

Risk of selected gastrointestinal toxicities associated with poly (ADP-ribose) polymerase (PARP) inhibitors in the treatment of ovarian cancer: a meta-analysis of published trials

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Aims: We aimed to comprehensively assess the risk of gastrointestinal toxicities associated with poly (ADP-ribose) polymerase inhibitors (PARPis) in the treatment of ovarian cancer patients.

Materials and methods: We searched several databases for relevant trials. Eligible studies included prospective Phase II and III trials of ovarian cancer patients on the four PARPis (olaparib, veliparib, niraparib and rucaparib), describing events of nausea, vomiting, diarrhea, and constipation. Summary incidence, relative risk (RR), and 95% CIs were calculated employing fixed- or random-effects models.

Results: A total of 2,286 ovarian cancer patients from 12 trials were included for analysis. Our results showed that summary incidences of all-grade gastrointestinal events in ovarian cancer patients were nausea 68.8% (95% CI, 63.5%–73.6%), vomiting 36.2% (95% CI, 30.9%–41.8%), diarrhea 25.3% (95% CI, 21.2%–29.8%), and constipation 25.3% (95% CI, 17.9%–34.5%). The RRs of all-grade nausea, vomiting, diarrhea, and constipation were 2.00 (95% CI: 1.79–2.24; $P < 0.001$), 2.12 (95% CI: 1.75–2.58; $P < 0.001$), 1.20 (95% CI: 1.01–1.44; $P = 0.044$), and 1.20 (95% CI: 0.88–1.80; $P = 0.21$); respectively. While, the RRs of high-grade nausea, vomiting, diarrhea, and constipation were 3.74 (95% CI: 1.50–9.36; $P = 0.005$), 2.81 (95% CI: 1.17–6.74; $P = 0.02$), 0.56 (95% CI: 0.22–1.43; $P = 0.23$), 0.92 (95% CI: 0.34–2.49, $P = 0.87$); respectively.

Conclusion: Our study suggests that the risk of all-grade gastrointestinal toxicities associated with PARPis, excepting constipation, is significantly increased in ovarian cancer patients. And the use of PARPis significantly increased the risk of developing high-grade nausea and vomiting, but not for diarrhea and constipation. Close clinical monitoring is recommended when administering these drugs.

Keywords: poly (ADP-ribose) polymerase inhibitors, gastrointestinal toxicities, clinical trials, meta-analysis, targeted agents, gynaecological tumors, systematic review

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Introduction

Ovarian cancer is the second most common gynecologic malignancy and is the leading cause of death from gynecologic cancers worldwide.^{1,2} Typically, ovarian cancer presents with advanced stages at the time of diagnosis.³ Although most patients with advanced ovarian cancer initially receive platinum-based chemotherapy and achieve a clinical response, the effectiveness of the treatments diminishes over time, and most of these patients will ultimately relapse.^{4–6} The prognosis of these recurrent ovarian cancer patients is very poor, with a median survival ranging from 12 months to 24 months.⁷

Clearly, novel effective drugs or treatment strategies that can improve long-term disease control in recurrent ovarian cancer are urgently needed.⁸

Recent advances in the understanding of the molecular biology and mechanism of epithelial ovarian cancer have led to the development of a number of targeted therapies, including poly-ADP-ribose polymerase inhibitors (PARPis).^{9,10} PARPis are a novel class of therapeutic agents that target tumors with deficiencies in the homologous recombination DNA repair pathway. Until now, three PARPis olaparib,¹¹ niraparib,¹² and rucaparib¹³ have been approved for use in ovarian cancer by the US Food and Drug Administration. As these drugs have now entered routine clinical practice, more and more patients would receive PARPis, and concerns increase regarding the toxicities associated with the administration of PARPis. In a previously published meta-analysis conducted by Zhou et al,¹⁴ the authors found that treatment with the PARPis olaparib, veliparib, and niraparib was associated with a significant increase in the risk of developing hematologic toxicities in cancer patients. Gastrointestinal (GI) toxicities associated with PARPis have been reported in clinical trials, but the results are controversial.^{15,16} As a result, we conducted the present meta-analysis of all available trials to comprehensively assess the overall incidence and risk of selected GI toxicities (nausea, vomiting, diarrhea, and constipation) associated with PARPis in the treatment of ovarian cancer.

