

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

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## 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 received 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<sup>1</sup>. 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<sup>2</sup>. 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<sup>3</sup>. 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<sup>4</sup>. 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<sup>5</sup>. Concurrently a semi synthetic analogue of paclitaxel, docetaxel, was developed entering clinical trials in 1990<sup>6</sup>. Paclitaxel or docetaxel are currently used as part of combination chemotherapy for the treatment of ovarian, breast and non-small cell lung cancers<sup>7</sup>.

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<sup>8</sup>.

Similarly, many patients will relapse with disease resistant to paclitaxel therapy. Paclitaxel resistance can be mediated by P-glycoprotein export decreasing the cellular accumulation<sup>9</sup>. 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<sup>10</sup>.

Due to their differing mechanisms of action platinum 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<sup>11-13</sup>. Work in our laboratory has also suggested that when cells become resistant to platinum they often become sensitive to taxanes<sup>14,15</sup>. Preliminary reading of the literature suggested that the reverse is also true i.e. that taxane-resistant cell lines can be sensitive to platinum<sup>9,16</sup>. 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 platinum 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<sup>17,18</sup>. 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<sub>50</sub> (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:-

$$\text{Fold Resistance} = \text{IC}_{50} \text{ of Resistant Cell Line} / \text{IC}_{50} \text{ of Parental Cell Line}$$

The literature search for models of acquired resistance which report cross resistance data for both cisplatin and paclitaxel identified 137 cell lines<sup>9,11,13-16,19-83</sup>. 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<sup>84,85</sup>. 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<sub>50</sub> 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 a 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<sup>14,16,19,23,30,31,43,44,49,54,58,74,75,77,80-82,86-95</sup>. 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<sup>11,14,22,24,28,30,41,42,44,52,54,56, 62,67,71,72,76-79,96-107</sup>. 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<sup>14,23, 30,44,54,77,87,89,94,97,99,100,104</sup>. 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)<sup>11,14,23,24,28,30,41,42,44,54,62,72,76-78,87,89,94,96-98,100-103,106-135</sup>. 45 cell lines were also identified for paclitaxel and docetaxel of which 71.1% were cross resistant (Figure 3B)<sup>14,16,19,23,30,31,43,44,54,90,74,75,77,80-82,95,99,104,136-139</sup>. 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<sup>25,81</sup> and decreased accumulation of the drug<sup>21,24,79</sup>. However, some models have neither increased glutathione or decreased accumulation of cisplatin yet are hypersensitive to paclitaxel<sup>14</sup>. 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<sup>9</sup>, but others do not<sup>83</sup>. 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 sensitise platinum-resistant lung cancer cells to platinum treatment<sup>11-13</sup>. 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<sub>2</sub>/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<sup>12</sup>. 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<sup>140</sup>. Again, the A2780/CP cells are not hypersensitive to paclitaxel but non-cross resistant<sup>41</sup>. 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<sup>141</sup>. 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<sup>141</sup>. 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<sup>21</sup>. 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<sup>142</sup>. 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<sup>143</sup> 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<sup>144-147</sup>, NSCLC<sup>148,149</sup>, urothelial<sup>150</sup>, bladder<sup>151</sup> and endometrial carcinomas<sup>152</sup>.

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<sup>153,154</sup>. 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<sup>155-160</sup>. 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**

	Paclitaxel Naïve (2438 patients) 30 Studies		Paclitaxel Pre-treated (258 patients) 8 Studies	
Pooled Response Rate	Platinum Resistant 436/1918 (22.7%) Platinum Sensitive 202/520 (38.8%)		Platinum Resistant 82/232 (35.3%) Platinum Sensitive 15/26 (57.7%)	
	% Data*		% Data*	
Age	95.5%	Weighted Mean 57.65	84.9%	Weighted Mean 61.88
WHO Performance Status	90.0%	0 – 2 – 97% 3+ - 3%	47.3%	0 – 2 – 97.6% 3+ - 2.3%
FIGO Stage	15.0%	Stage I-II – 7% Stage III-IV – 93%	58.1%	Stage I-II – 9.5% Stage III-IV – 90.5%
Cycles Prior Chemotherapy	96.6%	1-2 Cycles – 61.8% 3+ Cycles – 38.2%	67.8%	1-2 Cycles – 65.7% 3+ Cycles – 34.25%
Histology	39.2%	Serous – 58.9% Non Serous – 41.1%	76.7%	Serous – 78% Non Serous – 22%
References	155-182		156, 183-189	

\* 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<sup>190</sup>.

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<sup>153,154</sup>. 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**

<b>Paclitaxel Naïve</b>	Paclitaxel/Other (300 patients) 8 Studies		Paclitaxel/Platinum (138 patients) 8 Studies	
Pooled Response Rate	Platinum Resistant 59/215 (27.4%) Platinum Sensitive 42/85 (49.4%)		Platinum resistant 15/47 (32%) Platinum sensitive 70/88 (79.5%)	
	% Data*		% Data*	
Age	100%	Weighted Mean 58.28	100%	Weighted Mean 55.92
WHO Performance Status	97%	0 – 2 – 100% 3+ - 0%	89.1%	0 – 2 – 100% 3+ - 0%
FIGO Stage	57.6%	Stage I-II – 4.6% Stage III-IV – 95.4%	37.7%	Stage I-II – 18% Stage III-IV – 82%
Cycles Prior Chemotherapy	100%	1-2 Cycles – 90.3% 3+ Cycles – 9.7%	100%	1-2 Cycles – 100% 3+ Cycles – 0%
Histology	47.6%	Serous – 70% Non Serous – 30%	98%	Serous – 60% Non Serous – 40%
References	163,170,191-196		197-204	
<b>Paclitaxel Pre-treated</b>	Paclitaxel/Other (109 patients) 3 Studies		Paclitaxel/Platinum (261 patients) 8 Studies	
Pooled Response Rate	Platinum Resistant 22/100 (22%) Platinum Sensitive 2/9 (22%)		Platinum resistant 3/8 (37.5%) Platinum sensitive 197/253(77.8%)	
	% Data		% Data	
Age	100%	Weighted Mean 56.66	76.2%	Weighted Mean 56.98
WHO Performance Status	100%	0 – 2 – 100% 3+ - 0%	50.5%	0 – 2 – 100% 3+ - 0%
FIGO Stage	15.5%	Stage I-II – 17.6% Stage III-IV – 82.3%	46%	Stage I-II – 18% Stage III-IV – 82%
Cycles Prior Chemotherapy	100%	1-2 Cycles – 100% 3+ Cycles – 0%	90%	1-2 Cycles – 96% 3+ Cycles – 4%
Histology	68.8%	Serous – 73% Non Serous – 27%	72.8%	Serous – 61.5% Non Serous – 38.5%
References	205-207		197,202,204,208-212	

\* 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<sup>213,214,186,215</sup>. There are several studies which have platinum-naïve patients receiving platinum salvage after taxane therapy<sup>216,217,218</sup> 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 platinum 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<sup>219</sup>, 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<sup>79</sup>. 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<sup>21</sup>.

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 antimetabolic agents including paclitaxel were found to have limited activity<sup>220</sup>. Gene polymorphism studies have also suggested that a mutation at Asn118 ERCC1 is associated with a decreased risk of platinum resistance in ovarian cancer<sup>221</sup>. A

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<sup>222</sup>. 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 platinum 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<sup>223</sup>. A greater understanding of the molecular characteristics of responders may also identify new therapeutic targets for cancer therapy.

## References

1. Lebowitz, D. and Canetta R. Clinical development of platinum complexes in cancer therapy: an historical perspective and an update. *Eur J Cancer* 1998;**34**:1522-1534.
2. Lokich, J. and Anderson N. Carboplatin versus cisplatin in solid tumors: an analysis of the literature. *Ann Oncol* 1998;**9**:13-21.
3. Wani, M.C., Taylor H.L., Wall M.E., Coggon P., and McPhail A.T. Plant antitumor agents. VI. The isolation and structure of taxol, a novel antileukemic and antitumor agent from *Taxus brevifolia*. *J Am Chem Soc* 1971;**93**:2325-2327.
4. Schiff, P.B., Fant J.A.N.E., and Horwitz S.B. Promotion of microtubule assembly in vitro by taxol. *Nature* 1979;**277**:665-667.
5. Tabata, H. Production of paclitaxel and the related taxanes by cell suspension cultures of *Taxus* species. *Curr Drug Targets*. 2006;**7**:453-461.
6. Bissett, D. and Kaye S.B. Taxol and taxotere--Current status and future prospects. *Eur J Cancer* 1993;**29**:1228-1231.
7. MIMS Online. 2007; [www.mims.com.au](http://www.mims.com.au)
8. Kartalou, M. and Essigmann J.M. Mechanisms of resistance to cisplatin. *Mutat Res* 2001;**478**:23-43.
9. Parekh, H., Wiesen K., and Simpkins H. Acquisition of taxol resistance via P-glycoprotein- and non-P-glycoprotein-mediated mechanisms in human ovarian carcinoma cells. *Biochem Pharmacol* 1997;**53**:461-470.
10. Orr, G.A., Verdier-Pinard P., McDaid H., and Horwitz S.B. Mechanisms of Taxol resistance related to microtubules. *Oncogene* 2003;**22**:7280-7295.
11. Locke, V.L., Davey R.A., and Davey M.W. Modulation of drug and radiation resistance in small cell lung cancer cells by paclitaxel. *Anti-cancer Drug* 2003;**14**:523-531.
12. Locke, V., Davey R., and Davey M. Paclitaxel sensitization of multidrug-resistant cells to chemotherapy is independent of the cell cycle. *Cytometry* 2001;**43**:170-174.
13. Su, G.M., Davey M.W., and Davey R.A. Induction of broad drug resistance in small cell lung cancer cells and its reversal by paclitaxel. *Int J Cancer* 1998;**76**:702-708.
14. Stordal, B.K., Davey M.W., and Davey R.A. Oxaliplatin induces drug resistance more rapidly than cisplatin in H69 small cell lung cancer cells. *Cancer Chemother Pharmacol* 2006;**58**:256-265.
15. Henness, S., Davey M.W., Harvie R.M., and Davey R.A. Fractionated irradiation of H69 small-cell lung cancer cells causes stable radiation and drug resistance with increased MRP1, MRP2, and topoisomerase II $\alpha$  expression. *Int J Radiat Oncol Bio Phys*. 2002;**54**:895-902.
16. Burns, B.S., Edin M.L., Lester G.E., Tuttle H.G., Wall M.E., Wani M.C, et al. Selective drug resistant human osteosarcoma cell lines. *Clin Orthop Rel Res* 2001;**259**:267.
17. Vermorken, J.B. The integration of paclitaxel and new platinum compounds in the treatment of advanced ovarian cancer. *Int J Gynecol Cancer* 2001;**11 Suppl 1**:21-30.

