



Research article

Effectiveness and toxicity of metronomic oral cyclophosphamide for recurrent or platinum-refractory ovarian cancer: A meta-analysis

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ABSTRACT

Purpose: To systematically assess the effectiveness and toxicity of metronomic oral cyclophosphamide (MOC) on recurrent or platinum-refractory ovarian cancer.**Methods:** We searched the Cochrane Library, Embase, PubMed, CNKI, Weipu, and Wanfang databases for eligible studies. A descriptive statistical method was used to analyze the pooled results. Ratios and means were merged to analyze the objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and the rate of serious adverse events (SAEs). Subgroup analysis, sensitivity analysis, and examination of publication bias were conducted for heterogeneity test and quality assurance of the results.**Results:** The ORR and DCR by MOC were 25% (95% CI 12–41) and 61% (95% CI 43–77), respectively. The median PFS and OS were 4.29 months (95% CI 2.62–5.97) and 11.26 months (95% CI 8.13–14.39), respectively. The rate of SAEs was 41% (95% CI 30–52). The most frequent SAEs were gastrointestinal toxicity 6% (95% CI 1–12), lymphopenia 6% (95% CI 1–13), and neutropenia 5% (95% CI 2–9). In the subgroup analysis, the ORR and DCR in the subgroup of MOC combined with bevacizumab/pazopanib were 42% (95% CI 26–58) and 82% (95% CI 63–95), respectively. The median PFS and OS were 7.32 months (95% CI 5.93–8.70) and 17.35 months (95% CI 12.89–21.82), respectively.**Conclusion:** MOC has a certain effect in clinical response on patients with recurrent or platinum-refractory ovarian cancers, especially when MOC combined with bevacizumab/pazopanib. However, there is a high risk of SAEs.

1. Introduction

Ovarian cancer (OC), including fallopian tube and primary peritoneal cancer, has become one of the primary causes of death among female malignancies. In 2020, about 210,000 women died of ovarian cancer, which had the second-highest mortality rate in gynecologic cancer [1]. The median age when diagnosed with ovarian cancer is 55, and most patients have a local or distant spread in initial diagnosis due to the insidious onset of cancer and the lack of efficient early screening methods [2]. The five-year survival rate is below 45% [3]. At present, chemotherapy occupy a primary status in the systemic therapy for ovarian cancer, and platinum-based doublets has already become the standard

method of therapy [4]. Approximately 70% of the patients show poor outcomes because of a relapse of the disease [5]. Platinum-based doublets are still the preferred regimens for patients who are platinum-sensitive (platinum-free-interval (PFI) > 6 months). But for the platinum-resistant (PFI < 6 months) or platinum-refractory (initial platinum therapy did not achieve remission of the disease) patients, non-platinum chemotherapy is useful. Targeted therapy and immune checkpoint inhibitors (ICIs) might be considered when specific biomarkers are present in the patients [6, 7, 8, 9]. However, as those drugs are generally unaffordable or unavailable, chemotherapy is still a common choice for most patients with advanced or recurrent ovarian cancer. Therefore, it is essential to assess the effectiveness and toxicity of

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chemotherapy. Furthermore, determining an effective, less harmful, economical, and convenient method is an improvement for traditional chemotherapy.

Metronomic chemotherapy (MCT), means administrating an anti-tumor agent continuously and regularly by using low dose for treatment to control the disease and reduce the effects of the adverse events [10]. MCT functions by promoting anti-angiogenesis, inhibiting tumor stem cells, and having immune-modulating effects [11]. Oral administration is generally performed because it is convenient and economical, and cyclophosphamide (CTX), capecitabine, etoposide, and vinorelbine have been extensively investigated in previous studies on MCT. Comprehensively and impressively studies have focused on breast cancer and lung cancer and those results have proved the effect and safety of MCT [12, 13]. In recent years, researchers have been also exploring MCT schemes for ovarian cancer, especially in patients with recurrent or platinum-refractory cancer. Most studies were phase I/II trials with small sample sizes or retrospective analyses. Hence, this meta-analysis was conducted for the prospective trials to collate existing information.

2. Methods

2.1. Search strategy

The Cochrane Library, Embase, PubMed, CNKI, Weipu, and Wanfang databases were checked for studies published till February 20, 2022. The keywords and the corresponding MeSH Terms used for searching were as follows: “gynecologic cancer” or “gynecologic carcinoma” or “ovarian tumor” or “ovarian carcinoma” or “ovarian cancer” or “ovarian neoplasms [MeSH Terms]” or “fallopian tube cancer [MeSH Terms]” or “primary peritoneal cancer” and “metronomic” or “low-dose”. To avoid the risk of omitting any relevant study, the reference lists of recent trials and reviews were searched, too.

