**Original Research Article**

**Meta-analysis on the PARP-inhibitor olaparib reveals therapeutic efficacy in ovarian cancer independent of BRCA1/2 mutation status**

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**Abstract:** Poly(ADP-ribose) polymerase (PARP) inhibitors are one of the most promising drugs for ovarian cancer treatment. This study investigated clinical trials of PARP inhibitors, in order to obtain a more complete prognosis of ovarian cancer patients, which is usually dependent on their BRCA1/2 mutation status. The PubMed database was searched using the key terms “PARP inhibitor OR olaparib OR veliparib OR niraparib OR rucaparib OR (BMN 673) AND (ovarian cancer OR solid tumors)”, while narrowing the selection of the article type to “clinical trial” only. Women included in the study had been histologically diagnosed with recurrent high-grade serous ovarian-, fallopian tube- or primary peritoneal-carcinoma, regardless of the presence of BRCA germline mutation or platinum-sensitive disease recurrence. Data from three Phase I and eight Phase II clinical trials were obtained, two of which evaluated veliparib, eight olaparib and one niraparib. A total of 1042 patients with either high-grade serous ovarian-, fallopian tube- or primary peritoneal cancer were enrolled, of which 587 had a BRCA1/2 germline mutation and at least 370 were platinum-sensitive. The overall response rate (ORR) for patients who underwent treatment with olaparib was 44.5% (95% confidence interval = 0.396–0.496). Patients with BRCA1/2 mutation and those with wild-type BRCA1/2 showed no significant difference in ORR (p = 0.35), even when considering solely Phase II trials (p = 0.13). PARP inhibitors, particularly olaparib, proved effective in the management of ovarian cancer patients. This study identified the existence of patients who presented wild-type BRCA1/2 and possibly BRCA-independent homologous-recombination deficient tumors, or patients with wild-type BRCA1/2 and tumors presenting other forms of BRCAneS, who benefit from treatment with olaparib.

**Keywords:** ovarian cancer; PARP inhibitors; olaparib; BRCA mutation; BRCA1/2; BRCAneS

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**Introduction**

Poly(ADP-ribose) polymerase (PARP) inhibitors are one of the most promising drugs for ovarian cancer treatment. BRCA1/2-defective ovarian cancer cells are unable to properly perform DNA repair through the homologous recombination pathway. This defectiveness provides more error-prone DNA repair mechanisms that lead to genetic abnormalities and genetic instability of the cancer cells. This phenotype is found in about 50% of ovarian cancer cells.[1] PARP inhibitors help to block these more error-prone mechanisms of DNA repair, which ultimately leads to cancer cell death.

PARP inhibitors were shown to have positive single agent activity in recurrent germline-mutated BRCA1/2 ovarian cancer[2,3] and are FDA-approved as monotherapy...
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Type of chemotherapy. The aim of this study was to investigate the available clinical trials that use PARP inhibitors for recurrent high-grade serous ovarian cancer in order to determine the overall recurrence rate (ORR) in these patients. Owing to other eventual underlying BRCA1/2 or other underlying BRCA-independent homologous-recombination defects, a sub-analysis was carried out to understand whether patients with wild-type BRCA1/2 would benefit from treatment with PARP inhibitors.

Materials and methods

Search strategy

The PubMed database was searched using the terms “PARP inhibitor OR olaparib OR veliparib OR niraparib OR rucaparib OR (BMN 673) AND (ovarian cancer OR solid tumors)”, while narrowing the article type selection to “clinical trial” only. The article titles and abstracts retrieved by the electronic searches were examined thoroughly. The full text of potentially relevant articles was obtained. Figure 1 elucidates the “Preferred Reporting Items of Systematic reviews and Meta-Analyses” (PRISMA) flowchart for the study.

Selection of patients

The study included women of any age with a histological diagnosis of recurrent advanced stage high-grade serous ovarian-, fallopian tube- or primary peritoneal-carcinoma, regardless of the presence of the BRCA 1/2 germline mutation and regardless of platinum-sensitive disease recurrence.

Data collection

Each relevant study was tabulated according to each characteristic, namely: (1) type of clinical trial, author, and year of publication; (2) study population (total number of patients diagnosed with late stage (anything other than stage I in both arms of the study), and patient’s age; (3) BRCA germline mutation status, platinum sensitivity and its outcomes (overall response rate, progression-free survival (PFS) and hazard ratio (HR) for progression with 95% confidence interval (CI)).

Statistical analysis

The primary endpoint was ORR based on the BRCA1/2 mutation status. The ORR was imputed using the raw data provided in the studies. It was defined by the number of patients showing either complete or partial response to treatment, divided by the total number of patients that underwent treatment. Pooled estimates were computed using the random-effects model via the Comprehensive Meta-Analysis software. The secondary endpoint of the study was the ORR for PARP inhibitors. The level of heterogeneity bias was formally evaluated by quantifying the inconsistency ($I^2$).

