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A SYSTEMATIC REVIEW OF PLATINUM AND TAXANE RESISTANCE FROM BENCH TO CLINIC: AN INVERSE RELATIONSHIP

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Abbreviated Title: Inverse relationship between platinum and taxane resistance

Keywords: Cisplatin, Carboplatin, Paclitaxel, Docetaxel, Resistance, Sensitivity, Cross-Resistance, Ovarian Cancer.
Abstract

We undertook a systematic review of the pre-clinical and clinical literature for studies investigating the relationship between platinum and taxane resistance. Medline was searched for 1) cell models of acquired drug resistance reporting platinum and taxane sensitivities and 2) clinical trials of platinum or taxane salvage therapy in ovarian cancer. 137 models of acquired drug resistance were identified. 68.1% of cisplatin-resistant cells were sensitive to paclitaxel and 66.7% of paclitaxel-resistant cells were sensitive to cisplatin. A similar inverse pattern was observed for cisplatin vs docetaxel, carboplatin vs paclitaxel and carboplatin vs docetaxel. These associations were independent of cancer type, agents used to develop resistance and reported mechanisms of resistance. 65 eligible clinical trials of paclitaxel-based salvage after platinum therapy were identified. Studies of single agent paclitaxel in platinum-resistant ovarian cancer where patients had previously recieved paclitaxel had a pooled response rate of 35.3% n=232, compared to 22% in paclitaxel naïve patients n=1918 (p<0.01 Chi-squared). Suggesting that pre-treatment with paclitaxel may improve the response of salvage paclitaxel therapy. The response rate to paclitaxel/platinum combination regimens in platinum-sensitive ovarian cancer was 79.5% n=88 compared to 49.4% n=85 for paclitaxel combined with other agents (p<0.001 Chi-squared), suggesting a positive interaction between taxanes and platinum. Therefore the inverse relationship between platinum and taxanes resistance seen in cell models is mirrored in the clinical response to these agents in ovarian cancer. An understanding of the cellular and molecular mechanisms responsible would be valuable in predicting response to salvage chemotherapy and may identify new therapeutic targets.
**Introduction**

The anti-tumour activity of cisplatin was 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. Cisplatin binds to the DNA strand hindering both DNA replication and RNA translation and eventually triggering apoptosis. Many cisplatin analogues were developed in an attempt to improve on cisplatin. Carboplatin was introduced into the clinic in 1992. Like cisplatin, carboplatin also binds to the DNA strand but in contrast it has a more favourable toxicity profile making it a popular choice in the clinic. However, cisplatin has been shown to have increased therapeutic efficacy in many tumours compared to carboplatin. Cisplatin or carboplatin are currently used as part of combination chemotherapy for the treatment of ovarian, testicular, head and neck cancers and gastro-esophageal cancers.

Paclitaxel, derived from the bark of the Pacific yew tree *Taxus brevifolia*, was first shown to have antitumour activity in 1971. All antimicrotubule agents disrupt mitosis however, paclitaxel was the first to stabilise polymerised microtubules in contrast to previous antimicrotubule agents such as vincristine and colchicine which depolymerise microtubules. The first phase I clinical trials of paclitaxel began in 1983 but were slow to progress with many paclitaxel hypersensitivity reactions reported and problems with supply of the drug. Paclitaxel is now produced in a renewable manner from plant cell culture. Concurrently a semi synthetic analogue of paclitaxel, docetaxel, was developed entering clinical trials in 1990. Paclitaxel or docetaxel are currently used as part of combination chemotherapy for the treatment of ovarian, breast and non-small cell lung cancers.

Initial responsiveness to cisplatin therapy is high, however the majority of patients ultimately relapse with resistant disease. Mechanisms of cisplatin resistance characterised in resistant cell models include, decreased cellular accumulation of drug, increased levels of glutathione, increased levels of DNA repair and increased anti-apoptotic activity.
Similarly, many patients will relapse with disease resistant to paclitaxel therapy. Paclitaxel resistance can be mediated by P-glycoprotein export decreasing the cellular accumulation\(^9\). Other mechanisms of paclitaxel resistance include altered expression or post-translational modification of \(\beta\)-tubulin, the target of paclitaxel, or other microtubule regulatory proteins. Any alteration in microtubule dynamics, paclitaxel binding sites or signalling pathways up or downstream of microtubule polymerisation can potentially mediate paclitaxel resistance\(^10\).

