TREATING CISPLATIN-RESISTANT CANCER: A SYSTEMATIC ANALYSIS OF OXALIPLATIN OR PACLITAXEL SALVAGE CHEMOTHERAPY

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Abstract

Objective: To examine the pre-clinical and clinical evidence for the use of oxaliplatin or paclitaxel salvage chemotherapy in patients with cisplatin-resistant cancer.

Methods: Medline was searched for 1) Cell models of acquired resistance reporting cisplatin, oxaliplatin and paclitaxel sensitivities and 2) Clinical trials of single agent oxaliplatin or paclitaxel salvage therapy for cisplatin/carboplatin-resistant ovarian cancer. **Results: Oxaliplatin -** Oxaliplatin is widely regarded as being active in cisplatin-resistant cancer. In contrast, data in cell models suggests that there is cross-resistance between cisplatin and oxaliplatin in cellular models with resistance levels which reflect clinical resistance (<10 fold). Oxaliplatin as a single agent had a poor response rate in patients with cisplatin-resistant ovarian cancer (8%, n=91). Oxaliplatin performed better in combination with other agents for the treatment of platinum-resistant cancer suggesting that the benefit of oxaliplatin may lie in its more favourable toxicity and ability to be combined with other drugs rather than an underlying activity in cisplatin resistance. Oxaliplatin therefore should not be considered broadly active in cisplatin-resistant cancer. **Paclitaxel** – Cellular data

suggests that paclitaxel is active in cisplatin-resistant cancer. 68.1% of cisplatin-resistant cells were sensitive to paclitaxel. Paclitaxel as a single agent had a response rate of 22% in patients with platinum-resistant ovarian cancer (n = 1918), a significant increase from the response of oxaliplatin ($p<0.01$). Paclitaxel-resistant cells were also sensitive to cisplatin, suggesting that alternating between agents may be beneficial. Studies of single agent paclitaxel in platinum-resistant ovarian cancer where patients had previously received paclitaxel had an improved response rate of 35.3% n=232 ($p<0.01$), suggesting that pre-treatment with paclitaxel improves the response of salvage paclitaxel therapy.

Conclusions: Cellular models reflect the resistance observed in the clinic as the cross resistant agent oxaliplatin has a lower response rate compared to the non-cross resistant agent paclitaxel in cisplatin-resistant ovarian cancer. Alternating therapy with cisplatin and paclitaxel may therefore lead to an improved response rate in ovarian cancer.

Keywords: Cisplatin, Oxaliplatin, Paclitaxel, Resistance, Ovarian Cancer, Salvage Chemotherapy

Chapter

Oxaliplatin has been widely regarded as potentially useful for the treatment of cisplatin-resistant cancer. The evidence cited for oxaliplatin's activity in cisplatin-resistant cancer comes in general from studies of highly cisplatin-resistant cell lines with low-level oxaliplatin resistance or review articles summarising these findings and oxaliplatin in general. While highly resistant models are useful to understand the possible mechanisms of resistance, drug resistance in the clinical setting typically occurs at lower levels of resistance (1;2) and may therefore involve different mechanisms of resistance.

Cisplatin and oxaliplatin target the DNA whereas paclitaxel, a taxane, causes toxicity by stabilising polymerised microtubules. Due to their differing mechanisms of action platinums and taxanes are often combined in cancer therapy. Our laboratory has found that when cells become resistant to platinum they often become sensitive to taxanes (3;4). Preliminary reading of the literature also suggested that the reverse is also true i.e. that taxane-resistant cell lines can be sensitive to platinum. We undertook this systematic review to identify, describe and critique the clinical and cellular evidence for the use of oxaliplatin or paclitaxel in patients with cisplatin-resistant cancer.

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 IC_{50} (drug concentration causing 50% growth inhibition) for these paired cell lines can be used to determine the increase in resistance known as fold resistance by the following equation:-

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

The literature search for models of acquired platinum resistance which report cross resistance data for both cisplatin and oxaliplatin identified 27 cell lines (5). For each cell line the fold oxaliplatin resistance was plotted against the fold cisplatin resistance, allowing an analysis of the pattern of cross resistance (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. For the purposes of this review we have defined cross resistance between cisplatin and oxaliplatin as greater than or equal to 2-fold resistance to both drugs. This definition is therefore based on what would be clinically observed as cross resistance.

