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Clinical Perspectives on Platinum Resistance

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Abstract

The platinum compounds cisplatin and carboplatin are widely used in the treatment of a number of solid malignancies. Although some platinum-sensitive tumours may be cured by combination chemotherapy (e.g. testicular cancer), most will relapse and subsequently prove resistant to platinum compounds. The mechanisms of platinum resistance in patients are still poorly understood. Clearly, when a tumour relapses a long time after successful first-line treatment, there is a high chance that it will still be sensitive to platinum compounds. A number of studies have attempted to assess the role of drug transport, the glutathione system, DNA repair and apoptosis genes in the development of resistance in tumours, but no conclusive evidence is available. Approaches to increasing the potency of platinum therapy (to overcome resistance) have been devised and some have proved to be effective; in particular, intraperitoneal administration of cisplatin has shown superiority over intravenous administration in selected patients with ovarian cancer. The development of drugs and techniques to reduce the adverse effects of platinum chemotherapy has greatly improved their administration. Investigations attempting to modulate platinum activity and toxicity have also been performed.

Further investigation of *in vivo* resistance mechanisms should be valuable in allowing prediction of clinical response to chemotherapy and may identify new treatments with the potential to improve outcomes for patients with a variety of platinum-resistant tumour types.

Resistance to platinum drugs has been studied in numerous preclinical studies, as described in detail in the accompanying paper by Kelland.[1] This paper provides a clinical perspective on resistance issues, including an overview of patterns of clinical resistance and definitions of clinical resistance/sensitivity, a review of relevant mechanistic data from patients, and an account of clinical approaches to overcoming resistance (see also the accompanying paper by Judson and Kelland[2] for a more detailed discussion of new drugs designed to circumvent resistance).

1. Inherent and Acquired Resistance to Cisplatin/Carboplatin

Resistance to platinum compounds varies between tumour types (table I). Some tumours, such as non-small cell lung cancer (NSCLC), are largely inherently resistant to cisplatin treatment, which results in low response rates. For example, treatment of NSCLC with cisplatin typically produces response rates of less than 20%.[3] Other solid tumour types, such as head and neck cancer, testicular cancer, ovarian cancer and small cell lung cancer (SCLC), are predominantly sensitive to

Table I. Sensitivity of various tumour types to standard platinum-based therapies

Sensitivity	Advanced tumour type	Treatment	Overall response (%)
High	Small cell lung cancer	Cisplatin/etoposide plus chest radiotherapy	80-95
	Ovarian	Cisplatin/paclitaxel or carboplatin/paclitaxel	70-80
	Testicular	Cisplatin/etoposide/bleomycin	80-99
	Head and neck	Cisplatin/fluorouracil	80-90
Low	Non-small cell lung cancer	Cisplatin/etoposide	≈20

platinum therapy, and response to first-line cisplatin treatment is high (table I).

The standard first-line treatment for patients with limited-disease SCLC is 4 to 6 cycles of cisplatin/etoposide plus concurrent early chest radiotherapy (4000 to 4500 cGy) or sequential chemotherapy followed by radiotherapy.[4] This typically results in overall response rates of 80 to 95% and a median survival time of 12 to 16 months.[5] The current treatment of stage II to IV ovarian cancer also relies on platinum-based therapies, either cisplatin (75 mg/m^2) and paclitaxel (135 mg/m^2) over 24 hours or carboplatin [dose adjusted to provide an area under the plasma concentration-time curve (AUC) of 5 to 7.5 mg/ml · min] with paclitaxel (175 mg/m^2) over 3 hours. These treatments generally result in overall response rates of 70 to 80%, complete response rates of about 50%, and a median survival duration of between 26 and 38 months (reviewed by McGuire and Ozols[6]). However, despite the high overall clinical response rates achieved with platinum-based therapy in these sensitive tumours, including a high proportion of complete responses, most patients (for example, up to 95% of patients with SCLC and 56% of those with stage 3 ovarian cancer) subsequently relapse because of acquired resistance to a range of cytotoxic agents, including cisplatin/carboplatin (reviewed by Huisman et al.[7] and Thigpen[8]).