Due to their differing mechanisms of action platinums and taxanes are often combined in cancer therapy. However, work in cell lines suggests that alternating between the two classes of drugs may be beneficial. Paclitaxel pre-treatment has also been shown to sensitise platinum-resistant cell lines\(^{11-13}\). Work in our laboratory has also suggested that when cells become resistant to platinum they often become sensitive to taxanes\(^{14,15}\). Preliminary reading of the literature suggested that the reverse is also true i.e. that taxane-resistant cell lines can be sensitive to platinum\(^{9,16}\). We undertook this systematic review to examine the pre-clinical evidence exploring the relationship between platinum and taxane resistance, and to examine the clinical evidence for taxane activity in patients with platinum-resistant cancer and the reverse, platinum activity in taxane-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. Conference presentations and abstracts were not included. The literature searches were last updated in May 2007.

**Literature searches for pre-clinical studies**

Medline was searched for human cell lines with acquired drug resistance describing the cross-resistance between at least two of the following compounds, cisplatin, carboplatin,
paclitaxel and docetaxel in models of acquired drug resistance. The following were used as keywords, ‘cisplatin’, ‘carboplatin’, ‘taxol’, ‘paclitaxel’, ‘taxotere’, ‘docetaxel’, ‘cross resistance’, ‘cross resistant’, ‘resistant’, ‘resistance’, ‘toxicity’ and ‘cell line’. 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 developed with platinums and taxanes were the most common found but resistant cell models developed to other compounds were included if they had cross resistance data for two or more compounds of interest. Resistant cell lines resulting from transfection were excluded. The name of each cell line found was also used as a medline keyword search to find cross resistance data over multiple publications. In some cases the same resistant cell line has been published with cross resistance data in multiple publications. In this case the key publication has been referenced.

**Literature searches for clinical studies**

Medline was searched for all controlled clinical trials using paclitaxel alone or in combination as treatment for patients who had previously received cisplatin or carboplatin based chemotherapy. Medline was also searched for clinical trials using cisplatin for the treatment of patients who had previously received taxanes. ‘paclitaxel’, ‘cisplatin’, ‘carboplatin’, ‘platinum’, ‘taxane’, ‘salvage’, ‘resistant’, ‘resistance’, ‘refractory’, ‘second line’ were used as keywords and studies were limited to any clinical trial type. The reference lists in included papers were also searched for additional studies. Studies using platinum or taxanes as first line therapy were excluded. Studies where prior chemotherapy treatment was not itemised were excluded. Studies where the platinum resistance status was not defined were also excluded. Studies including both cisplatin or paclitaxel pre-treated and chemotherapy naïve patients were eligible as long as the results for pre-treated patients were reported separately to allow data extraction.

We used the pooled response rate as a measure of drug activity. The pooled response rate for each cohort described was the combined complete and partial response rates of each
study based on the published response rate, assuming a standardised measure of response was used in the study. Patients recruited earlier than 1995 were assumed to be taxane naïve as platinum/paclitaxel combination therapy was only adopted as first-line therapy for ovarian cancer after several successful trials in 1996 showed the superiority of this regimen compared to the then standard therapy of cisplatin/cyclophosphamide\textsuperscript{17,18}. This group of patients were analysed separately as there is the possibility that this group may have received prior paclitaxel salvage therapy. There was no difference in response rate or other patient characteristics between these two groups.

Statistics

Linear regressions were performed on the scatter plots of the pre-clinical data. R values were calculated to show either a positive or negative correlation. The chi-squared test was used to test for significant differences between the pooled clinical data. p values of less than 0.05 were considered significant.

Results and Discussion

Platinum and taxane resistance in pre-clinical studies

Resistant cell models are developed in the laboratory by repeatedly exposing cancer cells in culture to chemotherapy. The surviving resistant cells are then compared to the parental sensitive cells using a cell viability assay such as the MTT or clonogenic assay. The platinum and taxane sensitivity of these paired cell lines is usually determined by exposing them to a range of drug concentrations and then assessing cell viability. The IC\textsubscript{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:-

\[
\text{Fold Resistance} = \frac{\text{IC}_{50} \text{ of Resistant Cell Line}}{\text{IC}_{50} \text{ of Parental Cell Line}}
\]
The literature search for models of acquired resistance which report cross resistance data for both cisplatin and paclitaxel identified 137 cell lines \textsuperscript{9,11,13-16,19-83}. For each cell line the fold paclitaxel resistance was plotted against the fold cisplatin resistance, allowing an analysis of the pattern of cross resistance between the two compounds (Figure 1A). 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. Studies which have developed cell lines from patients before and after chemotherapy have found that drug resistance in the clinic typically produces resistance of 2 to 3 fold \textsuperscript{84,85}. For the purposes of this review we have defined cross resistance between cisplatin and paclitaxel 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. 13.9\% of cell lines found in the literature review were below 2-fold resistance to both compounds and therefore classed as non-resistant indicated with black stars in Figure 1A.

