

Review Article

Extending platinum-free interval in partially platinum-sensitive recurrent ovarian cancer by a non-platinum regimen: Its possible clinical significance

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Abstract

Response to platinum retreatment in recurrent epithelial ovarian cancer is related to the platinum-free interval (PFI). The recommended and most accepted chemotherapy in the treatment of platinum-sensitive (PFI > 6 months) recurrence is platinum-based combination regimens. Patients with a PFI of 6–12 months are often considered partially platinum-sensitive (PPS) because lower response rates to subsequent platinum retreatment have been identified. Controversies and uncertainties still exist in this population of patients regarding the best treatment and the most effective therapeutic agents. It is proposed that extending the PFI with non-platinum agents may enhance the response to and the outcome of subsequent rechallenge with platinum. In this review, we discuss the treatment for PPS recurrent ovarian cancer and the possible clinical significance of extending PFI with intent to improve the medical care of PPS recurrence.

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Keywords: partially platinum sensitive; platinum sensitivity; recurrent ovarian cancer; progression free interval

Introduction

The standard upfront treatment for epithelial ovarian cancer consists of maximal cytoreductive surgery followed by adjuvant chemotherapy with platinum–taxane combination regimen. Although response rates (RRs) are in the range of 70–80%, the majority of these patients will eventually relapse and are then deemed incurable. With the increasing numbers of available therapies after recurrence, progression free survival (PFS) after first-line therapy has not increased, but overall survival (OS) is now longer [1]. Upon recurrence, most physicians' choice of second-line chemotherapy is guided by the duration of response to the prior platinum-based chemotherapy, that is, platinum-free interval (PFI). According to the data reported about 20 years ago, the probability of response to

retreatment with platinum or even non-platinum chemotherapeutic agents in recurrent ovarian cancer (ROC) depends on the PFI. The longer the PFI, the better RR can be expected [2–9]. The prognosis is poor for patients who progress during treatment (platinum-refractory) or for those whose disease recurs within 6 months (platinum-resistant). Patients with a PFI more than 6 months are thought to be platinum-sensitive so that platinum-based combination chemotherapy is recommended. However, in this group, patients with a PFI of 6–12 months are often considered partially platinum-sensitive (PPS) because the RR to subsequent platinum retreatment has been reported to be only 25–30%, which is obviously lower than that in patients who are thought to be definite platinum-sensitive (PFI of more than 12 months) [10–12]. Actually, controversies and uncertainties still exist in this population of patients regarding the best treatment and the most effective therapeutic agents. In this article, we review the treatment options for PPS recurrence and discuss the significance of using non-platinum agents to extend the PFI in improving the outcome.

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Can the PPS subgroup patients be treated with the same principle as those with definite platinum-sensitive relapse?

In platinum-sensitive ROC, platinum-based chemotherapy is recommended and has been shown to be superior to platinum monotherapy in several phase III trials. However, these studies usually did not report detailed or separate data for the PPS subgroup and should be interpreted with caution. Results of these clinical trials are summarized in Table 1.

The ICON4 AGO OVAR 2.2 phase III trial compared paclitaxel plus a platinum-based regimen (paclitaxel plus carboplatin in 80%) with conventional platinum-based chemotherapy in 802 women with ROC and a PFI of at least 6 months. The platinum–taxane regimen was associated with an improved RR (66% vs. 54%, $p = 0.06$), improved PFS (12 vs. 9 months; Hazard ratio (HR) = 0.76, $p = 0.0004$), and improved OS (29 vs. 24 months; HR = 0.82, $p = 0.02$). When the subgroup of patients with a PFI of 6–12 months was evaluated, the impact of combination therapy versus conventional platinum therapy on PFS seemed to be maintained, but the effect on OS appeared to be less when compared with those with a PFI of >12 months. However, the difference was not statistically significant [13–15]. In a recent retrospective study, a group of 39 patients who had ROC with a PFI ≥ 6 months were evaluated, and all of them received carboplatin and paclitaxel regimen for treatment of platinum-sensitive recurrence [16]. The authors found that the objective RR was higher in the subgroup of patients with a PFI ≥ 12 months (RR 86%) than that of the PFI 6–12 months subgroup (RR 68%) ($p = 0.05$). It was therefore concluded that reintroduction of carboplatin and paclitaxel should be recommended only in patients with a PFI of at least 12 months, and it would need more efforts to define the most optimal treatment for patients with PPS disease.

