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Efficacy and safety of paclitaxel with or without targeted therapy as second-line therapy in advanced gastric cancer

A meta-analysis

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Abstract

Backgroud: Paclitaxel (PTX) has become a widely used second-line therapy for advanced gastric cancer. There exists controversy whether targeted therapy combined with PTX can provide additional benefit over PTX alone. Therefore, a meta-analysis was carried out to evaluate the efficacy and safety of the two therapy regimes.

Methods: We searched systematically for studies from the databases of PubMed, Embase, Web of Science and the Cochrane Library published between January 2000 and August 2019. Only randomized controlled trials were eligible. Statistical analysis was performed by meta-analysis. The primary end points were progression-free survival and overall survival, objective response rate and adverse events were the secondary end points.

Results: A total of 4 randomized controlled trials with 1574 patients (PTX + targeted therapy, n = 786; PTX, n = 788) were included for the final analysis. As compared with PTX monotherapy, PTX + targeted therapy significantly improved progression-free survival (hazard ratio = 0.88, 95% confidence interval [CI] 0.84–0.92, $P < .001$), overall survival (hazard ratio = 0.90, 95% CI: 0.86–0.95, $P < .001$) and was associated with a better objective response rate (RR = 1.80; 95% CI: 1.45–2.24; $P < .001$). PTX+targeted therapy group significantly increased incidences of grade 3 to 5 neutropenia, fatigue and neuropathy ($P < .05$). No statistically significant differences were observed in the incidences of grade 3 to 5 anemia, decreased appetite, nausea, diarrhea and abdominal pain between the two treatments ($P > .05$).

Conclusions: Second-line PTX+targeted therapy is a more effective treatment option with tolerable safety profile for advanced gastric cancer as a result of improved survival, though with additional toxicity.

Abbreviations: AGC = advanced gastric cancer, CI = confidence interval, HR = hazard ratio, ORR = objective response rate, OS = overall survival, PFS = progression-free survival, PTX = paclitaxel, RCTs = randomized controlled trials, RR = risk ratio.

Keywords: advanced gastric cancer, meta-analysis, paclitaxel, targeted therapy

1. Introduction

As the fifth most common cancer, gastric cancer leads the third cause of malignant tumor deaths worldwide,[1,2] with more than 50% patients that occur in eastern Asia.[3] Although complete surgical resection is the only chance to offer a potentially curative treatment for patients with gastric cancer,[4] few patients are diagnosed at a sufficiently early stage eligible for operation. Moreover, the majority of patients who undergo curative resection eventually experience tumor recurrence or metastasis. Most patients are diagnosed as late malignant disease as a result of the advanced clinical manifestations. Five-year survival rate is only < 20% for patients with advanced gastric cancer (AGC). The prognosis is generally poor, and only palliative chemotherapy can provide a survival benefit.[5]

Currently, according to the human epidermal growth factor receptor 2 status, fluoropyrimidine plus platinum with or without trastuzumab are accepted worldwide as first-line chemotherapy.[6,7] After first-line failure, comparing with best supportive care, second-line chemotherapy also seems to show a significantly higher survival benefit.[8] Paclitaxel (PTX) has become a widely used standard second-line therapy.[9,10] PTX monotherapy often fails to provide adequate efficacy, with reported objective

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The datasets generated during and/or analyzed during the current study are publicly available.

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response rate (ORR) of 16% to 21%, median progression-free survival (PFS) of 2.6 to 3.6 months and overall survival (OS) of 5 to 9.5 months.[11,12] Therefore, more effective second-line treatment options are needed. In recent years, more and more targeted drugs have been used for AGC with the development of tumor cytobiology and molecular biology, epigenetic association studies, and genetic mechanism. Targeted therapies have magnified the effectiveness by combining with other treatments for many cancers, that consist of monoclonal antibodies and small molecular inhibitors.

