Comparative study of tegafur gimeracil and oteracil potassium (TS-1) plus docetaxel and oxaliplatin versus TS-1 plus oxaliplatin in postoperative adjuvant chemotherapy for gastric cancer

Ya Zhu, Zhenyong Zhang, Xinzong Zou

Department of Oncology, Affiliated Hospital of Jiangnan University, Wuxi, Jiangsu Province, China

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Abstract: Objective: The objective of this study was to comparatively study the effect of tegafur gimeracil and oteracil potassium (TS-1) plus docetaxel and oxaliplatin versus TS-1 plus oxaliplatin in postoperative adjuvant chemotherapy for gastric cancer. Methods: A total of 121 advanced patients received chemotherapy after radical gastrectomy were enrolled in this study and randomly assigned to two groups. Sixty-three patients received the chemotherapy regimen of TS-1 plus oxaliplatin and docetaxel were in observation group, while 58 patients received the regimen of TS-1 plus oxaliplatin were in control group. The short-term efficacy, long-term efficacy, Karnofsky performance status (KPS) score and toxic side effects were observed in both groups. Results: The total effective rate was 58.73%, and the total control rate was 87.30% in the observation group, which were significantly higher than those in the control group (39.66% and 72.41%), with statistical differences (both P<0.05). The progression-free survival and overall survival of the observation group were 5.73 and 11.18 months, respectively, which were not statistically significant from those of the control group (5.69 and 11.25 months; both P>0.05). The KPS scores of the observation group were higher than those of the control group after 3-week and 6-week chemotherapy (both P<0.05). There was no significant difference in the adverse reactions between the two groups after chemotherapy (P>0.05). Conclusions: The chemotherapy regimen of TS-1 plus docetaxel and oxaliplatin has significant effects in patients after gastrectomy, and improves patients’ physical condition with reliable safety.

Keywords: Post-gastrectomy, adjuvant chemotherapy, tegafur gimeracil and oteracil potassium (TS-1), docetaxel, oxaliplatin

Introduction

Gastric cancer, as a common malignant tumor in clinic, ranks the third among tumors that cause death. In the year of 2015, there were 1.3 million patients with gastric cancer worldwide [1]. The mortality of gastric cancer is high among all cancers [2, 3]. China is a country with a high risk of gastric cancer in East Asia for the incidence here is the second highest among all cancers [4, 5]. To date, the main treatment for gastric cancer is surgery [6]. But the resection rate of advanced gastric cancer is low, with high risk of postoperative recurrence and metastasis, and low 5-year survival rate, so the efficacy of surgical treatment alone is not promising [7]. In order to improve clinical efficacy, postoperative adjuvant chemotherapy is frequently carried out to reduce recurrence and metastasis. However, its application in clinic is greatly limited due to the large difference in the efficacy of chemotherapy drugs in cells and animal experiments and in humans [8]. At present, the common chemotherapy regimen for gastric cancer is a combination of two cytotoxic drugs or three cytotoxic drugs [9]. The combination of two drugs is fluoropyrimidine (tegafur gimeracil and oteracil potassium (TS-1) or capecitabine) + oxaliplatin or cisplatin. The combination of three drugs is paclitaxel + oxaliplatin or cisplatin + fluoropyrimidine or its improved replacement [9]. But the optimum choice of chemotherapy...
regimens is still controversial [10]. In this study, a double-drug regimen of TS-1 + oxaliplatin and a three-drug regimen of TS-1 + oxaliplatin + docetaxel were compared.

Materials and methods

Clinical data

A total of 128 patients with advanced gastric cancer received chemotherapy after radical gastrectomy from June 2017 to October 2018 were enrolled in our study and assigned to two groups using a random number table. Sixty-four patients received the chemotherapy regimen of TS-1 plus oxaliplatin and docetaxel were in the observation group, while 64 patients received the regimen of TS-1 plus oxaliplatin were in the control group. During the follow up, we lost 1 patient in the observation group and 6 patients in control group. Therefore, there were 121 patients included in the study analyses. All patients were 44-75 years old, with an average age of 53.4±8.9 years. Written informed consent form was obtained from all the subjects, and the study was approved by the Ethics Committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology.