2. Defining Cisplatin/Carboplatin Sensitivity and Resistance

In the preclinical setting, the definition of platinum resistance is usually relative to a particular reference cell line; for example, the ovarian cell line OD-129 is regarded as sensitive to cisplatin compared with a derivative cell line OD-129/DDP16, which is regarded as resistant to cisplatin.[9]

Definition of patients as cisplatin-sensitive or -resistant is based on the response to prior chemotherapy and the time to progression in the absence of chemotherapy.[10] However, this usually depends on the clinical setting and tumour type. For example, in ovarian cancer, the usual definition is that platinum-sensitive patients are those who have relapsed more than 6 months after completing cisplatin/carboplatin therapy; platinum-resistant patients include those who have relapsed within 6 months of prior platinum therapy.[11] Platinum-refractory disease can be defined as disease that progressed or was stable during platinum treatment.[11] However, in SCLC, sensitive patients tend to be defined as those who had a response to therapy lasting over 3 months after treatment termination.[7]

Because platinum compounds represent the backbone of treatment for ovarian cancer and SCLC, the definition of resistance is related specifically to these drugs, but this may very well be a broad definition of sensitivity to chemotherapy, at least for SCLC. In SCLC, the success of reinduction with the same chemotherapy or treatment with novel active agents has been shown to be unrelated to the specific drugs used in first line, but essentially linked to the response to first-line chemotherapy and the time since the end of previous chemotherapy (see section 3).[12]

3. The Platinum-Free Interval

Many studies have confirmed that the treatment-free or platinum-free interval is one of the most important predictors of response to second-line chemotherapy.[12-15]

For example, platinum-sensitive SCLC patients (i.e. those who relapsed more than 3 months after first-line chemotherapy) frequently respond to second-line chemotherapy (retreatment with their first-line therapy or topotecan). Objective response rates of 50 to 60% have been reported in these patients.[7] However, patients with SCLC who relapsed within 3 months have only a small chance (<10%) of responding to any drug.

In cisplatin-sensitive patients with ovarian cancer, the response to second-line chemotherapy with cisplatin is 27 to 59%, depending on the platinum-free interval.[8] Patients who do not respond to first-line platinum treatment or those who relapse within 6 months of therapy termination are also the most resistant to a second-line platinum therapy, but also to treatment with any other agent. Response rates to second-line platinum therapy for platinum-refractory or -resistant ovarian cancer are as low as 10%.[6] In patients who do not respond to cisplatin/carboplatin first-line therapy, paclitaxel achieves responses of 24 to 30%.[8] Second-line oral etoposide achieves response rates of 32% in platinum-resistant patients who received cisplatin/carboplatin and paclitaxel as first-line treatment.[8]

4. Clinical Studies of Resistance Mechanisms

Treatment of platinum-resistant cancer is a major problem which may be addressed to some degree by understanding the mechanisms that lead to resistance *in vivo*. As for most anticancer agents, cellular resistance to cisplatin is multifactorial. Among the many mechanisms of drug resistance described *in vitro*, increased repair of platinum-DNA damage appears to be the most important factor, whereas at levels of resistance >40-fold over baseline, increased levels of cellular glutathione (which result in thiol-substitution at the platinum centre and subsequent drug inactivation) appear to take on primary importance.[16] However, levels of drug resistance defined in preclinical models are rather difficult to translate into the clinical situation, as it is not clear whether drug concentrations *in vitro* approximate to those achieved in patients, nor is it clear whether tumour cells respond similarly to cisplatin *in vitro* and *in vivo*.

Accurate characterisation of resistance in the clinical setting is difficult, as some potential resistance mechanisms are not readily studied in patients. Studies of platinum resistance in patients are therefore relatively scarce, but the available data are reviewed in the following sections.

4.1 Transport

Although diffusion of cisplatin into cells is usually passive, alterations in uptake have been shown to influence sensitivity to platinum compounds in several preclinical models.[17] Lung resistance-related protein (LRP) is the major human vault protein; vault proteins are part of novel cellular organelles which are highly conserved among diverse eukaryotic cells. They localise to nuclear pore complexes and thus may play a role in drug resistance by regulating nucleocytoplasmic transport of several drugs.[18] The LRP-associated multidrug resistance (MDR) phenotype is broad, including drugs that are substrates of P-glycoprotein and the multiple drug–resistance-related protein (doxorubicin, vincristine) and also some nonclassical MDR-related drugs (e.g. cisplatin, carboplatin, melphalan).