2.2. Inclusion criteria

The inclusion criteria were as follows: (1) Prospective clinical trials for MCT in patients who were diagnosed with ovarian cancer, fallopian tube and primary peritoneal cancer in cytology or pathology. (2) Metronomic oral CTX. (3) Studies in which at least one of the following five results were presented or could be derived by calculation: objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS), overall survival (OS), and rate of SAEs related to chemotherapy.

2.3. Exclusion criteria

The exclusion criteria were as follows: basic research, case reports, reviews, retrospective analyses, conference papers, duplicated texts, and papers from which the information were impossible to be obtained.

2.4. Data extraction

The document retrieval methods were decided by the whole team. The literature search was conducted by one researcher. Two investigators cross-checked the relevant studies independently, selected the eligible articles, and extracted the information. Problems were solved by the whole team through discussion and negotiation. The extracted data were as follows: first author, year of publication, country of origin, clinical trial design, types of cancer, MCT schedules, median age, number of participants, median prior chemotherapy lines, ORR, DCR, median follow-up time, criteria for assessing effectiveness and toxicity, PFS, OS, SAEs, and incidence of SAEs.

2.5. Quality evaluation

All articles were read and assessed by two investigators independently. The Cochrane Handbook V5.1.0 was chosen for evaluating

randomized controlled trials (RCTs). For assessing non-RCTs, the MINORS (methodological index for non-randomized studies) score was used. All arguments regarding quality assessment were solved through discussion among all the investigators.

2.6. Statistical analysis

The merged ratio was used to calculate the ORR (the rate of participants showing complete response (CR) or partial response (PR)), DCR (the rate of participants with CR, PR, or stable disease), the rate of SAEs (the rate of participants with serious adverse events), and the rate of special SAEs (the rate of participants with special SAEs), along with the 95% CIs. The merged means were adopted to assess the PFS and OS and the corresponding 95% CIs. Cochrane's Q and I^2 statistics were adopted to quantify heterogeneity. The meta-analysis was performed by constructing random-effects models when there was significant heterogeneity ($I^2 > 50\%$ or $p < 0.10$). The subgroup analysis was performed by separating all participants according to the following conditions: multidrug MCT, MCT combined with bevacizumab/pazopanib, and MCT monotherapy/MCT combined with other drugs. Each experimental group was eliminated successively for sensitivity analyses. Finally, Egger's publication bias plots were used to evaluate possible impacts on the overall results; when the p -value was below 0.05 or the 95% CIs did not include 0, we considered that publication bias was absent. Statistical analyses were all conducted by STATA 16.0 software (Stata Corp LP, College Station, TX, USA).

3. Results

3.1. Eligible articles

The flow chart is presented in Figure 1. We found 327 studies, of which 321 were excluded for reasons such as duplicate publications (118), articles that were not relevant to our study (98), review articles (29), basic research articles (29), conference articles (14), retrospective analyses (20), and case reports (13). The remaining six articles were eligible.

3.2. Quality evaluation

RCTs were evaluated by the Cochrane Handbook Version 5.1.0. Non-RCTs were assessed using the MINORS scores. The studies by Sharma [14], Hall [15] and Gupta [16] were RCTs, where the allocation concealment and blinding were reported in detail, but reporting bias and any other possible bias were not mentioned. Regarding non-RCTs, the MINORS scores were from 7 to 11 (Table 1).

3.3. Pooled data analysis

This meta-analysis included information on 365 patients with recurrent or platinum-refractory ovarian cancer in nine cohorts from six trials [14, 15, 16, 17, 18, 19]. Five phase II trials and one phase I trial were included in our study. In all six trials, CTX was administered once a day, with 100 mg of CTX used in only one study and 50mg CTX used in the remaining five (Table 2). Patients with fallopian tube and primary peritoneal cancer were included along with those with epithelial ovarian cancer in five studies, while another one did not. Platinum-sensitive, platinum-resistant and refractory cancer were investigated in four studies, while either platinum-resistant or refractory cancer was investigated in the remaining two. Six trials reported detailed ORR and DCR. Five trials reported PFS and OS, and the OS data of Arm B could not be extracted from the study by Sharma. Five trials reported the rate of SAEs in detail (Table 1).

