A Bayesian Network Meta-Analysis for Identifying the Optimal Taxane-Based Chemotherapy Regimens for Treating Gastric Cancer

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Background: Several taxane-based chemotherapy regimens are effective in the treatment of gastric cancer; nevertheless, their comparative efficacy and safety remain disputed. This network meta-analysis (NMA) was designed to compare the efficacy and safety of different taxane-based chemotherapy regimens against gastric cancer.

Methods: A comprehensive search was conducted to identify all relevant randomized controlled trials (RCTs) in multiple electronic databases. A Bayesian NMA was performed to combine the direct and indirect evidence and estimate the comparative efficacy and safety of different taxane-based chemotherapy regimens simultaneously by utilizing WinBUGS 1.4.3 and Stata 13.1 software. The efficacy outcomes included overall survival rate (OS), progression-free survival (PFS), and overall response rate (ORR), and the safety outcomes were adverse reactions (ADRs), namely, neutropenia, leucopenia, vomiting, and fatigue.

Results: A total of 37 RCTs were identified involving 7,178 patients with gastric cancer, and 10 taxane-based chemotherapy regimens (RT, T, TC, TCF, TF, TO, TOF, mTCF, mTF, and mTOF) were collected in gastric cancer therapy. According to the results of cluster analysis, compared with other taxane-based chemotherapy regimens, the regimens of TOF, mTCF, and TF were associated with the most favorable clinical efficacy in improving OS, PFS, and ORR. On the other hand, the regimens of T and mTF had the potential to be the most tolerable and acceptable therapeutic alternative in terms of ADRs.

Conclusions: The current NMA provides the evidence that the combination of taxanes (paclitaxel or docetaxel) and fluorouracil is associated with the most preferable and beneficial option for patients with gastric cancer, although additional results from multicenter trials and high-quality studies will be pivotal for supporting our findings.

Keywords: gastric cancer, paclitaxel, docetaxel, chemotherapy, network meta-analysis
INTRODUCTION

As one of the most frequently diagnosed cancers, gastric cancer is the second leading cause of cancer mortality worldwide (de Martel et al., 2012; Ferro et al., 2014; Torre et al., 2015). Currently, surgical resection is still the primary curative treatment for gastric cancer. Nevertheless, the majority of patients will suffer from locoregional recurrence; it is a consensus that chemotherapy has been essential for achieving survival advantages and therapeutic benefit (Gunderson, 2002; Cunningham et al., 2006; Miceli et al., 2014). National comprehensive cancer network (NCCN) guidelines recommend that paclitaxel and docetaxel are listed as the standard first-line chemotherapeutic drugs for gastric cancer (Ajani et al., 2016). Paclitaxel and docetaxel are members of drugs called taxanes; taxanes have become key drugs for over a dozen malignancies since their antitumor activity was established in the early 1990s (Kudlowitz and Muggia, 2013). Additionally, paclitaxel, which was originally isolated from the North American Pacific yew tree (Taxus brevifolia), was approved by the U.S. Food and Drug Administration as Taxol against advanced ovarian cancer in 1992, and has recently been widely used for the treatment of solid tumors such as gastric cancer (Bocci et al., 2013; Howat et al., 2014; Khanna et al., 2015; Kundranda and Niu, 2015). Similarly, docetaxel has also shown encouraging results in gastric cancer with notable objective responses and meaningful survival advantage (Brower, 2015; Shah et al., 2015). Taxane-based chemotherapy regimens have been validated as promising effective treatments for gastric cancer due to significantly increasing the overall survival compared with placebo and possessing the favorable activity with acceptable adverse toxicities against gastric cancer (Constena et al., 2002; Wilke et al., 2014; Jiang et al., 2015). There is also increasing concern about the anticancer mechanisms of paclitaxel and docetaxel, and multiple studies have recognized that paclitaxel can arrest mitosis and the cell cycle to induce the death of cells by stabilizing microtubules and interfering with microtubule disassembly during cell division. According to a recent study, the antitumor activity of paclitaxel can be enhanced by exosomes from M1-polarized macrophages through activating macrophage-mediated inflammation (Wang et al., 2019). The encouraging activity of paclitaxel in the treatment of gastric cancer is associated with AKT/ERK activation, the TGF-β/Smad signaling pathway suppression (Tsukada et al., 2013; Wu et al., 2014). Forkhead box transcription factor 1 might be a new therapeutic target in docetaxel-resistant gastric cancer (Li et al., 2013). However, recent evidence has demonstrated that intratumoral concentrations of paclitaxel are too low to cause mitotic arrest and result in multipolar divisions instead (Weaver, 2014; Zhang et al., 2014; Song et al., 2015).

Network meta-analysis (NMA) can simultaneously synthesize direct and indirect comparisons in the absence of direct evidence and also produces inferences regarding the comparative efficacy or safety of multiple treatments and has the potential to rank competing interventions for different outcomes (Salanti et al., 2014; Rücker and Schwarzer, 2015). By virtue of its versatility, NMA is increasingly utilized to address knowledge gaps in medical sciences, especially the field of oncology. Recently, it has been applied to explore adjuvant therapy for pancreatic cancer, the optimal treatment for colorectal cancer, and others (Golfinopoulos et al., 2007; Wang et al., 2012; Liao et al., 2013).

