Int J Clin Exp Med 2016;9(3):5616-5629
www.ijcem.com /ISSN:1940-5901/IJCEM0021268

Original Article

Meta-analysis of TOMOX versus FOLFOX regimens for the treatment of advanced colorectal cancer

Chunlin Zhao, Hongyu Zhang, Yanwei Ye, Junfeng Sun, Penghui Li

Department of Gastrointestinal Surgery, The First Affiliated Hospital of Zhengzhou University, No. 1 East Jianshe Road, Erqi District, Zhengzhou, China

Received December 6, 2015; Accepted March 10, 2016; Epub March 15, 2016; Published March 30, 2016

Abstract: Objective: To compare the efficacy and safety of TOMOX and FOLFOX regimens for the treatment of advanced colorectal cancer. Methods: Electronic databases for randomized controlled trials comparing TOMOX and FOLFOX regimens for the treatment of advanced colorectal cancer were systematically searched using the following terms: "raltitrexed" or "Tomudex" or "TOMOX" and "fluorouracil" or "FOLFOX" and "advanced colorectal cancer" or "metastatic colorectal cancer". Conference proceedings and relevant journals were also screened. The outcomes included overall response rate, disease control rate, and toxicities. Results: Initial screening led to the selection of 19 studies, consisting of 1220 patients for the overall meta-analysis. The meta-analysis results showed that patients in TOMOX group had significantly higher overall response rate (RR 1.69, 95% CI 1.42-2.02, $P<0.00001$), disease control rate (RR 1.17, 95% CI 1.09-1.26, $P<0.0001$), partial response (RR 1.71, 95% CI 1.42-2.06, $P<0.00001$), and lower progressive disease (RR 0.59, 95% CI 0.48-0.72, $P<0.00001$) than those of FOLFOX group. The grade 1-2 toxicity analysis suggested that FOLFOX group had higher occurrence of nausea/vomiting, alopecia, diarrhea, mucositis and phlebitis, while TOMOX group had increased incidence of hepatic disorders. In addition, the grade 3-4 toxicity analysis revealed that FOLFOX group had significantly higher nausea/vomiting, while there were no statistically significant differences between the two groups for neutropenia, diarrhea, anemia, thrombocytopenia, peripheral neurotoxicity, asthenia, or hepatic disorders. Conclusion: TOMOX regimen is an effective and tolerable chemotherapy option for advanced colorectal cancer patients, particularly for those who cannot tolerate 5-Fu/capecitabine-based regimens.

Keywords: TOMOX, FOLFOX, advanced colorectal cancer, meta-analysis

Introduction

Colorectal cancer (CRC) is a commonly diagnosed malignancy and one of the leading causes of cancer-related deaths worldwide [1]. One-fourth of all the CRC patients have metastatic disease at the time of diagnosis, while one-third of those with early disease will eventually develop metastases [2]. For these metastatic patients, chemotherapy is the main therapeutic option. At present, 5-fluorouracil (5-Fu)-based chemotherapy continues to be the cornerstone treatment for metastatic CRC (mCRC). Oxaliplatin in combination with 5-Fu/leucovorin (FOLFOX) has already been considered to be a standard schedule in the treatment of advanced CRC [3, 4]. However, the continuous infusion of 5-Fu in the FOLFOX regimen causes some severe adverse effects, especially cardiovascular issues, which pose serious threat to the patient's life [5]. In addition, patients having either partial activity of the enzyme dihydropyrimidine dehydrogenase or its absolute deficiency develop adverse toxic events more easily because of suboptimal 5-Fu metabolism [6]. Moreover, 5-Fu requires a central venous catheter placement for prolonged infusion, which increases costs and provokes discomfort for patients. Therefore, a more convenient and safer schedule or chemotherapy drug could be an attractive option for both patients and doctors. In this context, raltitrexed (Tomudex), a quinazoline analogue of folinic acid and a thymidylate synthase (TS) inhibitor could be a potential treatment alternative.

Raltitrexed enters cells through the reduced-folate carrier and is then polyglutamated by

folypolyglutamate synthase, which increases its retention in the cell, and therefore results in prolonged TS inhibition, DNA fragmentation, and cell death [7, 8]. Also, raltitrexed has a convenient bolus 3-weekly schedule because of its long-lasting inhibition of TS [5]. In 1993, the first randomized multicenter, international phase III study including 439 untreated advanced colorectal cancer patients was conducted to compare the efficacy of raltitrexed (at the dose of 3.0 mg/m^2 every 3 weeks) with 425 mg/m^2 5-Fu and 20 mg/m^2 leucovorin (LV) for 5 days (the Mayo regimen) [9]. The response rate was higher in the raltitrexed group and these patients had a shorter stay in hospital due to the simple schedule. They also had significantly lower rates of grade 3 and 4 toxicities, such as leucopenia and mucositis. However, no statistically significant differences were observed between both groups in overall survival (OS) and time to progression (TTP). Later, studies about combined regimens of raltitrexed with either oxaliplatin (TOMOX) or irinotecan (TOMIRI) showed enhanced efficacy and less toxicities [10-15]. A recent study has demonstrated that raltitrexed, alone or in combination with oxaliplatin or irinotecan was associated with no significant cardiac toxicity in patients who had experienced prior cardiac toxicity from 5-Fu or capecitabine [16]. Therefore, the TOMOX regimen may be another reasonable option of chemotherapy for patients with advanced colorectal cancer. Thus, we performed a meta-analysis of all the randomized controlled trials (RCTs) to compare the efficacy of TOMOX and FOLFOX regimens in the treatment of advanced CRC.

Methods

Literature search

A systematic literature search until December 1st, 2015 was performed with terms "raltitrexed" or "Tomudex" or "TOMOX" and "fluorouracil" or "FOLFOX" and "metastatic colorectal cancer" or "advanced colorectal cancer" in the following databases: MEDLINE, EMBASE, the Cochrane Library, the Controlled Clinical Trials Database, CNKI, and WANFANG Database. The conference proceedings and relevant journals were also further screened for potentially relevant studies. There was no language restriction while screening for the relevant studies.

Selection criteria

Titles and abstracts of all the identified articles were screened and the studies were included according to the following criteria: a) RCTs that compared the TOMOX regimen with FOLFOX regimen; b) patients were ≥18 years with advanced colorectal cancer (metastatic disease); c) results included at least information about complete response, partial response, stable disease, progressive disease, or grades of toxicities (1-2 or 3-4); d) life expectancy of patients ≥3 months, adequate renal function, hepatic function and bone marrow, and normal ECG; and e) the first line chemotherapy regimen was either TOMOX or FOLFOX. Studies were excluded if they were retrospective and had no control arm or data regarding efficacy or toxicities.

Data extraction and quality assessment

Two authors (Zhang H.Y. and Zhao C.L.) independently extracted the data from all the included studies. This data consisted of patient characteristics, study design, inclusion and exclusion criteria, information about complete response, partial response, stable disease and progressive disease, and number of grade 1-2 and 3-4 toxicities. The details of the randomization (generation and concealment), the number of patients allocated to each group, chemotherapy regimen, and the number of lost to follow-up patients were also recorded. The overall methodological quality of each trial was assessed by the same two reviewers. If there were any discrepancies, a third author (Ye Y.W.) was consulted and consensus was reached by discussion. The quality of each study was assessed using the Jadad scoring system and the Cochrane Collaboration's tool for assessing risk of bias. High-quality trials were assigned a score of more than 2, while low-quality trials scored 2 or less (range 0-5).

Statistical analyses

The meta-analysis was performed based on the recommendations of the PRISMA statement [17], and the statistical analyses were carried out according to the Cochrane Collaboration Guidelines [18]. This study was based on intention-to-treat analysis.