Materials and methods

Data source

Several databases including PubMed, Web of Science and Cochrane library were searched for relevant trials. The search key words were PARPis, olaparib, veliparib, niraparib, rucaparib and ovarian cancer. Additionally relevant articles in the reference lists of recent meta-analyses that investigated PARPis in ovarian cancer patients were also searched. In order to avoid duplication, only the most complete or recent was considered for analysis. All results were input into Endnote X8 reference software (Thomson Reuters, Stamford, CT, USA) for duplication exclusion and further reference management. Finally, the most updated package inserts of olaparib, niraparib, and rucaparib were reviewed to identify other relevant information. Trials were chosen and reviewed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.¹⁷

Study selection

The primary objective of the present study was to evaluate the overall incidence of PARPis-related GI toxicities and the

risk of GI toxicities in ovarian cancer patients treated with PARPis; therefore, only prospective phase II and III trials evaluating PARPis in ovarian cancer patients with adequate data on GI toxicities were incorporated in the analysis. Phase I trials were omitted due to multiple dose level and limited sample sizes. Clinical trials that met the following criteria were included as follows: 1) prospective phase II and III trials, expanded access protocols (EAPs); 2) participants assigned to treatment with PARPis (alone or in combination at any dosage or frequency); and 3) available data regarding events or incidence of GI toxicities and sample size. Phase I trials were excluded because of inter-study variability in drug dosing as well as the small number of patients in these trials.

Data extraction

Two investigators independently conducted data abstraction, and any discrepancy between the reviewers was resolved by consensus. Most of the incorporated trials have used the common terminology criteria of adverse events version 4.0 for grading of the relevant adverse events. A checklist of necessary data to be extracted from each study included: first author's name, year of publication, phases of trials, number of enrolled subjects, treatment arms, number of patients in treatment and controlled groups, median age, median progression-free survival, and the number of each of the selected GI adverse events.

Statistical analysis

The primary summary measures were incidence, relative risk (RR), and corresponding 95% CIs of all grade (grade 1–4) and high-grade (grade 3–4) selected GI toxicities. All statistical analyses were performed by using Version 2 of the Comprehensive MetaAnalysis program (Biostat, Englewood, NJ, USA). For the calculation of incidence, the number of patients with selected GI toxicities in PARPis alone and the total number of patients receiving PARPis alone were extracted. To calculate RR, patients assigned to PARPis were compared only with those assigned to control treatment in the same trial. Between-study heterogeneity was estimated using the χ^2 -based Q statistic.¹⁸ Heterogeneity was considered statistically significant when $P_{\text{heterogeneity}} < 0.1$. The presence of publication bias was evaluated by using the Begg and Egger tests.^{19,20} A statistical test with a *P*-value < 0.05 was considered significant.

Results

Search results

Our search yielded 240 potentially relevant citations on PARPis from the searched databases. The details for the study

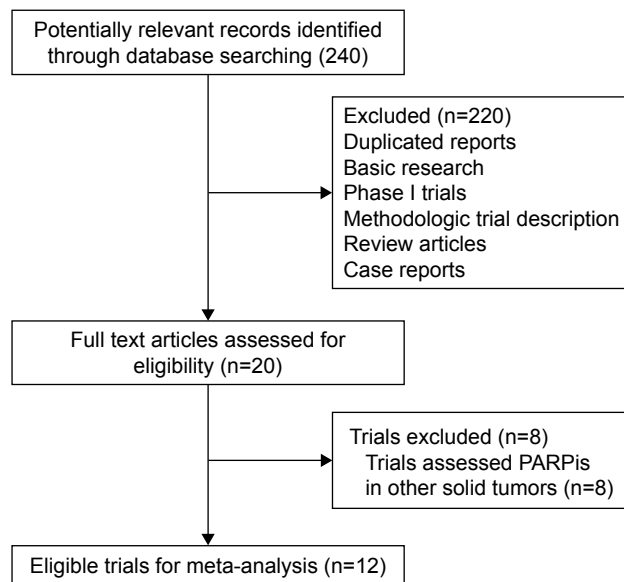


Figure 1 Studies eligible for inclusion in the meta-analysis.

inclusion/exclusion procedure are illustrated in Figure 1. A total of 12 trials were considered eligible for the analysis, including three Phase III trials^{21–23} and nine Phase II trials.^{24–32} A total of 2,286 patients were included in this analysis. Most patients had a performance score between 0 and 2 and competent liver, kidney and bone marrow function. The baseline patients' characteristics in each trial are described in Table 1.