Results

Selection of studies

Inclusion criteria: (1) Reports on phase I–III clinical trial; (2) Peer-reviewed; and (3) Published in English. Exclusion criteria: (1) Article publication of Phase I clinical trials that were in progress to Phase II trials. Thus, only the Phase II clinical trial was considered; (2) Studies that published several interim analyses. Thus, only the most recent analysis was considered.

Study selection

In total, 28 studies were identified that fulfilled our electronic-based search criteria. Of these, 16 article titles were fully retrieved by limiting the screening process to “title” and “abstract” only. Of the 16 full-text analyses, two studies were excluded because they did not include ovarian cancer patients. Another two studies were excluded as they involved Phase I clinical studies that were in progress towards readily established Phase II trials. One article was also excluded as it was a first interim analysis from a study that had already published its second interim analysis (Figure 1).
Studies evaluated the use of veliparib, niraparib, and olaparib. Two of the studies evaluated the use of veliparib, eight evaluated the use of olaparib and one evaluated the use of niraparib. A high heterogeneity between the included studies was found ($I^2 = 78.98\%$).

**Patient characteristics**

A total of 1042 patients with either high-grade serous ovarian-, fallopian tube- or primary peritoneal-cancer were enrolled, of which 587 patients had either a *BRCA1* or *BRCA2* germline mutation and at least 370 of them were platinum-sensitive. The mean/median age of the patients was in the fifth decade for all trials (Table 1).

**Overall response rate (ORR)**

Evaluation of the primary endpoint, for the *BRCA1/2* mutation status was based on the ORR analysis from five available clinical trials (*i.e.*, one Phase I trial and four Phase II trials). The pooled ORR for *BRCA1/2* germline mutation carriers and wild-type *BRCA1/2* patients were $56.6\%$ (95% CI = 0.483–0.645) and 57.9% (95% CI = 0.501–0.653), respectively. There was no significant difference in the ORR between patients having *BRCA1/2* germline mutation and those with wild-type *BRCA1/2* gene ($p = 0.35$) (Figure 2). Considering only data pooled from the four Phase II trials, *BRCA1/2* germline mutation carriers showed an ORR of 55.9% (95% CI = 0.471 – 0.644) and wild-type *BRCA1/2* patients showed an ORR of 59.7% (95% CI = 0.518–0.671) ($p = 0.13$). The secondary endpoint was the ORR for PARP inhibitors.

**Table 1. Summary of included trials**

| Study phase, Author, Year | Treatment arms | N Arm 1 | N Arm 2 | Mean age (range), years | BRCA status (N response / N mutated) | Platinum sensitivity (N response / N sensitive) | ORR, treatment arm (%) | Mean PFS (months) | HR (95% CI) |
|---------------------------|----------------|---------|---------|------------------------|--------------------------------------|-----------------------------------------------|------------------------|------------------|-------------|
| II, Coleman, 2015\[1\]    | Veliparib 400 mg orally bid until progression | 52      | Single arm | 57 (median) (37–94) | 11/52                                | 7/20                                           | 26                     | 8.18             | n.a.        |
| II, Kaufman, 2015\[1\]   | Olaparib 400 mg bid | 193     | Single arm | 57 (29–79) | 60/193                                | n.a.                                           | 31.1                   | 7                | n.a.        |
| II, Kummar, 2015\[1\]     | Oral cyclophosphamide 50 mg once daily in combination with veliparib 60 mg once daily vs. cyclophosphamide alone | 35      | 37       | 58 (median) (37–79) | 5/31                                | n.a.                                           | 14.8 (Arm 1) | 22.2 (Arm 2)   | 2.1         |
| II, Oza, 2015\[1\]       | Maintenance with olaparib 400 mg bid vs. no therapy | 81      | 81       | 59 (27–78) | 13/20                                | n.a./83                                         | 41.2                   | 12.2             | 0.51 (0.34–0.77) |
| I, del Conte, 2014\[6\]   | Olaparib (7 olaparib dose cohorts (50–400 mg bid)) plus PLD (40 mg m(-2)) | 26      | Single arm | 55.5 (31–74) | 11/18                                | 10/14                                         | 53.8                   | n.a.             | n.a.        |
| II, Ledermann, 2014\[11\] | Olaparib 400 mg bid vs. placebo | 136     | 128      | 55.0–63.0 (21–89) | 48/71                                | n.a./115                                        | 55.8                   | 8.4 (Arm 1) vs. 4.8 (Arm 2) | 0.18 (0.1–0.31) |
| I, Sandhu, 2014\[12\]    | Niraparib (10 niraparib dose cohorts (30–400 mg bid)) | 49      | Single arm | 59 (39–75) | 8/20                                | 5/10                                           | 31.0                   | 12.9             | n.a.        |
| II, Liu, 2014\[13\]      | Olaparib 400 mg bid vs. Olaparib vs. Olaparib + cediranib | 46      | 44       | 58.1 and 57.8 | Arm 1: 7/24 Arm 2: 16/23 | Arm 1: 20 Arm 2: 21 47.8 (Arm 1) 9.0 (Arm 1) and 17.7 (Arm 2) | 0.42 (0.23–0.76) | n.a.             | n.a.        |
| II, Lee, 2014\[14\]      | Olaparib (dose escalation) plus Carboplatin AUC 3-5 | 37      | Single arm | 52 (35–73) | 16/37                                | 14                                             | 44.1                   | 16               | n.a.        |
| II, Kaye, 2012\[15\]     | Olaparib 200 mg bid vs. Olaparib 400 mg bid vs. PLD 40 mg m(-2) | 32      | 32       | 51.5 (39–69) | Arm 1: 8/32 Arm 2: 10/32 Arm 2: 16/32 Arm 3: 6/32 | Arm 1: 18/32 Arm 2: 26/32 Arm 3: 14/32 Arm 3: 18 | 44.1                   | 16               | n.a.        |
| II, Gelmon, 2011\[16\]   | Olaparib 400 mg bid | 65      | Single arm | 58 (39–84) | 7/17                                | 13/25                                         | 29.0                   | n.a.             | n.a.        |

