Systematic Review and Meta-Analysis

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Effect of molecular targeted agents in chemotherapy for treating platinum-resistant recurrent ovarian cancer

A systematic review and meta-analysis

Luting Liu, PhD*, Wanchun Xiong, MM

Abstract

This study aimed to investigate the effect of molecular targeted agents (MTAs) in chemo on platinum-resistant recurrent ovarian cancer (ROC). We performed this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statements. Randomized controlled trials reporting data about platinum-resistant ovarian cancer treated by MTAs were included. The endpoints for the present study included overall survival and progression-free survival. We analyzed 9 randomized controlled trials including 3631 patients with ROC. The pooled analysis indicated that a combination of MTAs with chemo could markedly increase objective response rate in those patients ($P = .012$). Nevertheless, the survival rate of those patients was not markedly changed ($P = .19$). Besides, the combination of MTAs with chemo dramatically aggravated the occurrence of adverse events ($P < .05$). Moreover, it resulted in the termination of treatment ($P = .044$) in those patients, but it had no effect on fatal adverse events ($P = .16$). Our results indicated that the combination of MTAs with chemo notably improved objective response rate in patients with platinum-resistant ROC, but its benefit did not translate into survival benefits.

Abbreviations: AEs = adverse events, CI = confidence interval, HRs = hazard ratio, MTAs = molecular targeted agents, OC = ovarian carcinoma, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCTs = randomized controlled trials, ROC = recurrent ovarian cancer.

Keywords: chemotherapy, molecular targeted agents, platinum-resistant, recurrent ovarian cancer

1. Introduction

Ovarian carcinoma (OC) is a common lethal gynecological cancer, and it has been reported that more than 280,000 new cases and 180,000 deaths are being identified annually.[1] Symptoms of ovarian are usually developed into late-stage due to its biology. As a result, over 70% have already had advanced-stage disease among patients with OC when they were diagnosed.[2,3] The current treatment methods include surgical resection and chemotherapy, which contain carboplatin and paclitaxel.[4,5] Although most patients have fewer symptoms after treatment, most of them eventually suffer from relapse and drug resistance.[6,7] For patients with platinum-resistant recurrent ovarian cancer (ROC), the treatment effects of the current schemes are similar. Unfortunately, there is no standard or effective chemotherapy for platinum-resistant ROC.[8–11] Therefore, novel effect treatment options are needed for ROC patients.

In the past few decades, the emerging understandings of the underlying molecular mechanisms of carcinogenesis led to the identification of novel drugs for the treatment of OC. These drugs treat OC by acting on key factors or signaling pathways related to tumor cell proliferation and invasion. Several molecularly targeted agents (MTAs) have been developed. There are memorable therapeutic effects of them on patients with OC,[12–16] which results in the application of bevacizumab and poly(ADP)-ribose polymerase inhibitors for treating advanced OC.[17–19] However, there are still doubts about the efficacy of the new MTAs in treating platinum-resistant ROC remains contentious. Therefore, in the present study, randomized controlled studies relating to ROC were included to assess the effect of combined use of MTAs with chemotherapy for platinum-resistant ROC patients by meta-analysis.

2. Materials and methods

2.1. Study design

We performed this meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statements.[20] Ethical approval was avoided in this study.

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The datasets generated during and/or analyzed during the present study are available from the corresponding author on reasonable request.

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2.2. Definition of the study results

We included the studies in which MTAs were used as an experimental group while the others were the control group. The endpoints of treatment in this study included: (1) overall survival (OS), which was the period between enrolled group and death, examining subjects who were survival; (2) progression-free survival (PFS), which was the period between enrolled group and development recorded for the first time; and (3) objective response rate (ORR), including partial or whole response rate and stabilization rate.

2.3. Search strategy

Electronic databases were searched, including PubMed, Embase, and Cochrane Library to select related studies published before April, 2019, in which MTAs were the second treatment for ROC. The key terms to search studies included: ("ovarian carcinoma" or "ovarian cancer," or "gynecological cancer," or "gynecological carcinoma" or "ovarian epithelial cancer") and ("recurrent" or "refractory") and ("molecularly targeted agents," or "sunitinib," or "vandetanib," "pazopanib," or "trebananib," or "trabectedin," or "axitinib," or "aflibercept," or "seribantumab"). The studies we searched only included randomized controlled trials (RCTs) in humans. There was no language restriction.

