The Impact of Pegylated Liposomal Doxorubicin in Recurrent Ovarian Cancer: An Updated Meta-Analysis of Randomized Clinical Trials

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Abstract

**Background:** Pegylated Liposomal Doxorubicin (PLD) could improve the survival rate of patients with recurrent ovarian cancer in previous meta-analysis studies. The aim of the present meta-analysis was to further update the role of PLD in the treatment of recurrent ovarian cancer.

**Methods:** Literature search was performed by using the electronic databases Medicine, EMBASE, Web of Science, and Cochrane library until 27 July 2020. We only restricted the randomized clinical trials. Study specific hazard ratios and 95% confidence level (HR/95% CI), risk ratios and 95% confidence level (RR/95% CI), were pooled using a random effect model.

**Results:** 10 studies (12 trials) were included after screening of 940 articles. We categorized the eligible studies into two groups: the doublet regimens (four trials, 1767 patients) resulted that PLD plus carboplatin(carbo) provided superior progression free survival (PFS) (HR, 0.85; 95% CI, 0.74-0.97) and similar overall survival (OS) (HR, 1.00; 95% CI, 0.88-1.14) compared PAC plus carbo. PLD plus carboplatin was associated with significantly more anemia and Thrombocytopenia, other side effects well-tolerated. In platin resistant patients, the monotherapy regimens (eight trials, 1980 patients) resulted that PLD had similar PFS (HR, 1.02; 95% CI, 0.90–1.16) and OS (HR, 0.88; 95% CI, 0.77–1.01) to other monotherapies. PLD alone was more associated with mucositis/stomatitis and hand-foot syndrome, other side effects well-tolerated.

**Conclusion:** In platinum-sensitive recurrent ovarian cancer, PLD plus carbo is more effective than PAC plus carbo. In platinum-resistant or refractory recurrent ovarian cancer, PLD has similar survival to others monotherapies. For side effects, PLD plus carbo or monotherapy chemotherapy both were well-tolerated.

Introduction

Ovarian cancer is one of the most common gynecological malignancies, with the third highest incidence of gynecological tumors and the highest mortality rate. Because ovarian cancer is not easy to detect in the early stage, it is usually diagnosed as advanced stage and its 5-year relative survival rate is relatively low. The lifetime risk of ovarian cancer is approximately 1 in 75, and the likelihood of dying from this malignancy is 1 in 100 [1, 2]. Cytoreductive surgery followed by platinum-based chemotherapy remains the mainstay of treatment in ovarian cancer. Despite complete remission through the best upfront treatment, approximately 70% to 80% of patients experience a relapse within 5 years [3, 4]. So ovarian cancer is still a serious threat to women's health in the world.

For patients with platinum-sensitive recurrent ovarian cancer, we usually choose carboplatin in combination with paclitaxel (PAC) as first-line standard chemotherapy regimen, but this regimen has more non-hematologic toxicity resulting in early discontinuation of treatment. Specifically, this regimen has high rates of alopecia, hypersensitivity and neurotoxicity [5]. Platinum re-challenge therapy in platinum-refractory or resistant patients usually results in low response rates and short survival. In that setting, chemotherapy with single agents shows activity and lower toxicity than combination chemotherapy [6]. Single agent second-line treatments include non-platinum compounds such as paclitaxel, topotecan, PLD, gemcitabine, etoposide, vinorelbine, and bevacizumab, we usually choose the sequential use of single chemotherapeutic agents dependent on the different conditions of the patients. While treatment options for recurrent ovarian cancer have increased, most of these patients will still eventually die from ovarian cancer. Therefore, goal of therapy in recurrent setting should not only focus on improving the length of life, but also include a thoughtful review of anticipated side effects and the quality of life.