The Review Manager software (RevMan, version 5.3 for Windows) provided by the Cochrane

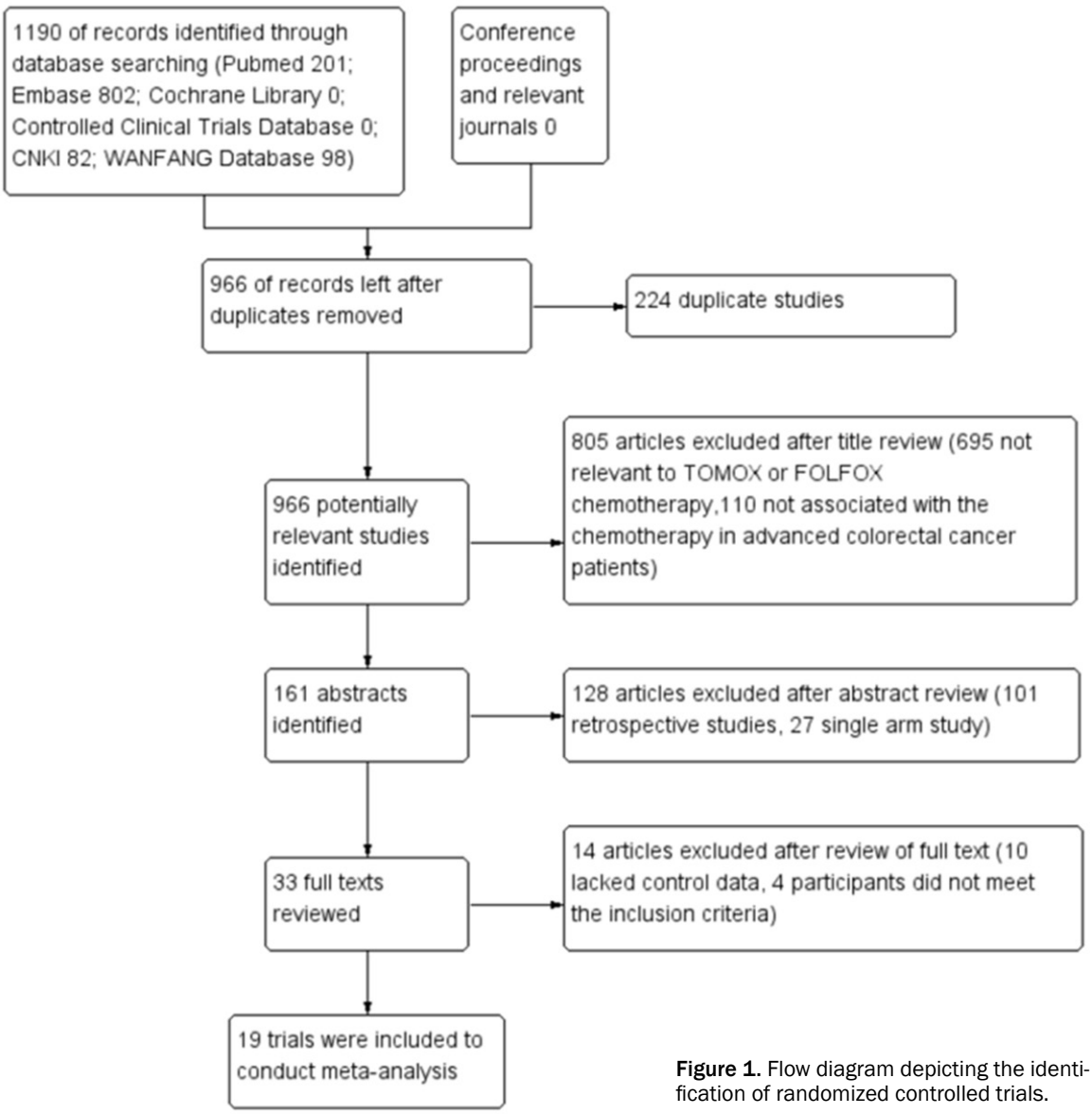

Figure 1. Flow diagram depicting the identification of randomized controlled trials.

Collaboration was used to conduct the meta-analysis. Dichotomous outcomes were presented as relative risk (RR) and the 95% confidence interval (CI) was quantified for all the analyses. Heterogeneity was assessed with Cochran's χ^2 test and the I^2 test. $P<0.10$ and I^2 value >50% represented statistically significant heterogeneity. The data were analyzed using the fixed effects model, if there was no significant statistical heterogeneity (χ^2 $P>0.10$ and $I^2<50\%$), or the random effects model was applied if there was heterogeneity [19]. Publication bias was assessed by creating funnel plots. Subgroup analysis was conducted based on the two different response evaluation criteria about tumors, the World Health Organization (WHO) criteria or the Response Evaluation Criteria in Solid Tumors (RECIST).

Results

Initial screening resulted in identification of a total of 1190 potentially relevant studies. Further analysis revealed that only 19 studies with 1220 patients met all the inclusion criteria and underwent a full analysis (**Figure 1**). The characteristics of the included trials are shown in **Table 1**. All the included trials were RCTs and were carried out between 2007 and 2015. In these RCTs, 612 patients were identified to have received TOMOX regimen, while 608 patients received FOLFOX regimen. The treat-

Table 1. General characteristics of the included trials

Study	n. (TOMOX/ FOLFOX)	Treatment regimen	Response evaluation criteria	median PFS/ TTP (months)	median OS (months)	n. of Lost follow-up	Jadad
Chen YY 2014 [20]	22/21	TOMOX*/FOLFOX*	RECIST	Not Available	Not Available	2	3
Feng L2012 [21]	21/24	TOMOX/FOLFOX	WHO	8.6/5.3	10.8/9.4	2	3
Fu XY 2012 [22]	20/20	TOMOX/FOLFOX	WHO	Not Available	Not Available	0	2
Gravalos 2012 [23]	92/91	TOMOX/FOLFOX4	RECIST	7.7/8.7	15.7/17.2	8	4
Hang ZK 2014 [24]	18/18	TOMOX/FOLFOX	WHO	Not Available	Not Available	0	2
Hu J 2011 [25]	30/30	TOMOX/FOLFOX	WHO	7.5/5.2	Not Available	0	2
Li CY 2013 [26]	15/15	TOMOX/mFOLFOX	WHO	8.2/4.9	Not Available	2	3
Liu D 2015 [27]	32/32	TOMOX*/FOLFOX*	RECIST	8.3/4.2	9.8/8.2	0	2
Liu WZ 2015 [28]	23/22	TOMOX/FOLFOX*	Not Available	Not Available	Not Available	3	3
Nin C 2011 [29]	21/20	TOMOX/FOLFOX	WHO	8.3/5.2	Not Available	2	4
Niu N 2013 [30]	25/24	TOMOX*/FOLFOX*	RECIST	8/4.2	9.8/8.1	2	3
Shi SZ 2013 [31]	20/20	TOMOX/FOLFOX	RECIST	Not Available	Not Available	0	2
Wang JL 2012 [32]	112/102	TOMOX/FOLFOX	WHO	Not Available	Not Available	11	4
Wu JB 2007 [33]	20/20	TOMOX/FLOFOX	WHO	7.8/5.0	Not Available	3	4
Wu YM 2013 [34]	42/48	TOMOX/FOLFOX	WHO	Not Available	Not Available	0	4
Xia BJ 2014 [35]	30/30	TOMOX/FOLFOX	RECIST	Not Available	Not Available	0	4
Xue HJ 2011 [36]	25/25	TOMOX/FOLFOX4	WHO	11.0/9.0	Not Available	2	4
Zhang X 2014 [37]	20/22	TOMOX**/FOLFOX**	Not Available	7.5/5.2	14/13.3	0	2
Zhuang ZX 2010	23/22	TOMOX/FOLFOX	Not Available	8.9/5.6	12.9/10.7	3	3

