Poly(ADP-Ribose) Polymerase Inhibitors (PARPi) for Patients With Advanced Breast Cancer: a Meta-analysis of Randomized Controlled Trials

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Research

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Abstract

BACKGROUND: Poly(ADP-ribose) polymerase (PARP) inhibitors are new class of drugs that are currently being studied in several malignancies. However, datas about the efficacy and safety of the PARP inhibitors are limited. Therefore, we conducted a meta-analysis of randomized controlled trials (RCT) in patients with breast cancer.

METHODS: Pubmed/Medline, Embase, Cochrane Library, and abstracts presented at the annual meeting of the American Society of Clinical Oncology (ASCO) were searched for articles published from 2000 to June 2018. Summary incidences and the RR, HR with 95% confidence intervals, were calculated by using a random-effects or fixed-effects model.

RESULTS: The summary HR indicated PARPi was not associated with OS (HR=0.83, 95%CI 0.66–1.06, Z=1.49, P=0.14), while it could significantly improve PFS and time to deterioration (TTD) of global health status/quality of life(GHS/QoL) as compared with traditional standard therapy, the HR was 0.60(95%CI 0.50-0.72; Z=5.52, P=0.00001) and 0.4 (95%CI 0.29–0.54,z=5.80 ,p=0.000),respectively. The RR of grade 3 or more anemia ,fatigue and headache was 3.02 (95% CI, 0.69–13.17;p = 0.14,,I²=90%),0.77 (95%CI, 0.34–1.73;p=0.52,I²=7%) and 1.13 (95% CI,0.30–4.18;p=0.86,I²=0%),respectively.

CONCLUSION: The findings of this meta-analysis showed that PARPi has no significant effect on OS, while it could significantly improve in PFS and TTD of GHS/QoL for patients with advanced or metastatic breast cancer. Furthermore,our findings also demonstrated that the PARPi treatment is connected with an increased risk of grade 3 or more anemia adverse events.

Introduction

Breast tumor is the most popular female malignancy, with an estimated 1 million new cases diagnosed in 2012 (a quarter of all cancers[1]. In 2016, there were approximately 246 660 women diagnosed with breast tumor within America. Recent decades have shown significant progress with the therapy of breast tumor. Human epidermal growth factor receptor type 2 (HER2)-targeted therapies and Endocrine treatment have received a substantial improvement in overall survival(OS) in patients with HER2-positive and hormone receptor(HR) positive breast tumor[1]. Despite extensive research, triple-negative (estrogen receptor (ER),progesterone receptor (PR) negative,and HER2-negative) breast cancers (TNBC), still lack specific methods for therapy[3]. At present, the mainstay of treatment for triple-negative breast cancer and BRCA associated triple-negative is still chemotherapy.

Poly (adenosine diphosphate-ribose) polymerase (PARP) is a novel therapeutic target in cancer,which can bind to DNA breaks and attract DNA repair proteins to the site of damage to facilitates DNA repair[4]. Poly (adenosine diphosphate-ribose) polymerase (PARP) is a novel therapeutic target in cancer,which can bind to DNA breaks and attract DNA repair proteins to the site of damage to facilitates DNA repair[5]. Those people whose breast cancer susceptibility genes (BRCA1 and BRCA2) mutations,have a high risk of developing breast tumor[6].

PARP inhibitors have played a crucial role in the repair of DNA single-strand breaks by the base excision repair (BER) pathway[7]. PARP inhibitors are oral small-molecule inhibitors of PARP enzymes 1, 2, and 3, which can improve the clinical activity of DNA-damaging Chemotherapy by blocking DNA damage repair[8]. PARP inhibition could cause “synthetic lethality” in BRCA mutant tumor cells, which leads to profound cytotoxicity to tumor cells while sparing healthy cells[4, 9]. Because only the tumors in BRCA 1/2 mutated patients are defective in homologous recombination, therapy with PARP inhibitors appears to be highly tumour-specific[4].

Olaparib is a newfangled of PARP inhibitor which can induce synthetic lethality in homozygous BRCA-deficient cells[10]. Olaparib was permitted to treat advanced ovarian cancer patients with malignant germline BRCA-mutated, who have been treated with three or more prior lines of chemotherapy[11]. Furthermore the SOLO1 trial showed that BRCA1/2 mutation and newly diagnosed advanced ovarian cancer patients who have accepted platinum-based chemotherapy, the use of maintenance therapy with olaparib would provide a substantial benefit concerning progression free survival(PFS)[12]. The SOLO1 trial, which approved olaparib as maintenance therapy of ovarian cancer patients who were sensitive to platinum therapy.