In the AGO OVAR 2.5 phase III trial, 356 patients with platinum-sensitive disease (PFI ≥ 6 months) were randomized to the treatment of either carboplatin alone or carboplatin plus gemcitabine combination regimen. In overall population, PFS was significantly longer (8.6 vs. 5.8 months; HR 0.72; $p = 0.0031$) and RR was significantly higher (47.2% vs. 30.9%, $p = 0.0016$) in patients receiving combination regimen. OS was similar in the two groups (18.0 vs. 17.3 months), but the study was not powered for an OS endpoint. Of note, the study demonstrated improved PFS in patients with a PFI <12 months (7.9 vs. 5.2 months; HR 0.69; $p = 0.0311$) [14,17]. However, relative to therapy with taxanes, gemcitabine plus carboplatin exhibited a preferable toxicity profile because greatly diminished neuropathy and alopecia had been shown, which are of importance for the affected women, making gemcitabine plus carboplatin another treatment option for patients with platinum-sensitive ROC.

In the CALYPSO (Caelyx in Platinum Sensitive Ovarian patients) randomized, multicentric, phase III non-inferiority trial, a total of 976 patients who relapsed more than 6 months after first- or second-line platinum and taxane-based therapies were randomly assigned to carboplatin plus pegylated liposomal doxorubicin (PLD) (CD arm) or carboplatin plus paclitaxel (CP arm) for at least 6 cycles. The non-inferiority PFS primary endpoint was not only met, but CD was associated with a statistically significant improvement in PFS over CP (11.3 vs. 9.4 months; HR = 0.82; $p = 0.005$). Furthermore, severe toxicities and bothersome side effects associated with CP—including carboplatin hypersensitivity reactions, peripheral neuropathy, and alopecia—were markedly reduced with CD regimen [18–22]. The benefits observed in the whole CALYPSO population for CD could also be noted in the PPS subgroup (median PFS = 9.4 months in the CD arm vs. 8.8 months in the CP arm), which comprised 35% of the 976 patients. In addition, the risk reduction of

Table 1
Randomized clinical trials assessing combination regimens for second-line treatment of patients with platinum-sensitive relapsed ovarian cancer.

Study	ICON4 AGO OVAR 2.2 [13]	AGO OVAR 2.5 [17]	CALYPSO [18,23,25]	OVA-301 [45,47]
Experimental arm (E)	Paclitaxel + Carboplatin	Gemcitabine + Carboplatin	PLD + Carboplatin	PLD + Trabectedin
Control arm (C)	Carboplatin	Carboplatin	Paclitaxel + Carboplatin	PLD
Patient number (E vs. C)	392 vs. 410	178 vs. 178	486 vs. 507	337 vs. 335
Distribution based on PFI				
PFI < 6 mo	0	0.5% vs. 0%	0	35% vs. 35%
PFI 6–12 mo	23% vs. 27%	39.9% vs. 39.9%	35% vs. 36.1%	37% vs. 28%
PFI > 12 mo	77% vs. 73%	59.6% vs. 60.1%	65% vs. 63.9%	29% vs. 37%
Efficacy results (total platinum-sensitive population/subgroup PFI 6–12 mo)				
Response rate	6.6% [#] /NR	47.2% [#] /NR	NR/39%	35.2% [#] /NR
PFS, median (mo)	13 [#] /NR	8.6 [#] /7.9 [#]	11.3 [#] /9.4 [#]	9.2 [#] /7.4 [#]
Overall survival (mo)	29 [#] /NR	18 [#] /NR	Immature data	22.4 [#] /23 [#]
Conclusion	Combination therapy significantly improves PFS and OS. Data for subgroup of PFI 6–12 mo not reported separately (maintained effect on PFS but less positive on OS; difference of effects on PFS and OS not reached significantly)	Combination therapy significantly improves PFS not only in total platinum-sensitive population but also in the subgroup of PFI 6–12 mo.	Combination therapy significantly improves PFS not only in total platinum-sensitive population but also in the subgroup of PFI 6–12	Combination therapy significantly improves PFS in platinum-sensitive patients with a more pronounced positive impact on PFI 6–12 mo subgroup

NR = not reported; OS = overall survival; PFI = progression free interval; PFS = progression free survival; PLD = pegylated liposomal doxorubicin.

[#] Significantly different when compared to control arm; * Not significantly different when compared to control arm.

disease progression seemed to be higher (27% in PPS subgroup vs. 18% in the overall population) [23–25].