Clinical studies on childhood acute lymphocytic leukaemia and on acute myelocytic leukaemia and ovarian carcinoma showed that LRP might be a clinically relevant marker of drug resistance; in particular, LRP overexpression was a better marker of platinum resistance than P-glycoprotein or MRP in advanced ovarian cancer.[19] For example, patients with LRP-positive tumours had a significantly poorer response to chemotherapy ($p = 0.004$) and shorter progression-free ($p = 0.003$) and overall ($p = 0.007$) survival than those with LRP-negative tumours.[19]

Although the canalicular multispecific organic anion transporter cMOAT2/MRP3 has been shown to be overexpressed in cisplatin-resistant cell lines, its role in clinical platinum resistance has still to be investigated.[20]

4.2 Detoxification

Cellular inactivation of platinum drugs may occur through binding of platinum to metallothioneins or the nonprotein thiol glutathione. Although several preclinical studies indicate that metallothionein levels are correlated with cisplatin resistance, the relevance of this in the clinic is currently unknown.[17] Glutathione is the most abundant cellular thiol and may be present at intracellular concentrations approaching 10 mmol/L. The conjugation of cisplatin with glutathione is catalysed by glutathione-S-transferases (GSTs), and overexpression of GSTπ has been studied in biopsies, although without consistent results.[21]

4.3 DNA Repair

The measurement of DNA damage in clinical samples is arduous and therefore only a limited number of studies have been published. The development of enzyme-linked immunosorbent assays which use monoclonal antibodies raised to the major intrastrand cisplatin-DNA adduct has recently allowed interesting studies in patients treated with platinum-containing regimens. However, studies reviewed in the rest of this section did not use this method.

The formation and repair of DNA-platinum adducts has been studied in various groups of patients. Increased repair of cisplatin-DNA adducts has been demonstrated in tumour cells from patients with clinical signs of cisplatin resistance.[22] A 2.8-fold increase in repair rate was observed in human malignant glioma cells obtained at disease progression after cisplatin therapy, as compared with before treatment.[22] In a cohort of patients with ovarian cancer, responders had higher platinum-DNA adduct levels than nonresponders, although there was substantial overlap between the groups.[23] Ma et al.[24] showed that platinum-DNA adducts in white blood cells were measurable in the 24 hours following a standard dose of cisplatin. In a series of 45 patients, the same investigators found that cisplatin exposure expressed as AUC was closely correlated with both peak DNA adduct level and the area under the adduct level-time curve. These measures were significant predictors of response, suggesting that individualised administration of cisplatin using AUC or the level of adduct formation could lead to increased response rates.[25]

Within the complexity of DNA repair mechanisms, nucleotide excision repair (NER) appears to be the pathway of major importance for cisplatin-DNA damage, and within NER, the excision repair cross-complementing (ERCC) gene ERCC1 appears to be a critical gene.[26] Using a reverse-transcriptase polymerase chain reaction method, Dabholkar et al.[27] investigated NER gene expression in fresh tumour samples from patients who received platinum-based therapy. These studies examined ERCC1, ERCC2 (XPD), and XPA transcripts (XP = the xeroderma pigmentosum gene involved in hypersensitivity to UV light).

In ovarian cancer, high ERCC1 messenger RNA levels were correlated with resistance to platinum-based chemotherapy.[27] This result has been confirmed by a more recent study in patients with gastric cancer treated with cisplatin plus fluorouracil.[28] In this study, the levels of ERCC1 were on average 2-fold lower in responsive patients than in nonresponders. The coordinated expression of genes involved in DNA repair in normal tissue, in contrast to the uncoordinated expression in tumour tissue, is also of interest.[29]

The clinical implications of mismatch repair (MMR) are at present unclear.[30] Loss of MMR in human colon cancer cells resulted in a 2-fold increase in cisplatin resistance.[31,32] The hMLH1 protein, which is involved in the recognition of DNA damage, was expressed at a lower level (statistically significant) after platinum treatment compared with no treatment: 36% of samples from patients with ovarian carcinoma treated with cisplatin combination chemotherapy were negative for the hMLH1 subunit, compared with only 10% of samples from untreated patients.[33]

4.4 Apoptosis

Decreased ability of cells to undergo programmed cell death (apoptosis) after exposure to anticancer agents represents another type of broad-spectrum drug resistance mechanism. The p53 gene, a major player in this process, is frequently mutated in solid tumours. For example, p53 is the most frequently mutated gene in ovarian cancer (50 to 70% of patients), and 60% of NSCLC patients have p53 mutations.[34]

In fresh tumour biopsies from patients with ovarian cancer, increased p53 levels were found for patients who later appeared to be resistant to cisplatin.[35] However, conflicting data are present in the literature,[34] and it is clear that other molecules are also involved in this complex process. The relationship between p53 status and resistance to platinum compounds is unclear, although several preclinical studies indicate that mutant p53 leads to platinum resistance and resistance to DNA-damaging agents in general.[34]

5. Circumvention of Drug Resistance

Several different approaches are currently being investigated to increase the efficacy of platinum compounds. The most important are summarised in table II.