PLD, an anthracycline chemotherapy derived from doxorubicin, and is the first FDA-approved cancer nanomedicine [7]. As early as in 2014, has been approved for the treatment of ovarian and breast cancer, multiple myeloma, and Kaposi sarcoma [8]. The 2017 NCCN Guidelines recommend that carbo combined with PLD be added as one of the initial chemotherapy regimens for ovarian cancer. Carbo combined with PLD is recommended for patients with recurrent platinum-sensitive ovarian cancer patients, and PLD monotherapy is recommended for relapsed platinum-resistant ovarian cancer patients. The 2018 NCCN Guidelines include PLD as a first-line chemotherapy regimen for ovarian cancer, and carboplatin/liposomal doxorubicin for advanced ovarian cancer patients (category 2A recommendation). The 2019 NCCN Guidelines recommend that PLD plus Bevacizumab is a potential treatment option for patients with platinum-resistant recurrent ovarian cancer. Clinical studies have shown that compared with other standard chemotherapy regimens, PLD has a non-inferior survival rate and is well-tolerated, especially with lower alopecia and neurotoxicity [9].
The previous studies [10, 11] clarified that PLD is effective and well tolerated in the treatment of ovarian cancer. Because these two meta-analysis are earlier and less trials included, we added the latest trials and performed an updated meta-analysis. this study results will help in the selection of chemotherapy regimens for recurrent ovarian cancer patients.

Methods

1. Search strategy

We conducted this meta-analysis framework under the guidance of PRISMA. Queries of literature were performed by using the electronic databases Medicine, EMBASE, Web of Science, and Cochrane library until 27 July 2020. The search MeSH terms and free words used were: 1) "Pegylated Liposomal Doxorubicin," "Caelyx," "Lipodox," "Doxil" and 2) "ovarian cancer," "ovarian neoplasm," "ovarian carcinoma" and 3) "Randomized Controlled Trial." In this study, language for the searching and inclusion studies were not limited. The detail of the search strategy is presented in the Supplementary Material 1. This study does not involve patient knowledge and ethics.

2. Eligibility criteria

The abstracts of all articles retrieved in the initial search were independently screened by two authors (X.R.L and L.X.P). Both processes were executed by independent reviewers according to the following criteria. The inclusion criteria were: 1) involved patients with histologically confirmed recurrent ovarian cancer; 2) included interventions were PLD alone versus other monotherapy or PLD plus carboplatin versus paclitaxel plus carboplatin; 3) involved outcomes measures were survival outcome and adverse events; 4) all studies were RCTs. The exclusion criteria were: 1) no PLD was performed; 2) no ovarian cancer patients were examined; 3) the study was conducted in pediatric population (<18 years old); 4) animal/laboratory study; 5) review articles, case reports, letters, commentaries, or conference proceedings; 6) recurrent ovarian cancer histology was not confirmed. Disagreements were discussed with a third author (Prof. G.N.Z) to achieve consensus.

For the study, The same two authors, who performed full-text screening, independently conducted data extraction, and all inconsistencies were resolved by consensus. Selected full text manuscripts were reviewed to determine their relevance in detail. The exclusion criteria were: 1) not within the research purpose; 2) data is missing; 3) overlapping studies.

3. Data Extraction

Data were extracted from the included studies. Data included: first author, journal, year of publication, number, age and characteristics of patients, study design, outcomes.

4. Statistical Analysis

For survival variables such as Progression Free Survival (PFS) and Overall Survival (OS), we used the hazard ratios (HR), and 95% CI, which are presented as forest plots. For categorical variables, we used the risk ratios (RR) and 95% CI, which are presented as forest plots. Heterogeneity across studies was evaluated using the \( I^2 \) metric and chi-square test. We used the random-effect model to calculate the summary estimate if heterogeneity existed (\( I^2 > 50\% \)) across studies. Otherwise, the fix-effect model was used (\( I^2 \leq 50\% \)). If heterogeneity existed across studies, we performed subgroup analyses based on study design and analyzed the subgroup results. We used Egger's linear regression test, as well as Begg's funnel plot to assess potential publication bias existed across studies. All statistical testing was conducted using the Review Manager 5.3 (Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and stata.15.0 (Stata-Corp, College Station, TX). All tests were two-sided with \( P < 0.05 \) considered statistically significant, except for heterogeneity test (\( P < 0.1 \)) and publication bias (\( P < 0.1 \)) in meta-analyses.

