Original Article

Therapeutic effect of biweekly cetuximab combined with first-line chemotherapy on KRAS/RAS wild-type advanced colorectal cancer

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Abstract: Objective: To observe the efficacy of biweekly cetuximab combined with first-line chemotherapy for the treatment of KRAS/RAS wild-type advanced colorectal cancer. Methods: A retrospective study was performed in 72 patients with KRAS/RAS wild-type advanced colorectal cancer, confirmed by gene detection. According to the regiments the patients received, they were divided into the biweekly cetuximab group and the weekly cetuximab group, with 36 cases in each group. Patients in the two groups were assigned in two subgroups, left-sided colorectal cancer and right-sided colorectal cancer, according to the primary site of tumor. The efficacy and side effects in the two groups were evaluated. Results: In terms of efficacy, the objective remission rate was better in the biweekly cetuximab group than that in the weekly cetuximab group (P<0.05). The difference in overall survival time was not significant between the two groups (P>0.05). The objective remission rate, disease control rate and overall survival time in the two left-sided colorectal cancer subgroups were higher than those in the right-sided colorectal cancer subgroups (all P<0.05). In terms of adverse reactions, only the incidence of rash was higher in the biweekly cetuximab group than in the weekly cetuximab group (P<0.05). Conclusion: Biweekly cetuximab combined chemotherapy has significant curative effects on patients with KRAS/RAS wild-type advanced colorectal cancer. The biweekly regimen is more beneficial and safer for the left colon, which is worthy of clinical application and further research.

Keywords: Colorectal cancer, cetuximab, chemotherapy, therapeutic effect

Introduction

Colorectal cancer, including tumor of the rectum, is the most common malignant lesion in the digestive system. The latest data of global epidemiology show that it’s the third most common cancer with an incidence rate of 8% among all cancers [1]. In 2017, 135,000 people in the United States developed colorectal cancer [2]. A study in 2015 also found an increased incidence of colorectal cancer, and 191,000 people died of colorectal cancer [3]. Studies showed that cancer metastasis was found in 1/3 of patients at diagnosis. Chemotherapy is currently the main treatment for advanced colorectal cancer. mFOLFOX6 chemotherapy is the first choice for treatment and it can improve patients’ progression-free survival and overall survival [4, 5].

Increasing studies have found that angiogenesis plays an important role in the occurrence and development of tumors [6, 7]. Therefore, how to inhibit neovascularization has become a hot spot of research. Vascular endothelial growth factor (VEGF) is an important mediator in promoting angiogenesis in tumors, and plays an important role in tumor growth and metastasis [8, 9]. Thus, inhibition of VEGF has become a new target for the treatment of tumors [10]. For colorectal cancer, the commonly used drug that inhibits VEGF is cetuximab. The use of cetuximab in combination with first-line chemotherapy to treat KRAS/RAS wild-type advanced colorectal cancer has become the focus of attention [11]. In the past, the normal regimen of cetuximab was weekly use; which increases patients’ hospitalization, as well as time and economic costs, and then reduces patient compliance. Recent studies have found that cetuximab has a long half-life of up to 213 hours, and an average elimination half-life of 97 hours, and its pharmacokinetics are nonlinear, resulting in...
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slow metabolism in the body. There were studies showing that biweekly and weekly treatment plans showed similar effects, overall survival time and side effects [12-14]. But there are few studies on the comparison of the two regimens in Chinese patients. Thereafter, this study aimed to evaluate the effect and adverse reactions of biweekly cetuximab combined with first-line chemotherapy in Chinese patients with colorectal cancer, so as to provide more evidence for the clinic.

Materials and methods

Clinical data

A total of 72 patients with KRAS/RAS wild-type advanced colorectal cancer (confirmed by gene detection) treated in the Department of Oncology from December 2012 to December 2017 were enrolled. According to different regimens, patients were divided into the biweekly cetuximab group and the weekly cetuximab group with 36 cases in each group. Besides the chemotherapy, biweekly cetuximab was given to the biweekly cetuximab group, while weekly cetuximab was performed for the weekly cetuximab group. Patients in the two groups were assigned into two subgroups, left-sided colorectal cancer and right-sided colorectal cancer, according to the primary site of tumor. All patients were 18-75 years old, with an average age of 53.5±8.7 years.