$N$ = Number of patients, PFS = Progression-free survival, ORR = Overall response rate, HR = Hazard ratio, CI = Confidence interval, n.a. = information not available

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Owing to the low outcome numbers of other PARP inhibitor studies, only the ORR for olaparib monotherapy was pooled, thereby precluding statistical analysis. Regarding the Phase II trial by Kaye et al., the 400 mg bid arm was considered for analysis because this has been established as the most efficient dose of olaparib. The ORR for patients who underwent treatment with olaparib was 41.2% (95% CI = 0.364–0.462). It is noteworthy that only the combination treatment with cediranib presented a significantly higher ORR of 79.6%.

**Discussion**

PARP inhibitors represent a paradigm shift in the treatment of BRCA mutation-related ovarian cancer. PARP inhibitor development and introduction into the clinical trial phase was initially hampered by a negative outcome with iniparib, a drug that is no longer considered to be a PARP inhibitor. Nonetheless, PARP inhibitors have come a long way, having proved to be active anti-cancer drugs and the only novel drug approved for ovarian cancer since 2006. Currently, PARP inhibitors are only approved for patients with an underlying BRCA1/2 germline mutation.

This study includes all the published data of Phase I and Phase II clinical trials on PARP inhibitors in recurrent high-grade serous ovarian-, fallopian tube- or primary peritoneal-cancer. It includes a large cohort of more than 1000 patients; mostly recurrent high-grade serous ovarian cancer patients. It also includes more than 500 patients presenting a BRCA1/2 germline mutation. Most of the studies (80%) evaluated the PARP inhibitor olaparib, and obtained a pooled ORR of 41.2%. Olaparib proved to be a highly active drug in ovarian cancer, an otherwise virtually untreatable disease. Results with veliparib are less encouraging, with ORRs of 14.8%–26.0% and mean PFS rates of 2.1–8.2 months. On the other hand, the study is limited by the inclusion of only Phase I and II clinical trials, as no Phase III trials were identified in the database. This resulted in a small and possibly biased population of both over-represented and heavily pre-treated patients.

This study raises several important issues. While PARP inhibitors are traditionally seen as favorable drugs for the treatment of BRCA-mutated high-grade serous ovarian carcinoma owing to their mechanism of action, this study revealed no significant difference in the pooled ORR between patients having BRCA1/2 mutation and those that possessed wild-type BRCA1/2 gene (p = 0.35). This indicates that ovarian cancer patients who would potentially benefit from this form of therapy are excluded from this treatment option. It is possible that those patients who responded to olaparib, despite possessing a wild-type BRCA-gene, had some other form of BRCA inactivation (BRCAness) such as promoter hyper-methylation. All BRCAness phenotypes, not restricted to BRCA germline mutations, should be taken into account in future clinical trials of this drug. Alternatively, some patients may have some other form of BRCA-independent homologous-recombination deficiency, such as RAD51C deficiency.

Another important point refers to the apparent synergistic activity with cediranib. The Phase II clinical trial that evaluated this combination treatment reported an almost 80% ORR, almost 18 months PFS and HR of 0.42 (0.23–0.76). These exceptional results support the inclusion of cediranib in future trials. Bevacizumab, which has been used successfully in advanced ovarian cancer,
could also be of potential interest and should be evaluated.

Regarding the overall survival (OS) rate, only three clinical trials included complete datasets\(^5\)\(^-\)\(^7\). The OS information for these trials was not reported although it remains the ultimate treatment goal. Could it be achieved by inserting PARP-inhibitors only after chemotherapy-induced remission, particularly in platinum-sensitive patients? Extrapolation from other tumor types suggests that this treatment option deserves further exploration.

**Conclusion**

In summary, PARP inhibitors, particularly olaparib, proved to be effective in the management of BRCA1/2 germline-mutated ovarian cancer. Nonetheless, fine-tuning is still necessary to identify patients with wild-type BRCA1/2 genes and other forms of BRCAAness or BRCA-independent homologous recombination-deficient tumors, who may respond to therapy with olaparib. Equal importance should be given to the rational development of combinatorial treatment involving chemotherapy and PARP inhibition.

**Conflict of interest**

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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