18. McGuire, W.P., Hoskins W.J., Brady M.F., Kucera P.R., Partridge E.E., Look K.Y. et al Cyclophosphamide and Cisplatin Compared with Paclitaxel and Cisplatin in Patients with Stage III and Stage IV Ovarian Cancer. *N Engl J Med* 1996;**334**:1-6.
19. Bergman, A.M., Giaccone G., van Moorsel C.J., Mauritz R., Noordhuis P., Pinedo H.M. et al Cross-resistance in the 2',2'-difluorodeoxycytidine (gemcitabine)-resistant human ovarian cancer cell line AG6000 to standard and investigational drugs. *Eur J Cancer* 2000;**36**:1974-1983.
20. Perego, P., Romanelli S., Carenini N., Magnani I., Leone R., Bonetti A. et al Ovarian cancer cisplatin-resistant cell lines: multiple changes including collateral sensitivity to Taxol. *Ann Oncol* 1998;**9**:423-430.
21. Yamamoto, K., Kikuchi Y., Kudoh K., and Nagata I. Modulation of cisplatin sensitivity by taxol in cisplatin-sensitive and -resistant human ovarian carcinoma cell lines. *J Cancer Res Clin Oncol* 2000;**126**:168-172.
22. Sawada, S., Mese H., Sasaki A., Yoshioka N., and Matsumura T. Combination chemotherapy of paclitaxel and cisplatin induces apoptosis with Bcl-2 phosphorylation in a cisplatin-resistant human epidermoid carcinoma cell line. *Cancer Chemother Pharmacol* 2003;**51**:505-511.
23. Ikubo, S., Takigawa N., Ueoka H., Kiura K., Tabata M., Shibayama T. et al In vitro evaluation of antimicrotubule agents in human small-cell lung cancer cell lines. *Anticancer Res* 1999;**19**:3985-3988.
24. Johnson, S.W., Shen D., Pastan I., Gottesman M.M., and Hamilton T.C. Cross-resistance, cisplatin accumulation, and platinum-DNA adduct formation and removal in cisplatin-sensitive and -resistant human hepatoma cell lines. *Exp Cell Res* 1996;**226**:133-139.
25. Parekh, H. and Simpkins H. Cross-resistance and collateral sensitivity to natural product drugs in cisplatin-sensitive and -resistant rat lymphoma and human ovarian carcinoma cells. *Cancer Chemother Pharmacol* 1996; **37**:457-462.
26. Davey, R.A., Locke V.L., Henness S., Harvie R.M., and Davey M.W. Cellular models of drug- and radiation-resistant small cell lung cancer. *Anticancer Res* 2004;**24**:465-471.
27. Ling, Y.H., Donato N.J., and Perez-Soler R. Sensitivity to topoisomerase I inhibitors and cisplatin is associated with epidermal growth factor receptor expression in human cervical squamous carcinoma ME180 sublines. *Cancer Chemother Pharmacol* 2001;**47**:473-480.
28. Li, L., Luan Y., Wang G., Tang B., Li D., Zhang W. et al Development and characterization of five cell models for chemoresistance studies of human ovarian carcinoma. *Int J Mol Med* 2004;**14**:257-264.
29. Liang, Y., Meleady P., Cleary I., McDonnell S., Connolly L., and Clynes M. Selection with melphalan or paclitaxel (Taxol) yields variants with different patterns of multidrug resistance, integrin expression and in vitro invasiveness. *Eur J Cancer* 2001;**37**:1041-1052.
30. Kelland, L.R. and Abel G. Comparative in vitro cytotoxicity of taxol and Taxotere against cisplatin-sensitive and -resistant human ovarian carcinoma cell lines. *Cancer Chemother Pharmacol* 1992;**30**:444-450.
31. Nomura, T., Yamasaki M., Nomura Y., and Mimata H. Expression of the inhibitors of apoptosis proteins in cisplatin-resistant prostate cancer cells. *Oncol Rep* 2005;**14**:993-997.
32. Ma, J., Murphy M., O'Dwyer P.J., Berman E., Reed K., and Gallo J.M. Biochemical changes associated with a multidrug-resistant phenotype of a human glioma cell line with temozolomide-acquired resistance. *Biochem Pharmacol* 2002;**63**:1219-1228.

33. Smith, V., Raynaud F., Workman P., and Kelland L.R. Characterization of a human colorectal carcinoma cell line with acquired resistance to flavopiridol. *Mol Pharmacol* 2001;**60**:885-893.
34. Pu, Y.S., Chen J., Huang C.Y., Guan J.Y., Lu S.H., and Hour T.C. Cross-resistance and combined cytotoxic effects of paclitaxel and cisplatin in bladder cancer cells. *J Urol* 2001;**165**:2082-2085.
35. Pu, Y.S., Tsai T.C., Cheng A.L., Tsai C.Y., Tseng N.F., Su I.J. et al Expression of MDR-1 gene in transitional cell carcinoma and its correlation with chemotherapy response. *J Urol* 1996;**156**:271-275.
36. Chung, Y.M., Park S., Park J.K., Kim Y., Kang Y., and Yoo Y.D. Establishment and characterization of 5-fluorouracil-resistant gastric cancer cells. *Cancer Lett* 2000;**159**:95-101.
37. Chu, J.J., Chiang C.D., Rao C.S., Chang W.M., and Lai Y.K. Establishment and characterization of a paclitaxel-resistant human non-small cell lung cancer cell line. *Anticancer Res* 2000;**20**:2449-2456.
38. Heuser, M., Kopun M., Rittgen W., and Granzow C. Cytotoxicity determination without photochemical artifacts. *Cancer Lett* 2005;**223**:57-66.
39. Cole, S.P., Bhardwaj G., Gerlach J.H., Mackie J.E., Grant C.E., Almquist K.C, et al. Overexpression of a transporter gene in a multidrug-resistant human lung cancer cell line. *Science* 1992;**258**:1650-1654.
40. Cole, S.P., Downes H.F., Mirski S.E., and Clements D.J. Alterations in glutathione and glutathione-related enzymes in a multidrug-resistant small cell lung cancer cell line. *Mol Pharmacol* 1990;**37**:192-197.
41. Hamaguchi, K., Godwin A.K., Yakushiji M., O'Dwyer P.J., Ozols R.F., and Hamilton T.C. Cross-resistance to diverse drugs is associated with primary cisplatin resistance in ovarian cancer cell lines. *Cancer Res* 1993;**53**:5225-5232.
42. Takara, K., Obata Y., Yoshikawa E., Kitada N., Sakaeda T., Ohnishi N. et al Molecular changes to HeLa cells on continuous exposure to cisplatin or paclitaxel. *Cancer Chemother Pharmacol* 2006;**58**:785-793.
43. Yabuki, N., Sakata K., Yamasaki T., Terashima H., Mio T., Miyazaki Y. et al Gene amplification and expression in lung cancer cells with acquired paclitaxel resistance. *Cancer Genet Cytogenet* 2007;**173**:1-9.
44. Samimi, G., Kishimoto S., Manorek G., Breaux J.K., and Howell S.B. Novel mechanisms of platinum drug resistance identified in cells selected for resistance to JM118 the active metabolite of satraplatin. 2007; *Cancer Chemother Pharmacol* **59**:301-312.
45. Lourda, M., Trougakos I.P., and Gonos E.S. Development of resistance to chemotherapeutic drugs in human osteosarcoma cell lines largely depends on up-regulation of Clusterin/Apolipoprotein J. *Int J Cancer* 2007;**120**:611-622.
46. Materna, V., Stege A., Surowiak P., Priebsch A., and Lage H. RNA interference-triggered reversal of ABC2-dependent cisplatin resistance in human cancer cells. *Biochem Biophys Res Commun* 2006;**348**:153-157.
47. Bruzek, L.M., Poynter J.N., Kaufmann S.H., and Adjei A.A. Characterization of a human carcinoma cell line selected for resistance to the farnesyl transferase inhibitor 4-(2-(4-(8-chloro-3,10-dibromo-6,11-dihydro-5H-benzo-(5,6)-cyclohepta(1,2-b)-pyridin-11(R)-yl)-1-piperidiny)-2-oxo-ethyl)-1-piperidinecarboxamide (SCH66336). *Mol Pharmacol* 2005;**68**:477-486.
48. Perego, P., Gatti L., Righetti S.C., Beretta G.L., Carenini N., Corna E. et al Development of resistance to a trinuclear platinum complex in ovarian carcinoma cells. *Int J Cancer* 2003;**105**:617-624.

49. Kamazawa,S., Kigawa J., Kanamori Y., Itamochi H., Sato S., Iba T. et al Multidrug resistance gene-1 is a useful predictor of Paclitaxel-based chemotherapy for patients with ovarian cancer. *Gynecol Oncol* 2002;**86**:171-176.
50. Smith,V., Rowlands M.G., Barrie E., Workman P., and Kelland L.R. Establishment and characterization of acquired resistance to the farnesyl protein transferase inhibitor R115777 in a human colon cancer cell line. *Clin Cancer Res* 2002;**8**:2002-2009.
51. Komuro,Y., Udagawa Y., Susumu N., Aoki D., Kubota T., and Nozawa S. Paclitaxel and SN-38 overcome cisplatin resistance of ovarian cancer cell lines by down-regulating the influx and efflux system of cisplatin. *Jpn J Cancer Res* 2001;**92**:1242-1250.
52. Levasseur,L.M., Greco W.R., Rustum Y.M., and Slocum H.K. Combined action of paclitaxel and cisplatin against wildtype and resistant human ovarian carcinoma cells. *Cancer Chemother Pharmacol* 1997;**40**:495-505.
53. Dunn,T.A., Grunwald V., Bokemeyer C., and Casper J. Pre-clinical activity of taxol in non-seminomatous germ cell tumor cell lines and nude mouse xenografts. *Invest New Drugs* 1997;**15**:91-98.
54. Ma,J., Maliepaard M., Kolker H.J., Verweij J., and Schellens J.H. Abrogated energy-dependent uptake of cisplatin in a cisplatin-resistant subline of the human ovarian cancer cell line IGROV-1. *Cancer Chemother Pharmacol* 1998;**41**:186-192.
55. Toffoli,G., Corona G., Tolusso B., Sartor F., Sorio R., Mini E. et al Resistance to methotrexate in SKOV-3 cell lines after chronic exposure to carbamazepine is associated with a decreased expression of folate receptor. *Int J Cancer* 2000;**85**:683-690.
56. Zaffaroni,N., Silvestrini R., Orlandi L., Bearzatto A., Gornati D., and Villa R. Induction of apoptosis by taxol and cisplatin and effect on cell cycle-related proteins in cisplatin-sensitive and -resistant human ovarian cells. *Br J Cancer* 1998;**77**:1378-1385.
57. Flandina,C., Flugy A., Borsellino N., and D'Alessandro N. Development and partial characterization of a human T-lymphoblastic leukemic (CCRF-CEM) cell line resistant to etoposide. Analysis of possible circumventing approaches. *J Chemother* 1996;**8**:465-471.
58. Gosland,M.P., Gillespie M.N., Tsuboi C.P., Tofiq S., Olson J.W., Crooks P.A. et al Reversal of doxorubicin, etoposide, vinblastine, and taxol resistance in multidrug resistant human sarcoma cells by a polymer of spermine. *Cancer Chemother Pharmacol* 1996;**37**:593-600.
59. Yang,X. and Page M. P-glycoprotein expression in ovarian cancer cell line following treatment with cisplatin. *Oncol Res*1995;**7**:619-624.
60. Doyle,L.A., Ross D.D., Ordonez J.V., Yang W., Gao Y., Tong Y. et al An etoposide-resistant lung cancer subline overexpresses the multidrug resistance-associated protein. *Br J Cancer* 1995;**72**:535-542.
61. Smith,C.D., Zilfou J.T., Stratmann K., Patterson G.M., and Moore R.E. Welwitindolinone analogues that reverse P-glycoprotein-mediated multiple drug resistance. *Mol Pharmacol* 1995;**47**:241-247.
62. Xu,B.H., Gupta V., and Singh S.V. Characterization of a human bladder cancer cell line selected for resistance to mitomycin C. *Int J Cancer* 1994;**58**:686-692.
63. Kijima,T., Kubota N., and Nishio K. Establishment of a CPT-11-resistant human ovarian cancer cell line. *Anticancer Res*1994;**14**:799-803.

