OXALIPLATIN FOR THE TREATMENT OF CISPLATIN-RESISTANT CANCER: A SYSTEMATIC REVIEW

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Abstract

Oxaliplatin is widely regarded as being active in cisplatin-resistant cancer. We undertook a systematic review of the literature to identify, describe and critique the clinical and pre-clinical evidence for the use of oxaliplatin in patients with "cisplatin-resistant" cancer. We identified 25 pre-clinical cell models of platinum resistance and 24 clinical trials reporting oxaliplatin based salvage therapy for cisplatin-resistant cancer. The pre-clinical data suggests that there is cross-resistance between cisplatin and oxaliplatin in low-level resistance models. In models with high level resistance (>10 fold) there is less cross resistance between cisplatin and oxaliplatin, which may be a reason why oxaliplatin is thought to be active in cisplatin-resistant cancer. In clinical trials where oxaliplatin has been used as part of salvage therapy for patients who have failed cisplatin or carboplatin combination chemotherapy, there was a much lower response rate in patients with platinum-refractory or resistant cancers compared to platinum-sensitive cancers. This suggests that there may be cross-resistance between cisplatin and oxaliplatin in the clinic. Oxaliplatin as a single agent had a poor response rate in cisplatin refractory and resistant cancer. Oxaliplatin performed better in combination with other agents for the treatment of platinum resistant/refractory cancer suggesting that the benefit of oxaliplatin may lie in its more favourable toxicity and ability to be combined with other drugs rather than an underlying activity in cisplatin resistance. Oxaliplatin therefore should not be considered broadly active in cisplatin-resistant cancer.

Introduction

The anti-proliferative properties of cisplatin were first observed in the 1960s. The first cancer patient received cisplatin in April 1971. Cisplatin quickly progressed through clinical trials becoming the first platinum compound approved for cancer therapy and has been used widely in cancer patients since 1978 [1]. Cisplatin is used in combination with other drugs to treat a variety of solid tumours and is one of the most successful chemotherapeutics used today. However, for those patients who do not respond to first line treatment or those who relapse with resistant disease, the prognosis is very poor [2]. The past 30 years have seen extensive research into the mechanism of action of cisplatin, the development of new platinum drugs and research into the mechanisms of platinum drug resistance.

Many other platinum drugs have been developed in an attempt to improve on cisplatin. Oxaliplatin is part of the 'dach' family of platinum compounds. This group of platinum compounds were first synthesised in 1972 by substituting the amine radicals of cisplatin with a 'dach' radial [3]. The prototypes of this group showed promising anti-tumour activity but low solubility in water, limiting their potential use in the clinic. Modifications to improve water solubility were made and oxaliplatin was first synthesised in the late 1970s. Oxaliplatin demonstrated both aqueous solubility and anti-tumour activity [4]. Oxaliplatin was shown to have activity against colon cancer *in vitro* [4] and is now used as a treatment for colon cancer in combination with 5-fluorouracil [5,6]. Oxaliplatin is a better tolerated chemotherapeutic than cisplatin, while both cause neurotoxicity, the toxicity of oxaliplatin is more rapidly reversible [7,8].

Oxaliplatin has been widely regarded as potentially useful for the treatment of cisplatin-resistant cancer. Numerous clinical trials have been published using oxaliplatin as part of salvage therapy for cisplatin-resistant tumours. The pre-clinical evidence cited by these clinical studies for oxaliplatin's activity in cisplatin-resistant cancer comes in general from studies of highly cisplatin-resistant cell lines with low-level oxaliplatin resistance [9,10] or review articles summarising these findings and oxaliplatin in general [11,12]. While highly resistant models are useful to understand the possible mechanisms of resistance, drug resistance in the clinical setting typically

occurs at lower levels of resistance [13,14] and may therefore involve different mechanisms of resistance.

Other pre-clinical data cited as evidence of oxaliplatin's activity in cisplatin resistant cancer is the differential activity of cisplatin and oxaliplatin in the National Cancer Institute's panel of 60 cell lines [4,15]. Oxaliplatin shows activity in colon carcinoma whereas cisplatin does not. Although these studies have been used to suggest a different profile of cross resistance between the two compounds, they only demonstrate that colon carcinoma cells are more sensitive to oxaliplatin and do not shed any light on the pattern of cross resistance between the two compounds in resistant cancers or other types of cancer.

Oxaliplatin has been thought to have differing activity to cisplatin due to structural differences between the two molecules, yet both bind to and create adducts in GC rich areas of the DNA strand. There are many mechanisms by which cancer cells acquire resistance to platinum drugs, many of which have been characterised in resistant cell models. Mechanisms of platinum resistance common to both drugs include increased cellular glutathione leading to increased detoxification [16,17] or decreased accumulation of the drug within the cell [18,17] yet some models have neither of these mechanisms [19]. The activity of oxaliplatin in some cisplatin-resistant cell lines is thought to be due to DNA repair or damage recognition processes that discriminate between cisplatin and oxaliplatin adducts. A loss of mismatch repair increases resistance to cisplatin adducts, but has no effect on oxaliplatin adducts in cell lines [20]. However, this relationship remains to be confirmed in the clinic where studies show decreases in mismatch repair genes as prognostic of both increased [21] and decreased survival [22] in response to cisplatin based therapy. Mismatch repair genes have not as yet been examined in the clinic in response to oxaliplatin therapy.

