Biweekly CAPOX versus Triweekly CAPOX in the adjuvant therapy of post-surgery CRC: a randomized controlled trial

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Research Article

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Abstract

**Background:** Adjuvant CAPOX (capecitabine plus oxaliplatin) provided significant disease-free survival (DFS) benefit in patients with high-risk stage II or stage III colorectal cancer (CRC). Conventional triweekly CAPOX results in 14-38% 3-4 grade hematological toxicity. Modified biweekly CAPOX was observed to be generally well-tolerated in previous studies.

**Methods:** High-risk stage II and stage III post-surgery CRC patients were randomized in the control triweekly group (intravenous infusion of oxaliplatin 130 mg/m² on day 1 and oral capecitabine 1000 mg/m², twice daily from d1 to d14) and the experimental biweekly group (intravenous infusion of oxaliplatin 85 mg/m² on day 1 and oral capecitabine 1000 mg/m², twice daily from d1 to d10). The primary endpoint was incidence of thrombocytopenia. The secondary endpoint was 18-month DFS rate.

**Results:** Between Jul 25, 2018, and May 14, 2021, 160 patients were 1:1 randomly enrolled and received treatment. The primary endpoint thrombocytopenia occurred 33% and 49% in biweekly and triweekly group (P=0.02). The second endpoint 18-month DFS in 3-month group was 94.1% in biweekly CAPOX group, and 93.8% in triweekly CPOX group (P=0.96). Neutropenia was 36% and 51% in biweekly and triweekly group, respectively (P=0.04). The rate of uncomplete therapy patient was 7% and 15% in biweekly and triweekly group, respectively (P=0.13).

**Conclusion:** Biweekly CAPOX presented significant less thrombocytopenia and neutropenia than triweekly CAPOX regimen. And biweekly CAPOX did not affect the 18-month DFS rate.

**Clinical trial registration:** First registration date: 21/06/2018. ClinicalTials.gov (NCT03564912).

Introduction

Colorectal cancer (CRC) was estimated to be the fourth most common cancer and the second leading cause of cancer deaths worldwide(1). A large proportion of CRC patients are diagnosed in advanced stage cause no warning symptoms(2). Surgery remains the foundation of curative treatment, and perioperative chemotherapy, especially postoperative adjuvant chemotherapy plays particularly important role. To improve overall and disease-free survival, adjuvant chemotherapy is widely applied in high-risk stage II and stage III CRC patients.

Since the MOSAIC study(3), CAPOX (capecitabine and oxaliplatin) and FOLFOX (fluorouracil plus leucovorin and oxaliplatin) had become the standard adjuvant regimens for high-risk stage II and stage III CRC(4). However, whether adjuvant chemotherapy improves clinical outcomes of patients with stage II or curatively resected stage IV colon cancer, and whether duration lasts for 3 months or 6 months, are still controversial. Recently years, a few studies(5, 6) have focused on the duration course, hoping to reduce treatment-related adverse events while providing intact clinical benefits. Peripheral sensory neuropathy (PSN) is the most criticized adverse event in these studies and its incidence was significantly lower with 3-month therapy than with 6-month therapy(7, 8). Indeed, hematologic toxicity, especially thrombocytopenia, is an equally important factor affecting the integrity of adjuvant treatment. It is reported that grade ≥ 3
thrombocytopenia was about 5% in CAPOX adjuvant treated patients(9), compared with 0-1.7% in FOLFOX adjuvant treated patients(3, 5). Previous studies have not paid sufficient attention to the difference between the two treatment regimens and the proportion of thrombocytopenia leading to treatment intolerance. Indeed, biweekly CAPOX was reported to have no incidence of grade 3 thrombocytopenia in first-line treatment of metastases CRC in several studies(10, 11). This may be related to a modified single dose of oxaliplatin, which has not been validated in adjuvant therapy.

Therefore, we conducted this pilot study of biweekly CAPOX versus triweekly CAPOX for high-risk stage II and stage III colon cancer to assess the potential implications in modified single dose oxaliplatin for Asian patients. One of the key objectives of our study was to provide data to confirm the treatment related adverse events difference between the two regimens and its impact on treatment tolerability. Another objective was to explore whether modified biweekly CAPOX could affect disease free survival (DFS) in adjuvant CRC patients.

