REVIEW ARTICLE

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New Developments and Approaches in the Platinum Arena

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Abstract

Following the introduction of cisplatin and the demonstration of its importance in the treatment of testicular and ovarian cancer, there was a need to develop less toxic analogues. Compared with cisplatin, carboplatin proved markedly less toxic to the kidneys and nervous system and caused less nausea and vomiting, while generally (and certainly for ovarian cancer) retaining equivalent antitumour activity. In many situations, carboplatin is now the drug of choice in view of the improved quality of life it offers patients.

Many drug combinations involving platinum complexes have been explored, but those with taxanes are particularly noteworthy. Paclitaxel in combination with a platinum agent is now accepted as a standard component of first-line treatment for ovarian cancer, and produces improved survival.

Preclinical studies suggested that drugs containing the diaminocyclohexane ligand would be capable of overcoming intrinsic or acquired resistance. However, this outcome was not realised in the clinic until the development of oxaliplatin, which appears to have a different spectrum of activity compared with cisplatin and carboplatin. Oxaliplatin improves the response rate and progression-free survival when given with fluorouracil for the treatment of advanced colorectal cancer, and its activity in other tumour types is under investigation.

ZD0473 is a platinum analogue that relies on steric hindrance to overcome thiol-mediated detoxification. It has a good tolerability profile, is currently undergoing phase II testing, and its activity in combination with other agents is being explored.

The trinuclear platinum complex BBR3464 also looks promising in preclinical studies and will shortly be evaluated in phase II trials.

Although much research remains to be done, these new developments in platinum-based chemotherapy should translate into significant improvements in treatment for patients with a broad range of tumour types.

The original platinum-based coordination complex, *cis*-dichlorodiammine platinum (II) [cisplatin], is one of the most widely used cytotoxic cancer drugs and possesses a very broad spectrum of activity. Although activity was reported against tumours such as refractory testicular teratoma and ovarian cancer, the incidence of severe adverse effects (such as kidney damage and nausea and vomiting) was initially unacceptable.[1] While these adverse effects have been alleviated to some extent [e.g. by using hyperhydration with isotonic saline for nephrotoxicity, and with the advent of the serotonin (5-hydroxytryptamine) type-3 (5-HT_3) antagonists for nausea and vomiting], there has been a major synthetic drive to develop platinum analogues with a more acceptable toxicity profile.

Foremost among less toxic platinum analogues is carboplatin [*cis*-diammine-1,1-cyclobutane

dicarboxylate platinum (II)], the dose-limiting toxicity of which is myelosuppression, principally thrombocytopenia. Randomised trials have demonstrated equivalent activity between cisplatin and carboplatin both as a single agent and in combination with other drugs for the treatment of ovarian cancer (reviewed by Go & Adjei[2]). A meta-analysis has subsequently combined data from 10 studies and confirmed equivalence in the treatment of suboptimally debulked ovarian cancer.[3] However, in 4 studies in patients with good-risk germ cell tumours in which carboplatin was used in place of cisplatin (in combination with etoposide with or without bleomycin), relapse-free survival favoured cisplatin.[2] Carboplatin has now replaced cisplatin in many clinical situations, on the basis of its broadly similar activity profile and improved tolerability.

This review describes new developments and approaches since the development of carboplatin. The major focus has been on broadening the clinical utility of platinum-based chemotherapy to include tumours that are or may become resistant to cisplatin/carboplatin. The mechanisms by which such resistance occurs are described in an article by Kelland elsewhere in this supplement.[4] Broadly, circumvention of resistance has been attempted through either novel combination chemotherapy regimens (e.g. with paclitaxel) or platinum analogue development (e.g. oxaliplatin, ZD0473, BBR3464) as described in this review. There have also been efforts to develop an oral platinum drug [satraplatin (JM216)] and liposomal forms of cisplatin [e.g. cisplatin-liposomal-Alza (SPI077)]. Chemical structures of registered platinum drugs plus those of developmental drugs which have reached clinical trials are provided in figure 1.