Recently, some clinical trials investigating the efficacy of PTX + targeted therapy in AGC have been conducted. However, the results of these studies were conflicting that whether adding targeted agents to second-line PTX can improve the clinical benefit remains controversial. Therefore, we carried out a meta-analysis based on randomized controlled trials (RCTs) to examine the question of whether PTX + targeted therapy is more effective than PTX monotherapy as a second-line therapy in AGC.

2. Materials and methods

The meta-analysis was performed based on previous published studies, thus, ethical approval and patient consent are not necessary.

2.1. Search strategy

The databases of PubMed, Web of Science, Embase and the Cochrane Library were systematically searched for articles published in English from January 2000 to August 2019. The keywords used were as following: "gastric or stomach", "cancer or tumor or carcinoma or adenocarcinoma", "paclitaxel or taxol". All possibly relevant articles and their related references were searched on the basis of the following eligible criteria.

2.2. Selection criteria

Inclusion criteria for eligible studies in the meta-analysis were presented as follows:

(1) RCTs (phase II or III studies);
(2) at least 20 patients involved in the studies;
(3) comparing PTX + targeted therapy with PTX alone as second-line chemotherapy;
(4) reporting sufficient data of ORR, PFS, OS and incidence of adverse events;
(5) published in English.

The exclusion criteria for this meta-analysis were non-randomized trials, conference abstracts, studies without a full-text, single-arm trials, case reports, reviews, letters, animal experimental studies, or with insufficient data. For duplicated literature reports, we selected the most comprehensive one.

2.3. Data extraction and quality assessment

The data from all the included studies were independently screened and extracted by the 2 reviewers (Ting Zheng, Jianjiang Jin). A third reviewer will independently analyze the data of the full text articles to settle any disagreements between the 2 reviewers. Extracted data of the eligible studies were as follows:

(1) study characteristics (first author, publication year, country, research time, phase of trial, NCT number, published journal);
(2) patient characteristics (number, age, gender);
(3) treatment regimens;
(4) treatment outcomes (ORR, PFS, OS), incidence of adverse events.
(5) Quality of each included study was assessed independently by 2 reviewers (Ting Zheng, Jianjiang Jin) using Cochrane Risk of Bias tool.[13]

2.4. Statistical analysis

All statistical analyses were performed strictly utilizing the meta-analysis program of STATA software (version 15.1 for Windows; Stata Corporation, College Station, TX). The primary end points of this analysis included OS and PFS. ORR and grade 3 to 5 adverse events were the second end points. The pooled risk ratio (RR) for ORR, and hazard ratios (HRs) for PFS and OS were calculated. We considered statistical significance if the test of pooled analysis with $P < .05$. The Cochran Q-test and the I^2 statistic were using to measure the statistical heterogeneity among the included trials.[14] Heterogeneity existed when the P value was $< .10$ for the Q-test or I^2 statistic was $> 50\%$, then a random effect model was using for pooled analysis, else a fixed effect model was needed. Publication bias was measured by using Begg and Egger test.[15,16]

3. Results

3.1.1. Study selection

The detail flowchart of the search and selection results is presented in Figure 1. The search strategy identified 2195 articles that were screened for inclusion.1218 articles were excluded because of duplication. Based on title and abstract review, 925 articles were excluded according to the inclusion criteria.16 articles were considered suitable and assessed for eligibility, however, 12 studies were conference abstracts. Finally, 4 RCTs[17–20] were included for further meta-analysis.

3.1.2. Study Characteristics and quality assessment

The basic characteristics of included studies are showed in Table 1. Four RCTs were available for this analysis. Two

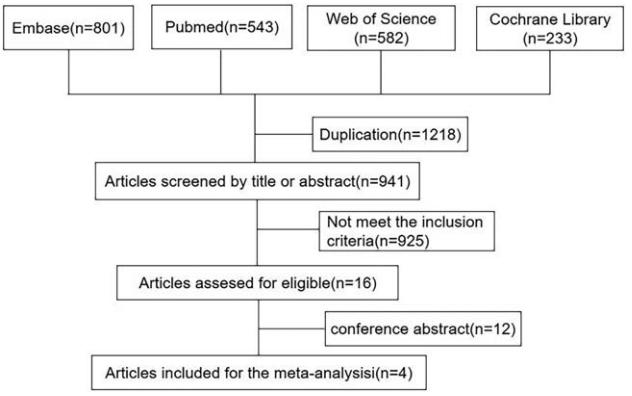

Figure 1. Flowchart of selection of studies for the meta-analysis.