As a cornerstone of chemotherapy for gastric cancer, paclitaxel and docetaxel are used as the standard of care alone or in combination with other anticancer drugs in more than 30 regimens. However, the choice of taxane-based chemotherapy regimens in the initial treatment of gastric cancer is an important issue, and it was still unclear which taxane-based chemotherapy regimens were the most effective and tolerable against gastric cancer. To address these issues, an NMA was designed to summarize the efficacy and safety of different taxane-based chemotherapy regimens, which may aid clinical decision-making.

METHODS

The procedure of the current NMA was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines “NMA extended version” (Hutton et al., 2015). The completed PRISMA checklist was presented as additional file (Presentation S1).

Retrieval Strategies

First, the electronic databases of Embase, PubMed, Cochrane Library, and OVID were searched for all eligible randomized controlled trials (RCTs) from inception to May 29, 2017. There were no limitation for publication years, languages, and blinding methods. For relevant publications, the following terms of gastric cancer were adopted: “Stomach Neoplasms [MeSH Terms],” “Stomach Neoplasm,” “Gastric Neoplasms,” “Gastric Neoplasm,” “Stomach Cancer,” “Stomach Tumor,” “Gastric Cancer,” “Gastric Tumor,” “Gastric Carcinoma,” and “Stomach Carcinoma.” More specific retrieval strategies were provided in Presentation S1. Second, manual searching was supplemented to identify the potential enrolled RCTs from the references of relevant meta-analyses and the retrieved review articles. In addition, the specialists in information retrieval were invited to amend our searching strategies. We appropriately adjusted our retrieval strategies in light of different electronic databases.

Inclusion and Exclusion Criteria

All the articles were reviewed by two investigators independently. RCTs were included if they satisfied the following criteria: 1) human participants were diagnosed as gastric cancer; 2) taxane-based chemotherapy regimens were used in either arm of the treatment; 3) the presence of a control was treated by the chemotherapeutic drugs in NCCN guideline; 4) the relative efficacy outcomes in the present NMA included OS, progression-free survival (PFS), and overall response rate (ORR), and the safety outcomes were adverse drug reactions (ADRs), such as neutropenia, leucopenia, vomiting, and fatigue; 5) all the trials should be designed as RCTs that compared the relative outcomes of taxane-based chemotherapy regimens.

Two investigators perused the titles and abstracts of the identified RCTs to exclude the irrelevant clinical trials; the
exclusion criteria were listed as follows: 1) except for gastric cancer, patients suffered from other cancers; 2) the interventions of trials contained surgery, radiotherapy, or chemotherapeutic drugs that were not recommended by NCCN guidelines; without taxane-based chemotherapy regimens were not in either arm; the arms were different in therapy duration or drug administration; 3) insufficient data were available to estimate the outcomes; 4) type of study was non-RCT, for example, single-arm trial, pharmacological experiments, and reviews; duplications; and unavailable full-text.

Data Extraction and Quality Assessment
Two investigators screened the initial search results for potentially eligible studies independently. All identified articles were then retrieved in full, and the corresponding data were extracted by Microsoft Excel (Microsoft Corp, Redmond, WA) as follows: 1) the publication information, including the name of first author, publication year, literature databases, and country; 2) the characteristics of the enrolled patients with gastric cancer: number, age, gender, type, and other information of cancer; 3) the information of intervention: the dosage, duration, and treatment cycle; 4) outcomes: the measured data about the efficacy and safety outcomes. The Kaplan–Meier curves of OS and PFS were digitized using Engauge Digitizer (www.digitizer.sourceforge.net). These outcomes were calculated by the following formula: ORR = (number of complete response patients + partial response)/the total number of patients × 100%; the incidence of ADRs = (number of patients occurred ADRs/total number of patients) × 100%; 4) the description of study design: blinding, randomization allocation methods, and other items for quality assessment. For analysis purposes, taxane-based chemotherapy regimens were considered as the experimental arm, and other chemotherapy treatments were considered to be the control arm. Similarly, docetaxel and paclitaxel were merged to the taxanes (T) drug class, and other chemotherapeutic drugs were defined as their initials in the NMA.

The two investigators independently examined the quality of all included trials according to the Cochrane risk of bias tool (Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0) (Higgins et al., 2011). Discrepancies were resolved either by consensus or through adjudication by a third investigator. The quality evaluation items of each trial included selection bias (random sequence generation and allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting), and other biases, and these items were scored as low, high, or unclear risk of bias.

This present NMA does not require ethical approval because it only gathered the data from relevant published trials.