2.4. Inclusion criteria

Inclusion criteria were: (1) pathological confirm of platinum-resistant ROC patients; (2) ROC patients received systematic or combination chemotherapy with MTAs randomly; and (3) results including treatment effect, survival, or toxicity, were reported in included trials.

2.5. Data extraction

Two investigators (XWC and YCR) searched and extracted the data from the trials independently. There was no difference between title, summary, and the trial to be studied. If the 2 reviewers had different suggestions, the third reviewer (LLT) will make a final decision. We summed up those data from each trial enrolled in this study, including the authors, publishing time, follow-up period, sample size, median age, chemotherapy regimens, and survival outcomes.

2.6. Statistical analysis

The critical outcome included OS, and the subordinate endpoint included PFS, ORR, and toxicities. The fixed-effects model or random-effects model was carried out to analyze the patients treated with combination MTAs with chemotherapy with hazard ratios (HRs) and 95% confidence interval (CI) when minimal or significant heterogeneity existed in the variables, respectively. There were statistical significances in heterogeneity when $P < .1$ (X^2 test) and $>50\%$ (I^2 test). Comprehensive Meta-Analysis program (Biostat, Englewood, NJ) was used to perform Forest plots to sum up the included studies. The publication bias was assessed using Egger regression asymmetry, the Begg rank correlation, and the funnel plots.

3. Results and discussion

3.1. Search outcomes

There were 606 clinical trials including PubMed 408, ASCO 128, ESMO 70, relevant to MTAs as methods to treating advanced ROC. There were 9 prospective RCTs in this study (Fig. 1), with 2388 patients with platinum-resistant ROC.[21–29] Sample size included in every included study was 91 (range: 22–703 patients). Jadad scale was carried out to evaluate the quality of each trial, and the results showed 4 trials with 5 scores and 5 trials with 3 scores.

3.2. Efficacy of MTAs in platinum-resistant ROC

Nine included trials reported the PFS data. The pooled analysis showed that MTAs could ameliorate PFS in patients with platinum-resistant ROC with HR 0.83 ($P = .067$, Fig. 2). Significant heterogeneity existed among those 9 studies ($I^2 = 92.0\%$, $P < .001$). Compared with chemotherapy alone, the combined analysis showed that MTAs in chemotherapy used to treat ROC significantly ameliorated OS with HR 0.94 ($P = .19$, Figure S1, Supplemental Digital Content, http://links.lww.com/MD/G352). Heterogeneity test showed that I^2 was 0% and P was .87, so that we carried out a fixed-effects model. In addition, we found that MTAs in chemotherapy used to treat platinum-resistant ROC remarkably decreased ORR in comparison with treatment without MTAs ($P = .012$, Fig. 3). Heterogeneity testing showed I^2 was 0%, and P was .72.

3.3. Toxicities

Due to multiple adverse events (AEs) of included targeted agents, we only analyzed the risk difference of any AEs which resulted in permanent discontinuation or fatal AEs between chemotherapy with MTAs and without MTAs. No significant heterogeneity of included trials was found so the fixed-effects model was used to analyze pooled results. Our results showed that combined use of MTAs with chemo notably raised the risk of any AEs resulting in discontinuation ($P = .044$, Fig. 4), but not influencing fatal AEs ($P = .16$, Figure S2, Supplemental Digital Content, http://links.lww.com/MD/G353).

3.4. Publication bias

The results of the funnel plot indicated the absence of remarkable asymmetry for PFS and OS analyzed by Begg or Egger test ($P = .63$ or $P = .70$) (Figure S3, Supplemental Digital Content, http://links.lww.com/MD/G354 and Figure 4, Supplemental Digital Content, http://links.lww.com/MD/G355).