It is the minority of cell models of acquired resistance shown in Figure 1A which are cross-resistant (open circles) to both cisplatin and paclitaxel (16.8\%). The majority of cells are either non-cross resistant (grey circles 40.9\%), with no gain of resistance to the other compound, or hypersensitive (black circles 28.5\%) becoming more sensitive than the parental cancer cell line they were derived from. 71 cell lines were resistant to cisplatin, 48 of these were non-cross resistant or hypersensitive to paclitaxel (67.6\%). 69 cell lines were resistant to paclitaxel, 46 of these were non-cross resistant or hypersensitive to cisplatin (66.6\%). This suggests an inverse relationship between cisplatin and paclitaxel resistance in resistant cell models where resistance to one leads to sensitivity to the other. The resistant cell lines found in the systematic review were diverse in type of carcinoma (Figure 1B). Ovarian (45.3\%) and SCLC (21.2\%) were the most common carcinomas used to develop cell lines, however, the other 16 types of carcinoma suggest that the inverse relationship between cisplatin and paclitaxel resistance is not cell type specific and could apply to all cancers. The chemotherapeutics used to develop the resistant models were also diverse, the most common were cisplatin (37.2\%) and paclitaxel (20.4\%) (Figure 1C). The other 31 agents are diverse mechanistically.
suggesting that when cells become resistant to any agent there are two distinct paths available, one which leads to cross resistance to cisplatin and the other to paclitaxel.

The methods used to determine the IC\textsubscript{50} of the resistant models, as well as the exposure time of the toxicity assays also varied between the studies found in this systematic review. The consistency of the inverse relationship between cisplatin and paclitaxel resistance despite such experimental variability suggests that there is a fundamental molecular process involved in this relationship. We then sought to examine the resistance relationship between other platinum and taxane chemotherapy agents.

To examine if the inverse relationship between cisplatin and paclitaxel extended to other platinum and taxane drugs, the cross resistance pattern between cisplatin vs docetaxel, carboplatin vs paclitaxel and carboplatin vs docetaxel were examined. The literature search for models of acquired resistance which report cross resistance data for both cisplatin and docetaxel identified 59 cell lines\textsuperscript{14,16,19,23,30,31,43,44,49,54,58,74,75,77,80-82,86-95}. A similar inverse relationship was observed between cisplatin and docetaxel as for cisplatin and paclitaxel (Figure 2A). 20 cell lines were resistant to cisplatin, 14 of these were non-cross resistant or hypersensitive to docetaxel (70.0%). 26 cell lines were resistant to docetaxel, 20 of these were non-cross resistant or hypersensitive to cisplatin (76.9%). A similar array of cancer types and selecting agents were also found. 47 cell lines were identified for carboplatin vs paclitaxel\textsuperscript{11,14,22,24,28,30,41,42,44,52,54,56,62,67,71,72,76-79,96-107}. A similar inverse relationship was observed between carboplatin and paclitaxel (Figure 2B). 31 cell lines were resistant to carboplatin, 19 of these were non-cross resistant or hypersensitive to paclitaxel (67.6%). 18 cell lines were resistant to paclitaxel, 6 of these were non-cross resistant or hypersensitive to carboplatin (33.3%). This last percentage is unusually low compared to the other inverse relationships due to the limited number of cell lines found in the systematic review process. 20 cell lines were identified for carboplatin vs docetaxel\textsuperscript{14,23,30,44,54,77,87,89,94,97,99,100,104}. A similar inverse relationship was observed between carboplatin and docetaxel (Figure 2C). 10 cell lines were resistant to carboplatin, 6 of these were non-cross resistant or hypersensitive to docetaxel (60.0%).
9 cell lines were resistant to docetaxel, 5 of these were non-cross resistant or hypersensitive to carboplatin (55.6%).

To highlight how different the inverse relationship between platinum and taxanes is to cross-resistance between agents the pattern of cisplatin and carboplatin as well as paclitaxel and docetaxel were analysed. The literature search for models of acquired resistance which report cross resistance data for both cisplatin and carboplatin identified 98 cell lines of which 76.5% were cross resistant (Figure 3A) 11,14,23,24,28,30,41,42,44,54,62,72,76-78,87,89,94,96-98,100-103,106-135. 45 cell lines were also identified for paclitaxel and docetaxel of which 71.1% were cross resistant (Figure 3B) 14,16,19,23,30,31,43,44,54,90,74,75,77,80-82,95,99,104,136-139. Cross resistance was observed between these similar compounds over a large range of fold resistances. A large array of cancer types were represented in both these comparisons. The selecting agents used in the cell lines reporting platinum cross resistant data were predominately platinum based, cisplatin 71.4% and carboplatin 7.1%. The selecting agents in the taxane comparison were more diverse with paclitaxel and docetaxel representing 24.4 and 11.1% of cell lines respectively.

