Effects of Cetuximab Combined with Modified FOLFIRI on Advanced Gastric Cancer in Second-line Treatment

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ABSTRACT Objective: To observe the effects of Cetuximab combined with modified FOLFIRI on advanced gastric cancer in second-line treatment and evaluate its efficacy and adverse reactions, and to investigate the relationship between its efficacy and prognosis. Methods: Tumor lesions and adverse reactions were observed every 2 cycles of treatment, and the progress of tumor and survival were followed up. Tumor remission assessment were performed in accordance with Response Evaluation Criteria in solid Tumors (RECIST) and the adverse event were classified according to the Common adverse events evaluation criteria version 3.0 (NCI a CTCAE3.0) by National Cancer Institute. Calculate the tumor remission rate, median time to progression and median overall survival. Results: Among the 38 patients who completed at least 2 cycles of treatment and received efficacy evaluation, one case was observed in complete remission (CR), accounting for 0.03%; 13 cases were in partial remission (PR), accounting for 34.00%; the overall remission rate (ORR = CR + PR) was 37.00%. 20 cases were in status of stable disease (SD), accounting for 53.00%; disease control rate (Disease Control Rate, DCR = CR + PR + SD) was 89.00%. Disease progression (PD) was occurred in 4 cases, accounting for 11.00%. The overall safety is good, for no case of treatment-related death occurred. The III / IV neutropenia incidence was 52.5%, incidence of febrile due to particle missing 13.1%, incidence of III / IV degree severe anemia 29.5%, incidence of III / IV degree of thrombocytopenia decline 8.2%. III / IV degree of non-hematologic toxicity included nausea (8.2%), vomiting (6.6%), stomatitis (1.6%), diarrhea (6.6%), infection (4.9%), fatigue (4.9%), ileus (6.6 %), elevated aminotransferases (l.6%), allergic reactions (l.6%) and rash (9.8%). Conclusion: This study showed that Cetuximab combined with modified FOLFIRI is a safe and effective program in second-line treatment of advanced gastric cancer patients. It is required to further research and find its effective biomarkers.

Key words: Cetuximab Alone; Gastric Cancer; Second-Line Treatment; FOLFIRI Program

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Forewords

Although the incidence of gastric cancer is declining worldwide, adenocarcinoma in the junction of proximal stomach and lower esophageal has been gradually increased over the past 10 years [1]. The clinical manifestations of gastric cancer are not clear and the cancer cannot be diagnosed in early period. Most gastric cancers are diagnosed as advanced gastric cancer, and chemotherapy is the main method to treat advanced gastrio cancer (AGc) [2]. Several randomized clinical studies have shown that the combined chemotherapies can significantly prolong median survival time and improve quality of life in AGC patients compared with best supportive care. However, in the field of first-line chemotherapy for patients with AGc, no program is globally accepted as standard treatment because it is not significantly superior to other programs. Cetuximab (C225) is a human mouse chimeric anti-EGFR monoclonal antibody, and it has a significant effect in metastatic colorectal cancer, head and neck squamous cell carcinoma and non-small cell carcinoma [3]. Preliminary experiments have shown that in gastric cancer cells, cetuximab combined with irinotecan has synergistic anti-tumor effect, which further provided a theoretical basis for clinical studies. Therefore, in phase II of this prospective clinical study, cetuximab will be combined with FOLFIRI to treat patients with locally advanced or metastatic gastric cancer who were not successfully treated in first line. Their efficacy and adverse reactions will be observed, and their correlation with efficacy and prognosis will also be investigated.

1 Material and Method

1.1 Clinical data

48 patients with gastric cancer were observed and treated from November 2008 to February 2010 in our hospital, all of whom were conformed to the following standards: aged from 18 to 70 years old; They were confirmed by pathological histology having metastatic or advanced gastric adenocarcinoma which were locally recurrent; Had measurable lesions, target lesions through spiral CT should be ≥ 10 mm, through ordinary CT and MRI should be ≥ 20 mm; ECOGPS score was three points; Informed consent forms were signed; They were failed in first line chemotherapy treatment with locally advanced or metastatic gastric cancer. The laboratory check at baseline: routine blood ≥ 2.0×10^9/L, PLI ≥ 80×10^9 / L; Kidney function: Cr ≥ 1.0 × upper normal limit (UNL); Liver function: total bilirubin ≤ 1 × UNL, ALT and AST ≤ 1.5 × UNL; Period after the last chemotherapy time ≥ 1

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month. Patients with similar clinical conditions were randomly divided into two groups according to age and courses: 25 cases in control group; 23 cases in treatment group. There were no statistical differences in sex, age, weight index and other general situations between the two groups.