The OlympiAD trial demonstrated that compared to standard therapy, olaparib provided a remarkable benefit among patients with a germline BRCA mutation and HER2-negative metastatic breast tumor[13]. OlympiAD trial that gave the approval of olaparib by the FDA for the therapy of patients with BRCA-mutated HER2-negative metastatic breast tumor patients[14].

Talazoparib, is another oral inhibitor of PRAP. The phase III trial EMBRACA showed that compared to standard chemotherapy, single-agent talazoparib provided a significant benefit concerning PFS among patients with germline BRCA1/2 mutation advanced breast cancer. Talazoparib was recently approved as the therapy of people with malignant or suspected malignant germline BRCA-mutated, HER2-negative, locally advanced or metastatic breast cancer by FDA and the European Medicines Agency (EMA)[15, 16].

As a new drug, it is vital to understand its adverse effects profile better to optimize its use. However, data about the efficacy and safety of the PARPi are limited. Few studies have investigated the PARPi in any systematic way. Therefore, the purpose of this meta-analysis is to review recent research to evaluate the efficacy and safety of PARP inhibitors.

Materials And Methods

2.1. Data source

A literature search was independently performed by two investigators using electronic databases including Pubmed/Medline,

Embase and Cochrane Library, using the following search keywords: “Olaparib” or “PARPi” or “Talazoparib” and “Randomized” and “Advanced Breast Cancer” restricted to randomized controlled trials

(RCT) published in English. We also searched abstracts and virtual meeting presentations from the American Society of Clinical Oncology (<http://www.asco.org/ASCO>) conferences held between January 2000 and September 2019. What's more, we searched the clinical trial registration website (<http://www.ClinicalTrials.gov>) to obtain information on prospective registration trials. When more than one publication was identified from the same clinical trial, we used the most recent or complete report of that trial. When data could not be determined, we would contact the authors.

2.2. Selection criteria

Studies should meet the following criteria of eligibility: 1) articles published in English language, 2) prospective phase II or III randomized controlled trials (RCT) design in advanced breast cancer patients; 3) participants assigned to treatment with PARPi or control (placebo, chemotherapy or other therapies) and, 4) studies with available safety data reporting adverse events.

2.3. Data extraction and quality assessment

Two experienced investigators independently performed data extraction[17]. Different variables from each eligible study were extracted: first author's name, publication year, trial phase, number of enrolled patients, dosing schedules used in PARPi and control arms, CTCAE (Common Terminology Criteria for Adverse Events) version, median progression-free survival, median overall survival, number of patients for analysis and number of the selected adverse events. We assessed the methodological quality of the included trials using the Cochrane Collaboration tool[18]. Studies were graded as having a "low risk", "high risk", or "unclear risk" of bias across the seven specified domains. We also used the seven-point Jadad ranking system that included randomization, double-blinding, and withdrawals, a practice in agreement with other meta-analyses done in this context[19].

2.4. Statistical analysis

In this meta-analysis, the software Stata 15.0 and review manager 5.3 as used to pool the results of eligible studies. The H.R. with its 95% CI was used to evaluate the influence strength of the PARPi on the prognosis of advanced breast cancer patients for each study. Q statistics and I^2 statistics evaluated the heterogeneity among the independent studies[20], and it is considered to be heterogeneous if P-value ≤ 0.1 or $I^2 \geq 50\%$. The fixed-effects model would be adopted if there was no heterogeneity among studies; otherwise, we would use the random-effects model[21]. Publication bias was evaluated through funnel plots and quantified by the Begg [22] and Egger tests. A symmetrical plot and P-value of Egger's test (≥ 0.05) suggested that there was no publication bias in all studies[23].

Results

3.1. Search results

The search strategy yielded a total of 130 publications. Fig. 1 provides an overview of the literature search and study selection. After removal of duplicates, 82 studies remained for the screening of titles and abstracts. Of these, 31 potentially relevant publications were selected for full-text reading. After the full-text screening, 3 RCTs reported in 8 publications were included in the systematic review[24-31], and all of them provided sufficient data for quantitative synthesis of the overall survival of advanced breast cancer patients by meta-analysis.