We undertook this systematic review to identify, describe and critique the clinical and pre-clinical evidence for the use of oxaliplatin in patients with "cisplatin-resistant" cancer.

Methods

We conducted literature searches for pre-clinical and clinical studies using Medline. Review articles and articles not published in English were excluded. The reference lists in included papers were also searched for additional studies. Conference presentations and abstracts were not included. The literature searches were last updated in October 2006.

Literature searches for pre-clinical studies

Medline was searched for studies describing the cross-resistance between cisplatin and oxaliplatin in platinum-resistant cell lines using 'cisplatin', 'oxaliplatin', 'cross resistance', 'cross resistant', 'resistant', 'resistance' and 'cell line' as keywords. Resistance studies looking at a panel of cancer cell lines and the relative resistance between them were excluded, as these studies examine innate platinum resistance and not resistance developed from chemotherapy. Resistant cell lines resulting from transfection of cells were also excluded. Resistant cell lines developed using multiple drugs were also excluded, as this would introduce other factors to the cross resistance analysis between cisplatin and oxaliplatin. In some cases the same platinum-resistant cell line has been published with cisplatin and oxaliplatin cross resistance data in multiple publications. In this case the key publication has been listed in the table.

Literature searches for clinical studies

Medline was searched for all controlled clinical trials using oxaliplatin alone or in combination as treatment for patients who had previously received cisplatin or carboplatin based chemotherapy. 'Oxaliplatin', 'cisplatin' and 'platinum' were used as keywords and studies were limited to any clinical trial type. Studies using oxaliplatin as first line therapy were excluded. Studies where patients had no prior treatment with cisplatin or carboplatin were excluded. Studies including both cisplatin pre-treated and chemotherapy naïve patients were eligible as long as the results for platinum pre-treated patients were reported separately to allow data extraction.

Cisplatin and oxaliplatin resistance in pre-clinical studies

The cellular models of platinum resistance can be divided into three groups. The first contain cell lines developed from patients before and after chemotherapy [13,14]. The platinum sensitivity of these paired cell lines is usually determined by exposing them to a range of platinum concentrations and assessing cell viability with either an MTT or clonogenic assay. The IC_{50} (drug concentration causing 50% growth inhibition) for these paired cell lines can be used to determine the increase in resistance known as fold resistance by the following equation:-

Fold Resistance = IC_{50} of Platinum Resistant Cell Line / IC_{50} of Parental Cell Line

These studies have found that drug resistance in this clinical setting typically produces resistance of 2 to 3 fold [13,14].

The second group contains those cell lines developed in a clinically relevant way with doses of 1-10 μg/ml as determined by pharmacokinetic studies [23,24]. The scheduling of treatments may also be important since continuous exposure to drug is likely to produce higher levels of resistance as it does not mimic clinical therapy which is delivered in a pulsed manner with cycles of treatment. The third group contains the highly drug resistant models. Although these are valuable models for studying potential resistance mechanisms, they are less appropriate to study the activity of oxaliplatin at clinical levels of cisplatin resistance.

The literature search for models of acquired platinum resistance which report cross resistance data for both cisplatin and oxaliplatin identified 25 platinum-resistant cell lines (Table 1). The majority of these cell lines are from the third group of cell models with high levels of resistance. The major mechanisms of resistance to platinum for each cell line in Table 1 is also listed. The resistance mechanism was not determined for some of the cell lines listed as most of these studies were aimed at showing a differential activity between cisplatin and oxaliplatin rather than determining the mechanisms of platinum resistance.

Table 1 -Cell Lines With Acquired Platinum Drug Resistance – Fold Resistance Data for Cisplatin and Oxaliplatin

