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Overcoming Platinum Resistance in Ovarian Carcinoma

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Abstract

Importance of the field—Ovarian cancer remains a deadly malignancy because most patients develop recurrent disease that is resistant to chemotherapy, including platinum. Because response rates for current treatment regimens are relatively similar and unfortunately low, no standard chemotherapy for platinum-resistant ovarian cancer exists.

Areas covered in this review—A systematic literature review of clinical studies published between January 2005 and March 2010 was conducted using search engines, PubMed and MEDLINE with the entry keywords, ovarian cancer and platinum resistance. This search revealed 40 clinical trials (1793 patients).

What the reader will gain—Gemcitabine was the most common drug used in clinical trials reporting higher response rates, $\geq +1$ SD of overall response rate (5 out of 8). Gemcitabine-based combination therapy showed an average response rate of 27.2% (95%CI 22.4–32.0). Combination of gemcitabine and pegylated liposomal doxorubicin (PLD) was the most common regimen (n=3) and was associated with possible additive effects in platinum-resistant ovarian cancer patients: response rate, gemcitabine alone 6.1%, PLD alone 19.8%, and gemcitabine with PLD 28.7% (95% CI 20.4–37.0), respectively.

Take home message—Analysis of recent clinical trials showed that gemcitabine-based combination chemotherapy was associated with the highest anti-tumor effects in platinum-resistant ovarian cancer patients during the study period.

Keywords

clinical trial; gemcitabine; ovarian cancer; platinum resistance; recurrence; review

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Declaration of interest

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1. Introduction

In 2009, an estimated 21,550 women in the United States were diagnosed with ovarian cancer and approximately 14,600 died from this disease.¹ The majority of ovarian cancer patients respond to initial therapy with tumor cytoreductive surgery and platinum-based chemotherapy.² However, approximately 70% of advanced stage patients will develop recurrent cancer and eventually succumb to recurrent disease typically characterized by multiple drug resistance.^{3–4} Nevertheless, platinum-based chemotherapy remains the mainstay for treatment of recurrent disease. Platinum resistance, defined as tumor progression during or within six months after completion of prior platinum therapy, is common in recurrent disease.^{5–6} Due to the poor survival of women with platinum-resistant ovarian cancer, understanding the mechanisms contributing to platinum resistance as well as improved therapeutic approaches are urgently needed. Historically, a number of chemotherapeutic agents have been used for patients with platinum-resistant ovarian cancer. However, due to relatively similar response rates with salvage therapy, no standardized treatment exists for these patients. The current study presents a systematic review of contemporary clinical studies in platinum-resistant ovarian cancer to evaluate the effectiveness of various therapies tested.

2. Methods

A systematic review of literature was conducted using public search engines, PubMed and MEDLINE, with entry keywords: ovarian cancer and platinum resistance. The review was limited to the English literature published between January 1, 2005 and March 1, 2010. This time period was chosen to focus on contemporary clinical studies for platinum-resistant ovarian cancer. Of the 319 studies identified during the 5-year period, 60 (18.9%) were original clinical articles that were further evaluated. Only the patients with platinum-resistant epithelial ovarian cancer were evaluated for these analyses. Patients with platinum-sensitive cancer as well as trials presented only in an abstract form were excluded from this study. The following parameters were identified for each article: year of publication, study design (clinical trial or non-trials such as, case series and retrospective reviews), type of chemotherapy regimen, class of drug, number of patients enrolled, number of patients that responded to therapy, and response rate (defined as sum of rates for complete response and partial response by RECIST criteria).⁷ Stable disease as defined by RECIST criteria was not included in response rate. Survival outcomes for progression-free survival (PFS) and overall survival (OS) from the start of current chemotherapy for the recruited clinical studies were also abstracted. Studies reporting survival outcomes only for the responding patients were not included. Cross-comparison analyses among clinical trials that used the same chemotherapy regimen unifying the variables (subject number enrolled and patients responding to therapy) were performed in our study. Statistical comparisons of response rates to chemotherapy regimens were compared between the trials and between the non-trial studies. Correlation of the response rate to chemotherapy and survival outcome was determined using the curve of best fit. Continuous variables were tested for normality using the Kolmogorov-Smirnov (KS) test and expressed either by mean ($\pm$ SD) or by median (range), as appropriate. Student *t*-test or Mann-Whitney *U* test was performed to determine the statistical significance of observed differences between study groups. Categorical variables were evaluated using Fisher's exact test with odds ratios and 95% confidence intervals (95%CI). All statistical tests were 2-tailed, and a *p* value <0.05 was considered statistically significant. The statistical significance of the data was determined using Statistical Package for Social Scientists software (SPSS, version 18.0, Chicago, IL). Information for type of chemotherapy for ongoing clinical trials was abstracted from the public website (<http://clinicaltrials.gov>).

