

## Original Research Article

# Effect of the combination of trastuzumab, paclitaxel and carboplatin in the treatment of uterine serous carcinoma: A systematic review and meta-analysis

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### Abstract

**Purpose:** To systematically review the efficacy of paclitaxel-carboplatin versus trastuzumab in combination with paclitaxel/carboplatin for the treatment of uterine serous carcinoma (USC) with high Her2/neu expression, in order to obtain an evidence-based reference for clinical treatment.

**Methods:** Publications were obtained from China Knowledge Network (CNKI), VIP database (VIP), Wanfang database, PubMed, Embase, Cochrane Library, and Web of Science. The retrieval period was from the establishment of database to May 2022, and the efficacy of paclitaxel-carboplatin combination with trastuzumab (study group) versus paclitaxel-carboplatin (control group) for the treatment of Her2/neu high-expressing USC was collected. Two reviewers independently screened, extracted data, and evaluated the quality of evidence of included studies. RevMan 5.3 statistical software was used for meta-analysis. Outcomes included overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and adverse events.

**Results:** Meta-analysis showed that the study group had significantly longer OS than control group ( $p = 0.004$ ), and PFS of study group was significantly longer than that of control group ( $p < 0.0001$ ). In terms of ORR, there was no difference between the two groups ( $p = 0.42$ ). However, in terms of total and high-risk adverse events, the number of patients with adverse events in study group was higher than in control group ( $p = 0.05$ ), ( $p = 0.0001$ ).

**Conclusion:** Paclitaxel-carboplatin combination with trastuzumab significantly prolongs OS and PFS in USC patients with high Her2/neu expression, but it may increase the incidence of adverse events.

**Keywords:** Endometrial cancer, Uterine serous carcinoma, Paclitaxel-carboplatin, Trastuzumab, Meta-analysis

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## INTRODUCTION

Endometrial cancer (EC) is the most common malignancy among females. Paclitaxel-carboplatin (PC) is the current gold-standard chemotherapy for patients with advanced and

recurrent endometrial cancer [1]. Uterine serous carcinoma (USC), a rare pathological type of EC with a high mortality rate and poor prognosis, is characterized by strong invasiveness, high postoperative recurrence rate, and multifocal recurrence, and is mostly located outside the

pelvic cavity [2-4]. Trastuzumab (T), a monoclonal antibody against the human epidermal growth factor receptor (HER2/neu), showed clinical benefits for breast cancer and gastric cancer in several randomized controlled trials (RCTs) [5]. Recently, PC plus T, which was further assessed in a randomized phase II trial showed improved effectiveness in USC patients with high HER2/neu compared to T [6,7]. However, despite the demonstrated benefits of PC + T, there is still a lack of evidence-based support for the treatment of USC.

To address this, a systematic review and meta-analysis were performed to comprehensively evaluate the efficacy and safety of PC or PC + T in the treatment of USC.

## METHODS

### Search strategy and selection criteria

A comprehensive search was conducted on PubMed, EMBase, Medline, Cochrane Library, CNKI Chinese Academic Journals Network, VIP Chinese Scientific Journals Database, and Wanfang Database until up to May 2022, using search terms such as endometrial cancer, uterine serous carcinoma, paclitaxel-carboplatin, paclitaxel-carboplatin-trastuzumab and/or trastuzumab.

### Inclusion criteria

Retrospective studies on randomized clinical trials (RCTs), comparative studies of PC and PC + T, and single-arm reports of PC + T were included for qualitative analysis. Reports on recurrent or advanced USC patients with high her2/neu expression without age, race, region, and other restrictions were also included.

### Exclusion criteria

Studies without results of PC + T and the required outcome indicators, systematic reviews, meta-analyses, or reviews, animal experiments or laboratory research and reports not in Chinese or English were excluded.

### Parameters measured

The primary outcomes were overall survival (OS), progression-free survival (PFS), objective response rate (ORR), overall adverse events (OAEs), and high-risk adverse events (HAEs). The classification of adverse events (AEs) was as defined by the Medical Dictionary for Regulatory Activities (MedDRA) [8], with Grades 1-2 representing low-risk adverse events and

Grades 3-5 representing high-risk adverse events.

### Data extraction and quality assessment

Two investigators independently assessed all studies and identified those that met the inclusion criteria by reading the title, abstract, or full text. Discrepancies in title, abstract, and full-text selection were resolved by discussion between two reviewers or consensus with a third reviewer. If data were missing or unclear, the corresponding authors were contacted to obtain data.