1. New Drug Combinations

Platinum anticancer agents have been combined successfully with many other anticancer drugs including fluorouracil, etoposide, doxorubicin, gemcitabine, ifosfamide and mitomycin. However, one particular drug combination, cisplatin plus paclitaxel, deserves special mention.

Paclitaxel was initially identified as a promising anticancer drug by the US National Cancer Institute (NCI) as part of its screening programme. Early trials demonstrated activity against platinum-refractory ovarian cancer.[5] A phase III trial (study GOG 111) conducted by the Gynecologic Oncology Group demonstrated superior progression-free and overall survival for patients with stage III or IV ovarian cancer treated with cisplatin plus paclitaxel compared with those receiving cisplatin plus cyclophosphamide.[6] These results have been confirmed by a European-Canadian study[7] and there is a broad consensus that cisplatin plus paclitaxel represents a significant advance in the treatment of advanced ovarian cancer.[8]

The combination of carboplatin with paclitaxel is also worthy of special note. The principal dose-limiting toxicity of carboplatin is thrombocytopenia, whereas for paclitaxel given by short infusion it is neutropenia. When these drugs are given in combination, thrombocytopenia is less common than with carboplatin alone, the dose interval for carboplatin can be reduced from 4 to 3 weeks and both drugs can be administered at their respective standard doses or above.[9-11] Carboplatin plus paclitaxel appears highly active against urothelial cancer[12] and endometrial cancer.[13]

There is an increasing consensus that radiotherapy plus concurrent platinum-based chemotherapy offers a significant advance in the treatment of locally advanced cervical cancer compared with chemotherapy alone.[14] The NCI has recently made a 'Clinical Announcement' concerning the preliminary results of 5 controlled clinical trials which indicate that this approach appears to result in a worthwhile survival advantage.[15]

2. Platinum Analogue Development

2.1 Oxaliplatin

As mentioned in the introduction to this paper, a key goal in the development of analogues of cisplatin/carboplatin has been to overcome drug resistance. About 20 years ago, Burchenal and colleagues[16] observed that agents in which the ammine