Table 1

Characteristics of included study.

Study	Research time	Country	Phase	Regimen	Number	Male (%)	Mean age (range)	NCT number	Published journal
Wilke.2014	Dec 2010 to Sept 2012	27 countries	III	Ramucirumab + paclitaxel	330	229 (69%)	61 (25–83)	NCT01170663	Lancet Oncol
				Placebo + paclitaxel	335	243 (73%)	61 (24–84)		
Satoh.2014	March 2008 to January 2012	Asia	III	Lapatinib + paclitaxel	132	101 (77%)	60.8 (32-79)	NCT00486954	J Clin Oncol
				paclitaxel	129	106 (82%)	60.4 (22–80)		
Bang.2015	February 2010 to May 2012	Korea	II	olaparib + paclitaxel	62	49 (79%)	63.0 (31–77)	NCT01063517	J Clin Oncol
				Placebo + paclitaxel	62	44 (71%)	60.5 (25–79)		
Bang.2017	Sept 2013 to March 2016	Asia	III	olaparib + paclitaxel	263	174 (66%)	58 (49–67)	NCT01924533	Lancet Oncol
				Placebo + paclitaxel	262	185 (71%)	59 (50–65)		

Dec = december, J Clin Oncol = journal of clinical oncology, Sept = september.

studies[19,20] compared Olaparib plus PTX with PTX, one[17] compared ramucirumab plus PTX with PTX. one[18] compared lapatinib plus PTX with PTX. Among the 4 RCTs, 3 were phase III trials and 1 was phase II trial. They all published in worldwide top journals. As shown in Table 1, a total of 1574 patients from the 4 studies were analyzed ultimately. Among them, 786 patients were in the PTX+targeted therapy group and 788 patients in the PTX alone group. Patients were all pathologically confirmed AGC (including gastro-oesophageal junction cancer) and aged ≥20 years with ECOG performance status ≤2 and with acceptable renal, liver, and bone marrow function. The median age and the proportion of male between the 2 treatment regimens were similar.

In terms of the Cochrane Risk of Bias assessment, only 1 study has not described the blinding of participants and personnel, so it has "unclear" risk of corresponding bias. No other additional risk of bias was present in all trials. Hence, all the included trials were of high quality. (Table 2)

3.2. Efficacy

3.2.1. ORR. The ORR was comprised of complete response (CR) and partial response (PR). The values of ORR were reported in all eligible studies. The meta-analysis of the ORR was calculated by fixed effect model because of no significant heterogeneity observed among the studies ($I^2 = 21.5\%$; $P = .281$). There was a significant increase in the ORR by addition of targeted therapy (RR = 1.80; 95% confidence interval [CI]: 1.45–2.24; $P < .001$) (Fig. 2).

3.2.2. PFS. PFS was defined as the time from random assignment to tumor progression or until death. Overall, It indicated that targeted therapy combined with PTX significantly improved the PFS when compared with the PTX alone (HR = 0.88, 95% CI 0.84–0.92, $P < .001$) (Fig. 3). After the pooled analysis, the result of the test for heterogeneity of the therapeutic effect was not significant ($I^2 = 48.5\%$; $P = .120$). So, a fixed effect model was employed.

3.2.3. OS. The heterogeneity between the 2 groups regarding the outcome of OS was low ($I^2 = 0\%$, $P = .486$). The estimated pooled HR for OS of the 4 trials was 0.90(95% CI: 0.86–0.95, $P < .001$) (Fig. 4), which indicated that targeted therapy combined with PTX significantly prolonged the OS time.