3.2. Study quality

All included trials were randomized, with 1 phase 2 trials[30] and 2 phase 3 trials[24, 29] were published in full manuscript, and one trial was presented at the ASCO meeting[32]. Using the Cochrane Collaboration tool for risk of bias classification, we found the quality of the included studies to be generally good and fair(fig.2). Trials were also ranked for the Jadad score, with all trials categorized as being of good quality (achieving a score of 4 or more)[19]. All three trials reported adverse events according to the National Cancer Institute's CTCAE version 3 or 4 criteria.

3.3. Patients

The baseline characteristics of the enrolled studies are presented in table 1. A total of 926 patients were available for the meta-analysis (PARPi: 587; controls/placebo: 339)with median age ranging from 44 to 50 years. The most commonly mutated gene was BRCA1, in 757 of patients, followed by BRCA2 in 329. All three included studies reported safety data on adverse events and were included in the analysis. In one trial, randomization was between chemotherapy/control and PARPi olaparib[33]. Another study, PARPi Talazoparib, was compared to Standard-Therapy for advanced breast cancer[24]. Since there are few randomized controlled trials related to PARPi monotherapy for advanced breast cancer, to improve the reliability of our conclusion, we added another trial that PARPi Veliparib was combined with Carboplatin/Paclitaxel[30]. All of the three included studies provided OS and PFS data of patients with breast cancer. (table1).

3.4 Data synthesis

The primary endpoint of OS in patients with advanced breast cancer was evaluated in 926 patients. No significant heterogeneity was found (chi-squared=0.54,df=2,P=0.76,I²=0%), and fixed effects model was utilized to calculate the pooled HR and 95% CI. The combined results indicated that PARPi was associated with lower mortality (HR 0.83, 95%CI 0.66–1.06, Z=1.49, P=0.14 deficient quality of evidence). Patients with advanced breast cancer who received PARPi had 17% lower mortality than those who received other Standard-Therapy during the study period, but this difference was not statistically significant (fig 3.)

The primary endpoint of progression-free survival in patients with advanced breast cancer was evaluated in 926 patients. No significant heterogeneity was found (chi-squared=2.55,df=2,P=0.28,I²=22%), so we used fixed-effects model to calculate the pooled HR and 95% CI. The pooled results demonstrated that

PARPi group could significantly decrease the risk of death from patients with advanced breast cancer compared with the control group, which was only 60% of the control group (HR 0.60, 95% CI 0.50 to 0.72; $Z=5.52$, $P<0.00001$) and the results were statistically significant. (fig4.)

Two studies assessed the time to deterioration (TTD) of global health status/quality of life (GHS/QoL), the HR for TTD was 0.4 (95% CI 0.29–0.54, Supplementary Fig.1). No significant heterogeneity was found ($P=0.671$, $I^2=0\%$), the pooled HR suggested that PARPi treatment can lead to a statistically significant delay in TTD in patients with advanced breast cancer.

3.5 Sensitivity Analysis

The root of heterogeneity was assessed by sensitivity analysis, and there was not apparent heterogeneity was detected as described above. Besides, the pooled HR was not affected by any individual study, as shown in sensitivity analyses, which demonstrated that the results of our meta-analysis were robust and stable (fig.5.)

3.6 Publication bias

No evidence of publication bias was detected for OS or PFS of PARPi group by either the Begg's or the Egger's test (for PFS of PARPi group Begg's $P=0.296$ and Egger's $P=0.116$; for OS of PARPi group Begg's $P=1.000$ and Egger's $P=0.653$) [22, 23].

