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Evaluation of efficacy and safety of PARP inhibitors in breast cancer: A systematic review and meta-analysis

Xiao-Fei Chang [a, 1], Xiao-Lu Ren [b, 1], Jie-Quan Yang [a], Jian-Jun Shi [a], Jun-Heng Bai [a], Meng-Sheng Cui [a, *], Wen-Wen Dong [a, **]

[a] Department of Breast, Heping Hospital Affiliated to Changzhi Medical College, Changzhi, China
[b] Department of Radiation Oncology, Shanxi Cancer Hospital, Taiyuan, China

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ABSTRACT

Background: Many breast cancer clinical trials with PARPi have been completed or are currently carried out, either by monotherapy or combined with chemotherapy. We aim to assess the efficacy and safety of PARPi in breast cancer patients as compared to chemotherapy.
Methods: A comprehensive literature search of PubMed, EMBASE, CENTRAL, conference meetings and clinical trial registry was performed. The primary outcomes were progression-free survival (PFS), overall survival (OS), overall response rate (ORR). The secondary outcome was safety profile. The comparative effects were measured using hazard ratio (HR) or relative risk (RR) with 95% confidence interval. Subgroup analyses were conducted based on types of intervention and baseline characteristics of patients.
Results: Six RCTs (n = 1953) were included. Two RCTs were recognized as high risk. PARPi was associated with an improved PFS (HR, 0.65; 95% CI, 0.56–0.74), OS (HR, 0.86; 95% CI, 0.73–1.01), and a higher ORR (RR, 1.38; 95% CI, 1.05–1.82). PARPi, however, significantly increased risk of grade 3–4 thrombocytopenia (RR, 1.63; 95% CI, 1.06–2.52). Monotherapy was observed with lower risk of disease progression and higher ORR rate than combination therapy, 0.56 to 0.65 and 2.21 to 1.05, respectively. For patients without prior platinum treatment, PARPi significantly improved PFS (HR, 0.64; 95% CI, 0.52–0.79).
Conclusions: PARPi was observed with a significantly improved efficacy in aspects of PFS and ORR, but also higher risk of grade 3–4 thrombocytopenia as compared to chemotherapy. PARPi was a better choice for patients who had not received previous platinum treatment.

1. Introduction

Breast cancer is the most common cancer in women, accounting for an estimated 2.09 million cases in 2018, with an increasing trend [1]. This disease is also one of the main causes of death in women [2]. There are many risk factors of breast cancer, among which, genetic factors are particularly important. Gene mutations in either BRCA1 or BRCA2 are profound in women, increasing the risk of breast cancer that is about five times than the normal. It is estimated that among women with mutation in BRCA1 and BRCA2, about 50–65% and 40–57%, respectively, will develop breast cancer by age 70 [3]. Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer with poor prognosis, testing negative for estrogen receptors, progesterone receptors, and excess HER2 protein [4]. One known cause of TNBC is germline mutations. Breast cancer with BRCA1 mutation is more likely to be triple negative while BRCA2 mutation is associated with estrogen receptor positive, HER2 negative [5].

Although traditional treatment regimen is based on the characteristics of breast cancer, now that genetic testing for BRCA mutations is available, treatment decisions for breast cancer can be made more precisely [6]. Poly-ADP-ribose polymerase (PARP) inhibitors are a novel class of DNA repair defect target therapeutics

Keywords abbreviations: PFS, progression-free survival; OS, overall survival; ORR, overall response rate; HR, hazard ratio; RR, relative risk; TNBC, triple-negative breast cancer; PARP, Poly-ADP-ribose polymerase; pCR, pathological complete response; AE, adverse event; RCT, randomized controlled trial; CI, confidence interval.

* Corresponding author. No. 110, South Yan an road, Luzhou district, Changzhi, 046000, Shanxi Province, China.
** Corresponding author.
E-mail addresses: cmsrxk@163.com (M.-S. Cui), 13109925499@sina.cn (W.-W. Dong).
[1] These authors are co-first authors and contributed equally to this study.