Statistical Analysis
Odds ratios (ORs) were calculated for dichotomous data with corresponding 95% credible intervals (CIs). On the one hand, a Bayesian NMA was designed to obtain estimates for the comparative efficacy and safety of taxane-based chemotherapy regimens against gastric cancer. WinBUGS 1.4.3 software (MRC Biostatistics Unit, Cambridge, UK) was utilized to perform statistical analysis. The posterior densities were estimated through the Markov Chain Monte Carlo simulations in the random-effects model (Achana et al., 2014; Stephenson et al., 2015; Greco et al., 2016). The choice of random-effects model for outcomes was mainly associated with the within-study and between-study methodological and clinical variation in current NMA (Jackson et al., 2014; Chan, 2016). The results of analysis procedure were based on 200,000 simulation iterations and 10,000 adaptation iterations. On the other hand, Stata version 13.1 software (Stata Corp, College Station, TX) was adopted to present the results and graphs from the NMA (Shim et al., 2017). The network graph could display the relationship of observed comparisons. The thickness of the lines in the network graph was proportional to the number of trials used for comparisons; node sizes corresponded to total sample sizes for treatments (Chairmani et al., 2013; Donegan et al., 2013). Moreover, the Surface Under the Cumulative Ranking (SUCRA) curve was employed to rank the different taxane-based chemotherapy regimens towards each outcome. The value of SUCRA ranged from 0% to 100%, and the larger the SUCRA value of comparisons was regarded as the better treatment option (Rücker and Schwarzer, 2015; Trinquart et al., 2016). In terms of the publication bias, SUCRA values were graphically accessed via a comparison-adjusted funnel plot, and Egger’s regression test and Begg regression test were applied to measure the asymmetry; the results of Egger test (P > .05) and Begg test (P > .05) were defined as non-significant publication bias among included RCTs (Trinquart et al., 2012). Besides, the inconsistency between indirect and direct comparisons was calculated with the inconsistency factors (IFs) and their 95% CIs in node-splitting analysis for each loop of evidence, and it was regarded as a better consistency when the lower bound of 95% CIs was equal to zero (Hans-Peter, 2014; Krahn et al., 2014; Movridis et al., 2014). Additionally, the cluster analysis was conducted for choosing the optimal taxane-based chemotherapy regimens in consideration of two different outcomes simultaneously, and the interventions located in the upper right corner were superior to others (Veroniki et al., 2015).

RESULTS

Literature Search and Study Characteristics
Initially, a total of 2406 citations were yielded through comprehensive searching according to the searching strategy as mentioned. After screening the titles and abstracts, we excluded the irrelevant and duplicate articles; 872 potentially eligible papers were selected for full-text reading. Ultimately, we included 37 RCTs, which were subject to data extraction and analysis. All the 37 eligible studies were published between 1999 and 2016. In addition, this NMA incorporated 10 taxane-based chemotherapy regimens (RT, T, TC, TCF, TF, TO, TOF, mTCF, mTF, and mTOF). The process of the study selection is shown in Figure 1. The references and reasons for excluding articles from full-text assessment are listed in Presentation S1.
Table 1 summarizes the baseline characteristics of RCTs included in the NMA from 13 different countries. Overall, 7,178 patients with gastric cancer from 37 RCTs were involved, and the number of participants in the trials varied from 24 to 714 and their ages ranged from 19 to 87 years old. The network plots of evidence with respect to efficacy outcome are illustrated in Figure 2.

Assessment of Methodological Quality
We critically appraised the methodological quality of the included RCTs in accordance with the Cochrane risk of bias tool. In random sequence generation, a total of 21 RCTs (56.76%) were rated as low risk in randomization owing to the fact that authors stated the principles of randomization in detail, and the remaining 16 trials were defined as high risk. Only 14 trials (37.84%) provided information on allocation concealment, and thus they were regarded as low risk. Among included RCTs, the appropriate blinding procedure was introduced in 2 RCTs (5.41%); therefore, they were evaluated as low risk in performance bias and detection bias. Since all the trials included in the NMA disclosed the specific information about withdrawals, the attrition bias was minimized. In terms of selective reporting, only 1 RCT (2.70%) explicitly had a reporting bias. Other bias sources were not identified. A summary of the risk of bias for each included RCT is shown in Figure 3.

The Efficacy Outcomes
The 1-year OS data were available for 30 RCTs involving 19 chemotherapy regimens (CF, ECF, EOF, F, I, IC, IF, OF, RT, T, TC, TCF, TF, TO, TOF, mCF, mTCF, mTF, and mTOF). According to the results of NMA illustrated in Table 2, there were 11 comparisons with statistically significant differences with respect to 1-year
### TABLE 1 | Characteristics of included RCTs.