	Cell Line	Cancer	Treatment Dose and Strategy	Cis Fold	Ox Fold	Resistance Mechanism	Reference
Cisplatin	A431/Pt	Cervical	Continuous 0.1 μg/ml – 1 μg/ml	2.6	0.96	↓Acc (Cis), ↓Adducts (Cis), ↓MSH2	[25,26]
	KB-3-1/KCP4	Epidermoid	Continuous 7 μg/ml	51.3	94.5	↑GSH ↓Acc (Cis), ↑NER, ↓MSH6	[16]
	H12DDP	Germ Cell	Unknown dose Pulsed exposure over 49 weeks	8.0	2.0	ND	[9]
	P388/DDP	Leukemia*	Single Dose 6-8 mg/kg	7.0	8.0	ND	[27]
	L1210/DDP	Leukemia*	Single Dose 6-8 mg/kg	40.0	1.0	↑Replicative bypass of adducts (Cis)	[27,28]
	PC-9/CDDP	NSCLC	15 months 0.5 μg/ml	18.3	5.1	ND	[10]
	PC-14/CDDP	NSCLC	15 months 1.5 μg/ml	7.7	2.3	ND	[10]
	A2780-E(80)	Ovarian	Continuous 0.075 μg/ml -24 μg/ml	92.0	4.7	↓Acc(Cis and Ox)	[4]
	KB CP(20)	Ovarian	Continuous 0.075 μg/ml - 6 μg/ml	78.0	2.7	↓Acc(Cis and Ox)	[4]
	A2780/CP	Ovarian	Unclear from previous literature	10.9	2.0	↓Acc(Cis and Ox), ↑DNA Repair	[29]
	SKOV3-cis	Ovarian	Continuous stepwise to 20 μg/ml	4.0	5.3	↓Acc(Cis), ↓P-gp	[18]
	A2780-cis	Ovarian	Continuous stepwise to 20 μg/ml	3.0	20.0	↓Acc(Cis), ↑P-gp	[18]
	H69CIS200	SCLC	8 4-day pulses 0.2 μg/ml	1.7	1.6	No change GSH or Acc	[19]
	(SCLC1)SR-2	SCLC	5 ng/ml 24 hour pulses then continuous 0.1 μg/ml	16.0	1.0	Increase in mutated MRP4	[30]
Oxaliplatin	HCT116/R1	Colon	Continuous stepwise to 1.99 μg/ml	2.1	27.8	ND	[31]
	HCT116/R2	Colon	Continuous stepwise to 4 μg/ml	2.9	68.4	↓ pro-apoptotic Bax	[31]
	HCT116oxaliR	Colon	Pulsed 0.051 – 0.103 μg/ml	0.8	15.8	No change GSH or Pt Acc	[32]
	HT29oxaliR	Colon	Pulsed 0.131 – 0.262 μg/ml	0.6	13.3	No change GSH or Pt Acc	[32]
	A2780/C25	Ovarian	Continuous 0.04 μg/ml – 9.93 μg/ml	5.1	8.4	↓Acc (Cis and Ox), ↑GSH	[29,17]
	CH1oxaliR	Ovarian	Pulsed 0.079 – 0.159 μg/ml	3.9	3.0	No change GSH or Pt Acc	[32]
	A2780/C10	Ovarian	Continuous 0.04 μg/ml – 3.97 μg/ml	3.0	18.0	↑GSH	[33,17]
	A2780oxaliR	Ovarian	Pulsed 0.030-0.060 μg/ml	1.2	3.7	No change GSH or Pt Acc	[32]
	H69OX400	SCLC	8 4-day pulses 0.4 μg/ml	1.8	1.8	No change GSH or Acc	[19]
Carboplatin	SKOV3-car	Ovarian	Continuous stepwise to 100 μg/ml	1.5	4.0	↓Accumulation(Car), ↓P-gp	[18]
	A2780-car	Ovarian	Continuous stepwise to 100 μg/ml	4.0	12.5	↓Acc(Car), ↑P-gp	[18]

Acc – accumulation, Car – carboplatin, Cis – cisplatin, GSH – glutathione, ND – Not Determined, NER – nucleotide excision repair, NSCLC – non-small cell lung cancer, MRP4 – multidrug resistance associated protein 4, Ox – oxaliplatin, P-gp – P-glycoprotein, Pt – Platinum, Tax - taxol. * Murine cells.

For each cell line in Table 1 the fold oxaliplatin resistance was plotted against the fold cisplatin resistance, allowing an analysis of the pattern of cross resistance between the two compounds (Figure 1). The definition of cross resistance is a matter of debate in the literature. Some studies consider two drugs cross-resistant only if a similar level of resistance is observed. For the purposes of this review we have defined cross resistance between cisplatin and oxaliplatin as greater than or equal to 2-fold resistance to both drugs. This definition is therefore based on what would be clinically observed as cross resistance.

Figure 1 shows that the majority of models of acquired platinum resistance are cross-resistant to both cisplatin and oxaliplatin having at least 2-fold resistance to both drugs. The lower level resistant models, below 10-fold, tend to be cross-resistant to a similar level to both drugs. However, the higher level resistant models, above 10-fold indicated by grey shading, are highly resistant to their selecting drug and then exhibit a lower level of resistance to the other drug. This suggests that a common mechanism of low-level resistance to both cisplatin and oxaliplatin develops at clinical levels of drug treatment. Whereas the resistance mechanisms that develop at higher drug concentrations are likely to be more specific for the selecting drug. Figure 1 also shows that there is a limited number of clinically relevant models of cisplatin and oxaliplatin resistance, as most are well in excess of 2 to 3-fold.