3. Recent clinical studies

Sixty clinical studies were published during the study period. Of those, 40 (66.7%) were clinical trials (phase II, 37 studies) and the remaining 20 (33.3%) were non-trial studies. A total of 35 drugs over 17 classes were evaluated, which resulted in 40 regimens (Table 1). The most commonly used drugs are shown in Table 2. Among recent studies, gemcitabine was studied in 10 (25%) out of 40 clinical trials and 6 (30%) out of 20 non-trial studies, respectively, making it the most common drug studied. Topotecan-based therapies showed the lowest response rates among the most commonly used drugs (19.9% in clinical trials and 17.8% in non-trials, respectively). Tables 3 and 4 list all the studies evaluated for the analyses of clinical trials and non-trial studies, respectively. Figure 1 demonstrates the response rate based on type of regimen (monotherapy *versus* combination therapy). There were 1793 patients enrolled in clinical trials, and an average response rate of 16.0% (± 12.0) was noted in the 40 trials. The response rate was normally distributed (K-S test, $p=0.75$). There were 505 patients evaluated in 20 non-trial clinical studies with an average response rate of 26.3% (± 16.2) and a normal distribution (K-S test, $p=0.97$). Average response rate in clinical trials was significantly lower than that found in non-trial clinical studies ($p=0.02$). The response rate to therapy was significantly lower in platinum-resistant compared to platinum-sensitive ovarian cancer patients. For example, the response rate to topotecan-based therapy in platinum-resistant patients was only 18% whereas the response rate was 44% in platinum-sensitive recurrent ovarian cancer patients.⁸ Use of gemcitabine (5 out of 8) or pegylated liposomal doxorubicin (4 out of 8) was commonly seen in clinical trials that showed higher response rates ($\geq +1$ SD [$\geq 28\%$] above overall response rate, Table 3 and Figure 1). Conversely, monotherapy (7 out of 8) was commonly seen in the clinical trials that showed substantially lower response rates (≤ -1 SD [$\leq 4\%$] below overall response rate). Non-trial studies that showed $\geq +1$ SD of response rate ($\geq 42.5\%$) were common in regimens using paclitaxel (2 out of 4, Table 4). The mean value of median PFS among the evaluated studies was 4.1 (± 1.7) months in clinical trials and 4.4 (± 2.0) months in non-trial studies, respectively. Mean value of median OS among the evaluated studies from the start of the current treatment was 12.3 (± 3.3) months in clinical trials and 13.4 (± 5.1) months in non-trial studies, respectively. The proportion of studies with mono- or combination therapy for platinum-resistant ovarian cancer was similar (30 studies, respectively). The efficacy of combination therapy was statistically higher than monotherapy for platinum-resistant ovarian cancer patients (clinical trials, 21.7 vs. 10.1%, $p=0.009$; non-trial studies, 33.7 vs. 18.9%, $p=0.038$).

4. Approaches for Treating Platinum Resistance

4.1. Gemcitabine

Gemcitabine was the most commonly used drug for the treatment of platinum-resistant ovarian cancer patients during the study period. This finding is interesting because gemcitabine has been commonly used in platinum-sensitive recurrent ovarian cancer, but less commonly in platinum-resistant disease. In these studies with gemcitabine-based therapy, 571 subjects were enrolled in 16 gemcitabine-based studies (Table 2). Gemcitabine is a deoxycytidine analog, disrupting DNA polymerization after incorporation during DNA synthesis into cancer cells.⁹ Gemcitabine also shows cytotoxic activity by inhibiting ribonucleotide reductase thereby disrupting DNA repair mechanisms.⁹ This approach is useful for platinum-resistant cancers because enhanced DNA repair is commonly observed in recurrent tumors previously exposed to platinum-based treatment.¹⁰ Furthermore, the combination of gemcitabine with cisplatin has been shown to have synergistic activity with regard to platinum-DNA adduct formation in pre-clinical studies.¹¹

Gemcitabine monotherapy resulted in among the lowest response rates in platinum-resistant ovarian cancer, as demonstrated in a phase III randomized controlled trial (6.1%).¹² However,

once combined with other cytotoxic agents, response rates were significantly higher: combination therapy with any cytotoxic agents *versus* monotherapy, 27.2 vs. 6.1%, odds ratio 5.79, 95%CI 2.45–13.7, $p<0.0001$ (Figure 2). Gemcitabine-based therapy combined with epirubicin (48.1%, $p<0.0001$),¹³ with pegylated liposomal doxorubicin (28.7%, $p<0.0001$),^{14–16} with oxaliplatin (28.2%, $p=0.0001$),^{17–18} or with cisplatin (21.7%, $p=0.003$)^{19–20} demonstrated significantly higher response rates than treatment with gemcitabine alone. Combination therapy with gemcitabine and pegylated liposomal doxorubicin also showed a higher response rate than monotherapy with pegylated liposomal doxorubicin alone although it did not reach statistical significance (28.7 vs 19.8%, $p=0.087$). These studies suggest a possible additive or synergistic effect in the combined use of gemcitabine and pegylated liposomal doxorubicin. There were no trials that investigated monotherapy with cisplatin, oxaliplatin, or topotecan alone for platinum-resistant ovarian cancer patients during the study period. Combination of gemcitabine with topotecan did not reach statistical significance compared to gemcitabine monotherapy (17.4%, $p=0.093$).²¹

Among the five types of combination therapy, gemcitabine with epirubicin showed a significantly higher response rate compared to gemcitabine with cisplatin (48.1 vs. 21.7%, odds ratio 3.36, 95% CI 1.36–8.25, $p=0.013$) and compared to gemcitabine with topotecan (48.1 vs. 17.4%, odds ratio 4.41, 95%CI 1.18–16.4, $p=0.036$). The remaining combination therapies did not show statistically significant differences between gemcitabine with pegylated liposomal doxorubicin, oxaliplatin, cisplatin, and topotecan. Epirubicin is a new generation anthracycline; therefore, no previous studies investigating its efficacy in combination with gemcitabine in ovarian cancer patients had been reported. Although anti-tumor activity with gemcitabine and epirubicin was the highest among the 40 clinical trials in platinum-resistant ovarian cancer (response rate 48.1%, 95%CI 29.3–67.0), the study size was relatively small, making it susceptible to type II error ($n=30$).¹³ Further trials are needed to better characterize the efficacy of this combination treatment among patients with platinum-resistant ovarian cancer. Combination gemcitabine with pegylated liposomal doxorubicin was the most common regimen ($n=3$, 7.5%) in the 40 clinical trials during the study period.^{14–16} This regimen was also associated with the third highest response rate among the evaluated chemotherapy regimens in the recent clinical trials (28.7%, 95%CI 20.4–37.0). The combination of these two agents was chosen because of differing mechanisms of action, possible synergistic effects, and minimally overlapping toxicity profiles.¹⁴ Although topotecan was commonly used in recent clinical trials, only one study evaluated the efficacy of gemcitabine combined with topotecan.²¹ The response rate of this trial was below the average of other clinical trials utilizing combination therapies (17.4 vs. 21.7%, Figure 1), and no statistical difference was seen in the response rate between gemcitabine alone and gemcitabine with topotecan (Figure 2). Prior to this study period, only one other study evaluating the combination of gemcitabine and topotecan in platinum-resistant ovarian cancer had been published,²² and a similar response rate was reported (12.5%). Therefore, in these limited clinical studies, adding gemcitabine with topotecan does not appear to confer any additional therapeutic benefit in platinum-resistant ovarian cancer.

