255.
130 S. C. White, P. Lorigan, G. P. Margison, F. Martin, N. Thatcher, H. Anderson and M. Ranson, *Br. J. Cancer*, 2006, **95**, 822–828.
131 S. Bandak, D. Goren, A. Horowitz, D. Tzemach and A. Gabizon, *Anti-Cancer Drugs*, 1999, **10**, 911–922.
132 M. S. Newman, G. T. Colbern, P. K. Working, C. Engbers and M. A. Amantea, *Cancer Chemother. Pharmacol.*, 1999, **43**, 1–7.
133 P. K. Working, M. S. Newman, T. Sullivan, M. Brunner, M. Podell, Z. Sahenk and N. Turner, *Toxicol. Sci.*, 1998, **46**, 155–165.
134 J. Vaage, D. Donovan, E. Wipff, R. Abra, G. T. Colbern, P. Uster and P. Working, *Int. J. Cancer*, 1999, **80**, 134–137.

135 K. J. Harrington, C. R. Lewanski, A. D. Nothcote, J. Whittaker, H. Wellbank, R. G. Vile, A. M. Peters and J. S. W. Stewart, *Ann. Oncol.*, 2001, **12**, 493.
136 M. D. DeMario, N. J. Vogelzang, L. Janisch, M. Tonda, M. A. Amantea, L. Pendyala and M. J. Ratain, *Proc. Am. Soc. Clin. Oncol.*, 1998 (1998 ASCO Annual Meeting).
137 J. H. Schellens, G. Groenewegen, T. J. M. Meeru, M. Maliepaard, M. M. Tinbben, D. Pluim, H. W. W. ten Bokke, M. Schot, H. Welbank, G. H. Blijham and J. H. Bleijnen, *Proc. Am. Soc. Clin. Oncol.*, 1999 (1999 ASCO Annual Meeting).
138 G. J. Veal, M. J. Griffin, A. Parry, G. S. Dick, M. A. Little, S. M. Yule, B. Morland, E. J. Estlin, J. P. Hale, A. D. J. pearson, H. Welbank and A. V. Boddy, *Br. J. Cancer*, 2001, **84**, 1029–1035.
139 J. M. M. Terwogt, G. Groenewegen, D. Pluim, M. Maliepaard, M. M. Tibben, A. Huisman, H. W. W. Ten Bokke, M. Schot, H. Welbank, E. E. Voest, J. H. Beijnen and J. H. M. Schellens, *Cancer Chemother. Pharmacol.*, 2002, **49**, 201–210.
140 L. Liu, D. Hershock, M. Machtay, K. M. Algazy, R. S. Weber, G. S. Weinstein, A. A. Chalian, L. K. Miller, K. Rockwell, M. Tonda, E. Schnipper and D. I. Rosenthal, *Proc. Am. Soc. Clin. Oncol.*, 2001, 20.
141 D. I. Rosenthal, S. S. Yom, L. Liu, M. Machtay, K. Algazy, R. S. Weber, G. S. Weinstein, A. A. Chalian, L. K. Miller, K. Rockwell, M. Tonda, E. Schnipper and D. Hershock, *Invest. New Drugs*, 2002, **20**, 343–349.
142 E. E. Vokes, G. S. Gordon, A. M. Mauer, C. M. Rudin, S. A. Krauss, L. Szeto, H. M. Golomb and P. C. Hoffman, *Clin. Lung Cancer*, 2000, **2**, 128–132.
143 E. S. Kim, C. Lu, F. R. Khuri, M. Tonda, B. S. Glisson, D. Liu, M. Jung, W. K. Hong and R. S. Herbst, *Lung Cancer*, 2001, **34**, 427–432.
144 D. M. Vail, I. D. Kurzman, P. C. Glawe, M. G. O'Brien, R. Chun, L. D. Garrett, J. E. Obradovich, R. M. Fred, C. Khanna, G. T. Colbern and P. K. Working, *Cancer Chemother. Pharmacol.*, 2002, **50**, 131–136.
145 A. Schroeder, Y. Avnir, S. Weisman, Y. Najajreh, A. Gabizon, Y. Talmon, J. Kost and Y. Barenholz, *Langmuir*, 2007, **23**, 4019–4025.
146 A. Schroeder, R. Honen, K. Turjeman, A. Gabizon, J. Kost and Y. Barenholz, *J. Controlled Release*, 2009, **137**, 63–68.
147 J. Lauterzstain, R. Perez-Soler, A. R. Khokhar, R. A. Newman and G. Lopez-Berestein, *Cancer Chemother. Pharmacol.*, 1986, **18**, 93–97.