TOMOX: Tom: 3 mg/m^2+Ox: 130 mg/m^2 (d1;q3w), TOMOX*: Tom: 2.5 mg/m^2+Ox: 100 mg/m^2 (d1;q3w), TOMOX**: Tom: 3 mg/m^2+Ox: 100 mg/m^2 (d1;q3w), FOLFOX: 5-Fu: 375-425 mg/m^2 (d1-5)+LV: 200 mg/m^2 (d1-5)+Ox: 130 mg/m^2 (d1)q3w, FOLFOX*: 5-Fu: 375 mg/m^2 (d1-5)+LV: 200 mg/m^2 (d1-5)+Ox: 100 mg/m^2 (d1)q3w, FOLFOX**: LV: 200 mg/m^2 (d1)+Ox: 130 mg/m^2 (d1)+5-Fu bolus: 400 mg/m^2+5-Fu infusion: 3000 mg/m^2 (d1) q3w, mFOLFOX: LV: 200 mg/m^2 (d1)+Ox: 130 mg/m^2 (d1)+5-Fu bolus: 400 mg/m^2+5-Fu infusion: 3000 mg/m^2 (d1) q3w.

ment regimen was uniform in 11 of the 19 included trials, but their dosage in remaining studies was slightly adjusted. According to the Jadad scoring system, 13 studies had a score greater than 2 (high-quality), while 6 studies had a score equal to 2 (low-quality). The mean score was about 3, therefore, the overall quality of the included studies was relatively high.

Analysis of efficacy outcomes

Complete response (CR): A total of eighteen trials reported complete response data and we observed a RR of 1.44, 95% CI: 0.74-2.82, P=0.29, and no heterogeneity between these trials (I^2=0%). Also, there was no significant difference between outcomes of TOMOX and FOLFOX regimens as seen in **Figure 2A**.

Partial response (PR): Partial response was also assessed from the eighteen studies and the observed RR was 1.71, 95% CI: 1.42-2.06, and P<0.00001, with no heterogeneity (I^2=0%). The partial response rate was significantly higher with TOMOX regimen as compared to FOLFOX regimen as seen in **Figure 2B**.

Stable disease (SD): Stable disease data were reported in the eighteen trials. Based on their analyses, we observed a RR of 0.94, 95% CI: 0.81-1.08, and P=0.37. Again, no heterogeneity (I^2=0%) was found in SD. We did not observe any statistically significant differences between outcomes of TOMOX and FLOFOX regimens as seen in **Figure 3A**.

Progressive disease (PD): This analysis was again based on the data from eighteen studies. We observed a RR value of 0.59, 95% CI: 0.48-0.72, and P<0.00001, with no heterogeneity (I^2=0%). The data suggested that the rate of progressive disease was significantly reduced with TOMOX regimen when compared to FOLFOX as shown in **Figure 3B**.

Overall response rate (ORR=CR+PR): Overall response rate, which is defined as the combination of complete response and partial response, was also assessed. The data revealed a RR value of 1.69, 95% CI: 1.42-2.02, and P<0.00001, which suggested that patients receiving TOMOX regimen had significantly higher ORR compared with FOLFOX (**Figure 4A**). There was no heterogeneity (I^2=0%) between the trials.

Disease control rate (DCR=CR+PR+SD): The disease control rate calculated as the sum of

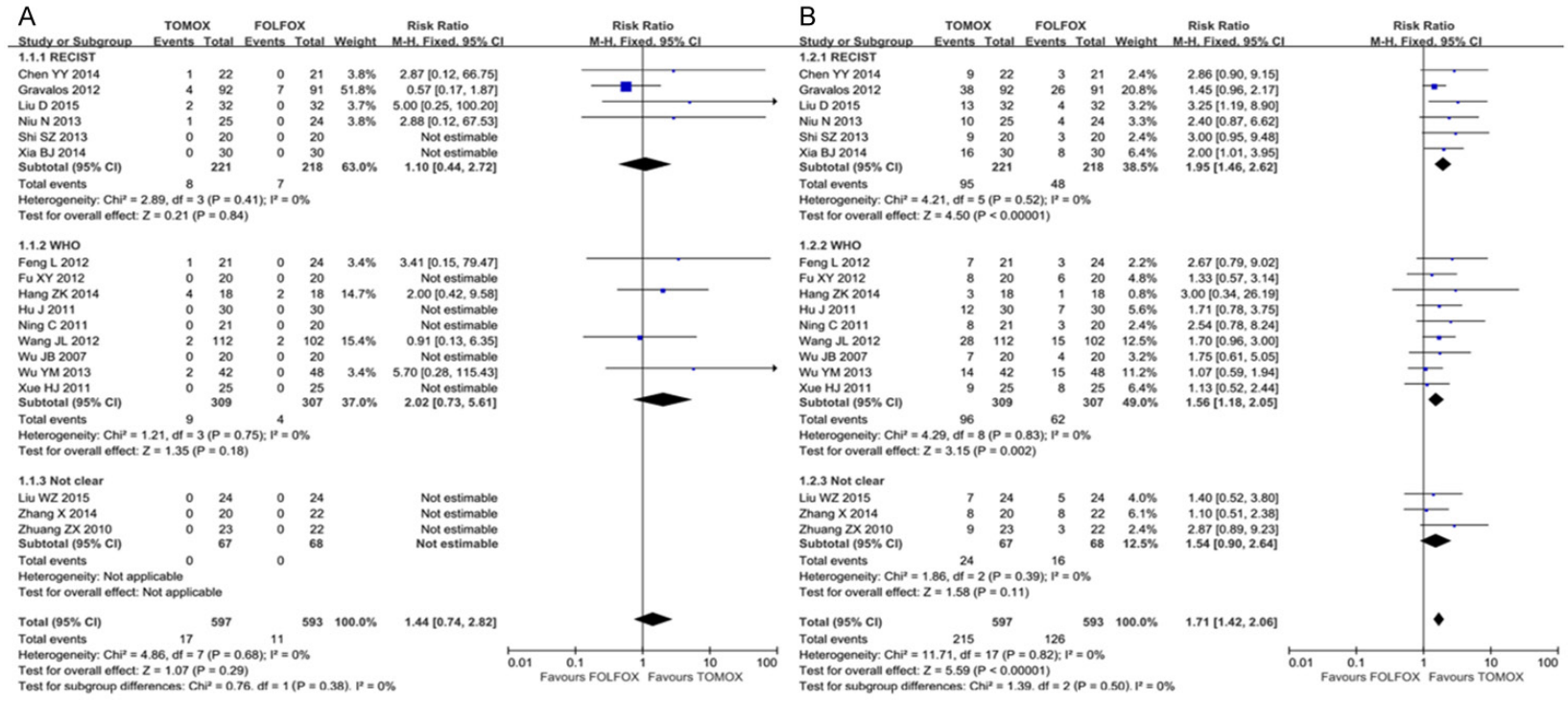

Figure 2. Forest plots representing the relative risk (RR) stratified by tumor response evaluation criteria for (A) complete response (CR) or (B) partial response (PR).