Results

1. Literature Search

A total of 940 articles were confirmed using our electronic database search. After removing duplicate articles and screening the studies titles and abstracts, 56 articles meeting the inclusion criteria underwent full-text assessment resulting in 10 relevant studies [13-22]. Flowchart of the selection procedure (Fig. 1).
2. Study Characteristics

In 2 studies treatment arms were evaluated separately: PLD plus carbo vs PAC plus carbo (four trials [13-16]: 851 PLD plus carbo and 916 PAC plus carbo). PLD vs other monotherapy (eight trials [17-22]: 963 PLD and 1,017 other monotherapy), Vergote2009 [19] was categorized into both trials: PLD vs Topotecan and PLD vs Canfosfamide; Kaye2012 [22] was categorized into both trials: PLD vs 200mg Olaparib and PLD vs 400mg Olaparib. All features of the included studies are demonstrated in Table.1. We assessed the study quality based on The Cochrane Collaboration's tool and the criteria specified in Chapter 8 of the Cochrane Handbook for Systematic Reviews of Interventions [12]. Table.2. Each study was evaluated for potential bias and quality by two independent authors experienced. Disagreements were resolved by consensus.

3. Extraction of Data

3.1 Doublet Regimens overall analysis: PLD plus carbo vs PAC plus carbo

PLD plus carbo was associated with a significant improvement in PFS (HR, 0.85; 95% CI, 0.74-0.97; $I^2=28\%$; $p=0.02$). And OS was similar to standard chemotherapy regimen PAC plus carbo (HR, 1.00; 95% CI, 0.88-1.14; $I^2=0\%$; $p=0.99$). (Fig.2)

Grade 3-4 toxicities: PLD plus carbo was associated with a decreased risk of an allergic reaction (RR,0.38; 95% CI,0.19-0.78; $I^2=0\%$; $p<0.01$), Arthralgia/myalgia (RR, 0.19; 95% CI, 0.05-0.68; $I^2=0\%$; $p=0.01$), and neutropenia (RR, 0.76; 95% CI, 0.67-0.86; $I^2=0\%$; $p<0.01$). PLD plus carbo was associated with an increased risk of anemia (RR,1.82; 95% CI,1.22-2.71; $I^2=0\%$; $p<0.01$) and thrombocytopenia (RR,2.67; 95% CI,1.94-3.67; $I^2=0\%$; $p<0.01$). There was no difference risk of fatigue/asthenia (RR, 1.10; 95% CI, 0.78-1.56; $I^2=0\%$; $p=0.01$), hand-foot syndrome (RR,2.76; 95% CI,0.50-15.16; $I^2=0\%$; $p=0.24$) and vomiting (RR, 1.38; 95% CI, 0.72-2.66; $I^2=44\%$; $p=0.33$). (Fig.4)

3.2 Monotherapy Regimens overall analysis: PLD vs Single agent

PLD was similar in PFS (HR,1.02; 95% CI,0.90–1.16; $I^2=0\%$; $p=0.72$) and OS (HR,0.88; 95% CI, 0.77–1.01; $I^2=0\%$; $p=0.07$) to other single agent. (Fig.3)

Grade 3-4 toxicities: PLD was associated with an significant increased risk of mucositis/stomatitis (RR, 0.10; 95% CI, 0.04–0.23; $I^2=0\%$; $p<0.01$), and Hand-foot syndrome (RR, 0.03; 95% CI, 0.01–0.09; $I^2=0\%$; $p <0.01$) compared with the other monotherapies. There were no difference risk of anemia(RR, 1.26; 95% CI, 0.86–1.83; $I^2=0\%$; $p=0.23$), vomiting (RR, 0.97; 95% CI, 0.57–1.66; $I^2=38\%$; $p=0.91$), fatigue/asthenia (RR, 1.09; 95% CI, 0.73–1.64; $I^2=19\%$; $p=0.66$), thrombocytopenia (RR, 1.73; 95% CI, 0.93–3.24; $I^2=4\%$; $p=0.08$) and neutropenia (RR, 1.32; 95% CI, 0.59–2.96; $I^2=86\%$; $p =0.50$). (Fig.5)