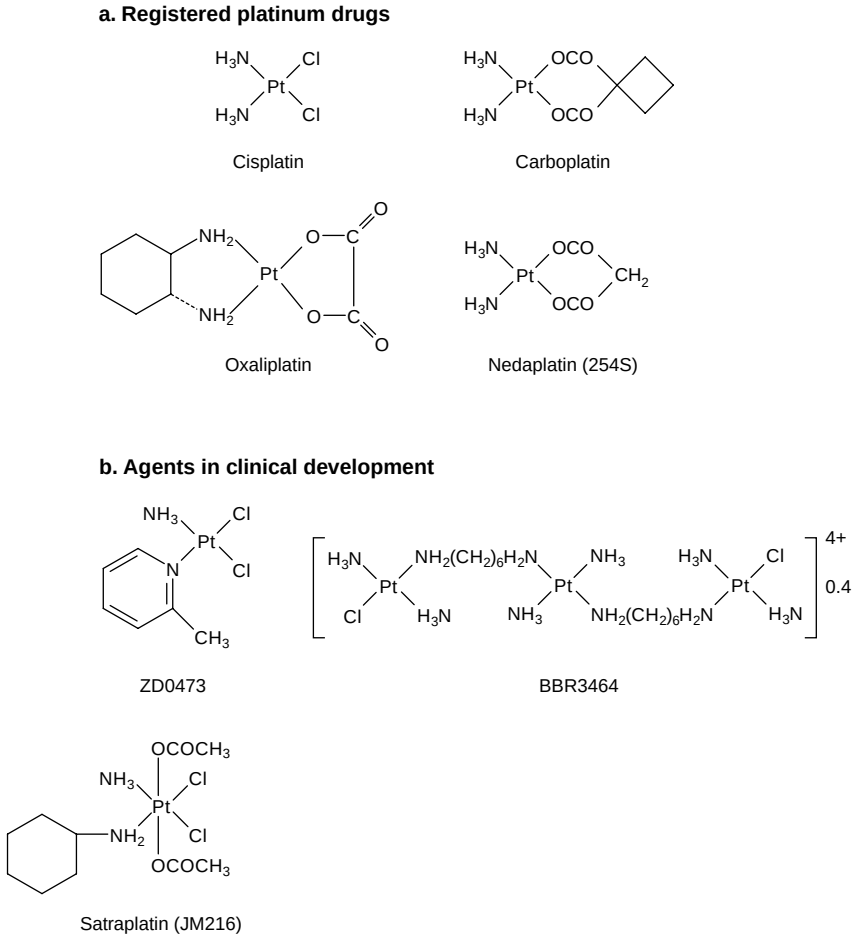

Fig. 1. Structures of platinum drugs currently registered for use and developmental drugs undergoing clinical trials (liposomal cisplatin not included).

ligands were replaced by a diamminoclycohexane (DACH) group were active against cisplatin-resistant cell lines, such as the P388 murine leukaemia line. This led to the development of a range of such agents, a number of which underwent clinical testing. These included a platinum (IV) complex with 4 chlorine atoms, initially called tetraplatin but subsequently designated ormaplatin. This proved highly neurotoxic and was also nephrotoxic, and failed to demonstrate clinical activity against cisplatin-resistant tumours.[17,18]

However, another of the DACH-type analogues, oxaliplatin, while not tested in the setting of cisplatin-resistant tumours, appears to have a somewhat different and potentially useful spectrum of antitumour activity.[19] This agent has shown activity in advanced colorectal cancer both as monotherapy[20] and in combination with fluorouracil.[21] Randomised clinical trials have demonstrated improved response rates and progression-free survival with the addition of oxaliplatin.[22,23] In addition, responses have been obtained with oxaliplatin monotherapy in patients whose disease was refractory to standard fluorouracil plus leucovorin regimens.[24]

In the setting of combined therapy, there is some evidence in favour of chronomodulation using programmable pumps to deliver fluorouracil and

folinic acid (leucovorin) maximally at 4.00am and oxaliplatin at 4.00pm. When this approach was used, antitumour activity was higher (objective response rate 53%) and toxicity was lower than with standard daily infusion protocols.[21]

Oxaliplatin produces a curious pattern of neurotoxicity, including facial dysaesthesia, which may be provoked by exposure to cold.[25] Peripheral sensory neuropathy may also occur but is reversible and rarely dose limiting. The drug does not cause significant nephrotoxicity.[25]

Although the full potential of oxaliplatin has yet to be determined, it represents a significant advance in the treatment of advanced colorectal cancer, as it is the only platinum complex to have shown activity against this malignancy. The drug is registered for use in advanced colorectal cancer in France, the UK and some other European countries.

2.2 ZD0473

ZD0473 (formerly AMD473, JM473) [*cis*-amminedichloro(2-methylpyridine) platinum (II)] is a novel platinum complex developed from a research programme designed to identify a platinum anticancer drug with the capacity to overcome acquired or intrinsic (*de novo*) resistance to cisplatin. Emphasis was placed upon the establishment and use of human ovarian cancer cell lines and xenografts which were representative of both intrinsic and acquired cisplatin resistance and were well characterised in terms of their major mechanism(s) of resistance.[26]

A commonly found mechanism of resistance to cisplatin (including in our own studies[27]) is an increase in cytoplasmic levels of thiol-containing species (especially glutathione – see the paper by Kelland in this supplement[4]), which can result in thiol substitution at the platinum centre of the anticancer drug. It has been found that thiol substitution is hindered by the introduction of steric bulk in the molecule; ZD0473, which has a methyl-substituted pyridine side chain, was synthesised with this feature in mind.[28]