The cited evidence for the activity of oxaliplatin in cisplatin-resistant cancers comes from highly cisplatin-resistant cell models, where there is above 10-fold resistance to cisplatin and below 10-fold resistance to oxaliplatin [4,29,10] (indicated in grey in Figure 1). However Figure 1 shows that the reverse is also true; where there is greater than 10-fold resistance to oxaliplatin there is less than 10-fold resistance to cisplatin [33,18]. This suggests that in high level drug resistance to either cisplatin or oxaliplatin there will be limited activity to the other drug. Furthermore, if the same degree of cross resistance occurred at high and low drug concentrations it is likely that more than one highly cross resistant cell line would have been found in the systematic review process. The only highly cross resistant cell line found was the KB-3-1/KCP4 cells which were 51.3-fold resistant to cisplatin and 94.5-fold resistant to oxaliplatin [16].

Interestingly, two oxaliplatin-resistant colon carcinoma cell lines HCT116oxaliR and HT29oxaliR, shown in Figure 1, have become hypersensitive to cisplatin with a fold resistance for cisplatin of less than 1 [32]. This finding may relate to oxaliplatin's unique activity in colon carcinoma [4]; however, this hypersensitivity is not the case in all oxaliplatin resistant colon carcinomas found in the systematic review as HCT116/R1 and HCT116/R2 show low-level cisplatin resistance [31]. This suggests that cisplatin may have activity in oxaliplatin-resistant colon cancer. Further studies could be undertaken to examine this, although the clinical utility of cisplatin following oxaliplatin is likely to be low, due to cisplatin's neurotoxicity [34].

Oxaliplatin shows a lower level of cross resistance in the majority of highly cisplatin-resistant cells (Figure 1). This does not represent an increase in activity in cisplatin resistance as this would be demonstrated by cell lines becoming hypersensitive to oxaliplatin which was not the case in the vast majority of cell lines found. Cisplatin and oxaliplatin-resistant cell lines are often hypersensitive to other non-platinum containing chemotherapeutics such as paclitaxel and taxotere [19,35]. Paclitaxel has also shown promising results in the treatment of patients resistant to cisplatin [36,37,38]. Therefore, paclitaxel and taxotere appear to have increased activity in platinum-resistant cancer, although the mechanism of this activity is not fully understood. This is quite different to the pattern observed for the activity of oxaliplatin in cisplatin-resistant cells.

Oxaliplatin in the treatment of patients with cisplatin-resistant cancers

Oxaliplatin has been used as a single agent and in combination with other chemotherapeutics for the treatment of cancers that are unresponsive to cisplatin or carboplatin based combination chemotherapy. Clinical platinum resistance is variably defined in the clinic and as such it is difficult to make comparisons of treatment activity between trials. The definition of platinum resistance is more critical in highly platinum sensitive diseases such as ovarian and testicular cancer. Many trialists define primary platinum resistance as disease progression during first-line treatment with a platinum containing regimen. However there is less agreement for secondary platinum resistance or potentially platinum sensitive patients, where it is common to use a platinum free interval, e.g. At least 6 months, to try to define patients as "potentially

sensitive". Markman [39] describes a classification system to assist patient selection in second-line ovarian cancer studies. The relevance of this system to other cancers is however dependent on the innate platinum sensitivity of the underlying tumour type.

Cisplatin combination chemotherapy is the cornerstone of treatment of ovarian and testicular carcinomas. Testicular carcinomas are exquisitely sensitive to cisplatin which cures > 80% of patients, however when resistance does occur the prognosis is usually poor [40]. Similarly initial platinum responsiveness in ovarian cancer is high, but 80% of patients will eventually relapse and be cisplatin resistant [41].

Interpreting drug activity after platinum treatment even in these two highly platinum sensitive cancer types is further complicated by the common use of platinum in combination with other agents. Here, resistance to combination chemotherapy involves more than just resistance to platinum agents and the response to second line platinum containing regimens is influenced by the non-platinum agents used in both first and second line therapy.

In our search of the literature for published controlled clinical trials describing the activity of oxaliplatin either as a single agent or in combination in the treatment of patients having previously received cisplatin based combination chemotherapy, we identified 24 studies. Using Markman's criteria as a template, the patients within these studies were classified into five groups according to the following definitions.

A) Platinum Refractory – Progression of disease or failure to achieve a partial response during last platinum based combination chemotherapy.
B) Platinum Resistant – Progression of disease within 6 months after platinum based combination chemotherapy.
C) Platinum Sensitive – Progression of disease greater than 6 months after platinum based combination chemotherapy.
D) Non-Platinum Refractory – Patients who do not progress during platinum therapy but their individual time of disease progression after platinum treatment is not itemised in the study. These patients can therefore not be classified as platinum resistant (B) or platinum sensitive (C).

E) Unclassified – Patients who had been previously treated with platinum chemotherapy but where there was not enough information to classify in A, B, C or D.