64. Chou, T.C., Motzer R.J., Tong Y., and Bosl G.J. Computerized quantitation of synergism and antagonism of taxol, topotecan, and cisplatin against human teratocarcinoma cell growth: a rational approach to clinical protocol design. *J Natl Cancer Inst* 1994;**86**:1517-1524.
65. Ding, Z., Yang X., Chernenko G., Tang S.C., and Pater A. Human papillomavirus type 16-immortalized endocervical cells selected for resistance to cisplatin are malignantly transformed and have a multidrug resistance phenotype. *Int J Cancer* 2000;**87**:818-823.
66. Ishii, M., Iwahana M., Mitsui I., Minami M., Imagawa S., Tohgo A. et al Growth inhibitory effect of a new camptothecin analog, DX-8951f, on various drug-resistant sublines including BCRP-mediated camptothecin derivative-resistant variants derived from the human lung cancer cell line PC-6. *Anti-cancer Drug* 2000;**11**:353-362.
67. Klaassen, U., Harstrick A., Schleucher N., Vanhoefer U., Schroder J., Wilke H. et al Activity- and schedule-dependent interactions of paclitaxel, etoposide and hydroperoxy-ifosfamide in cisplatin-sensitive and -refractory human ovarian carcinoma cell lines. *Br J Cancer* 1996;**74**:224-228.
68. Masanek, U., Stamm G., and Volm M. Messenger RNA expression of resistance proteins and related factors in human ovarian carcinoma cell lines resistant to doxorubicin, taxol and cisplatin. *Anti-cancer Drug* 1997;**8**:189-198.
69. Metzinger, D.S., Taylor D.D., and Gercel-Taylor C. Induction of p53 and drug resistance following treatment with cisplatin or paclitaxel in ovarian cancer cell lines  
267. *Cancer Lett* 2006;**236**:302-308.
70. Minagawa, Y., Kigawa J., Itamochi H., Kanamori Y., Shimada M., Takahashi M. et al Cisplatin-resistant HeLa cells are resistant to apoptosis via p53-dependent and -independent pathways. *Jpn J Cancer Res* 1999;**90**:1373-1379.
71. Rogers, P., Boxall F.E., Allott C.P., Stephens T.C., and Kelland L.R. Sequence-dependent synergism between the new generation platinum agent ZD0473 and paclitaxel in cisplatin-sensitive and -resistant human ovarian carcinoma cell lines. *Eur J Cancer* 2002;**38**:1653-1660.
72. Tanaka, T., Toujima S., and Umesaki N. Growth-inhibitory signals by activin A do not affect anticancer drug-sensitivity and acquired multi-drug-resistance in human ovarian endometrioid adenocarcinoma OVK-18 cells. *Oncol Rep* 2004;**11**:667-671.
73. Yen, W.C. and Lamph W.W. A selective retinoid X receptor agonist bexarotene (LGD1069, Targretin) prevents and overcomes multidrug resistance in advanced prostate cancer. *Prostate* 2006;**66**:305-316.
74. Kitazaki, T., Oka M., Nakamura Y., Tsurutani J., Doi S., Yasunaga M. et al Gefitinib, an EGFR tyrosine kinase inhibitor, directly inhibits the function of P-glycoprotein in multidrug resistant cancer cells. *Lung Cancer* 2005;**49**:337-343.
75. Guo, B., Villeneuve D.J., Hembruff S.L., Kirwan A.F., Blais D.E., Bonin M, et al. Cross-resistance studies of isogenic drug-resistant breast tumor cell lines support recent clinical evidence suggesting that sensitivity to paclitaxel may be strongly compromised by prior doxorubicin exposure. *Breast Cancer Res Treat* 2004;**85**:31-51.
76. Helleman, J., Burger H., Hamelers I.H., Boersma A.W., de Kroon A.I., Stoter G. et al Impaired cisplatin influx in an A2780 mutant cell line: evidence for a putative, cis-configuration-specific, platinum influx transporter. *Cancer Biol Ther* 2006;**5**:943-949.



77. Takara, K., Sakaeda T., Yagami T., Kobayashi H., Ohmoto N., Horinouchi M. et al Cytotoxic effects of 27 anticancer drugs in HeLa and MDR1-overexpressing derivative cell lines. *Biological & Pharmaceutical Bulletin* 2002;**25**:771-778.
78. Slapak, C.A., Mizunuma N., and Kufe D.W. Expression of the multidrug resistance associated protein and P-glycoprotein in doxorubicin-selected human myeloid leukemia cells. *Blood* 1994;**84**:3113-3121.
79. Christen, R.D., Jekunen A.P., Jones J.A., Thiebaut F., Shalinsky D.R., and Howell S.B. In vitro modulation of cisplatin accumulation in human ovarian carcinoma cells by pharmacologic alteration of microtubules. *J Clin Invest* 1993;**92**:431-440.
80. Ark-Otte, J., Samelis G., Rubio G., Lopez Saez J.B., Pinedo H.M., and Giaccone G. Effects of tubulin-inhibiting agents in human lung and breast cancer cell lines with different multidrug resistance phenotypes. *Oncol Rep.* 1998;**5**:249-255.
81. Jensen, P.B., Holm B., Sorensen M., Christensen I.J., and Sehested M. In vitro cross-resistance and collateral sensitivity in seven resistant small-cell lung cancer cell lines: preclinical identification of suitable drug partners to taxotere, taxol, topotecan and gemcitabin. *Br J Cancer* 1997;**75**:869-877.
82. Jaffrezou, J.P., Dumontet C., Derry W.B., Duran G., Chen G., Tsuchiya E. et al Novel mechanism of resistance to paclitaxel (Taxol) in human K562 leukemia cells by combined selection with PSC 833. *Oncol Res* 1995;**7**:517-527.
83. Ohta, S., Nishio K., Kubo S., Nishio M., Ohmori T., Takahashi T. et al Characterisation of a vindesine-resistant human small-cell lung cancer cell line. *Br J Cancer* 1993;**68**:74-79.
84. Kawai, H., Kiura K., Tabata M., Yoshino T., Takata I., Hiraki A. et al Characterization of non-small-cell lung cancer cell lines established before and after chemotherapy. *Lung Cancer* 2002;**35**:305-314.
85. Kuroda, H., Sugimoto T., Ueda K., Tsuchida S., Horii Y., Inazawa J. et al Different drug sensitivity in two neuroblastoma cell lines established from the same patient before and after chemotherapy. *Int J Cancer* 1991;**47**:732-737.
86. Liang, Y., O'Driscoll L., McDonnell S., Doolan P., Oglesby I., Duffy K. et al Enhanced in vitro invasiveness and drug resistance with altered gene expression patterns in a human lung carcinoma cell line after pulse selection with anticancer drugs. *Int J Cancer* 2004;**111**:484-493.
87. Chikamori, M., Takigawa N., Kiura K., Tabata M., Shibayama T., Segawa Y. et al Establishment of a 7-ethyl-10-hydroxy-camptothecin-resistant small cell lung cancer cell line. *Anticancer Res* 2004;**24**:3911-3916.
88. Wyler, B., Shao Y., Schneider E., Cianfriglia M., Scheper R.J., Frey B.M. et al Intermittent exposure to doxorubicin in vitro selects for multifactorial non-P-glycoprotein-associated multidrug resistance in RPMI 8226 human myeloma cells. *Br J Haematol.* 1997;**97**:65-75.
89. Mellish, K.J., Barnard C.F., Kelland L.R., and Harrap K.R. Circumvention of acquired tetraplatin resistance in a human ovarian carcinoma cell line by a novel trans platinum complex, JM335 [trans ammine (cyclohexylamine) dichloro dihydroxo platinum (IV)]. *Int J Cancer* 1994;**59**:65-70.
90. Sato, S., Kigawa J., Kanamori Y., Itamochi H., Oishi T., Shimada M. et al Activity of docetaxel in paclitaxel-resistant ovarian cancer cells. *Cancer Chemother Pharmacol* 2004;**53**:247-252.
91. Grosse, P.Y., Bressolle F., and Pinguet F. In vitro modulation of doxorubicin and docetaxel antitumoral activity by methyl-beta-cyclodextrin. *Eur J Cancer* 1998;**34**:168-174.