As this inverse relationship between platinum and taxanes occurs in so many resistant cell models the individual mechanisms of resistance are many and varied. The major mechanisms of cisplatin resistance in cells with a lack of cross resistance to paclitaxel include, increased glutathione 25,81 and decreased accumulation of the drug 21,24,79. However, some models have neither increased glutathione or decreased accumulation of cisplatin yet are hypersensitive to paclitaxel 14. This suggests that cisplatin-resistant cell lines are sensitive to paclitaxel irrespective of their major mechanism of platinum resistance. The ABC transporter P-glycoprotein transports paclitaxel out of a cell but does not transport cisplatin. Many of the paclitaxel-resistant cell lines, with a sensitivity to cisplatin, have increased P-glycoprotein expression leading to increased efflux of paclitaxel 9, but others do not 83. This suggests that the sensitivity to cisplatin is independent of P-glycoprotein mediated resistance, and that there is a fundamental molecular process involved in this relationship that is yet to be elucidated. An
understanding of this response could lead to improved treatment strategies for both cisplatin- and paclitaxel-resistant cancer.

Pre-treatment with a low dose of paclitaxel can also sensitispe platinum-resistant lung cancer cells to platinum treatment\textsuperscript{11-13}. These cisplatin resistant cell lines are not hypersensitive to paclitaxel, they are non-cross resistant showing the same level of resistance as the parental cell line. Maximal sensitisation was achieved with a low 10 ng/ml dose of paclitaxel, whereas a paclitaxel induces a G\textsubscript{2}/M block at doses greater than 12.5 ng/ml. The sensitisation due to paclitaxel was therefore independent of the cell cycle mediated effect of the drug\textsuperscript{12}. This suggests that other signalling pathways, independent of the cell cycle effects of paclitaxel, may be involved in the sensitisation to cisplatin treatment.

This same sensitisation effect has also been observed in platinum-resistant A2780/CP ovarian carcinoma cells with 3nM paclitaxel pre-treatment\textsuperscript{140}. Again, the A2780/CP cells are not hypersensitive to paclitaxel but non-cross resistant\textsuperscript{41}. Pre-treatment with paclitaxel therefore has the potential to render cisplatin-resistant cells sensitive to platinum therapy. This systematic review has shown that 67.6\% of cisplatin-resistant cell lines are hypersensitive or non-cross resistant to paclitaxel. The clinical challenge is to identify which patients are likely to respond to single agent paclitaxel and those who require paclitaxel pre-treatment before recommencing platinum therapy.

The success of paclitaxel pre-treatment has also been demonstrated in an animal model\textsuperscript{141}. In KF28 chemotherapy naïve cells implanted into nude mice the sequence of paclitaxel then cisplatin or the paclitaxel/cisplatin combination was superior to either agent alone or cisplatin first followed by paclitaxel. In KF13 cisplatin resistant cells in the same nude mice model, single agent paclitaxel and any paclitaxel combination regimen was superior to cisplatin treatment\textsuperscript{141}. This is what was predicted to occur from toxicity testing of the KF13 cells in vitro, the cells are 4.84 fold resistant to cisplatin but hypersensitive to paclitaxel 0.56 fold\textsuperscript{21}. The cell models summarised in this systematic review have shown that there is an inverse relationship between cisplatin and paclitaxel
resistance. The question we would now like to examine is does this pattern extend to the clinical treatment of drug-resistant cancer?

**Paclitaxel in the treatment of patients with platinum-resistant ovarian cancer**

Cisplatin combination chemotherapy is the cornerstone of treatment of ovarian carcinomas. Initial platinum responsiveness in ovarian cancer is high, but up to 80% of patients will eventually relapse and become cisplatin resistant. Clinical platinum resistance is variably defined in the clinic and as such it is difficult to make comparisons of treatment activity between trials. However, many second-line ovarian carcinoma studies use Markman’s criteria where disease progression with a platinum free interval of less than 6 months is considered platinum resistant. Paclitaxel resistance is a concept that is not clearly defined in the literature. Where paclitaxel resistance is defined it is usually defined in the same manner as platinum resistance, disease progression with a taxane-free interval of < 6 months.