Inclusion criteria

Patients were eligible if they were diagnosed with primary advanced gastric cancer of stage IIB-IIIC and received laparoscopic surgery [11]; had normal cardiopulmonary function; did not receive other tumor treatment before laparoscopic surgery and chemotherapy; had normal coagulation and bone marrow function; had complete clinical data.

Exclusion criteria

Patients who received or was receiving 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 the chemotherapy drugs; patients who were not cooperative; patients with incomplete clinical data.

Clinical and pathological staging

Clinical staging and pathological staging were evaluated according to UICC/AJCC diagnostic criteria (version 7) [11].

Methods

The chemotherapy was given one week after surgery. The regimen for the observation group was as follows. During a chemotherapy period, which was 21 days, over 3 h of oxaliplatin (130 mg/m², from Nanjing-pharma, Jiangsu, China) and 1 h of docetaxel (75 mg/m², from Ao-saikang, Jiangsu, China) were intravenously infused on day 1; TS-1 (40 mg/m², from Haiwangfu Pharma, Fujian, China) was orally taken from day 1 to day 14, 2 times a day. The regimen for the control group in a 21-day chemotherapy period was as follows. Over 3 h of oxaliplatin (130 mg/m²) was intravenously infused on day 1; TS-1 (40 mg/m²) was orally taken from day 1 to day 14, 2 times a day. In both groups, allergy prevention was given 12 h before chemotherapy with intravenous injection of 20 mg dexamethasone (Hasen-modern, Shanghai, China), and 30 min before chemotherapy with intramuscular injection of 25 mg promethazine (Shharvest, Shanghai, China). To protect the stomach, intravenous infusion of 300 mg cimetidine (Nanguo pharma, Guangdong, China) was given 30 min before chemotherapy. The efficacy in both groups was evaluated after 4 periods of chemotherapy.

Follow-up was performed monthly by reviewing the visit record or telephone. The disease-free survival (DFS) period was from the first day after surgery to the date of recurrence or progression. The overall survival (OS) was from the first day after clarifying of pathology after surgery to patient’s death date or the last follow up.

Outcome measures

The short-term efficacy was evaluated after 4 periods of chemotherapy [12]. The treatment efficacy was divided into complete remission (CR), partial remission (PR), stability of disease (SD), and progression of disease (PD). Effective rate (%) = (CR + PR)/total number of patients × 100%. Disease control rate (%) = (CR + PR + SD)/total number of patients × 100%.

The long-term efficacy was evaluated according to progression-free survival (PFS) and overall survival (OS). PFS referred to the time during which the tumor progressed to other parts of the body in the study period. OS referred to the time from the start of chemotherapy treatment to the death of the patient or the end of the study period.
The Karnofsky performance status (KPS) score was used to evaluate patients’ condition before chemotherapy, after chemotherapy, and 3 weeks after surgery, with a total score of 100 points [13]. The higher the score was, the better the physical condition was. Score less than 60 points indicated poor physical condition, which was not conducive to the treatment.

Toxic reaction was recorded according to the NCI-CTC 4.0 classification after 4 cycles of chemotherapy [14]. The toxic reactions included toxic symptoms in blood system and other systems such as nausea and vomiting, diarrhea, constipation, abnormal liver function, abnormal renal function, abnormal cardiac function, alopecia, and toxicity in peripheral nervous system. The above toxic reactions were classified into grade 0-4 according to different conditions. Comparison was carried out between patients with grade 1-2 and with grade 3-4 in the two groups.