92. Mueller, H., Kassack M.U., and Wiese M. Comparison of the usefulness of the MTT, ATP, and calcein assays to predict the potency of cytotoxic agents in various human cancer cell lines. *J Biomol Screen* 2004;**9**:506-515.
93. Hill, B.T., Whelan R.D., Shellard S.A., McClean S., and Hosking L.K. Differential cytotoxic effects of docetaxel in a range of mammalian tumor cell lines and certain drug resistant sublines in vitro. *Invest New Drug* 1994;**12**:169-182.
94. Mellish, K.J., Kelland L.R., and Harrap K.R. In vitro platinum drug chemosensitivity of human cervical squamous cell carcinoma cell lines with intrinsic and acquired resistance to cisplatin. *Br J Cancer* 1993;**68**:240-250.
95. Traunecker, H.C., Stevens M.C., Kerr D.J., Ferry D.R., Traunecker H.C., Stevens M.C. et al The acridonecarboxamide GF120918 potently reverses P-glycoprotein-mediated resistance in human sarcoma MES-Dx5 cells. *Br J Cancer* 1999;**81**:942-951.
96. Mese, H., Sasaki A., Alcalde R.E., Nakayama S., and Matsumura T. Establishment and characterization of cisplatin-resistant human epidermoid carcinoma cell line, A431 cell. *Chemotherapy* 1998;**44**:414-420.
97. Yonei, T., Ohnoshi T., Hiraki S., Ueoka H., Kiura K., Moritaka T. et al Antitumor activity of platinum analogs against human lung cancer cell lines and tumor specimens. *Acta Med Okayama* 1993;**47**:233-241.
98. Shen, D.W., Goldenberg S., Pastan I., and Gottesman M.M. Decreased accumulation of [<sup>14</sup>C]carboplatin in human cisplatin-resistant cells results from reduced energy-dependent uptake. *J Cell Physiol.* 2000;**183**:108-116.
99. Glynn, S.A., Gammell P., Heenan M., O'Connor R., Liang Y., Keenan J. et al A new superinvasive in vitro phenotype induced by selection of human breast carcinoma cells with the chemotherapeutic drugs paclitaxel and doxorubicin. *Br J Cancer* 2004;**91**:1800-1807.
100. Kelland, L.R., Mistry P., Abel G., Loh S.Y., O'Neill C.F., Murrer B.A. et al Mechanism-related circumvention of acquired cis-diamminedichloroplatinum(II) resistance using two pairs of human ovarian carcinoma cell lines by ammine/amine platinum(IV) dicarboxylates. *Cancer Res* 1992;**52**:3857-3864.
101. Harstrick, A., Bokemeyer C., Scharnofk M., Hapke G., Reile D., and Schmoll H.J. Preclinical activity of a new platinum analogue, lobaplatin, in cisplatin-sensitive and -resistant human testicular, ovarian, and gastric carcinoma cell lines. *Cancer Chemother Pharmacol* 1993;**33**:43-47.
102. Behrens, B.C., Hamilton T.C., Masuda H., Grotzinger K.R., Whang-Peng J., Louie K.G. et al Characterization of a cis-diamminedichloroplatinum(II)-resistant human ovarian cancer cell line and its use in evaluation of platinum analogues. *Cancer Res* 1987;**47**:414-418.
103. Hotze, A.C., Bacac M., Velders A.H., Jansen B.A., Kooijman H., Spek A.L. et al New cytotoxic and water-soluble bis(2-phenylazopyridine)ruthenium(II) complexes. *J Med Chem* 2003;**46**:1743-1750.
104. Makarovskiy, A.N., Siryaporn E., Hixson D.C., and Akerley W. Survival of docetaxel-resistant prostate cancer cells in vitro depends on phenotype alterations and continuity of drug exposure. *Cell Mol Life Sci* 2002;**59**:1198-1211.
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.
106. Mirski, S.E., Gerlach J.H., and Cole S.P. Multidrug resistance in a human small cell lung cancer cell line selected in adriamycin. *Cancer Res* 1987;**47**:2594-2598.

107. Isonishi,S., Ohkawa K., Tanaka T., and Howell S.B. Depletion of protein kinase C (PKC) by 12-O-tetradecanoylphorbol-13-acetate (TPA) enhances platinum drug sensitivity in human ovarian carcinoma cells. *Br J Cancer* 2000;**82**:34-38.
108. Hong,W.S., Saijo N., Sasaki Y., Minato K., Nakano H., Nakagawa K. et al Establishment and characterization of cisplatin-resistant sublines of human lung cancer cell lines. *Int J Cancer* 1998;**41**:462-467.
109. Twentyman,P.R., Wright K.A., Mistry P., Kelland L.R., and Murrer B.A. Sensitivity to novel platinum compounds of panels of human lung cancer cell lines with acquired and inherent resistance to cisplatin. *Cancer Res* 1992;**52**:5674-5680.
110. Jain,N., Lam Y.M., Pym J., and Campling B.G. Mechanisms of resistance of human small cell lung cancer lines selected in VP-16 and cisplatin. *Cancer* 1996;**77**:1797-1808.
111. Hospers,G.A., Mulder N.H., de Jong B., de Ley L., Uges D.R., Fichtinger-Schepman A.M. et al Characterization of a human small cell lung carcinoma cell line with acquired resistance to cis-diamminedichloroplatinum(II) in vitro. *Cancer Res* 1988;**48**:6803-6807.
112. Kelland,L.R., Mistry P., Abel G., Freidlos F., Loh S.Y., Roberts J.J. et al Establishment and characterization of an in vitro model of acquired resistance to cisplatin in a human testicular nonseminomatous germ cell line. *Cancer Res* 1992;**52**:1710-1716.
113. Walker,M.C., Povey S., Parrington J.M., Riddle P.N., Knuechel R., and Masters J.R. Development and characterization of cisplatin-resistant human testicular and bladder tumour cell lines. *Eur J Cancer* 1990;**26**:742-747.
114. Song,I.S., Savaraj N., Siddik Z.H., Liu P., Wei Y., Wu C.J. et al Role of human copper transporter Ctr1 in the transport of platinum-based antitumor agents in cisplatin-sensitive and cisplatin-resistant cells. *Mol Cancer Ther* 2004;**3**:1543-1549.
115. Hong,W.S. and Son Y.S. Biochemical characterization of cisplatin-resistance in MKN-45 human stomach adenocarcinoma cell line. *Anticancer Res* 1996;**16**:3031-3036.
116. Osmak,M., Bizjak L., Jernej B., and Kapitanovi S. Characterization of carboplatin-resistant sublines derived from human larynx carcinoma cells. *Mutation Research* 1995;**347**:141-150.
117. Xu,H., Choi S.M., An C.S., Min Y.D., Kim K.C., Kim K.J. et al Concentration-dependent collateral sensitivity of cisplatin-resistant gastric cancer cell sublines. *Biochem Biophys Res Commun* 2005;**328**:618-622.
118. Asada,N., Tsuchiya H., Ueda Y., and Tomita K. Establishment and characterization of an acquired cisplatin-resistant subline in a human osteosarcoma cell line. *Anticancer Res* 1998;**18**:1765-1768.
119. Son,Y.S., Suh J.M., Ahn S.H., Kim J.C., Yi J.Y., Hur K.C. et al Reduced activity of topoisomerase II in an Adriamycin-resistant human stomach-adenocarcinoma cell line. *Cancer Chemother Pharmacol* 1998;**41**:353-360.
120. Liang,X.J., Shen D.W., and Gottesman M.M. A pleiotropic defect reducing drug accumulation in cisplatin-resistant cells. *J Inorg Biochem* 2004;**98**:1599-1606.
121. Zhao,R., Rabo Y.B., Egyhazi S., Andersson A., Edgren M.R., Linder S. et al Apoptosis and c-jun induction by cisplatin in a human melanoma cell line and a drug-resistant daughter cell line. *Anti-cancer Drug* 1995;**6**:657-668.

122. Misawa,T., Kikkawa F., Maeda O., Obata N.H., Higashide K., Suganuma N. et al Establishment and characterization of acquired resistance to platinum anticancer drugs in human ovarian carcinoma cells. *Jpn J Cancer Res* 1995;**86**:88-94.
123. Sharp,S.Y., Mistry P., Valenti M.R., Bryant A.P., and Kelland L.R. Selective potentiation of platinum drug cytotoxicity in cisplatin-sensitive and -resistant human ovarian carcinoma cell lines by amphotericin B. *Cancer Chemother Pharmacol* 1994;**35**:137-143.
124. Nakagawa,M., Nomura Y., Kohno K., Ono M., Mizoguchi H., Ogata J. et al Reduction of drug accumulation in cisplatin-resistant variants of human prostatic cancer PC-3 cell line. *J Urol* 1993;**150**:1970-1973.
125. Kimiya,K., Naito S., Soejima T., Sakamoto N., Kotoh S., Kumazawa J. et al Establishment and characterization of doxorubicin-resistant human bladder cancer cell line, KK47/ADM. *J Urol* 1992;**148**:441-445.
126. Kobayashi,H., Takemura Y., Miyachi H., and Ogawa T. Antitumor activities of new platinum compounds, DWA2114R, NK121 and 254-S, against human leukemia cells sensitive or resistant to cisplatin. *Invest New Drugs* 1991;**9**:313-319.
127. Hospers,G.A., Meijer C., de Leij L., Uges D.R., Mulder N.H., and de Vries E.G. A study of human small-cell lung carcinoma (hSCLC) cell lines with different sensitivities to detect relevant mechanisms of cisplatin (CDDP) resistance. *Int J Cancer* 1990;**46**:138-144.
128. Bedford,P., Shellard S.A., Walker M.C., Whelan R.D., Masters J.R., and Hill B.T. Differential expression of collateral sensitivity or resistance to cisplatin in human bladder carcinoma cell lines pre-exposed in vitro to either X-irradiation or cisplatin. *Int J Cancer* 1987;**40**:681-686.
129. Teicher,B.A., Holden S.A., Kelley M.J., Shea T.C., Cucchi C.A., Rosowsky A. et al Characterization of a human squamous carcinoma cell line resistant to cis-diamminedichloroplatinum(II). *Cancer Res* 1987;**47**:388-393.
130. Chang,J.Y., Liu J.F., Juang S.H., Liu T.W., Chen L.T., Chang J.Y. et al Novel mutation of topoisomerase I in rendering cells resistant to camptothecin. *Cancer Res* 2002;**62**:3716-3721.
131. Hill,B.T., Shellard S.A., Hosking L.K., Fichtinger-Schepman A.M., Bedford P., Hill B.T. et al Enhanced DNA repair and tolerance of DNA damage associated with resistance to cis-diammine-dichloroplatinum (II) after in vitro exposure of a human teratoma cell line to fractionated X-irradiation. *Int J Radiat Oncol Bio Phys* 1990;**19**:75-83.
132. Lai,S.L., Hwang J., Perng R.P., and Whang-Peng J. Modulation of cisplatin resistance in acquired-resistant nonsmall cell lung cancer cells. *Oncol Res* 1995;**7**:31-38.
133. Meijer,C., Mulder N.H., Timmer-Bosscha H., Sluiter W.J., Meersma G.J., and de Vries E.G. Relationship of cellular glutathione to the cytotoxicity and resistance of seven platinum compounds. *Cancer Res* 1992;**52**:6885-6889.
134. Rixe,O., Ortuzar W., Alvarez M., Parker R., Reed E., Paull K. et al Oxaliplatin, tetraplatin, cisplatin, and carboplatin: spectrum of activity in drug-resistant cell lines and in the cell lines of the National Cancer Institute's Anticancer Drug Screen panel. *Biochem Pharmacol* 1996;**52**:1855-1865.
135. Fukuda,M., Ohe Y., Kanzawa F., Oka M., Hara K., and Saijo N. Evaluation of novel platinum complexes, inhibitors of topoisomerase I and II in non-small cell lung cancer (NSCLC) sublines resistant to cisplatin. *Anticancer Res* 1995;**15**:393-398.