1.2 Treatment protocol

Cetuximab were provided by German Merck with free of charge. First dose was 400 mg/m^2, with more than 120 minutes of intravenous drip; after that the dosage was 250 mg weekly, at dl and d8, with more than 60 minutes of intravenous drip. Antihistamine and corticosteroids drugs should be given to prevent allergic reactions before the use of Cetuximab, and the vital signs should be monitored before drug use, during drug use, right after drug use and 1 hour after drug use. The dose of Irinotecan was 150mg/ m^2, with 2 hours of intravenous drip, d2. It was not recommended to use drugs to prevent choline syndrome at the first time. When tears, sweat, abdominal pain and other diarrhea acetylcholine syndrome appeared in patients within 24 hours after use of irinotecan, 0.25 mg of atropine would be recommended by subcutaneous injection, or intramuscular injection. After that, atropine would be conventionally used to prevent acetylcholine syndrome. The folic acid calcium dose is 200 mg/m^2, d2, with intravenous drip before 5-fluorouracil. 5-fluorouracil dose was 400 mg/m^2, with bolus administration, after that, 2.4 g/m^2 with intravenous bolus administration for continuous 46 hours, d2. The above three drugs were repeatedly used in every 2 weeks, 2 times for a cycle of treatment. The program would continue until disease progression or adverse reactions appeared and could not be tolerated by patients or patients required to withdraw from the research initiatively. Chemotherapy would continue if there was delay treatment because of skin toxicity related with Cetuximab, patients would be out from research if they had delayed treatment because of other toxicity correlated with Cetuximab and the researchers would decide the next step of treatment.

1.3 Clinical Efficacy Evaluation

The situation of tumor lesions was evaluated per 2 cycles of treatment, and adverse reactions were observed, tumor progression and survival time were followed up. Tumor remission was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST). Adverse events were classified according to the National Cancer Institute common adverse event evaluation criteria version 3.0 (NCI -CTCAE3.0). The tumor remission rate, median time to progression and overall median survival time were calculated.

1.4 Statistical Methods

SPSS 13.0 statistical package was applied for statistical analysis for all samples. Data were presented with the mean ± standard deviation ($\bar{x}\pm s$). Analysis of variance was used to compare the differences between groups. When $P<0.05$, the difference was considered statistically significant.

2 Results

2.1 Basic situation of patients

In all 48 patients, male 21 cases, females 27 cases, ratio of male to female was 1.3:1; patients aged between 26 and 69 years old, average age was 52 years, and patients > 59 years of age accounted for 28 %; ECOGPS score between 0 and 1, in whom patients with a score of 0 were accounted for 28%; patients' first-line chemotherapy protocol mainly consisted of four kinds, most of which were the ECF program (epirubicin, cisplatin, 5-fluorouracil) and variants (oxaliplatin instead of cisplatin, capecitabine instead of 5-fluorouracil), accounting for 56% . Fluorouracil combined with platinum drugs were accounted for 21%, taxanes combined with 5-fluorouracil drugs were accounted for 21%. Only one patient was treated with single-agent Xeloda in first-line chemotherapy, accounting for 2% (Table 1).

2.2 Treatment situation

In all of the 48 patients, 38 patients completed at least two cycles of treatment. Two patients failed to complete two cycles of therapy and withdrew from the study, in whom one patient was only transfused with cetuximab once, and was out of the research because obstructive jaundice was found out when liver and kidney function were checked before chemotherapy. Five patients suffered IV neutropenia fever after one cycle of treatment, and required initiatively to withdraw from the study. Two patients had intestinal obstruction after one cycle of treatment, and were out of study because delayed treatment time was longer than that required by the program.

2.3 Remission rate

As shown in Table 2, 38 cases completed at least two cycles of therapy and efficacy evaluation. Among them, one case had complete remission (CR), accounting for 0.03%; 13 cases had partial remission (PR), accounting for 34.00%; overall remission rate (ORR = CR + PR) was 37.00%. Patients with stable disease (SD) had 20 cases, accounting for 53.00%; disease control rate (Disease Control Rate, DCR = CR + PR + SD) was 89.00%; Patients with disease progression (PD) were 4 cases, accounting for 11.00%.