4.2. Pegylated liposomal doxorubicin

Pegylated liposomal doxorubicin is polyethylene glycol coated liposomal doxorubicin.²³ The strength of pegylated liposomal doxorubicin is that monotherapy alone produces sufficient anti-tumor effects in platinum-resistant ovarian cancer. In our analyses of clinical trials for platinum-resistant ovarian cancer, average response rate from 3 studies in which monotherapy was given was among the highest of all tested monotherapy agents (response rate 19.4%, Figure 1).^{12, 24–25} Of note, the average response rate of monotherapy in the setting of platinum-resistant cancer was only 10.1% (95%CI 8.4–11.8). The average response rate of pegylated liposomal doxorubicin monotherapy was similar to the average response rate from 13 clinical

trials with combination therapy given to platinum-resistant ovarian cancer patients (21.7%, 95% CI 18.3–25.0). This information is useful for patients treated with pegylated liposomal doxorubicin because adverse effects during chemotherapy are often associated with multi-drug regimens and can be a limiting factor for discontinuation of chemotherapy.

Despite the multiple trials with pegylated liposomal doxorubicin, the second most commonly tested drug during the study period, there were only two types of combination therapy that were used with it (2 studies with topotecan^{26–27}, 3 studies with gemcitabine^{14–16}). The rationale to combine topotecan and pegylated liposomal doxorubicin originated from differences in dose-limiting toxicity profiles.²⁶ However, the addition of topotecan to pegylated liposomal doxorubicin does not appear to confer additional therapeutic benefit (monotherapy *versus* topotecan combination, 19.4 vs. 19.1%, $p=1.0$).^{26–27} Conversely, the combination of pegylated liposomal doxorubicin with gemcitabine may result in additional benefit. Although it did not reach statistical significance, this is most likely due to the small sample size and the fact that the average response rate among trials with gemcitabine tended to be higher than trials with pegylated liposomal doxorubicin alone (response rate, 28.7 vs. 19.4%, odds ratio 1.67, 95% CI 0.96–2.9, $p=0.087$). These observations provide a rationale for developing additional combination regimens with pegylated liposomal doxorubicin.

The sequence of drug administration in the two trials of pegylated liposomal doxorubicin and topotecan was: pegylated liposomal doxorubicin followed by topotecan (response rate 28%)²⁶; and simultaneous initiation of both drugs in each cycle (response rate 9.1%, $p=0.14$ compared to the other regimen).²⁷ Although these two regimens did not demonstrate a statistically significant difference, the response rate of the regimen with simultaneous delivery was lower than the sequentially dosed regimen. Prior to the study period, there was a phase II clinical trial that showed a higher response rate with sequential administration of topotecan followed by etoposide (response rate 38%) in platinum-resistant ovarian cancer.²⁸ In that study, pretreatment with topotecan was postulated to increase inhibition of topoisomerase II- α , which would allow sensitization to etoposide.²⁸ Taken together, the sequence of administration of topotecan appears to be a potentially important factor affecting response to therapy. Due to the limited number of studies on this topic, a definitive answer remains to be determined. Further investigations are needed to determine the optimal sequence of topotecan-based chemotherapy.

4.3. Platinum agents

Platinum-based chemotherapeutics elicit their cytotoxic effects by forming intra-strand cross-links of DNA and platinum that induces cell apoptosis.²⁹ Platinum remains the mainstay of treatment of recurrent disease in ovarian cancer patients. Current active members of available platinum agents include cisplatin, carboplatin, and oxaliplatin. In our analyses of published studies, 10 (16.7%) of the 60 clinical studies used platinum agents for patients with platinum resistance.^{17–20, 30–35} Among clinical trials, 6 (10%) studies used platinum-based therapies such as cisplatin ($n=3$),^{19–20, 30} carboplatin ($n=1$),³¹ and oxaliplatin ($n=2$).^{17–18} None of these studies used solely platinum-based monotherapy. Rather, all were combined with other cytotoxic agents such as gemcitabine ($n=4$), ifosfamide ($n=1$), paclitaxel ($n=1$), cyclosporine ($n=1$), and interferon ($n=1$) (Table 3). Among the non-trial studies, 4 (20%) studies evaluated cisplatin ($n=1$)³⁶ or carboplatin ($n=3$).^{32–33, 35} One of 4 studies tested carboplatin monotherapy,³⁵ and the remaining three tested combination therapy with paclitaxel (Table 4).