Inclusion criteria

Patients who were diagnosed with KRAS/RAS wild type advanced colorectal cancer according to the Standard for Diagnosis and Treatment of Colorectal Cancer issued by the Medical Authority of National Health and Family Planning Commission of the People's Republic of China in 2015 [15]; patients with tumor lesions that can be measured or evaluated by CT or PET/CT; patients with expected lifetime of more than 6 months; patients with normal coagulation, bone marrow, and cardiopulmonary functions; patients without central nervous system metastasis and major vascular involvement according to imaging examination; patients with physical fitness score of 0-2 points according to the criterion of US Eastern Cooperative Oncology Group [16]; patients with complete clinical data.

Exclusion criteria

Patients who received or were receiving other chemotherapy; patients with severe cardiopulmonary disease, other primary malignant tumors or abnormal blood coagulation or bone marrow functions; patients with liver or kidney dysfunction; patients who were allergic to chemotherapy drugs; patients who did not cooperative; patients with incomplete clinical data.

Methods

The biweekly cetuximab group was treated with biweekly cetuximab combined with mFOLFOX6 chemotherapy. On the first day, intravenous infusion of oxaliplatin (Sanofi, China) was given at a dose of 85 mg/m² for more than 2 h, and intravenous infusion of calcium folate (Jiangsu Hengrui Medicine Co., Ltd., China) and fluorouracil (Shanghai Xudong Haipu Pharmaceutical Co., Ltd., China) were administered both at a dose of 400 mg/m². After that, intravenous fluorouracil at a dose of 2,400 mg/m² was given for 46-48 h of maintenance treatment. Intravenous drip of 500 mg/m² cetuximab was given once every two weeks. Every 14 days was one course of treatment.

The weekly cetuximab group received weekly intravenous drip of cetuximab in combination with mFOLFOX6 chemotherapy. The chemotherapy regimen was the same as the above, and only cetuximab was administered once a week for the first dose of 400 mg/m², followed by 250 mg/m² per week. Every 14 days was one course of treatment.

The efficacy of patients was evaluated after 4 courses of treatment.

Evaluation of therapeutic effect

Short-term efficacy: therapeutic effects were divided into complete remission (CR), partial remission (PR), stabilization of disease (SD), and progression of disease (PD) [17]. CR inferred that all lesions disappeared, with no new lesions. All tumor markers were below the upper limit for at least 4 weeks. PR referred to the sum of the maximum diameters of tumors being reduced by at least 30% and maintained for more than 4 weeks. PD referred to a maximum increase in the sum of diameters of tumor
target lesions by at least 20% compared to the minimum during the observation period, or the discovery of new lesions. SD referred to the change of tumor between the state of PR and PD, that is, the sum of the maximum diameter of the lesion did not reduce to the PR standard, or the sum of the maximum diameter of the lesion did not increase to the PD standard. Objective remission rate (%) = (CR + PR)/total number of cases * 100%; disease control rate (%) = (CR + PR + SD)/total number of cases * 100%.

Long-term efficacy was evaluated according to the 5-year overall survival time (from the chemotherapy to death). The cut-off date of follow-up was March 1, 2019. Overall survival of patients whose survival date exceeded the follow-up deadline was recorded as 5 years.

Toxic reaction

According to the NCI-CTC4.0 toxic reaction classification, the toxic side effects of chemotherapeutic drugs included: toxicity of the blood system, of peripheral nervous system, and of other systems such as nausea and vomiting, diarrhea, constipation, abnormal liver function, abnormal renal function, abnormal cardiac function, hair loss, and acne [18]. The above reactions were classified into degree 0-4 according to different conditions, and comparison was performed between patients with toxic reaction grade 0-2 and with grade 3-4. The detailed classifications were as follows.

The toxic reaction in leukocytes was graded as grade 0: ≥4.0 * 10^9/L; grade 1: 3.0-3.9 * 10^9/L; grade 2: 2.0-2.9 * 10^9/L; grade 3: 1.0-1.9 * 10^9/L; grade 4: <1.0 * 10^9/L.

Toxic reaction in hemoglobin was graded as grade 0: ≥110 g/L; grade 1: 95-109 g/L; grade 2: 80-94 g/L; grade 3: 65-79 g/L; grade 4: <65 g/L.

Nausea and vomiting were graded as grade 0: none; grade 1: nausea; grade 2: temporary vomiting; grade 3: vomiting and in need of treatment; grade 4: uncontrolled vomiting.

