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Review Article

Efficacy and safety of combination of poly-ADP-ribose polymerase inhibitor (PARPi) and chemotherapy compared with chemotherapy alone in treatment of recurrent ovarian carcinoma: a systematic review.

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Abstract

Platinum-based chemotherapy after surgical cytoreduction is the universal treatment for advanced ovarian cancer (OC), however, about eighty percent of patients experienced relapse and progression-free survival remained poor. Patients who relapsed within one year of treatment eventually become resistant to second-line chemotherapy. Poly-ADP-ribose polymerase inhibitors are a novel class of targeted therapy that could overcome these challenges by augmenting the chemotherapeutic activity of other cytotoxic agents. Cumulative Index to Nursing and Allied Health Literature (CINHAL), Cochrane and PubMed databases were searched for potentially relevant primary publications from 2011 to 2022 reporting on efficacy and safety of combination of a PARP inhibitor and chemotherapy versus chemotherapy in recurrent OC and reviewed. The outcomes of interest assessed qualitatively were progression-free survival (PFS) and grade 3 or higher adverse events (AEs) as measures of efficacy and safety respectively. Eight randomized controlled trials (RCTs) were included in the systematic review comprising 3,021 patients evaluated efficacy and safety of PARP inhibitors: Olaparib, niraparib and veliparib with combinations of bevacizumab, carboplatin, cisplatin, cediranib, cyclophosphamide and paclitaxel. 824 patients had 33 BRCA mutation while 1,430 had wild-type BRCA, an allele that confers increased risk of cancer. Most patients had platinum-sensitive cancers. There was significant prolongation of PFS with PARP inhibitor and chemotherapy combination compared to chemotherapy in all included trials except one which combined veliparib with cyclophosphamide. The prolongation of PFS was more remarkable in patients with BRCA mutation and occasionally patients with wild-type BRCA. Niraparib and veliparib were notably associated with grade 3 or higher anaemia, neutropenia, and thrombocytopenia, olaparib caused fatigue and gastrointestinal disturbances while bevacizumab and cediranib caused hypertension. This review suggested combined PARP inhibitor and chemotherapy significantly prolonged progression-free survival especially in patients with BRCA mutation compared to chemotherapy and the combined therapy is safe.

Keywords: Combined PARP Inhibitor; Chemotherapy; Efficacy, Safety, Ovarian Cancer

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Quick Response Code:

Introduction

Ovarian carcinoma is the deadliest female genital tract malignancy with less than 30% of women with advanced stage surviving 5 years after diagnosis. [1] There were around 240,000 new cases globally three years ago [2], and about 152,000 women die annually from causes related to ovarian cancer placing it eight on the list of causes of cancer-related mortalities in women. [3] Ovarian cancer has no classical clinical features, hence more than 75% of cases present late.[3] For a patient in whom the diagnosis is made early, the goal of treatment is cure.[4]

The conventional treatment for advanced-stage disease is platinum-taxane chemotherapy after surgical debulking[5]with remarkable response in about 20% of patients, the remaining 80% develop relapse with a progression-free survival (PFS) of one year to 18 months with a significant proportion becoming resistant to second-line chemotherapy.[6] Relapse within 1 year of platinum-based chemotherapy have is associated with response to subsequent chemotherapy[7], especially those with platinum resistance.[8] There is therefore an unmet need to optimize treatment approaches to develop therapies that would improve response to treatment and survival.

Poly-ADP-ribose polymerase inhibitors are a novel therapeutic approach in the treatment of ovarian cancer to bridge this gap to improve outcome.[9, 10] PARP is a protein responsible for the repair of single-strand DNA breaks (ssDNA),[11-13] and has an influence in the repair of double-strand DNA (dsDNA) breaks in the presence of homologous recombination deficiency (HRD).[13, 14] The mechanism of action of PARPi is by preventing ssDNA repair and resulting in the formation of dsDNA breaks that are not meticulously repaired in cancer cells with HRD such as BRCA1/2.[5, 12] Such inaccurately repaired cancer cells undergo apoptosis and are removed by autophagy. The mechanism of tumor cell death is the result of combination of toxic pharmacological activity of the PARPi and the mutation in the tumor cells and this is referred to as synthetic lethality.[12, 13]HRD is not exclusively confined to tumours with BRCA1/2 mutations, defects in other co-factors that play a role in homologous recombination repair pathway such as PALB2, RAD51D[15] and ATM[16] are also categorized as HRD states and this give support to the response of patients with wild-type BRCA and even non-mutated cancers to PARPi.[5]