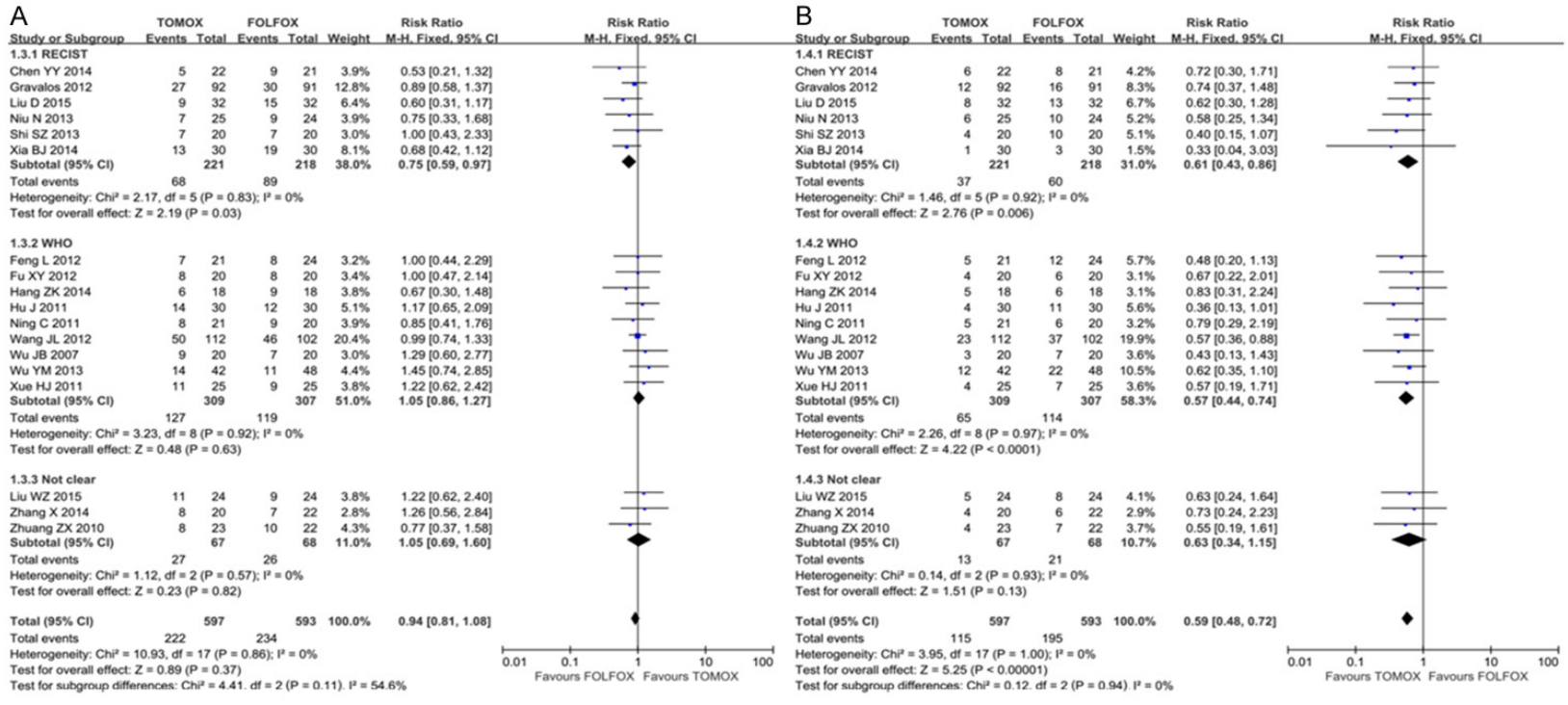

Figure 3. Forest plots representing the relative risk (RR) stratified by tumor response evaluation criteria for (A) stable disease (SD) or (B) progressive disease (PD).

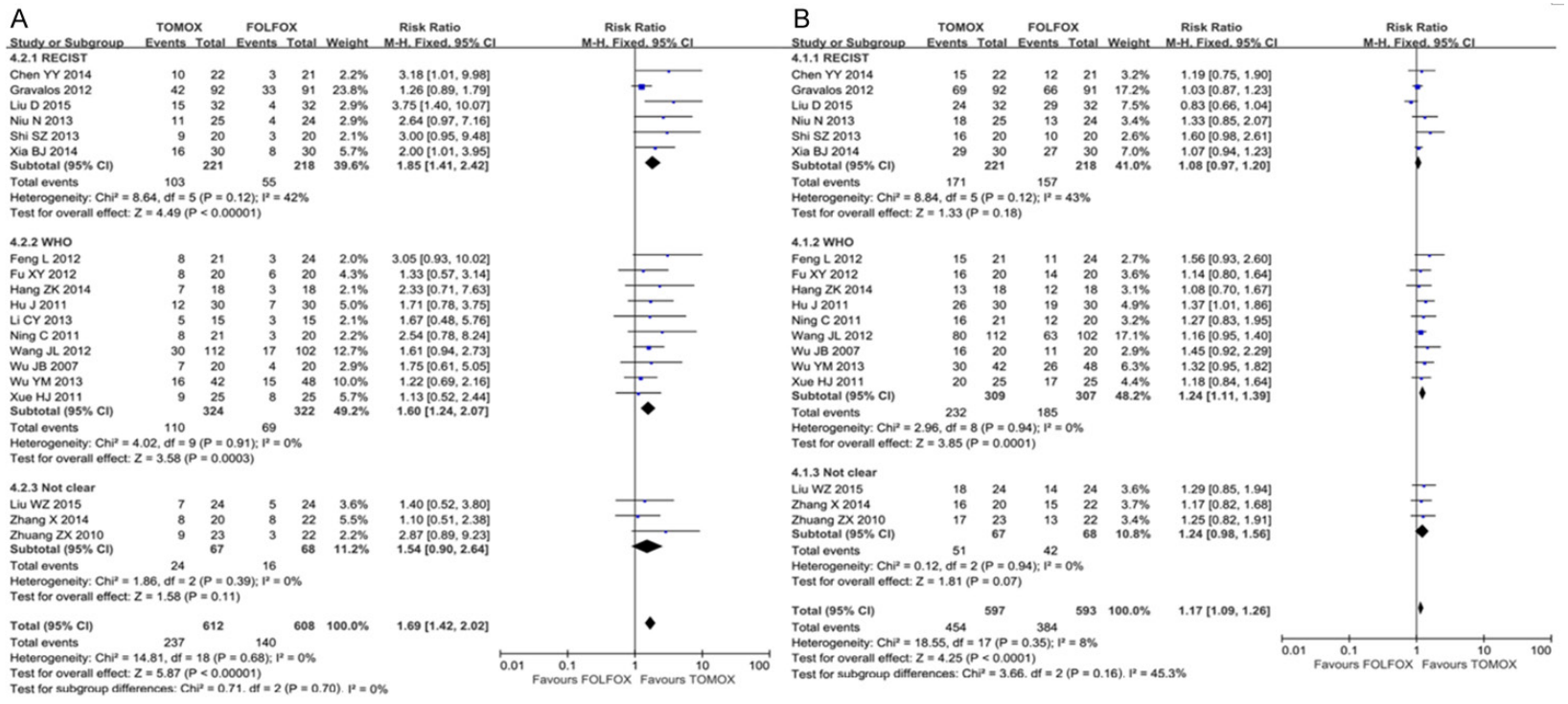

Figure 4. Forest plots representing the relative risk (RR) stratified by tumor response evaluation criteria for (A) overall response rate (ORR) or (B) disease control rate (DCR).

Table 2. Comparison of grade 1-2 toxicities in TOMOX and FOLFOX group

Toxicities	No. of study	TOMOX Events/Total	FOLFOX Events/Total	RR (95% CI)	*P* values	Heterogeneity I^2
Neutropenia	13	157/398 (39.4%)	145/396 (36.6%)	1.08 (0.90-1.29)	0.40	37%
Nausea/vomiting	13	141/398 (35.4%)	203/396 (51.3%)	0.69 (0.58-0.81)	<0.0001	0%
Diarrhea	11	80/359 (22.3%)	107/357 (30.0%)	0.75 (0.59-0.96)	0.02	0%
Anemia	8	78/271 (28.8%)	63/258 (24.4%)	1.17 (0.88-1.56)	0.27	0%
Thrombocytopenia	9	87/304 (28.6%)	77/300 (25.7%)	1.12 (0.87-1.44)	0.39	0%
Neurotoxicity	12	111/378 (29.4%)	133/376 (35.4%)	0.83 (0.68-1.02)	0.08	0%
Asthenia	7	90/272 (33.1%)	95/268 (35.4%)	0.92 (0.73-1.16)	0.48	0%
Hepatic disorders	13	141/398 (35.4%)	96/396 (24.2%)	1.44 (1.16-1.78)	0.0009	1%
Mucositis	3	4/61 (6.6%)	13/60 (21.7%)	0.30 (0.11-0.87)	0.03	0%
Alopecia	7	19/263 (7.2%)	37/263 (14.1%)	0.55 (0.36-0.84)	0.006	0%
Phlebitis	2	0/36 (0%)	16/35 (45.7%)	0.06 (0.01-0.41)	0.004	0%