Paclitaxel has been used as a single agent and in combination with other chemotherapeutics for the treatment of platinum-resistant ovarian cancer. Ovarian carcinoma was chosen for this analysis as our preliminary literature searches showed it had by far the most studies of paclitaxel salvage therapy in platinum-resistant patients. Furthermore, platinum resistance is usually clearly defined in ovarian cancer. Hence our study populations were more likely to be homogenous. Other platinum-resistant carcinomas which have been treated with paclitaxel based salvage therapy include testicular, NSCLC, urothelial, bladder and endometrial carcinomas.

Our search of the literature for paclitaxel salvage therapy in platinum-resistant ovarian carcinoma identified 98 studies. 56 studies were using single agent paclitaxel, 26 studies a paclitaxel/platinum combination and 16 studies were other paclitaxel based combination chemotherapy. In order to analyse if the inverse relationship between cisplatin and paclitaxel resistance observed in resistant cell models is apparent in clinical trials the studies were divided into two groups, paclitaxel naïve ovarian cancer or
paclitaxel pre-treated ovarian cancer. The patients from these studies were then divided into platinum resistant or platinum sensitive groups where resistance was defined as a platinum free interval of < 6 months. Those studies which did not define the platinum-free interval of their patients were excluded. Those studies which had paclitaxel both naïve and pre-treated patients and reported a combined response rate were excluded. Of the 98 studies identified in the literature search 65 were suitable for analysis. These studies were all Phase I and II controlled clinical trials.

Figure 4A is a summary of the pooled response rate for each cohort of patients divided on their platinum-resistance status and paclitaxel pre-treatment status. As expected the response rate of platinum-sensitive patients is higher than the platinum-resistant group across both paclitaxel groupings. What was unexpected was platinum-resistant patients who have previously received paclitaxel therapy respond better to single agent paclitaxel (RR 35.3% n = 232) than paclitaxel naïve patients (RR 22.7% n = 1918) (p <0.01 Chi-squared). Similarly in platinum-sensitive patients the paclitaxel pre-treated cohort (RR 57% n = 26) had a higher response rate than the paclitaxel naïve (RR 38.8% n = 520), however this was not significant due to low patient numbers. Usually if patients have received a drug and experienced disease progression, they are less likely to respond to therapy with a subsequent exposure to the same drug. Although one must be cautious in interpreting these summary findings due to the potential for biases in pooling of patients across studies, if the findings do reflect the true clinical response to these agents they suggest that initial co-treatment with platinum and paclitaxel may improve the outcome of paclitaxel salvage therapy. Paclitaxel may be acting as a response modifier, altering the kind of platinum resistance rendering the cancer sensitive to paclitaxel therapy. This hypothesis could be tested prospectively in a well designed clinical trial addressing drug sequencing.

Table 1 examines the patient characteristics from the paclitaxel naïve and pre-treated cohorts to determine if any other factor may have contributed to the unexpected higher response rate of the paclitaxel pre-treated patients. The cohorts of patients have very similar age, performance status, FIGO stage, and number of cycles of prior
chemotherapy. There was however a histological difference between the two groups, in
the paclitaxel naïve group 59% were serous adenocarcinomas whereas in the paclitaxel
pre-treated group 78% were serous adenocarcinomas. Serous histology has been shown to
be prognostic of response to paclitaxel salvage chemotherapy in platinum pre-treated
ovarian cancer \(^{153,154}\). Only 16 of the 30 studies in the paclitaxel naïve group reported
tumour histology representing 39.2% of patients, therefore the lack of data in this cohort
may be responsible for this apparent difference between the two groups. Studies which
had serous histology of 60% or less were then eliminated from this group leaving 6
studies with a combined serous histology of 70% representing 353 patients \(^{155-160}\). This
subgroup of paclitaxel naïve patients had a pooled response rate of 21% (platinum
resistant patients) and 39% (platinum sensitive patients), similar to that of the whole
paclitaxel naïve cohort. This result suggests that the higher response rate of the paclitaxel
pre-treated cohort is not explained entirely by the higher percentage of serous histology.
# Table 1 - Single Agent Paclitaxel in Platinum Pre-treated Ovarian Carcinoma