The issue of re-treatment with platinum agents in the setting of recurrent platinum-resistant ovarian cancer has been extensively debated. See and colleagues evaluated the effectiveness of re-treatment with carboplatin monotherapy in 34 patients diagnosed with platinum-resistant recurrent ovarian cancer.³⁵ This approach was based on the premise that a prolonged platinum-free interval of more than 1 year may restore sensitivity to platinum drugs in patients with

previously diagnosed platinum-resistant ovarian cancer. However, this study reported only 2 (5.9%) patients with a partial response, which was one of the lowest response rates in our analyses (more than 1 SD below the average response rate). Although some effect with platinum-monootherapy re-treatment may be evident in patients with platinum-resistant ovarian cancer, the broad use of this therapeutic strategy must be carefully evaluated prior to clinical implementation. On the other hand, when platinum agents were combined with other cytotoxic agents, these regimens were among the more effective treatments in platinum-resistant disease (response rate, 6 clinical trials 21.3%, 95% CI 16.0–26.7; and 3 non-trial studies 43.2%, 95% CI 28.5–57.8). A newer generation of platinum, oxaliplatin, was developed with the goal of overcoming platinum resistance. Indeed, oxaliplatin as a single agent or in combination with other agents in ovarian cancer demonstrated minimal cross-resistance with cisplatin or carboplatin,³⁷ while simultaneously showing some therapeutic activity in recurrent ovarian cancer.³⁸ In our analyses of clinical trials, oxaliplatin combined with gemcitabine showed similar response rates to cisplatin combined with gemcitabine (28.7 vs. 21.7%, $p=0.37$); however, many on-going pre-clinical studies are actively investigating new synthetic platinum compounds that may have future clinical applications.^{39–40}

4.4. Taxanes

Paclitaxel and docetaxel are both taxanes that inhibit microtubule dis-aggregation. Both agents are commonly used in first line chemotherapy after primary cytoreductive surgery in ovarian cancer. Paclitaxel monootherapy showed the highest response rate among the tested monootherapy drugs in clinical trials given to platinum-resistant recurrent ovarian cancer patients (20.9%).⁴¹ Though not clinical trials, paclitaxel-based regimens employing a weekly dosing schedule also resulted in the two highest response rates (60% and 53%, respectively, Table 4).^{32, 42} Dose-dense combination therapy with carboplatin and paclitaxel to platinum-resistant ovarian cancer patients also showed a high response rate although it showed a wide 95% CI due to the limited subject number tested ($n=8$, response rate 37.5%, 95% CI 4–71%).³³ While the original basis for the once weekly dose-dense schedule for paclitaxel administration was to maintain intense and prolonged exposure of the drug to the target cells,⁴² emerging data contends that the therapeutic effects may also reflect semi-metronomic dosing resulting in anti-angiogenic effects rather than purely a dose-density effect. In this setting, combination of paclitaxel with bevacizumab may be an attractive approach for patients with platinum-resistant disease. A retrospective analysis of 55 patients with recurrent ovarian cancer treated with weekly paclitaxel and biweekly bevacizumab showed a 60% (95% CI 47.1–72.9) response rate including a 25% complete response rate.⁴³ Future clinical development of this regimen is expected in platinum-resistant patients. Although docetaxel did not demonstrate a favorable therapeutic response in our analyses during the study period, this was most likely due to the limited patient sample size ($n=7$).⁴⁴ Prior to the study period, 4 published phase II clinical trials evaluating docetaxel monootherapy in platinum-resistant ovarian cancer reported a wide range of response rates ranging from 6.9% to 35%.^{45–48} The overall response rate with docetaxel in platinum-resistant ovarian cancer patients among these five trials was 17.6% (95% CI 10.9–24.3) in 125 patients, which was comparable to paclitaxel monootherapy.^{44–48}

4.5. Bevacizumab

Bevacizumab is a human monoclonal antibody against the critical pro-angiogenic factor, vascular endothelial growth factor (VEGF) that contributes to angiogenesis, tumor growth, and metastasis.⁴⁹ In an analysis of recent clinical trials, bevacizumab monootherapy showed one of the highest response rates in platinum-resistant disease (bevacizumab *versus* all other monootherapy agents evaluated in our study, 15.9 vs. 10.1%, Figure 1).⁵⁰ Although there were no published clinical trials evaluating combination therapy with bevacizumab during the study period, a retrospective analysis of 2 studies studying bevacizumab-based combination therapy

(with cyclophosphamide, 5-fluorouracil, docetaxel, or gemcitabine + liposomal doxorubicin) reported promising response rates in platinum-resistant disease (37.5%, 95% CI 20.7–54.3, Table 4).^{51–52} Currently, multiple phase II clinical trials testing bevacizumab-based combination therapy either with docetaxel, topotecan, temsirolimus, pemetrexed, sorafenib, or erlotinib for platinum-resistant disease are ongoing.