Materials and Methods

Study design

This study is an open-label, randomized, single-center pilot study conducted in China. Patients who had complete resection for high-risk stage II and stage III colon cancer were randomized 1:1 assigned to receive either biweekly CAPOX or triweekly CAPOX. The duration time of chemotherapy refer to the recently published adjuvant studies(12) (high-risk stage II and low-risk stage III population received 3-month CAPOX therapy, high-risk stage III population received 6-month CAPOX therapy). The inclusion criteria of patients were curatively resection of high-risk stage II and stage III colon cancer patients, the age range from 18–75 years, ECOG performance status 0–2, adequate renal, hepatic and bone marrow function. The major exclusion criteria were those who received neoadjuvant treatment before surgery or unstable heart disease, active inflammation, etc. The Ethics Committee of the First Affiliated Hospital of Zhejiang University School of Medicine approved the protocol. This study is registered at the Clinical Trials (NCT 03564912). The primary endpoint was incidence of thrombocytopenia. The secondary endpoint was 18-month DFS rate defined as the proportion of patients who relapse or death from any case patients within 18 months.

Treatment

Patients were 1:1 randomized to the biweekly group or triweekly group via blocked randomization with random block size of 4 to balance enrolled participants. Triweekly CAPOX include intravenous infusion of oxaliplatin 130 mg/m2 on day 1 and oral capecitabine 1000 mg/m2, twice daily from d1 to d14, biweekly CAPOX include intravenous infusion of oxaliplatin 85 mg/m2 on day 1 and oral capecitabine 1000 mg/m2, twice daily from d1 to d10. Patients were evaluated for disease recurrence by abdominal computed tomography (CT) scans and serum CEA every 3 months, chest CT scans every 6 months, and colonoscopy every 12 months. The Common Terminology Criteria for Adverse Events Version (CTCAE) 5.0 was used to evaluate AEs every single cycle of treatment till one month later after final treatment. Therapeutic dose was planned to reduce by 20% when grade ≥ 3 adverse events happened.
Sample size

Sample size calculation was performed with thrombocytopenia as the primary outcome, use a significant level of 5% and a power level of 80%. 80 participants were required for each group based on 0.44 effect size.

Statistical analysis

DFS curve was derived by Kaplan-Meier estimation. Cox proportional hazard model was used to calculate the HRs and 95% CIs between biweekly group and triweekly group. The AE frequency was compared using chi-square test. For all tests, P < 0.05 was defined as statistically significant. The IBM SPSS Statistics (Version 26; IBM Corp., New York, USA) was used for the analyses. The GraphPad Prism 8 (GraphPad Software, Inc., La Jolla, CA, USA) was used for chart making.

Results

Patients

Between 25 July 2018 and 14 May 2021, 160 patients were enrolled in our study 1:1 randomized received biweekly CAPOX or triweekly CAPOX adjuvant chemotherapy as shown in CONSORT diagram (Fig. 1). All enrolled patients received at least one cycle therapy and were included in final analysis. The last follow-up time was 25 December 2022, and the median follow-up period was 27 months.