3.3 Subgroup analysis

We perform neutropenia side effect subgroup analyze based on different drugs in Monotherapy Regimens ($I^2=86\%$), one subgroup [19, 20] showed that Canfosfamide and Patupilone were lower risk than PLD (RR, 0.39; 95% CI, 0.21–0.72; $I^2=33\%$; $p<0.01$), the other subgroup [17-19, 21] showed that Gemcitabine, Topotecan, LiFA and Olaparib were higher risk than PLD (RR, 2.26; 95% CI, 1.61–3.17; $I^2=0\%$; $p<0.01$). And perform subgroup for the differences of bad toxic and side effects based on the different doses of PLD: In doublet regimens: anemia, 30mg/m^2 vs 45mg/m^2 PLD ($I^2=0\%$); thrombocytopenia, 30mg/m^2 vs 45mg/m^2 PLD ($I^2=0\%$). There were no difference in the incidence of adverse reactions at different doses of PLD. In monotherapy regimens: mucositis/stomatitis, 40mg/m^2 vs 50mg/m^2 PLD ($I^2=60.5\%$); Hand-foot syndrome, 40mg/m^2 vs 50mg/m^2 PLD ($I^2=30.2\%$). There were difference in the incidence of adverse reactions at different doses of PLD.

3.4 Publication bias

To assess all studies PFS potential publication bias, we used Egger's linear regression test ($p=0.635$), as well as Begg's funnel plot ($p=0.592$). The tests results showed that this updated meta-analysis was no significant publication bias. (Supplementary Material 2.)

Discussion
To the best of our knowledge, this study is the most recently updated meta-analysis about PLD curative effect and side effects in recurrent ovarian cancer chemotherapy. The main results suggest that PLD is effective for the treatment of recurrent ovarian cancer, even better. The secondary indicators show that most patients well tolerated and has no serious adverse reactions.

1. Doublet Regimens

Because of studies results showed that platinum doublets of carbo plus PAC, carbo plus gemcitabine, and carbo plus PLD superior to single-agent platinum, and carbo plus PLD were as effective as carbo plus PAC in women with high-sensitive relapsed ovarian cancer [4, 23-25]. So we only selected and compared doublet regimens based on platinum in platinum-sensitive recurrent ovarian cancer. PLD plus carbo had superior in PFS and has no obvious different in OS. We found that in four doublet regimens trials, only the results of Pujade-Lauraine2010 and Gladieff 2012 showed that PFS in the PLD plus carbo group had significant superiors. This results may due to in Pujade-Lauraine2010, 90% of women received post-progression treatment and the proportion of women in the PAC plus carbo arm who received PLD as post-study therapy (68%) was significantly higher than the proportion of women in the PLD plus carbo arm who received PAC (43%;P < 0.01); this may have influenced OS HR in the direction of the PAC plus carbo arm [11]. However, in Gladieff 2012, OS was not counted due to overall survival data was immature, so there is no exact comparison between PFS and OS. There is another perspective, it is possible that tumor cells that survive treatment with PLD plus carbo maybe more aggressive or may be resistant to subsequent therapies. when the disease does recur, it may progress more quickly or maybe resistant to other therapies, thus negating any benefits for OS [10]. We also guess Bafaloukos 2010 And was phase II study that was not powered to assess OS and may affect the final result. But the specific reasons are not clear, and further research is needed.

We compared the different of PFS and OS based on different PLD doses. PLD 30mg/m² every 4weeks compared with PLD 45mg/m² every 4weeks, the results showed PFS and OS no significant difference. Therefore, we support PLD 30mg/m² every 4weeks can be used as the initial dose in PLD plus carbo doublet regimens.