<table>
<thead>
<tr>
<th></th>
<th>Paclitaxel Naïve (2438 patients)</th>
<th>Paclitaxel Pre-treated (258 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>30 Studies</td>
<td>8 Studies</td>
</tr>
<tr>
<td><strong>Pooled Response Rate</strong></td>
<td>Platinum Resistant 436/1918 (22.7%)</td>
<td>Platinum Resistant 82/232 (35.3%)</td>
</tr>
<tr>
<td></td>
<td>Platinum Sensitive 202/520 (38.8%)</td>
<td>Platinum Sensitive 15/26 (57.7%)</td>
</tr>
<tr>
<td><strong>% Data</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>95.5%</td>
<td>84.9%</td>
</tr>
<tr>
<td>WHO Performance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Status</td>
<td>90.0%</td>
<td>47.3%</td>
</tr>
<tr>
<td></td>
<td>0 – 2 – 97%</td>
<td>0 – 2 – 97.6%</td>
</tr>
<tr>
<td></td>
<td>3+ - 3%</td>
<td>3+ - 2.3%</td>
</tr>
<tr>
<td>FIGO Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>15.0%</td>
<td>58.1%</td>
</tr>
<tr>
<td></td>
<td>Stage I-II – 7%</td>
<td>Stage I-II – 9.5%</td>
</tr>
<tr>
<td></td>
<td>Stage III-IV – 93%</td>
<td>Stage III-IV – 90.5%</td>
</tr>
<tr>
<td>Cycles Prior</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>96.6%</td>
<td>67.8%</td>
</tr>
<tr>
<td></td>
<td>1-2 Cycles – 61.8%</td>
<td>1-2 Cycles – 65.7%</td>
</tr>
<tr>
<td></td>
<td>3+ Cycles – 38.2%</td>
<td>3+ Cycles – 34.25%</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>39.2%</td>
<td>76.7%</td>
</tr>
<tr>
<td></td>
<td>Serous – 58.9%</td>
<td>Serous – 78%</td>
</tr>
<tr>
<td></td>
<td>Non Serous – 41.1%</td>
<td>Non Serous – 22%</td>
</tr>
<tr>
<td>References</td>
<td>155-182</td>
<td>156, 183-189</td>
</tr>
</tbody>
</table>

*Percentage of patients where study reported each characteristic*
The response rate of single agent paclitaxel in platinum-resistant ovarian cancer (22.7%) may seem low for a drug which appears to be non-cross resistant in the platinum-resistant cell models. However, this response rate compares favourably to the reported response rate of the potentially cross-resistant oxaliplatin in platinum-resistant ovarian cancer (9%) examined in a recent review.

Figure 4B summarises the response of ovarian cancer to salvage paclitaxel combination therapy. The studies have been divided into two groups: combination regimens which include a platinum compound and those which do not. These are further subdivided into paclitaxel naïve or pre-treated and platinum resistant or sensitive groupings. Here, the pooled response rate of paclitaxel naïve platinum-resistant patients to paclitaxel combination therapy paclitaxel/other 27.4% and paclitaxel/platinum 32% are higher compared to paclitaxel monotherapy (22.7% RR), however this difference is not significant. Interestingly, the response of paclitaxel naïve platinum-sensitive patients to platinum/paclitaxel combination therapy (79.5% n = 88) is also superior to paclitaxel combined with other agents (49.4% n = 85) (p < 0.001 Chi-squared). This result is again surprising as patients resistant to platinum would be considered to be less likely to respond to a platinum containing regimen than a non-platinum regimen. This suggests that the combination of platinum and taxanes may be additive in achieving a higher response rate in a platinum resistant cohort. However, there does not appear to be any benefit of pre-treatment with paclitaxel as observed in the response to single agent paclitaxel (Figure 4A). Table 2 examines the patient characteristics across the different cohorts. The only apparent difference is a lower percentage of serous histology in the paclitaxel/platinum cohorts (~ 60%) versus the paclitaxel/other cohorts (~70%). This difference would suggest that the paclitaxel/other cohort should have a higher response rate if serous histology was a significant predictive factor. However, the paclitaxel/platinum cohort is the group with the higher response rate. Suggesting that this response may be due a positive interaction between agents rather than any difference in patient characteristics.
### Table 2 - Combination Paclitaxel in Platinum Pre-treated Ovarian Carcinoma