Diarrhea was graded as grade 0: none; grade 1: short-term (≤2 days); grade 2: tolerable (>2 days); grade 3: intolerable, and in need of treatment; grade 4: bloody diarrhea.

Constipation was graded as grade: 0: none; grade 1: mild; grade 2: moderate; grade 3: bloating; grade 4: bloating and vomiting.

Hepatic dysfunction (bilirubin or alanine aminotransferase) was graded as grade 0: ≤1.25 * N; grade 1: 1.26-2.50 * N; grade 2: 2.6-5.0 * N; grade 3: 5.1-10.0 * N; grade 4: >10 * N.

Renal dysfunction (urea nitrogen or creatinine) was graded as grade 0: ≤1.25 * N; grade 1: 1.26-2.50 * N; grade 2: 2.6-5.0 * N; grade 3: 5.1-10.0 * N; grade 4: >10 * N.

Cardiac dysfunction was graded as grade 0: normal function; grade 1: asymptomatic, but with abnormal cardiac signs; grade 2: short-term insufficiency of cardiac function, but no need of treatment; grade 3: symptomatic, insufficient cardiac function, and can be effectively treated; grade 4: symptomatic, insufficient cardiac function, and cannot be treated effectively.

Bleeding was graded as grade 0: none; grade 1: mild, and no need of blood transfusion; grade 2: obvious, and in need of each transfusion of PLT1-2U; grade 3: obvious, and in need of each transfusion of PLT3-4U; grade 4: large amount, and in need of each transfusion of PLT >4U.

Acne was graded as grade 0: none; grade 1: asymptomatic but with scattered macules, papules, and erythema; grade 2: scattered macules, papules, and erythema, with itching or other related symptoms; grade 3: systemic macules, pimples or herpes; grade 4: exfoliative dermatitis or ulcerative dermatitis.

Statistical analyses

Statistical analyses were performed using SPSS 17.0 software. The continuous variables were expressed as mean ± standard deviation (mean ± sd). The data conformed to a normal distribution and homogeneity of variance were compared with the use of t test, while data not conforming to a normal distribution and homogeneity of variance were analyzed with the use of rank sum test. The count data were processed using Pearson chi-square test, expressed as chi-square. Survival analysis was performed using Kaplan-Meier analysis and Log-rank test. The difference was statistically significant at P<0.05.
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### Results

#### Comparison of general data

There was no statistically significant difference in gender, age, BMI, tumor differentiation, cTMN stage, primary tumor location, and physical fitness score between the two groups (all P>0.05). See Table 1.

#### Comparison of clinical effective rate

The comparison of therapeutic effects between the two groups showed that the objective remission rate of the biweekly cetuximab group was 36.11%, which was higher than that of the weekly cetuximab group (13.89%, P<0.05). In terms of the total control rate, the biweekly cetuximab group was 86.11%, which was higher than that of the weekly cetuximab group (75.00%), but the difference was not significant (P>0.05). See Table 2.

#### Comparison of long-term efficacy

The 5-year overall survival time of the two groups showed that the survival time in the

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**Table 1. Comparison of general and baseline data**

<table>
<thead>
<tr>
<th>Item</th>
<th>Biweekly cetuximab group (n=36)</th>
<th>Weekly cetuximab group (n=36)</th>
<th>χ²/t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male: female)</td>
<td>21:15</td>
<td>20:16</td>
<td>0.057</td>
<td>0.812</td>
</tr>
<tr>
<td>Age (year)</td>
<td>53.6±9.1</td>
<td>53.3±8.3</td>
<td>0.236</td>
<td>0.813</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.60±7.96</td>
<td>22.61±7.48</td>
<td>0.692</td>
<td>0.490</td>
</tr>
<tr>
<td>Differentiation (n)</td>
<td></td>
<td></td>
<td>0.322</td>
<td>0.851</td>
</tr>
<tr>
<td>Well-differentiated</td>
<td>7</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderately differentiated</td>
<td>16</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poorly differentiated</td>
<td>13</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cTMN stage (n)</td>
<td></td>
<td></td>
<td>0.551</td>
<td>0.458</td>
</tr>
<tr>
<td>III</td>
<td>25</td>
<td>22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>11</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary tumor location</td>
<td></td>
<td></td>
<td>0.084</td>
<td>0.772</td>
</tr>
<tr>
<td>Right side</td>
<td>8</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left side</td>
<td>28</td>
<td>29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical fitness score</td>
<td></td>
<td></td>
<td>0.335</td>
<td>0.551</td>
</tr>
<tr>
<td>0-1 point</td>
<td>30</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 points</td>
<td>6</td>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: BMI, body mass index.