Tables 2 and 3 summarise the results on patients from clinical trials which have used oxaliplatin as a single agent and in combination respectively for the treatment of patients who have previously received cisplatin or carboplatin based chemotherapy. Patients from each study have been categorised as group A-E according to the above definitions. The pooled response rate (RR) of patients grouped by their platinum resistance status in 460 ovarian and 75 testicular cancer patients is presented in Figure 2. Other cancer types found in the systematic review included, bladder, cervical, gastric, mesothelioma and NSCLC. However, only one study was found for each of these cancer types.

Table 2 – Single agent oxaliplatin in platinum pre-treated cancer

Cancer	Treatment Regimen	Respondents	Study Criteria for Platinum Resistance	Reference
Bladder	Oxaliplatin 130 mg/m^2 every 21 days	B) 0/8 platinum resistant C) 1/10 platinum sensitive	Resistance defined as progressive disease within 6 months of a platinum regimen	[15]
Cervical	Oxaliplatin 130 mg/m^2 every 21 days	B) 0/15 platinum resistant C) 2/9 platinum sensitive	Resistance defined as progressive disease within 6 months of a platinum regimen	[42]
Ovarian	Oxaliplatin 130 mg/m^2 every 21 days	B)1/23 platinum resistant	Resistance defined as progressive disease within 6 months of a platinum regimen	[43]
Ovarian	Oxaliplatin 130 mg/m^2 every 21 days	A) 1/18 platinum refractory C) 10/16 platinum sensitive D) 0/8 non-platinum refractory	Resistance defined by Markman's Criteria	[41]
Ovarian	Oxaliplatin 130 mg/m^2 every 21 days	B) 2/32 platinum resistant C) 5/13 platinum sensitive	Resistance defined as progressive disease within 6 months of a platinum regimen	[44]
Ovarian	Oxaliplatin median dose of 100 mg/m^2 every 21 days	A) 3/18 platinum refractory D) 6/13 non-platinum refractory	Resistance defined by Markman's Criteria	[45]
Testicular	Oxaliplatin 130 mg/m^2 every 14 days or 60 mg/m^2 every 7 days for 3 cycles	A) 0/7 platinum refractory B) 6/20 platinum resistant E) 0/5 unclassified	Resistance defined as progressive disease within 4 weeks of a platinum regimen or absolute defined as failure during therapy	[46]

Table 3 - Oxaliplatin combination chemotherapy in platinum pre-treated cancer

Cancer	Treatment Regimen	Respondents	Study Criteria for Platinum Resistance/Sensitivity	Reference
Gastric	Oxaliplatin 85mg/m^2 and 5-FU 400 mg/m^2 Day 1 and Leucovorin 150 mg/m^2 and 2.4-3 g/m^2 Day 3 every 14 days	A) 6/20 platinum refractory D) 0/6 non-platinum refractory	Resistance defined as progression during platinum therapy	[47]
Mesothelioma	Oxaliplatin 130 mg/m^2 and Raltitrexed 3 mg/m^2 every 21 days	E) 3/15 Unclassified	Not defined by study	[48]
Ovarian	Oxaliplatin 130 mg/m^2 and Cisplatin 100 mg/m^2 every 21 days	A) 3/13 Platinum refractory D) 7/12 non-platinum refractory	Resistance defined by Markman's Criteria	[49]
Ovarian	Taxol 135 mg/m^2 Day 1, Oxaliplatin 100 mg/m^2 and Cisplatin 75 mg/m^2 Day 2, CGSF 5µg/kg/d Days 6-13 every 21 days	C) 6/7 platinum sensitive	Sensitivity defined as > 12 months with progression free disease	[50]
Ovarian	Oxaliplatin 85 mg/m^2, 5-FU 400 mg/m^2 and Leucovorin 200 mg/m^2 Day1 and 5-FU 600 mg/m^2 infusion Day 1 and 2 every 21 days	B) 11/38 platinum resistant	Resistance defined as progressive disease within 6 months of a platinum regimen	[51]
Ovarian	Oxaliplatin 100-130 mg/m^2 and Taxol 135-175 mg/m^2 every 21-28 days	A) 6/18 platinum refractory D) 9/13 non-platinum refractory	Resistance defined by Markman's Criteria	[52]
Ovarian	Oxaliplatin 130 mg/m^2 and Taxol 175 mg/m^2 every 21 days	C) 79/98 platinum sensitive	Sensitivity defined as 6 months with progression free disease	[53]
Ovarian	Oxaliplatin 70 mg/m^2 and Liposomal Doxorubicin 30-35 mg/m^2 every 28 days	B) 4/14 platinum resistant C) 18/27 platinum sensitive	Resistance defined as progressive disease within 6 months of a platinum regimen	[54]
Ovarian	Oxaliplatin 85 mg/m^2 Day 1, 5-FU 370 mg/m^2 and Leucovorin 30 mg/m^2 Days 1 and 8 – repeated every 14 days	A) 0/2 platinum refractory B) 3/12 platinum resistant C) 3/6 platinum sensitive	Resistance defined as progressive disease within 6 months of a platinum regimen. Refractory defined as progression during platinum therapy	[55]
Ovarian	Oxaliplatin 85 mg/m^2, Liposomal Doxorubicin 30 mg/m^2 and Cyclophosphamide 750 mg/m^2 every 21 days	B) 10/27 platinum resistant C) 8/12 platinum sensitive	Resistance defined as progressive disease within 6 months of a platinum regimen.	[56]
Ovarian	Oxaliplatin 85 mg/m^2 Day 1and Gemcitabine 1000 mg/m^2 Day 1 and 8 every 21 days	A) 0/3 platinum refractory B) 5/17 platinum resistant	Resistance defined as progressive disease within 6 months of a platinum regimen. Refractory defined as progression during platinum therapy	[57]
Ovarian and NSCLC	Oxaliplatin 70-100 mg/m^2 and Gemcitabine 800-1500 mg/m^2 every 14 days	B) 3/4 platinum resistant	Resistance defined as progressive disease within 6 months of a platinum regimen	[58]
Testicular	Oxaliplatin 85 mg/m^2 Day 1and Gemcitabine	B) 9/28 platinum resistant	Resistance defined as progressive disease within	[59]