<table>
<thead>
<tr>
<th>Paclitaxel Naïve</th>
<th>Paclitaxel/Other (300 patients)</th>
<th>8 Studies</th>
<th>Paclitaxel/Platinum (138 patients)</th>
<th>8 Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pooled Response Rate</strong></td>
<td>Platinum Resistant 59/215 (27.4%)</td>
<td>Platinum Sensitive 42/85 (49.4%)</td>
<td>Platinum resistant 15/47 (32%)</td>
<td>Platinum sensitive 70/88 (79.5%)</td>
</tr>
<tr>
<td>% Data*</td>
<td>% Data*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>100%</td>
<td>Weighted Mean 58.28</td>
<td>100%</td>
<td>Weighted Mean 55.92</td>
</tr>
<tr>
<td>WHO Performance Status</td>
<td>97%</td>
<td>0 – 2 – 100%</td>
<td>89.1%</td>
<td>0 – 2 – 100%</td>
</tr>
<tr>
<td></td>
<td>3+ - 0%</td>
<td></td>
<td>3+ - 0%</td>
<td></td>
</tr>
<tr>
<td>FIGO Stage</td>
<td>57.6%</td>
<td>Stage I-II – 4.6%</td>
<td>37.7%</td>
<td>Stage I-II – 18%</td>
</tr>
<tr>
<td></td>
<td>Stage III-IV – 95.4%</td>
<td></td>
<td>Stage III-IV – 82%</td>
<td></td>
</tr>
<tr>
<td>Cycles Prior Chemotherapy</td>
<td>100%</td>
<td>1-2 Cycles – 90.3%</td>
<td>100%</td>
<td>1-2 Cycles – 100%</td>
</tr>
<tr>
<td></td>
<td>3+ Cycles – 9.7%</td>
<td></td>
<td>3+ Cycles – 0%</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>47.6%</td>
<td>Serous – 70%</td>
<td>98%</td>
<td>Serous – 60%</td>
</tr>
<tr>
<td></td>
<td>Non Serous – 30%</td>
<td></td>
<td>Non Serous – 40%</td>
<td></td>
</tr>
<tr>
<td>References</td>
<td>163,170,191-196</td>
<td></td>
<td>197-204</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Paclitaxel Pre-treated</th>
<th>Paclitaxel/Other (109 patients)</th>
<th>3 Studies</th>
<th>Paclitaxel/Platinum (261 patients)</th>
<th>8 Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pooled Response Rate</strong></td>
<td>Platinum Resistant 22/100 (22%)</td>
<td>Platinum Sensitive 2/9 (22%)</td>
<td>Platinum resistant 3/8 (37.5%)</td>
<td>Platinum sensitive 197/253(77.8%)</td>
</tr>
<tr>
<td>% Data</td>
<td>% Data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>100%</td>
<td>Weighted Mean 56.66</td>
<td>76.2%</td>
<td>Weighted Mean 56.98</td>
</tr>
<tr>
<td>WHO Performance Status</td>
<td>100%</td>
<td>0 – 2 – 100%</td>
<td>50.5%</td>
<td>0 – 2 – 100%</td>
</tr>
<tr>
<td></td>
<td>3+ - 0%</td>
<td></td>
<td>3+ - 0%</td>
<td></td>
</tr>
<tr>
<td>FIGO Stage</td>
<td>15.5%</td>
<td>Stage I-II – 17.6%</td>
<td>46%</td>
<td>Stage I-II – 18%</td>
</tr>
<tr>
<td></td>
<td>Stage III-IV – 82.3%</td>
<td></td>
<td>Stage III-IV – 82%</td>
<td></td>
</tr>
<tr>
<td>Cycles Prior Chemotherapy</td>
<td>100%</td>
<td>1-2 Cycles – 100%</td>
<td>90%</td>
<td>1-2 Cycles – 96%</td>
</tr>
<tr>
<td></td>
<td>3+ Cycles – 0%</td>
<td></td>
<td>3+ Cycles – 4%</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>68.8%</td>
<td>Serous – 73%</td>
<td>72.8%</td>
<td>Serous – 61.5%</td>
</tr>
<tr>
<td></td>
<td>Non Serous – 27%</td>
<td></td>
<td>Non Serous – 38.5%</td>
<td></td>
</tr>
<tr>
<td>References</td>
<td>205-207</td>
<td></td>
<td>197,202,204,208-212</td>
<td></td>
</tr>
</tbody>
</table>

* Percentage of patients where study reported each characteristic
Platinum in the treatment of patients with taxane-resistant cancers

Taxane resistance is not discussed as widely in the literature as platinum resistance. However, a small group of studies have examined platinum salvage therapy for taxane resistant cancers. The most common carcinoma examined is ovarian, where the majority of patients have failed combination platinum/taxane therapy. There are several studies which have platinum-naïve patients receiving platinum salvage after taxane therapy but there are not enough studies from a single type of carcinoma to pool data to allow comparisons to be made.

Molecular Mechanism of Inverse Relationship between Platinum and Taxanes

From the systematic review of resistant cell models it appears that the observed inverse relationship between platinums and taxanes is independent of the currently known major mechanisms of resistance to both agents. Cisplatin is known to bind to microtubules and alter their dynamics, which may contribute to paclitaxel hypersensitivity in cisplatin resistant cell lines. Many cisplatin-resistant cell models could have alterations in tubulin or microtubule dynamics but this is not often studied. One study found that paclitaxel pre-treatment of their cisplatin-resistant cell lines increased the accumulation of cisplatin and was associated with tubulin alterations. If paclitaxel-resistant cell lines have similar tubulin alterations they may accumulate more cisplatin and become more sensitive to cisplatin treatment. KF28TX and KFr13TX paclitaxel-resistant cells have increased accumulation of cisplatin associated with cisplatin sensitivity.