Statistical analyses

Statistical analyses were performed using SPSS 17.0 software. The continuous variables were expressed as mean ± standard deviation. The data conformed to normal distribution and homogeneity of variance were compared with the use of independent sample t test, denoted as t. The enumeration data were processed using Pearson chi-square test, denoted as χ². Survival analysis was performed using Kaplan-Meier analysis and Log-rank test. The difference was statistically significant at P<0.05.

Results

Comparison of general and baseline data

There were no differences in gender, age, tumor size, pathological type, and UICC stage between the two groups (all P>0.05), so the two groups were comparable. See Table 1.

Comparison of clinical efficacy

The total effective rate was 58.73%, and the total control rate was 87.30% in the observation group, which were significantly higher than those in the control group (39.66% and 72.41%), with statistical differences (both P<0.05). See Table 2.

Table 1. Comparison of general and baseline data

<table>
<thead>
<tr>
<th>Item</th>
<th>Observation group (n=63)</th>
<th>Control group (n=58)</th>
<th>χ²/t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male: female)</td>
<td>35:28</td>
<td>34:24</td>
<td>0.116</td>
<td>0.734</td>
</tr>
<tr>
<td>Age (year)</td>
<td>53.2±9.1</td>
<td>53.6±8.8</td>
<td>0.243</td>
<td>0.808</td>
</tr>
<tr>
<td>Tumor size (cm)</td>
<td></td>
<td></td>
<td>0.163</td>
<td>0.683</td>
</tr>
<tr>
<td>&gt;5 cm</td>
<td>36</td>
<td>31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5 cm</td>
<td>27</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pathological type</td>
<td></td>
<td></td>
<td>0.011</td>
<td>0.917</td>
</tr>
<tr>
<td>Differentiated</td>
<td>60</td>
<td>55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>3</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UICC stage</td>
<td></td>
<td></td>
<td>0.358</td>
<td>0.949</td>
</tr>
<tr>
<td>IIIB</td>
<td>19</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIA</td>
<td>18</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIB</td>
<td>12</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIC</td>
<td>14</td>
<td>15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: CR, complete remission; PR, partial remission; SD, stability of disease; PD, progression of disease.

Table 2. Comparison of clinical efficacy

<table>
<thead>
<tr>
<th>Group</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>Total effective rate (%)</th>
<th>Total control rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group (n=63)</td>
<td>5 (7.94)</td>
<td>32 (50.79)</td>
<td>18 (28.57)</td>
<td>8 (12.70)</td>
<td>37 (58.73)</td>
<td>55 (87.30)</td>
</tr>
<tr>
<td>Control group (n=58)</td>
<td>0 (0.00)</td>
<td>23 (39.66)</td>
<td>19 (32.76)</td>
<td>16 (27.59)</td>
<td>23 (39.66)</td>
<td>42 (72.41)</td>
</tr>
<tr>
<td>χ²</td>
<td>8.975</td>
<td></td>
<td></td>
<td></td>
<td>4.395</td>
<td>4.210</td>
</tr>
<tr>
<td>P</td>
<td>0.030</td>
<td></td>
<td></td>
<td></td>
<td>0.036</td>
<td>0.040</td>
</tr>
</tbody>
</table>
TS-1 plus docetaxel with or without oxaliplatin

**Comparison of PFS**

The PFS of the observation group was 5.73 months (95% CI: 5.290-6.180), and of the control group was 5.69 months (95% CI: 5.213-6.170), with no statistical difference between the two groups ($\chi^2 = 0.107, P = 0.774$). See Figure 1.

**Comparison of OS**

The OS in the observation group was 11.18 months (95% CI: 9.835-12.525), which was not significantly different from 11.25 months in the control group (95% CI: 10.043-12.471) ($\chi^2 = 0.008, P = 0.928$). See Figure 2.

**Comparison of KPS score**

A repeated measures analysis of variance in KPS scores between the two groups found that there were differences in KPS scores between the two groups at 3 weeks and 6 weeks postoperatively, and scores were higher in the observation group than those in the control group ($P < 0.05$). See Table 3.