148 R. Perez-Soler, L. Y. Yang, B. Drewinko, J. Lauterzstain and A. R. Khokhar, *CancerRes.*, 1988, **48**, 4509–4512.
149 A. R. Khokhar, S. Al-Baker, T. Brown and R. Perez-Soler, *J. Med. Chem.*, 1991, **34**, 325–329.
150 R. Perez-Soler, J. Lauterzstain, L. C. Stephens, K. Wright and A. R. Khokhar, *Cancer Chemother. Pharmacol.*, 1989, **24**, 1–8.
151 I. Han, Y.-H. Ling, S. Al-Baker, A. R. Khokhar and R. Perez-Soler, *Cancer Res.*, 1993, **53**, 4913–4919.
152 I. Han, A. R. Khokhar and R. Perez-Soler, *Cancer Chemother. Pharmacol.*, 1996, **39**, 17–24.
153 I. Han, T. Nguyen, L. Y. Yang, A. R. Khokhar and R. Perez-Soler, *Anti-Cancer Drugs*, 1994, **5**, 64.
154 R. Perez-Soler, A. R. Khokhar and G. Lopez-Berestein, *Cancer Res.*, 1987, **47**, 6462–6466.
155 R. Perez-Soler, G. Lopez-Berestein, J. Lauterzstain, S. Al-Baker, K. Francis, D. Macais-Kiger, M. N. Raber and A. R. Khokhar, *Cancer Res.*, 1990, **50**, 4254–4259.
156 T. Dragovich, D. Mendelson, S. Kurtin, K. Richardson, D. Von Hoff and A. Hoos, *Cancer Chemother. Pharmacol.*, 2006, **58**, 759–764.
157 M. L. Rothenberg, A. M. Oza, R. H. Bigelow, J. D. Berlin, J. L. Marshall, R. K. Ramanathan, L. L. Hart, S. Gupta, C. A. Garay, B. G. Burger, N. Le Bail and D. G. Haller, *J. Clin. Oncol.*, 2003, **21**, 2059–2069.
158 R. Perez-Soler, D. B. Shin, Z. H. Siddik, W. K. Murphy, M. Huber, J. S. Lee, A. R. Khokhar and W. K. Hong, *Clinical Cancer Res.*, 1997, **3**, 373–379.
159 C. Lu, R. Perez-Soler, B. Piperdi, G. L. Walsh, S. G. Swisher, W. R. Smythe, H. J. Shin, J. Y. Ro, L. Feng, M. Truong, A. Yalamanchili, G. Lopez-Berestein, W. K. Hong, A. R. Khokhar and D. M. Shin, *J. Clin. Oncol.*, 2005, **23**, 3495–3501.
160 C. F. Verschraegen, S. Kumagai, R. Davidson, B. Feig, P. Mansfield, S. J. Lee, D. S. Maclean, W. Hu, A. R. Khokhar and Z. H. Siddik, *J. Cancer Res. Clin. Oncol.*, 2003, **129**, 549–555.
161 N. J. Wheate and J. G. Collins, *Curr. Med. Chem.: Anti-Cancer Agents*, 2005, **5**, 267–279.
162 P. Di Blasi, A. Bernareggi, G. Beggiolin, L. Piazzoni, E. Menta and M. L. Formento, *Anticancer Res.*, 1998, **18**, 3113–3118.
163 J. D. Roberts, G. Beggiolin, C. Manzotti, L. Piazzoni and N. Farrell, *J. Inorg. Biochem.*, 1999, **77**, 47–50.
164 J. D. Roberts, J. Peroutka and N. Farrell, *J. Inorg. Biochem.*, 1999, **77**, 51–57.
165 P. Perego, L. Gatti, C. Caserini, R. Supino, D. Colangelo, R. Leone, S. Spinelli, N. Farrell and F. Zunino, *J. Inorg. Biochem.*, 1999, **77**, 59–64.
166 T. D. McGregor, A. Hegmans, J. Kasparkova, K. Neplechova, O. Novakova, H. Penazova, O. Vrana, V. Brabec and N. Farrell, *JBIC, J. Biol. Inorg. Chem.*, 2002, **7**, 397–404.
