RESEARCH ARTICLE

Clinical Study of Nimotuzumab Combined with Chemotherapy in the Treatment of Late Stage Gastric Cancer

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Abstract

Objective: To explore the clinical effects of nimotuzumab combined with chemotherapy in the treatment of late gastric cancer. Methods: A total of 34 reoccurrence or metastatic patients with late stage gastric cancer who were confirmed by histopathology and/or cytology were selected and randomly divided into observational and control groups, of 17 cases each. Patients in the control group were treated with the standard DCF plan, while patients in observational group additionally received nimotuzumab. The short-term and long-term efficacy and adverse reactions in the 2 groups were followed. Results: The objective response rate (ORR) and disease control rate (DCR) were 64.7% (11/17) and 82.4% (14/17) in observational group and 25.0%(4/16) and 37.5%(6/16) in the control group(ORR and DCR between 2 groups, χ^2=5.2412, *P*=0.0221 and χ^2=6.9453, *P*=0.0084). The median progression-free survival (PFS) time and median overall survival (OS) time were 6.50 months and 12.50 months in observational group and 4.50 months and 8.25 months in the control group (*P*=0.0212; *P*=0.0255). The main toxic and side effects in the 2 groups were reduced leukocytes and hemoglobin, gastrointestinal reactions and hair loss and these were relieved after symptomatic treatment and nutrition support therapy. There were no differences in the occurrence of toxic and side effects between the 2 groups. Conclusions: Nimotuzumab combined with DCF plan is effective in treating late stage gastric cancer. A larger scale study is now warranted for confirmation of the findings.

Keywords: Nimotuzumab - chemotherapy-gastric cancer - progression-free survival - toxic and side effects

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Introduction

Gastric cancer, one of common malignant tumors, has high modality in Asian. Most patients are found in late gastric cancer when clinically diagnosed and lose the chance of surgery because the early clinical symptoms of gastric cancer are easy to be ignored. Chemotherapy-based comprehensive treatment is adopted for the treatment of late gastric cancer, but the curative effect is not ideal. In recent years, in order to improve the efficacy and the survival time of the patients, targeted drugs combined with chemotherapy regimens come into being. Nimotuzumab, the first humanized monoclonal antibody, which regards epidermal growth factor receptor (EGFR) as the target, can competitively inhibit the combination of endogenous ligand and EGFR and block EGFR-mediated signal transduction pathway and cytological effect, thus inhibiting tumor cell proliferation, angiogenesis, infiltration and metastasis and promoting tumor cell apoptosis (Barta et al., 2013). In addition, nimotuzumab can enhance the chemoradiotherapy effects (Diaz-Miqueli et al., 2013; Lin et al., 2014; Song et al., 2014). So far, multiple studies at home and abroad have proved that nimotuzumab are effective in treatment of head and neck neoplasm, colorectal cancer, pancreatic cancer, non-small cell lung cancer (NSCLC) and breast cancer (Diaz-Miqueli et al., 2013; Lin et al., 2014; Song et al., 2014). Moreover, nimotuzumab combined with chemotherapy or radiology is approved for treating head and neck squamous cell carcinoma, glioma in children, nasopharynx cancer (Ciardiello et al., 2008). In order to explore the efficacy of nimotuzumab in the treatment of advanced malignant neoplasm, nimotuzumab combined with chemotherapy was adopted for treating 34 patients with advanced gastric cancer in our hospital since February 2012, with good effect. Here are the results.

Materials and Methods

General data

This study was approved by Ethics Committees of People's Hospital of Rizhao, Shandong. A total of 34 reoccurred or metastatic patients with late gastric cancer from February, 2012 to May, 2013, who were confirmed by histopathology and/or cytology were selected, of which, there were 20 males and 14 females, aged 32~74 years old with the median age being 57 years; 9 with initial treatment and 25 with retreatment; 13 with family history and 21 without family history; all with adenocarcinoma in stage IV; 5 with high differentiation, 8 with moderate