Although non-platinum single chemotherapeutic agents, including topotecan and PLD, are most commonly used in platinum-resistant disease, they have been shown to have better RR in the setting of platinum-sensitive disease. As a matter of fact, these drugs have been approved by the Food and Drug Administration in the treatment of both platinum-sensitive and platinum-resistant ROC [26]. In patients with a PFI of >6 months, although topotecan and PLD had similar RR, median PFS (28.9 months for PLD vs. 23.3 months for topotecan, $p = 0.037$) and OS (108 vs. 71.1 weeks, $p = 0.008$) significantly favored PLD [27,28]. Further analysis demonstrated that the survival benefit was more prominent in patients with a PFI of 6–12 months ($n = 122$; HR = 1.58; $p = 0.021$) than in patients with a PFI of >12 months ($n = 97$; HR = 1.15; $p = 0.057$) [29].

Based on these studies, the UK National Institute for Clinical Excellence recommends a platinum–taxane combination or single-agent PLD for the treatment of PPS ROC [30]. On the other hand, the National Comprehensive Cancer Network recommends using similar treatment regimens (platinum based) for patients whose disease recurs after >6 months (platinum-sensitive patients) and does not mention different treatment strategy for PPS relapse, but emphasizes that no single therapeutic agent should be currently recommended as the treatment of choice for recurrence [31].

Can platinum-sensitivity be increased in a partially platinum-sensitive group by using non-platinum drugs to defer the reintroduction of platinum to a later time?

It has been hypothesized that platinum sensitivity can be restored by prolonging PFI. *In vitro* tumor models have shown that platinum resistance is an unstable, reducible, and perhaps reversible phenomenon. Treatment with non-platinum drugs to extend the PFI may make cells sensitive to platinum drugs again [32]. The results of some retrospective clinical studies or small series also imply the feasibility of this strategy. According to the series reported by Kavanagh et al [33], in which 33 patients with ovarian cancers refractory to platinum–taxane combination were treated with single agent taxane at next relapse, followed by single-agent carboplatin once the disease progressed on a taxane, the RR of carboplatin

reintroduction was 21%. However, responses were noted only in patients with a PFI of at least 12 months and an initial sensitivity to a taxane. The authors proposed that the finding may be secondary to taxane therapy that leads to the reversal of platinum resistance, or the prolonged PFI makes the tumors lose their resistance to platinum. A more recent retrospective review, reported by See et al [34], identified 34 patients with ovarian cancer who had previously progressed on platinum therapy and were considered platinum resistant or refractory. The median PFI from the time platinum was last received to retreatment with carboplatin was 15.2 months. Partial response was found in two patients (5.9%), while 21 patients (61.7%) had a stable disease. It seems that patients who have been deemed platinum resistant may still benefit from platinum retreatment after a period of treatment with non-platinum agents.

In order to determine the impact of extending PFI with intervening non-platinum agents on subsequent platinum retreatment in platinum-sensitive ROC, Italian investigators in the SOCRATES study retrospectively identified 428 patients who had ROC with a PFI of >6 months [35]. The interval from the end of the first line to relapse was 6–12 months in 164 patients (39.5%) and >12 months in 251 cases (60.5%). At second line, 282 (65.9%) received platinum (group A), while 146 (34.1%) received non-platinum chemotherapy (group B). In the latter group, 67 patients received platinum at later progression (group B1), while 79 never received platinum (group B2) (Table 2) [35]. The initial PFI at the time of receiving second-line chemotherapy was 19, 9.6, and 8.4 months in patients of groups A, B1, and B2, respectively. Median time to platinum retreatment was 19 and 23.1 months in patients of groups A and B1, respectively. The RR to the first platinum received was 74.4% and 57.4% in groups A and B1, respectively ($p = 0.02$). Although the results of SOCRATES study made the authors question the hypothesis that extending the PFI with an intervening non-platinum therapy improves the RR of a further platinum retreatment, we should notice the difference in baseline PFI in each group. Actually, group A (PFI 20 months) represented ROC with PFI >12 months, while group B1 (PFI 9.6 months) and group B2 (PFI 8.4 months) represent ROC patients with PFI 6–12 months. Patients in the two subgroups had different baseline of PFI and thus, cannot be compared fairly. Although a better RR was found in group A, the median OS was similar in group A and

Table 2
Summary of the SOCRATES study [35].