Figure 1A shows that the majority of models of acquired platinum resistance are cross-resistant to both cisplatin and oxaliplatin having at least 2-fold resistance to both drugs. The lower level resistant models, below 10-fold, tend to be cross-resistant to a similar level to both drugs. However, the higher level resistant models, above 10-fold, are highly resistant to their selecting drug and then exhibit a lower level of resistance to the other drug. This suggests that a common mechanism of low-level resistance to both cisplatin and oxaliplatin develops at clinical levels of drug treatment. Whereas the resistance mechanisms that develop at higher drug concentrations are likely to be more specific for the selecting drug. This is in contrast with the cross resistance relationship between cisplatin and carboplatin which shows cross resistance at low and high level resistance, indicated by grey shading (6) (Figure 1B).

The literature search for models of acquired resistance which report cross resistance data for both cisplatin and paclitaxel identified 137 cell lines (6). 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 2A). 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 2A. It is the minority of cell models of acquired resistance 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. A similar inverse relationship was observed between cisplatin and docetaxel, carboplatin and paclitaxel and carboplatin and docetaxel, suggesting that an inverse resistance relationship exists between platinum and taxane chemotherapy (6).

The resistant cell lines found in the cisplatin/paclitaxel systematic review were diverse in type of carcinoma (Figure 2B). 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 2C). 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.

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 platinum resistant (7). 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 (8) where disease progression with a platinum free interval of less than 6 months is considered platinum resistant. Our search of the literature for single agent oxaliplatin salvage therapy in platinum-resistant ovarian carcinoma identified 4 studies. The response rate (RR) of the platinum- resistant cohort was very low RR 8%, n = 91 compared to the platinum-sensitive cohort RR 42%, n = 50 ($p < 0.05$ Chi-squared) (5). This suggests that there is no special activity of oxaliplatin in cisplatin-resistant cancer and correlates with the in vitro data suggesting that there is cross-resistance between cisplatin and oxaliplatin at clinically relevant levels of resistance. Oxaliplatin performed better in combination with other agents for the treatment of cisplatin-resistant cancer suggesting that the benefit of oxaliplatin may lie in its more favourable toxicity and ability to be combined with other drugs rather than an underlying activity in cisplatin resistance (5). Oxaliplatin therefore should not be considered broadly active in cisplatin-resistant cancer.

Our search of the literature for single agent paclitaxel salvage therapy in platinum-resistant ovarian carcinoma identified 56 studies. 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 paclitaxel naïve cisplatin resistant patients had a higher response rate of 22%, n = 1918 compared to the 8% response rate to oxaliplatin ($p < 0.01$). This again correlates with the in vitro data, there is a better response to the non-cross resistant agent paclitaxel than the cross resistant agent oxaliplatin (Figure 3). What was unexpected was platinum-resistant patients who have previously received paclitaxel therapy responded better to single agent paclitaxel (RR 35.3% n = 232) than the paclitaxel naïve patients (RR 22.7% n = 1918) ($p <0.01$ Chi-squared) (Figure 3) (6). Both cohorts of patients had very similar age, performance status, FIGO stage, and number of cycles of prior chemotherapy, there was a difference in histology but this did not account for this difference in response rates (6). 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.

Conclusions

Oxaliplatin is not highly active in cisplatin resistant cancer, this appears to be due to cross resistance between cisplatin and oxaliplatin at clinically relevant levels of resistance. This provides some insight into the mechanisms of resistance to these agents, low level resistance provides cross resistance to both but at higher levels of resistance the mechanisms diverge. Paclitaxel has higher activity in cisplatin-resistant ovarian cancer, supporting the inverse resistance phenotype observed in cell models. Paclitaxel salvage chemotherapy has higher activity in ovarian cancer patients who have received prior paclitaxel therapy suggesting that alternating between agents could improve response rates.