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[7]. PAPR inhibitors have been approved for treatment in breast cancer, specifically in BRCA mutation-associated breast cancer and triple-negative breast cancer. Current clinical trials in PARP inhibitors are monotherapy or combined therapy [8]. On the other hand, chemotherapy is an alternative treatment, frequently used as adjuvant or neoadjuvant therapy [9]. Common chemotherapy drugs include anthracyclines, taxanes, capecitabine, gemcitabine, eribulin, etc. Besides, DNA-damaging agents such as platinum agents can be effective based on preclinical and clinical experiments [10].

To date, many breast cancer clinical trials with PARP inhibitors have been completed, either by monotherapy or combined with chemotherapy. OlympiAD trial was the first randomized phase III trial in HER2 negative metastatic breast cancer with BRCA mutations, comparing Olaparib alone to chemotherapy. Median PFS was significantly longer in the PARP inhibitor group than in the standard chemotherapy group [11]. However, when evaluating the addition of PARP inhibitors to chemotherapy, the results of BrighTNess trial showed that adding veliparib to carboplatin and paclitaxel did not improve the pathological complete response (pCR) rate [12]. Given the controversial results from different trials, there is a need to define whether the benefit from PARP inhibitors is superior to chemotherapy. In addition, the only existing systematic review and meta-analysis was performed to assess the activity, efficacy and safety of single-agent PARP inhibitor compared to standard monochemotherapy. As a result, only 2 trials were included and analyzed [13].

Here, in this systematic review and meta-analysis, we aim to assess the efficacy and safety of PARP inhibitors in breast cancer patients as compared to chemotherapy. The comparison could be single-agent PARP inhibitor versus monochemotherapy as well as addition or not of PARP inhibitor to standard therapy. The primary outcomes were progression-free survival (PFS), overall survival (OS), overall response rate (ORR). The secondary outcome was safety profile: any-grade adverse events (AEs), treatment discontinuation, dose reduction, death due to AEs, grade 3–4 AEs, and a number of specific AEs. Study design is limited to randomized controlled trials (RCTs).

2. Materials and methods

The present systematic review and meta-analysis was conducted following the PRISMA checklist [14].

2.1. Information sources and search strategy

Eligible studies were identified by a systematic search of PubMed, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) from their respective inception to 21 September 2020, limited to “clinical trial” wherever possible, with no restrictions on the time, language or publication. The keywords for search were “breast cancer” and “PARP inhibitor”. Relevant reports from American Society of Clinical Oncology meeting were reviewed and trial registration website (https://clinicaltrials.gov/) was searched for potential studies as well. Also, reference lists of eligible studies were examined to identify additional trials.

2.2. Study selection

All identified studies were screened for titles and abstracts, and full texts were further scrutinized to judge their eligibility. Inclusion criteria: 1) RCTs in breast cancer patients with published or present results; 2) PARP inhibitor as the intervention and chemotherapy as the control, either in monotherapy or combination therapy but comparable; 3) with sufficient data for statistical analysis on at least one of the outcomes: PFS, OS, ORR. Duplicate studies were excluded and updated results of the same study were combined. Study selection was implemented independently by two reviewers. Disagreements were resolved by discussion till consensus was achieved or by referring to a third expert.

2.3. Data extraction and quality assessment

Data to be extracted from the selected studies included:

1) bibliographic information: first author, publication year
2) clinical and pathological characteristics of patients for both groups: number of patients, age, BRCA mutation status, hormone receptor status, prior cytotoxic therapy, previous platinum-based therapy
3) type of intervention and control
4) results of PFS, OS, ORR and AEs
5) data for assessment of study quality

The risk of bias in RCTs was assessed following the Cochrane Collaboration's RoB 2 tool. Judgement was presented as high, low or some concerns, following five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in measurement of the outcome and bias in selection of the reported result [15]. Similarly, two reviewers extracted information and assessed trial quality independently and in duplicate.

2.4. Data synthesis and analysis

The comparative effects of PARP inhibitors and chemotherapy on PFS and OS were measured using hazard ratio (HR) with 95% confidence interval (CI). HR < 1 means that the efficacy of intervention group is superior to control group and HR > 1 means the opposite. Relative risk (RR) and 95% CI were reported for the effect on ORR and safety. RR > 1 indicates that ORR of PARP inhibitor group is higher than that of control group. In terms of safety profile, RR > 1 means that the PARP inhibitor group had worse adverse events than in the reference group. For each outcome, the effect estimates of HR and RR were then pooled to produce a summary effect estimate using random-effects model [16]. Statistical heterogeneity was measured by I^2 statistic and Cochrane's Q test [17]. I^2 statistic >50% and p-value for Cochrane's Q test $\leq$0.1 suggested significant heterogeneity. Subgroup analyses were conducted based on types of intervention (monotherapy or combination therapy), baseline characteristics of patients (BRCA mutation status and hormone receptor status), or other potential factors that could contribute to heterogeneity. Sensitivity analysis was carried out to check robustness of the summary estimate by excluding studies with high risk of bias. All analyses were performed with RevMan software, version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). A p-value < 0.05 was considered statistically significant except for the heterogeneity test.