We evaluated the Grade 2 or higher toxicities: PLD plus carbo was associated with a decreased risk of alopecia (RR, 0.09; 95% CI, 0.07-0.12; I^2=0%; p< 0.01), neuropathy (RR, 0.19; 95% CI, 0.14-0.27; I^2=19%; p<0.01) compared with PAC plus carbo. PLD plus carbo was associated with an increased risk of mucositis/stomatitis (RR,2.12; 95% CI,1.54-2.93; I^2=0%; p<0.01), and hand-foot syndrome (RR,6.12; 95% CI,3.84-9.76; I^2=0%; p<0.01).

Compared with Grade 3-4 severe toxicities, Hand-foot syndrome and mucositis/ stomatitis both mainly focused on low grade toxicities, the patient's adverse symptoms are mild. Anemia and thrombocytopenia both mainly focused on severe toxicities. Fortunately, the adverse incidence is not high (8.2% and 14.7%). We laterally compared the incidence of side effects at two different PLD doses (Grade 3-4 toxicity). For anemia, 30mg/m² vs 45mg/m² PLD (8.0% vs 9.5%). For thrombocytopenia, 30mg/m² vs 45mg/m² PLD (15.0% vs 12.0%). These two adverse reactions did not show significant dose-dependence of PLD, which may be because the combination of carbo reduced the toxic and side effects of PLD.

The updated meta-analysis results show that PLD plus carbo has a non-inferior survival rate and is well-tolerated. Hence, PLD plus carbo emerged as a favorable potion for platinum-sensitive patients in the recurrent setting.

2. Single Regimens

In platinum-resistant or refractory recurrent ovarian cancer, PLD has similar non-inferior survival results as other single agents. So platinum-resistant women are challenged with non-platinum drugs. Study showed that gemcitabine plus PLD is a very attractive combination given that they have different mechanisms of action and different toxicity profiles [28]. This combination does not reduce the effect of each other, but also increases the additive activity of the drug. This therapy was well tolerated by most platinum resistant ovarian cancer patients, and patients with higher levels of baseline deoxycytidine kinase had longer PFS. The usage recommended PLD 35 mg/m² on day 1, and gemcitabine 1000 mg/m² on days 1, 15 q4weeks. But this study is a phase I b study need further study. Another study showed that Olaparib combined with PLD were well tolerated but did not result in significant prolongation of PFS or OS in platinum resistant or refractory ovarian cancer [29]. The 2019 NCCN Guidelines showed that PLD plus Bevacizumab is a potential treatment option for patients with platinum-resistant recurrent ovarian cancer. The 2020 NCCN Guidelines suggest that bevacizumab is effective in both platinum-sensitive and platinum-resistant recurrent ovarian cancer. Treatment of platinum-resistant or refractory recurrent ovarian cancer as a palliative care still need more potential chemotherapy options.
The mainly common adverse effect of monotherapy PLD were mucositis/stomatitis and Hand-foot syndrome. We laterally compared the incidence of side effects at two different PLD doses (Grade 3-4 toxicity). For mucositis/stomatitis, 40mg/m$^2$ vs 50mg/m$^2$ PLD (4.2% vs 10.2%). the result showed mucositis/stomatitis is a dose-dependent side effect of PLD. For Hand-foot syndrome, 40mg/m$^2$ vs 50mg/m$^2$ PLD (3.4% vs 17.6%). the result showed Hand-foot syndrome is also a significantly dose-dependent side effect of PLD.

This updated meta-analysis show that PLD is well-tolerated in 40mg/m$^2$ lower dose regimens, and which do not adversely affect survival compared with other single regimens, and confirm PLD as a good choice for women in whom monotherapy is a treatment option.