3.7 Incidence and relative risk of adverse events

Using a random-effects model, the summary incidence of all-grade and grade 3 or more adverse events in PARPi-treated patients was 98% (heterogeneity: $I^2=0\%$, $p=0.43$) and 47% (heterogeneity: $I^2=98\%$, $p<0.00001$), while in non-PARPi patients was 97% (heterogeneity: $I^2=0\%$, $p=0.66$) and 53% (heterogeneity: $I^2=100\%$, $p<0.00001$). The relative-risk (RR) of all-grade and grade 3 or more adverse events compared to non-PARPi was 1.02 (95% CI, 0.99–1.04; $p=0.16$) and 0.90 (95% CI, 0.78–1.03; $p=0.13$) while this difference was not statistically significant. (Fig. 7)

We were also using a random-effects model to calculate the summary incidence of all-grade and grade 3 or more anemia, fatigue and headache events in PARPi-treated patients. the RRs of all-grade anemia, fatigue and headache events were 1.68 (95% CI, 0.93–3.03; $p=0.08$, $I^2=89\%$), 1.05 (95% CI, 0.83–1.34; $p=0.67$, $I^2=50\%$) and 1.29 (95% CI, 1.01–1.65; $p=0.04$, $I^2=0\%$) (Fig. 9). There were significant heterogeneity in anemia ($P=0.0001$, $I^2=89\%$) and fatigue ($P=0.13$, $I^2=50\%$), when evaluating only trials that PARPi was given as monotherapy, the RR of all-grade anemia or fatigue events were 2.09 (95% CI, 1.10–3.97; $p=0.02$, $I^2=82\%$) and 1.19 (95% CI, 0.97–1.45; $p=0.10$, $I^2=0\%$) (Fig. 8).

The RRs of grade 3 or more anemia, fatigue and headache events were 3.02 (95% CI, 0.69–13.17; $p=0.14$, $I^2=90\%$), 0.77 (95% CI, 0.34–1.73; $p=0.52$, $I^2=7\%$) and 1.13 (95% CI, 0.30–4.18; $p=0.86$, $I^2=0\%$), respectively. Significant heterogeneity in anemia was found, when excluded the trial

that PARPi was in combination with chemotherapy , the RR of grade 3 or more anemia was 5.88 (95% CI, 3–10.36;p=0.00001,I²=7%) .(Fig. 9).

As a consequence,PARPi treatment was associated with a significant increase in the incidence and risk of any-grade anemia(RR=2.09 95% CI, 1.10–3.97;p=0.02,I²=82%) and headache(RR=1.29, 95% CI 1.01-1.65;p =0.04,I²=0%),the RR of PARPi associated all-grade anemia has significant heterogeneity(Fig.9).Moreover,PARPi treatment was associated with a significant increase in the incidence and risk of grade 3 or more anemia events (RR=5.88 95% CI, 3–10.36;p=0.00001,I²=7%) ,and this difference was statistically significant.

Discussion

The meta-analysis identified 3 RCTs involved 926 advanced or metastatic breast cancer patients. The summary HRs indicated PARP inhibitors were not associated with OS (HR= 0.83, 95%CI 0.66-1.06, Z=1.49, P=0.14 shallow quality of evidence), while it could significantly improve PFS compared to patients treated with traditional standard therapy(HR= 0.60,95%CI 0.50 - 0.72; Z=5.52, P=0.00001).Moreover, according to results of global health status/quality of life(GHS/QoL),we also observed a significant delay in time to deterioration (TTD) compared to patients who were treated with traditional standard chemotherapy.

Concerning all-grade and grade 3 or more adverse events,there are not statistically remarkable differences between PARP inhibitors and control group.The relative risk (RR) of all-grade and grade 3 or more adverse events compared to control group was 1.02 (95% CI,0.99-1.04; p= 0.16) and 0.90 (95% CI, 0.78-1.03; p = 0.13)(Fig. 8). significantly increased risk of all-grade and grade 3 or more anemia events associated with PARPi treatment in advanced or metastatic breast cancer patients. The RR of all-grade and grade 3 or more anemia was(RR=2.09 95% CI, 1.10–3.97;p=0.02,I²=82%) and 5.88 (95% CI, 3–10.36;p=0.00001,I²=7%),respectively.Whereas there was significant heterogeneity in all-grade anemia.

Our findings also suggest that the PARP inhibitors treatment are connected with a growing risk of all-grade headache ,the pooled RR was 1.29 (95% CI,1.01–1.65;p =0.04,I²=0%),the results were statistically significant.

MEDIOLA Trial ,a Phase II study of olaparib and durvalumab in patients with germline BRCA-mutated metastatic breast tumor.The updated results of MEDIOLA Trial showed that the most common grade 3 or more adverse events were anemia ,neutropenia and pancreatitis.And the data also suggest that patients with two prior lines of chemotherapy had shorter median PFS ,median duration of response (mDoR), and median OS ,lower objective response rate (ORR) than those with fewer prior lines of chemotherapy[34].Furthermore,the updated results in the phase 3 EMBRACA and phase 2 ABRAZO trial showed that a higher TALA exposure was related to a higher risk of anemia and thrombocytopenia[35].All these findings support the conclusion of this meta-analysis.