3.5. Discussion

OC is the leading cause of cancer-related mortality in gynecological malignancies worldwide.[30] At present, the first-line chemo for OC is on the basis of the combined use of platinum-derived cytotoxic agents and paclitaxel. Despite high response rate and median PFS, over 70% of these patients would finally suffer disease progression.[31] The emergency of resistance to platinum-resistant chemo mainly accounts for the deaths with recurrent OC. Currently, object response rates to frequently use of cytotoxic agents in platinum-refractory patients, such as pegylated liposomal doxorubicin,[32] gemcitabine,[33] topotecan,[34] and etoposide[35,36] are modest with a median overall survival of 9 to 12 months.[7,37] As combination cytotoxic agents for ROC did not show consistent benefits, no standard doublet combination therapy, except for bevacizumab, is recommended for ovarian cancer in this setting. Clearly, novel drugs or

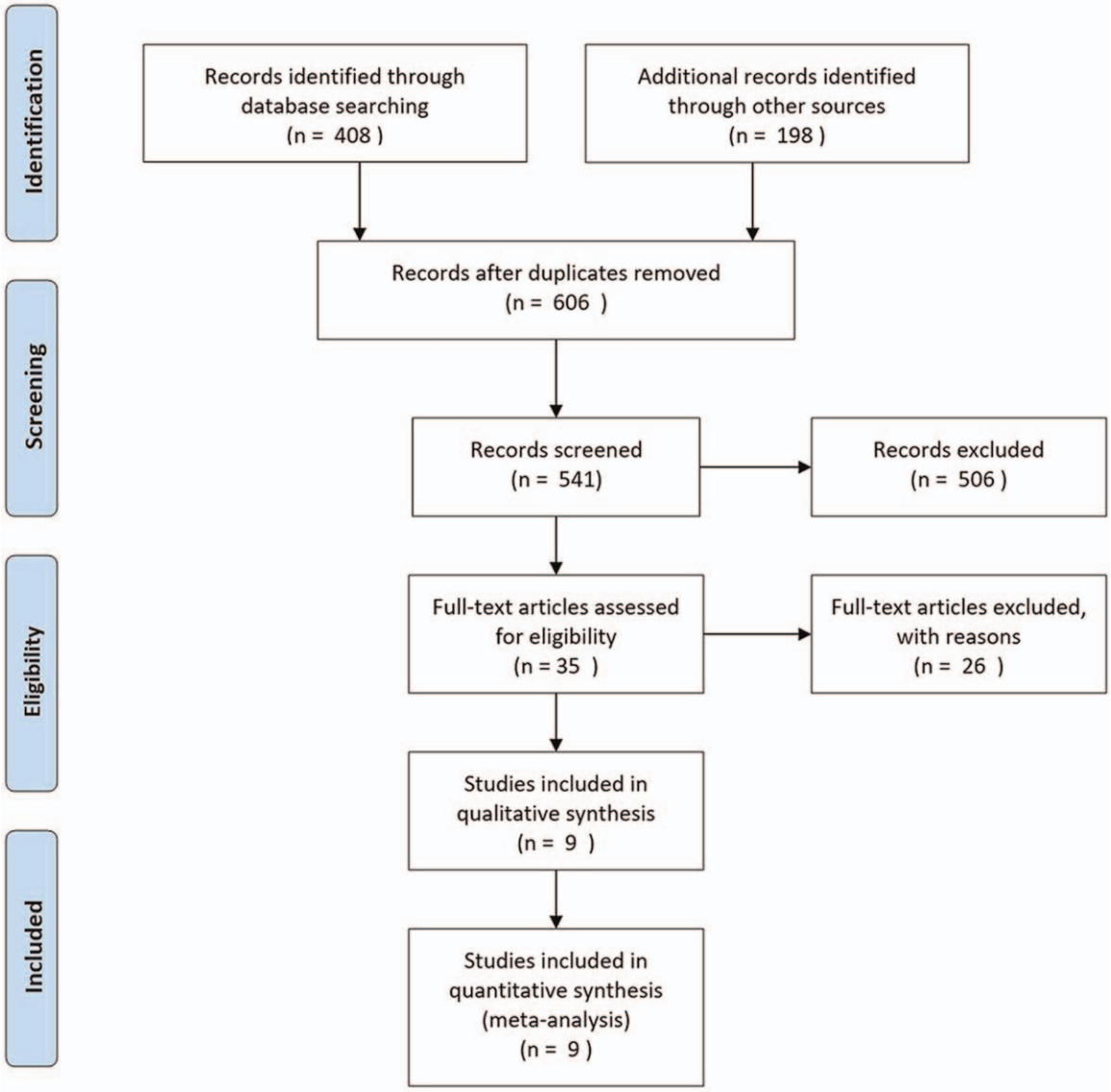

Figure 1. PRISMA flow diagram. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