167 M. B. G. Kloster, J. C. Hannis, D. C. Muddiman and N. Farrell, *Biochemistry*, 1999, **38**, 14731–14737.
168 V. Brabec, J. Kasparkova, O. Vrana, O. Novakova, J. W. Cox and N. Farrell, *Biochemistry*, 1999, **38**, 6781–6790.
169 J. Kasparkova, J. Zehnulova, N. Farrell and V. Brabec, *J. Biol. Chem.*, 2002, **277**, 48076–48086.
170 Y. Qu, N. J. Scarsdale, M.-C. Tran and N. P. Farrell, *JBIC, J. Biol. Inorg. Chem.*, 2003, **8**, 19–28.
171 Y. Qu, N. J. Scarsdale, M. C. Tran and N. Farrell, *J. Inorg. Biochem.*, 2004, **98**, 1585–1590.
172 A. Hegmans, S. J. Berners-Price, M. S. Davies, D. S. Thomas, A. S. Humphreys and N. Farrell, *J. Am. Chem. Soc.*, 2004, **126**, 2166–2180.
173 Y. Qu, M.-C. Tran and N. P. Farrell, *JBIC, J. Biol. Inorg. Chem.*, 2009, **14**, 969–977.
174 R. A. Ruhayel, J. J. Moniodis, X. Yang, J. Kasparkova, V. Brabec, S. J. Berners-Price and N. P. Farrell, *Chem.–Eur. J.*, 2009, **15**, 9365–9374.
175 T. D. McGregor, Z. Balcarova, Y. Qu, M.-C. Tran, R. Zaludova, V. Brabec and N. Farrell, *J. Inorg. Biochem.*, 1999, **77**, 43–46.
176 T. D. McGregor, W. Bousfield, Y. Qu and N. Farrell, *J. Inorg. Biochem.*, 2002, **91**, 212–219.
177 S. Komeda, T. Moulaei, K. K. Woods, M. Chikuma, N. P. Farrell and L. D. Williams, *J. Am. Chem. Soc.*, 2006, **128**, 16092–16103.
178 Q. Liu, Y. Qu, R. Van Antwerpen and N. Farrell, *Biochemistry*, 2006, **45**, 4248–4256.
179 C. Billecke, S. Finniss, L. Tahash, C. Miller, T. Mikkelsen, N. P. Farrell and O. Bogler, *Neuro-Oncology*, 2006, **8**, 215–226.
180 L. Orlandi, G. Colella, A. Bearzatto, G. Abolafio, C. Manzotti, M. G. Daidone and N. Zaffaroni, *Eur. J. Cancer*, 2001, **37**, 649–659.
181 A. Riccardi, D. Meco, C. Ferlini, T. Servidei, G. Carelli, G. Segni, C. Manzotti and R. Riccardi, *Cancer Chemother. Pharmacol.*, 2001, **47**, 498–504.
182 G. Colella, M. Pennati, A. Bearzatto, R. Leone, D. Colangelo, C. Manzotti, M. G. Daidone and N. Zaffaroni, *Br. J. Cancer*, 2001, **84**, 1387–1390.
183 T. Servidei, C. Ferlini, A. Riccardi, D. Meco, G. Scambia, G. Segni, C. Manzotti and R. Riccardi, *Eur. J. Cancer*, 2001, **37**, 930–938.
184 C. Manzotti, G. Pratesi, E. Menta, R. Di Domenico, E. Cavalletti, H. H. Fiebig, L. R. Kelland, N. Farrell, D. Polizzi, R. Supino, G. Pezzoni and F. Zunino, *Clin. Cancer Res.*, 2000, **6**, 2626–2634.
185 P. Perego, C. Caserini, L. Gatti, N. Carenini, S. Romanelli, R. Supino, D. Colangelo, I. Viano, R. Leone, S. Spinelli, G. Pezzoni, C. Manzotti, N. Farrell and F. Zunino, *Mol. Pharm.*, 1999, **55**, 528–534.
186 G. Pratesi, P. Perego, D. Polizzi, S. C. Righetti, R. Supino, C. Caserini, C. Manzotti, F. C. Giuliani, G. Pezzoni, S. Tognella, S. Spinelli, N. Farrell and F. Zunino, *Br. J. Cancer*, 1999, **80**, 1912–1919.
187 C. Sessa, G. Capri, L. Gianni, F. Peccatori, G. Grasselli, J. Bauer, M. Zucchetti, L. Vigano, A. Gatti, C. Minoia, P. Liati, S. Van Den Bosch, A. Bernareggi, G. Camboni and S. Marsoni, *Ann. Oncol.*, 2000, **11**, 977–983.
188 P. Calvert, A. N. Hughes, A. Azzabi, M. Verill, G. Camboni, E. Verdi, A. Bernareggi, M. Zucchetti, C. Minoia, C. Sessa, J. Carmichael and A. Calvert, *Proc. Am. Soc. Clin. Oncol*, 2000, **19**, abstr 921F.