Among patients with platinum resistance who harbour BRCA1/2 mutations, only 31-33% experience a favourable response when olaparib, a PARP was administered as single agent for maintenance therapy. [17,18] In order to improve the efficacy of PARPi as maintenance chemotherapeutics in recurrent ovarian carcinoma, several trials have been carried out combining PARPi with other cytotoxic medications. However, these combinations as doublet or triplet raised the concern of worse adverse events when several cytotoxic agents are used concurrently.[8] Rotterberg et al. [19] suggested olaparib has the potential to enhance the efficacy of cytotoxic agents that cause DNA damage like carboplatin, and carboplatin-paclitaxel doublet is an established regime for the platinum-sensitive recurrent ovarian cancer. PARP inhibitors alone have not significantly prolonged overall survival in a meta-analysis.[20] Inhibition of angiogenesis is crucial in cancer therapeutics, blocking the receptors of vascular endothelial growth factor (VEGF) or platelet derived growth factor (PDGF) that triggers neovascularization.[7] Anti-angiogenesis agents such bevacizumab and cediranib when combined with PARPi significantly improved progression-free survival (PFS) in patients with relapsed ovarian carcinoma when compared with olaparib alone therapy.[21] This might be as a result of the synergistic effect of anti-angiogenesis induced hypoxic effect of bevacizumab or cediranib and the synthetic lethality property unique to PARPi in HRD tumor cells.[21] According to Kaplan et al., anti-angiogenesis induced hypoxia could disrupt homologous recombination repair thereby increasing the sensitivity of tumours with wild-type BRCA to PARP inhibitors.[22] Furthermore, a combination of veliparib and cyclophosphamide offered about 50%

of patients with BRCA-mutated solid tumours a significant though incomplete response and another 25% had their disease stabilized over prolonged period.[23] Therefore, addition of a PARPi could be an important strategy in the management of platinum-sensitive or platinum-resistant recurrent ovarian carcinoma and since these could improve PFS irrespective of presence or absence of homologous recombination deficiency, patients with other forms of epithelial ovarian cancers could benefit from their use.

The aim of this systematic review is to compare the efficacy and safety of a combination of PARPi and chemotherapy with chemotherapy in patients with recurrent ovarian cancer.

Methodology.

A scoping search of the literature was done to identify a relevant topic for the systematic review and help to develop an appropriate search strategy. A thorough search was carried out in electronic databases using key terms from the research questions, after relevant keywords were identified. The databases CINHAL, Cochrane and PubMed were searched for articles eligible for this systematic review in March and April 2022 and an updated search was carried out on May 19, 2022. Combinations of keywords and synonyms were used, incorporating Boolean operators (AND/OR), truncation, MeSH, title (TI) and abstract (AB) and search ran on the databases. The keywords and term used were: ovarian cancer, ovarian neoplasm, ovarian malignancy, ovarian carcinoma, carcinoma of ovary, ovary cancer, platinum-sensitive ovarian cancer, ovarian cancer recurrence, olaparib, veliparib, MK4872, niraparib, rucaparid, talazoparid, PARP inhibitor, poly-ADP-ribose polymerase inhibitor, PARP inhibitor, cyclophosphamide, cediranib, paclitaxel, bevacizumab, doxorubicin, cisplatin, carboplatin, gemcitabine, docetaxel, efficacy, safety, side effects, adverse events, survival, disease-free survival, mortality, recurrence-free survival, overall survival, progression-free survival and death. The systematic review complied with the Preferred Reporting item for Systematic review and Meta-analysis recommendation statement PRISMA-2020.[24] The reference list of all selected articles was manually searched for relevant articles. The identified articles were recorded and exported into Endnote citation manager.