	1000 mg/m^2 Day 1 and 8 every 21 days		4 weeks of a platinum regimen	
Testicular	Oxaliplatin 85 mg/m^2 Day 1and Gemcitabine 1000 mg/m^2 Day 1 and 8 every 21 days	A) 2/9 platinum refractory B) 5/13 platinum resistant D) 9/13 non-platinum refractory	Resistance defined as progressive disease within 4 weeks of a platinum regimen or absolute defined as failure during therapy	[60]
Testicular	Oxaliplatin 85 mg/m^2 Days 1 and 15, Irinotecan 80 mg/m^2 Days 1, 8 and 15, prophylactic GCSF Days 3-6, 10-13 and 20-25 every 28 days	E) 7/18 unclassified	Defined as failure to achieve a durable CR to a cisplatin-based regimen time to progression not itemised	[61]
Testicular	Oxaliplatin 130 mg/m^2 and Cisplatin 100 mg/m^2 every 21-28 days with up to four other drugs in combination	A) 4/9 platinum refractory B) 0/1 platinum resistant C) 2/2 platinum sensitive	Resistance defined as progressive disease during last platinum based regimen	[62]
Testicular	Oxaliplatin 80 mg/m^2, Taxol 70 mg/m^2 and Gemcitabine 800 mg/m^2 Days 1, 8 and 15 every 28 days	E) 1/7 unclassified	Failure to respond to a platinum containing regimen time to progression not itemised	[63]

The pooled RR for single agent oxaliplatin in platinum refractory (n = 36, RR 11%) and platinum-resistant (n = 55, RR 5.5 %) ovarian cancer patients was similarly low (Figure 2i). However, the pooled RR was much higher for platinum-sensitive ovarian cancer patients (n = 29, RR = 51.7%). This observation suggests that in ovarian cancer, oxaliplatin as a single agent is not significantly active in cisplatin-resistant or refractory patients. Interpretation of the higher RR in the non-platinum refractory classification (n = 21, RR 28.6%) is confounded by the potential for misclassification of platinum-resistant versus platinum-sensitive patients due to lack of detail in the studies from which their data was extracted. However, the RR of the non-platinum refractory patients is higher than the platinum refractory patients. The RR of the non-platinum refractory patients also falls between the RR for platinum-resistant and platinum-sensitive groups suggesting that there is a mixture of both groups of patients in this cohort.

Figure 2i shows that oxaliplatin when used in combination achieves a higher response rate in all four groups of ovarian cancer patients than when used as a single agent. The pooled response rate of the platinum resistant (n = 108, RR = 30.55%) and refractory patients (n = 36, RR 25.0%) is similar and much lower than the platinum-sensitive patients (n=150, RR 76.0%). In the highly platinum-sensitive testicular cancers (Figure 2ii), the pooled RR for oxaliplatin combination chemotherapy was the same for platinum-refractory patients (n = 18, RR 33.3%), and platinum-resistant patients (n = 42, RR 33.3%). The response rate of platinum sensitive (n = 2, RR = 100%) and non-platinum refractory testicular cancers (n = 13, RR 69.2%) was higher but should be viewed with caution considering the low numbers of patients in these groups. In both ovarian and testicular cancer patients, the pooled RR was higher for platinum sensitive than platinum resistant or refractory patients. This suggests that oxaliplatin has less activity in cisplatin-resistant cancers.