Group	A	B1	B2
Patient number (persons)	282	67	79
Definition	Platinum as second-line CT	Non-platinum as second-line CT followed by platinum as third-line CT	Non-platinum as second-line CT and platinum never being used thereafter
PFI at the time when receiving second-line CT (mo)	19	9.6	8.4
Response rate to non-platinum agents	—	44.6%	28.8%
Median time to platinum retreatment (mo)	19	23.1	—
Response rate to platinum retreatment	74.4%	57.4%	—
Mean overall survival (mo)	27.2	26.1	16.8

PFI = progression-free interval.

group B1, that is, 27.2 versus 26.1 months, respectively. Group B2 was characterized by having the worst RR (28.8%) and survival (16.8 months).

Currently, an Italian multicentric randomized phase III trial [Multicenter Italian Trials in Ovarian Cancer group 8 (MITO-8)] is ongoing and is aimed to test the hypothesis that artificial prolongation of PFI with a non-platinum treatment will improve the effectiveness of overall therapy in patients with ovarian cancer progression occurring 6–12 months after first-line treatment with a platinum-based regimen (Fig. 1). Patients will be randomized to receive either PLD monotherapy followed by paclitaxel–carboplatin at the next progression or the reverse (paclitaxel–carboplatin and then PLD monotherapy at the second progression). The primary endpoint will be OS [36]. Only when there is solid evidence from prospective randomized trials can we confirm the benefit of extending PFI in the treatment of PPS recurrence.

Non-platinum agents may be a more effective alternative to platinum-based regimen in the treatment of patients with partially platinum-sensitive relapse

In addition to PLD, the combination regimen of PLD and trabectedin is gaining attention in the treatment of ROC, especially in the subset of PPS relapse. Trabectedin (Yondelis; PharmaMar, Colmenar Viejo, Spain) is a synthetic, marine-derived anticancer agent, originally isolated from the Caribbean sea tunicate, *Ecteinascidia turbinata*. Trabectedin was initially approved in soft tissue sarcoma by the European Medicines Agency in 2007, and in combination with PLD for the treatment of patients with recurrent platinum-sensitive ovarian cancer in September, 2009. The drug has been approved in 60 countries worldwide and is being developed for treating breast and other solid tumors. Trabectedin uniquely binds covalently to the minor groove of DNA, bends the DNA toward the major groove, interrupts transcription, and results in G2-M cell cycle block, leading to apoptosis [9,37–41]. Three phase II studies have demonstrated the activity and efficacy of single agent trabectedin [42–44]. Furthermore, the randomized phase III OVA-301 trial ($n = 672$), which

included patients with platinum-sensitive relapse (PFI >6 months) and platinum-resistant recurrence (PFI <6 months) (but excluded patients who had disease progression during frontline therapy, that is, platinum-refractory disease), demonstrated that trabectedin plus PLD combination significantly improves PFS (median PFS 7.3 months with trabectedin/PLD vs. 5.8 months with PLD; HR = 0.79; $p = 0.019$) and overall RR (27.6% for trabectedin/PLD vs. 18.8% for PLD, $p = 0.008$) over PLD alone. The toxicity related to trabectedin/PLD was acceptable. No difference was found in the interim analysis for OS (22.4 vs. 19.5 months for PLD, $p = 0.092$) [45,46]. In the subgroup analysis for platinum-sensitive patients, the median PFS was 9.2 and 7.5 months, respectively (HR = 0.73; $p = 0.017$) and the RR was 35.3% and 22.6% ($p = 0.0042$), both favoring the trabectedin/PLD combination. As for OS, a positive trend in favor of the combination was observed (22.4 vs. 19.5 months, $p = 0.0920$). For the platinum-resistant subgroup, there was no difference regarding RR, PFS, and OS.

In the *post-hoc*, exploratory, and hypothesis-generating analysis, the subgroup of patients with a PFI of 6–12 months, who comprised one-third ($n = 214$) of the 672 randomized patients in the OVA-301 trial, were analyzed. Trabectedin/PLD resulted in a 35% risk reduction of disease progression or death [HR = 0.65, 95% confidence interval (CI), 0.45–0.92; $p = 0.0152$; median PFS 7.4 vs. 5.5 months], and a significant 41% decrease in the risk of death (HR = 0.59; 95% CI, 0.43–0.82; $p = 0.0015$; median survival 23.0 vs. 17.1 months). The safety of trabectedin/PLD in this subset did not differ from that of the overall population. Importantly, time from randomization to subsequent platinum was significantly longer (HR = 0.64; $p = 0.0167$; median 9.8 vs. 7.9 months) for patients in the trabectedin/PLD combination arm, who also survived significantly longer after subsequent platinum (HR = 0.63; $p = 0.0357$; median 13.3 vs. 9.8 months) [47].