| Study ID | Country     | Size     | M/F | Age (median/ range) | Regimen       | Intervention                                                                 | Duration | Outcome       |
|----------|-------------|----------|-----|---------------------|---------------|-------------------------------------------------------------------------------|----------|---------------|
| Amani et al., 2005 | USA         | 76/79    | 114/41 | 57/21–83           | TC/TCF        | TC (docetaxel 85 mg/m² + cisplatin 75 mg/m²); TCF (docetaxel 85 mg/m² + cisplatin 75 mg/m² + 5-FU 750 mg/m²) | 3 w      | OS, PFS, ADRs |
| Al-Batran et al., 2013 | Germany     | 71/72    | 96/47 | 69.5               | OF/TOF        | OF (oxaliplatin 85 mg/m² + leucovorin 200 mg/m² + 5-FU 2600 mg/m²); TCF (oxaliplatin 85 mg/m² + leucovorin 200 mg/m² + docetaxel 50 mg/m² + 5-FU 2600 mg/m²) | 3 w      | OS, PFS, ADRs |
| Casak et al., 2015 | USA         | 330/335  | /    | /                   | RT/T          | RT (paclitaxel 80 mg/m² + ramucirumab 8 mg/kg); T (paclitaxel 80 mg/m²)        | 4 w      | OS            |
| Gómez-Martín et al., 2012 | Spain       | 41/32/27/58 | 112/46 | 61/20–79          | CF/ECF/EOF/TCF | CF (cisplatin 80 mg/m²/day + capecitabine); ECF (epirubicin 50 mg/m² + cisplatin 60 mg/m² + 5-FU 2400 mg/m²) | 3 w      | OS, PFS, ADRs |
| Guo et al., 2015 | China       | 174/96/127 | 286/111 | /                   | TF/TOF/TOF    | TF (paclitaxel 135 mg/m² + 5-FU 2400 mg/m² + leucovorin 400 mg/m²); TO (paclitaxel 135 mg/m² + oxaliplatin 85 mg/m² + leucovorin 400 mg/m²) | 3 w      | OS, PFS, ADRs |
| Hironaka et al., 2013 | Japan       | 108/111  | 171/48 | 65/37–75           | T/I           | T (paclitaxel 80 mg/m²); l (irinotecan 150 mg/m²)                             | 4 w      | OS, PFS, ADRs |
| Inal et al., 2012 | Turkey      | 85/22    | 69/38 | 54/23–76           | TCF/mTCF      | TCF (docetaxel 75 mg/m² + cisplatin + 5-FU 750 mg/m²); mTCF (docetaxel 60 mg/m² + cisplatin + 5-FU 600 mg/m²) | 3 w      | OS, PFS, ADRs |
| Kim et al., 2015 | Korea       | 27/25    | 42/10 | /                   | T/TO          | T (docetaxel 36 mg/m²); TO (docetaxel 36 mg/m² + oxaliplatin 80 mg/m²)        | 3 w      | OS, PFS, ADRs |
| Kim et al., 2014 | Korea       | 38/39    | 54/22 | 57/35–75           | TC/TO         | TC (docetaxel 35 mg/m² + cisplatin 60 mg/m²); TO (docetaxel 35 mg/m² + oxaliplatin 120 mg/m²) | 3 w      | OS, PFS, ADRs |
| Kos et al., 2011 | Turkey      | 30/40    | 48/22 | 53.5/23–69         | CF/mTOF       | CF (cisplatin 50 mg/m² + leucovorin 200 mg/m² + 5-FU 400 mg/m²); mTCF (docetaxel 60 mg/m² + cisplatin 60 mg/m² + 5-FU 600 mg/m²) | 3 w      | OS, PFS, ADRs |
| Li et al., 2009 | China       | 52/52    | 63/41 | /                   | TCF/OF        | TCF (docetaxel 75 mg/m² + oxaliplatin 15 mg/m² + 5-FU 500 mg/m²); OF (oxaliplatin 85 mg/m² + leucovorin 200 mg/m² + 5-FU 400 mg/m²) | 3 w      | OS, PFS, ADRs |
| Li et al., 2011 | China       | 50/44    | 63/31 | 58.5/20–75         | TCF/OF        | TCF (paclitaxel 50 mg/m² + cisplatin 20 mg/m² + 5-FU 750 mg/m²); OF (oxaliplatin 85 mg/m² + leucovorin 200 mg/m² + 5-FU 400 mg/m²) | 4 w      | OS, PFS, ADRs |
| Lim et al., 2010 | Korea       | 77/72/37 | 116/70 | 57                 | mCF/TC/OF     | mCF (cisplatin 60–100 mg/m² + capecitabine 1000 mg/m²); TC (docetaxel 75 mg/m² + cisplatin 60–100 mg/m²); CF (cisplatin 60–100 mg/m² + 5-FU 800–1000 mg/m²) | 3 w      | OS, PFS, ADRs |
| Liu et al., 2015 | China       | 57/63    | 59/61 | 58.9/48–75         | TC/TCF        | TC (docetaxel 65–75 mg/m² + cisplatin 15–20 mg/m²); TCF (docetaxel 65–75 mg/m² + cisplatin 15–20 mg/m² + capecitabine 1000 mg/m²) | 3 w      | OS, PFS, ADRs |
| Lu et al., 2016 | China       | 34/30    | 38/26 | 64/38–77           | TCF/TF        | TCF (paclitaxel 135 mg/m² + capecitabine 2000 mg/m² + 5-FU 350 mg/m²); TF (paclitaxel 135 mg/m² + 5-FU 350 mg/m²) | 3 w      | OS, PFS, ADRs |
TABLE 1 | Continued