ZD0473 was studied *in vitro* in human tumour cell lines with a range of sensitivities to platinum agents and in the same cell lines with acquired resistance to cisplatin. It was able to overcome platinum resistance to a significant degree in cell lines with differing mechanisms of resistance (fig. 2).[29] Moreover, good retention of activity was observed in cell lines manipulated to possess relatively high levels of either glutathione or metallothioneins.[30] Interestingly, in addition to reduced susceptibility to inactivation by glutathione, ZD0473 also showed the ability to overcome resistance in the 41McisR ovarian line in which resistance to cisplatin is due to reduced uptake of the drug. Investigations into the nature of interactions between ZD0473 and DNA demonstrated differences in the sequence specificity of DNA adduct formation compared with that for cisplatin and carboplatin and the presence of a unique ZD0473 binding site.

In vivo animal studies of human tumour xenografts have shown the activity of ZD0473 to be at least comparable and in some cases superior to that of cisplatin[31] (fig. 3). ZD0473 was active against a cisplatin-resistant CH1 ovarian tumour xenograft, even when the tumour was progressing after cisplatin treatment. Activity against murine

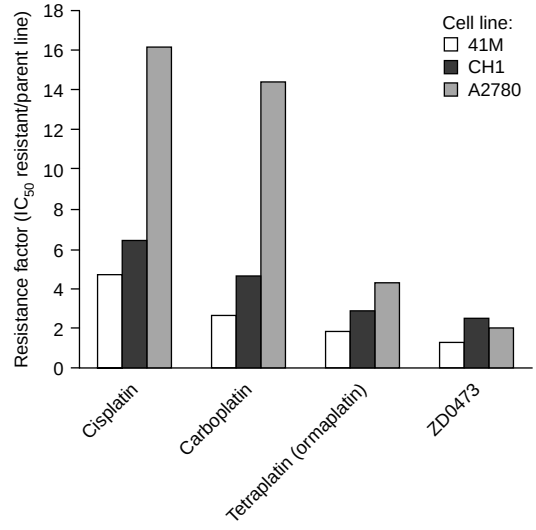

Fig. 2. Circumvention of acquired cisplatin resistance by ZD0473. Resistance factors for 3 cell lines (ratio of IC_{50} values for cell line with acquired platinum resistance versus parent cell line). **IC_{50}** = concentration required to inhibit cell growth by 50% *in vitro*.

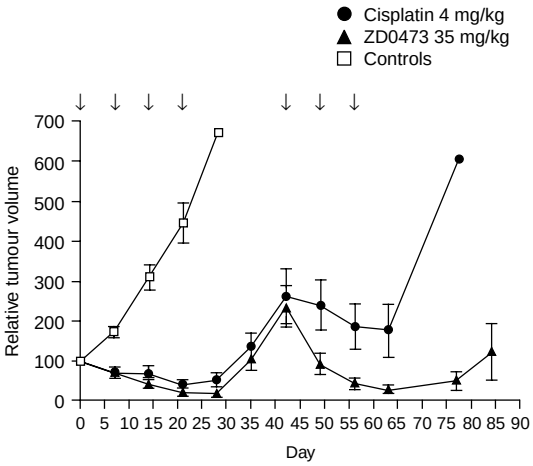

Fig. 3. *In vivo* antitumour activity of ZD0473 versus cisplatin (each given on days 42, 49 and 56 following initial treatments) against CHI human ovarian carcinoma xenografts at regrowth after treatment with cisplatin (3 to 4 mg/kg on days 0, 7, 14 and 21). Data points are means ± SD; arrows indicate days of drug administration. From Raynaud et al.,[31] with permission.

tumours was retained when the drug was administered orally and some activity was seen against the acquired cisplatin-resistant ADJ/PC6cisR tumour, which is totally resistant to other platinum agents.