Overall incidence of relevant adverse events

For the incidence analysis, we considered ovarian cancer patients receiving PARPis monotherapy. The pooled

incidence of all-grade nausea, vomiting, diarrhea, and constipation was 68.8% (95% CI, 63.5%–73.6%), 36.2% (95% CI, 30.9%–41.8%), 25.3% (95% CI, 21.2%–29.8%), and 25.3% (95% CI, 17.9%–34.5%), respectively. There was significant heterogeneity among trials, and we thus performed the meta-analysis by using a random-effects model (Table 2). As for high-grade GI toxicities, the pooled incidence of GI toxicities associated with PARPis was nausea 3.4% (95% CI, 2.6%–4.5%), vomiting 2.0% (95% CI, 1.4%–3.0%), diarrhea 1.7% (95% CI, 1.0%–3.0%), and constipation 1.4% (95% CI, 0.9%–2.3%), respectively. There was no significant heterogeneity among included trials, and we thus performed the meta-analysis by using a fixed-effects model (Table 2).

RR of all-grade relevant GI toxicities

A meta-analysis of the RR of all-grade adverse events was performed on the included randomized controlled trials (RCTs), which contained a direct comparison between PARPis and control treatment. The RRs of all-grade nausea, vomiting, diarrhea, and constipation were 2.00 (95% CI: 1.79–2.24; $P < 0.001$, Figure 2A), 2.12 (95% CI: 1.75–2.58; $P < 0.001$, Figure 2B), 1.20 (95% CI: 1.01–1.44; $P = 0.044$, Figure 2C), 1.26 (95% CI: 0.88–1.20); $P < 0.001$, Figure 2D); respectively. Thus, patients treated with PARPis had an increased risk of developing all-grade nausea, vomiting, diarrhea, and constipation. The fixed effects model was used for all the evaluated toxicities, except for constipation.

RR of high-grade relevant GI toxicities

RCTs directly comparing PARPis with control treatment were included to calculate RRs of high-grade GI toxicities. The RR

Table 1 Baseline characteristics of included trials

Author	Patient enrolled	Phase	Treatment regimes	Median age, years	Median PFS, months	No for analysis
Audeh et al, 2010 ²⁷	57	II	Olaparib 400 mg bid	54	NR	57
Gelmon et al, 2011 ²⁶	65	II	Olaparib 400 mg bid	58	7.1	65
Kaye et al, 2012 ²⁵	97	II	Olaparib 200 mg bid	58.5	6.5	64
Ledermann et al, 2012 ²⁴	265	II	Pegylated liposomal doxorubicin	53	7.1	33
			Olaparib 400 mg bid po	58	8.4	136
Liu et al, 2014 ³¹	90	II	Placebo	59	4.8	128
			Olaparib 400 mg bid po	57.8	9	46
Coleman et al, 2015 ³⁰	50	II	Veliparib 400 mg bid po	57	8.18	50
Bell-McGuinn et al, 2016 ²⁹	12	II	Iniparib 8 mg/kg	NR	NR	12
Domchek et al, 2016 ²⁸	154	II	Olaparib 400 mg bid po	58	NR	154
Mirza et al, 2016 ²¹	553	III	Niraparib 300 mg qd po	57	21	367
			Placebo	58	5.5	179
Pujade-Lauraine et al, 2017 ²³	295	III	Olaparib 150 mg bid po	56	19.1	195
			Placebo	56	5.5	99
Swisher et al, 2017 ³²	206	II	Rucaparib 600 mg bid po	NR	NR	206
Coleman et al, 2017 ²²	564	III	Rucaparib 600 mg bid po	61	16.6	375
			Placebo	62	5.4	189