**Comparison of adverse reactions**

We compared the incidence of adverse reactions between patients with grade 1-2 and with grade 3-4 in the two groups and found no difference in the adverse reactions after chemotherapy between the two groups (all $P > 0.05$). All the adverse reactions occurred were tolerable and properly treated. See Table 4.

**Discussion**

At present, it has become a research hotspot to optimize the radiotherapy and chemotherapy regimen for patients with advanced gastric cancer to reduce postoperative recurrence and metastasis and improve survival [12, 15]. With the advent of new chemotherapeutic drugs and protocols, the most commonly used drugs in the clinic now are fluoropyrimidines, platinum, taxanes, and trastuzumab, but the optimal chemotherapy regimen remains controversial [10]. The compound preparation composed of tegafur, gimeracil and oteracil potassium can inhibit the activity of orotate phosphoribosyltransferase in the gastrointestinal tract, thereby lessening its decomposition in the gastrointestinal tract, prolonging the action time *in vivo*, and maintaining the blood concentration, which promotes the transformation and absorption of the drug, and eventually achieves the purpose of inhibiting tumor growth [16]. A study found that the distribution of TS-1 was selective, mainly in the gastrointestinal tract, so the drug was able to alleviate gastrointestinal symptoms such as nausea and vomiting [17]. Additionally, TS-1 is an oral drug that can avoid or reduce the toxicity of intravenous injection on the heart and kidney [18]. Other study showed that the compound preparation of tegafur, gimeracil and oteracil potassium had a significant effect on advanced gastric cancer [19]. Oxaliplatin is a third-generation platinum drug that targets DNA and effectively prevents DNA replication and transcription [20]. Docetaxel is a taxol drug that has been shown to lead an improved effective rate for patients with advanced gastric cancer when combining with chemotherapy drugs [21].

In terms of efficacy, previous study showed that TS-1 combined with oxaliplatin regimen for the treatment of 41 patients with gastric cancer...
TS-1 plus docetaxel with or without oxaliplatin

had a total effective rate of 53.7% and a median survival of 7.8 months [22]. Another study also used the combination of the two drugs for gastric cancer patients and showed an effective rate of 55.8% and PFS of 7 months [23]. Previous study that applied the three-drug combination of paclitaxel, oxaliplatin and TS-1 found an effective rate of 66.7% and PFS of 7.1 months [24]. In this study, the total effective rate of the observation group, using the combination of three drugs, was 58.73%, and the total control rate was 87.30%, which were significantly higher than those in the control group (39.66% and 72.41%), with statistical difference. The PFS and OS of the observation group were 5.73 months and 11.18 months, which were not significantly different from 5.69 months and 11.25 months, respectively in the control group.

The KPS score was used to evaluate the physical condition of the patient after treatment, and the higher the score, the better the physical condition [13]. In the study, it was found that the KPS score of the observation group was higher than that of the control group after three-week and six-week chemotherapy, indicating that the combination of the three drugs was beneficial to the recovery of the patient’s physical condition, which may be related to the higher effective rate and control rate of the observation group.

In terms of adverse reactions, the common reactions after chemotherapy in the two groups were symptoms in blood system and digestive system. Statistical comparison showed no significant difference between the two groups in leukopenia, hemoglobin reduction, thrombocytopenia, nausea and vomiting, abnormal liver function, alopecia, neurotoxicity, and hand-foot syndrome. A study showed that the main adverse reactions in patients with gastric cancer treated with TS-1 combined with oxaliplatin were leukopenia and thrombocytopenia [23]. The reactions in patients treated with the three-drug regimen were leukopenia and alopecia [25]. The adverse reactions appeared in this study were tolerated, and the incidence was similar to the above studies.

The sample size of this study was small, so further expansion of the sample size is needed. Additionally, this study was a retrospective but not a prospective study, so a multicenter prospective study should be performed to further confirm the effect of three-drug chemotherapy regimen.