136. Hari,M., Loganzo F., Annable T., Tan X., Musto S., Morilla D.B. et al Paclitaxel-resistant cells have a mutation in the paclitaxel-binding region of beta-tubulin (Asp26Glu) and less stable microtubules. *Mol Cancer Ther* 2006;**5**:270-278.
137. Myer,M.S., Joone G., Chasen M.R., and van Rensburg C.E. The chemosensitizing potential of GF120918 is independent of the magnitude of P-glycoprotein-mediated resistance to conventional chemotherapeutic agents in a small cell lung cancer line. *Oncol Rep* 1999;**6**:217-218.
138. Giannakakou,P., Gussio R., Nogales E., Downing K.H., Zaharevitz D., Bollbuck B. et al A common pharmacophore for epothilone and taxanes: molecular basis for drug resistance conferred by tubulin mutations in human cancer cells. *Proc Natl Acad Sci USA*. 2000;**97**:2904-2909.
139. Bhalla,K., Huang Y., Tang C., Self S., Ray S., Mahoney M.E. et al Characterization of a human myeloid leukemia cell line highly resistant to taxol. *Leukemia* 1994;**8**:465-475.
140. Parker,R.J., Dabholkar M.D., Lee K.B., Bostick-Bruton F., and Reed E. Taxol effect on cisplatin sensitivity and cisplatin cellular accumulation in human ovarian cancer cells. *J Natl Cancer Inst* 1993;**Monographs**:83-88.
141. Yamamoto,K., Kikuchi Y., Kudoh K., Hirata J., Kita T., and Nagata I. Treatment with paclitaxel alone rather than combination with paclitaxel and cisplatin may be selective for cisplatin-resistant ovarian carcinoma. *Jpn J Clin Oncol* 2000;**30**:446-449.
142. Dieras,V., Bougnoux P., Petit T., Chollet P., Beuzeboc P., Borel C. et al Multicentre phase II study of oxaliplatin as a single-agent in cisplatin/carboplatin +/- taxane-pretreated ovarian cancer patients. *Ann Oncol* 2002;**13**:258-266.
143. Markman,M. and Hoskins W. Responses to salvage chemotherapy in ovarian cancer: a critical need for precise definitions of the treated population. *J Clin Oncol* 1992;**10**:513-514.
144. Bokemeyer,C., Beyer J., Metzner B., Ruther U., Harstrick A., Weissbach L. et al Phase II study of paclitaxel in patients with relapsed or cisplatin-refractory testicular cancer. *Ann Oncol* 1996;**7**:31-34.
145. Bokemeyer,C., Schmoll H.J., Natt F., Knoche M., Beyer J., and Souchon R. Preliminary results of a phase I/II trial of paclitaxel in patients with relapsed or cisplatin-refractory testicular cancer. *J Cancer Res Clin Oncol* 1994;**120**:754-757.
146. McNeish,I.A., Kanfer E.J., Haynes R., Giles C., Harland S.J., Driver D. et al Paclitaxel-containing high-dose chemotherapy for relapsed or refractory testicular germ cell tumours. *Br J Cancer* 2004;**90**:1169-1175.
147. De Giorgi,U., Rosti G., Aieta M., Fochess, i F., Paoluzz, et al. Weekly gemcitabine, paclitaxel, oxaliplatin combination chemotherapy in patients with Cisplatin-refractory germ cell tumor: preliminary experience. *Am J Clin Oncol* 2004;**27**:457-460.
148. Buccheri,G., Ferrigno D., and Cuneo Lung Cancer Study Group. Second-line weekly paclitaxel in patients with inoperable non-small cell lung cancer who fail combination chemotherapy with cisplatin. *Lung Cancer* 2004;**45**:227-236.
149. Ceresoli,G.L., Gregorc V., Cordio S., Bencardino K.B., Schipani S., Cozzarini C. et al Phase II study of weekly paclitaxel as second-line therapy in patients with advanced non-small cell lung cancer. *Lung Cancer* 2004;**44**:231-239.

150. Takahashi, T., Higashi S., Nishiyama H., Segawa T., Nakamura E., Kinoshita H. et al Biweekly paclitaxel and gemcitabine for patients with advanced urothelial cancer ineligible for cisplatin-based regimen. *Jpn J Clin Oncol* 2006;**36**:104-108.
151. Otto, T., Bex A., Krege S., Walz P.H., and Rubben H. Paclitaxel-based second-line therapy for patients with advanced chemotherapy-resistant bladder carcinoma (M1): a clinical Phase II study. *Cancer* 1997;**80**:465-470.
152. Akizuki, S., Katsumata N., Yamanaka Y., Andoh M., Fujiwara Y., and Watanabe T. Weekly paclitaxel in patients with CAP-resistant advanced or recurrent endometrial carcinoma: a series of four patients. *Int J Clin Oncol* 2005;**10**:272-275.
153. Eisenhauer, E.A., Bokkel Huinink W.W., Swenerton K.D., Gianni L., Myles J., van der Burg M.E. et al European-Canadian randomized trial of paclitaxel in relapsed ovarian cancer: high-dose versus low-dose and long versus short infusion. *J Clin Oncol* 1994;**12**:2654-2666.
154. Eisenhauer, E.A., Vermorken J.B., and Van Glabbeke M. Predictors of response to subsequent chemotherapy in platinum pretreated ovarian cancer: A multivariate analysis of 704 patients. *Ann Oncol* 1997;**8**:963-968.
155. Omura, G.A., Brady M.F., Look K.Y., Averette H.E., Delmore J.E., Long H.J, et al. Phase III trial of paclitaxel at two dose levels, the higher dose accompanied by filgrastim at two dose levels in platinum-pretreated epithelial ovarian cancer: an intergroup study. *J Clin Oncol* 2003;**21**:2843-2848.
156. Ghamande, S., Lele S., Marchetti D., Baker T., and Odunsi K. Weekly paclitaxel in patients with recurrent or persistent advanced ovarian cancer. *Int J Gynecol Cancer* 2003;**13**:142-147.
157. Cantu, M.G., Buda A., Parma G., Rossi R., Floriani I., Bonazzi C. et al Randomized controlled trial of single-agent paclitaxel versus cyclophosphamide, doxorubicin, and cisplatin in patients with recurrent ovarian cancer who responded to first-line platinum-based regimens. *J Clin Oncol* 2002;**20**:1232-1237.
158. Uziely, B., Groshen S., Jeffers S., Morris M., Russell C., Roman L, et al. Paclitaxel (Taxol) in heavily pretreated ovarian cancer: Antitumor activity and complications. *Ann Oncol* 1994;**5**:827-833.
159. Blom, R., Palm N., and Simonsen E. Paclitaxel (Taxol) monotherapy in the treatment of progressive and recurrent ovarian carcinoma after platinum-based chemotherapy. *Acta Oncol.* 1996;**35**:733-736.
160. Gore, M.E., Preston N., A'Hern R.P., Hill C., Mitchell P., Chang J. et al Platinum-Taxol non-cross resistance in epithelial ovarian cancer. *Br J Cancer* 1995;**71**:1308-1310.
161. Piccart, M.J., Green J.A., Lacave A.J., Reed N., Vergote I., Benedetti-Panici P. et al Oxaliplatin or paclitaxel in patients with platinum-pretreated advanced ovarian cancer: A randomized phase II study of the European Organization for Research and Treatment of Cancer Gynecology Group. *J Clin Oncol* 2000;**18**:1193-1202.
162. Markman, M., Webster K., Kulp B., and Peterson G. Prolonged disease-free and treatment-free survival in platinum-resistant ovarian cancer following extended (>1 year) administration of single-agent paclitaxel: A case report and discussion of potential clinical implications. *Cancer Invest.* 2005;**23**:33-35.
163. Bolis, G., Parazzini F., Scarfone G., Villa A., Amoroso M., Rabaiotti E. et al Paclitaxel vs epidoxorubicin plus paclitaxel as second-line therapy for platinum-refractory and -resistant ovarian cancer. *Gynecol Oncol* 1999;**72**:60-64.

164. Tay,S.K. and Thilagam M.D. Single agent paclitaxel in resistant and relapsed epithelial ovarian cancer after first-line platinum-based chemotherapy--experience in an Asian population. *Annals of the Academy of Medicine, Singapore* 1998;**27**:645-649.
165. ten Bokkel,H.W., Gore M., Carmichael J., Gordon A., Malfetano J., Hudson I. et al Topotecan versus paclitaxel for the treatment of recurrent epithelial ovarian cancer. *J Clin Oncol* 1997;**15**:2183-2193.
166. Rosenberg,P., Andersson H., Boman K., Ridderheim M., Sorbe B., Puistola U. et al Randomized trial of single agent paclitaxel given weekly versus every three weeks and with peroral versus intravenous steroid premedication to patients with ovarian cancer previously treated with platinum. *Acta Oncol.* 2002;**41**:418-424.
167. McGuire,W.P., Rowinsky E.K., Rosenshein N.B., Grumbine F.C., Ettinger D.S., Armstrong D.K. et al Taxol: a unique antineoplastic agent with significant activity in advanced ovarian epithelial neoplasms. *Ann Intern Med* 1989;**111**:273-279.
168. Planner,R.S., Allen D.G., Brand A.H., Grant P.T., Toner G.C., and Sykes P.H. Paclitaxel (Taxol) as salvage therapy for relapsed ovarian cancer. *Australian & New Zealand Journal of Obstetrics & Gynaecology.* 1996;**36**:168-170.
169. Markman,M., Hakes T., Barakat R., Curtin J., Almadrones L., and Hoskins W. Follow-up of Memorial Sloan-Kettering Cancer Center patients treated on National Cancer Institute Treatment Referral Center protocol 9103: paclitaxel in refractory ovarian cancer. *J Clin Oncol* 1996;**14**:796-799.
170. Buda,A., Floriani I., Rossi R., Colombo N., Torri V., Conte P.F. et al Randomised controlled trial comparing single agent paclitaxel vs epidoxorubicin plus paclitaxel in patients with advanced ovarian cancer in early progression after platinum-based chemotherapy: an Italian Collaborative Study from the Mario Negri Institute, Milan, G.O.N.O. (Gruppo Oncologico Nord Ovest) group and I.O.R. (Istituto Oncologico Romagnolo) group. *Br J Cancer* 2004;**90**:2112-2117.
171. Phillips K.A., Friedlander M., Olver I., Evans B., Smith J., Fitzharris B., et al. Australasian multicentre phase II study of paclitaxel (Taxol) in relapsed ovarian cancer. *Australian and New Zealand Journal of Medicine.* 1995;**25**:337-343.
172. Trope,C., Hogberg T., Kaern J., Bertelsen K., Bjorkholm E., Boman K. et al Long-term results from a phase II study of single agent paclitaxel (Taxol(R)) in previously platinum treated patients with advanced ovarian cancer: The Nordic experience. *Ann Oncol* 1998;**9**:1301-1307.
173. Aravantinos,G., Skarlos D.V., Kosmidis P., Athanassiades A., Bafaloukos D., Giannakakis T. et al A phase II study of paclitaxel in platinum pretreated ovarian cancer. A hellenic cooperative oncology group study. *Eur J Cancer* 1997;**33**:160-163.
174. Thigpen,J.T., Blessing J.A., Ball H., Hummel S.J., and Barrett R.J. Phase II trial of paclitaxel in patients with progressive ovarian carcinoma after platinum-based chemotherapy: a Gynecologic Oncology Group study. *J Clin Oncol.* 1994;**12**:1748-1753.
175. Mayerhofer,K., Kucera E., Zeisler H., Speiser P., Reinthaller A., and Sevelde P. Taxol as second-line treatment in patients with advanced ovarian cancer after platinum-based first-line chemotherapy. *Gynecol Oncol* 1997;**64**:109-113.
176. Nardi,M., Aloe A., De Marco S., Cognetti F., Iacovelli A., Atlante G. et al Paclitaxel as salvage therapy in advanced pretreated ovarian cancer: a phase II study. *Am J Clin Oncol* 1997;**20**:230-232.
177. Gore,M.E., Levy V., Rustin G., Perren T., Calvert A.H., Earl H. et al Paclitaxel (Taxol) in relapsed and refractory ovarian cancer: the UK and Eire experience. *Br J Cancer* 1995;**72**:1016-1019.