Studies for which no data or information is available after contacting the corresponding authors were excluded. The quality of each study was assessed by the Jadad scale [9], which included criteria such as random number generation, allocation concealment, blind method, and follow-up (dropped out or loss follow-up).

### Statistical analysis

The RevMan 5.3 software was used for literature quality rating, mapping, and data analysis. For time events, the hazard ratio (HR) and the associated 95 % confidence interval (CI) were used to describe OS and PFS. For dichotomous outcomes, ORR, OAEs, and HAEs were performed using relative risk (RR) and its associated 95 % CI. Heterogeneity test was quantified using I<sup>2</sup> and Q statistics, and if  $p > 0.10$ ,  $I^2 \leq 50\%$ , evidence was analyzed using fixed-effect models. Otherwise, the random-effect models were used. In addition, if the available data could not be analyzed using meta-analysis, descriptive analysis was performed.

## RESULTS

### Literature research

A total of 1858 relevant studies were initially identified, and 4 eligible full-text studies were selected for detail analysis, including 3 RCTs [6,7,10] and 1 case report [11], as shown in Figure 1.

### Characteristics and quality evaluation of eligible studies

Overall, a total of 118 patients were involved, 62 in PC + T group (experimental group) and 56 patients in PC group (control group). The characteristics of the prospective studies included in this study are presented in Table 1.

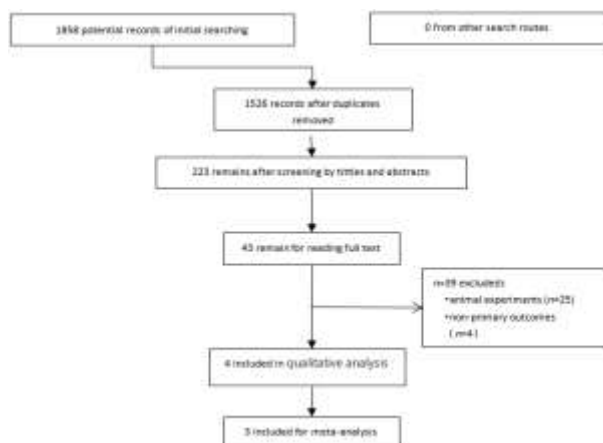


Figure 1: Flow diagram of the study selection

**Efficacy parameters**

**Overall survival (OS)**

Two studies evaluated OS in USC patients treated with PC or PC + T, with a total of 116 subjects. There was no heterogeneity between the two studies ( $p = 0.33$ ,  $I^2 = 0\%$ ), and the fixed-effect model with combined effect size was used for further analysis. As shown in Figure 2, treatment with PC + T significantly resulted in the lengthening of the OS when compared with PC {HR=0.51, 95 % CI (0.32, 0.81),  $p = 0.004$ }.

**Progression-free survival (PFS)**

Data from two studies involving 116 USC patients were analyzed to identify the impact of

PC + T treatment on PFS when compared to PC [6,7]. PC + T treatment was superior in prolonging PFS when compared to PC {HR = 0.45, 95 % CI (0.31, 0.65),  $p < 0.0001$ }, a similar result was found in fixed-effect model meta-analysis ( $p = 0.91$ ,  $I^2 = 0\%$ ).

**Objective response rate (ORR)**

As shown in Table 1, only one study assessed this outcome [6]; thus, descriptive analyses were used.

**Adverse events (AEs)**

One hundred and eighteen patients in two studies reported a total of 1,055 AEs, including 180 high-risk adverse events. For OAEs, there was significant statistical heterogeneity among the studies ( $p = 0.02$ ,  $I^2 = 80\%$ ), and the random effect model was used to analyze the combined effect size. The results showed that the incidence of OAEs in the experimental group was higher than in the control group {RR = 1.49 95 % CI (1.00, 2.29),  $p = 0.05$ }, and the difference between the two groups was statistically significant (Figure 4). For HAEs, there was no statistical heterogeneity among the studies ( $p = 0.54$ ,  $I^2 = 0$ ). High-risk adverse events in experimental group were also higher than in control group {RR = 1.73 95 % CI (1.32, 2.26),  $p < 0.0001$ }, and the difference between the two groups was statistically significant (Figure 5).