therapies will be used to increase platinum-resistant ROC patients' survival. So far, a number of prospective trials have been conducted to extensively investigate the efficacy of several novel targeted agents, including aromatase inhibitors[38,39] and poly(ADP)-ribose polymerase inhibitors[40] for treating ROC in this setting. However, as far as we know, it is not clear whether MTAs in chemotherapy were effective in treating platinum-resistant ROC.

This study is the most comprehensive analysis, in which we clearly explore the effect of MTAs in chemotherapy for treating advanced platinum-resistant ROC. There were 3631 participates in 9 prospective clinical trials included in this study. Our combined results showed that MTAs in chemotherapy markedly increased ORR in patients with platinum-resistant ROC, but it had no effect on survival benefits, including PFS and OS. We also assess the toxicities associated related to the combination of MTAs with chemo, and the results indicated that MTAs with chemo markedly raised the risk of AEs, but it did not influence fatal AEs in platinum-resistant ROC. According to those results, we detect a significant ORR benefit and a tendency to improve PFS in patients with platinum-resistant ROC who were treated with MTAs, but the risk of developing severe toxicities was increased.

There are several strengths in this analysis. First, it is the first and most comprehensive study to determine the effect of MTAs with chemotherapy on the treatment of ROC. The quality of included trials was high according to the Jadad score. Additionally, all included trials are prospective RCTs. Finally, there are relatively limited heterogeneity and inconsistency of included trials and we also perform subgroup analysis to assess the potential heterogeneity.

However, several limitations of the present study are needed to be concerned. First, fatal AEs are not the primary endpoint and are extracted from clinical trials. The process of attribution of causality by investigators would be biased. Second, we analyzed

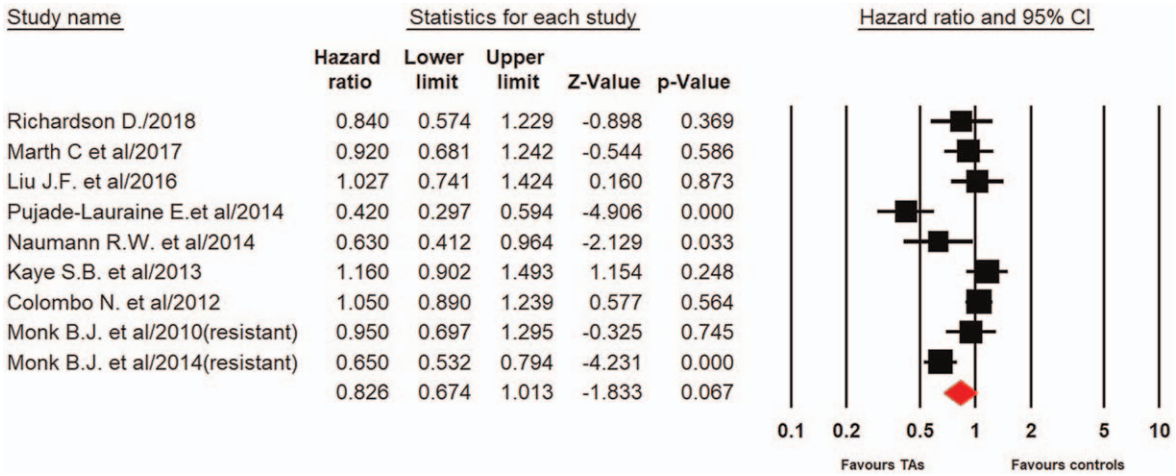

Figure 2. Random-effect model of hazard ratio (95%CI) of PFS associated with chemotherapy with or without TAs in ROC patients. CI = confidence interval, PFS = progression-free survival, ROC = recurrent ovarian cancer, TAs = targeted agents.