| Study ID | Country     | Size   | M/F   | Age (median/ range) | Regimen       | Intervention                                                                 | Duration | Outcome        |
|----------|-------------|--------|-------|--------------------|---------------|------------------------------------------------------------------------------|----------|----------------|
| Maruta et al., 2007 | Japan | 12/12 | 18/6  | 62                 | T/TF           | T (docetaxel 60 mg/m²); TF (docetaxel 60 mg/m² + 5-FU 600 mg)                | 3 w      | OS, ORR, ADRs  |
| Muro et al., 2016 | Argentina | 330/335 | 472/190 | 61/24–84          | RT/T           | RT (ramucirumab 8 mg/kg + paclitaxel 80 mg/m²); T (paclitaxel 80 mg/m²)       | 3 w      | OS, PFS, ORR, ADRs |
| Nishina et al., 2016 | Japan | 49/51 | 33/16 | 59/30–74          | F/T            | F (5-FU 800 mg/m²); T (paclitaxel 80 mg/m²)                                  | 4 w      | OS, PFS, ADRs  |
| Ochenduszko et al., 2015 | Poland | 29/27 | 29/27 | 59                 | ECF/mDCF       | ECF (epirubicin 50 mg/m² + oxaliplatin 130 mg/m² + capecitabine 625 mg/m²); mDCF (docetaxel 40 mg/m² + leucovorin 400 mg/m² + 5-FU 400 mg/m² + cisplatin 40 mg/m²) | 3 w      | OS, PFS, ADRs  |
| Roth and Ajani, 2003 | Switzerland | 76/79 | 117/164 | 54.5              | TC/TCF         | TC (docetaxel 85 mg/m² + cisplatin 75 mg/m²); TCF (docetaxel 75 mg/m² + cisplatin 75 mg/m² + 5-FU 750 mg/m²) | 3 w      | ORR, ADRs      |
| Roth et al., 2007 | Switzerland | 40/38/41 | 89/30 | 59/32–78          | ECF/TCF/TCF   | ECF (epirubicin 50 mg/m² + cisplatin 60 mg/m² + 5-FU 200 mg/m²); TCF (docetaxel 85 mg/m² + cisplatin 75 mg/m² + 5-FU 300 mg/m²) | 3 w      | ORR, ADRs      |
| Teker et al., 2014 | Turkey | 44/42 | 52/34 | 56/25–77          | TCF/ECF        | TCF (docetaxel 50–75 mg/m² + cisplatin 50–75 mg/m² + 5-FU 250–750 mg/m²); ECF (epirubicin 50 mg/m² + cisplatin 60 mg/m² + 5-FU 200 mg/m²) | 3 w      | OS, PFS, ORR, ADRs |
| Thuss-Patience et al., 2005 | Germany | 45/45 | 65/25 | 62/34–75          | mTF/ECF       | mTF (docetaxel 75 mg/m² + 5-FU 200 mg/m²); ECF (epirubicin 50 mg/m² + cisplatin 60 mg/m² + 5-FU 200 mg/m²) | 3 w      | OS, PFS, ORR, ADRs |
| Thuss-Patience et al., 2011 | Germany | 40/51 | 68/23 | 62/32–79          | mTF/TF        | mTF (docetaxel 60 mg/m² + capecitabine 800 mg/m²); TF (docetaxel 75 mg/m² + capecitabine 1000 mg/m²) | 3 w      | OS, PFS, ORR, ADRs |
| Tsuburaya et al., 2014 | Japan | 359/355 | 486/228 | /                | F/TF           | F (5-FU 267 mg/m²); TF (paclitaxel 80 mg/m² + 5-FU 267 mg/m²)               | 3 w      | OS, ADRs       |
| Van Cutsem et al., 2006 | Russia | 221/224 | 317/128 | 55/25–79          | TCF/CF         | TCF (docetaxel 75 mg/m² + cisplatin 75 mg/m² + 5-FU 750 mg/m²); CF (cisplatin 100 mg/m² + 5-FU 1,000 mg/m²) | 4 w      | OS, PFS, ORR, ADRs |
| Van Cutsem et al., 2015 | Belgium | 79/89/96 | 175/79 | 59               | TO/TOF/mTOF   | TO (docetaxel 75 mg/m² + oxaliplatin 130 mg/m²); TOF (docetaxel 50 mg/m² + oxaliplatin 85 mg/m² + 5-FU 2400 mg/m² + leucovorin 400 mg/m²); mTOF (docetaxel 50 mg + oxaliplatin 100 mg + capecitabine 625 mg/m²) | 3 w      | OS, PFS, ORR, ADRs |
| Wang et al., 2016 | China | 119/115 | 169/65 | 56.1/19–80        | CF/mTOF       | CF (cisplatin 75 mg/m² + 5-FU 600 mg/m²); mTOF (docetaxel 60 mg/m² + cisplatin 60 mg/m² + 5-FU 600 mg/m²) | 3 w      | OS, ORR, ADRs  |
| Wilke et al., 2014 | Germany | 330/335 | 472/193 | 61/25–84          | RT/T           | RT (ramucirumab 8 mg/kg + paclitaxel 80 mg/m²); T (paclitaxel 80 mg/m²)       | 4 w      | OS, PFS, ORR, ADRs |
| Yang et al., 2005 | China | 60/60/60 | 118/62 | 62/22–87          | CF/TCF/TO     | CF (cisplatin 50 mg/m² + 5-FU 200 mg/m²); TCF (Taxol 100 mg/m² + cisplatin 50 mg/m² + 5-FU 200 mg/m²); TO (Taxol 100 mg/m² + oxaliplatin 100 mg/m²) | 3 w      | ORR, ADRs      |
| Ye et al., 2008 | China | 60/72 | 86/46 | 51                | OF/TF         | OF (oxaliplatin 85 mg/m² + leucovorin 200 mg/m² + 5-FU 400 mg/m²); TF (paclitaxel 75 mg/m² + leucovorin 200 mg/m² + 5-FU 400 mg/m²) | 4 w      | ORR, ADRs      |
| Zhang et al., 2009 | China | 37/30/35 | 71/31  | /                | F/TF/CF       | F (capecitabine 1000 mg/m²); TF (paclitaxel 175 mg/m² + capecitabine 1000 mg/m²) | 3 w      | ORR, ADRs      |
| Zhao et al., 2016 | China | 78/78 | 80/76 | 39.40             | CF/TCF        | CF (cisplatin 25 mg/m² + 5-FU 400 mg/m²); TCF (paclitaxel 80 mg/m² + cisplatin 25 mg/m² + 5-FU 400 mg/m²) | 3 w      | ORR, ADRs      |
OS, namely, TO vs. mTCF (OR = 3.04, 95% CI = 1.13–7.75), T vs. TF (OR = 2.72, 95% CI = 1.19–6.33), TC vs. TF (OR = 2.79, 95% CI = 1.26–5.87), I vs. TF (OR = 3.88, 95% CI = 1.27–12.98), TO vs. TOF (OR = 2.90, 95% CI = 1.63–5.04), TF vs. TO (OR = 0.25, 95% CI = 0.14–0.48), TF vs. mTOF (OR = 0.28, 95% CI = 0.11–0.77), TCF vs. TO (OR = 0.40, 95% CI = 0.20–0.86), TOF vs. mTOF (OR = 0.39, 95% CI = 0.17–0.89), RT vs. T (OR = 0.61, 95% CI = 0.41–0.91), and OF vs. TO (OR = 0.41, 95% CI = 0.19–0.93). Based on the SUCRA in Figure S1, the TF regimen had the greatest possibility of achieving a considerable improvement in 1-year OS. In addition, the taxane-based chemotherapy regimens were ranked as follows: TF (92.15%) > mTCF (78.88%) > TOF (75.49%) > TCF (68.06%) > mTF (66.67%) > RT (61.47%) > TC (34.35%) > T (32.13%) > TOF (24.22%) > TO (16.31%).
Regard the endpoint of 1-year PFS, 21 eligible RCTs with 17 chemotherapy regimens (CF, ECF, EOF, F, I, IC, OF, RT, T, TC, TCF, TF, TO, TOF, mTCF, mTF, and mTOF) reported the 1-year PFS. As the results indicate in Supplementary File 3, the significant differences were observed between the chemotherapy regimens of TO vs. TOF (OR = 3.80, 95% CI = 1.00–17.87), F vs. RT (OR = 24.38, 95% CI = 1.07–1227), as well as F vs. TOF (OR = 41.09, 95% CI = 1.09–3852). Besides that, the TOF regimen was associated with the remarkable option for improving the 1-year PFS in the light of SUCRA (Figure S1), and the ranks of different taxane-based chemotherapy regimens in the 1-year PFS were listed below: TOF (85.91%) > TO (84.14%) > TCF (62.34%) > mTF (56.84%) > TOF (54.09%) > T (32.09%) > RT (26.91%) > mTCF (18.77%).