4.6. Other new agents

Several new agents have been evaluated for platinum-resistant disease (Table 1). Response rates of monotherapy with ixabepilone (14.3%), 9-aminocamptothecin (14%), pemetrexed (13.4%), and LY355703 (12.5%) were comparable or higher across 19 evaluated regimens (overall response rate 10.1%, Figure 1). Ixabepilone is a microtubule-stabilizing epothilone B analog with anti-tumor activity in taxane-resistant breast cancer.⁵³ DeGeest and colleagues extended these observations and reported the anti-tumor efficacy of ixabepilone in platinum-resistant ovarian cancer to be higher than average compared to other monotherapies tested.⁵³ No published studies reporting the efficacy of combination therapy of ixabepilone were identified. 9-aminocamptothecin, a camptothecin analog, inhibits the activity of topoisomerase I.⁵⁴ Despite its better than average anti-tumor activity among evaluated monotherapy agents in our study, the authors concluded that the prolonged infusion schedule (continuous infusion for 120 hours) may be a barrier to adopting this treatment in the future.⁵⁴ Pemetrexed is an anti-folate agent that inhibits all folate-dependent metabolic enzymes involved in thymidine and purine nucleotide pathways.^{55–56} One of the studies that used pemetrexed monotherapy reported encouraging anti-tumor activity with a response rate among the highest of evaluated monotherapy regimens (21%, Table 3).⁵⁵ Clinical trials for recurrent platinum-resistant and -sensitive ovarian cancer testing pemetrexed in combination with bevacizumab and with carboplatin are currently ongoing. LY355703 is a cytotoxic cryptophycin analog that destabilizes microtubules during mitosis.⁵⁷ This mechanism of action is opposite to the one of taxanes. In pre-clinical experiments, LY355703 elicited anti-tumor effects in multidrug resistant cells, including taxane-resistant cells.⁵⁷ CKD-602 is a newly developed camptothecin analog that inhibits topoisomerase I. CKD-602 showed superiority over parental drugs by overcoming the difficulty of toxicity and poor water solubility.⁵⁸ Although the overall response rate of CKD-602 monotherapy was encouraging, the relatively small number of subjects (n=5) mandates further exploration of this agent before treatment recommendations can be developed. Tamoxifen-based therapy demonstrates very low response rates in platinum-resistant ovarian cancer in our analyses (average response rate, 3.6%).^{59–60}

5. Role of evaluating progression-free survival in chemotherapy response

Chemotherapy response is generally determined by RECIST criteria, the mainstay of the standard evaluation of solid tumors, including ovarian cancer. These evaluations are based on the change in the size of tumors, and do not include survival functions such as PFS. Because PFS directly reflects the durability of the effect of a given chemotherapy in trials or studies, we evaluated potential relationships between PFS and chemotherapy response rates. As expected, PFS significantly correlated with chemotherapy response rates in platinum-resistant ovarian cancer studies (clinical trials, $p < 0.001$; non-trial studies, $p = 0.01$, Figure 3). However, a select sub-group of studies did not fit the results of this correlation and merit special attention. First, we divided results of clinical trials into 4 categories based on the cutoff values of PFS and response rate as determined by the mean values, 4.1 months and 16%, respectively. These cutoffs divide the trials into the following categories: Category A, both response rate and PFS were above the average; Category B, although response rate is above the average, PFS is below the average; Category C, although response rate is below the average, PFS is above the average; and Category D, both parameters were below the average (Figure 3). We established that Category A trials included desirable regimens while Category D regimens were not desirable.

Category B regimens merit special attention because these studies actually, yet unexpectedly, showed significantly shorter PFS than studies with Category A regimens despite reportedly higher response rates (mean PFS in clinical trials, Category B vs. A, 3.1 vs. 5.1 months, $p<0.001$, Figure 3). Category C therapies, on the other hand, hold some promise of anti-tumor effects because these regimens resulted in longer PFS than average despite somewhat lower response rates. There was no statistical difference in PFS in Category C studies compared to Category A trials (mean PFS Category C vs. A, 5.8 vs. 5.1 months, $p=0.24$). Categories B or C, regarded as “gray zone regimens,” comprised approximately one third of the regimens with response rates higher or lower than the average of clinical trials, respectively (Category B, 30.8% in Category A+B; and Category C 27.3% in Category C+D). Table 5 shows the actual chemotherapy regimens based on response rates and PFS. Gemcitabine-based combination therapy remained a favorable regimen in more than half of trials in Category A (5 out of 9).

Platinum resistance, as defined by the Gynecologic Oncology Group (GOG), covers a relatively broad range of time frame for tumor recurrence. It is possible that the biology of tumors growing during postoperative chemotherapy administration (i.e., platinum refractory) may differ from tumors that recur at around the six month time period following completion of postoperative chemotherapy. It is also possible that tumors in Category B were more aggressive than Category A while tumors in Category C were less aggressive than Category D. In this setting, it may be useful to refine the definition of platinum resistance to cover a more narrow range of time than the current 6 months time frame. Some groups such as Gynecologic Cancer Intergroup (GCIg) are considering the 3 month time point for defining platinum-resistance instead of 6 months. In the current study, we proposed grouping PFS and response rate into 4 categories, which we believe may provide a more biologically pertinent classification. However, the classification of regimens into four categories based on chemotherapy response and PFS may potentially be arbitrary (Table 5). Due to the limited number of patients, it cannot be excluded that certain regimens may have been misclassified above or below average just by chance. Our classification describes the common observation that some patients may obtain a significant, but short response, while others may demonstrate modest but durable remissions. The general impression is that this phenomenon could be due to different biological behavior of the tumor rather than truly different activity of the treatment. The latter hypothesis could safely be tested only in the context of large prospective randomized trials.

6. Conclusion

We conducted a systematic review of 60 recent clinical studies that included a total of 2298 patients with platinum-resistant ovarian cancer. All together, the chemotherapy response rate in clinical trials for patients receiving any type of chemotherapy for platinum-resistant recurrent ovarian cancer was 16.0% (± 12.0) in clinical trials, and 26.3% (± 16.2) in non-trial clinical studies, respectively. As expected, combination therapy showed higher anti-tumor activity than monotherapy (clinical trial, 21.7 vs. 10.1%; and non-trial studies, 33.7 vs. 18.9%, respectively). Gemcitabine-based therapy was the most common regimen and reported the highest response rates to platinum-resistant ovarian cancer. Gemcitabine with pegylated liposomal doxorubicin and with platinum agents were well-studied regimens that demonstrated sufficient anti-tumor activity with possible synergistic effects demonstrated in relatively large study populations.