Inclusion criteria

Primary Research articles, full-texts and abstracts, limited to human adult females published from May 2011 to May 2022 and in English that evaluated the efficacy and safety of a combination of a PARP inhibitor and chemotherapy as doublet or triplet compared with chemotherapy were included in this systematic review. The patients had recurrent ovarian carcinoma and the result has PFS and adverse events as outcome measures for efficacy and safety respectively, and diagnosis was histologically confirmed as primary ovarian cancer; and participants had not received a PARP inhibitor previously. Studies were considered eligible for inclusion when they have data on BRCA mutational status, HRD or wild-type BRCA.

Exclusion criteria

Excluded from the review were publications on benign ovarian tumours or secondary cancers. Studies with insufficient data, no definite number of participants who experienced adverse events, a PARP inhibitor monotherapy in intervention arm or placebo alone in the control arm and single arm studies were excluded for inclusion. Phase 1 trials were excluded because they assessed dose and route of drug administration. Also excluded were theses, reports, reviews, personal views, guidelines, case reports, letter for authors and abstracts with insufficient data on intervention and outcomes.

Review process.

After removal of duplicates, the identified articles were screened from their titles and abstracts by applying the inclusion and exclusion criteria. Irrelevant articles were excluded and full text of articles that

remained were retrieved and reviewed, and inclusion and exclusion criteria applied to determine relevant articles for inclusion in the systematic review.

Data Extraction

A single reviewer extracted data from the included studies on Microsoft Excel spreadsheet complying with PRISMA guideline and saved it in duplicates. Data extracted included: last name of first author, study design, the year study was published, number of patients and medications in intervention and control arms, PFS, grade ≥3 adverse events, death, mutation status of patients and response to previous platinum-based chemotherapy.

Definition of outcomes

1. Progression-free survival is the time from unplanned allocation of cases to when cancer becomes advanced or death occurs,[20] this measures efficacy.
2. Grade 3 or worse adverse events: an adverse event (AE) is any undesirable inadvertent clinical features or laboratory abnormality that is not permanent and related to treatment or medical intervention, and grade 3 or worse refers to those AEs that are severe or

3. Life threatening or leading to death,[25] these three parameters measure safety.

Risk of Bias Assessment

The reviewer assessed the quality of included studies using the five-point Jadad score for evaluation of quality of randomized controlled trials (RCTs)[26] and was based on randomization, blinding, method of blinding and if the was dropout or withdrawal from the study. The Jadad score of the 8 trials ranged between 3 and 5 indicating that trials were of fairly good quality (Table I).

Table I. Showing Jadad score for included studies.

Author	Year	Was the study described as randomized?	Was the method used to generate the sequence of randomization described and appropriate?	Was the study described as double blind?	Was the method of double blinding described and appropriate?	Was there a description of withdrawals or dropouts	Total
Coleman *et al.*[33]	2019	1	1	1	1	1	5
Colombo *et al.*[30]	2019	1	1	0	0	1	3
Kummar*e t al.*[32]	2015	1	1	0	0	1	3
Lui *et al.*[29]	2019	1	1	0	0	1	3

Lui *et al.*[31]	2020	1	1	0	0	1	3
Mizra*et al.*[27]	2019	1	1	0	0	1	3
Oza *et* al.[28]	2015	1	1	0	0	1	3
Ray-Coquard*et* al.[4]	2019	1	1	1	0	1	4

Outcome

Progression-free survival

There was significant improvement in most patients irrespective of their mutational status. In the niraparib-bevacizumab versus bevacizumab study (Table II), the combination prolonged PFS relative to bevacizumab alone (11.9 versus 5.5months).[27]PFS was similarly prolonged in the olaparib-paclitaxel and was 12.2months compared with 9.6 months in the paclitaxel alone arm and this benefit was more in patients with BRCA mutation.[28] Furthermore, olaparib combined with cediranib prolonged PFS to 17.7 months relative to 9 months with olaparib alone, and with further analysis, patients with wild-type BRCA having longer PFS (16.5 versus 5.7 months) and a lower direction PFS in those with BRCA mutation, 19.4 versus 16.5 months.[29] Similarly, this trend was reported in another included trial except that olaparib-cediranib combination prolonged PFS to 5.8 months compared with 2.1 months for olaparib alone[30],and also and 10.4 versus 8.2 months.[31]Likewise, olaparib when combined with bevacizumab prolonged PFS to 22.9 months compared with 16.6 months in the bevacizumab-placebo arm with HRD positive patients having longer PFS (37.2 versus 17.7 months).[4] In contrast, veliparib-cyclophosphamide combination produced a marginally lower PFS of 2.1 months compared to 2.3 months for cyclophosphamide alone.[32]