### Supplementary File 3

Moreover, the TF regimen was believed to be particularly beneficial for improving ORR for patients with gastric cancer according to the SUCRA. The rankings of taxane-based chemotherapy regimens based on their SUCRA value were as follows: TF (85.91%) > TO (84.14%) > TCF (62.34%) > mTF (56.84%) > TOF (54.09%) > T (32.09%) > RT (26.91%) > mTCF (18.77%).

### The Safety Outcomes

Twenty-five RCTs involving 16 chemotherapy regimens (CF, ECF, EOF, F, I, OF, RT, T, TC, TCF, TF, TO, TOF, mTCF, mTF, and mTOF) described neutropenia. The pooled results in Table 2 showed that 16 comparisons were associated with significant differences in neutropenia as follows: CF vs. TOF, TF vs. mTF, F vs. mTF, EOF vs. TOF, TO vs. mTF, EOF vs. TOF, TOF vs. mTOF, TF vs. mTOF, TF vs. mTOF, TF vs. mTOF, TO vs. mTOF, TF vs. mTOF, TO vs. mTOF, TF vs. mTOF, and TF vs. mTOF. The SUCRA of neutropenia for different taxane-based chemotherapy regimens was arranged as follows: mTCF (93.51%) > T (65.52%) > TOF (57.45%) > TC (54.09%) > TCF (53.82%) > TOF (33.21%) > TO (27.93%) > mTF (24.13%) > RT (21.09%) > mTOF (1.70%); these results indicated that the mTCF regimen had the highest probability of being the most favorable treatment in terms of relieving neutropenia.
There were 29 trials with 18 chemotherapy regimens (CF, ECF, EOF, F, I, IC, IF, OF, RT, T, TC, TCF, TF, TO, TOF, mTCF, mTF, and mTOF) concerning leucopenia. As summarized in Table 2, there were significant differences between 17 comparisons, and 15 of them were taxane-based chemotherapy regimens, namely, IF vs. mTCF, ECF vs. mTCF, IC vs. mTCF, I vs. mTCF, TOF vs. mTCF, TO vs. mTCF, TF vs. mTCF, TCF vs. mTCF, T vs. mTCF, TC vs. mTCF, OF vs. mTCF, F vs. mTCF, CF vs. mTCF, mTCF vs. mTF, and mTCF vs. TOF. According to SUCRA for leucopenia, taxane-based chemotherapy regimens were ranked as follows: T (68.23%) > TOF (63.16%) > TC (58.86%) > TF (49.33%) > TCF (46.91%) > mTOF (44.96%) > TOF (39.4%) > TO (38.9%) > RT (33.26%) > mTCF (2.629%). It was suggested that only receiving paclitaxel or docetaxel appeared to have the highest SUCRA value of the decrease in the risk of leucopenia.

The analysis of vomiting included the data from 29 trials with 18 chemotherapy regimens (CF, ECF, EOF, F, I, IC, IF, OF, RT, T, TC, TCF, TF, TO, TOF, mTCF, mTF, and mTOF). The results of NMA demonstrated in Table 2 that significant differences were detected between these nine comparisons: EOF vs. TOF, TF vs. TOF, ECF vs. TOF, TF vs. TOF, IF vs. TOF, F vs. IF, CF vs. TO, CV vs. IF, and TOF vs. mTCF. Furthermore, TO regimen possessed the great possibility of significantly reduced risk of vomiting compared to other taxane-based chemotherapy regimens, and their ranks were presented as follows based on SUCRA: TO (74.08%) > mTF (63.35%) > mTCF (61.83%) > mTOF (58.02%) > TF (56.27%) > TC (45.72%) > TCF (37.87%) > RT (37.34%) > T (35.02%) > TOF (14.51%).