The baseline characteristics were shown in Table 1. There were 80 patients in biweekly group and another 80 patients in triweekly group, with balanced characteristics between two groups. Sixty-three percent of patients (100/160) were high-risk stage II and low-risk stage III patients and received 3-month treatment, and thirty-seven percent of patients were high-risk stage III patients and received 6-month treatment. There were 47 patients had right-side primary tumor and 103 patients had left-side primary tumor. The proportion of elevated serum CEA and CA19-9 before surgery were 30% and 19%.
<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of all enrolled patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Biweekly CAPOX (n = 80)</td>
</tr>
<tr>
<td></td>
<td>Triweekly CAPOX (n = 80)</td>
</tr>
<tr>
<td></td>
<td>P value</td>
</tr>
<tr>
<td>Duration of treatment</td>
<td></td>
</tr>
<tr>
<td>6-month</td>
<td>31 (38)</td>
</tr>
<tr>
<td>3-month</td>
<td>49 (62)</td>
</tr>
<tr>
<td>Age, median(range), years</td>
<td>58 (32–77)</td>
</tr>
<tr>
<td>&lt;70</td>
<td>68 (85)</td>
</tr>
<tr>
<td>≥70</td>
<td>12 (15)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>45 (56)</td>
</tr>
<tr>
<td>Female</td>
<td>35 (46)</td>
</tr>
<tr>
<td>Location of primary tumor</td>
<td></td>
</tr>
<tr>
<td>Right</td>
<td>25 (31)</td>
</tr>
<tr>
<td>Left</td>
<td>52 (65)</td>
</tr>
<tr>
<td>NA</td>
<td>3 (4)</td>
</tr>
<tr>
<td>T stage</td>
<td></td>
</tr>
<tr>
<td>T1-3</td>
<td>68 (85)</td>
</tr>
<tr>
<td>T4</td>
<td>12 (15)</td>
</tr>
<tr>
<td>N stage</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>16 (20)</td>
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<tr>
<td>N1</td>
<td>40 (50)</td>
</tr>
<tr>
<td>N2</td>
<td>24 (30)</td>
</tr>
<tr>
<td>Number of harvested lymph nodes</td>
<td></td>
</tr>
<tr>
<td>&lt;12</td>
<td>2 (2)</td>
</tr>
<tr>
<td>≥12</td>
<td>70 (88)</td>
</tr>
<tr>
<td>NA</td>
<td>8 (10)</td>
</tr>
<tr>
<td>CEA before surgery</td>
<td></td>
</tr>
<tr>
<td>&lt;5</td>
<td>45 (56)</td>
</tr>
</tbody>
</table>
Biweekly CAPOX
(n = 80)  
Triweekly CAPOX
(n = 80)  
\(P\) value

<table>
<thead>
<tr>
<th></th>
<th>Biweekly CAPOX</th>
<th>Triweekly CAPOX</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\geq 5)</td>
<td>26 (32)</td>
<td>22 (57)</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>9 (12)</td>
<td>11 (88)</td>
<td></td>
</tr>
<tr>
<td>CA199 before surgery</td>
<td></td>
<td></td>
<td>0.83</td>
</tr>
<tr>
<td>&lt;37</td>
<td>56 (70)</td>
<td>54 (68)</td>
<td></td>
</tr>
<tr>
<td>(\geq 37)</td>
<td>15 (19)</td>
<td>15 (19)</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>9 (11)</td>
<td>11 (13)</td>
<td></td>
</tr>
<tr>
<td>Recurrence patient</td>
<td>13 (16)</td>
<td>9 (11)</td>
<td>0.35</td>
</tr>
<tr>
<td>Uncomplete therapy patient</td>
<td>6 (7)</td>
<td>12 (15)</td>
<td>0.13</td>
</tr>
</tbody>
</table>

**Thrombocytopenia and other adverse events**

All grade thrombocytopenia occurred 33% in biweekly group and 49% in triweekly group (\(P = 0.02\)). In the biweekly group, 3-month treatment subgroup presented 28% thrombocytopenia and 6-month treatment subgroup was 38%. In the triweekly group, 3-month treatment group presented 43% thrombocytopenia and 6-month treatment subgroup was 58%. However, grade \(\geq 3\) thrombocytopenia was 5% versus 9% in biweekly and triweekly group with no significant difference (\(P = 0.35\)).