189 D. I. Jodrell, T. R. J. Evans, W. Steward, D. Cameron, J. Prendiville, C. Aschele, C. Noberasco, M. Lind, J. Carmichael, N. Dobbs, G. Camboni, B. Gatti and F. De Braud, *Eur. J. Cancer*, 2004, **40**, 1872–1877.
190 T. A. Hensing, N. H. Hanna, H. H. Gillenwater, M. G. Camboni, C. Allievi and M. A. Socinski, *Anti-Cancer Drugs*, 2006, **17**, 697–704.
191 G. Scagliotti, S. Novello, L. Crino, F. De Marinia, M. Tonato, C. Noberasco, G. Selvaggi, F. Massoni, B. Gatti and G. Camboni, *Lung Cancer*, 2003, **41**, S223.
192 A. H. Calvert, H. Thomas, N. Colombo, M. Gore, H. Earl, L. Sena, G. Camboni, P. Liati and C. Sessa, *Eur. J. Cancer*, 2001, **37**, S260.
193 L. R. Kelland, G. Abel, M. J. McKeage, M. Jones, P. M. Goddard, M. Valenti, B. A. Murrer and R. H. Kenneth, *Cancer Res.*, 1993, **53**, 2581–2586.

194 G. Samimi and S. B. Howell, *Cancer Chemother. Pharmacol.*, 2006, **57**, 781–788.
195 H. Choy, C. Park and M. Yao, *Clin. Cancer Res.*, 2008, **14**, 1633–1638.
196 E. Fokkema, H. J. M. Groen, M. N. Helder, E. G. E. Vries and C. Meijer, *Biochem. Pharmacol.*, 2002, **63**, 1989–1996.
197 A. J. Cmelak, H. Choy and B. A. Murphy, *Proc. Am. Soc. Clin. Oncol.*, 1999, 18.
198 G. B. Inc, Orplanta. Satraplatin Capsules, in *Advisory Committee Briefing Document*, USA Food and Drug Administration, 2007.
199 *European Medicines Agency, Withdrawal assessment report for orplanta*, 2008, pp. 1–37.
200 http://www. clinicaltrials.gov, U.S National Library of medicine, Bethesda, 1993.
201 J. Holford, F. Raynaud, B. Murrer, K. Grimaldi, J. Hartley, M. Abrams and L. Kelland, *Anti-cancer Drug Des.*, 1998, **13**, 1–18.
202 A. Battle, R. Choi, D. Hibbs and T. Hambley, *Inorg. Chem.*, 2006, **45**, 6317–6322.
203 P. Beale, I. Judson, A. O'Donnell, J. Trigo, C. Rees, F. Raynaud, A. Turner, L. Simmons and L. Etterley, *Br. J. Cancer*, 2003, **88**, 1128–1134.
204 Y. Chen, Z. Guo, S. Parsons and P. J. Sadler, *Chem.–Eur. J.*, 1998, **4**, 672–676.
205 J. Holford, S. Sharp, B. Murrer, M. Abrams and L. Kelland, *Br. J. Cancer*, 1998, **77**, 366–373.
206 S. Sharp, C. O'Neill, P. Rogers, F. Boxall and L. Kelland, *Eur. J. Cancer*, 2002, **38**, 2309–2315.
207 F. Raynaud, F. Boxall, P. Goddard, M. Valenti, M. Jones, B. Murrer, M. Abrams and L. Kelland, *Clin. Cancer Res.*, 1997, **3**, 2063–2074.
208 K. Gelmon, T. Vandenberg, L. Panasci, B. Norris, M. Crump, L. Douglas, W. Walsh, S. Matthews and L. Seymour, *Ann. Oncol.*, 2003, **14**, 543–548.
209 J. Treat, J. Schiller, E. Quoix, A. Mauer, M. Edelman, M. Modiano, P. Bonomi, R. Ramlau and E. Lemarie, *Eur. J. Cancer*, 2002, 38.
210 *The Design and Development of the Tumour-Targeting Nanopolymer DACH Platinum Conjugate AP5346 (Prolindac™)*, S. B. Howell, *in Platinum and other heavy metal compounds in cancer chemotherapy: Molecular mechanism and clinical applications*, eds. A. Bonetti, R. Leone, F. Muggia and S. B. Howell, Humana Press, New York, 2009, 33–39.
211 P. Sood, K. B. Thurmond, J. E. Jacob, L. K. Waller, G. O. Silva, D. R. Stewart and D. Nowotnik, *Bioconjugate Chem.*, 2006, **17**, 1270–1279.