5.1 High Dose Cisplatin or Carboplatin

The use of high dose cisplatin has been attempted in several malignancies but particularly in testicular and ovarian cancer. In ovarian cancer, a randomised trial[36] in 165 patients showed that cisplatin 100 mg/m^2 was superior to 50 mg/m^2 in combination with cyclophosphamide 750 mg/m^2. This study was closed after an interim analysis showed a highly significant improvement in survival in the high dose group ($p = 0.0008$ at 2 years; relative death rate for high versus low dose = 0.52).[36] However, at longer term follow-up (median 4 years and 9 months), the difference in survival was reduced (relative death rate 0.68, $p = 0.043$). In light of long term toxicity, particularly neurotoxicity, the authors recommended a cisplatin dose of 75 mg/m^2 in further studies.[37] However, in testicular cancer, no increase in complete remission rate was shown with high dose cisplatin compared with a standard dose regimen.[38] In general, however, schedules for the treatment of testicular tumours already involve relatively high doses of cisplatin (100 mg/m^2 over 5 days).

The dose of carboplatin can be increased much more than that of cisplatin, because of its lower nonhaematological toxicity; indeed, regimens involving high dose carboplatin (at doses up to 3-fold the standard dose) plus peripheral stem cell support

Table II. Approaches to increase the efficacy of platinum compounds

Approach	Examples
Increase dose and intensity	High dose carboplatin with PSCT
	Intraperitoneal cisplatin
Combination chemotherapy	Using platinum drugs with other anticancer agents
	Using modulators of platinum resistance (see table III)
Investigate molecules that inhibit known mechanisms of platinum resistance	Drugs that prevent efflux of platinum compounds from cells
	DNA repair inhibitors
	Drugs that interfere with the glutathione system
Reduce adverse effects, allowing higher doses to be administered	Serotonin (hydroxytryptamine; 5-HT$_3$) antagonists to reduce vomiting
	BNP7787 (dimesna) to reduce renal toxicity
	Amifostine to reduce neurotoxicity
Develop more potent and less toxic platinum compounds	Oxaliplatin
Develop novel platinum compounds which are insensitive to the major mechanisms underlying intrinsic and acquired cisplatin resistance in solid tumours	ZD0473

PSCT = peripheral stem cell support

Table III. Modulators of platinum resistance

Modulator	Effect
Cyclosporin	Decreased drug efflux and gene expression (*c-fos*)
Dipyridamole	Decreased drug efflux
Amphotericin B	Increased drug accumulation
Trifluoperazine	Calmodulin inhibition – increased drug uptake
Hyperthermia	Increased drug uptake and platinum-DNA adduct levels
Buthionine sulfoximine	Glutathione depletion
Aphidicolin	Decreased DNA polymerase α activity
Novobiocin	Decreased topoisomerase II activity

are in use.[39] Carboplatin in combination with paclitaxel is normally administered with dose adjustment to an AUC of 7.5 mg/ml · min. A maximum safe and effective dose of 1600 mg/m^2 has been reported for carboplatin in this setting[39] (AUC dosing to a target of 12 to 16 mg/ml · min may be preferred). Ongoing trials are comparing this high dose chemotherapy regimen (plus stem cell support) with standard treatments in ovarian cancer.

5.2 Localised Administration

The feasibility of intra-arterial or intracavitary administration of high dose cisplatin (100 mg/m^2) has been demonstrated. Higher response rates have been achieved with intra-arterial cisplatin than with intravenous cisplatin in solid tumours, such as head and neck squamous cell carcinomas[40] and brain metastases.[41] A recent randomised trial demonstrated that intraperitoneal cisplatin administration was superior to intravenous administration in combination with intravenous cyclophosphamide in ovarian cancer patients.[42] The median survival duration was significantly longer in patients receiving intraperitoneal cisplatin (49 months) compared with those receiving intravenous cisplatin (41 months) [p = 0.02].[42] However, given the technical difficulties involved in intraperitoneal administration, this route is not often used in the treatment of this disease.

5.3 Improved Delivery

Liposomal formulations may increase the uptake of cisplatin, and such formulations are under clinical investigation. Sterically stabilised liposomes can improve drug delivery, as it has been shown that liposomes extravasate and localise in the extracellular space of tumours in animal models.[43] Administration of liposomal cisplatin resulted in prolonged circulation time, increased tumour platinum disposition, and significantly improved antitumour effect compared with standard cisplatin administration in a preclinical tumour model.[44]

5.4 Modulation

There are a number of biochemical modulators of cisplatin resistance (table III). These include the combination of cisplatin with cyclosporin to modulate (improve) drug transport by reducing drug efflux. Cyclosporin has also been shown to decrease the resistance of cancer cells to cisplatin by suppressing cisplatin-induced oncogene (*c-fos*) expression.[45] Cisplatin and cyclosporin A had minimal activity in 26 patients with recurrent and platinum-resistant ovarian cancer.[46]