**Table 2. Comparison of clinical effective rate (n, %)**

<table>
<thead>
<tr>
<th>Group</th>
<th>CR (0.00)</th>
<th>PR (13.61)</th>
<th>SD (50.00)</th>
<th>PD (13.89)</th>
<th>Objective remission rate</th>
<th>Total control rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biweekly cetuximab group (n=36)</td>
<td>0</td>
<td>13 (36.11)</td>
<td>18 (50.00)</td>
<td>5 (13.89)</td>
<td>13 (36.11)</td>
<td>31 (86.11)</td>
</tr>
<tr>
<td>Weekly cetuximab group (n=36)</td>
<td>0</td>
<td>5 (13.89)</td>
<td>22 (61.11)</td>
<td>9 (25.00)</td>
<td>5 (13.89)</td>
<td>27 (75.00)</td>
</tr>
<tr>
<td>χ²</td>
<td>4.550</td>
<td>2.203</td>
<td>1.183</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.031</td>
<td>0.043</td>
<td>0.237</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


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**Figure 1.** Comparison of long-term efficacy.
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Table 3. Comparison of the efficacy on left-sided and right-sided colorectal cancer in the biweekly cetuximab group (n, %)

<table>
<thead>
<tr>
<th>Group</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>Objective remission rate</th>
<th>Total control rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left-sided subgroup (n=28)</td>
<td>0 (0.00)</td>
<td>13 (46.43)</td>
<td>15 (53.57)</td>
<td>0 (0.00)</td>
<td>13 (46.43)</td>
<td>28 (100.00)</td>
</tr>
<tr>
<td>Right-sided subgroup (n=8)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>3 (37.50)</td>
<td>5 (62.50)</td>
<td>0 (0.00)</td>
<td>3 (37.50)</td>
</tr>
<tr>
<td>χ²</td>
<td>21.536</td>
<td></td>
<td></td>
<td></td>
<td>5.841</td>
<td>20.323</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td>0.016</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


Table 4. Comparison of the efficacy on left-sided and right-sided colorectal cancer in the weekly cetuximab group (n, %)

<table>
<thead>
<tr>
<th>Group</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>Objective remission rate</th>
<th>Total control rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left-sided subgroup (n=29)</td>
<td>0 (0.00)</td>
<td>5 (17.24)</td>
<td>22 (75.86)</td>
<td>2 (6.90)</td>
<td>5 (17.24)</td>
<td>27 (93.10)</td>
</tr>
<tr>
<td>Right-sided subgroup (n=7)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
<td>7 (100.00)</td>
<td>0 (0.00)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>χ²</td>
<td>22.609</td>
<td></td>
<td></td>
<td></td>
<td>4.123</td>
<td>22.593</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
<td>0.049</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


Figure 2. Comparison of 5-year total survival time between the left-sided and right-sided subgroups of the biweekly cetuximab group.

The comparison of the efficacy showed that the objective remission rate and overall control rate of the left-sided subgroups were higher than those of the right-sided subgroups (all P<0.05). See Table 3 and Table 4.

Comparison of the long-term efficacy on left-sided and right-sided colorectal cancer

In the biweekly cetuximab group, the 5-year overall survival time of the left-sided subgroup was 22.2 months (95% CI: 20.448-23.887), which was longer than that of the weekly cetuximab group (21.5 months; 95% CI: 19.645-23.312), but the difference was not statistically significant (χ²=0.335, P=0.563). See Figure 1.

Comparison of adverse reactions

Only the incidence of rash was significantly higher in the biweekly cetuximab group than in the weekly cetuximab group (P<0.05). There was no statistical difference between the two groups in terms of other adverse reactions (all P>0.05). All the adverse reactions were tolerated after symptomatic treatment. See Table 5.

Discussion

A study found that abnormal vascular proliferation of tumor tissue expedites tumor growth
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and metastasis, so, cetuximab, which inhibits vascular proliferation is used in the clinic [8]. Some studies believed that cetuximab combined with any chemotherapy can improve the survival time of patients with wild-type colorectal cancer [19, 20]. Clinically, the usual regimen of cetuximab was weekly use, which will increase the patients' time and economic costs. Since cetuximab has a long half-life and nonlinear metabolism in the body, some researchers proposed a biweekly treatment plan, and found that the efficacy was equivalent to that of weekly treatment. The biweekly regimen reduced the time and economic costs, without increasing the toxic side effects [12-14].

