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

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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
Comparison of TOMOX with FOLFOX

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/m² every 3 weeks) with 425 mg/m² 5-Fu and 20 mg/m² 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
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 $\chi^2$ 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 ($\chi^2$ $P>0.10$ 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-
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 FLOFOX 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

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### Table 1. General characteristics of the included trials

<table>
<thead>
<tr>
<th>Study</th>
<th>n. (TOMOX/FOLFOX)</th>
<th>Treatment regimen</th>
<th>Response evaluation criteria</th>
<th>median PFS/TTP (months)</th>
<th>median OS (months)</th>
<th>n. of Lost follow-up</th>
<th>Jadad</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feng L2012 [21]</td>
<td>21/24</td>
<td>TOMOX/FOLFOX</td>
<td>WHO</td>
<td>8.6/5.3</td>
<td>10.8/9.4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Fu X 2012 [22]</td>
<td>20/20</td>
<td>TOMOX/FOLFOX</td>
<td>WHO</td>
<td>Not Available</td>
<td>Not Available</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Gravalos 2012 [23]</td>
<td>92/91</td>
<td>TOMOX/FOLFOX4</td>
<td>RECIDIST</td>
<td>7.7/8.7</td>
<td>15.7/17.2</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Hang ZK 2014 [24]</td>
<td>18/18</td>
<td>TOMOX/FOLFOX</td>
<td>WHO</td>
<td>Not Available</td>
<td>Not Available</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Hu J 2011 [25]</td>
<td>30/30</td>
<td>TOMOX/FOLFOX</td>
<td>WHO</td>
<td>7.5/5.2</td>
<td>Not Available</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Li CY 2013 [26]</td>
<td>15/15</td>
<td>TOMOX/mFOLFOX</td>
<td>WHO</td>
<td>8.2/4.9</td>
<td>Not Available</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Liu D 2015 [27]</td>
<td>32/32</td>
<td>TOMOX*/FOLFOX*</td>
<td>RECIDIST</td>
<td>8.3/4.2</td>
<td>9.8/8.2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Nin C 2011 [29]</td>
<td>21/20</td>
<td>TOMOX/FOLFOX</td>
<td>WHO</td>
<td>8.3/5.2</td>
<td>Not Available</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Shi SZ 2013 [31]</td>
<td>20/20</td>
<td>TOMOX/FOLFOX</td>
<td>WHO</td>
<td>Not Available</td>
<td>Not Available</td>
<td>0</td>
<td>2</td>
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<tr>
<td>Wu JB 2007 [33]</td>
<td>20/20</td>
<td>TOMOX/FOLFOX</td>
<td>WHO</td>
<td>7.8/5.0</td>
<td>Not Available</td>
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<td>4</td>
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<tr>
<td>Wu YM 2013 [34]</td>
<td>42/48</td>
<td>TOMOX/FOLFOX</td>
<td>WHO</td>
<td>Not Available</td>
<td>Not Available</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Xia BJ 2014 [35]</td>
<td>30/30</td>
<td>TOMOX/FOLFOX</td>
<td>WHO</td>
<td>Not Available</td>
<td>Not Available</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Zhang X 2014 [37]</td>
<td>20/22</td>
<td>TOMOX*/FOLFOX**</td>
<td>Not Available</td>
<td>7.5/5.2</td>
<td>14/13.3</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Zhuang ZX 2010 [38]</td>
<td>23/22</td>
<td>TOMOX/FOLFOX</td>
<td>Not Available</td>
<td>8.9/5.6</td>
<td>12.9/10.7</td>
<td>3</td>
<td>3</td>
</tr>
</tbody>
</table>

TOMOX: Tom: 3 mg/m2 (d1)+5-Fu bolus: 400 mg/m2 (d1)+5-Fu infusion: 3000 mg/m2 (d1) q3w, FOLFOX: 5-Fu: 375 mg/m2 (d1)+5-Fu: 200 mg/m2 (d1)+5-Fu: 130 mg/m2 (d1)+5-Fu: 375 mg/m2 (d1)+5-Fu: 200 mg/m2 (d1)+5-Fu: 100 mg/m2 (d1) q3w, FOLFOX*: LV: 200 mg/m2 (d1)+5-Fu: 130 mg/m2 (d1)+5-Fu: 100 mg/m2 (d1) q3w, mFOLFOX: LV: 200 mg/m2 (d1)+5-Fu: 130 mg/m2 (d1)+5-Fu: 100 mg/m2 (d1) q3w, FOLFOX**: LV: 200 mg/m2 (d1)+5-Fu: 130 mg/m2 (d1)+5-Fu: 100 mg/m2 (d1) q3w.
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).
Comparison of TOMOX with FOLFOX

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).
Comparison of TOMOX with FOLFOX

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 (Ι²=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,