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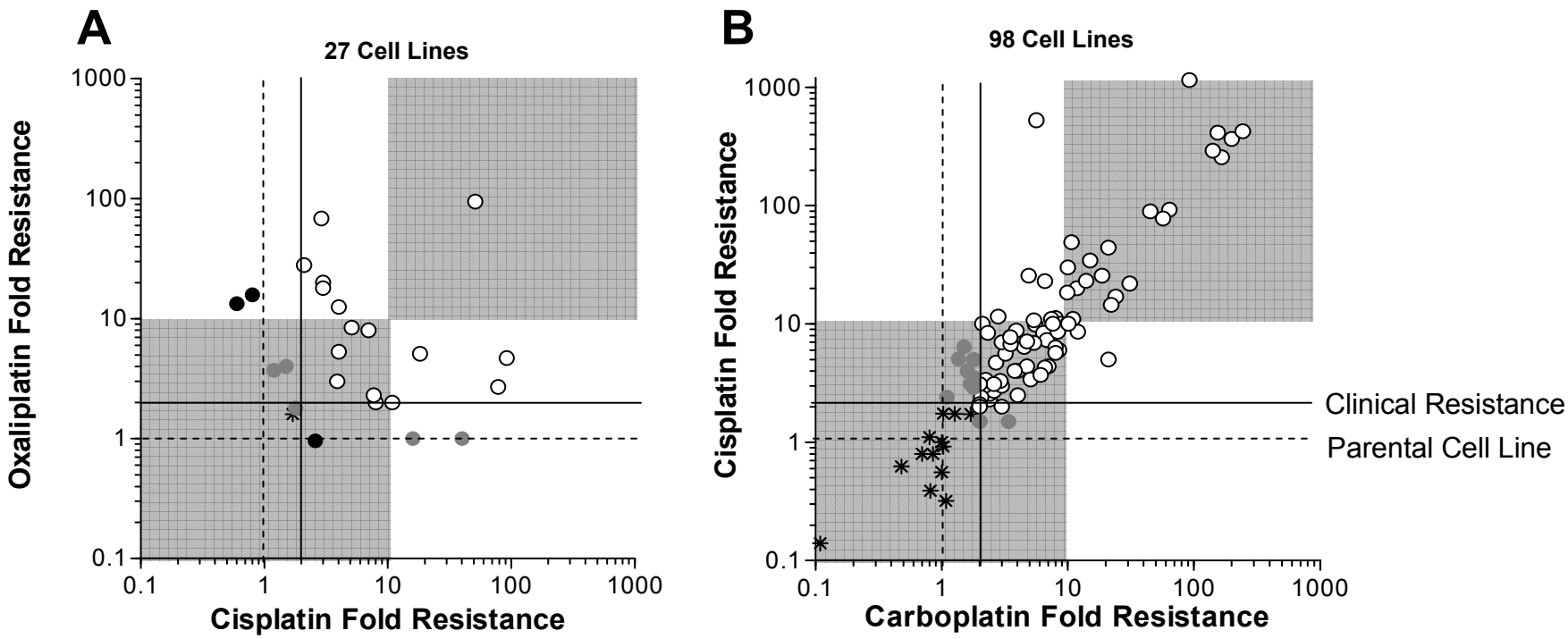

Figure 1 – Cross resistance between A) cisplatin and oxaliplatin and B) cisplatin and carboplatin in cell models of acquired platinum resistance. The dotted line at 1 indicates the fold resistance of the parental cell lines. The solid line at 2 indicates the level of clinical platinum resistance.