3. Strength and Limitation of PLD for the treatment of ovarian cancer

The most concerning potential side effect of doxorubicin and PLD is often cited as congestive heart failure. Doxorubicin is closely related to congestive heart failure. PLD’s parent drug is doxorubicin, but PLD can effectively reduce cardiac toxicity. Studies show that PLD reduced incidence of cardiotoxicity by five-to six fold even in doses≥500 mg/m$^2$. It is because of pegylation, coating the liposome with a hydrophilic protective coating, allows a prolonged time of the drug in circulation due to its ability to evade immunologic elimination. Both lower plasma levels and improved ability to target tumor tissue allow for the sparing of cardiac toxicity with PLD [26]. One study surfaced that even with high cumulative doses of PLD up to 2500 mg, there were no significant incidences of cardiotoxicity by 2D strain on 3D left ventricular ejection fraction, so long-term use is safe [27]. So PLD had a cardioprotection, and is more beneficial for patients with poor heart function and elderly patients.

Recurrent studies showed that prolonged treatment with PLD has been associated with the development of secondary oral Mucosal squamous cell carcinoma in a number of case reports, but the specific mechanism of action is unknown [9]. Another trial showed that The cumulative doses of PLD in our patients before the development of squamous cell carcinoma were 1350mg/m$^2$ and 1142 mg/m$^2$ respectively, so reduce the amount dose, prolonged administration and regular oral cavity examinations along with complete skin examinations was necessary [30]. So we should use PLD dose as low as possible and prolonged administration to reduce the incidence of Hand-Foot Syndrome, thereby reducing the incidence of secondary oral Mucosal squamous cell carcinoma.

Conclusion

PLD plus carbo for platinum-sensitive disease it shows a better PFS than standard regimens PAC plus carbo and well-tolerated. However, there is no difference in overall survival. The findings of this meta-analysis support the continued use of PLD plus carbo as doublet regimens chemotherapy for platinum-sensitive recurrent ovarian cancer and PLD 30mg/m$^2$ every 4weeks can be used as the initial dose. As single agent therapy, PLD shows similar survival to other agent and well-tolerated. The findings of this meta-analysis support the continued use of PLD monotherapy as first line chemotherapy for platinum-resistant or refractory recurrent ovarian cancer and recommend PLD 40mg/m$^2$ every 4weeks can be used as the initial dose.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The dataset used or analyzed in this study is available from the corresponding author upon reasonable request.

Competing interests

All the authors declare no competing interests.
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Author contributions
All authors contributed to the design of the review. X.R.L and L.X.P completed the initial data search. Y.Z and J.M.H designed methods and completed the Statistical analysis. G.N.Z co-designed methods and revised the article. X.R.L wrote the first manuscript draft and all authors approved the final manuscript.