3.3. Toxicity

The meta-analysis results of the major grade 3 to 5 adverse events are listed in Table 3. Eight types of adverse events that the 4 RCTs all reported were pooled analysis. Except for neutropenia, decreased appetite and diarrhea, no evidence of heterogeneity was observed among the studies of other grade 3 to 5 adverse events ($I^2 < 50\%$). Therefore, the fixed effects model was used for calculating. Otherwise, the random effects model was used for pooling instead. Comparing with PTX alone, PTX + targeted therapy proved higher risks of grade 3 to 5 neutropenia (RR = 1.69; 95% CI:1.32–2.15; $P < .001$), fatigue (RR = 2.11; 95% CI:1.36–3.30; $P < .001$) and neuropathy (RR = 1.72; 95% CI:1.02–2.91; $P = .043$). Otherwise, it showed no statistical significance in the incidences of grade 3 to 5 anemia, decreased appetite, nausea, diarrhea, and abdominal pain.

3.4. Publication Bias

There was no evidence of publication bias found for the ORR of included study by either the Begg or Egger (Begg, $P = .734$; Egger, $P = .747$)

4. Discussion

Radical resection was considered as the main curative treatment for early gastric cancer, whereas, most patients present at an

Table 2

Quality assessment by Cochrane risk of bias.

Study	Random sequence generation	Allocation concealment	Blinding	Imcomplete outcome data	Selective reporting	Other bias
Wilke.2014	L	L	L	L	L	L
Satoh.2014	L	L	U	L	L	L
Bang.2015	L	L	L	L	L	L
Bang.2017	L	L	L	L	L	L

L = lower risk, U = unclear.

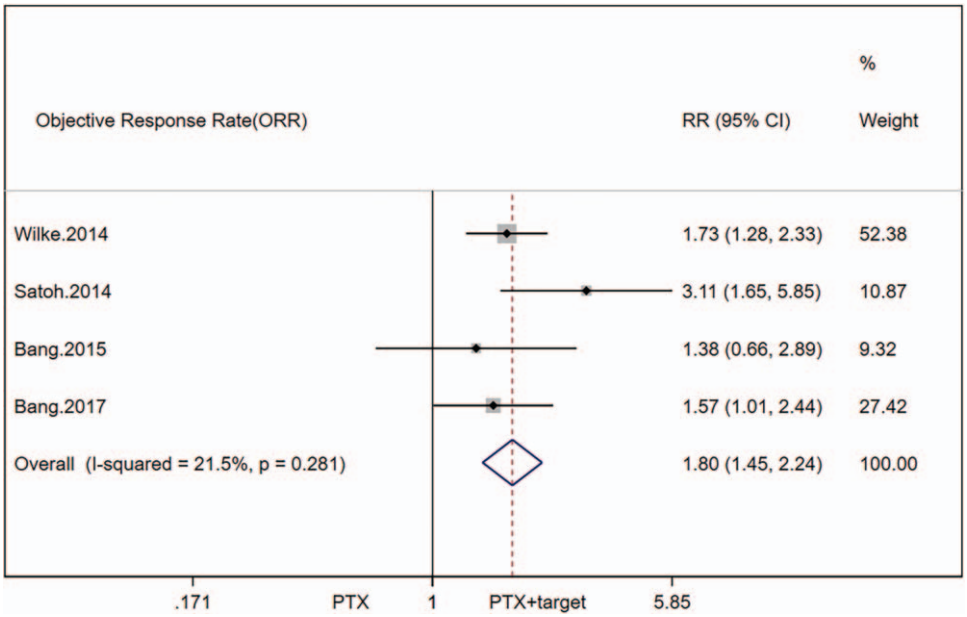

Figure 2. Forest Plot of objective response rate between PTX + targeted therapy and PTX. PTX = paclitaxel.

advanced stage because of its late clinical manifestation and commonly relapse. The prognosis of AGC shows extremely poor. Only 10% to 15% of the 5-year survival rate in Japan, Korea, and the Western countries.[21] Systematic chemotherapy is recommended as the basic therapeutic approach for AGC that can provide improved survival and enhance life quality. Fluoropyrimidine combined with oxaliplatin or cisplatin are the preferred regimens for first-line therapy with median PFS of 6 to 7 months and OS of 10 to 13 months.[22,23] The majority of patients originally respond to chemotherapy, but then experience progression after the first-line chemotherapy. According to NCCN guideline, category 1 preferred options for second-line therapy include PTX,[10] docetaxel[24] and irinotecan.[25] Although as a widely used second-line therapy, the effect of PTX alone is limited. Therefore, altering the existing therapeutic regimens and finding more effective strategies seem to be significance important for AGC. In recent years, some targeted drugs in combination with PTX have been researched as second-line therapies. However, many clinical trials have conflicting outcomes.