The pooled ORR and DCR by MOC for recurrent or platinum-refractory ovarian cancer were 25% (95% CI 12–41) and 61% (95% CI 43–77). The PFS and OS were 4.29 months (95% CI 2.62–5.97) and 11.26

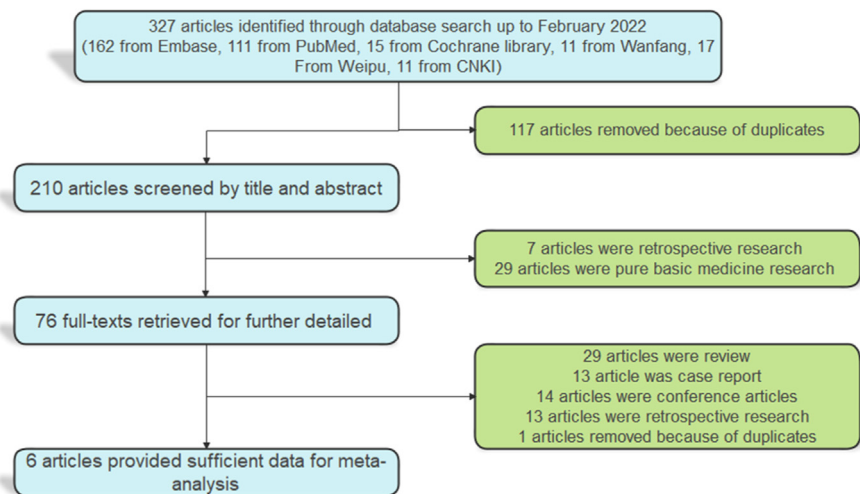


Figure 1. Flowchart of the article retrieval and selection.

months (95% CI 8.13–14.39), respectively. The rate of SAEs was 41% (95% CI 12–41). Among them, the SAEs with >5% incidence were: gastrointestinal toxicity 6% (95% CI 1–12), lymphopenia 6% (95% CI 1–13), and neutropenia 5% (95% CI 2–9). The rate of fatigue, hepatotoxicity, hypertension, mucositis, anemia, and thrombocytopenia were 3% (95% CI 1–6), 2% (95% CI 0–5), 1% (95% CI 0–5), 1% (95% CI 0–4), 0% (95% CI 0–2), and 0% (95% CI 0–1), respectively (Table 3 and Figure 2).

3.4. Subgroup analysis, sensitivity analysis and examination of publication bias

One subgroup analysis was conducted. The participants were classified according to the following criteria for subgroup analysis: multidrug MCT, MCT combined with bevacizumab/pazopanib, and MCT monotherapy/MCT combined with other drugs. We found significant differences regarding ORR and DCR in the subgroup of MCT combined with bevacizumab/pazopanib ($p = 0.01$ and $p = 0.00$, respectively), while among other subgroups, parameters were similar (Figure 3). The results of DCR and ORR in the group of MCT combined with bevacizumab/pazopanib were 42% (95% CI 26–58) and 82% (95% CI 63–95), respectively. The PFS and OS in this subgroup were 7.32 months (95% CI 5.93–8.70) and 17.35 months (95% CI 12.89–21.82), respectively. The SAEs were 31% (95% CI 22–42) in this subgroup. The sensitivity analysis indicated that none of the trials were the root cause of heterogeneity, and all pooled data were stable (Figure 4). In the analysis of publication bias, based on the Egger's publication bias plots, the p -values and their 95% CIs of ORR, DCR, PFS, OS, and rate of SAEs were: $p = 0.540$ (95% CI 3.73–6.52), $p = 0.702$ (95% CI 6.13–4.79), $p = 0.112$ (95% CI 0.96–7.3), $p = 0.000$ (95% CI 3.18–5.23), and $p = 0.133$ (95% CI 6.08–1.03), respectively. The results were not affected except those of OS (Figure 5).

4. Discussion

Since metronomic chemotherapy was proposed in 2000 [20], researchers have administered it for treating several types of cancer [12, 13, 21]. All the studies showed that MCT was effective and had low levels of toxicity. The therapeutic regimens for ovarian cancer are limited, and cancer relapse occurs easily after the treatment. Some patients have platinum-resistant or refractory disease, they cannot tolerate the toxicity of other high-dose cytotoxic agents. This results in a poor prognosis. In

such cases, MCT might provide a new therapeutic strategy for salvage therapy in patients with platinum-resistant or refractory ovarian cancer and for palliative care in advanced cancer. Several clinical trials were performed on the effect of MCT for ovarian cancer. However, those were retrospective analyses or phase I/II trials, whose results might have been influenced by small sample sizes and different inclusion or exclusion criteria. Thus, we conducted the meta-analysis for evaluating the effect and toxicity of MCT.