The total adverse events are shown in Table 2. Overall patients randomly assigned to triweekly CAPOX treatment had significantly more adverse events than patients receiving biweekly CAPOX treatment, especially all grade neutropenia (\(P = 0.04\)). No significant differences were observed in more than grade 3 neutropenia (\(P = 0.17\)). In the biweekly group, 6 patients (7.5%) failed to complete adjuvant chemotherapy due to treatment intolerance. In the triweekly group, the discontinue patients was 12 (15%), including 11 patients with treatment intolerance and 1 patient found to have leukemia during the treatment. In patients receiving 6-month CAPOX, 21% (13/60) of the patients experienced grade \(\geq 2\) PSN, whereas 10% (10/100) of the patients in the 3-month CAPOX group experienced grade \(\geq 2\) PSN. There was no treatment related death.
Table 2
Adverse events by regimen and treatment duration in all patients

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Biweekly CAPOX group (n = 80)</th>
<th></th>
<th>Triweekly CAPOX group (n = 80)</th>
<th></th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3-month treatment (N = 49)</td>
<td>6-month treatment (N = 31)</td>
<td>total</td>
<td>3-month treatment (N = 51)</td>
<td>6-month treatment (N = 29)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>19(38)</td>
<td>10(32)</td>
<td>29(36)</td>
<td>24(47)</td>
<td>17(58)</td>
</tr>
<tr>
<td>Neutropenia(≥ 3)</td>
<td>1(2)</td>
<td>0</td>
<td>1(1)</td>
<td>2(4)</td>
<td>2(7)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>14(28)</td>
<td>12(38)</td>
<td>26(33)</td>
<td>22(43)</td>
<td>17(58)</td>
</tr>
<tr>
<td>Thrombocytopenia(≥ 3)</td>
<td>1(2)</td>
<td>3(10)</td>
<td>4(5)</td>
<td>5(10)</td>
<td>2(7)</td>
</tr>
<tr>
<td>Anemia</td>
<td>10(20)</td>
<td>8(25)</td>
<td>18(22)</td>
<td>7(14)</td>
<td>13(45)</td>
</tr>
<tr>
<td>PNS</td>
<td>24(49)</td>
<td>16(52)</td>
<td>40(50)</td>
<td>32(62)</td>
<td>15(52)</td>
</tr>
<tr>
<td>PNS(≥ 2)</td>
<td>5(10)</td>
<td>6(19)</td>
<td>11(14)</td>
<td>7(14)</td>
<td>4(14)</td>
</tr>
<tr>
<td>Liver dysfunction</td>
<td>15(30)</td>
<td>7(22)</td>
<td>22(27)</td>
<td>22(43)</td>
<td>10(34)</td>
</tr>
<tr>
<td>Hyperbilirubinemia</td>
<td>5(10)</td>
<td>6(19)</td>
<td>11(14)</td>
<td>5(10)</td>
<td>7(24)</td>
</tr>
<tr>
<td>Diarrhea (≥ 3)</td>
<td>0</td>
<td>1(3)</td>
<td>1(1)</td>
<td>0</td>
<td>1(3)</td>
</tr>
<tr>
<td>Vomiting (≥ 3)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2(4)</td>
<td>0</td>
</tr>
</tbody>
</table>

Disease-free survival

At the time of analysis, 21 events had been reported (13 in the biweekly group and 9 in the triweekly group). The Kaplan-Meier plots for DFS among 3-month and 6-month groups are shown in Fig. 2–3. The 18-month DFS rate was 94.1% in 3-month biweekly CAPOX group, and 93.8% in the 3-month triweekly CPOX group (P = 0.96). The 18-month DFS rate was 89.6% in the 6-month biweekly CAPOX group, and 93.5% in the 6-month triweekly CAPOX group (P = 0.61). The median disease-free survival time of 13 relapse patients is 13.3 months (range 1.7–52.5 months). There were two patients died due to disease progression in triweekly group.

Discussion

Our study is the first study explore the safety and efficacy of biweekly CAPOX and triweekly CAPOX in colorectal adjuvant treatment. Previous study had shown that biweekly CAPOX had modest efficacy and an
acceptable safety profile in the treatment of advanced gastric cancer\(^{(13)}\). In our study, we enrolled high-risk stage II and stage III post-surgery colorectal cancer patients to certify its advantage of biweekly CAPOX in adjuvant area.