2.4 Time to progression (TTP)

The patients were followed up until February 2010, in all of the 48 patients, 10 patients still did not appear disease progression (21%). According to intend-to-treat analysis, the median time to progression was 4.6 months, 95% CI was 3.5 months to 5.7 months (Table 3). Figure 1 shows the patients' TTP curve by Kaplan-Meier method.

2.5 Adverse reactions

In this study, the overall safety of this program was good, no treatment-related death occurred. The incidence rate of III / IV grade neutropenia was 52.5%. The incidence rate of febrile neutropenia was 13.1% . Grade III - IV anemia rate was 29.5% .

Table 1 Basic situation of patients

	Number of cases	Percentage(%)
Total cases at baseline	48	100
Gender		
Male	21	43
Female	27	57
Age		
≤ 59	35	72
>59	13	28
ECOGPS		
0	13	28
1	35	72
First-line chemotherapy		
SFu/Xeloda,L-OHP	11	21
ECF/EOF/EOX	21	56
SFu,TXT/P TX	11	21
Xeloda	5	2

Table 2 The remission status of patients with gastric cancer

	Cases(N=38)	Percentage(%)
Overall remission	14	37.00
Complete remission	1	0.03
Partial remission	13	34.00
Disease stable	20	53.00
Disease progression	4	11.00

Table 3 TTP of the patients with gastric cancer

	Median TTP	S.E.	95%CI	
			LL	UL
Time(Months)	4.600	0.581	3.461	5. 739

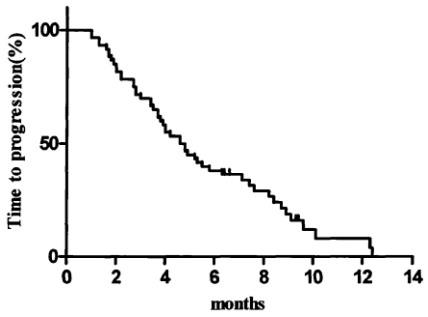

Fig.1 TTP curve of patients with gastric cancer

Grade III- IV platelet decreasing rate was 8.2%. Non-hematologic toxicity of Grade III-IV included nausea (8.2%), vomiting (6.6%), stomatitis (1.6%), diarrhea (6.6%), infection (4.9%), fatigue (4.9%), intestinal obstruction (6.6 %), elevated aminotransferases (l.6%), allergic reactions (l.6%) and rash (9.8%).

3 Discussion

Advanced gastric cancer (AGC) of chemotherapy began in the 1960s, the effect of 5-fluorouracil (SFu) was studied most, but the effect of single drug application was not satisfied. The remission rate was 21%. The combined chemotherapy began in 1970s, among which EAM (fluorouracil, doxorubicin, mitomycin) programs were widely used [4]. However, randomized controlled studies have shown that there was no significant difference in remission rate and survival time between the use of FAM, FA (SFu, doxorubicin), and single-SFu treatment for gastric cancer. Later the response rate and median survival time in patients with FAMTx (fluorouracil, doxorubicin, methotrexate) were found to

be better than those with FAM. FAMTX was once regarded as a standard chemotherapy protocol in Europe and America.

Epidermal growth factor receptor (EGFR) were normally expressed in squamous cells of esophagus, head and neck, while they had no expressions in the gastrointestinal tract, breast and other epithelial cells [5]. Studies have shown that the expression of EGFR has increased in gastric epithelial dysplasia and gastric cancer, especially in severe dysplasia and advanced gastric cancer. This indicates that EGFR was closely related with the incidence and progression of gastric cancer [2,6]. Studies have shown that the prognosis of patients with gastric cancer was worse if expressions of EGFR were positive. Gastric cancer occurs mainly in the elderly, because the elder patients usually have poor general conditions and nutritional status due to gastrointestinal dysfunction. Cetuximab is superior to other EGFR inhibitors because of its security. The side effects of Cetuximab monotherapy were mild, and mainly were acne-like rash. However, the side effects of irinotecan were severe, and mainly were diarrhea and myelosuppression [7]. Therefore, cetuximab combined with irinotecan may reduce the dose of irinotecan so as to reduce the adverse effects of irinotecan. Based on these results, we further carried out the phase II clinical study on combined use of cetuximab with improved FOLFI program in second-line treatment for patients with advanced gastric cancer[8].