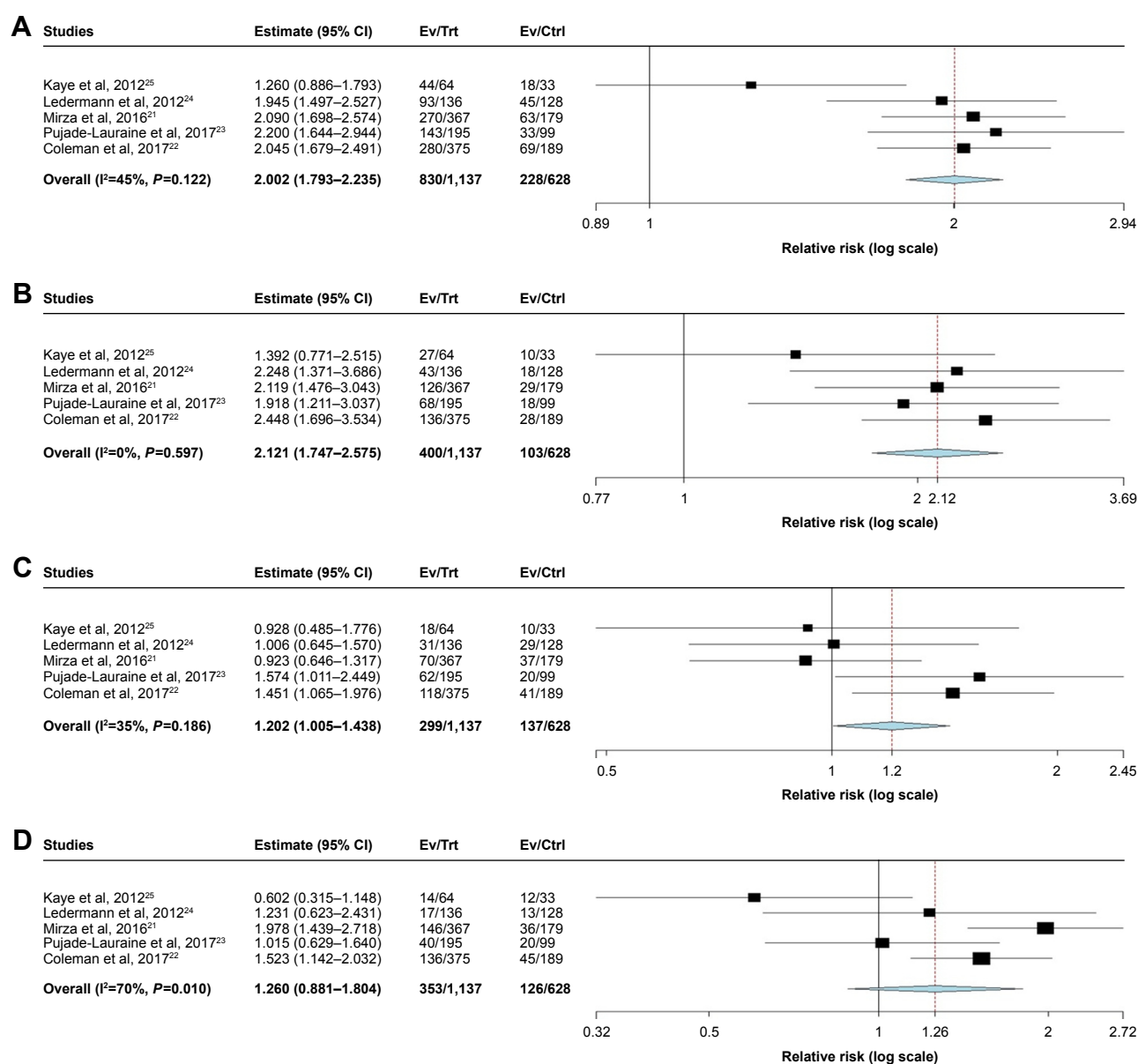
Abbreviations: NR, not reported; PFS, progression-free survival; Bid, bis in die; Po, per os.

Table 2 Incidence of adverse outcomes for clinical trials included in the meta-analysis

Adverse outcome	Grade	Trials	Events	No of patients	Incidence, % (95% CI)	I ²
Nausea	All-grade	12	1,225	1,727	68.8 (63.5–73.6)	76
	Grade 3 and 4	12	53	1,727	3.4 (2.6–4.5)	0
Vomiting	All-grade	10	611	1,669	36.2 (30.9–41.8)	76
	Grade 3 and 4	10	39	1,669	2.0 (1.4–3.0)	0
Diarrhea	All-grade	11	433	1,677	25.3 (21.2–29.8)	70
	Grade 3 and 4	11	21	1,677	1.7 (1.0–3.0)	38
Constipation	All-grade	9	476	1,566	25.3 (17.9–34.5)	92
	Grade 3 and 4	9	16	1,566	1.4 (0.9–2.3)	0

of high-grade nausea, vomiting, diarrhea, and constipation were 3.74 (95% CI: 1.50–9.36; $P=0.005$, Figure 3A), 2.81 (95% CI: 1.17–6.74; $P=0.02$, Figure 3B), 0.56 (95% CI: 0.22–1.43; $P=0.23$, Figure 3C), 0.92 (95% CI: 0.34–2.49, $P=0.87$,