When veliparib was combined with paclitaxel, PFS was 34.7 months compared with 22 months in the paclitaxel alone group, with a lower PFS period in patients with HRD (31.9 versus 20.5 months).[33]

Adverse events (AEs)- grade 3 or more

The most frequent with AEs olaparib-cediranib combination included fatigue (27% and 11%), diarrhoea (23% and 0%), and hypertension (41% and 0%) in the olaparib-combined and olaparib groups respectively.[29] Five serious adverse events occurred in a similar study that used paclitaxel in the control arm instead of olaparib with one death in both arms of the study.[30] Olaparib-paclitaxel-carboplatin combination caused 10% more frequent AEs than paclitaxel-carboplatin; the most frequent grade ≥3 AEs were neutropenia (43% and 35%), and anaemia (9% and 7%) in the intervention and control groups correspondingly[28] (Table II). Veliparib-paclitaxel combination is associated with serious AEs in 84% of cases compared with 72% in paclitaxel alone group and cause grade 3 or more neutropenia (62% versus 57%), anaemia (40% versus 36%) and fatigue (4% versus 4%) in the intervention and control arms respectively.[33] Furthermore, the combination of veliparib and cyclophosphamide cause more serious

AEs than cyclophosphamide alone (Table II). [32]The most common AEs in olaparib-bevacizumab versus bevacizumab-placebo study was hypertension and was 35% in the bevacizumab-placebo arm compared to 9% in the olaparib-bevacizumab arm.[4] Fatal AEs led to discontinuation in less than 1% and 1% in the olaparib-bevacizumab and bevacizumab-placebo groups respectively.[4] In another study that compared niraparib-bevacizumab with bevacizumab, the most frequent grade ≥3 AEs were anaemia (15% versus 18%), thrombocytopenia (10% and 12%) and hypertension (21% and 0%) in the niraparib-bevacizumab and bevacizumab arms respectively. [27] Additionally, niraparib-bevacizumab combination is associated with proteinuria (21% and 0%), and hypertension (56% and 22%) compared to niraparib only treatment (Table II).

Table II showing characteristics of randomized controlled trials included in the systematic review.

Author	**Year**	**Study design**	**No. of patients** **Treatment/ control**	**Intervention**	**Control**	**Response to platinum-** **Based chemotherapy**	**No. of Patients with** **BRCA mutation**	**No. of patients with BRCA wild-type**	**No. Patients with HRD**	**PFS (months) (treatment/** **control)**	**AE grade 3 and above** **Intervention/control (%)**
Coleman et al.[33]	2019	Double-blind phase III RCT	382/383/375	Veliparib + paclitaxel + veliparib maintenance, Veliparib+ paclitaxel+ placebo maintenance	Paclitaxel + placebo, then placebo	NA	298	742	627	34.7/22.0	Serious AEs 84/72 Anaemia 40/36 Fatigue 4/4 Neutropenia 62/57

Colombo et al.[30]	2019	Open-label phase II RCT	123	Olaparib + cediranib continuous(A) Olaparib + cediranib weekly(B)	Paclitaxel weekly	Recurrent	0	123	0	HRD cohorts 31.9/20.5	5, 2 deaths 1:1
Kummar et al.[32]	2015	Open-label phase II RCT	37/38	Veliparib + cyclophosphamide	cyclophosphamide	Sensitive and resistant	31	-	1	5.8, 3.8/2.1	Anaemia 5/0 Fatigue 10/0 Leucopenia 5/0 Lymphopenia 35/8
Lui et al.[29]	2019	Open-label phase II RCT	44/46	Olaparib + cediranib	Olaparib	Sensitive and relapsed	47	-	43	2.1/2.3	Fatigue 27/11 Diarrhoea 23/0 Hypertension 41/0
Lui et al.[31]	2020	Open-label phase III RCT	176/176/176	Olaparib + cediranib	Olaparib SOC	Sensitive	123	-	-	10.4/8.2/10.3	GIT 30/8.4 Hypertension 31.7/1.8 Fatigue 17.5/1.8