7. Expert Opinion

In 2006, the US Food and Drug Administration (FDA) approved the use of gemcitabine only for platinum-sensitive recurrent ovarian cancer patients. As of 2009, the FDA approved the use of gemcitabine combined with another cytotoxic agent for patients with advanced ovarian cancer who do not show response to other chemotherapy agents. Because gemcitabine-based combination therapy was among the most effective regimens for platinum-resistant ovarian

cancer in our analyses (5 out of 8 clinical trials with $\geq +1$ SD improved response rates were gemcitabine-based therapy, Table 3), a gemcitabine-based combination therapy appears to be a favorable approach to overcome platinum-resistance in ovarian cancer patients. In our analyses combining PFS with response rate, gemcitabine-based combination therapy was the most common regimen in the subgroup showing substantial response rates and PFS (Category A in Table 5 and Figure 3). While modest improvements in response rates with combination chemotherapy may be attractive, the decision to use such regimens must carefully balance the potential for increased toxicity in a setting where cure is unattainable. Indeed, gemcitabine-based therapy was associated with considerable incidence of grade 3 or 4 neutropenia, and 62.5% of clinical trials with gemcitabine-based therapy reported a 50% or higher incidence of grade 3 or 4 neutropenia (range 26% to 80%).^{12–21} Furthermore, more toxicity was associated with gemcitabine-based therapy compared to non gemcitabine-based therapy. For example, in a phase III randomized trial, gemcitabine therapy was associated with increased risk of severe neutropenia compared to pegylated liposomal doxorubicin (grade 3 or 4, 38.4 vs. 18.8%, $p=0.003$).¹² This toxicity profile associated with gemcitabine-based therapy could explain the reason for its lack of integration as the standard therapy for recurrent ovarian cancer. Further trials are expected to elucidate the efficacy of gemcitabine-based combination therapy.

The development of liposomal doxorubicin has resulted in improvement of drug delivery with a concomitant decrease in toxicity compared to free doxorubicin alone.²³ A liposomal carrier is designed to have a longer circulating half-life and thus enhance the tumoral uptake of drug. Increased efflux of platinum is one of the known mechanisms associated with developing platinum-resistance in ovarian cancer.⁶¹ Therefore, developing mechanisms to either increase the uptake of cytotoxic agents into tumor cells or improve retention of cytotoxic agents within tumor cells may be an attractive approach to overcome platinum resistance. Pre-clinical studies of a newly synthesized pegylated liposomal cisplatin showed promising results with regard to increased intracellular cisplatin concentrations.⁶² Additional clinical development with pegylated liposomal cisplatin is warranted in platinum-resistant ovarian cancer. One delivery mechanism of liposomal drugs includes the endocytotic pathway. Inducing cellular endocytosis with macromolecular drug complexes was associated with increased drug uptake into platinum-resistant cell lines.³⁹ Developing targeted drug delivery systems with developing new liposomal carriers is an important strategy to overcome platinum resistance and requires further investigation in this area.

Targeting DNA repair mechanisms is an attractive therapeutic approach in platinum-resistant ovarian cancer. Most of the platinum-based combination therapies in our analyses are fundamentally expected to have the additional benefit of targeting one of the major mechanisms of platinum resistance (i.e., enhanced repair mechanism of damaged DNA).¹⁰ The platinum and gemcitabine regimen was the most common combination among platinum-based trials, and this pairing was designed to inhibit ribonucleotide reductase to then block the repair of damaged DNA by gemcitabine.⁹ The response rates of platinum with gemcitabine were overall higher than the average response rates across all trials using combination therapy (24.5%, 95% CI 17.9–31.1). Other approaches targeting DNA repair mechanisms in platinum-resistant tumors in recent published trials have added cyclosporine to platinum.³¹ Cyclosporine alters the expression of oncogenes as well as other genes associated with the DNA repair mechanism, thereby reversing platinum resistance.³¹ Important molecular targets in the DNA repair mechanism in ovarian cancer include poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP),⁶³ excision repair cross-complementation group 1 (ERCC1),⁶⁴ and breast cancer gene (BRCA).⁶⁵ Multiple pre-clinical studies have demonstrated that alterations of these enzymes are associated with platinum resistance in ovarian cancer, and phase II clinical trials with PARP inhibitors are underway in ovarian cancer patients. Future clinical trials are expected to further evaluate the efficacy of targeting DNA repair mechanisms. Of additional interest may be to further evaluate the combination of a platinum agent with an inhibitor of the DNA damage

repair mechanism. Bearing in mind that altered DNA repair mechanisms are not the only pathways of platinum resistance, other mechanisms contributing to platinum resistance worthy of exploration include abnormal platinum transport.⁶¹ Increased expression of ATP7B, a metal transporter, is associated with platinum-resistant ovarian cancer. Inhibiting ATP7B with small interference RNA (siRNA) reversed cisplatin resistance in platinum-resistant cells.⁶¹ RNA interference therapy with siRNA offers a unique therapeutic option because (i) many important targets are not “drugable” by other methods, (ii) the functional protein structure is not known for many targets, (iii) many tyrosine kinases also have known and unknown kinase-independent functions, and (iv) multiple important and functionally relevant phosphorylation sites often exist within a target. Although RNA interference therapy is currently in pre-clinical stages, the potential clinical utility of RNA interference therapy deserves special consideration.