In this meta-analysis, the ORR and DCR by MOC were 25% (95% CI 12–41) and 61% (95% CI 43–77), respectively. Regarding survival outcomes, PFS and OS were 4.9 months (95% CI 2.62–5.97) and 11.26 months (95% CI 8.13–14.39), respectively. Our results were similar to those of a systematic literature analysis of MCT in solid tumors, where the mean RR and DCR were 26.03% (95% CI 21.4–30.7) and 56.3% (95% CI 50.9–61.6), respectively [21]. And the median PFS was 4.6 months (interquartile range (IQR) 2.9–7.0). Our results showed that MOC has a certain effect in the clinical response of recurrent or platinum-refractory ovarian cancer. Specifically, it showed a DCR of 61% (95% CI 43–77). A subgroup analysis based on multidrug MCT, MCT combined with bevacizumab/pazopanib, and MCT monotherapy/MCT combined with other drugs was performed to lower the heterogeneity arising from the pooled analyses. We found that when combined with bevacizumab/pazopanib, the ORR, DCR, PFS, and OS were better, with the evaluated outcomes as 42% (95% CI 26–58), 82% (95% CI 63–95), 7.32 months (95% CI 5.93–8.70), and 17.35 months (95% CI 12.89–21.82), respectively. Barber discovered that MOC combined with bevacizumab had promising effects on platinum-resistant ovarian cancer in a retrospective study [22]. The ORR, DCR, median PFS, and OS in his study were 42.4%, 65.1%, five months, and nine months, respectively. The patients who showed a clinical response had a long OS of 20 months (2–56). These results were quite close to the results of our study, which suggested that MOC in conjunction with anti-angiogenic agents might be effective. Regarding safety, the rate of SAEs was 41% (95% CI 30–52), which was higher than that found in previous studies of MCT. All the patients in our study underwent high-dose chemotherapy, and combination regimens were used in almost all trials when MCT was performed. Thus, we argue that SAEs should be focused on. Further optimization and adjustments need to be made in this direction. The common SAEs were lymphopenia 6% (95% CI 1–13), gastrointestinal toxicity 6% (95% CI 1–12), and neutropenia 5% (95% CI 2–9). Yangyang Liu also found a similar phenomenon on patients with metastatic breast cancer. They did not find significant difference in

Table 1. Basic information and specific characteristics of the eligible clinical trials.

Author	Year	Country	Trial Design	Cancer	MCT Drugs	Age	Total Patients	Prior CT Lines	CR	PR	ORR	SD	DCR	Median Follow Up (Months)	PFS (Months)	OS (Months)	SAEs	Efficacy Evaluation Criteria	AE Evaluation Criteria	MINORS Score
Aparna Sharma	2021	India	II/RCT	Platinum Resistant/ Refractory Epithelial Ovarian Cancer	Arm A: etoposide; CTX	53 (33–74)	37	2 (1–4)	11	10	21	1	22	22.2 (95% CI 20.3–25.4)	3.4 (95% CI 3–6.53)	11.2 (95% CI 5.66– NR)	9	RECIST 1.1	NCI CTCAE 4.03	11
					Arm B: pazopanib; etoposide; CTX;	54 (36–73)	38	2 (1–3)	11	9	20	2	22	5.1 (95% CI 3.13–10.33)	NR	12				
M.R. Hall	2020	UK	II/RCT	Advanced Ovarian, Fallopian Tube Or Primary Peritoneal Cancer	ArmA: nintedanib; CTX;	62.4 (54.7–70.2)	59	4 (2–NA)	1	4	5	24	29	19 (IQR17–23)	2.9 (95% CI 1.03–5.62)	6.8 (95% CI 4.34–10.52)	38	RECIST 1.1	NCI CTCAE 4.1	11
					Arm B: CTX	65.7 (IQR 56.4–69.8)	55	4 (2–NA)	1	5	6	13	19	2.6 (95% CI 1.26–4.83)	6.4 (95% CI 3.88–9.86)	30				
Agustin A. Garcia	2008	USA	II/ non-RCT	Recurrent Ovarian Cancer, Fallopian Tube Or Primary Peritoneal Cancer	bevacizum; CTX	60 (31–83)	70	2 (1–3)	0	17	17	44	61	23.2 (3.7–32.7)	7.2 (95% CI 5.3–8.7)	16.9 (95% CI 11.4–25.2)	NA	RECIST	NCI CTCAE 3.0	7
Rohan Gupta	2019	USA	II/RCT	Recurrent Epithelial Ovarian, Fallopian Tube, and Primary Peritoneal Cancer	Arm A: CTX	60 (27–79)	26	3.5 (1–12)	0	1	1	8	9	NA	1.84 (95% CI 1.17–3.68)	9.69 (95% CI 3.84–13.18)	9	RECIST 1.0	NCI CTCAE 2.0	10
					Arm B: CTX; celecoxib	61 (48–80)	26	4 (1–8)	0	1	1	9	10	2.02 (95% CI 1.68–5.42)	12.55 (95% CI 6.67–17.61)	8				
C. Dinkic	2017	Germany	I/non-RCT	Recurrent, Platinum-Resistant, Previously Treated Ovarian, Peritoneal, or Fallopian Tube Cancer	pazopanib; CTX	68.5	14	3 (2–4)	1	6	7	4	11	NA (Follow-up:24 months)	8.35 (95% CI 4.14–12.47)	24.95 (95% CI 5.29–35.30)	4	RECIST	NCI CTCAE	8
Emese Zsiros	2020	USA	II/ non-RCT	Epithelial Ovarian, Fallopian Tube, or Primary Peritoneal Cancer	pembrolizumab; bevacizumab; CTX	62 (45–89)	40	NA	3	16	19	19	38	25.5 (90% CI 2.5–34.0)	10.0 (90% CI 6.5–17.4)	16.0 (12.5, 26.1)	13	RECIST 1.1	NCI CTCAE 5.0	11