The metabolism of ZD0473 is relatively simple; the major biotransformation products are the aquated *cis* and *trans* species.[30]

Preclinical studies showed that the dose-limiting toxicity of ZD0473 was myelosuppression, with no evidence of renal impairment or neurotoxicity.[31] A phase I study of the drug (administered intravenously by 1-hour infusion) confirmed that the dose-limiting toxicity in humans is bone marrow suppression.[32] Both neutropenia and thrombocytopenia are observed, but recovery is quite rapid and patients who have not been heavily pretreated can be treated at 3-weekly intervals. Cumulative anaemia but not thrombocytopenia is seen. There has been no evidence of peripheral neurotoxicity, ototoxicity or renal toxicity. Several phase I clinical trials of ZD0473 as part of combination regimens are ongoing.

A phase II study programme is underway to determine the activity and safety profile of ZD0473 in non-small cell lung cancer, small cell lung cancer, mesothelioma and ovarian cancer. The recommended monotherapy dose and schedule for phase II studies is 120 mg/m^2 every 3 weeks. Patients who have been heavily pretreated with cytotoxic agents which damage bone marrow stem cells may require dose reductions and may not be able to tolerate the drug every 3 weeks. Conversely, some patients will tolerate higher doses, e.g. 150 mg/m^2. We have observed evidence of antitumour activity (unpublished data) in our preliminary studies in patients with a variety of malignancies including non-small cell lung cancer, mesothelioma, head and neck and ovarian cancers.

2.3 Trinuclear Platinums: BBR3464

Farell and coworkers[33] have recently described a novel charged trinuclear platinum complex, BBR3464, which entered clinical trials during 1998. The molecule contains 2 *trans*- $PtCl(NH_3)_2$ units linked by a $NH_2(CH_2)_6(NH_2$-*trans*-$Pt(NH_3)_2$-$NH_2(CH_2)_6NH_2$ diamine chain; as such, it represents a significant structural departure from cisplatin and carboplatin (see fig. 1). BBR3464 binds to DNA more rapidly than cisplatin (binding half-time 40 *vs* 240 minutes) and forms long range interstrand and intrastrand crosslinks.[34] It was about 20-fold more potent than cisplatin in terms of *in vitro* growth inhibition across a range of tumour cell lines and showed a unique pattern of activity compared with other platinum agents across the NCI's 60-cell line drug screen.[35] BBR3464 also showed promising *in vivo* antitumour activity, independent of p53 status, in a range of human tumour xenografts.[35,36]

The findings of 2 phase I studies have recently been reported. With a 1-hour infusion of 1.1 mg/m^2 given every 28 days, diarrhoea and neutropenia were evident as dose-limiting toxicities.[37] No significant nephrotoxicity, neurotoxicity or pulmonary toxicity was observed. BBR3464 showed signs of antitumour activity in a patient with colorectal cancer and in another with pancreatic cancer. The second study used 0.17 mg/m^2/day given daily for 5 days, with similar dose-limiting toxici-

ties to those observed with monthly administration.[38] Phase II trials are now beginning.

3. Other Platinum Drugs

3.1 Nedaplatin (254S)

Nedaplatin (254S) [*cis*-diammine(glycolato) platinum] is a 'cisplatin-like' compound which is registered for use in Japan. Thrombocytopenia is the dose-limiting toxicity, although occasional severe nephrotoxicity has been reported.[39] Phase II studies have shown activity in a similar range of tumour types to those responsive to cisplatin.[39] Nedaplatin failed to demonstrate useful activity as a single agent against non-small cell lung cancer.[40]

3.2 Satraplatin (JM216, BMS182751)

Satraplatin (JM216, BMS182751) is an orally available platinum drug with carboplatin-like dose-limiting toxicity.[41] In phase I clinical trials, it demonstrated saturable oral bioavailability and dose-limiting myelosuppression; no nephro-, oto- or neurotoxicity was observed.[42-44] Daily administration for 5 days proved the most suitable for phase II evaluation.[42] Although a phase III study in prostate cancer was performed, no data are available from this trial and the drug is not being actively developed at present.