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

<table>
<thead>
<tr>
<th>Toxicities</th>
<th>No. of study</th>
<th>TOMOX Events/Total</th>
<th>FOLFOX Events/Total</th>
<th>RR (95% CI)</th>
<th>P values</th>
<th>Heterogeneity Ι²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>13</td>
<td>157/398 (39.4%)</td>
<td>145/396 (36.6%)</td>
<td>1.08 (0.90-1.29)</td>
<td>0.40</td>
<td>37%</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>13</td>
<td>141/398 (35.4%)</td>
<td>203/396 (51.3%)</td>
<td>0.69 (0.58-0.81)</td>
<td>&lt;0.0001</td>
<td>0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>11</td>
<td>80/359 (22.3%)</td>
<td>107/357 (30.0%)</td>
<td>0.75 (0.59-0.96)</td>
<td>0.02</td>
<td>0%</td>
</tr>
<tr>
<td>Anemia</td>
<td>8</td>
<td>78/271 (28.8%)</td>
<td>63/258 (24.4%)</td>
<td>1.17 (0.88-1.56)</td>
<td>0.27</td>
<td>0%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>9</td>
<td>87/304 (28.6%)</td>
<td>77/300 (25.7%)</td>
<td>1.12 (0.87-1.44)</td>
<td>0.39</td>
<td>0%</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>12</td>
<td>111/378 (29.4%)</td>
<td>133/376 (35.4%)</td>
<td>0.83 (0.68-1.02)</td>
<td>0.08</td>
<td>0%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>7</td>
<td>90/272 (33.1%)</td>
<td>95/268 (35.4%)</td>
<td>0.92 (0.73-1.16)</td>
<td>0.48</td>
<td>0%</td>
</tr>
<tr>
<td>Hepatic disorders</td>
<td>13</td>
<td>141/398 (35.4%)</td>
<td>96/396 (24.2%)</td>
<td>1.44 (1.16-1.78)</td>
<td>0.0009</td>
<td>1%</td>
</tr>
<tr>
<td>Mucositis</td>
<td>3</td>
<td>4/61 (6.6%)</td>
<td>13/60 (21.7%)</td>
<td>0.30 (0.11-0.87)</td>
<td>0.03</td>
<td>0%</td>
</tr>
<tr>
<td>Alopecia</td>
<td>7</td>
<td>19/263 (7.2%)</td>
<td>37/263 (14.1%)</td>
<td>0.55 (0.36-0.84)</td>
<td>0.006</td>
<td>0%</td>
</tr>
<tr>
<td>Phlebitis</td>
<td>2</td>
<td>0/36 (0%)</td>
<td>16/35 (45.7%)</td>
<td>0.06 (0.01-0.41)</td>
<td>0.004</td>
<td>0%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Toxicities</th>
<th>No. of study</th>
<th>TOMOX Events/Total</th>
<th>FOLFOX Events/Total</th>
<th>RR (95% CI)</th>
<th>P values</th>
<th>Heterogeneity Ι²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>14</td>
<td>57/490 (11.6%)</td>
<td>54/487 (11.1%)</td>
<td>1.23 (0.50-3.01)</td>
<td>0.66</td>
<td>70%</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>14</td>
<td>11/490 (2.2%)</td>
<td>37/487 (7.6%)</td>
<td>0.34 (0.19-0.63)</td>
<td>0.0006</td>
<td>0%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>12</td>
<td>13/451 (2.9%)</td>
<td>12/448 (2.7%)</td>
<td>1.09 (0.54-2.20)</td>
<td>0.82</td>
<td>0%</td>
</tr>
<tr>
<td>Anemia</td>
<td>8</td>
<td>11/271 (4.1%)</td>
<td>12/258 (4.7%)</td>
<td>0.87 (0.40-1.88)</td>
<td>0.73</td>
<td>0%</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10</td>
<td>26/396 (6.6%)</td>
<td>30/391 (7.7%)</td>
<td>0.86 (0.52-1.42)</td>
<td>0.55</td>
<td>4%</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>13</td>
<td>10/470 (2.1%)</td>
<td>22/467 (4.7%)</td>
<td>0.50 (0.25-1.01)</td>
<td>0.05</td>
<td>0%</td>
</tr>
<tr>
<td>Asthenia</td>
<td>8</td>
<td>28/364 (7.7%)</td>
<td>22/359 (6.1%)</td>
<td>1.32 (0.78-2.22)</td>
<td>0.30</td>
<td>0%</td>
</tr>
<tr>
<td>Hepatic disorders</td>
<td>14</td>
<td>30/490 (6.1%)</td>
<td>21/487 (4.3%)</td>
<td>1.43 (0.86-2.38)</td>
<td>0.17</td>
<td>8%</td>
</tr>
<tr>
<td>Mucositis</td>
<td>3</td>
<td>0/61 (0%)</td>
<td>0/60 (0%)</td>
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<td>—</td>
<td>Not applicable</td>
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<tr>
<td>Alopecia</td>
<td>7</td>
<td>0/263 (0%)</td>
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<td>—</td>
<td>Not applicable</td>
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<tr>
<td>Phlebitis</td>
<td>2</td>
<td>0/36 (0%)</td>
<td>0/35 (0%)</td>
<td>Not estimable</td>
<td>—</td>
<td>Not applicable</td>
</tr>
</tbody>
</table>
Comparison of TOMOX with FOLFOX

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-
Comparison of TOMOX with FOLFOX

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.
Comparison of TOMOX with FOLFOX

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 transaminase 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.

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Disclosure of conflict of interest

None.

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