In summary, the OVA-301 trial demonstrated that trabectedin/PLD combination brings in significantly superior PFS and a positive trend in OS over PLD alone. Benefits appeared more evident in the platinum-sensitive subset (PFI > 6 months) and even more pronounced in patients with PPS disease. The investigators postulated that the enhanced survival benefits with trabectedin/PLD over single agent PLD in OVA-301, particularly in patients with PPS disease, may be due to an extension of the PFI which helps in the improvement of response to subsequent platinum-based therapy [48]. This hypothesis will be tested in the ongoing phase III prospective, multicentric, randomized trial, INOVATYON Study (International, Randomized Study in Patients With Ovarian Cancer), which has started to recruit participants since June 2011, by the Mario Negri Gynecologic Oncology group (Fig. 2). The objective is to demonstrate the superiority, in terms of prolonged survival, of trabectedin and PLD (regimen evaluated in OVA-301 trial) versus carboplatin and PLD (regimen evaluated in CALYPSO trial) in patients with advanced and progressive ovarian cancer 6–12 months after completion of first-line treatment with platinum-based chemotherapy [49]. At disease progression, the trabectedin/PLD arm is allowed to

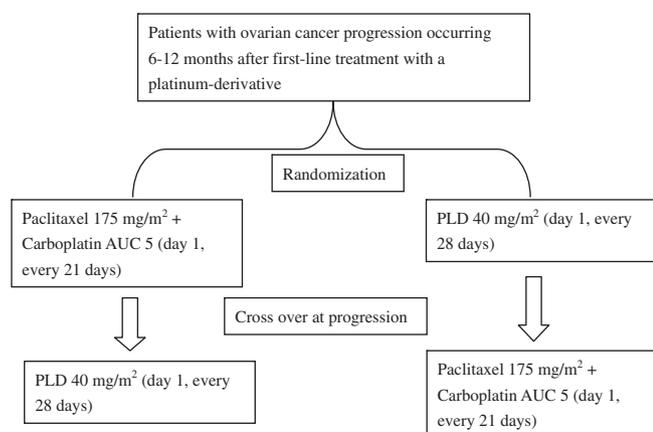


Fig. 1. Multicenter Italian Trials in Ovarian Cancer group 8 (MITO-8) study design.

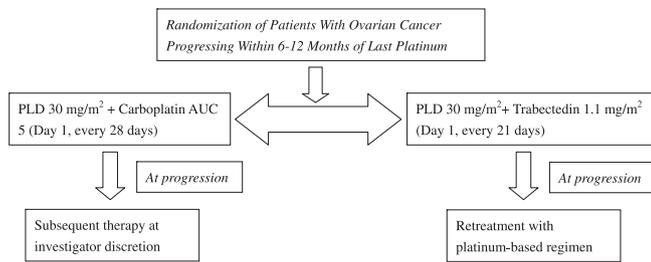


Fig. 2. International, Randomized Study in Patients with Ovarian Cancer (INOATYON) Study design.

be used in retreatment with platinum-based regimen, and subsequent therapy of the carboplatin/PLD arm will be based on investigator discretion. This would allow the prospective evaluation of the effect of PFI extension with a non-platinum combination on response to subsequent platinum.

Conclusion

Current recommendations for the treatment of ROC with a PFI 6–12 months are the same as those for a PFI of >12 months, but the best therapy option for the PPS disease remains to be determined. Although platinum-based combinations are recommended, the possibility of unsatisfactory response is frequently expected because it has been observed—and thus believed by most gynecology oncologists—that the response to platinum retreatment is closely related to the duration of PFI.

The emergence and use of non-platinum agents, such as PLD, topotecan, or trabectedin, may help improve the care of this subpopulation for two potential reasons. One would be that non-platinum agents may have better treatment efficacy than platinum-based therapy in the PPS subset. The other possible benefit might be due to the prolongation of PFI, which is believed to be capable of reversing platinum resistance, or increasing sensitivity to and response to subsequent platinum retreatment. Preclinical or retrospective clinical studies as well as some small series have provided evidence on the feasibility and potential benefits of this strategy. The data from OVA-301 trial are encouraging because they have validated trabectedin plus PLD combination as a new valuable and promising treatment option in the treatment of relapsed ovarian cancer, especially for patients with a PFI of 6–12 months. However, only after evidences from prospective studies, such as MITO-8 study or INOVATYON study, have been made available can we confirm the hypothesis.

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