3.3 Liposomal Cisplatin: SPI077

Liposomal cisplatin (SPI077; cisplatin-liposomal-Alza) contains cisplatin packaged in liposomes which have been modified by the incorporation of polyethylene glycol, rendering them less susceptible to removal by the reticulo-endothelial system.[45] Liposomal delivery may have the capacity to exploit the enhanced permeability and tumour retention phenomenon which result from the immature vasculature in tumours. These characteristics allow large molecules, or in this case the liposomes, to escape from the circulation and become trapped in the interstitial spaces of the tumour. Subsequent slow release of the drug from the liposome may then occur. Liposomal cisplatin has a very small volume of distribution and extremely long plasma elimination half-life. However, no dose-limiting toxicity has been observed in phase I studies of liposomal cisplatin,[45] and there is some concern that release of the drug from the liposomes is too restricted. Nevertheless, liposomal cisplatin did demonstrate improved antitumour activity with reduced toxicity compared with cisplatin in certain animal tumour model systems.[45] Clinical investigation of liposomal cisplatin beyond phase I has been halted pending assessment of possible alternative formulations.

3.4 *Trans*-Platinum Complexes

A major dogma for structure-activity relationships of platinum complexes had been that *trans*-platinum complexes are inactive as antitumour agents. However, during the 1990s, at least 3 independent groups have described *trans*-platinum compounds, some endowed with promising *in vitro* antitumour properties (including retention of potency against some cell lines with acquired cisplatin resistance) [see Kelland et al.[46] and references therein]. One *trans*-platinum complex, JM335 [*trans*-ammine (cyclohexylaminedichlorodihydroxo) platinum (IV)], showed marked *in vivo* antitumour efficacy against both murine and human subcutaneous tumour models.[46] However, to date no *trans*-platinum complex has reached clinical trial, with the possible exception of BBR3464, which is not, strictly speaking, comparable.

4. Conclusions

Platinum complexes have played an important role in cancer treatment for more than 2 decades. In addition to being of fundamental importance in the treatment of ovarian and testicular cancer, they are now established in the routine therapy of cancers of the lung, head and neck, bladder and upper GI tract. With some exceptions, carboplatin appears to have activity similar to that of cisplatin, but has a lower potential for nausea and vomiting and lacks the marked toxicity to the kidneys and peripheral nerves seen with the parent compound. Combinations with taxanes, mainly

paclitaxel, have confirmed this crucial role, with proven benefit in the first-line treatment of ovarian cancer and good results in non-small cell lung cancer.

In addition to the need to overcome the serious toxicities associated with cisplatin, a goal of recent analogue development has been to overcome resistance associated with thiol-induced detoxification, reduced drug uptake and altered DNA repair pathways.

Oxaliplatin, a new agent containing the diaminocyclohexane moiety, appears to possess a spectrum of activity different from that of other platinum drugs; it has shown activity in fluorouracil-resistant advanced colorectal cancer and substantial activity in first-line treatment when combined with fluorouracil.

ZD0473 has been developed specifically to overcome the resistance associated with thiol-induced detoxification (through a mechanism of steric hindrance). It also retains the advantages of reduced toxicity seen with carboplatin, causing dose-limiting myelosuppression but no other serious adverse effects. This has important implications for patients' quality of life. It may be possible to administer this agent orally; experience with satraplatin suggests that this is a feasible approach. ZD0473 also appears to possess other pharmacological advantages, including enhanced transport and distinct DNA specificity with regard to adduct formation, and may thus be able to overcome other resistance mechanisms.

The trinuclear platinum complex BBR3464 has a markedly different mechanism of DNA binding compared with other platinum agents and may also display a different spectrum of antitumour activity. There are already hints of this in early clinical trials.

There is much work to be done to confirm the activity of these new agents, to define more fully their spectrum of activity and to identify the optimum chemotherapy combinations. Nevertheless, it appears that this group of anticancer agents is likely to continue to yield significant improvements in cancer treatment for some years to come.

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