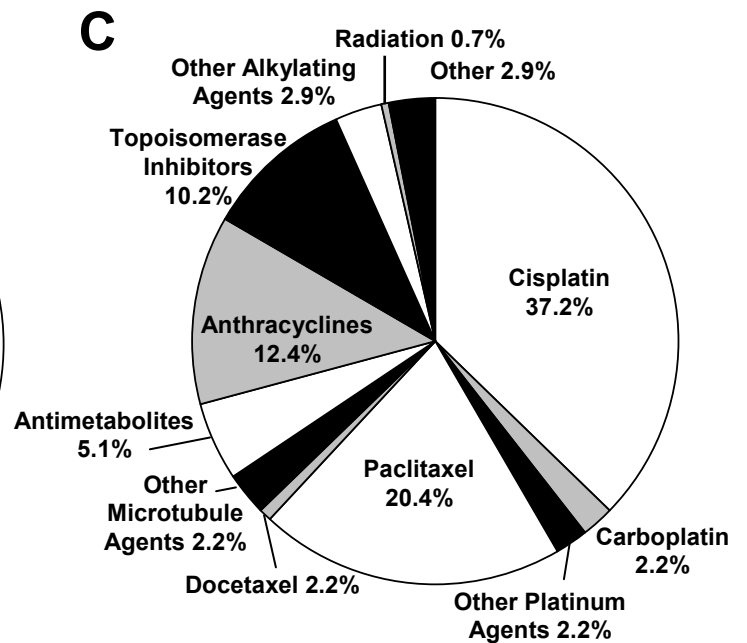
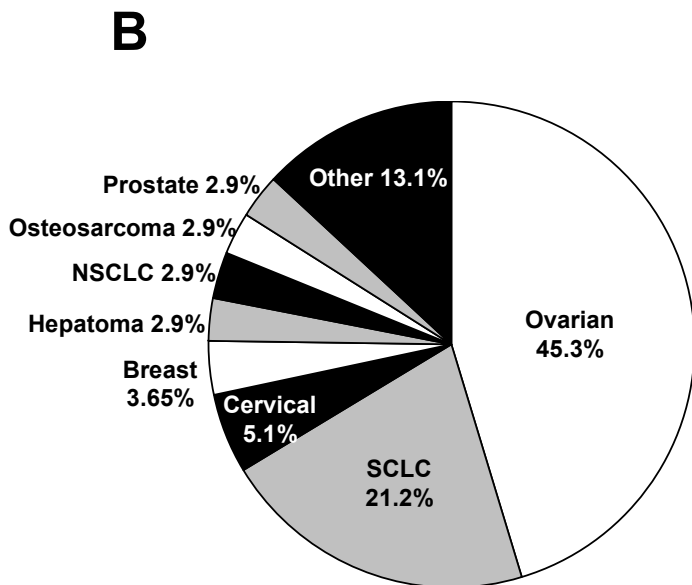
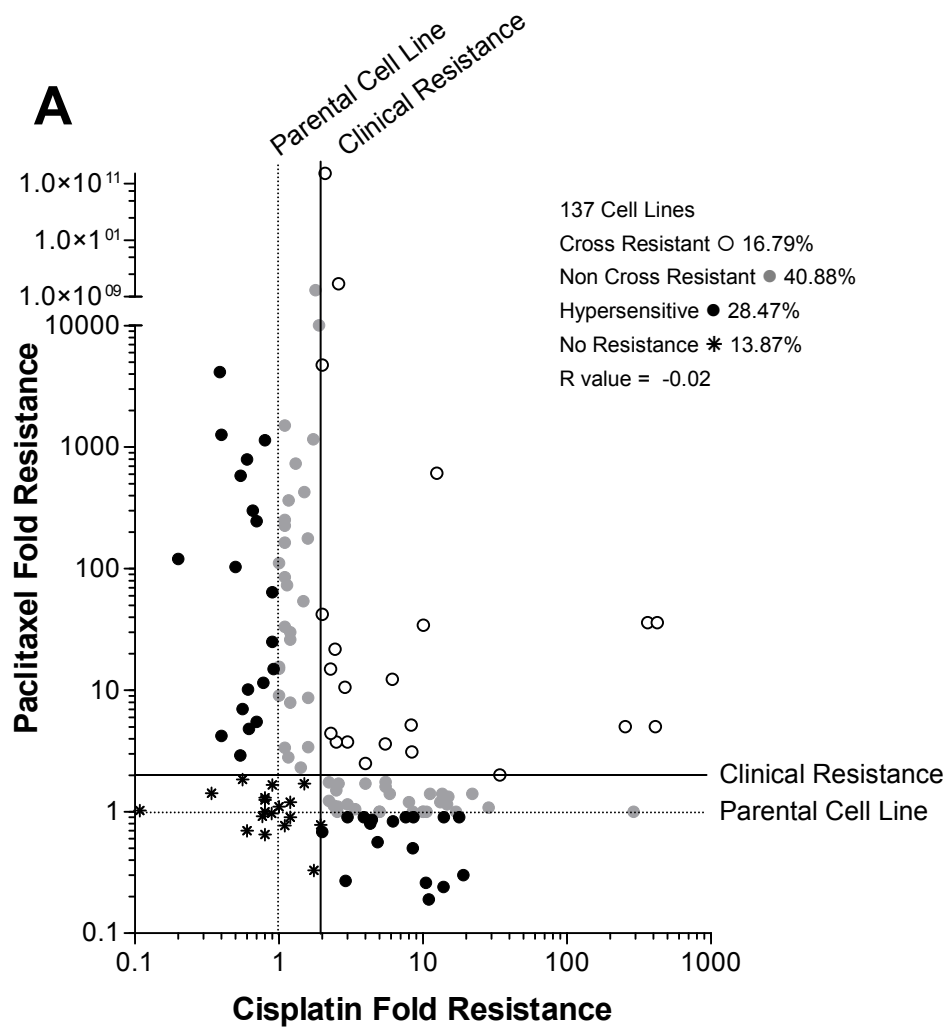
178. Bruzzone,M., Catsafados E., Miglietta L., Amoroso D., Pedulla F., Giannessi P.G. et al Salvage chemotherapy with paclitaxel in platinum-resistant advanced ovarian cancer patients. *Oncology* 1996;**53**:349-353.
179. Seewaldt,V.L., Greer B.E., Cain J.M., Figge D.C., Tamimi H.K., Brown W.S. et al Paclitaxel (Taxol) treatment for refractory ovarian cancer: phase II clinical trial. *Am J Obstet Gynecol.* 1994;**170**:1666-1670.
180. Sarosy,G., Kohn E., Stone D.A., Rothenberg M., Jacob J., Adamo D.O. et al Phase I study of taxol and granulocyte colony-stimulating factor in patients with refractory ovarian cancer. *J Clin Oncol* 1992;**10**:1165-1170.
181. Trimble,E.L., Adams J.D., Vena D., Hawkins M.J., Friedman M.A., Fisherman J.S. et al Paclitaxel for platinum-refractory ovarian cancer: results from the first 1,000 patients registered to National Cancer Institute Treatment Referral Center 9103. *J Clin Oncol* 1993;**11**:2405-2410.
182. Kohn,E.C., Sarosy G., Bicher A., Link C., Christian M., Steinberg S.M. et al Dose-intense taxol: high response rate in patients with platinum-resistant recurrent ovarian cancer. *J Natl Cancer Inst.* 1994;**86**:18-24.
183. Le,T., Hopkins L., Baines K.A., Rambout L., Al Hayki M., and Kee Fung M.F. Prospective evaluations of continuous weekly paclitaxel regimen in recurrent platinum-resistant epithelial ovarian cancer. *Gynecol Oncol* 2006;**102**:49-53.
184. Tresukosol,D., Kudelka A.P., Gonzales d.L., Edwards C.L., Freedman R.S., Mante R. et al Paclitaxel retreatment in patients with platinum and paclitaxel resistant ovarian cancer. *Eur J Gynaecol Oncol* 1996;**17**:188-191.
185. Zanotti,K.M., Belinson J.L., Kennedy A.W., Webster K.D., and Markman M. Treatment of Relapsed Carcinoma of the Ovary with Single-Agent Paclitaxel Following Exposure to Paclitaxel and Platinum Employed as Initial Therapy. *Gynecol Oncol* 2002;**79**:211-215.
186. Gynecologic Oncology Group, Markman M., Blessing J., Rubin S.C., Connor J., Hanjani P. et al Phase II trial of weekly paclitaxel (80 mg/m<sup>2</sup>) in platinum and paclitaxel-resistant ovarian and primary peritoneal cancers: a Gynecologic Oncology Group study. *Gynecol Oncol* 2006;**101**:436-440.
187. Kaern,J., Baekelandt M., and Trope C.G. A phase II study of weekly paclitaxel in platinum and paclitaxel-resistant ovarian cancer patients. *Eur J Gynaecol Oncol* 2002;**23**:383-389.
188. Boruta,D.M., Fowler W.C., Jr., Gehrig P.A., Boggess J.F., Walton L.A., and Van Le L. Weekly paclitaxel infusion as salvage therapy in ovarian cancer. *Cancer Invest* 2003;**21**:675-681.
189. Markman,M., Hall J., Spitz D., Weiner S., Carson L., Van Le L. et al Phase II trial of weekly single-agent paclitaxel in platinum/paclitaxel-refractory ovarian cancer. *J Clin Oncol* 2002;**20**:2365-2369.
190. Stordal,B., Pavlakis N., and Davey R. Oxaliplatin for the treatment of cisplatin-resistant cancer: A systematic review. *Cancer Treat Rev* 2007;**33**:347-357.
191. Miglietta,L., Amoroso D., Bruzzone M., Granetto C., Catsafados E., Mammoliti S. et al Paclitaxel plus ifosfamide in advanced ovarian cancer: a multicenter phase II study. *Oncology* 1997;**54**:102-107.
192. Dimopoulos,M.A., Papadimitriou C., Gennatas C., Akrivos T., Vlahos G., Voulgaris Z. et al Ifosfamide and paclitaxel salvage chemotherapy for advanced epithelial ovarian cancer. *Ann Oncol* 1997;**8**:195-197.