Table 1: Characteristics and quality evaluation of eligible studies (Jadad scale = 6)

Reference	Phase	Treatment	Sample (N)	Age (years)	Outcome
[6]	II	PC + T	28	73(45-88)	OS, PFS, ORR, AEs
		PC	30	67(57-85)	
[7]	III-IV	PC + T	28	73(45-88)	OS, PFS
		PC	30	67(57-85)	
[10]	III-IV	PC + T	28	73(68-78)	AEs
		PC	32	66(64-69)	

**Abbreviations:** PC: Paclitaxel-carboplatin; PC + T: Paclitaxel-carboplatin plus trastuzumab; OS: Overall survival; PFS: Progression-free survival; ORR: Objective response rate; AEs: Adverse events

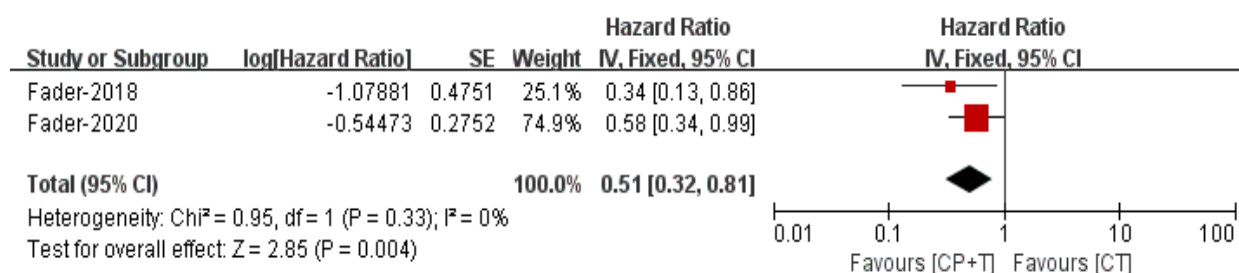


Figure 2: Overall survival in USC patients treated with PC or PC + T. Results are from a fixed-effect model meta-analysis

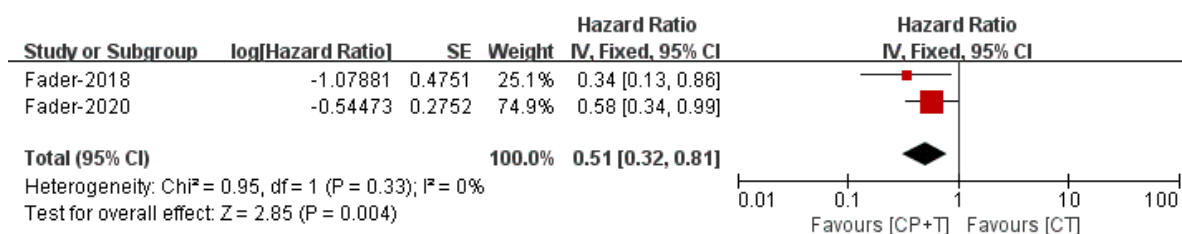


Figure 3: Progression-free survival (PFS) in USC patients treated with PC or PC + T

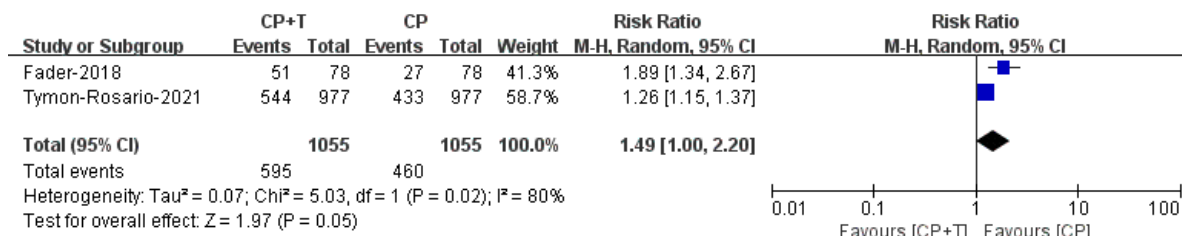


Figure 4: Overall adverse events (OAEs) in USC patients treated with PC or PC + T

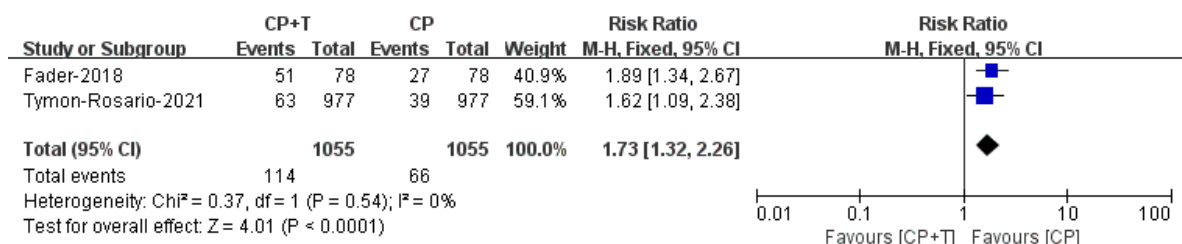


Figure 5: High-risk adverse events (HAEs) in USC patients treated with PC or PC + T