3. Results

3.1. Study selection and characteristics

The flow diagram of study selection was shown in Fig. 1. A total of 6 studies were identified eligible from 533 records of entry by our literature research [11,12,18–21]. One additional study which identified from clinical trial registry was excluded because only simple results were presented on the website (https://clinicaltrials.gov/) without any further publication [22]. To be specific, there were no baseline characteristics of the patients and no detailed

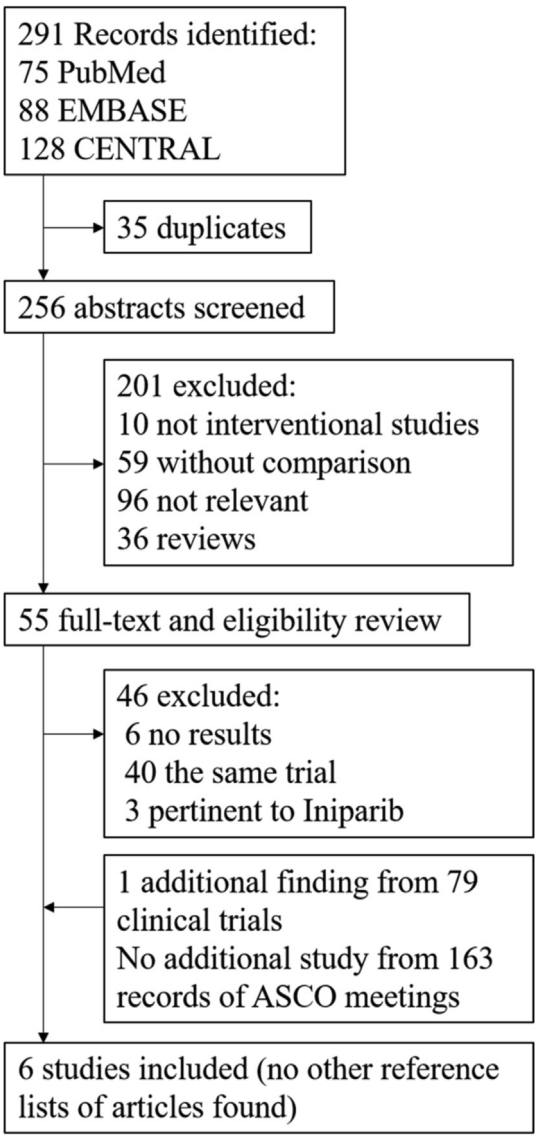

Fig. 1. Flow chart of study selection.

results like hazard ratio of PFS or vision of survival curves. The inclusion of studies of Iniparib could be controversial. Recent preclinical experiments showed that this compound did not possess PARP inhibitory activity [23]. Despite that it was at first investigated as a PARP inhibitor in phase I/II clinical trials, we decided to exclude studies pertinent to Iniparib [24–26] and perform sensitivity analysis to have a better understanding of its effect.

The main characteristics of studies were displayed in Table 1. The total sample size of patients included in our study was 1953, among which 1263 patients were received PAPR inhibitors treatment and 690 patients were received chemotherapy treatment. The PARP inhibitors investigated included Talazoparib, Olaparib, and Veliparib. Only two studies compared single agent PARP inhibitor and monochemotherapy while others compared the combination therapy, investigating whether addition of PARP inhibitor can improve the outcome. All studies specified BRCA mutation status in the report, but information on BRCA mutation status was incomplete in one study because of not mandatory collection. Two studies targeted on triple negative patients while there were no restrictions of hormone receptor in the other four studies. Four studies provided data on number of patients who had prior received chemotherapy, and among them, three studies were available for number of patients who were treated with platinum-based therapy. Also, one study excluded patients with previous anti-cancer treatment.