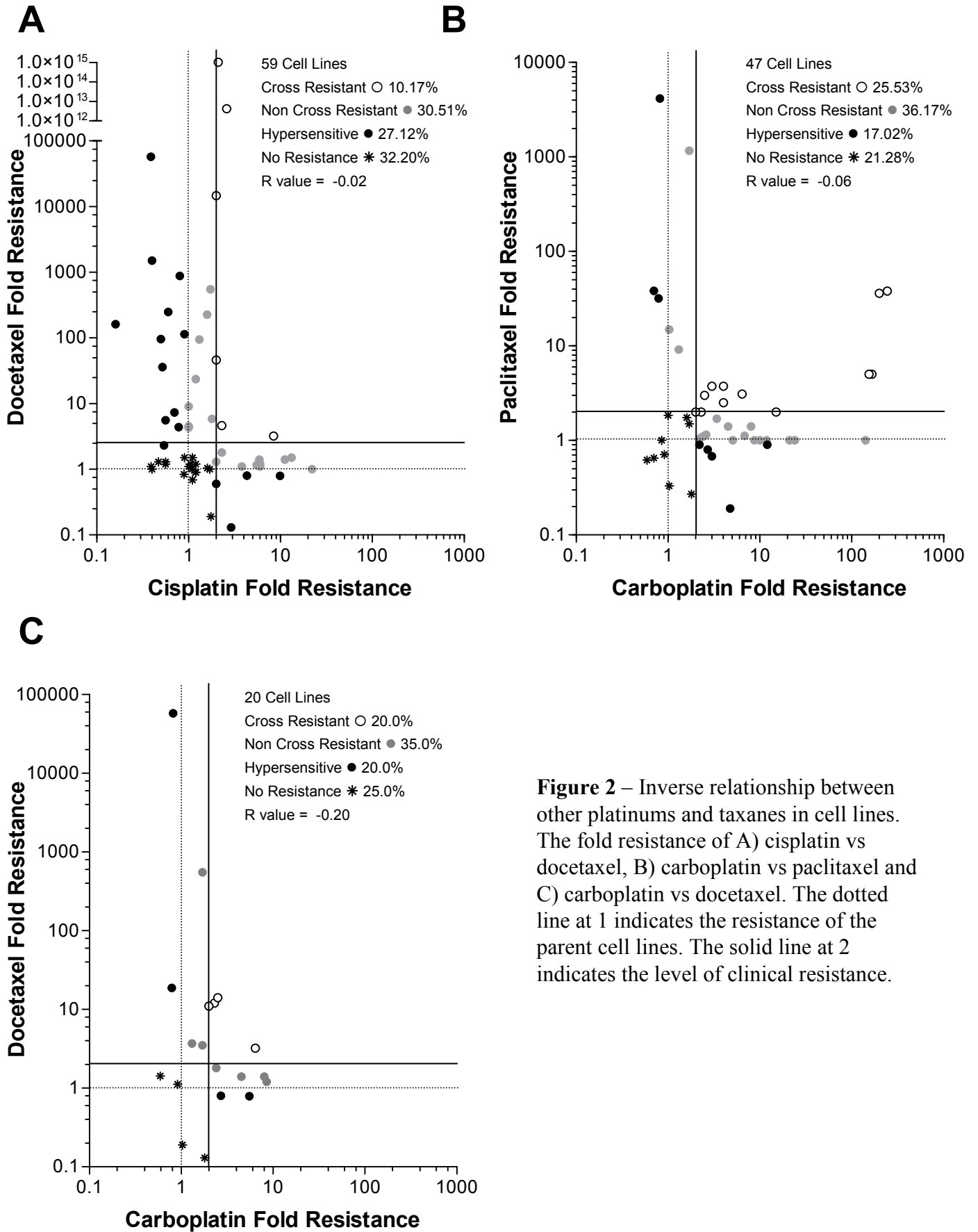
193. O'Reilly,S., Fleming G.F., Barker S.D., Walczak J.R., Bookman M.A., McGuire W.P., III et al Phase I trial and pharmacologic trial of sequences of paclitaxel and topotecan in previously treated ovarian epithelial malignancies: a Gynecologic Oncology Group study. *J Clin Oncol* 1997;**15**:177-186.
194. Lauria,R., Ferrari E., Tramontana S., Morabito A., Perrone F., Maffeo A. et al A phase I study of paclitaxel and epirubicin, without and with filgrastim, for the treatment of platinum-resistant advanced ovarian cancer. *Oncology* 1999;**56**:267-273.
195. Kurtz,J.E., Deplanque G., Duclos B., Eichler F., Giron C., Limacher J.M. et al Paclitaxel-Anthracycline Combination Chemotherapy in Relapsing Advanced Ovarian Cancer after Platinum-Based Chemotherapy: A Pilot Study. *Gynecol Oncol* 1998;**70**:414-417.
196. Olver,I., Davy M., Luftner D., Park S.H., Egorin M., Ellis A. et al A phase I study of paclitaxel and altretamine as second-line therapy to cisplatin regimens for ovarian cancer  
27. *Cancer Chemother Pharmacol* 2001;**48**:109-114.
197. Viens,P., Petit T., Yovine A., Bougnoux P., Deplanque G., Cottu P.H. et al A phase II study of a paclitaxel and oxaliplatin combination in platinum-sensitive recurrent advanced ovarian cancer patients. *Ann Oncol* 2006;**17**:429-436.
198. Delaloge,S., Laadem A., Taamma A., Chouaki N., Cvitkovic E., Pautier P. et al Pilot study of the paclitaxel, oxaliplatin, and cisplatin combination in patients with advanced/recurrent ovarian cancer. *Am J Clin Oncol* 2000;**23**:569-574.
199. Ohtani,K., Sakamoto H., Masaoka N., Shimada K., Kanaeda T., Kurihara M. et al A case of rapidly growing ovarian squamous cell carcinoma successfully controlled by weekly paclitaxel-carboplatin administration. *Gynecol Oncol* 2000;**79**:515-518.
200. Pujade-Lauraine,E., Guastalla J.P., Weber B., Cure H., Orfeuvre H., Mousseau M. et al Efficacy and safety of the combination paclitaxel/carboplatin in patients with previously treated advanced ovarian carcinoma: a multicenter French Groupe des Investigateurs Nationaux pour l'Etude des Cancers Ovariens phase II study. *Sem Oncol* 1997;**24**:S15-S15.
201. Guastalla,J.P., Pujade-Lauraine E., Weber B., Cure H., Orfeuvre H., Mousseau M. et al Efficacy and safety of the paclitaxel and carboplatin combination in patients with previously treated advanced ovarian carcinoma: A multicenter GINECO (Groupe d'Investigateurs Nationaux pour l'Etude des Cancers Ovariens) phase II study. *Ann Oncol* 1998;**9**:37-43.
202. Dizon,D.S., Hensley M.L., Poynor E.A., Sabbatini P., Aghajanian C., Hummer A. et al Retrospective analysis of carboplatin and paclitaxel as initial second-line therapy for recurrent epithelial ovarian carcinoma: application toward a dynamic disease state model of ovarian cancer. *J Clin Oncol* 2002;**20**:1238-1247.
203. de Jongh,F.E., de Wit R., Verweij J., Sparreboom A., van den Bent M.J., Stoter G. et al Dose-dense cisplatin/paclitaxel. a well-tolerated and highly effective chemotherapeutic regimen in patients with advanced ovarian cancer. *Eur J Cancer* 2002;**38**:2005-2013.
204. Utsunomiya,H., Akahira J., Tanno S., Moriya T., Toyoshima M., Niikura H. et al Paclitaxel-platinum combination chemotherapy for advanced or recurrent ovarian clear cell adenocarcinoma: a multicenter trial. *Int J Gynecol Cancer* 2006;**16**:52-56.
205. Fracasso,P.M., Brady M.F., Moore D.H., Walker J.L., Rose P.G., Letvak L. et al Phase II study of paclitaxel and valspodar (PSC 833) in refractory ovarian carcinoma: a gynecologic oncology group study. *J Clin Oncol* 2001;**19**:2975-2982.

206. Garcia,A.A., O'Meara A., Bahador A., Facio G., Jeffers S., Kim D.Y. et al Phase II study of gemcitabine and weekly paclitaxel in recurrent platinum-resistant ovarian cancer. *Gynecol Oncol* 2004;**93**:493-498.
207. Duska,L.R., Penson R., Supko J.G., Finkelstein D.M., Makastorsis T., Gallagher J. et al A Phase I study of continuous infusion doxorubicin and paclitaxel chemotherapy with granulocyte colony-stimulating factor for relapsed epithelial ovarian cancer. *Clin Cancer Res* 1999;**5**:1299-1305.
208. Gronlund,B., Hogdall C., Hansen H.H., and Engelholm S.A. Results of Reinduction Therapy with Paclitaxel and Carboplatin in Recurrent Epithelial Ovarian Cancer. *Gynecol Oncol* 2001;**83** :128-134.
209. Havrilesky,L.J., Alvarez A.A., Sayer R.A., Lancaster J.M., Soper J.T., Berchuck A. et al Weekly low-dose carboplatin and paclitaxel in the treatment of recurrent ovarian and peritoneal cancer. *Gynecol Oncol* 2003;**88**:51-57.
210. Rose,P.G., Fusco N., Fluellen L., and Rodriguez M. Second-line therapy with paclitaxel and carboplatin for recurrent disease following first-line therapy with paclitaxel and platinum in ovarian or peritoneal carcinoma. *J Clin Oncol* 1998;**16**:1494-1497.
211. Rose,P.G., Smrekar M., and Fusco N. A phase II trial of weekly paclitaxel and every 3 weeks of carboplatin in potentially platinum-sensitive ovarian and peritoneal carcinoma  
12. *Gynecol Oncol* 2005;**96**:296-300.
212. Balbi,G., Di Prisco L., Musone R., Menditto A., Cassese E., Balbi C. et al Second-line with paclitaxel and carboplatin for recurrent disease following first paclitaxel and platinum compounds in ovarian carcinoma. *Eur J Gynaecol Oncol* 2002;**23**:347-349.
213. Papadimitriou,C.A., Fountzilias G., Aravantinos G., Kalofonos C., Mouloupoulos L.A., Briassoulis E. et al Second-line chemotherapy with gemcitabine and carboplatin in paclitaxel-pretreated, platinum-sensitive ovarian cancer patients. A Hellenic Cooperative Oncology Group Study. *Gynecol Oncol* 2004;**92**:152-159.
214. Ghamande,S.A. and Piver M.S. Role of salvage chemotherapy with topotecan and cisplatin in patients with paclitaxel- and platinum-resistant recurrent ovarian or primary peritoneal cancer: a phase II pilot study. *J Surg Oncol* 1999;**72**:162-166.
215. Markman,M., Webster K., Zanotti K., Peterson G., Kulp B., and Belinson J. Phase 2 trial of carboplatin plus tamoxifen in platinum-resistant ovarian cancer and primary carcinoma of the peritoneum. *Gynecol Oncol* 2004;**94**:404-408.
216. Petit,T., Benider A., Yovine A., Bougnoux P., Spaeth D., Maindrault-Goebel F. et al Phase II study of an oxaliplatin/vinorelbine combination in patients with anthracycline- and taxane-pre-treated metastatic breast cancer. *Anti-cancer Drug* 2006;**17**:337-343.
217. De Pas,T., de Braud F., Mandala M., Curigliano G., Catania C., Ferretti G. et al Cisplatin and vinorelbine as second-line chemotherapy in patients with advanced non-small cell lung cancer (NSCLC) resistant to taxol plus gemcitabine. *Lung Cancer* 2001;**31**:267-270.
218. Varker,K.A., Phelps S.H., King M.M., and Williams C.L. The small GTPase RhoA has greater expression in small cell lung carcinoma than in non-small cell lung carcinoma and contributes to their unique morphologies. *Int J Oncol* 2003;**22**:671-681.
219. Boekelheide,K., Arcila M.E., and Eveleth J. cis-diamminedichloroplatinum (II) (cisplatin) alters microtubule assembly dynamics. *Toxicol App Pharm* 1992;**116**:146-151.