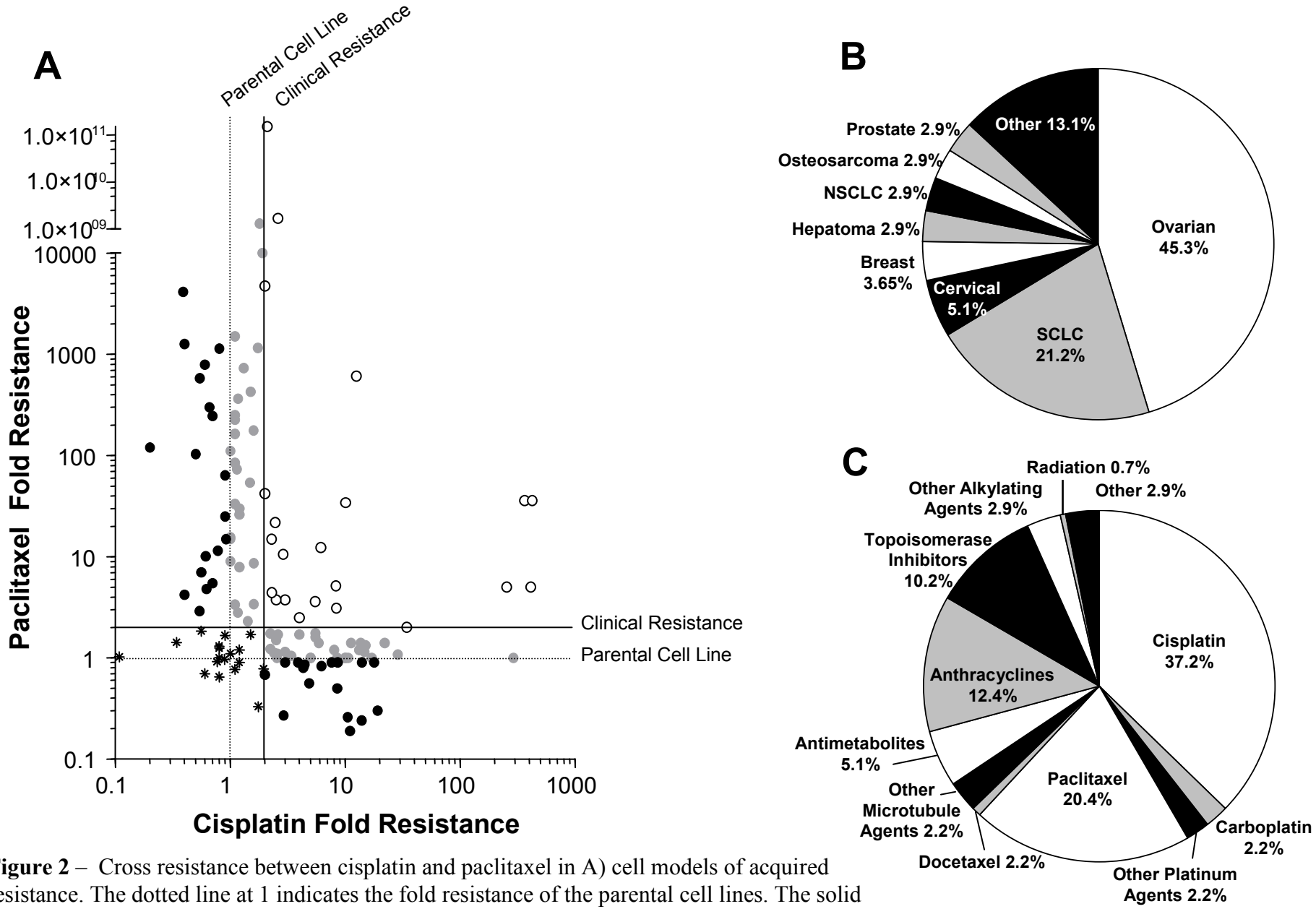

Figure 2 – Cross resistance between cisplatin and paclitaxel in A) cell models of acquired resistance. The dotted line at 1 indicates the fold resistance of the parental cell lines. The solid line at 2 indicates the level of clinical platinum resistance. Characteristics of the resistant models in the cisplatin/paclitaxel systematic review B) Types of carcinoma and C) Chemotherapeutics used to develop the resistant models. Reproduced from Stordal et al 2007, Cancer Treatment Reviews with permission from Elsevier Limited (6).