Glutathione-platinum complexes are actively transported out of cells, which could contribute to drug efflux. In addition, glutathione may directly or indirectly participate in DNA repair.[47,48] Depletion of glutathione levels by buthionine sulfoximine (BSO) inhibits DNA repair in cisplatin-resistant cell lines.[48] The limited availability of BSO for clinical trials has so far impeded relevant attempts to revert cisplatin resistance. Inhibitors of glutathione synthesis are also under investigation,[49] as are inhibitors of repair processes (e.g. aphidicolin, a DNA polymerase α inhibitor, and novobiocin, a topoisomerase II inhibitor).

5.5 Reduction of Adverse Effects

Reducing the toxicity of chemotherapy can allow higher doses to be administered, which may contribute to prevention of resistance. Approaches to reducing the adverse effects of platinum-based therapy, and toxicity issues relating to currently used platinum drugs, are discussed in more detail in the accompanying paper by O'Dwyer.[50]

The introduction of serotonin (hydroxytryptamine; 5-HT_3) antagonists to treat and prevent drug-induced emesis has provided a major improvement in the administration of cisplatin and several other anticancer drugs. The value of thiosulfate to reduce nonhaematological toxicity of intracavitary cisplatin has also been demonstrated.[51] However, the concern that thiosulfate may also reduce the antitumour effect of cisplatin has greatly limited its use.

5.6 New Agents and Combinations

Although carboplatin has replaced cisplatin in the treatment of most solid tumours, the possibility of developing novel platinum analogues with a different spectrum of activity has stimulated research.[52] New platinums which have a low level of cross-resistance with cisplatin or carboplatin have been developed (e.g. oxaliplatin) and this remains an area in which further improvement can be expected (see the accompanying paper by Judson and Kelland.[2])

Combinations of platinum agents with DNA repair inhibitors such as cytarabine, hydroxyurea, gemcitabine and arabinosyl-2-fluoroadenine have all been shown to work synergistically in experimental models.[53] The combination of gemcitabine with cisplatin has also shown synergy in patients with NSCLC.[54] *In vitro*, exposure of breast and ovarian tumour cells to cisplatin in combination with a monoclonal antibody against the c-erb-2 protein resulted in a significantly enhanced cytotoxic effect.[55] Phase II trials of this combination in breast cancer gave higher objective clinical response rates than those reported for cisplatin alone.[56]

6. Discussion

Cisplatin/carboplatin resistance remains a major problem for the treatment of patients with many tumour types. These include patients who have a high intrinsic resistance to cisplatin/carboplatin, such as those with NSCLC and colorectal cancer, and patients who are initially sensitive but acquire resistance, such as those with SCLC and ovarian cancer. More than 95% of patients with SCLC relapse after initial treatment because of acquired drug resistance, resulting in extremely low 5-year survival rates. Although much of our understanding of resistance is based on preclinical studies, much effort is now being made in characterising determinants of resistance in patients.

Although several mechanisms of resistance to platinum chemotherapy have been defined in *in vitro* models, corresponding studies in patients have not been conclusive. Transport defects may have a role in platinum resistance, but convincing studies need to be performed using tumours from patients. Several studies using clinical samples have suggested a role for glutathione in the development of resistance in patients, and this has led to attempts to reduce glutathione synthesis in clinical trials. More recently, studies on the role of DNA repair as a resistance mechanism for platinum and other anticancer compounds have been performed using clinical material. Measurement of levels of DNA-platinum adducts appears to be a good predictor of response to platinum compounds. Furthermore, data are now available to indicate that certain genes involved in DNA repair may also be important in the resistance of solid tumours to platinum compounds. However, confirmatory studies are necessary. Various attempts have been made in the clinic to reduce resistance to platinum compounds, including improving the tolerability of chemotherapy (so higher doses can be used), modulating drug resistance mechanisms and new or improved delivery methods. Some of these methods have entered common clinical practice (e.g. antiemetic therapy), whereas others remain largely investigational at present (e.g. drug resistance mod-

ulation) or are difficult to implement routinely (e.g. intraperitoneal chemotherapy).

Further understanding of resistance mechanisms *in vivo* will facilitate prediction of clinical response to chemotherapy and may identify novel treatment strategies to overcome resistance mechanisms. Resulting new treatment strategies have the potential to significantly affect the outcome of patients with both inherent and acquired cisplatin/carboplatin resistance in many tumour types.

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