Table 2: Qualitative analysis of Adverse events (AEs)

Reference	LAEs	HAEs
[6]	None	78 cases in total, including blood or lymphatic disorders (6 cases), neutropenia (9 cases), severe anemia (6 cases)
[10]	875 treatment-related AEs, 146 AEs for common gastrointestinal reactions, 65 AEs for blood and lymphatic system disorders, 80 AEs for drug-related skin and subcutaneous tissue diseases, 70 AEs for metabolic and nutritional disorders, 75 AEs for musculoskeletal and connective tissue diseases and 67 times of nervous system disorders	102 treatment-related AEs, common: blood and lymphatic system disorders 24 times, vascular related diseases 11 times
[11] (a case report)	A 74-year-old woman presented with lower limb weakness, abdominal discomfort, and anemia during the treatment	None

Abbreviations: LAEs: Low-risk Adverse Events; HAEs: High-risk Adverse Events

**Qualitative analysis of adverse events (AEs)**

A total of three studies [6,9,11] were included for AEs qualitative analysis. Santin *et al* [11] reported a case study of a USC patient who relapsed after PC treatment, and immunohistochemistry showed Her2/neu overexpression (3+). After 3 months of PC + T treatment, the metastatic lesions completely disappeared, with no recurrence or evident HAEs. Notably, Fader *et al* [6] and Tymon *et al*

[10] also reported AEs after PC or PC + T treatment (Table 2).

**DISCUSSION**

Although USC accounts for only a small part of EC, it is responsible for nearly 40 % of endometrial cancer-related deaths [3]. Currently, the common treatment for USC is surgery, followed by radiotherapy and chemotherapy, as needed [12]. The significance of Her2/neu

overexpression has been fully confirmed in the pathogenesis and targeted therapy of many cancers, including breast, stomach, and gastroesophageal junction. Moreover, Her2/neu in endometrial cancer has been studied for more than 20 years and has been demonstrated to have the highest expression in USC [13]. Trastuzumab, a monoclonal antibody against Her2/neu receptor, produces good clinical efficacy in the treatment of breast cancer and gastric cancer [14]. However, based on the current data, the evidence of clinical efficacy of trastuzumab on recurrent USC patients with Her2/neu overexpression is scarce [15].

In this study, meta-analysis and systematic review was performed to estimate the efficacy of Paclitaxel-carboplatin in combination with trastuzumab for USC patients with Her2/neu overexpression, so as to identify the most preferable chemotherapy treatment in clinical setting. A total of 4 articles were eligible, 3 of which were prospective studies, and one case report was used for meta-analysis. Results showed that PC + T significantly prolonged the overall survival and progression-free survival of Her2/neu hyperexpressive USC patients compared to classical PC chemotherapy. Meanwhile, a case report suggests that patients with late-relapsed Her2/neu overexpression (3+) USC achieved complete clearance of abdominal metastases with trastuzumab. Combined with previous reports on treatment of USC, the above results have certain guiding relevance to clinical practice. Furthermore, these encouraging results are in line with the NCCN guidelines [16], which state that trastuzumab is the preferred treatment in addition to PC chemotherapy for women with advanced or recurrent Her2/neu positive USC.

### Limitations of this study

There are some limitations in this study: Firstly, because there are few reports on PC + T treatment of USC, only a few studies meet the inclusion criteria. Secondly, most studies had diverse research objectives, making it difficult to make a precise quantitative analysis. Furthermore, the findings may not be generalizable, since all of the studies included in this meta-analysis were conducted in the United States. Finally, there are several ongoing clinical trials relating to PC + T treatment of USC, and further prospective studies are required to validate the findings of this study.

### CONCLUSION

The incidence of adverse events in USC patients treated with PC + T is higher than in PC alone.

The most common LAEs and HAEs are gastrointestinal reactions, and blood and lymphatic disorders, respectively. However, more clinical studies are needed to confirm these findings. Furthermore, large-scale, high-quality, long-term follow-up clinical trials are required to confirm the long-term efficacy and safety of PC + T treatment in Her2/neu overexpression (3+) USC patients.

### DECLARATIONS

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None provided.

#### **Ethical approval**

None provided.

#### **Availability of data and materials**

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

#### **Conflict of Interest**

No conflict of interest associated with this work.

#### **Contribution of Authors**

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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