Table 3. Comparison of grade 3-4 toxicities in TOMOX and FOLFOX group

Toxicities	No. of study	TOMOX Events/Total	FOLFOX Events/Total	RR (95% CI)	*P* values	Heterogeneity I^2
Neutropenia	14	57/490 (11.6%)	54/487 (11.1%)	1.23 (0.50-3.01)	0.66	70%
Nausea/vomiting	14	11/490 (2.2%)	37/487 (7.6%)	0.34 (0.19-0.63)	0.0006	0%
Diarrhea	12	13/451 (2.9%)	12/448 (2.7%)	1.09 (0.54-2.20)	0.82	0%
Anemia	8	11/271 (4.1%)	12/258 (4.7%)	0.87 (0.40-1.88)	0.73	0%
Thrombocytopenia	10	26/396 (6.6%)	30/391 (7.7%)	0.86 (0.52-1.42)	0.55	4%
Neurotoxicity	13	10/470 (2.1%)	22/467 (4.7%)	0.50 (0.25-1.01)	0.05	0%
Asthenia	8	28/364 (7.7%)	22/359 (6.1%)	1.32 (0.78-2.22)	0.30	0%
Hepatic disorders	14	30/490 (6.1%)	21/487 (4.3%)	1.43 (0.86-2.38)	0.17	8%
Mucositis	3	0/61 (0%)	0/60 (0%)	Not estimable	----	Not applicable
Alopecia	7	0/263 (0%)	0/263 (0%)	Not estimable	----	Not applicable
Phlebitis	2	0/36 (0%)	0/35 (0%)	Not estimable	----	Not applicable

CR, PR, and SD, was analyzed using eighteen trials and. The observed RR value was 1.17, 95% CI: 1.09-1.26, and *P*<0.0001. The TOMOX group showed better and statistically significant DCR than the FOLFOX group. Here, we observed a low degree of heterogeneity (I^2= 26%) as seen in **Figure 4B**.

Analysis of progression free survival and overall survival

The median progression-free survival (PFS)/time to progression (TTP) and overall survival (OS) were reported in 11 and 6 studies, respectively. The range of median PFS/TTP was 7.5 months to 11.0 months in the TOMOX group, while 4.2 months to 9.0 months in the FOLFOX group. Similarly, the median OS ranged between 9.8-15.7 months for TOMOX group patients and 8.1-17.2 months for FOLFOX group patients. We could not perform a pooled analysis due to the limited availability of complete data, which restricted our study to only a descriptive analysis about these two outcomes. One randomized Phase-II study showed no statistically significant difference in PFS (7.7 vs. 8.7 months, *P*=0.292) and OS (15.6 vs. 17.2 months, *P*= 0.475) between the TOMOX arm and FOLFOX arm [23]. The other two studies also showed no significant differences in OS between the two arms [37, 38]. However, other remaining trials showed a significantly longer PFS/TTP (10 trials) and OS (3 trials) in TOMOX group patients than FOLFOX group.

Toxicity analysis

The patients receiving FOLFOX regimen sustained significantly greater grade 1-2 toxicities, like occurrence of nausea/vomiting (RR=0.69,

95% CI: 0.58-0.81, *P*<0.0001), diarrhea (RR= 0.75, 95% CI: 0.59-0.96, *P*=0.02), mucositis (RR=0.30, 95% CI: 0.11-0.87, *P*=0.03), alopecia (RR=0.55, 95% CI: 0.36-0.84, *P*=0.006), and phlebitis (RR 0.06, 95% CI: 0.01-0.41, *P*=0.004). In contrast, the TOMOX group patients had increased frequency of hepatic disorders (RR=1.44, 95% CI: 1.16-1.78, *P*=0.0009). These data are described in **Table 2**. Furthermore, the analysis of grade 3-4 toxicities revealed that FOLFOX group patients had significantly higher nausea/vomiting rate (RR= 0.34, 95% CI: 0.19-0.63, *P*=0.0006) than that of the TOMOX group as shown in **Table 3**. No other toxicities had any statistically significant differences between the TOMOX and the FOLFOX group patients.

Subgroup analysis

The subgroup analysis for the treatment response was performed based on two different response evaluation criteria about tumors. The evaluation based on RECIST involved data from 6 studies, while evaluation with WHO criterion had 10 studies. The other 3 studies did not have clear information about these criteria. Based on the RECIST subgroup analysis, it was observed that patients in the TOMOX arm had significantly higher ORR (RR=1.85, 95% CI: 1.41-2.42, *P*<0.00001), PR (RR=1.95, 95% CI: 1.46-2.62, *P*<0.00001), and lower PD (RR= 0.61, 95% CI: 0.43-0.86, *P*=0.006), while the rate of SD was increased in the FOLFOX arm (RR=0.75, 95% CI: 0.59-0.97, *P*=0.03). Similarly, WHO subgroup analysis also revealed that patients with TOMOX treatment had significantly higher ORR (RR=1.60, 95% CI: 1.24-2.07, *P*=0.0003), DCR (RR=1.24, 95% CI: 1.11-1.39, *P*=0.0001), PR (RR=1.56, 95% CI: 1.18-2.05, *P*=0.002), and lower PD (RR=0.57, 95% CI: 0.44-0.74, *P*<0.0001). All these data have been shown in **Figures 2**-**4**. No statistical differences were observed for other efficacy outcomes between the two regimens.

Assessment of publication bias

We performed the funnel plot analysis for each of our outcomes and observed no noticeable asymmetry, as seen in **Figure 5**. Therefore, these plots suggested that there is no significant publication bias about these outcomes in the included trials.

Discussion

This meta-analysis involving 1220 patients from 19 RCTs found that TOMOX regimen had better ORR and DCR compared with FOLFOX regimen. In contrast, a recent meta-analysis based on 5 studies and comparing single raltitrexed regimen with LV5FU2 concluded equivalent response rate for overall survival and disease control rate between the two regimens [39]. This study suggested that combination of raltitrexed with other regimen results in differential efficacy.

Oxaliplatin is a third-generation platinum derivative with a unique mechanism of action, and has been proved to have a synergistic cytotoxic effect when combined with thymidylate synthase inhibitors, such as fluorouracil [40]. Of note, raltitrexed and oxaliplatin have different mechanisms of action and toxicity profiles. The schedule of raltitrexed combined with oxaplatin (TOMOX) in the treatment of advanced colorectal cancer has been explored in two phase II studies showing an ORR, median PFS, and median OS of 50%, 6.5 months, >9 months and 54%, 6.2 months, 14.6 months, respectively [10, 11]. The main hematological and non-hematological toxicities were of grade III/IV neutropenia (17% and 30%) and liver function test abnormalities (17% and 34%), respectively. This study also confirmed the feasibility of the TOMOX regimen and its activity in advanced colorectal cancer patients. Similarly, in our analysis raltitrexed plus oxaliplatin combination (TOMOX) also showed a significantly higher ORR (38.7% vs. 23.0%) and DCR (76.0% vs. 64.8%) as compared to FOLFOX regimen. The range of median PFS/TTP was 7.5 months to 11.0 months in the TOMOX group, while 4.2 months to 9.0 months in the FOLFOX group. The median OS of the two groups ranged between 9.8-15.7 months and 8.1-17.2 months, respectively. Therefore, based on these observations, it would be sufficed to conclude that the schedule of TOMOX is feasible and effective in patients with advanced colorectal cancer.