Mizra et al.[27]	2019	Open-label phase II RCT	48/49	Niraparib + bevacizumab	Niraparib	sensitive	43	-	-	11.9/5.5	Anaemia 15/18 Thrombocytopenia 10/12 Hypertension 21/0
Oza et al.[28]	2015	Open-label Phase II RCT	81/81	Olaparib + paclitaxel + carboplatin then olaparib maintenance	Paclitaxel +carboplatin	sensitive	41	-	66	12.2/9.6	Anaemia 9/7 Neutropenia 43/35 Serious AEs 15/21
Ray-coquard et al.[4]	2019	Double-blind phase III RCT	537/269	Olaparib + bevacizumab	Bevacizumab	NA	241	565	387	22.1/16.1	Hypertension 9/13 Serious AEs 31/31 Myelodysplasia 1/0.4

Keys to abbreviation in table 2.

Adverse events (AEs)Progression-free survival (PFS), hazard ratio (HR), Not available (NA), Germline BRCA mutation (gBRCAm), Gastrointestinal tract (GIT), Standard of care (SOC), Confidence interval (CL), Number (No.)

Results

Three hundred and ten (310) records were identified from the three electronic databases and 37 duplicate publications were removed, the titles and abstracts of the 273 articles were screened for eligible studies for exclusion and 196 articles were excluded after reading their title and abstract. The full-texts of the remaining 77 articles were retrieved and reviewed extensively and 69 full-text articles did not meet the criteria were therefore excluded (refer to PRISMA flow diagram below). The 8 articles remaining were RCTs with a total of 3,021 patients included in the systematic review, the vast majority had platinum-sensitive cancers. Two of the RCTs are phase III double-blinded while six of the trials were phase II open-label RCTs, 824 patients had BRCA mutation while 1430 had wild-type BRCA (an allele that influence cancer occurrence) (Table II).