RCT randomized controlled trial, MCT metronomic chemotherapy, CTX cyclophosphamide, CT chemotherapy, CR complete response, PR partial response, SD stable disease, SAEs serious adverse events or grade \geq 3 adverse events, QD once a day, BID two times a day, NR not reach, NA not available, RECIST Response Evaluation Criteria in Solid Tumors, CTCAE Common Terminology Criteria for Adverse Events.

Table 2. MCT Schedule of the eligible clinical trials.

Number	Author	Single Arm	CTX Dose	CTX Administration	Combination Therapy	Combination Of Drugs
1	Aparna Sharma	NO	50mg	PO D1-28; Q4W	YES	Arm A: etoposide PO 50mg D1-14;
2			50mg	PO D1-28; Q4W	YES	Arm B: pazopanib 400mg QD; etoposide PO 50 mg D1-14;
3	M.R. Hall	NO	100mg	PO QD; Q6W	YES	Arm A: nintedanib 200mg PO BID;
4			100mg	PO QD; Q6W	NO	Arm B: NO
5	Agusti-n A. Garcia	YES	50mg	PO QD Q4W	YES	bevacizumab 10 mg/kg IV QW (first 3 weeks) then 10 mg/kg IV Q2W;
6	Rohan Gupta	NO	50mg	PO QD	NO	Arm A: NO
7			50mg	PO QD; Q4W	YES	Arm B: celecoxib 400mg PO BID; Q4W
8	C. Dinkic	YES	50mg	PO QD	YES	pazopanib 400mg, 600 mg, 800mg PO QD; CTX 50mg QD;
9	Emese Zsiros	YES	50mg	PO QD	YES	(pembrolizumab iv 200mg; bevacizumab iv 15 mg/kg) Q3W

MCT metronomic chemotherapy, CTX cyclophosphamide.

Table 3. Incidence of special SAEs caused by metronomic chemotherapy.

	No. of clinical trials	Incidence % (95% CI)	I ² %	p value
Neutropenia	9	5 (2–9)	57.74	0.02
Thrombocytopenia	9	0 (0–1)	0.00	0.96
Anaemia	9	0 (0–2)	25.78	0.21
Lymphopenia	9	6 (1–13)	80.48	0.00
Gastrointestinal toxicity	9	6 (1–12)	78.20	0.00
Hepatotoxicity	9	2 (0–5)	53.81	0.03
Hypertension	9	1 (0–5)	64.85	0.00
Fatigue	9	3 (1–6)	48.00	0.05
Mucositis	9	1 (0–4)	49.58	0.04

the clinical benefit rate (CBR), six-month PFS, twelve-month PFS, the six-month OS, twelve-month OS, and twenty-four-month OS between MCT group and MCT combined with anti-angiogenic agents' group, but the rate of SAEs was higher in combination therapy. In preclinical studies, there were many reports about the combination of MCT with anti-angiogenic agents [23, 24]. Mechanistically, MCT decreases the level and activity of bone-marrow-derived endothelial progenitor cells, lowers the potential of angiogenesis, and activates thrombospondin-1 to inhibit circulating endothelial cells, thereby affecting angiogenesis. MCT can also keep cancer in a dormant state to maintain a vascular-free state. The combination of MCT and anti-angiogenic agents can enhance the inhibition of blood vessels in cancer and, therefore, effectively arrest cancer progression. But are the combination regimens suitable for all MCT schemes? To elucidate this, a mathematical model of MCT was constructed by Hahnfeldt, who found that maintaining the maximum threshold concentration of anti-angiogenesis might be the optimal MCT scheme. However, no method has been developed to determine its optimal dose in practice [25, 26, 27, 28]. Neither biological principles nor mathematical models showed that clinical responses were positively correlated with an increase in drug dosage after reaching the upper limit

of anti-angiogenesis. Thus, the dose of MCT drugs and the specific clinical application scenarios should be noted while administering combination therapy.