We performed a meta-analysis of 4 RCTs of PTX with or without targeted anticancer agents for AGC. The potential

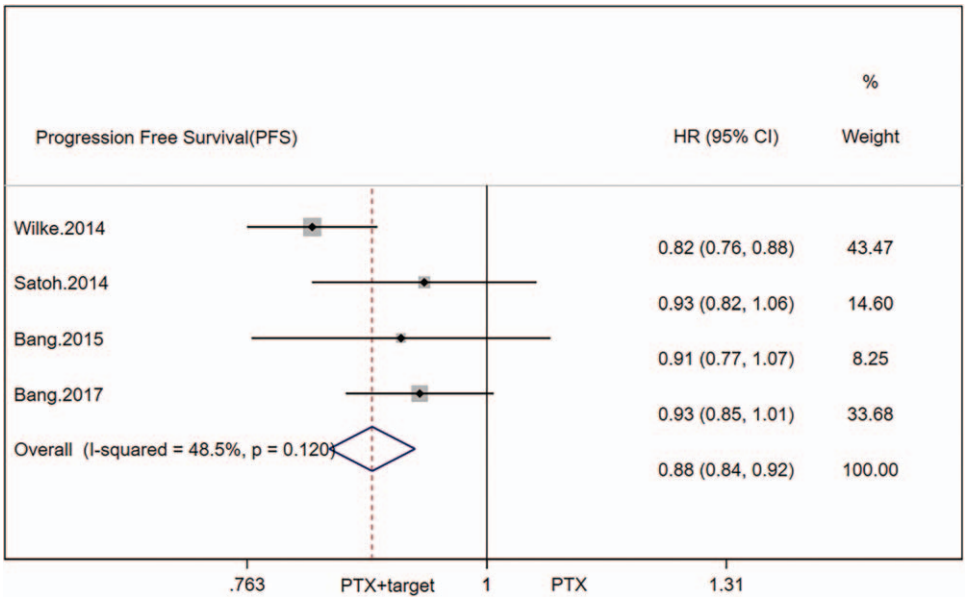

Figure 3. Forest Plot of progression-free survival between PTX + targeted therapy and PTX. PTX = paclitaxel.