With regard to toxicities, previous studies have reported that the most common toxicities associated with raltitrexed regimens were elevated transaminase levels, anemia, and asthenia [41-43]. The analysis of grade 1-2 toxicities in our meta-analysis revealed significantly higher inci-

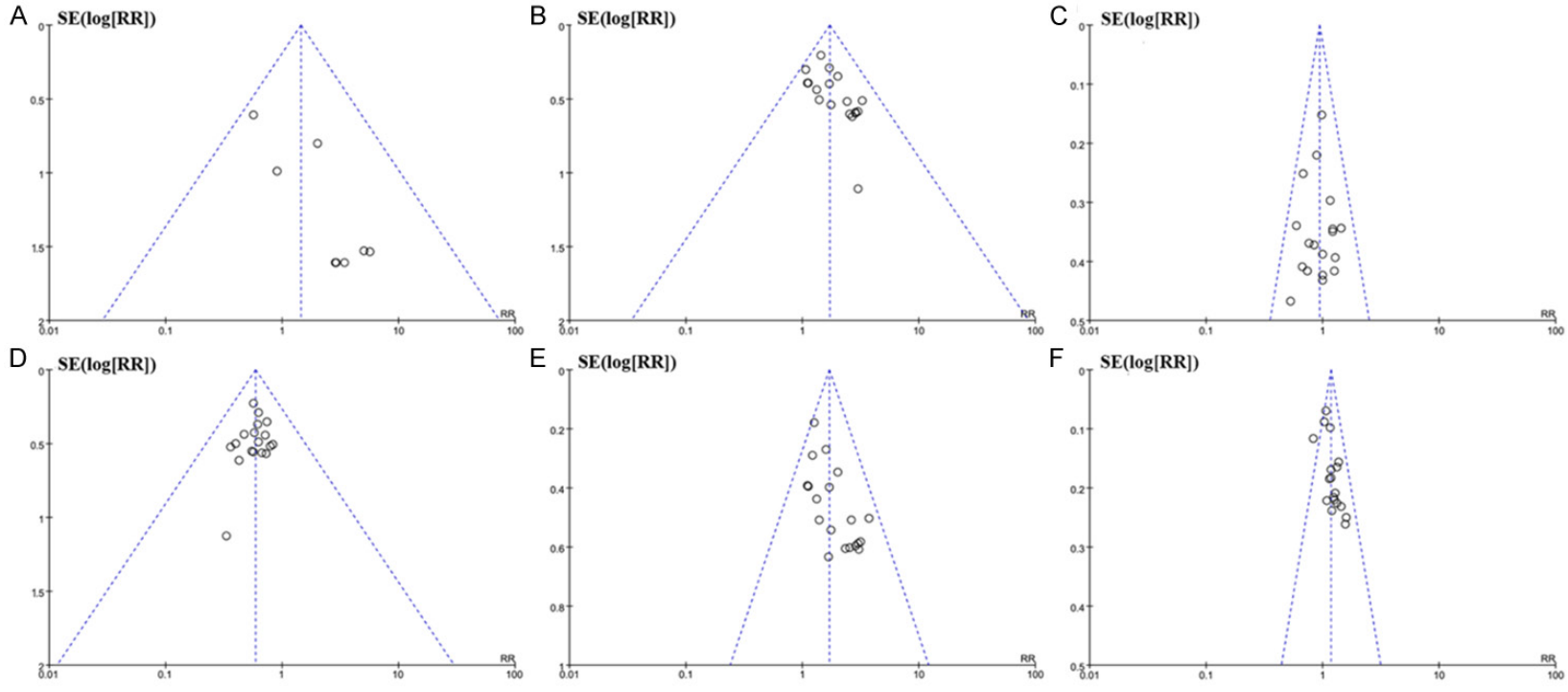

Figure 5. Funnel plots of (A) complete response (CR), (B) partial response (PR), (C) stable disease (SD), (D) progressive disease (PD), (E) overall response rate (ORR), and (F) disease control rate (DCR). RR = relative risk, SE = standard error.

dence of hepatic disorders in the TOMOX group, while nausea/vomiting, diarrhea, mucositis, alopecia, and phlebitis occurred more frequently in the FOLFOX group. The most common grade 1-2 adverse effect was neutropenia in the TOMOX group, but the difference did not reach statistical significance when compared with the FOLFOX group. Within grade 3-4 toxicities, frequency of nausea/vomiting was significantly higher in the FOLFOX group than the TOMOX group. Although neutropenia, asthenia, thrombocytopenia, and hepatic disorders occurred commonly in both groups, there were no significant differences.

TOMOX regimen has been observed to be associated with a statistically significant higher incidence of grade 1-2 hepatic disorders, though these can be predicted, diagnosed, and treated. The predictive factors of hepatotoxicity in TOMOX regimen were elevated baseline transminase levels, raltitrexed cumulative dose combined with oxaliplatin, chemotherapy cycles, and un-extended intervals between courses [44]. In addition, one of the included studies reported two treatment-related deaths in the FOLFOX group (one because of neutropenic sepsis, the other one due to pancitopenia plus septic shock) and one in the TOMOX group (because of septic shock) [23]. Treatment-related mortality has been a bottleneck issue for widespread application of raltitrexed since the PETACC-1 trial was stopped early because of 17 drug-related deaths (1.9%) in the raltitrexed (RTX) arm. However, 11 of the 17 RTX-related deaths were found to be due to serious protocol deviation (creatinine clearance was not measured or RTX dose was not modified based on creatinine clearance) [43]. If these patients were excluded, then the overall mortality was not significantly different between the RTX arm (1%) and the 5-FU/FA arm (0.9%). Therefore, evaluating renal function before each and every cycle, dosage adjustment in the presence of renal impairment, and monitoring closely with prompt treatment for toxicities could make the raltitrexed treatment safer [45].

Another point that needs attention is the importance of raltitrexed for the treatment of patients with heart disease or for those who have developed cardiotoxicity with 5-Fu chemotherapy. A systematic review has indicated that the overall incidence of cardiotoxicity associated with 5-Fu varied between 0.55% and 19% (mean: 5.0%, median: 3.85%) [46]. However, no literature has reported cases of cardiotoxicity associated with raltitrexed. In fact, one retrospective systematic review [46] has shown that a total of 111 patients with gastrointestinal cancer and heart disease history or 5-Fu/capecitabine-related cardiotoxicity showed a favorable incidence of cardiac events (4.5%) when receiving raltitrexed treatment. Besides, the ARCTIC study reported that 42 patients initially treated with 5-Fu/capecitabine-based chemotherapy experienced cardiac toxicity. When they were then switched to the raltitrexed-based chemotherapy schedule, it was observed that no further cardiac events occurred [16]. Altogether, these studies suggest that raltitrexed could be a safe treatment option for advanced colorectal patients with cardiovascular risk factors or prior cardiac events caused by 5-Fu/capecitabine-based chemotherapy.

The FOLFOX group in our analysis also showed a remarkably high incidence (45.7%) of phlebitis caused by central venous catheter. Compared with prolonged 5-Fu infusion regimens, the convenient bolus 3-weekly schedules of raltitrexed avoided some of these complications such as catheter-related thrombosis and phlebitis [47]. A patient preference study conducted by Young *et al.* showed that 91% of the patients with advanced colorectal cancer selected raltitrexed to be their preferred regimen compared with 6% for Mayo regimen, based on the administration schedule and/or side-effect attributes [47]. Thus, raltitrexed can be a reasonable, and possibly better-tolerated, chemotherapeutic drug for advanced colorectal cancer patients who are unable to receive 5-Fu/capecitabine-based chemotherapy.

The overall efficacy and tolerability appeared to be better for the TOMOX regimen than the FOLFOX based on our meta-analysis data. Raltitrexed can be an agent of choice in the adjuvant phase in patients with contraindications to 5-Fu/capecitabine-based chemotherapy, such as those who suffer from heart disease or who have experienced 5-Fu/capecitabine-related cardiotoxicity. Importantly, renal function should be monitored during treatment with TOMOX and dosage should be adjusted accordingly to avoid severe toxicities. Moreover, the convenience of a 3-weekly schedule

for raltitrexed was accepted more easily by patients than the prolonged infusion required for 5-Fu.