With respect to fatigue, 29 trials involving 17 chemotherapy regimens (CF, ECF, EOF, F, I, IC, IF, OF, RT, T, TC, TCF, TF, TO, TOF, mTCF, mTF, and mTOF) were enrolled. Disappointingly, the results revealed that no significant difference was found among these comparisons (Table 2). Moreover, mTF exhibited great possibility with the lowest risk of fatigue incidence, and the rankings of taxane-based chemotherapy regimens based on their SUCRA value were as follows: mTF (82.26%) > mTCF (53.82%) > TOF (51.81%) > TCF (52.92%) > TF (50.71%) > T (49.82%) > TOF (44.98%) > TOF (38.34%) > mTOF (32.87%) > RT (27.8%). Additionally, the SUCRA values of each chemotherapy regimen for efficacy and safety outcomes are summarized in Table 3, and the NMA results from outcomes are described in Presentation S1.

### Table 3

| Intervention | OS       | PFS      | ORR       | Neutropenia | Leukopenia | Vomiting | Fatigue |
|--------------|----------|----------|-----------|-------------|------------|----------|---------|
| CF           | 48.83    | 39.62    | 23.82     | 84.34       | 72.7       | 29.67    | 74.86   |
| ECF          | 51.51    | 49.26    | 31.37     | 38.94       | 44.77      | 67.72    | 77.23   |
| EOF          | 58.26    | 66.09    | 86.74     | 70.69       | 9.822      | 80.6     | 34.8    |
| F            | 54.55    | 3.541    | 3.719     | 52.54       | 83.96      | 13.8     | 58.21   |
| I            | 20.66    | 52.94    | 20.49     | 51.32       | 67.36      | 67.8     | 12.3    |
| IC           | 1.29E-02 | 34.36    | 70.03     | 58.64       | 21.39      | 43.1     | 25.71   |
| IF           | 67.29    | 47.31    | 43.05     | 88.35       | 25.71      |          |         |
| OF           | 65.03    | 71.43    | 62.83     | 71.71       | 74.08      | 46.65    | 51.82   |
| RT           | 61.47    | 56.87    | 28.91     | 21.09       | 33.26      | 37.9     | 27.8    |
| T            | 32.13    | 32.69    | 32.09     | 65.82       | 88.23      | 35.02    | 49.82   |
| TO           | 34.35    | 37.59    | 64.3      | 54.09       | 58.86      | 45.72    | 53.11   |
| TCF          | 68.06    | 44.96    | 62.34     | 57.46       | 49.61      | 37.87    | 52.9    |
| TF           | 92.15    | 53.06    | 85.91     | 53.82       | 49.33      | 56.27    | 50.71   |
| TO           | 16.31    | 46.95    | 84.14     | 27.93       | 38.9       | 74.08    | 42.88   |
| TOF          | 75.49    | 81.29    | 54.09     | 31.22       | 39.4       | 14.51    | 38.1    |
| mCF          | 34.11    | 68.28    | 1.699     | 4.94        | 58.02      | 32.87    |         |
| mTCF         | 78.88    | 56.22    | 18.77     | 93.51       | 2.629      | 61.83    | 53.82   |
| mTF          | 66.67    | 44.00    | 56.84     | 24.13       | 63.16      | 63.35    | 82.26   |
| mTOF         | 24.22    | 78.13    |           | 1.699       | 44.96      | 58.02    | 32.87   |

The values in bold font have higher SUCRA values for different outcomes.
1.60, \( P = .109 > .05 \), respectively. Also, the symmetric remaining part was used to estimate the center value of the funnel plot, and the parts along the center sides made up the sheared part and missing parts. According to the funnel plot, after being patched the actual value of the combined effect was estimated, and the number of RCTs increased while no qualitative change was produced in the results of publication bias ultimately. Thus, there was no significant publication bias among the included RCTs in the present NMA.

**Consistency Test**

The consistency test was preformed for the outcome of 1-year OS (Figure S2); this NMA involved 12 triangular loops and 4 quadrangle loops. The 95% CIs of IF values were truncated at zero for 15 closed loops, indicating that there is no evidence of significant inconsistency. Nevertheless, the significant inconsistency was observed in the quadrangle loop of (TC-TCF-TF-TO) (IF = 2.13, 95% CI = 0.57–3.69). Collectively, there was some inconsistency in this study.

**DISCUSSION**

For the comparative efficacy and safety of different taxane-based chemotherapy regimens against gastric cancer, we adopted the approach of NMA for providing the overwhelming evidence from published RCTs. In summary, the results of the present NMA indicated that the combination of taxanes (paclitaxel or docetaxel) and fluorouracil was associated with the most preferable and beneficial option for patients with gastric cancer in consideration of both efficacy and safety. Moreover, the choice of specific taxane-based chemotherapy regimens should simultaneously rely on the high-quality evidence-based research, the clinical practice of oncologists, and the physique of patients with gastric cancer. Attention should be given to the ADRs caused by paclitaxel and docetaxel to achieve the highest clinical benefits to avoid or decrease the occurrence of adverse effects.