Many molecular markers will be required to conclusively predict if a particular tumour is platinum or taxane sensitive. However, several markers have already been identified which could form the beginning of such a panel. DNA damaging drugs including cisplatin were found to be more active in wild-type p53 cells in the NCI-60 cancer cell line panel whereas antimitotic agents including paclitaxel were found to have limited activity. Gene polymorphism studies have also suggested that a mutation at Asn118 ERCC1 is associated with a decreased risk of platinum resistance in ovarian cancer.
panel of molecular markers for sensitivity to cisplatin/paclitaxel combination therapy comprising of IL6, Bcl-2, VEGF, ERCC1 and ABCB1 (p-glycoprotein) and 8 novel genes identified by microarray were examined in ovarian cancer cell lines and tumour samples. This study found that the novel microarray genes had a higher predictive power than that of the well characterised genes suggesting that there are many genes of unknown function which can be used as molecular markers.

Conclusions

This review article has highlighted an inverse relationship between platinum and taxane resistance. This phenomenon has been demonstrated in many resistant cell models diverse in type of carcinoma and agent used to develop resistance. This suggests that there may be a benefit in alternating between these two drugs in clinical cancer treatment. There is indirect clinical evidence to support this hypothesis as the response rate of single agent paclitaxel in platinum-resistant ovarian cancer studies is greater in patients having previously received paclitaxel. Paclitaxel combination therapy for platinum-resistant ovarian cancer is also greater when the second agent is platinum. This implies a positive interaction between platinums and taxanes when used in combination as well as in sequence.

The review of the cell lines exhibiting an inverse relationship between platinum and taxane resistance has revealed many different mechanisms of platinum and taxane resistance. This suggests that the mechanism of the inverse relationship between platinum and taxanes is independent of the major resistance mechanisms known for both compounds. If the wider phenomena of what causes the inverse resistance relationship between these compounds can also be understood, there is the potential to screen patients failing all kinds of chemotherapy to assess their potential to respond to platinum or taxane salvage therapy.

If molecular markers predicting the inverse relationship between platinum and taxanes can be identified in cell models using microarray and/or proteomic techniques, then these
have the potential to be translated to the clinic and be used to identify patients likely to respond to platinum or taxane salvage therapy. A predictive profile could then be used for individual patients to optimise their chemotherapy schedule and monitor response. An example of such an approach using pharmacogenomic drug resistance profiling is currently being explored in lung and ovarian cancer cell lines\textsuperscript{223}. A greater understanding of the molecular characteristics of responders may also identify new therapeutic targets for cancer therapy.
References


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105. NicAmhlaibh, R., Heenan, M., Cleary, I., Touhey, S., O'Loughlin, C., Daly, C. et al Altered expression of mRNAs for apoptosis-modulating proteins in a low level multidrug resistant variant of a human lung carcinoma cell line that also expresses mdr1 mRNA. *Int J Cancer* 1999; 82:368-376.


Figure 1 - Inverse relationship between cisplatin and paclitaxel resistance in cell lines. A) The fold resistance of cisplatin was plotted against the fold resistance for paclitaxel for 137 models of acquired drug resistance. The dotted line at 1 indicates the resistance of the parent cell lines. The solid line at 2 indicates the level of clinical resistance. B) Diversity of cancer type and C) Selecting agent used in the 137 models of acquired drug resistance.
Figure 2 – Inverse relationship between other platinums and taxanes in cell lines. The fold resistance of A) cisplatin vs docetaxel, B) carboplatin vs paclitaxel and C) carboplatin vs docetaxel. The dotted line at 1 indicates the resistance of the parent cell lines. The solid line at 2 indicates the level of clinical resistance.
Figure 3 – Cross Resistance between cisplatin and carboplatin and paclitaxel and docetaxel in cell lines. The fold resistance of A) cisplatin vs carboplatin and B) paclitaxel vs docetaxel. The dotted line at 1 indicates the resistance of the parent cell lines. The solid line at 2 indicates the level of clinical resistance.
Figure 4 – Pooled response rates of paclitaxel salvage therapy in ovarian carcinoma divided by platinum resistance status. A) Single agent paclitaxel divided into paclitaxel naïve or paclitaxel pre-treated patients. B) Combination paclitaxel therapy in paclitaxel naïve or pre-treated patients divided into paclitaxel/platinum combination therapy or other paclitaxel based combination therapy. The number above each bar represents the number of patients in the pooled cohort.