Figure 3D); respectively. Thus, patients treated with PARPis had an increased risk of developing high-grade nausea and vomiting, but not for high-grade diarrhea and constipation. The fixed effects model was used for all evaluated toxicities.

**Figure 2** Relative risk of all-grade GI toxicities in ovarian cancer treated with PARPis vs controls.

Notes: (A) Nausea. (B) Vomiting. (C) Diarrhea. (D) Constipation.

Abbreviations: Ev, events; Trt, treatment; Ctrl, controls; GI, gastrointestinal.

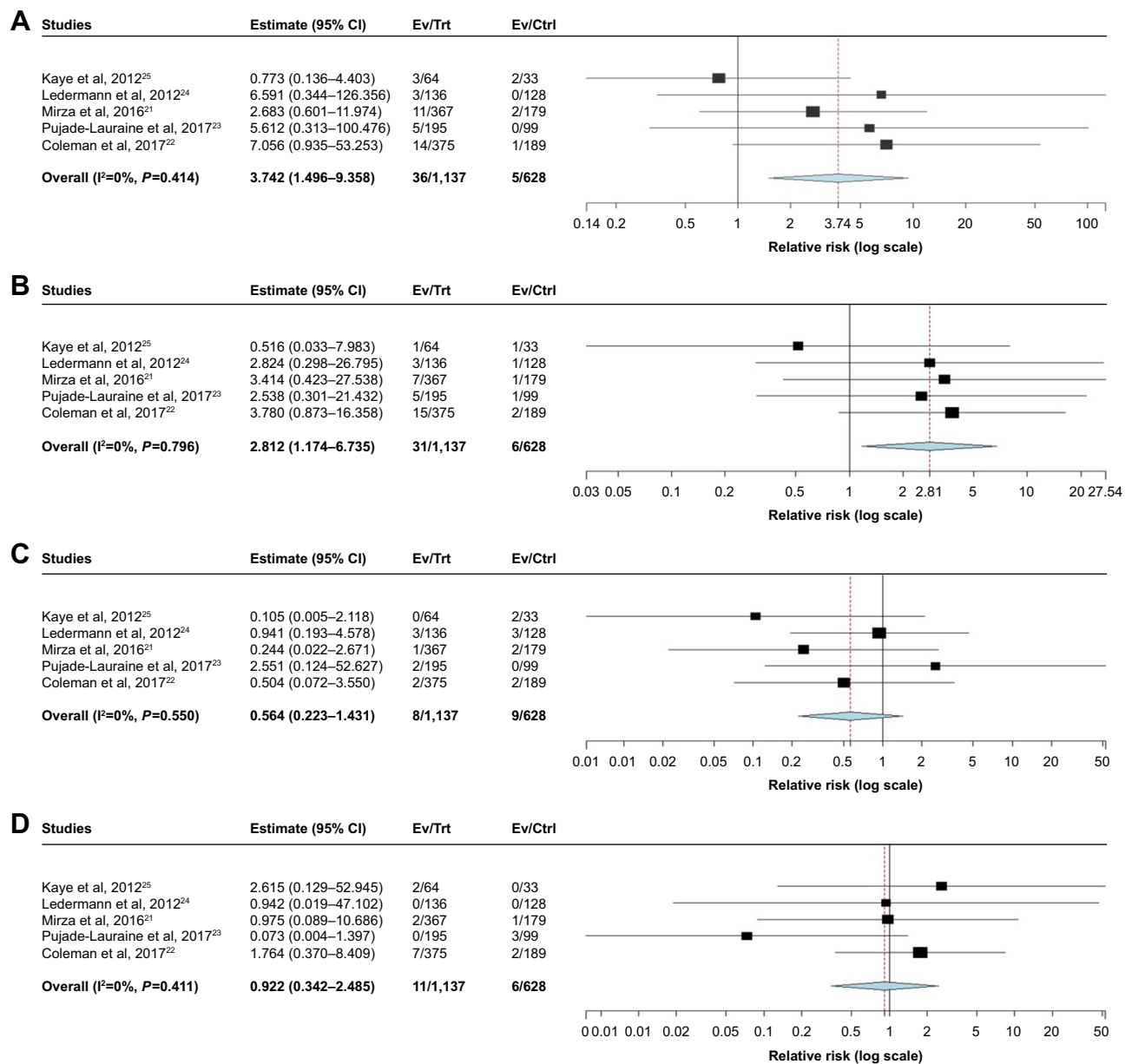


Figure 3 Relative risk of high-grade GI toxicities in ovarian cancer treated with PARPis vs controls.

Notes: (A) Nausea. (B) Vomiting. (C) Diarrhea. (D) Constipation.

Abbreviations: Ev, events; Trt, treatment; Ctrl, controls; GI, gastrointestinal.

Discussion

To the best of our knowledge, this is the most comprehensive and up-dated meta-analysis to provide an investigation of overall incidence and risk of GI toxicities in ovarian cancer patients treated with PARPis. Our analysis of data demonstrates that the risk of all-grade gastrointestinal toxicities associated with PARPis is significantly increased in the treatment of ovarian cancer. In addition, the use of PARPis in ovarian cancer significantly increases the risk of developing high-grade nausea and vomiting, but not for diarrhea and constipation. The four PARPis evaluated within our analysis are olaparib, veliparib, niraparib, and rucaparib. And three of

them olaparib, niraparib, and rucaparib have been approved for use in ovarian cancer due to their survival benefits. Additionally, a number of ongoing Phase II and III studies are assessing these agents in multiple other solid tumors indications.^{33,34} Therefore, the use of PARPis is anticipated to increase in the near future, and clinicians should pay particular attention to regular monitoring of GI toxicities related to PARPis during the administration of these drugs.

Until now, GI toxicities are considered an important cause for treatment interruption and/or permanent discontinuation in the clinical trials. Although high-grade GI toxicities are relatively uncommon, there are currently no methods to

predict patients at highest risk, and thus regular monitoring of clinical parameters during the administration of these drugs is warranted. Generally, administration of supportive therapy should be undertaken with the earliest manifestation of nausea and vomiting experienced by ovarian cancer patients treated by PARPis.