PRISMA FLOW CHART

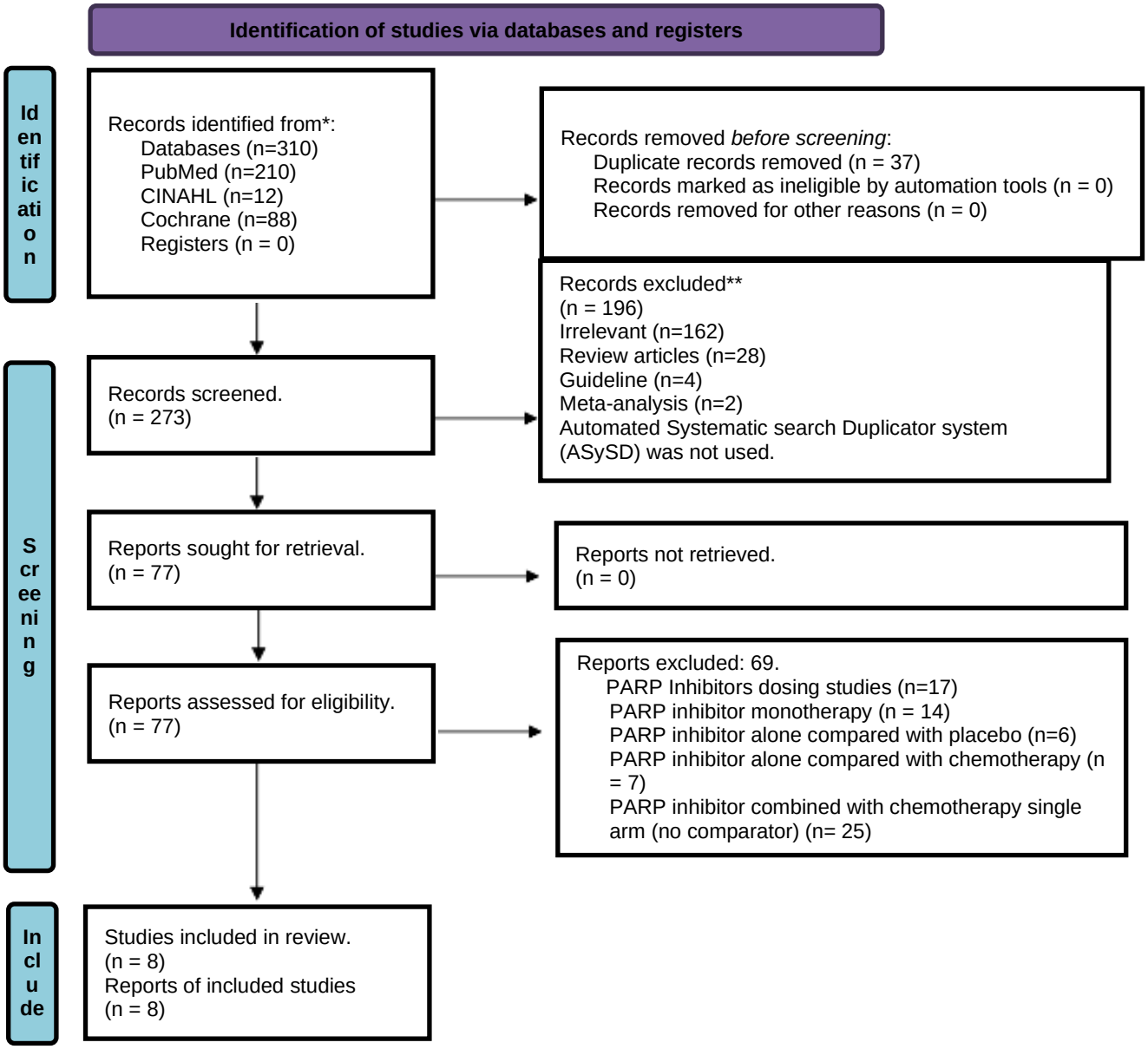

Figure 1. Flow diagram of study selection. Eight randomized controlled trials with complete date were included; studies reference 4, 27, 28,29,30,31, 32, 33.

Discussion

Originally used as radio-sensitizers in treatment of solid cancers, the PARP inhibitors are effective and safe alternative for patients with HRD cancers[12], especially patients with familial ovarian and breast cancers[34] because they induce apoptosis by synthetic lethality in BRCA-mutated and HRD cancers.[12, 13] The established management of advanced ovarian cancer is platinum-based chemotherapy and surgical cytoreduction with majority developing resistance after first-line chemotherapy.[22]

The olaparib-paclitaxel-carboplatin followed by olaparib improved PFS significantly compared to paclitaxel-carboplatin (Table II). [28] PFS was achieved most in BRCA-mutated cancers and was sustained despite longer follow-up period in the olaparib-paclitaxel-carboplatin group. Conventionally, carboplatin 4mg/ml AUC is combined with gemcitabine for treatment of relapsed cancer [35]. Addition of olaparib to paclitaxel-carboplatin had probably enhanced the cytotoxic activity of the low-dose carboplatin. Lederman et al. [36] However reported that olaparib monotherapy resulted in significant prolongation of PFS compared with placebo. On this ground, combining olaparib with paclitaxel-carboplatin may not have provided an edge over Olaparib alone but, the distinction here is the olaparib maintenance that followed the Olaparib-paclitaxel-carboplatin treatment. Accordingly, these studies may complement each other.

Anti-angiogenesis induced hypoxia could improve the efficacy of chemotherapy by enhancing the response of cancer cells to PARP inhibitors.[22] Two included studies [29, 30] on olaparib-cediranib compared with chemotherapy demonstrated significant improvement in PFS over paclitaxel or Olaparib alone, with PFS 5.8 versus 2.1 months and PFS of 17.7 versus 9.0 months, with improved trend in PFS in favour of patients with wild-type BRCA respectively. A similar trend was demonstrated in another phase III RCT[31] included, (Table II). Significant benefit in wild-type BRCAs emphasizes the role of co-factors like PALB2, RAD51D [15] and ATM[16], viewed as HRD states and lends support to the response of patients with wild-type BRCA to PARPi.[5]Two other reports[9, 37] used olaparib alone therapy demonstrated PFS of 6.4 and 8.8 months respectively but, the participants in both studies had dissimilar clinical characteristics. The similarity in the two studies suggested that the improved efficacy of olaparib-cediranib is unlikely due to inefficiency of the olaparib alone. The included studies did not however, have a cediranib alone arm. Furthermore, the PFS of cediranib alone in recurrent ovarian carcinoma in a reportwas 5.2 months, suggesting the clinical efficacy of cediranib as a single agent is less compared to olaparib-cediranib combination.[38]