212 E. Giansi, M. Wasil, E. Evagorou, A. Keddle, G. Wilson and R. Duncan, *Eur. J. Cancer*, 1999.
213 R. Duncan, *Chem. Ind.*, 1997, **7**, 262–264.
214 *In vitro Anti-proliferative Effects of Prolindac™, a Novel DACH-Platinum Linked Polymer Compound, as a Single Agent and in Combination with Other Anti-Cancer Drugs*, M. Serova, A. Ghoul, K. Rezai, F. Lokiec, E. Cvitkovic, D. Nowotnik, S. Faivre and E. Raymond, *in Platinum and other heavy metal compounds in cancer chemotherapy: Molecular mechanism and clinical applications*, eds. A. Bonetti, R. Leone, F. Muggia and S. B. Howell, Humana Press, New York, 2009, 41–47.
215 J. R. Rice, J. L. Gerberich, D. Nowotnik and S. B. Howell, *Clin. Cancer Res.*, 2006, **12**, 2248–2254.
216 M. Campone, J. M. Rademaker-Lakhai, J. Bennouna, S. B. Howell, D. Nowotnik, J. H. Beijnen and J. H. M. Schellens, *Cancer Chemother. Pharmacol.*, 2007, **60**, 523–533.
217 D. P. nowotnik and E. Cvitkovic, *Adv.Drug Delivery Rev.*, 2009, **61**, 1214–1219.
218 F. Joly, A. Madroszyk, A. Floquet, D. Gedouin, F. Bourdel and M. Campone, in *AACR-NCI-EORTC Symp.*, 2008.
219 P. Viens, P. Bougnoux, O. Rixe, T. Petit, A. Laadem, P. Cottu, R. Delva, F. Burki, A. Goupil and J. M. Extra, *Eur. J. Cancer*, 2001, **37**, S323.
220 http://www.regulon.org/company.html, accessed 27th January 2010.
221 T. Boulikas, *Oncol. Rep.*, 2004, **12**, 3–12.
222 T. Boulikas, *Cancer Ther.*, 2007, **5**, 351–376.
223 G. P. Stathopoulos, T. Boulikas, M. Vougiouka, G. Deliconstantinos, S. Rigatos, E. Darli, V. Villotou and J. G. Stathopoulos, *Oncol. Rep.*, 2005, **13**, 589–595.
224 P. Y. Kwok, *Annu. Rev. Genomics Hum. Genet.*, 2001, **2**, 235–258.
225 G. P. Stathopoulos, T. Boulikas, M. Vougiouka, S. K. Rigatos and J. G. Stathopoulos, *Oncol. Rep.*, 2006, **15**, 1201–1204.
226 M. E. Froudarakis, A. Pataka, P. Pappas, S. Anevlavis, E. Argiana, M. Nikolaidou, G. Kouliatis, S. Pozova, M. Marselos and D. Bouros, *Cancer*, 2008, **113**, 2752–2760.
227 T. Boulikas, G. P. Stathopoulos, N. Volakakis and M. Vougiouka, *Anticancer Res.*, 2005, **25**, 3031–3030.
228 A. Ravaioli, M. Papi, E. Pasquini, M. Marangolo, B. Rudnas, M. Fantini, S. V. L. Nicoletti, F. Drudi, I. Panzini, E. Tamburini, L. Gianni and G. Pasini, *J. Chemotherapy (Italy)*, 2009, **21**, 86–90.
229 N. Mylonakis, A. Athanasiou, N. Ziras, J. Angel, A. Rapti, S. Lampaki, N. Politis, C. Karanikas and C. Kosmas, *Lung Cancer*, 2010, **68**, 240–247.
230 C. Kosmas, J. Angel, A. Athanasiou, A. Rapti, C. Karanikas, S. Lambaki, N. Politis and N. Mylonakis, *Eur. J. Cancer Suppl.*, 2009, **7**, 531–531.
231 G. Karpathiou, E. Argiana, A. Koutsopoulos and M. E. Froudarakis, *Oncology*, 2007, **73**, 426–429.
232 S. Schildhauer, D. Pollmann, G. Pecher, K.-D. Wernecke, K. Possinger and D. Lüftner, *Eur. J. Cancer Suppl.*, 2005, **3**, 286–287.
233 C. Jehn, S. Siepmann, G. Pecher, K. D. Wernecke, K. Possinger and D. Lüftner, *Oral Oncology Supplement*, 2007, **2**, 118–118.
234 M. I. Koukourakis, A. Giatromanolaki, M. Pitiakoudis, G. Kouklakis, P. Tsoutsou, I. Abatzoglou, M. Panteliadou, K. Sismanidou, E. Sivridis and T. Boulikas, *Int. J. Radiat. Oncol., Biol., Phys.*, 2010, DOI: 10.1016/j.ijrobp.2009.07.1733.