Our meta-analysis study has several strengths. Our team performed a comprehensive search of the topic along with strict quality assessment. All of the included trials were prospective and randomized, which reduces selection bias and confounding. To our knowledge, this analysis including and analyzing 19 different RCTs is the largest analysis contrasting TOMOX to FOLFOX as first-line chemotherapy in the treatment of patients with advanced colorectal cancer. An earlier systematic review including 12 studies about raltitrexed-based first-line chemotherapy has also suggested that TOMOX and TOMIRI are effective, safe, and easy to administer for patients with metastatic colorectal cancer, but this study only included two randomized studies and 10 prospective single-arm trials, which resulted in a low level of evidence [5].

Nonetheless, there were several other limitations in this meta-analysis. Only less than half of the included trials reported median PFS/TTP or OS. Even when our team tried to contact the authors, we failed to get sufficient data to further analyze long-term outcomes, hence we only conducted a descriptive analysis. It should also be noted that a majority of the trials were carried out in Asia, what limits the generalizability of our analysis of toxicities. In addition, the dosage of chemotherapy was not consistent throughout, which makes it challenging to recommend a specific dosage based on our findings.

Our meta-analysis concluded that TOMOX regimen is an effective and tolerable chemotherapy option for advanced colorectal cancer patients, particularly for those who cannot tolerate 5-Fu/capecitabine-based regimens.

Acknowledgements

We acknowledge the work of polishing this manuscript by Medjaden Bioscience Limited.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Chunlin Zhao, Department of Gastrointestinal Surgery, The First Affiliated Hospital of Zhengzhou University, No. 1 East Jianshe Road, Erqi District, Zhengzhou 450052, Henan Province, China. Tel: +86 18339206109; E-mail: doctorzhaochunlin@126.com

References

[1] Siegel R, Naishadham D and Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013; 63: 11-30.

[2] Avallone A, Di Gennaro E, Silvestro L, Iaffaioli VR and Budillon A. Targeting thymidylate synthase in colorectal cancer: critical re-evaluation and emerging therapeutic role of raltitrexed. Expert Opin Drug Saf 2014; 13: 113-129.

[3] Engstrom PF, Arnoletti JP, Benson AB 3rd, Chen YJ, Choti MA, Cooper HS, Covey A, Dilawari RA, Early DS, Enzinger PC, Fakih MG, Fleshman J Jr, Fuchs C, Grem JL, Kiel K, Knol JA, Leong LA, Lin E, Mulcahy MF, Rao S, Ryan DP, Saltz L, Shibata D, Skibber JM, Sofocleous C, Thomas J, Venook AP, Willett C; National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: colon cancer. J Natl Compr Canc Netw 2009; 7: 778-831.

[4] Engstrom PF, Arnoletti JP, Benson AB 3rd, Chen YJ, Choti MA, Cooper HS, Covey A, Dilawari RA, Early DS, Enzinger PC, Fakih MG, Fleshman J Jr, Fuchs C, Grem JL, Kiel K, Knol JA, Leong LA, Lin E, Mulcahy MF, Rao S, Ryan DP, Saltz L, Shibata D, Skibber JM, Sofocleous C, Thomas J, Venook AP, Willett C; National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: rectal cancer. J Natl Compr Canc Netw 2009; 7: 838-881.

[5] Barni S, Ghidini A, Coinu A, Borgonovo K and Petrelli F. A systematic review of raltitrexed-based first-line chemotherapy in advanced colorectal cancer. Anticancer Drugs 2014; 25: 1122-1128.

[6] Omura K. Clinical implications of dihydropyrimidine dehydrogenase (DPD) activity in 5-FU-based chemotherapy: mutations in the DPD gene, and DPD inhibitory fluoropyrimidines. Int J Clin Oncol 2003; 8: 132-138.

[7] Zalcberg JR, Cunningham D, Van Cutsem E, Francois E, Schornagel J, Adenis A, Green M, Iveson A, Azab M and Seymour I. ZD1694: A novel thymidylate synthase inhibitor with substantial activity in the treatment of patients with advanced colorectal cancer. Tomudex Colorectal Study Group. J Clin Oncol 1996; 14: 716-721.

[8] Farrugia DC, Ford HE, Cunningham D, Danenberg KD, Danenberg PV, Brabender J, McVicar AD, Aherne GW, Hardcastle A, McCarthy K and Jackman AL. Thymidylate synthase expression in advanced colorectal cancer predicts for re-

sponse to raltitrexed. Clin Cancer Res 2003; 9: 792-801.
[9] Cunningham D, Zalcberg JR, Rath U, Olver I, Van Cutsem E, Svensson C, Seitz JF, Harper P, Kerr D, Perez-Manga G and et al. 'Tomudex' (ZD1694): results of a randomised trial in advanced colorectal cancer demonstrate efficacy and reduced mucositis and leucopenia. The 'Tomudex' Colorectal Cancer Study Group. Eur J Cancer 1995; 31A: 1945-1954.
[10] Cascinu S, Graziano F, Ferrau F, Catalano V, Massacesi C, Santini D, Silva RR, Barni S, Zaniboni A, Battelli N, Siena S, Giordani P, Mari D, Baldelli AM, Antognoli S, Maisano R, Priolo D, Pessi MA, Tonini G, Rota S and Labianca R. Raltitrexed plus oxaliplatin (TOMOX) as first-line chemotherapy for metastatic colorectal cancer. A phase II study of the Italian Group for the Study of Gastrointestinal Tract Carcinomas (GISCAD). Ann Oncol 2002; 13: 716-720.
[11] Seitz JF, Bennouna J, Paillot B, Gamelin E, Francois E, Conroy T, Raoul JL, Becouarn Y, Bertheault-Cvitkovic F, Ychou M, Nasca S, Fandi A, Barthelemy P and Douillard JY. Multicenter non-randomized phase II study of raltitrexed (Tomudex) and oxaliplatin in non-pretreated metastatic colorectal cancer patients. Ann Oncol 2002; 13: 1072-1079.
[12] Scheithauer W, Kornek GV, Ulrich-Pur H, Penz M, Raderer M, Salek T, Haider K, Kwasny W and Depisch D. Oxaliplatin plus raltitrexed in patients with advanced colorectal carcinoma: results of a Phase I-II trial. Cancer 2001; 91: 1264-1271.
[13] Scheithauer W, Kornek GV, Schuell B, Ulrich-Pur H, Penz M, Raderer M, Lang F, Schneeweiss B, Lenauer A and Depisch D. Second-line treatment with oxaliplatin + raltitrexed in patients with advanced colorectal cancer failing fluoropyrimidine/leucovorin-based chemotherapy. Ann Oncol 2001; 12: 709-714.
[14] Neri B, Doni L, Fulignati C, Perfetto F, Turrini M, Andreoli F, Pantalone D, Pernice LM, Taruffi F, Martini V, Poma A, Valeri A, Bacci G, Sancez L and Moretti R. Raltitrexed plus oxaliplatin as first-line chemotherapy in metastatic colorectal carcinoma: a multicentric phase II trial. Anticancer Drugs 2002; 13: 719-724.
[15] Carnaghi C, Rimassa L, Garassino I, Zucali PA, Masci G, Fallini M, Morenghi E and Santoro A. Irinotecan and raltitrexed: an active combination in advanced colorectal cancer. Ann Oncol 2002; 13: 1424-1429.
[16] Ransom D, Wilson K, Fournier M, Simes RJ, Gebski V, Yip D, Tebbutt N, Karapetis CS, Ferry D, Gordon S and Price TJ. Final results of Australasian Gastrointestinal Trials Group ARCTIC study: an audit of raltitrexed for patients with cardiac toxicity induced by fluoropyrimidines. Ann Oncol 2014; 25: 117-121.
[17] Moher D, Liberati A, Tetzlaff J, Altman DG; PRASMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010; 8: 336-341.
[18] Clarke M and Horton R. Bringing it all together: Lancet-Cochrane collaborate on systematic reviews. Lancet 2001; 357: 1728.
[19] DerSimonian R and Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-188.
[20] Chen YY, Liao JT and Wu J. Application research of raltitrexed and oxaliplatin in treatment of elderly patients with advanced colorectal cancer. China Modern Medicine 2014; 2: 78-82.
[21] Feng L. Clinical effect observation of raltitrexed plus oxaliplatin in treatment of advanced colorectal carcinoma. Clinical Misdiagnosis & Mistherapy 2012; 25: 43-46.
[22] Fu XY, Zhang HW, Li CL, Cui Y, Yang HM and Xiao Y. Raltitrexed combined with oxaliplatin in the treatment of advanced colorectal cancer. Journal of Clinical Medicine in Practice 2012; 16: 88-90.
[23] Gravalos C, Salut A, Garcia-Gircon C, Garcia-Carbonero R, Leon AI, Sevilla I, Maurel J, Esteban B, Garcia-Rico E, Murias A, Cortes-Funes H. A randomized phase II study to compare oxaliplatin plus 5-fluorouracil and leucovorin (FOLFOX4) versus oxaliplatin plus raltitrexed (TOMOX) as first-line chemotherapy for advanced colorectal cancer. Clin Translat Oncol 2012; 14: 606-612.
[24] Hang ZK. Effectiveness discussion of raltitrexed combined with oxaliplatin in the treatment of advanced colorectal cancer. China Modern Medcine 2014; 21: 75-76.
[25] Hu J, Wei YM, Wang YH, Wan XA, Hu Q and Ding HB. The application value of raltitreedd in the treatment of advanced colorectal cancer. Jilin Medicine 2011; 34.
[26] Li CY and Huang CX. Effacacy observation of raltitrexed combined with oxaliplatin in the treatment of advanced colorectal cancer. Zhejiang Clinical Medical Journal 2013; 15: 1112-1114.
[27] Liu D. Effect raltitrexed and oxaliplatin treatment of elderly patients with advanced colorectal cancer observed. China & Foreign Medical Treatment 2015; 119-120.
[28] Liu WZ, Li MK and Chen XM. Clinical research of raltitrexed combined with oxaliplatin in the treatment of colorectal liver metastases. Chin J Clinicians (Electronic Edition) 2015; 9: 146-148.
[29] Ning C, Wang Y and Wang ZG. Raltitrexed plus oxaliplatin in treatment of senile advanced colorectal carcinoma. Hainan Medical Journal 2011; 10: 61-63.