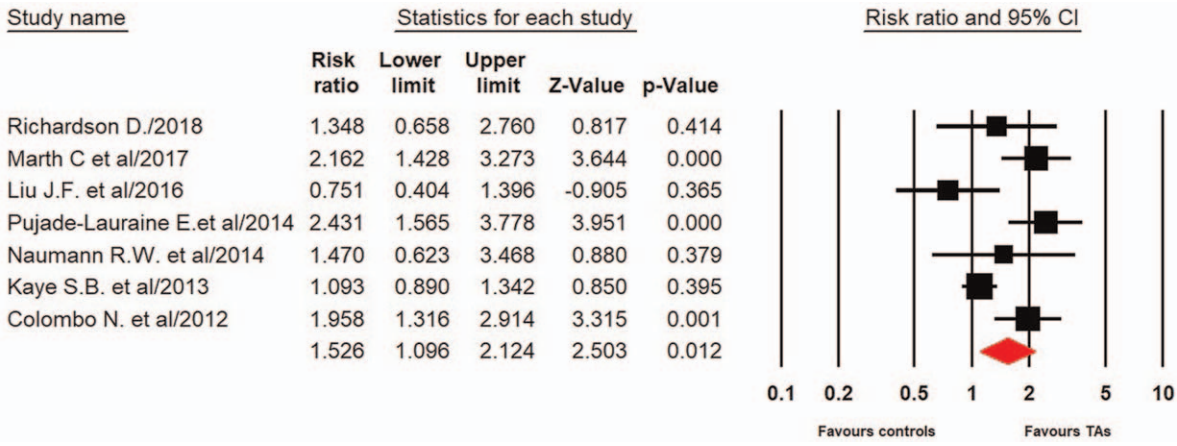

Figure 3. Fixed-effects model of relative ratio (95%CI) of ORR associated with chemotherapy with or without TAs in ROC patients. CI = confidence interval, ORR = objective response rate, ROC = recurrent ovarian cancer, TAs = targeted agents.

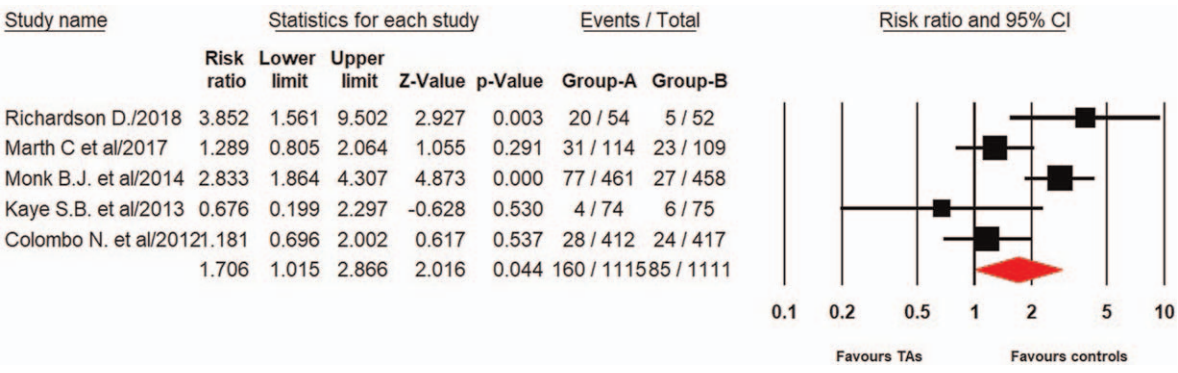

Figure 4. Fixed-effects model of relative ratio (95%CI) of AEs leads to treatment discontinuation associated with chemotherapy with or without TAs in ROC patients. AEs = adverse events, CI = confidence interval, ROC = recurrent ovarian cancer, TAs = targeted agents.

various factors and signaling pathways related to MTAs, and it may increase the heterogeneity among included trials. Finally, only published studies were included in our study.

4. Conclusion

In conclusion, we explored the effect of the combination of MTAs with chemotherapy on the treatment of advanced platinum-resistant ROC patients. Our pooled results suggested that MTAs in chemotherapy significantly improved ORR in platinum-resistant ROC, but its benefit did not translate into survival benefits (PFS and OS). Further high-quality randomized trials are still needed to investigate the treatment for ROC.

Author contributions

Writing – original draft: Luting Liu, Wanchun Xiong.
Writing – review & editing: Luting Liu, Wanchun Xiong.

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