MCT is a therapeutic strategy which is still being explored. No ongoing clinical trial is registered at clinicaltrials.gov; two clinical trials (NCT01175772 and NCT02387125) were terminated, and two (NCT00603460 and NCT03197584) were withdrawn. Most published MCT trials for ovarian cancer were phase I/II trials or retrospective studies, where the patients were administered at least second-line chemotherapy. Due to a high variation in the combination of drugs used, analyzing the survival benefits of MOC very accurately is challenging. With the integration of poly-ADP-ribose polymerase (PARP) inhibitors and ICIs, ovarian cancer therapy has developed rapidly in recent years [29]. Based on the mechanism of anti-angiogenesis and immunomodulation of MCT, its clinical benefits in combination with anti-angiogenic agents, ICIs, or both should be further investigated. Due to the lack of consensus regarding the potential benefits of MCT in ovarian cancer, drug selection, and optimal dose, further research is needed to resolve this issue. Additionally, the timing of MCT has been investigated not only in palliative care for advanced cancer but also in neoadjuvant chemotherapy and adjuvant chemotherapy. A study by Connie Rabanal for triple-negative breast cancer (TNBC) showed that a pathological complete response (pCR) rate of 47%–60% could be achieved by administering MCT with or without the combination of other drugs in neoadjuvant chemotherapy; however, severe toxicity was found. MCT could extend the disease-free survival (DFS) of TNBC patients who underwent adjuvant therapy and could be used in maintenance therapy of patients who were at high risk, especially those who did not achieve pCR [30]. Thus, whether other possible application opportunities for ovarian cancer could be investigated is worth discussing.

The number of cases that could be analyzed in this study was limited, and there was also publication bias in OS results. Few cohorts and low-quality scores of some studies might be regarded as the reasons for the analysis. By considering different regimens as an indicator, publication bias in OS was excluded by subgroup analysis. Only two trials were for platinum-resistant or refractory patients, and thus, more clinical trials should be performed to measure the effect of MCT for those key patients.

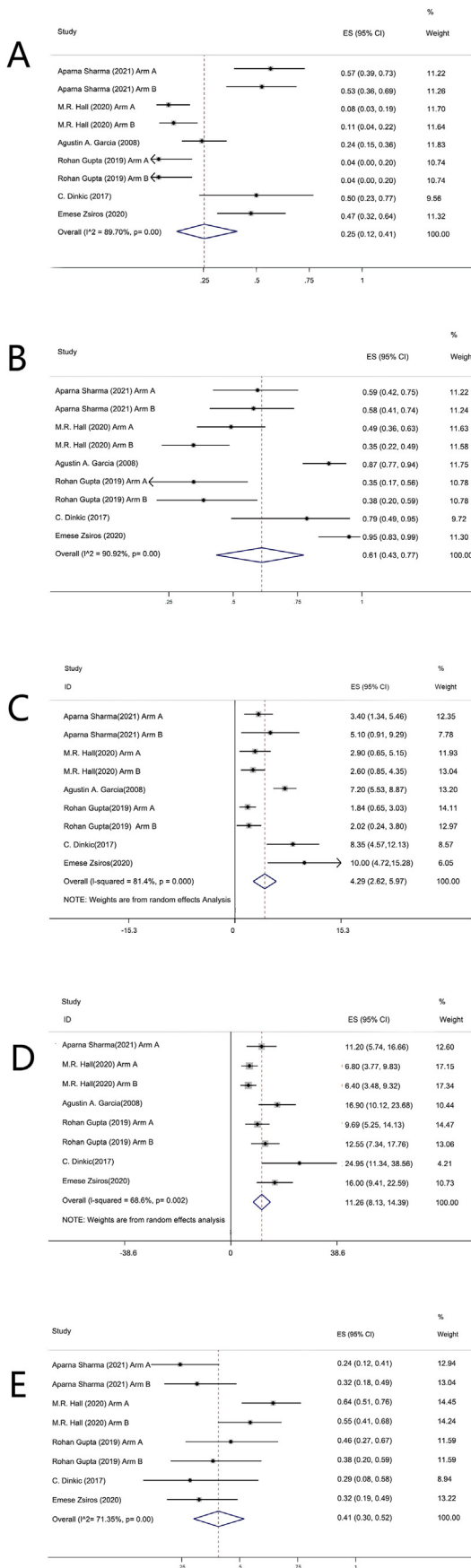


Figure 2. ORR, DCR, PFS, OS and SAEs incidence of metronomic chemotherapy for Ovarian cancer. a. ORR. b. DCR. c. PFS. d. OS. e. SAEs.