It is difficult to determine whether oxaliplatin alone or the combination of another drug with oxaliplatin is responsible for the response seen in cisplatin pre-treated patients. This question is unlikely to be resolved by further clinical trails as oxaliplatin used in combination therapy is associated with a greater response rate (Figure 2i). From the summary of cellular models of platinum resistance (Figure 1) and clinical trials of oxaliplatin as a single agent (Table 2), it appears that oxaliplatin alone lacks

sufficient activity to overcome cisplatin resistance. However, clinical trials demonstrating a response using oxaliplatin combination therapy in platinum-resistant patients often credit oxaliplatin's lack of cross resistance for the success of treatment [59,61]. The observed benefit from oxaliplatin combination regimens may well be due to the activity of the other agent or synergy between the two agents, rather than any innate ability for oxaliplatin to overcome cisplatin resistance. Furthermore, the more favourable toxicity profile of oxaliplatin lends itself for use in second-line combination regimens more readily than does cisplatin, and as such, cisplatin is not readily evaluated in this setting, even if it might be similarly active.

There are many different mechanisms of platinum resistance as illustrated by the cell models in Table 1. Perhaps when the particular mechanism of cisplatin resistance in a relapsed patient can be diagnosed, such as the loss of mismatch repair where oxaliplatin shows differential activity to cisplatin [20], the most appropriate platinum agent for a patient could be selected. This review highlights that oxaliplatin is not active in all types of cisplatin resistance. The ability to stratify cisplatin-resistant patients as potentially oxaliplatin sensitive based on specific markers of resistance within the tumour, will lead to an improved response rate of oxaliplatin in a subgroup of patients. However, there is a need to examine the role of other non-platinum chemotherapeutics in the treatment of cisplatin-resistant cancers to combat the multiple forms of resistance. Future trials of oxaliplatin in cisplatin-resistant cancers should also integrate the study of markers of platinum resistance within the resistant tumour such as ERCC1, MSH2, MLH1, glutathione and platinum uptake to begin the shift to tailoring salvage chemotherapy to individual mechanisms of resistance. This would be similar to, and complement the pharmacogenomic approach examining germline polymorphisms in genes associated with platinum resistance with the response to firstline chemotherapy [64].

Conclusions

The conclusion that oxaliplatin is active in cisplatin-resistant cancer has in general been overstated in the literature. Oxaliplatin has some activity in highly cisplatin-resistant cell lines however cisplatin has as much activity in highly-oxaliplatin resistant cell lines. The evidence from low-level platinum resistant cell lines and the

response of patients with cisplatin-resistant cancers suggest that there is cross-resistance between cisplatin and oxaliplatin. Oxaliplatin is useful for the treatment of some cisplatin-resistant cancers when used in combination with other agents. The clinical benefit of oxaliplatin for the treatment of cisplatin-resistant cancer may lie with its more preferable toxicity profile, which allows successful combination with other agents rather than any greater activity in cisplatin-resistance.

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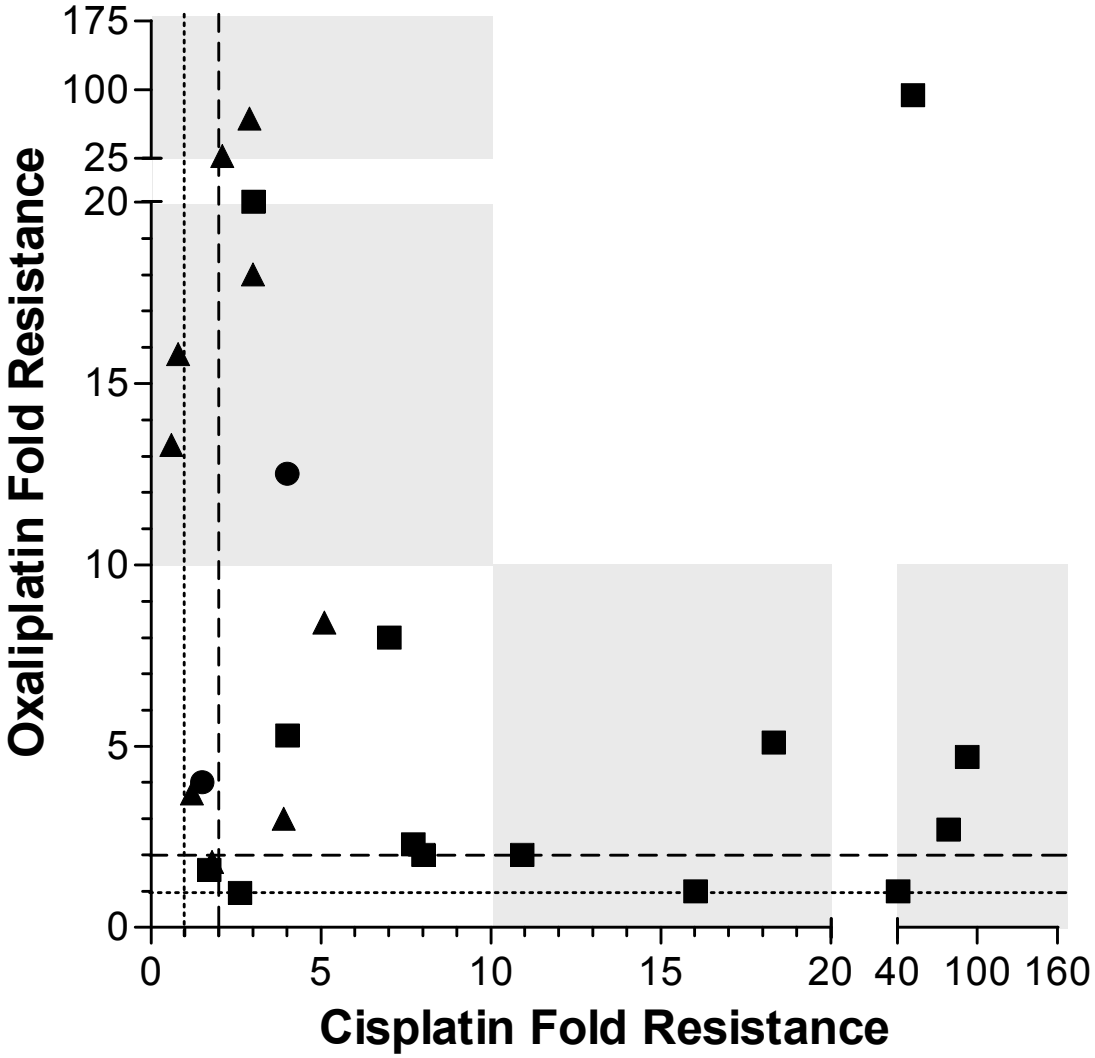