3.2. Risk of bias assessment

The methodological assessment of included studies was summarized in Table 2. All the studies were reported as randomized controlled trial. Three studies demonstrated open-label but analysis was based on intention-to-treat (ITT), which maintains the benefit of RCT: the effect of assignment to intervention was estimated by all randomized participants. There were two studies [11,18] assessed as high risk of bias due to missing outcome data. The differences between the proportion of missing outcome data in the two comparative groups were likely to cause bias. Since the patients were aware of the treatment, those in the chemotherapy group tended not to receive treatment and withdraw from the trial. Measurement of outcome was conformed to Response Evaluation Criteria in Solid Tumors (RESIST), and in some studies, conducted by independent central review. There was no overt evidence that the assessment of outcomes was influenced by knowledge of intervention groups. As a result, two RCTs [11,18] were removed in sensitivity analysis.

3.3. PARP inhibitors versus chemotherapy: efficacy

PFS was the primary end point in most studies, but cannot be obtained in one study [12]. By pooling the results of other five studies (Fig. 2), PARP inhibitors were associated with an improved effect on PFS, with HR 0.65 (95% CI, 0.56–0.74). No significant heterogeneity was observed ($I^2 = 0\%$, $p = 0.42$). OS was available in four studies [11,18–20]. Meta-analysis of the four trials showed significant improvement in OS comparing PARP inhibitors with chemotherapy, with HR 0.86 (95% CI, 0.73–1.01) and the heterogeneity is not significant, with $I^2 = 0\%$, $p = 0.66$ (Fig. 3). All the studies provided result of ORR. Although the weighted ORR was significant at RR 1.38 (95% CI, 1.05–1.82), the heterogeneity was significant as well, with $I^2 = 91\%$, $p < 0.00001$ (Fig. 4). The sample size in study [21] was quite small, leading to extreme large confidence interval.

Table 3 summarized the results of safety with regard to any grade AE, treatment discontinuation, dose reduction, death due to AE, as well as grade 3–4 AE in total and specific grade 3–4 AE in the PARP inhibitor group compared with chemotherapy group. Overall, PARP inhibitor group showed worse safety profile in treatment discontinuation (RR 1.11 95% CI [0.80, 1.53]) and dose reduction (RR 1.06, 95% CI [0.59, 1.91]). However, neither of the results showed statistical significance. In terms of specific grade 3–4 AE, PARP inhibitors were statistically significantly associated with thrombocytopenia (RR 1.63, 95% CI [1.06, 2.52], $p = 0.03$) compared to chemotherapy.

3.4. Subgroup analysis and sensitivity analysis

Results of subgroup analysis were presented in Table 4. In terms of monotherapy or combination therapy, PFS and ORR showed statistically significant subgroup differences but not for OS. Monotherapy was observed with lower risk of disease progression and higher ORR rate than combination therapy, 0.56 to 0.65 and 2.21 to 1.05, respectively. Results were homogeneous among each type of intervention, especially for ORR, which had significant heterogeneity in total population. As for BRCA mutation status, only 4 studies provided PFS of BRCA subtypes and the subgroup

Table 1
Characteristics of the included studies.