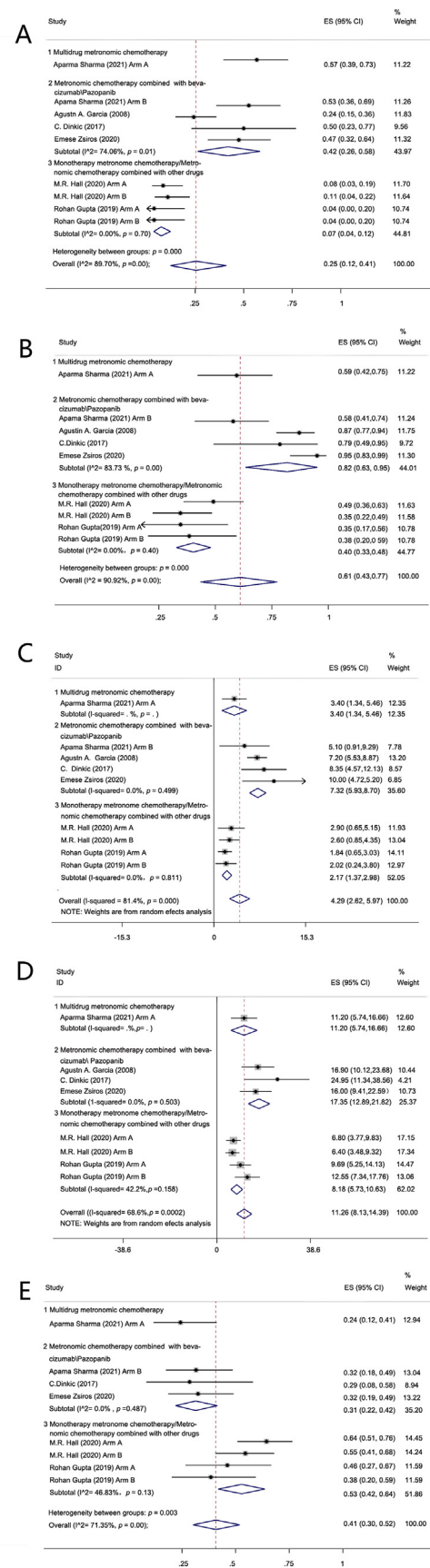


Figure 3. Subgroup analysis of metronomic chemotherapy for Ovarian cancer. a. ORR. b. DCR. c. PFS. d. OS. e. SAEs.

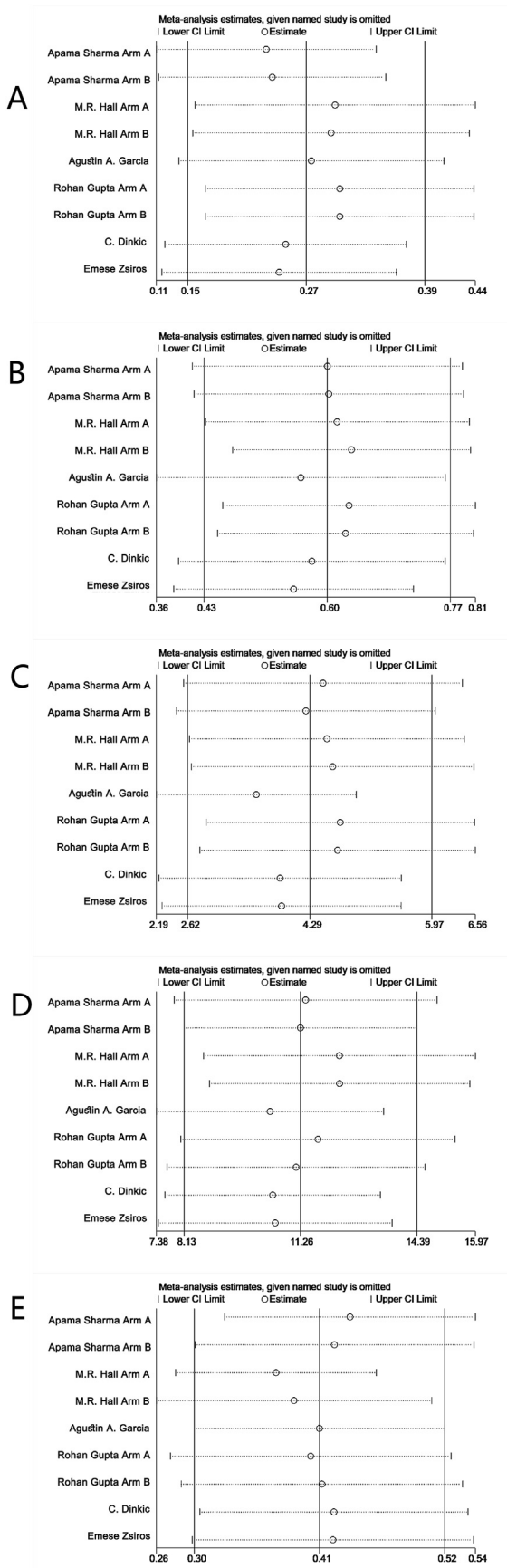


Figure 4. Sensitivity analysis tested the effects on overall results by omitting overall results by omitting each study. a. ORR. b. DCR. c. PFS. d. OS. e. SAEs.