Niraparib-bevacizumab combined therapy caused significant prolongation of PFS compared with bevacizumab alone, 11.9 and 5.5 months respectively.[27] Coleman et al. reportedcarboplatin-based therapy prolonged PFS from 12 to 14 months when bevacizumab was added. [10] The longer PFS of 11.9 months in the niraparib-bevacizumab arm of the study included in this review suggested addition of bevacizumab to niraparib have the potential of been used in patients with recurrent ovarian carcinoma. Similarly, Olaparib-bevacizumab combined therapy produced a remarkably improved PFS in the intervention than control arm with the benefit observed most in patients with BRCA mutation, a finding supported by another study.[39] Caution is necessary when drawing conclusions from such findings because the characteristics of the patients recruited in the two scenarios may vary. Conversely, a combination of veliparib and cyclophosphamide demonstrated good efficacy and safety profiles in patients receiving PARP treatment.[23] Veliparib alone therapy prolonged PFS marginally to 2.3 months compared to 2.1 months in the veliparib-cyclophosphamide arm(Table II).[32] However, the trial administered lower dose of veliparib 60mg daily, thus the lag in PFS might be due to the dosage being lower than 250mg to 400mg twice daily in the veliparib alone trial.[40]

The majority of AEs were mild to moderate grade not necessitating discontinuation of treatment in both intervention and control groups. Neutropenia was the most frequent grade ≥3 AE in the olaparib-paclitaxel-carboplatin arm than in the paclitaxel-carboplatin arm (Table II).[28] Olaparib is an efficacious and tolerable maintenance therapy.[9, 36] In the olaparib-cediranib combination trials[29-31], frequency of toxicities was similar in the intervention and control arms and most occurring grade ≥3 AEs were diarrhoea, fatigue and hypertension (Table II) consistent with the report in a trial.[21] Medical management was required for hypertension, though patients remained asymptomatic, the diarrhoea and fatigue resolved with dose reduction and symptomatic management.

Additionally, more frequent grade ≥3 AEs were experienced in the bevacizumab-placebo than in Olaparib-bevacizumab arm with 13% and 9% developing hypertension in the two arms respectively (Table II). [4] However, 1% of patients in olaparib-bevacizumab group developed myeloproliferative disease, acute lymphoblastic leukaemia or aplastic anaemia and incidence of primary malignancies was equal in both groups (Table II). Furthermore, 19% of patients discontinued bevacizumab while only 13% discontinued niraparib-bevacizumab in another included study.[27] This compares with rates of treatment interruption in two previous reports [41, 42] where gemcitabine or carboplatin was combined with bevacizumab. Treatment in the intervention and control arms were tolerated without serious impact on clinical condition or quality of life.

Cyclophosphamide and veliparib combination is safe and well tolerated in patients with refractory solid malignancies with no need of interrupting the veliparib because of unbearable toxicity.[23] Grade ≥3 leucopoenia and thrombocytopenia were noticed in 6.5% of patients in the veliparib-cyclophosphamide arm and was remedied by dosage adjustment and there more cases of myelosuppression compared with use of cyclophosphamide alone (Table II).[32]

Conclusion

Among 2,647 patients in the systematic review, combination of PARP inhibitor and chemotherapy caused significant prolongation of PFS compared with chemotherapy alone. Chemotherapy alone caused fewer grade ≥3 AEs compared to combination of PARP inhibitor and chemotherapy. Progression-free survival was more remarkable in patients with BRCA mutation and wild-type BRCA and this benefit was recorded in all trials included except one RCT in which cyclophosphamide and veliparib were combined, cyclophosphamide alone therapy offered a marginally prolonged PFS relative to the combination. The PARP inhibitor and chemotherapy combination are more efficacious; however, they caused more grade 3 or higher adverse events compared to chemotherapy but, most of the AEs were tolerated and ameliorated by dosage modification, discontinuation, or symptomatic management.

The limitations of this review are the small sample size in some of the trials and most were open-label phase II RCTs, the retrospective nature of systematic review and the fact that it was conducted by a single reviewer. In the future, involvement of many reviewers, inclusion of more double-blind RCTs with larger sample size could better provide a more evidence.

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