Study	Comparison	Patients, n (PARPi/ chemotherapy)	Age(yr), median(range)	BRCA status				Hormone-receptor −positive	Triple-negative	Prior cytotoxic therapy	Previous platinum-based therapy
				BRCA1+	BRCA2+	No mutation	Unknown				
Litton JK 2018	Talazoparib vs. monochemotherapy[a]	431 (287/144)	45 (27–84)/50 (24–88)	133 (46.3)/63 (43.8)	154 (53.7)/81 (56.2)	–	–	157 (54.7)/84 (58.3)	130 (45.3)/60 (41.7)	176 (61.3)/ 90 (62.5)	46 (16.0)/30 (20.8)
Robson M 2017	Olaparib vs. monochemotherapy[b]	302 (205/97)	44 (22–76)/45 (24–68)	121 (59.0)/51 (52.6)	88 (42.9)/ 46 (47.4)	–	–	103 (50.2)/49 (50.5)	102 (49.8)/48 (49.5)	146 (71.2)/ 69 (71.1)	60 (29.3)/26 (26.8)
Han HS 2017	VCP vs. PCP[c]	196 (97/99)	44 (25–65)/46 (24–66)	51 (52.6)/ 53 (53.5)	44 (45.4)/ 46 (46.5)	–	–	57 (58.8)/56 (56.6)	40 (41.2)/ 42 (42.4)	76 (78.4)/ 72 (72.7)	–
Dieras V 2019	VCP vs. PCP[c]	509 (337/172)	47 (39–54)/45 (39–54)	177 (52.5)/89 (51.7)	167 (49.6)/86 (50.0)	–	–	174 (51.6)/92 (53.5)	163 (48.4)/80 (46.5)	299 (88.7)/ 146 (84.9)	27 (8.0)/16 (9.3)
Loibl S 2018	VCP vs. PCP[c]	476 (316/160)	51 (41–59)/49 (40–57)	45 (14.2)/25 (15.6)		271(85.8)/ 135(84.4)	–	0	476 (100)	0	0
Kummar S 2016	Veliparib/ cyclophosphamide vs. cyclophosphamide	39 (21/18)	54 (34–77)	7 (17.9)		4 (10.3)	34 (87.2)	0	39 (100)	–	–

[a] capecitabine, eribulin, gemcitabine, or vinorelbine.
[b] capecitabine, eribulin, or vinorelbine.
[c] VCP: Veliparib/Carboplatin/Paclitaxel, PCP: Placebo/Carboplatin/Paclitaxel.

Table 2
Specific and overall risk-of-bias assessment for all included studies.

Study	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall risk-of-bias judgement
Litton 2018	Low: central randomization with stratification	Low: open-label, but crossover not allowed; ITT	High: 1 pt did not receive treatment, 10 withdrew and 7 lost to follow up in PARPi group; 18 pts did not receive treatment, 47 withdrew and 6 lost to follow up in control group	Low: the primary end point radiologic PFS was determined by blinded independent central review	Low: adhere to protocol	High
Robson 2017	Low: stratified randomization	Low: open-label, but crossover not permitted; ITT	High: 6 pts in control group did not receive treatment; 7 pts withdrew from the trial in PARPi group and 9 in control group	Low: the primary end point radiologic PFS was determined by blinded independent central review	Low: adhere to protocol	High
Han 2017	Low: stratified randomization	Low: double-blinded	Low: missing data did not differ much in two groups	Low: the primary end point PFS was determined by independent central review	No information	Low
Dieras 2019	Low: stratified randomization	Low: All parties were masked to treatment assignment	Low: missing data did not differ much in two groups	Low: Evaluation of tumor response was done by both the local investigator and by blinded independent central review.	Low: adhere to protocol	Low
Loibl 2018	Low: stratified randomization	Low: study funder, members of the academic steering committee, investigators, study site personnel, and patients remained masked to treatment	Low: 1 patient in PARPi group withdrew consent and none in control group	Low: Overall survival was defined as the number of days from the day of randomization to the date of death.	Low: adhere to protocol	Low
Kummar 2016	Low: randomized	Low: open label, efficacy on initial treatment was evaluated	Low: efficacy was evaluated on all patients	Low: Tumor response was assessed based on RESIST	Low: conduct followed regulations	Low

ITT: intention-to-treatment, pt: patient, PARPi: PARP inhibitor, RESIST: Response Evaluation Criteria in Solid Tumors.

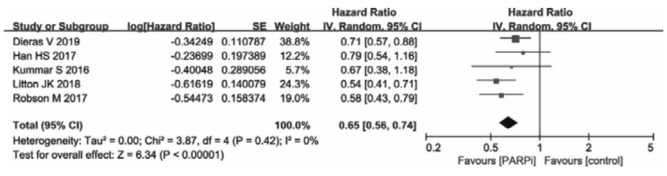

Fig. 2. Comparative effects of PARP inhibitors versus chemotherapy on progression-free survival of breast cancer patients. Results were presented as individual and pooled HR with 95% CI.

differences were not significant. Additionally, there was no significant subgroup difference among hormone receptor positive patients and triple negative patients in PFS or ORR. Of note, the higher ORR rate when treating with PARP inhibitors than with chemotherapy became statistically insignificant (RR 2.17, 95% CI [0.63, 7.49]) among subgroup TNBC patients and significant heterogeneity was still present. The impact of previous use of chemotherapy or platinum-based therapy was analyzed as well. No substantial subgroup differences were found according to stratification. Yet, for patients who received platinum-based therapy, the risk of disease