Throughout the past century, gastric cancer is one of the most common malignant tumors of the digestive system worldwide (Chen et al., 2016). Over the past three decades, the survival time of patients with gastric cancer has prolonged and their performance status has improved with the development of different therapeutic strategies for the treatment of advanced gastric cancer (MacDonald et al., 1980; Cocconi et al., 1994; Chao et al., 2004). Among various chemotherapeutic drugs, paclitaxel is an effective anticancer drug against a wide range of solid tumors (Blagosklonny and Fojo, 1999). The antitumor activity of paclitaxel was discovered in the 1970s and has been approved as a microtubule stabilizing agent since 1992, and evidence clearly indicates that paclitaxel can block progression of mitosis, promote tubulin polymerization, and stabilize microtubules from depolymerizing (De Furia, 1997; Rodríguez-Antona, 2010; Meng et al., 2016). Recently, it was reported that the mechanism of paclitaxel is associated with the downregulation of COX-2 expression to inhibit migration and invasion of gastric cancer cells more effectively (Sun et al., 2015).
Additionally, docetaxel resistance can be reversed via the inhibition of FOXM1, which might be a useful marker for predicting and monitoring docetaxel response and a new therapeutic target in docetaxel-resistant gastric cancer (Li et al., 2014). Based on several clinical trials, paclitaxel and docetaxel have been identified to improve the outcomes of patients with gastric cancer; in addition, paclitaxel or docetaxel significantly increases OS compared with placebo and has promising activity with acceptable adverse toxicities (Goel, 2012; Tsuburaya et al., 2013; Yamaguchi et al., 2013; Meng et al., 2014; Bang et al., 2015). Despite recent advancements aimed at optimizing taxane-based regimens, with respect to safety, anaphylactic reactions and hematologic toxicity have been frequently reported as the main adverse effects of paclitaxel or docetaxel, and these reactions could diminish with corticosteroids and antihistamine premedication (Blagosklonny and Fojo, 1999; Raisch et al., 2011).

To the best of our knowledge, this is the first systematic review with NMA that investigated the comparative efficacy and safety of the taxane-based chemotherapy regimens against gastric cancer. A total of 10 regimens (RT, T, TC, CF, TF, TO, TOF, mTFC; mTF, and mTOF) were evaluated for the efficacy and safety outcomes. The efficacy outcomes in the present study involve the 1-year OS, 1-year PFS, and ORR, and the safety outcomes were ADRs, such as neutropenia, leucopenia, vomiting, and fatigue. The hierarchy was calculated based on the SUCRA to identify the optimal treatment for each outcome; the cluster analysis was performed to estimate the superior taxane-based regimen account for both efficacy and safety. Besides, our search strategies were comprehensive to support our results, and the inclusion criteria were formulated and established strictly through the selection process of potential and eligible RCTs. Moreover, this NMA only focused on the chemotherapeutic drugs in NCCN guidelines to avoid clinical heterogeneity. Finally, the methodological quality assessment was conducted for the included RCTs; the comparison-adjusted funnel plots and Egger's test and Begg test were adopted to measure publication bias; the consistency test in node-splitting analysis for each loop was used to explore the reliability and credibility of both direct and indirect evidence.

Several limitations of this current NMA should be taken into consideration. First, the survival time or follow-up data were regarded as important for judging the therapeutic effects of patients with cancer; however, the majority of included RCT only provided the information on 1-year OR and PFS. The insufficient data about long-term endpoint were susceptible to interference in clinical heterogeneity; further study with final OS data will be essential. Therefore, the clinical trials of patients with cancer should focus on more meaningful endpoints. Besides, the information of intention-to-treat analysis was also not enough to perform the NMA among included trials. Second, the majority of RCTs included in the study exhibited a relatively high risk of bias in inadequate allocation concealment and blinding. Finally, we merged docetaxel and paclitaxel into the drug class of taxanes, and these two drugs might have slight differences for treating gastric cancer. We did not conduct a subgroup analysis for Asian and non-Asian patients because several of the included RCTs enrolled both Asian and non-Asian patients with gastric cancer. Hence, head-to-head RCTs comparing docetaxel and paclitaxel would be valuable in identifying the clinical benefits for the former and the latter. Future studies should be designed to address if Asian or non-Asian patients produce changes in receiving taxanes against gastric cancer.

**CONCLUSION**

In conclusion, the current evidence suggests that the combination of taxanes (paclitaxel or docetaxel) and fluorouracil was associated with the most preferable and beneficial option for patients with gastric cancer, although additional results from multicenter trials and high-quality studies will be pivotal for supporting our findings.

**AUTHOR CONTRIBUTIONS**

DZ, J-RW, K-HW, and X-JD contributed to the conception and design. DZ, J-RW, K-HW, X-JD, YZ, M-WN, X-MZ and S-YL contributed to the development of methodology. DZ, J-RW, K-HW, X-JD, YZ, M-WN, S-YL, and BZ contributed to the acquisition of data. DZ, J-RW, K-HW, X-JD, YZ, M-WN, S-YL, and BZ contributed to the analysis and interpretation of data. DZ, J-RW, and BZ performed the writing, review, and/or revision of the manuscript. Administrative, technical, or material support was provided by DZ, J-RW, K-HW, X-JD, X-MZ, and YZ. DZ, J-RW, K-HW, and X-JD performed study supervision.

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**SUPPLEMENTARY MATERIAL**

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