Some potential limitations of our study include the following: (i) The number of lines of chemotherapy administered to the patient is an important aspect that should be considered in reference to response rates; (ii) although our studies evaluated for the analysis were predominantly similar, that is, platinum-resistant ovarian cancer, indirect comparisons across different studies makes it difficult to draw definitive conclusions regarding the efficacy of chemotherapy. Nevertheless, our study offers valuable information for design of future trials; (iii) the primary end-point of therapy in the setting of recurrent ovarian cancer is palliation; therefore, the quality of life should also be considered.⁶⁶

8. Article Highlights

- Ovarian cancer remains the leading cause of death among gynecologic malignancies. Platinum resistance is commonly seen in recurrent ovarian cancer patients. There is currently no standard chemotherapy for recurrence.
- Overall chemotherapy response rate in clinical trials for patients who received any type of chemotherapy for platinum-resistant recurrent ovarian cancer was 16.0% with mean progression-free survival of 4.1 months from the treatment. Combination therapy showed higher response rates than monotherapy (21.7 vs. 10.1%).
- Gemcitabine was the most common drug used in clinical trials. Gemcitabine-based combination therapy showed an average response rate of 27.2%, and was the most common therapy among the group of regimens with above average response rate and progression-free survival.

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Figure 1.

Figure 2.

Figure 3.

Table 1

Drug agents used in recent clinical studies for platinum-resistant ovarian cancer.

Class							
Alkylating agents	canfosfamide		cyclophosphamide		ifosamide		irofulven
Anthracyclines	doxorubicin		epirubicin		PLD		sabarbucin
Cryptophycin analog	LY355703						
Cytokine	interferon- α						
Epothilone B analog	ixabepilone						
Folate antimetabolites.	pemetrexed						
5-Fu prodrug	capecitabine						
Hormonal related	goserelin		letrozole		2-methoxyestradiol		tamoxifen
Immunosuppressive	cyclosporine						
Marine-derived agent	trabectedin						
Monoclonal antibody	bevacizumab		matuzumab				
Nucleoside analog	gemcitabine						
Platinum agents	carboplatin		cisplatin		oxaliplatin		
Small molecular inhibitors	gefitinib		imatinib				
Taxanes	docetaxel		paclitaxel				
Topoisomerase inhibitors	9-aminocamptothecin		etoposide		irinotecan		topotecan
Vinca alkaloids	navelbine						

Shown in alphabetical order.
Abbreviation: PLD, pegylated liposomal doxorubicin

Table 2

Common drugs used in recent clinical studies for platinum-resistant ovarian cancer.

	Number (%)	Subjects	RR (%)
Clinical trials (n=40)			
Gemcitabine	10 (25%)	430	22.3
Pegylated liposomal doxorubicin	8 (20%)	339	22.4
Topotecan	4 (10%)	96	19.9
Cisplatin	3 (7.5%)	114	21.9
Docetaxel	3 (7.5%)	61	19.7
Non-trial studies (n=20)			
Gemcitabine	6 (30%)	141	22.7
Paclitaxel	4 (20%)	89	39.3
Topotecan	3 (15%)	113	17.8
Carboplatin	3 (15%)	62	27.4
Pegylated liposomal doxorubicin	2 (10%)	53	28.3
Bevacizumab	2 (10%)	32	37.5

Analysis of 60 clinical studies published between January 2005 and March 2010.

Abbreviations: Number, number of clinical studies; Subjects, sum of enrolled patients in clinical studies; and RR, average response rate in any regimens using the listed agent.

Table 3

Clinical trials conducted for platinum-resistant ovarian cancer.

Year	Chemotherapy regimen	Subjects	RR (%)
2006	gemcitabine + epirubicin ¹³	30	43.3
2008	pegylated liposomal doxorubicin (biweekly) ²⁴	50	40
2008	gemcitabine + pegylated liposomal doxorubicin ¹⁴	48	37.5
2009	gemcitabine + oxaliplatin ¹⁷	50	37
2007	gemcitabine + cisplatin (biweekly) ¹⁹	35	31.5
2007	irinotecan + doxorubicin ⁶⁷	13	30.8
2006	gemcitabine + pegylated liposomal doxorubicin ¹⁵	30	33.3
2006	topotecan + pegylated liposomal doxorubicin ²⁶	27	28
2009	topotecan + docetaxel (weekly) ⁶⁸	29 [†]	25
2006	pegylated liposomal doxorubicin ²⁵	29	23.1
2007	paclitaxel + ifosfamide + cisplatin ³⁰	22	22.7
2005	gemcitabine + pegylated liposomal doxorubicin ¹⁶	37	22
2009	pemetrexed ⁵⁵	51	21
2005	docetaxel + irinotecan ⁶⁹	30	20
2006	paclitaxel (weekly) ⁴¹	48	20.9
2008	CKD-602 (camptotecan analog) ⁵⁸	5	20
2008	gemcitabine + topotecan ²¹	23	17
2006	gemcitabine + cisplatin ²⁰	57	16
2007	bevacizumab ⁵⁰	44	15.9
2005	canfosfamide ⁷⁰	34	15
2010	ixabepilone ⁵³	49	14.3
2005	9-aminocamptothecin ⁵⁴	56	14
2006	LY355703 (cryptophycin analog) ⁵⁷	24	12.5
2005	tamoxifen + goserelin ⁵⁹	26 [*]	11.5
2007	carboplatin + cyclosporine + interferon- α ³¹	30 ^{**}	10
2009	pemetrexed ⁵⁶	91	9.9
2007	gemcitabine + oxaliplatin ¹⁸	21	9.5
2008	topotecan + pegylated liposomal doxorubicin ²⁷	22	9.1
2007	pegylated liposomal doxorubicin ^{†, 12}	96	8.3
2006	capecitabine ⁷¹	36	7.3
2007	trabectedin ⁷²	79	6.3

Year	Chemotherapy regimen	Subjects	RR (%)
2007	gemcitabine ^{†,12}	99	6.1
2005	sabirubicin ⁷³	19	5.3
2009	canfosamide ⁷⁴	232	4.3
2009	capecitabine ⁷⁵	32	3.1
2008	letrozole ⁷⁶	31	3
2006	irofulven ⁷⁷	58	1.7
2006	imatinib mesylate ⁷⁸	12	0
2007	tamoxifen + gefitinib ⁶⁰	56	0
2007	docetaxel (weekly) ⁴⁴	7	0
2007	matuzumab ⁷⁹	30	0

Analysis of 40 clinical trials published between January 2005 and March 2010.