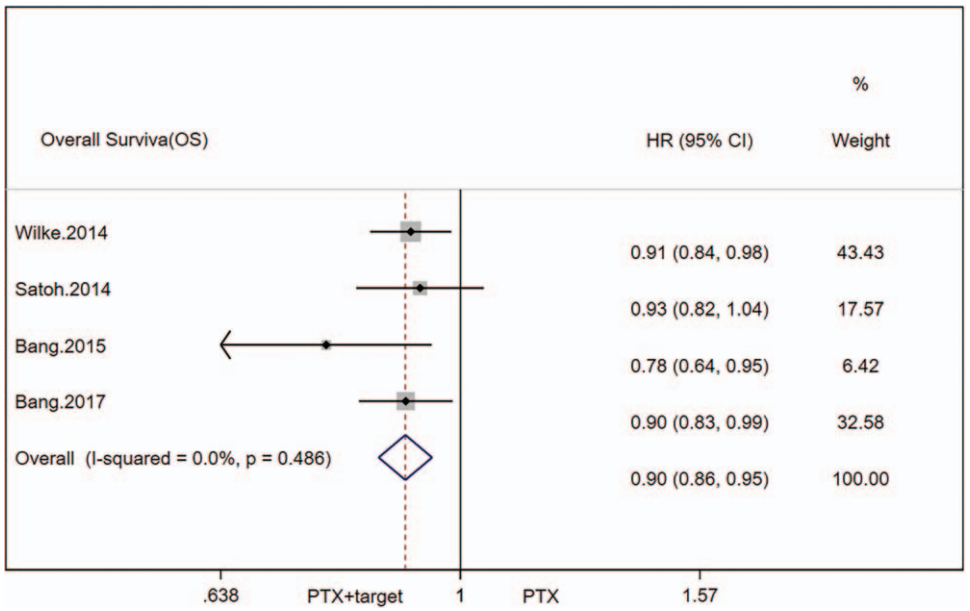

Figure 4. Forest Plot of overall survival between PTX + targeted therapy and PTX. PTX = paclitaxel.

efficacy and safety profile were systematically evaluated. In pooled analysis, A remarkable superiority of ORR (RR = 1.80; 95% CI: 1.45–2.24; $P < .001$) has been detected in PTX + targeted therapy group, a fixed effect model was used without significant heterogeneity. The addition of targeted therapy was also associated with significant improvement for PFS (HR = 0.88, 95% CI 0.84–0.92, $P < .001$) as well as OS (HR = 0.90,95% CI: 0.86–0.95, $P < .001$). No significant heterogeneity among the included studies of PFS and OS was observed, then a fixed effect model was performed. The results demonstrate that the targeted agents combined with PTX is associated with better OS benefit and treatment efficiency than the PTX alone for AGC.

Major adverse events were also evaluated in the meta-analysis including neutropenia, anemia, neuropathy, fatigue, decreased appetite, nausea, diarrhea and abdominal pain. As for grade 3 to 5 adverse events, the pooled data illustrated that PTX + targeted therapy had an obviously increased only in the incidence of fatigue, neutropenia and neuropathy. However, no statistically significant differences were observed in other grade 3 to 5 adverse events.

This meta-analysis has some limitations should be acknowledged. First, few RCTs (4 studies) were included and the sample size was not adequate enough to have a sufficient statistical power for the efficiency and safety of AGC between PTX + targeted therapy and PTX. We didn't divide these studies into subgroups because of the few studies. Additionally, some unknown bias may influence our selection strategies, although we detected none. Second, we only collected the published data that may limit us to fully research the effect and safety of target agents combined with PTX. Third, most studies were performed in Asia which are not completely transferable to the European patient population. The lastly, there were many details not available and could not be analyzed that may influenced the patient's outcomes. Therefore, caution should be exercised when interpreting the results of this meta-analysis because of the limitations mentioned above.

Table 3

Summary of Grade 3–5 Adverse Events.

AEs	RR	95%CI	I^2	P
Neutropenia	1.69	1.32–2.15	60.4%	<.001
Anemia	1.29	0.95–1.74	44.7%	.098
Neuropathy	1.72	1.02–2.91	0%	.043
Fatigue	2.11	1.36–3.30	0%	<.001
Decreased Appetite	1.37	0.63–2.99	51.3%	.431
Nausea	1.21	0.60–2.44	0%	.595
Diarrhoea	2.53	0.91–7.01	52.7%	.076
Abdominal Pain	1.49	0.81–2.75	0.7%	.202

AEs = adverse events, CI = confidence interval, RR = risk ratio.

5. Conclusions

In conclusion, PTX+targeted therapy showed significantly better survival outcomes compared with PTX alone due to the results of our meta-analysis of RCTs. Major grade 3 to 5 adverse events associated with PTX + targeted therapy were generally manageable and tolerable. Therefore, PTX + targeted therapy could be a considerable second-line option for AGC. In the future, more larger multicenter RCTs should be carried out to verify the efficacy and safety of PTX+targeted therapy.

Author contributions

Conceptualization: Ting Zheng, Li Zhou.
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Software: Ting Zheng, Jianjiang Jin.
Writing – original draft: Ting Zheng.
Writing – review & editing: Ting Zheng, Jianjiang Jin, Li Zhou.

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