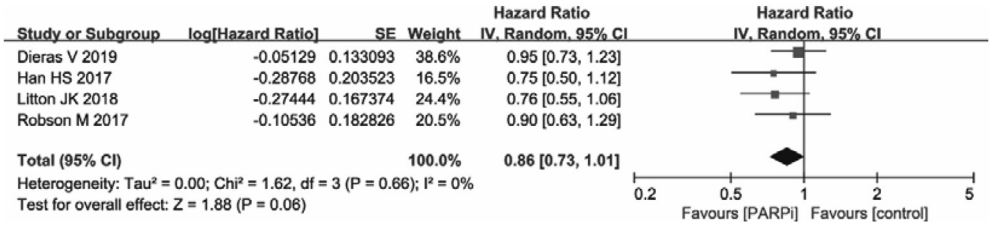

Fig. 3. Comparative effects of PARP inhibitors versus chemotherapy on overall survival of breast cancer patients. Results were presented as individual and pooled HR with 95% CI.

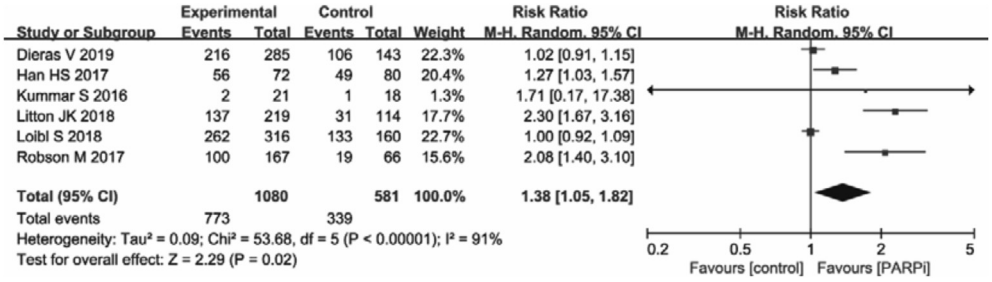

Fig. 4. Comparative effects of PARP inhibitors versus chemotherapy on overall response rate of breast cancer patients. Results were presented as individual and pooled HR with 95% CI. PARP inhibitors versus chemotherapy: safety.

Table 3
Safety profile of PARP inhibitor group versus control group.

Outcomes	Studies included	Events/total in PARPi group	Events/total in chemotherapy group	Risk ratio [95% CI], P value	Heterogeneity test
Any-grade adverse event	4	908/920	476/484	1.00 [0.99, 1.01], P = 0.90	I^2 = 6%, P = 0.36
Treatment discontinuation	5	123/1233	64/642	1.11 [0.80, 1.53], p = 0.54	I^2 = 20%, P = 0.29
Dose reduction	4	138/947	62/516	1.06 [0.59, 1.91], P = 0.84	I^2 = 72%, P = 0.01
Death due to adverse event	5	9/1161	5/564	0.89 [0.31, 2.55], P = 0.82	I^2 = 0%, P = 0.81
Grade 3-4 adverse event	6	774/1254	429/660	0.98 [0.88, 1.09], P = 0.67	I^2 = 60%, P = 0.03
Grade 3–4 neutropenia	6	583/1254	348/660	0.83 [0.65, 1.05], P = 0.12	I^2 = 80%, P = 0.0002
Grade 3–4 anemia	6	380/1254	123/660	1.83 [0.96, 3.48], P = 0.07	I^2 = 86%, P < 0.00001
Grade 3–4 thrombocytopenia	5	239/1049	85/569	1.63 [1.06, 2.52], P = 0.03	I^2 = 53%, P = 0.07
Grade 3–4 leukopenia	6	153/1254	86/660	0.91 [0.65, 1.28], P = 0.60	I^2 = 27%, P = 0.23

Table 4
PARP inhibitor group versus chemotherapy group: subgroup analysis of efficacy.