About EORTC QLQ-C30 symptoms and functioning subscales, the EMBRACA phase III trial showed that compared to the PCT arm, patients who treated with TALA significantly delayed TTD in all symptoms [25]. Meanwhile, there is similar result in the OlympiAD trial, except vomiting/nausea symptom score compared with TPC arm [36].

Our work has some limitations. First, there is significant heterogeneity between PARPi and all-grade fatigue, we failed to find the source of heterogeneity. Several reasons may account for the heterogeneity; 1) Differences in PARP inhibitors type and the dose may lead to heterogeneity; 2) fatigue is very subjective [37], the evaluated patient-reported outcomes in this regard seem to be better. Furthermore, we used adverse events data reported according to the NCI CTCAE grading system that also includes the subjectivity of the investigators when grading the event. All of these may partly explain the significant heterogeneity between studies. Second, randomized controlled trials about PARP inhibitors for patients with advanced breast cancer are too limited to perform a subgroup analysis study.

In conclusion, the findings of this meta-analysis showed that PARP inhibitors have no significant effect on OS, while it could significantly improve in PFS and TTD of GHS/QoL for patients with advanced or metastatic breast cancer. Furthermore, this meta-analysis also suggested that PARP inhibitors are associated with a significant increase in the risk of all-grade headache and anemia adverse events. Our findings demonstrated that the PARP inhibitors treatment is connected with an increased risk of grade 3 or more anemia adverse events.

Declarations

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Disclosure

The authors declared no conflicts of interest.

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Tables

Table1. Baseline characteristics of the included trials in final analysis

Author , year	Patients Enrolled	Treatment arms	Median age,(range)	BRCA- status		Hormone-receptor status		Median OS, months (95% CI)	Median PFS, months (95% CI)	Jadad score
				Brca- 1,n	Brca -2,n	Hormon e-recept or positive	Triple negative			
Robson 2019	205	Olaparib	44(22-76)	114	50	103	102	19.3(nr)	7 (5.7-8.3)	5
	97	Standard -chemotherapy	45(24-68)	84	45	49	48	17.1(nr)	4.2 (2.8-4.3)	
litton 2017	287	Talazoparib	45(27-84)	133	63	157	130	22.3(18.1 -26.2)	8.6 (7.2-9.3)	4
	144	Standard- Therapy	50(24-88)	154	81	60	84	19.5(16.3 -22.4)	5.6 (4.2-6.7)	
Han 2017		Veliparib+Carboplatin/Paclitaxel	44(25-65)	51	44	57	40	28.3(22.4 -nr)	14.1(11.5-16.2)	5
		Placebo+Carboplatin/Paclitaxel	46(24-66)	53	46	56	42	25.9(18.1 -34.8)	12.3(9.3-14.5)	

Figures

Figure 1

Study selection. PRISMA flow chart summarizing the process of selection of eligible studies.

Figure 2

A: Methodological Quality of Included Studies. B : Bias risk in the included randomized controlled trials.

Figure 3

Hazard Ratio for overall survival with Poly(ADP-Ribose) Polymerase Inhibitors (PARPi) vs. control.

Figure 4

Hazard Ratio for progression-free survival with Poly(ADP-Ribose) Polymerase Inhibitors (PARPi) vs. non-PARPi

Figure 5

Sensitivity analyses for included studies.a.all studies concerning PFS. b.all studies concerning OS

Figure 6

Relative risk of all-grade (a) and grade 3 or more (b) adverse events associated with PARPi versus non-PARPi.

Figure 7

Relative risk of all-grade anemia (a) ,fatigue (b) and headache (c)events associated with PARPi versus placebo/control in stratified analysis after excluding trial that PARPi was in combination with chemotherapy(a1)and(b1).

Figure 8

Relative risk of grade 3 or more anemia (a) , fatigue (b) and headache (c)events associated with PARPi versus placebo/control in stratified analysis, (a1)when evaluating only trials that PARPi was given as monotherapy.