The chemotherapy regimen of TS-1 plus docetaxel and oxaliplatin has significant effects in patients after gastrectomy and improves the patient’s physical condition, with reliable safety, so it is worthy of clinical investigation and promotion.

Table 3. Comparison of KPS score

<table>
<thead>
<tr>
<th>Group</th>
<th>At admission</th>
<th>3 weeks after operation</th>
<th>6 weeks after operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observation group (n=63)</td>
<td>68.48±5.27</td>
<td>85.43±5.10</td>
<td>90.00±2.84</td>
</tr>
<tr>
<td>Control group (n=58)</td>
<td>67.02±5.42</td>
<td>73.29±5.60</td>
<td>74.19±3.14</td>
</tr>
<tr>
<td>F</td>
<td>257.541</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.000</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: KPS, karnofsky performance status.

Table 4. Comparison of adverse reactions (n, %)

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Observation group (n=63)</th>
<th>Control group (n=58)</th>
<th>( \chi^2 )</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 1-2</td>
<td>Grade 3-4</td>
<td>Grade 1-2</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>8 (12.70)</td>
<td>4 (6.35)</td>
<td>10 (17.24)</td>
<td>8 (13.79)</td>
</tr>
<tr>
<td>Hemoglobin reduction</td>
<td>12 (19.05)</td>
<td>5 (7.94)</td>
<td>15 (25.86)</td>
<td>5 (8.62)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13 (20.63)</td>
<td>4 (6.35)</td>
<td>12 (20.69)</td>
<td>6 (10.34)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>20 (31.75)</td>
<td>5 (7.94)</td>
<td>19 (32.76)</td>
<td>4 (6.90)</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>8 (12.70)</td>
<td>2 (3.17)</td>
<td>8 (13.79)</td>
<td>6 (10.34)</td>
</tr>
<tr>
<td>Alopecia</td>
<td>12 (19.05)</td>
<td>13 (20.63)</td>
<td>15 (25.86)</td>
<td>13 (22.41)</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>5 (7.94)</td>
<td>7 (11.11)</td>
<td>8 (13.79)</td>
<td>4 (6.90)</td>
</tr>
<tr>
<td>Hand-foot syndrome</td>
<td>6 (9.52)</td>
<td>2 (3.17)</td>
<td>9 (15.52)</td>
<td>3 (5.17)</td>
</tr>
</tbody>
</table>

In terms of adverse reactions, the common reactions after chemotherapy in the two groups were symptoms in blood system and digestive system. Statistical comparison showed no significant difference between the two groups in leukopenia, hemoglobin reduction, thrombocytopenia, nausea and vomiting, abnormal liver function, alopecia, neurotoxicity, and hand-foot syndrome. A study showed that the main adverse reactions in patients with gastric cancer treated with TS-1 combined with oxaliplatin were leukopenia and thrombocytopenia [23]. The reactions in patients treated with the three-drug regimen were leukopenia and alopecia [25]. The adverse reactions appeared in this study were tolerated, and the incidence was similar to the above studies.

The sample size of this study was small, so further expansion of the sample size is needed. Additionally, this study was a retrospective but not a prospective study, so a multicenter prospective study should be performed to further confirm the effect of three-drug chemotherapy regimen.

The chemotherapy regimen of TS-1 plus docetaxel and oxaliplatin has significant effects in patients after gastrectomy and improves the patient’s physical condition, with reliable safety, so it is worthy of clinical investigation and promotion.
Disclosure of conflict of interest

None.

Address correspondence to: Xinzhong Zou, Department of Oncology, Affiliated Hospital of Jiangnan University, No.585 Xingyuan North Road, Wuxi 214041, Jiangsu Province, China. Tel: +86-0510-82606510; Fax: +86-0510-82606510; E-mail: zouxinzhong25zzx@163.com

References


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