Subgroup	Progression-free survival			Overall survival			Overall response rate (%)		
	Studies	HR [95%CI]	Heterogeneity	Studies	HR [95%CI]	Heterogeneity	Studies	RR [95%CI]	Heterogeneity
Types of intervention									
Subgroup differences			P = 0.06			P = 0.65			P < 0.00001
Monotherapy	2	0.56 [0.45, 0.68]	I^2 = 0%, P = 0.74	2	0.82 [0.64, 1.05]	I^2 = 0%, P = 0.50	2	2.21 [1.73, 2.84]	I^2 = 0%, P = 0.70
Combination therapy	3	0.65 [0.56, 0.74]	I^2 = 0%, P = 0.86	2	0.89 [0.71, 1.10]	I^2 = 0%, P = 0.33	4	1.05 [0.95, 1.16]	I^2 = 35%, P = 0.20
BRCA mutation status									
Subgroup differences			P = 0.77			–			–
BRCA1 mutation	4	0.65 [0.53, 0.78]	I^2 = 0%, P = 0.60	–	–	–	–	–	–
BRCA2 mutation	4	0.62 [0.51, 0.76]	I^2 = 0%, P = 0.42	–	–	–	–	–	–
Hormone receptor status									
Subgroup differences			P = 0.73			–			P = 0.71
Hormone-receptor positive	4	0.65 [0.52, 0.82]	I^2 = 24%, P = 0.27	–	–	–	2	1.71 [1.30, 2.26]	I^2 = 0%, P = 0.80
Triple-negative	5	0.62 [0.50, 0.77]	I^2 = 24%, P = 0.26	–	–	–	4	2.17 [0.63, 7.49]	I^2 = 93%, P < 0.00001
Prior cytotoxic therapy									
Subgroup differences			P = 0.63			–			P = 0.45
Yes	4	0.63 [0.51, 0.77]	I^2 = 0%, P = 0.55	–	–	–	2	1.97 [1.39, 2.78]	I^2 = 20%, P = 0.26
No	4	0.67 [0.55, 0.82]	I^2 = 0%, P = 0.47	–	–	–	2	2.82 [1.19, 6.69]	I^2 = 48%, P = 0.17
Previous platinum-based therapy									
Subgroup differences			P = 0.63			–			P = 0.60
Yes	4	0.72 [0.47, 1.09]	I^2 = 0%, P = 1.00	–	–	–	2	1.92 [1.08, 3.44]	I^2 = 0%, P = 0.90
No	4	0.64 [0.52, 0.79]	I^2 = 36%, P = 0.19	–	–	–	2	2.22 [1.73, 2.84]	I^2 = 0%, P = 0.94

progression in PARP inhibitor group relative to chemotherapy group became statistically insignificant, with HR 0.72 (95% CI, 0.47–1.09), while for those who did not receive platinum-based therapy, PARP inhibitors still significantly improved PFS (HR, 0.64; 95% CI, 0.52–0.79).

In sensitivity analysis, we first excluded studies with high risk of bias. The effect estimates were similar to overall analysis for PFS (HR 0.72, 95% CI 0.60–0.86, p = 0.0004; heterogeneity I^2 = 0%, p = 0.86) and OS (HR 0.89, 95% CI [0.71–1.10], p = 0.27; heterogeneity I^2 = 0%, p = 0.33) except for ORR (RR 1.05, 95% CI [0.95–1.16], p = 0.35; heterogeneity I^2 = 35%, p = 0.20). Then studies investigating iniparib were included to check the robustness of overall effect estimates. To note, one study [26] further assigned PARP inhibitor group to 2 dose schedules: iniparib once-weekly (PWI) (11.2 mg/kg, d1; n = 46); iniparib twice-weekly (PTI) (5.6 mg/kg, d1, 4; n = 48). For convenience of analyzing and interpreting, when evaluating the efficacy (specifically ORR because of absence of data regarding PFS and OS) and safety outcomes, the number of events and total number in the two intervention groups were combined and then compared to the control group. In general, sensitivity analysis produced similar results, with PFS (HR 0.67, 95% CI [0.60–0.76]) and ORR (HR 1.31, 95% CI [1.08–1.60]), but yielding significant difference in risk of survival comparing PARP inhibitors to chemotherapy, with HR 0.84 (95% CI, 0.73–0.95; p = 0.006).