However, as far as we know, there are no specific guidelines for the treatment of PARPis-induced GI toxicities due to lack of controlled studies addressing the subject. The philosophy of management of anticancer-related GI toxicities extends to employing some nutritional interventions. In a recent Cochrane review evaluating how to minimize the frequency of diarrhea associated with pelvic radiotherapy, the authors found that combinations of modified fat, lactose-restriction, fat-restriction and fiber supplementation was recommended to reduce to the frequency of diarrhea.³⁵ Additionally, according to the package insert of approved PARPis,^{36–38} if grade three or higher non-hematological toxicity occurs, temporary dose interruption and/or dose reduction to half the dose previously administered should be considered based on tolerability and severity.

A number of limitations are needed to be acknowledged: first, as with any similar meta-analysis, the pooled results of our study are significantly affected by the confounding factors of individual studies that are chosen. Second, this meta-analysis only includes published trials, and a meta-analysis of individual level data might define more clearly treatment benefits in specific subgroups. Third, heterogeneity is observed in some of the RR analyses. This may be related to the different PARPis for the RR analysis, and differences in sample size, although we have tried to minimize its influence by using the random-effect model. Finally, as the present meta-analysis excludes Phase I trials, the impact of PARPis dose/schedules on the risk of gastrointestinal toxicities could not be fully assessed in this analysis.

Conclusion

Our study suggests that the risk of all-grade gastrointestinal toxicities associated with PARPis is significantly increased in ovarian cancer patients receiving these drugs. And the use of PARPis significantly increased the risk of developing high-grade nausea and vomiting, but not for diarrhea and constipation. Although the rate of clinically high-grade GI toxicities is very low, clinicians should be aware of these risks and perform regular assessment for such toxicities during administration of these drugs. Additionally, further research into the pathogenesis of these toxicities is still needed.

Disclosure

The authors report no conflicts of interest in this work.

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