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Tables

Table 1. Characteristics of included studies.
| Study          | Intervention                  | No. of participants | Age, years Median (range) | Type of trial | Patient characteristics | Pretreatment status | Main outcomes |
|---------------|-------------------------------|---------------------|---------------------------|---------------|-------------------------|--------------------|--------------|
| Pujade-Lauraine 2010[14] | carbo(AUC5) + PLD 30 mg/m² q4wks | 466                 | 60.5 (24-82)              | phase III randomized multicenter, open-label trial | PS ROC               | After first-or second-line Platinum and taxane-based | PFS, OS, Toxicity |
|               | carbo(AUC5) + PAC 175 mg/m² q3wks | 509                 | 61 (27-82)                |               |                         |                    |              |
| Gladieff2012[15] | carbo(AUC5) + PLD 30 mg/m² q4wks | 161                 | 60 (24-82)                | phase III randomized non-inferiority trial | PS ROC               | After first- or second-line platinum- and taxane-based | PFS, Toxicity |
|               | carbo(AUC5) + PAC 175 mg/m² q3wks | 183                 | 60 (30-80)                |               |                         |                    |              |
| Mahner2014[16]  | carbo(AUC5) + PLD 30 mg/m² q4wks | 131                 | 60 (30-80)                | phase III randomized multicenter trial | PS ROC               | Platinum and taxane-pretreated | PFS, OS, Toxicity |
|               | carbo(AUC5) + PAC 175 mg/m² q3wks | 128                 | 63 (27-82)                |               |                         |                    |              |
| Bafaloukos2010[17] | carbo(AUC5) + PLD 45 mg/m² q4wks | 93                  | 62 (38-89)                | phase II randomized multicenter trial | PS ROC               | One cycle or more Of platinum-based | ORR, OS, Toxicity |
|               | carbo(AUC5) + PAC 175 mg/m² q3wks | 96                  | 63 (37-81)                |               |                         |                    |              |
| Mutch2007[18]  | PLD 50mg/m² IVI q4wks              | 96                  | 62 (28-83)                | phase III randomized multicenter open-label trial | PS ROC               | Prior platinum-based ≤ 2 prior regimens allowed | PFS, OS, Toxicity |
|               | Gemcitabine 1000mg/m² D1,8 q3wks | 99                  | 59 (38-85)                |               |                         |                    |              |
| Ferrandina2008[19] | PLD 40mg/m² IVI q4wks              | 76                  | 63 (28-80)                | phase III randomized multicenter trial | Partial PS and PR ROC | Failed first-line Platinum or paclitaxel | OS, Toxicity |
|               | Gemcitabine 1000mg/m² D1,5,8,15 q4wks | 77                | 63 (39-79)                |               |                         |                    |              |
| Vergote2009[20] | PLD 50mg/m² IVI q4wks              | 130                 | 60 (30-82)                | phase III randomized multicenter trial | platinum-refractory or PR ROC | Failed one second-Line therapy with either topotecan or PLD | Toxicity |
|               | Canfosfamide 1000mg/m² q3wks        | 231                 | 60 (26-85)                |               |                         |                    |              |
| Vergote2009[20] | PLD 50mg/m² IVI q4wks              | 130                 | 60 (30-82)                | phase III randomized multicenter trial | platinum-refractory or PR ROC | Failed one second-Line therapy with either Topotecan or PLD | Toxicity |
|               | Topotecan                           | 87                  | 60 (30-82)                |               |                         |                    |              |
| Study                        | Random sequence generation | Allocation concealment | Blinding of participants and personnel | Blinding of outcome assessment | Incomplete outcome data | Selective reporting | other bias |
|------------------------------|----------------------------|------------------------|----------------------------------------|-------------------------------|------------------------|---------------------|------------|
| Pujade-Lauraine2010[14]      | Low risk                   | Low risk               | High risk                              | Low risk                      | Low risk               | Low risk            | Low risk   |
| Gladieff2012[15]             | Low risk                   | Unclear risk           | High risk                              | Low risk                      | Low risk               | Low risk            | Low risk   |
| Mahner2014[16]               | Low risk                   | Low risk               | High risk                              | Low risk                      | Low risk               | Low risk            | Low risk   |
| Bafaloukos2010[17]           | Low risk                   | Low risk               | Unclear risk                           | Low risk                      | Low risk               | Low risk            | Low risk   |
| Mutch2007[18]                | Low risk                   | Low risk               | High risk                              | Unclear risk                  | Unclear risk           | High risk           | Low risk   |
| Ferrandina2008[19]           | Low risk                   | Low risk               | High risk                              | Low risk                      | Low risk               | Low risk            | Low risk   |
| Vergote2009[20]              | Low risk                   | Low risk               | High risk                              | Low risk                      | Low risk               | Low risk            | Low risk   |
| Colombo2012[21]              | Low risk                   | Low risk               | High risk                              | Low risk                      | Low risk               | Low risk            | Low risk   |
| Banerjee2018[22]             | Low risk                   | Low risk               | High risk                              | Low risk                      | Low risk               | Low risk            | Low risk   |
| Kaye2012[23]                 | Low risk                   | Low risk               | High risk                              | Low risk                      | Low risk               | Low risk            | Low risk   |

Note: OS, overall survival; PFS, progression-free survival; PS, platinum-sensitive; PR, Platinum-resistant; ROC, recurrent ovarian cancer.