[†] Different arms in the same study.

^{7/} 19 out of 29 were ovarian or peritoneal cancer.

* 17 out of 26 were platinum-resistant.

** 19 out of 30 were platinum-resistant.

Abbreviations: Subjects, number of patients enrolled in the trial; and RR, response rate (complete response rate + partial response rate or objective response rate if response rate is not available).

Table 4

Non-trial clinical studies for platinum-resistant ovarian cancer.

Year	Chemotherapy regimen	Subjects	RR (%)
2009	paclitaxel + carboplatin (extended weekly) ³²	20	60
2006	paclitaxel (weekly) ⁴²	32	53
2007	irinotecan + etoposide ⁸⁰	27	44.4
2008	bevacizumab + cyclophosphamide ⁵¹	9	44
2007	paclitaxel + carboplatin (dose-dense) ³³	8	37.5
2006	bevacizumab + cytotoxic agent *, ⁵²	23	34.8
2009	gemcitabine + pemetrexed ⁸¹	10	30
2006	irinotecan (weekly) ⁸²	28	29
2009	gemcitabine + pegylated liposomal doxorubicin ⁸³	35	28.6
2008	gemcitabine + pegylated liposomal doxorubicin (biweekly) ⁸⁴	18	28
2009	gemcitabine + cisplatin + ifosamide ³⁶	16	25
2008	gemcitabine (fixed dose) ⁸⁵	41	22
2008	docetaxel + imatinib ⁸⁶	23	21.7
2008	topotecan (weekly) ⁸⁷	69	20.3
2008	topotecan + navelbine ⁸	22	18
2007	tamoxifen ⁸⁸	29	10
2008	topotecan (weekly) ⁸⁹	22	9.1
2005	carboplatin ³⁵	34	5.9
2006	gemcitabine ⁹⁰	21	4.7
2009	2-methoxyestradiol ⁹¹	18	0

Analysis of 20 non-trial clinical studies published between January 2005 and March 2010.

* combined cytotoxic agents include in the study included: cyclophosphamide (65%), 5-fluorouracil (26%), docetaxel (4%), and gemcitabine + liposomal doxorubicin (4%).

Abbreviations: Subjects, number of patients enrolled in the study; and RR, response rate (complete response rate + partial response rate or objective response rate if response rate is not available).

Table 5

Combining response rate with PFS in evaluating chemotherapy.

Year	Chemotherapy regimen	RR (%)	PFS	OS
Category A: both RR and PFS above average (n=9)				
2006	gemcitabine + epirubicin ¹³	43.3	8	
2008	pegylated liposomal doxorubicin (biweekly) ²⁴	40	4.1	16.5
2008	gemcitabine + pegylated liposomal doxorubicin ¹⁴	37.5	6.9	18.2
2009	gemcitabine + oxaliplatin ¹⁷	37	4.6	11.4
2007	gemcitabine + cisplatin (biweekly) ¹⁹	31.5	4.9	13.2
2006	topotecan + pegylated liposomal doxorubicin ²⁶	28	7.5	10.3
2006	pegylated liposomal doxorubicin ²⁵	23.1	5.4	13.8
2005	docetaxel + irinotecan ⁶⁹	20	5	11
2006	gemcitabine + cisplatin ²⁰	16	5.4	14.9
Category B: RR above average but PFS below average (n=4)				
2006	gemcitabine + pegylated liposomal doxorubicin ¹⁵	33.3	3.8	15.8
2005	gemcitabine + pegylated liposomal doxorubicin ¹⁶	22	2.7	8.4
2009	pemetrexed ⁵⁵	21	2.9	11.4
2008	gemcitabine + topotecan ²¹	17	3	12.6
Category C: RR below average but PFS above average (n=6)				
2007	bevacizumab ⁵⁰	15.9	4.4	10.7
2005	canfosfamide ⁷⁰	15	7.2	14.1
2010	ixabepilone ⁵³	14.3	4.4	14.8
2006	LY355703 (cryptophycin analog) ⁵⁷	12.5	5.1	
2007	gemcitabine + oxaliplatin ¹⁸	9.5	5	9.2
2005	sabarubicin ⁷³	5.3	4.2	2.1
Category D: both RR and PFS below average (n=10)				
2005	9-aminocamptothecin ⁵⁴	14	2.9	10
2009	pemetrexed ⁵⁶	9.9	2.8	11.1
2008	topotecan + pegylated liposomal doxorubicin ²⁷	9.1	2	10.5
2007	pegylated liposomal doxorubicin ^{†, 12}	8.3	3.1	13.5
2007	gemcitabine ^{†, 12}	6.1	3.6	12.7
2009	canfosfamide ⁷⁴	4.3	2.3	13.5
2009	capecitabine ⁷⁵	3.1	2.3	
2007	tamoxifen + gefitinib ⁶⁰	0	1.9	8.4
2007	docetaxel (weekly) ⁴⁴	0	3.1	12.3

Year	Chemotherapy regimen	RR (%)	PFS	OS
2007	matuzumab ⁷⁹	0	1.8	13.3

Total 29 clinical trials that both response rate and PFS were available were classified into 4 groups based on the cutoff values of overall response rate (16%) and PFS (4.1 months) among clinical trials.

Abbreviations: RR, response rate; PFS, median progression-free survival (months); and OS, median overall survival (months).