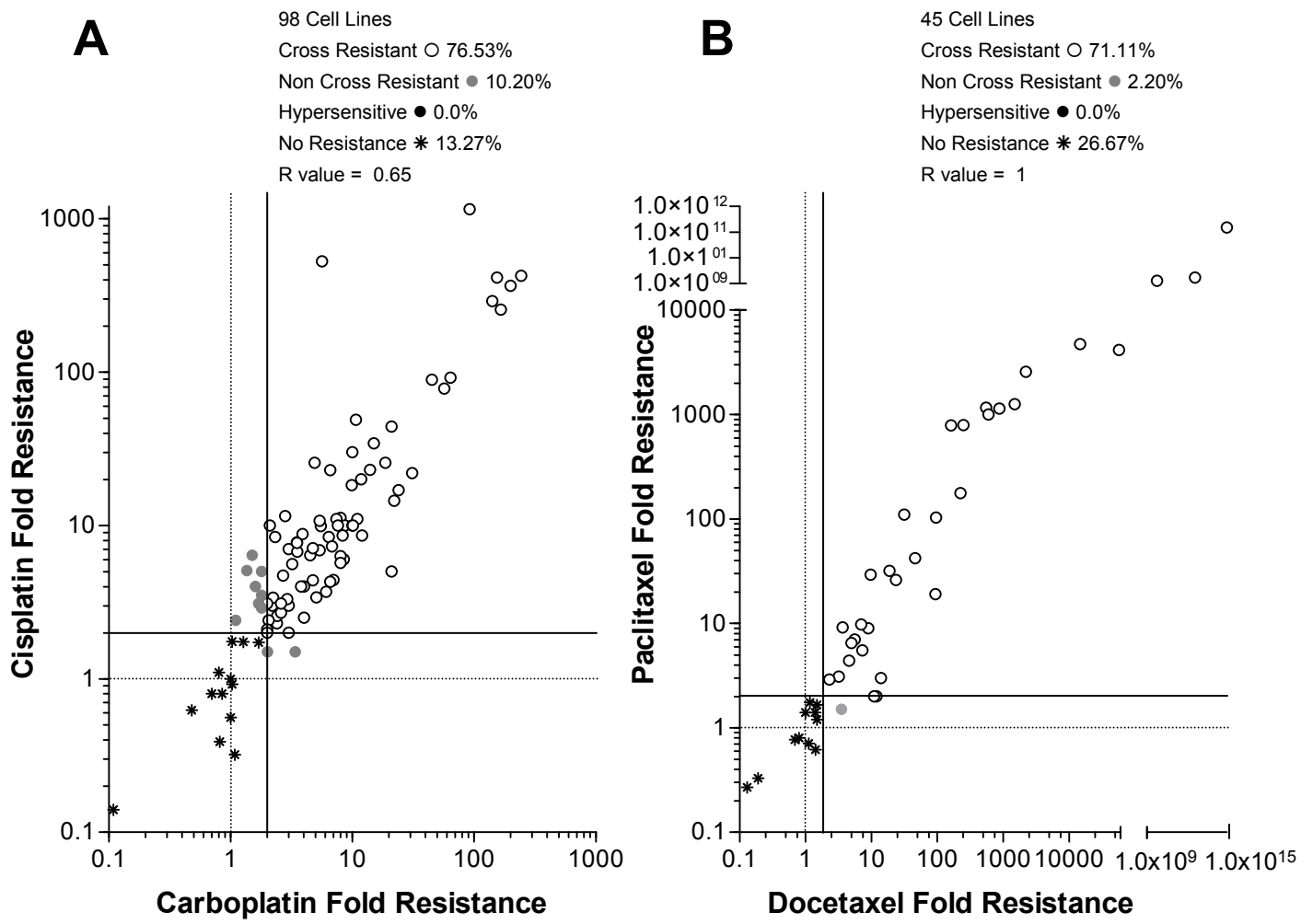
220. Weinstein, J.N., Myers T.G., O'Connor P.M., Friend S.H., Fornace A.J., Jr., Kohn K.W., et al. An information-intensive approach to the molecular pharmacology of cancer. *Science* 1997;**275**:343-349.
221. Kang, S., Ju W., Kim J.W., Park N.H., Song Y.S., Kim S.C., et al. Association between excision repair cross-complementation group 1 polymorphism and clinical outcome of platinum-based chemotherapy in patients with epithelial ovarian cancer. *Exp Mol Med* 2006;**38**:320-324.
222. Komatsu, M., Hiyama K., Tanimoto K., Yunokawa M., Otani K., Ohtaki M. et al Prediction of individual response to platinum/paclitaxel combination using novel marker genes in ovarian cancers. *Mol Cancer Ther* 2006;**5**:767-775.
223. Potti, A., Dressman H.K., Bild A., Riedel R.F., Chan G., Sayer R. et al Genomic signatures to guide the use of chemotherapeutics. *Nat Med* 2006;**12**:1294-1300.



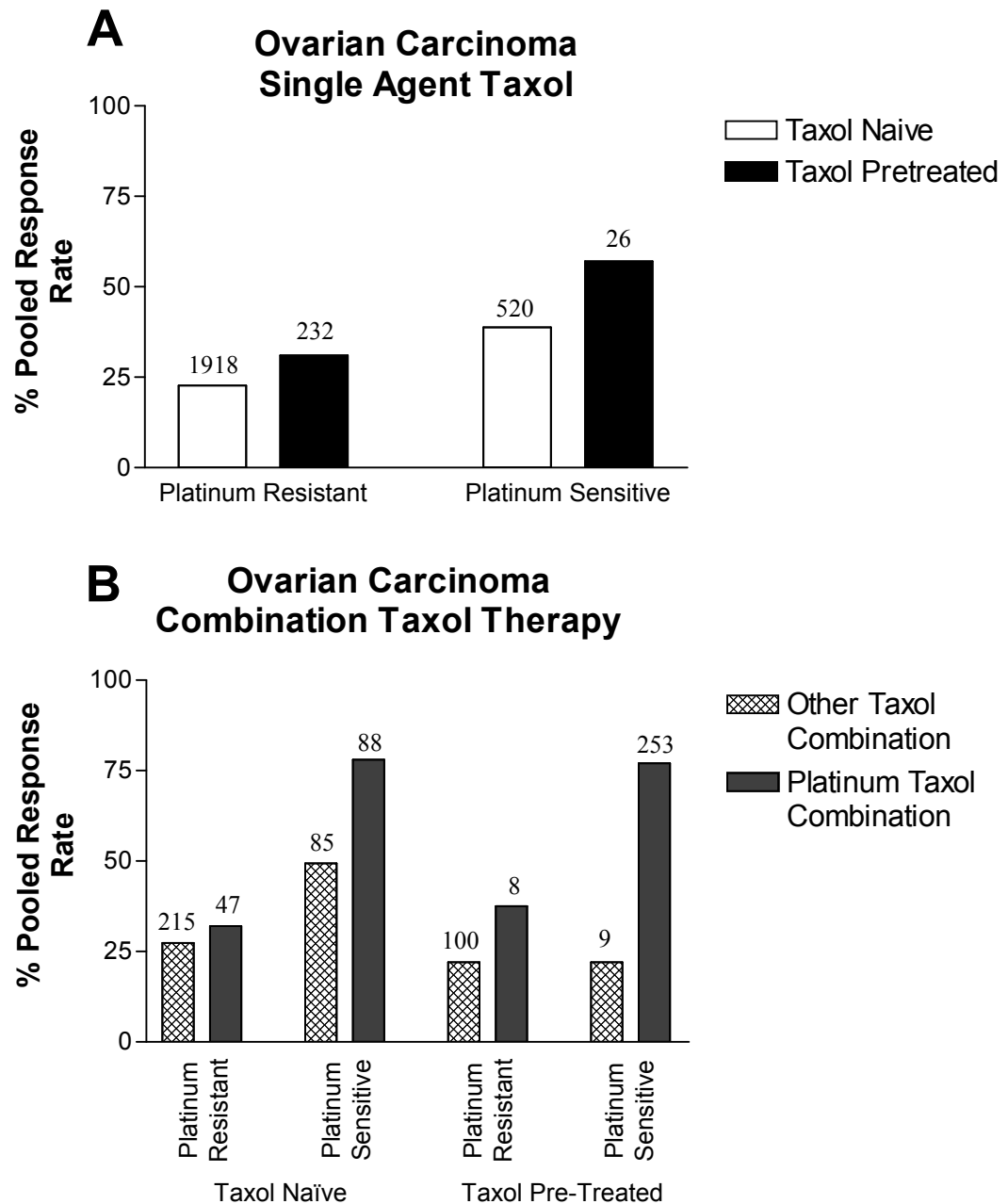
**Figure 1** - Inverse relationship between cisplatin and paclitaxel resistance in cell lines. A) The fold resistance of cisplatin was plotted against the fold resistance for paclitaxel for 137 models of acquired drug resistance. The dotted line at 1 indicates the resistance of the parent cell lines. 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 platinum 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.