The results showed that in 38 cases who completed at least two cycles of therapy and were received efficacy evaluation, one case had complete remission (CR), accounting for 0.03%; 13 cases had partial remission (PR), accounting for 34.00%; The total remission rate (ORR = CR + PR) was 37.00%. 20 cases were patients with stable disease (SD) , accounting for 53.00%; disease control rate (DCR = CR + PR + SD) was 89.00%; 4 cases were patients with disease progression (PD), accounting for 11.00%. The safety of this program was overall good, and no treatment-related death occurred. The incidence rate of III / IV grade neutropenia was 52.5%, the that of febrile neutropenia was 13.1%, that of III / IV grade anemia incidence was 29.5% , that of III / IV grade thrombocytopenia was 8.2%. III / IV grade non-hematologic toxicity included nausea (8.2%), vomiting (6.6%), stomatitis (1.6%), diarrhea (6.6%), infection (4.9%), fatigue (4.9%), intestinal obstruction (6.6 %), elevated aminotransferases (l.6%), allergic reactions (l.6%) and rash (9.8%). These results indicated that the joint use of cetuximab with FOLFIRI in second-line chemotherapy to treat advanced gastric cancer was safe and effective, and worthy of further randomized controlled studies to validate its efficacy.

In this study, the tumor remission rate was 37%, in all 48 patients, 10 patients still did not appear disease progression (21%). According to intend-to-treat analysis, the median time to progression was 4.6 months, 95% CI was 3.5 months to 5.7 months, suggesting that some patients were resistant to this program. Ineffective therapy on these patients can be avoided by looking for biomarkers to predict the efficacy, and gene targeting tailored therapy and targeted medicine therapy[9-10] can also be carried out to reduce the waste of economy and time, and avoid unnecessary side effects, which have important and practical significance. In conclusion, this study showed that the joint use of cetuximab with FOLFIRI in second-line treatment for patients with advanced gastric cancer was a safe and effective program; further studies were needed to find effective biomarkers.

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西妥昔单抗联合 FOLFIRI 方案治疗晚期胃癌的疗效观察

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摘要 目的：观察西妥昔单抗联合 FOLFIRI 方案用于一线治疗失败的局部晚期或转移性胃癌患者，观察其疗效和不良反应，并观察其与疗效和预后的相关性。方法：每 2 疗程评价肿瘤病灶情况，观察不良反应，随访肿瘤进展情况及生存期。按照实体瘤疗效评价标准(Response Evaluatione Criteria in solid Tumors，RECIST)进行肿瘤缓解评估，按照国立癌症研究所常见不良事件评价标准 3.0 版(NCI 一 CTCAE3.0)进行不良事件分级。计算肿瘤缓解率、中位至疾病进展时间和中位总生存期。结果：在 38 例至少完成了 2 个周期治疗并进行了疗效评价的患者中，观察到 1 例完全缓解(CR)，占 0.03%；13 例部分缓解(PR)，占 34.00%；总的缓解率(ORR=CR+PR)为 37.00%。疾病稳定(SD)的患者有 20 例，占 53.00%；疾病控制率 (Disease Control Rate，DCR=CR+PR+SD)为 89.00 %；疾病进展(PD)的患者为 4 例，占 11.00 %。本研究方案总体安全性良好，未发生一例治疗相关性死亡。其中 III/IV 度粒细胞减少的发生率为 52.5%，粒缺性发热的发生率为 13.1%，III/IV 度度贫血的发生率为 29.5%，III/IV 度度血小板下降的发生率为 8.2%。III/IV 度非血液学毒性包括恶心(8.2%)，呕吐(6.6%)，口腔炎(1.6%)，腹泻(6.6%)，感染(4.9%)，乏力(4.9%)，肠梗阻(6.6%)，转氨酶升高(l.6%)，过敏反应(l.6%)和皮疹(9.8%)。结论：本研究显示在晚期胃癌患者的二线治疗中西妥昔单抗联合 FOLFIRI 是一个安全有效的方案，需要进一步的研究寻找有效的生物标记物。

关键词：西妥昔单；胃癌；二线治疗；FOLFIRI 方案

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