4. Discussion

This meta-analysis assessed the efficacy and safety of PARP inhibitors in breast cancer patients as compared to chemotherapy. PARP inhibitors were associated with significantly improved effect in PFS and ORR. However, PARP inhibitors increased the risk of grade 3–4 thrombocytopenia, as compared to chemotherapy. The noteworthy efficacy of PARP inhibitors suggested that if patients are tolerable of thrombocytopenia, use of PARP inhibitors could improve the outcome of PFS as well as response rate.

Along with the two phase III trials [11,18] having reported greatly improved efficacy, FDA approved single agent PARP inhibitors olaparib and talazoparib for breast cancer. In the only previous meta-analysis [13], it summarized the efficacy and safety of the two studies. Compared with monochemotherapy, single-agent PARP inhibitor was observed to improve PFS (HR, 0.62) and ORR (OR, 4.15) but not OS. The conclusion is concordant with ours regardless of subtle discrepancy in magnitude which is attributed to exclusion of studies investigating combination therapy and alternative use of effect estimate OR.

Although single-agent PARP inhibitors have demonstrated great efficacy, they have limited activity in cancers without underlying DNA repair deficits, particularly in platinum resistant or hormone-receptor proficient cancers [27]. In order to augment anti-cancer ability and widen application population, recent studies focused more on combination therapies of both the PARP inhibitor and the chemotherapy for advanced breast cancer [27]. In a review evaluating the benefit of PARP inhibitors added to chemotherapy in the neoadjuvant setting. Taken all the few available trials together, the review concluded that PARP inhibitor added to chemotherapy did not show overt advantage over standard chemotherapy, either in TNBC, HR-positive or in BRCA mutated breast cancer patients [28]. Our study included 4 trials with combination therapy, of which the results were displayed in subgroup analysis. In contrast, combination therapy was observed with a lower efficacy compared to monotherapy especially in ORR. More evidence from the ongoing trials exploring the efficacy of combination therapy is warranted.

Our meta-analysis also provided a view of potential patients who could benefit more from PARP inhibitors. Patients with BRCA2 mutation and triple-negative tended to have a better outcome of PARP inhibitor than those with BRCA1 mutation and hormone-receptor positive, respectively, albeit that the subgroup differences were not statistically significant. Although TNBC patients responded more sensitively to chemotherapy, they have unfavorable prognosis instead, and variations among subgroups of TNBC could introduce heterogeneity on evaluation of ORR [29]. Of note, for patients who had received platinum-based therapy before, the outcome of PFS was not significantly improved in the comparison of PARP inhibitor and chemotherapy. One explanation could be that there was greater degree of cross-resistance once patients had prior platinum exposure [9]. This suggested that patients who did not have previous platinum treatment had more of a benefit of PARP inhibitors.

The findings in this meta-analysis have important clinical implications. When selecting treatment regimen for patients, one should consider the balance of efficacy benefits and safety risk. Addition of PARP inhibitors to standard chemotherapy brought about some adverse events, to be specific, myelosuppression. Grade 3–4 anemia and thrombocytopenia were more common in PARP inhibitor group than in chemotherapy group. Preclinical studies reported that inhibition of PARP2 impaired the erythroid progenitors and reduced life expectancy of erythrocytes [30]. Thrombocytopenia occurred in the context of PARP inhibitors was mainly caused by decrease in megakaryocyte proliferation and maturation [31].

Still, several limitations of our study should be acknowledged. Firstly, the available RCTs were limited for meta-analysis. The summary estimates herein may be inaccurate when generalized to a wider population. Nevertheless, our study included a total of 1953 patients and the sensitivity analysis demonstrated robustness of the results, the evidence from which can be convincing. Moreover, trials with different hypothesis generated various end points. For our specific primary and secondary outcomes, particularly in subgroup analysis, some trials lacked complete data. As a result, effect estimates were based on a smaller number of studies and paucity of long term outcome stratified by BRCA mutation status, hormone receptor status and prior therapy made us impossible to do the subgroup analysis.

In conclusion, this systematic review and meta-analysis compared the efficacy and safety of PARP inhibitor with chemotherapy either single-agent or in combination in breast cancer patients. PARP inhibitors were observed with a significantly improved efficacy in aspects of PFS and ORR. However, PARP inhibitors were associated with high risk of grade 3–4 thrombocytopenia. PARP inhibitor was a better choice for patients who had not received previous platinum treatment.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2021.05.009.

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