CAPOX is reported to have significant higher grade 3–4 thrombocytopenia than FOLFOX \((3−12\% \text{ vs. } 1−6\%)\) \(^{(14)}\). However, the negative effect of thrombocytopenia induced by CAPOX has not been paid enough attention. Indeed, not only grade 3–4 thrombocytopenia affects treatment, but grade 2 thrombocytopenia also requires drug intervention and may lead to delayed treatment\(^{(15)}\). Our study finds that all grade thrombocytopenia significant reduced by modified biweekly CAPOX, which has not been explored before. The incidence of all hematological AEs was lower in the biweekly group than in the triweekly group, concomitant lower treatment discontinuation. In the biweekly CAPOX group, 74 patients \(92.5\%\) completed all courses of adjuvant chemotherapy, which is higher than triweekly group and previous adjuvant study\(^{(16)}\). The completion rate of treatment is considered to be related to OS benefits\(^{(16)}\). The high completion rate of our study due to the high proportion of patients who underwent three-month treatment and the reduction of AEs of the modified biweekly CAPOX regimen. And it is shown that grade \(\geq 2\) PSN was more common in 6-month treatment patients, which was consistent with the finding of previous studies\(^{(17, 18)}\).

It is reported that the median DFS in relapsed patients aged less than 50 years was 13 months\(^{(19)}\). And in another retrospective study, the median recurrence free survival was 1.3 years\(^{(20)}\). Thus, we set 18-month DFS as second endpoint. In our study, the median DFS was 13.3 months in relapse patients. The DFS curves of biweekly and triweekly groups were similar, and the 18-month DFS rate did not reach significant difference between the two groups. However, the overall number of patients was too low to establish whether biweekly CAPOX is inferior to triweekly CAPOX.

There may have new revolution of adjuvant chemotherapy of CRC in the future. More and more studies support the use of ctDNA test to identify patients who are at increased risk of recurrence and are potential benefit from treatment\(^{(21, 22)}\). And it is reported that tumor deposits (TD) positive patients proven to have significantly worse outcomes, especially in N1a-b patients\(^{(23)}\). The role of TD deserves further scrutiny. And the best adjuvant treatment option of MSI-H CRC is still inconclusive. Although post-surgery CRC patients should be segmented in different groups, adjuvant treatment is still on the base of fluorouracil and oxaliplatin. We believe that modified biweekly CAPOX can reduce treatment-related AEs and turn out to be a better tolerance regimen for most CRC patients.

However, this is a pilot study with finite patients’ number, and did not have the statistical power to confirm the non-inferior of biweekly CAPOX to triweekly CAPOX. Further study still needed to confirm the advantages of biweekly CAPOX.

**Conclusion**

Our data suggests that biweekly CAPOX could be an acceptable alternative treatment option with favorable risk-benefit for CRC adjuvant chemotherapy. A modified biweekly CAPOX reduced hematological AEs and
improved treatment tolerance, and it did not compromise the DFS.

**Declarations**

**Ethics approval and consent to participate.**

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of The First Affiliated hospital of Zhejiang University. Informed consent was obtained from all individual participants included in the study.

**Consent for publication**

Not applicable.

**Availability of data and materials**

The datasets generated during and analyzed during the current study are available in link: https://pan.baidu.com/s/19-86yE2hxXxXUGljGSHzww code:gtn3

**Competing interests**

The authors have no relevant financial or non-financial interests to disclose.

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**Authors’ contribution**

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Hangyu Zhang, Danyang Wang, Zhou Tong, Tao Xiang, Xiaomeng Dai, Xuanwen Bao and Xudong Zhu. The first draft of the manuscript was written by Hangyu Zhang, Wenbin Chen, review and editing by Lulu Liu, Yi Zheng, Peng Zhao and Weijia Fang, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figures
160 patients enrolled in study

160 patients randomized

80 patients in triweekly group

51 patients 3-month
29 patients 6-month

80 patients in biweekly group

49 patients 3-month
31 patients 6-month

Figure 1

CONSORT flow diagram
Figure 2

Overall disease-free survival (DFS) according to biweekly and triweekly CAPOX in 3-month treatment duration group.
Figure 3

Overall disease-free survival (DFS) according to biweekly and triweekly CAPOX in 6-month treatment duration group.