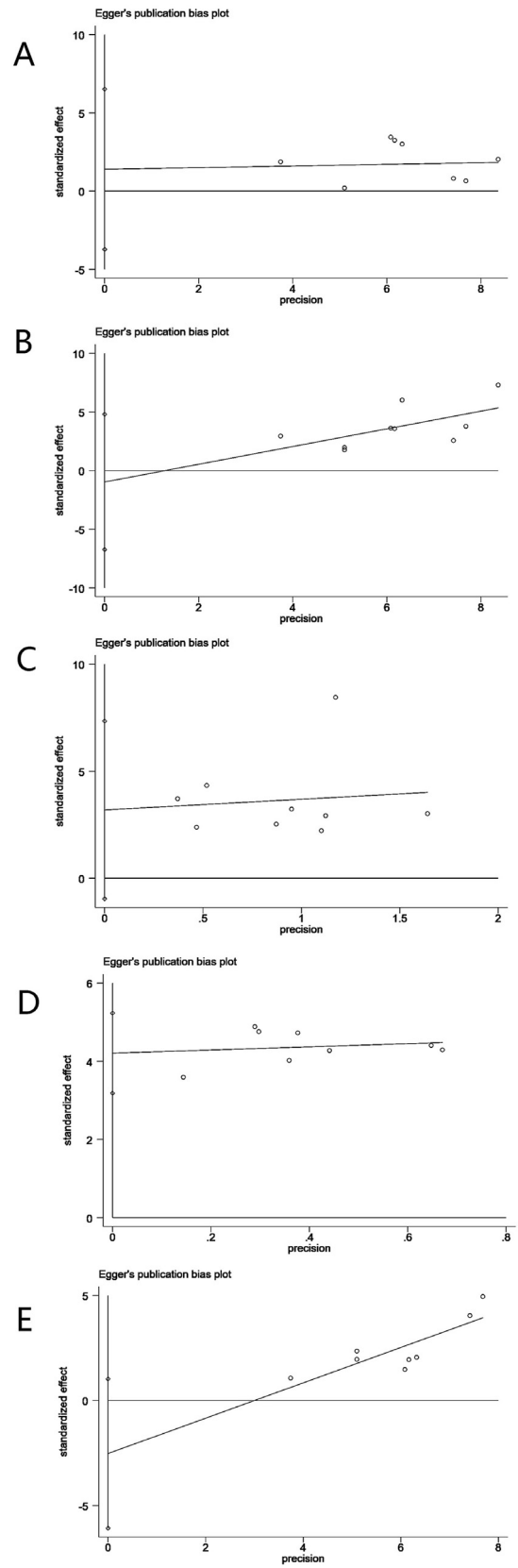


Figure 5. Egger's publication plots of ORR, DCR, PFS, OS and SADR rate of metronomic oral cyclophosphamide for ovarian tumour. a. ORR. b. DCR. c. PFS. d. OS. e. SAEs.

5. Conclusion

Nowadays, MCT have been shown to have potential anti-tumor effect in many cancers. Furthermore, some meta-analyses about the efficacy and toxicity of MCT in other solid tumors have been published. As a convenient and economical treatment option, MCT has a potential and extensive application prospect. This meta-analysis showed that MOC has a certain effect in the clinical response of recurrent or platinum-refractory ovarian cancers, especially when it is combined with bevacizumab/pazopanib. But be careful, the incidence of SAEs was relatively high in our study, which might be the controversy in further studies when MCT is combined with other treatment. In the future, more clinical trials for exploring the dose and the types of MCT drugs for ovarian cancer are warranted to provide more accurate and reliable evidence for precise clinical decision.

Declarations

Author contribution statement

Lili Huang; Ting Jiang: Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

Pengcheng Li; Fang Yang: Performed the experiments.

Jie Zhang; Xing Luo: Analyzed and interpreted the data.

Tao Ren: Contributed reagents, materials, analysis tools or data.

Ke Xu: Conceived and designed the experiments; Contributed reagents, materials, analysis tools or data; Wrote the paper.

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Data availability statement

Data will be made available on request.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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