A report on the treatment of wild-type colorectal cancer patients showed that the 99 patients receiving a first-line chemotherapy combined with biweekly cetuximab regimen had an overall survival time of 20.8 months [21]. Another study used the same treatment protocol to observe 60 patients, and found an overall survival time of 31.0 months [13]. A study compared the use of weekly and biweekly cetuximab, and found an overall survival time of 23.0 months and 25.8 months, respectively, and found no significant difference in the objective remission rate between the two groups [22]. In the present study, the overall survival of biweekly cetuximab group and weekly cetuximab group was 22.2 months and 21.5 months, respectively, with no statistical difference, which is similar to the above studies. However, in terms of the objective remission rate of the disease, our study found that the biweekly cetuximab group was 36.11% higher than 13.89% in the weekly cetuximab group.

A previous study found that left-sided and right-sided colorectal cancer have different pathological and molecular characteristics [23]. Studies have found that cetuximab for left-sided colorectal cancer, including rectal cancer, is superior to that for right-sided colorectal cancer treatment [24, 25]. In this study, the objective remission rate and overall control rate were significantly higher and the 5-year survival time was clearly longer in the two left-sided subgroups than those of right-sided subgroups, indicating that the therapeutic effect on left-sided colorectal cancer was better than that on right-sided colorectal cancer, which is consistent with the above studies.

In terms of adverse reactions, the common reactions to chemotherapy in the two groups were blood system and digestive system symptoms. Statistical comparison showed that there were no significant differences in leukopenia, hemoglobin reduction, thrombocytopenia, nausea and vomiting, abnormal liver function, paronychia, and bleeding. However, the incidence of rash in the biweekly cetuximab group was significantly higher than that in the weekly cetuximab group. Previous studies found that the most common side effect of cetuximab was grade III rash, with an incidence of 5-20% [26, 27]. The higher incidence of rash in the biweekly treatment group in this study may be related to the higher dose of cetuximab in this group and the relatively small sample size. The incidence of rash above grade III was low, and the symptom was tolerable.

The sample size of this study is small, so further expansion of the sample size is needed. Additionally, this study is a retrospective study, so a multicenter prospective study should be performed to observe the therapeutic effect of biweekly cetuximab combined with chemotherapy.

In conclusion, biweekly cetuximab combined chemotherapy has significant curative effects on patients with KRAS/RAS wild-type advanced colorectal cancer. The biweekly regimen is more beneficial and safer for patients with left-sided colorectal cancer, which is worthy of clinical application and further research.
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Table 5. Comparison of adverse reactions (n, %)

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Biweekly cetuximab group (n=36)</th>
<th>Weekly cetuximab group (n=36)</th>
<th>Z</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 0-2</td>
<td>Grade 3-4</td>
<td>Grade 0-2</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>4 (11.11)</td>
<td>2 (5.56)</td>
<td>5 (13.89)</td>
<td>4 (11.11)</td>
</tr>
<tr>
<td>Hemoglobin reduction</td>
<td>7 (19.44)</td>
<td>2 (5.56)</td>
<td>8 (22.22)</td>
<td>2 (5.56)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>6 (16.67)</td>
<td>2 (5.56)</td>
<td>6 (16.67)</td>
<td>5 (13.89)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>10 (27.78)</td>
<td>2 (5.56)</td>
<td>13 (36.11)</td>
<td>2 (5.56)</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>4 (11.11)</td>
<td>1 (2.78)</td>
<td>4 (11.11)</td>
<td>4 (11.11)</td>
</tr>
<tr>
<td>Paronychia</td>
<td>2 (5.56)</td>
<td>0 (0.00)</td>
<td>2 (5.56)</td>
<td>1 (2.78)</td>
</tr>
<tr>
<td>Rash</td>
<td>8 (22.22)</td>
<td>1 (2.78)</td>
<td>2 (5.56)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>Bleeding</td>
<td>4 (11.11)</td>
<td>0 (0.00)</td>
<td>1 (2.78)</td>
<td>0 (0.00)</td>
</tr>
</tbody>
</table>

Disclosure of conflict of interest

None.

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