[30] Niu N, Wu R, Chen W and Zeng YC. Clinical efficacy of raltitrexed plus oxaliplatinl in treatment of senile advanced colorectal carcinoma. Journal of China Medical University 2013; 42: 682-685.

[31] Shi SZ, Fu J and Dong XY. Recent effacacy observation of raltitrexed combined with oxaliplatin in the treatment of advanced colorectal cancer. Contemporary Medicine 2013; 19: 143-144.

[32] Wang JL, Li J, Qin SK, Chen Y, Zhang QY, Liu TS, Yang CK, Ye ZB, Xu N and Zheng LZ. Randomized multicenter phase III trial of oxaliplatin plus raltitrexed versus oxaliplatin plus fluorouraeil and leucovorin for advanced colorectal cancel. Chinese Clinical Oncology 2012; 17: 6-11.

[33] Wu JB, Wang HJ, Wang SJ, Li L and Feng L. Clinical efficacy comparison of raltitrexed plus oxaliplatinl and 5-fluorouracil/leucovorin plus oxaliplatin in treatment of advanced colorectal carcinoma. Cancer Research on Prevention and Treatment 2007; 34: 711-713.

[34] Wu YM. Clinical efficacy comparison of raltitrexed combined oxaliplatinl and 5-fluorouracil/leucovorin combined oxaliplatin in treatment of advanced colorectal carcinoma. Chin J Postgrad Med 2013; 24: 38-40.

[35] Xia BJ, Zhang FL and Ren W. Clinical observation of raltitrexed combined with oxaliplatin in the treatment of advanced colorectal cancer. Medical Information 2014; 27: 259.

[36] Xue HJ, Fan JQ, Cao RB, Zhu F and Yao J. Raltitrexed versus fluorouracil/leucovorin combined with oxaliplatin for advanced colorectal cancer: a prospective study. Chin J Postgrad Med 2011; 4: 7-10.

[37] Zhang X and Yin Y. Raltitrexed therapeutic efficacy of elderly patients with advanced colorectal cancer. Medcine and Philosophy 2014; 35: 23-24+59.

[38] Zhuang ZX, Shen XD, Shen LQ, Zhang YS, Lu YF and Chu X. Comparison of aaltitrexed plus oxaliplatin and 5-fluorouracil/leucovorin plus oxaliplatin in treatment of advanced colorectal carcinoma. Suzhou University Journal of Medical Science 2010; 30: 573-576+607.

[39] Liu Y, Wu W, Hong W, Sun X, Wu J and Huang Q. Raltitrexed-based chemotherapy for advanced colorectal cancer. Clin Res Hepatol Gastroenterol 2014; 38: 219-225.

[40] Raymond E, Chaney SG, Taamma A and Cvitkovic E. Oxaliplatin: a review of preclinical and clinical studies. Ann Oncol 1998; 9: 1053-1071.

[41] Cunningham D, Zalcberg JR, Rath U, Oliver I, van Cutsem E, Svensson C, Seitz JF, Harper P, Kerr D and Perez-Manga G. Final results of a randomised trial comparing 'Tomudex' (raltitrexed) with 5-fluorouracil plus leucovorin in advanced colorectal cancer. "Tomudex" Colorectal Cancer Study Group. Ann Oncol 1996; 7: 961-965.

[42] Cocconi G, Cunningham D, Van Cutsem E, Francois E, Gustavsson B, van Hazel G, Kerr D, Possinger K and Hietschold SM. Open, randomized, multicenter trial of raltitrexed versus fluorouracil plus high-dose leucovorin in patients with advanced colorectal cancer. Tomudex Colorectal Cancer Study Group. J Clin Oncol 1998; 16: 2943-2952.

[43] Popov I, Carrato A, Sobrero A, Vincent M, Kerr D, Labianca R, Raffaele Bianco A, El-Serafi M, Bedenne L, Paillot B, Mini E, Sanches E, Welch J, Collette L, Praet M and Wils J. Raltitrexed (Tomudex) versus standard leucovorin-modulated bolus 5-fluorouracil: Results from the randomised phase III Pan-European Trial in Adjuvant Colon Cancer 01 (PETACC-1). Eur J Cancer 2008; 44: 2204-2211.

[44] Massacesi C, Santini D, Rocchi MB, La Cesa A, Marcucci F, Vincenzi B, Delprete S, Tonini G and Bonsignori M. Raltitrexed-induced hepatotoxicity: multivariate analysis of predictive factors. Anticancer Drugs 2003; 14: 533-541.

[45] Cunningham D, Zalcberg J, Maroun J, James R, Clarke S, Maughan TS, Vincent M, Schulz J, Gonzalez Baron M and Facchini T. Efficacy, tolerability and management of raltitrexed (Tomudex) monotherapy in patients with advanced colorectal cancer. a review of phase II/III trials. Eur J Cancer 2002; 38: 478-486.

[46] Kelly C, Bhuva N, Harrison M, Buckley A and Saunders M. Use of raltitrexed as an alternative to 5-fluorouracil and capecitabine in cancer patients with cardiac history. Eur J Cancer 2013; 49: 2303-2310.

[47] Young A, Topham C, Moore J, Turner J, Wardle J, Downes M, Evans V and Kay S. A patient preference study comparing raltitrexed ('Tomudex') and bolus or infusional 5-fluorouracil regimens in advanced colorectal cancer: influence of side-effects and administration attributes. Eur J Cancer Care (Engl) 1999; 8: 154-161.