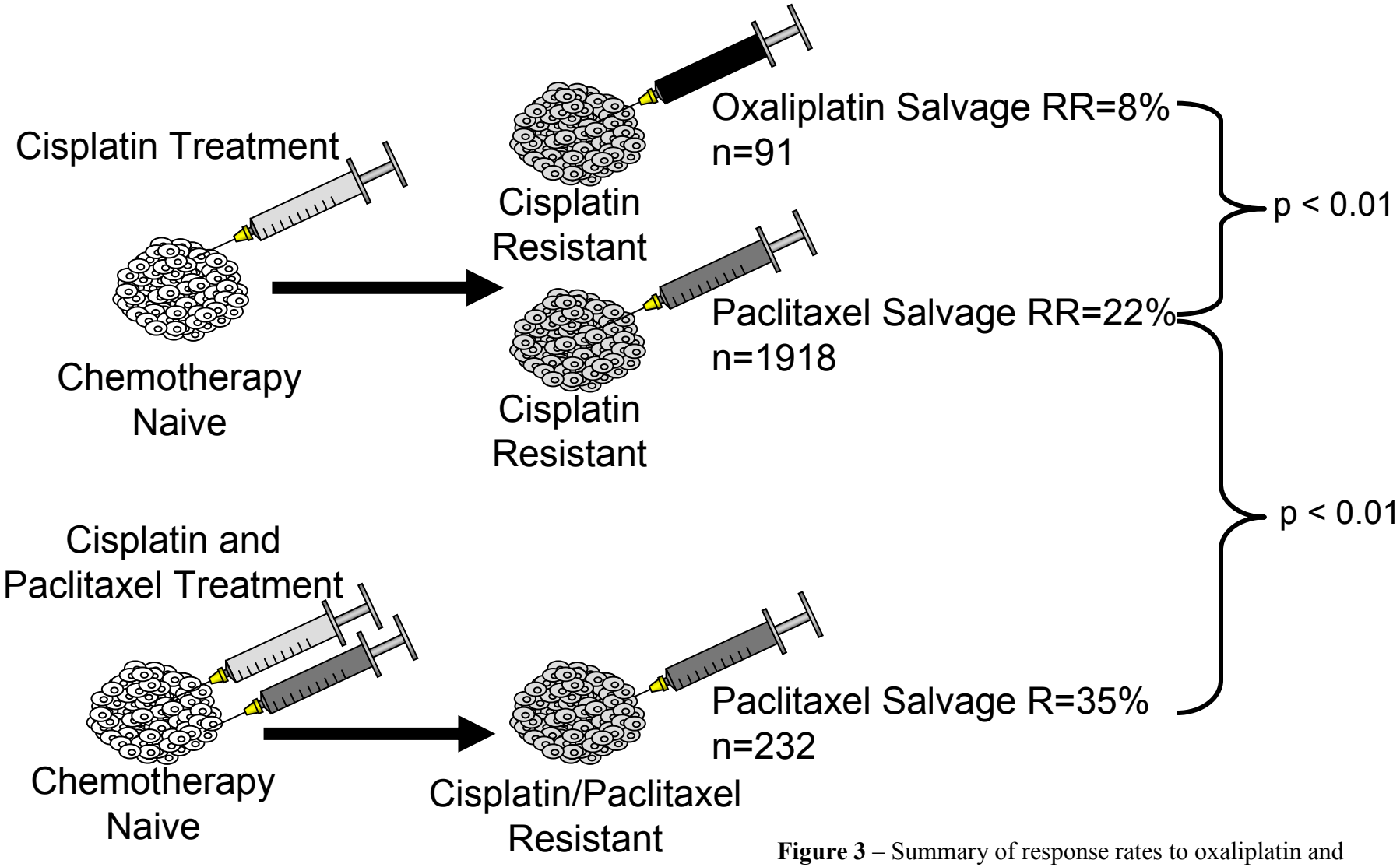

Figure 3 – Summary of response rates to oxaliplatin and paclitaxel salvage chemotherapy in cisplatin resistant ovarian cancer. Significant differences were determined by the Chi-squared test.