Figure 1 – Cross resistance between cisplatin and oxaliplatin in cell models of acquired platinum resistance. The fold resistance of cisplatin and oxaliplatin of each resistant cell line compared to the parental cell line it was derived from is plotted (from Table 1). Cells developed with cisplatin (■), oxaliplatin (▲) and carboplatin (●) are indicated. The dotted line (….) at 1 indicates the fold resistance of the parental cell lines. The dashed line (---) at 2 indicates the level of clinical platinum resistance.

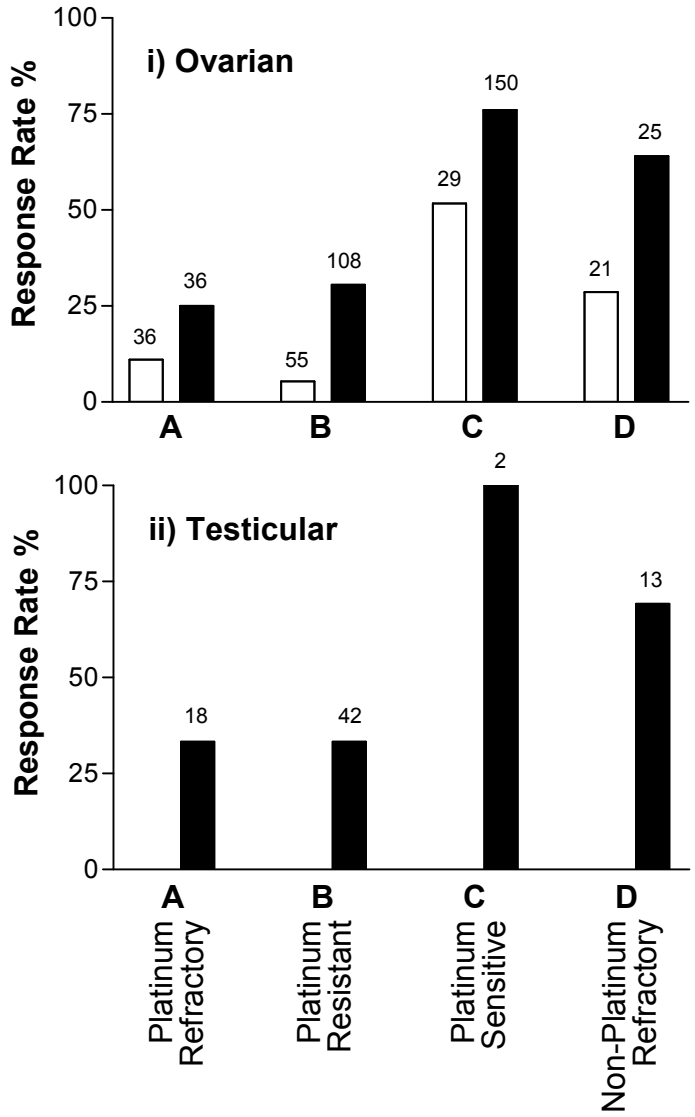

Figure 2 – Response rate of platinum pre-treated patients to oxaliplatin divided by resistance status. The pooled results for i) ovarian cancer and ii) testicular cancer are divided up into four patient groups A) Platinum refractory B) Platinum resistant C) Platinum sensitive and D) Non-platinum Refractory. The open bars are patients who received oxaliplatin as single agent (□), the closed bars are patients who received oxaliplatin combination chemotherapy (■). The number of patients pooled in each group is indicated above each bar.