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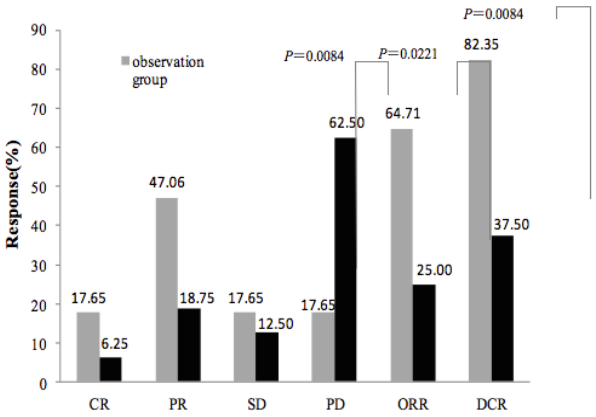

Figure 1. Comparison of Short-Term Efficacy of 2 Groups

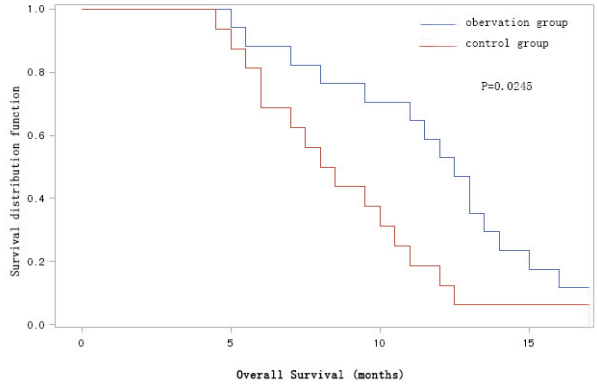

Figure 2. The PFS Curves of 2 Groups

differentiation and 21 with low differentiation; 23 with perigastric, abdominal cavity and peritoneal metastasis and 14 with liver metastasis, 9 with neck lymph node metastasis and 4 with other metastasis such as osseous metastasis. All patients were not accompanied by basic medical history and had normal routine blood examination and liver, kidney and ECG function. The Eastern Collaborative Oncology Group (ECOG) Karnofsky scores were ≥2. The expected lifetime were ≥3 months. All patients were divided into observational group and control group, 17 cases, respectively, and there were no differences in general data such as age, gender, Karnofsky scores and tumor differentiation degree (P>0.05), with comparability. All patients or relatives signed the informed consent.

Therapeutic method

Patients in control group were given DCF plan according to the comprehensive assessment of the clinical situation. DCF plan was as described below: intravenous drip of 60 mg/m^2 docetaxel for 1 h on d1 of treatment, dexamethasone 1 day before drug administration, 8 mg each time, twice daily, for 3 consecutive days, intravenous drip of 40 mg cisplatin on d1, continuous infusion of 600 mg/m^2 fluorouracil by portable infusion pump for 120 h, every 21 d as 1 cycle, and intravenous drip of 50 mL azasetron sodium chloride injection during 15 min before chemotherapy for gastrointestinal reaction. During chemotherapy, blood routine was examined weekly and liver and kidney functions were reviewed at the end of each cycle. If leukocyte or polymorphonuelear was reduced, supportive treatment of granulocyte colony-

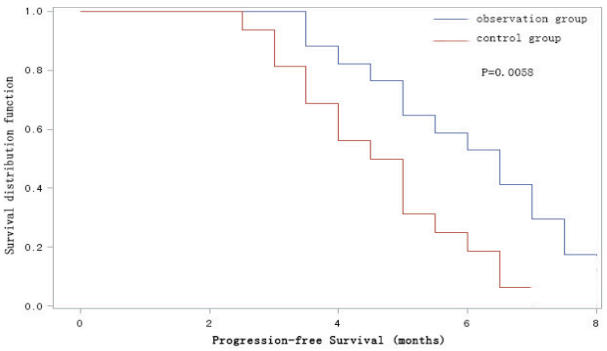

Figure 3. The OS Curves of 2 Groups

stimulating factor was given. Based on that, observational group was added with nimotuzumab. Intravenous drip of nimotuzumab (200 mg) plus normal saline (500 mL) was given for 2 h on the 1st day of chemotherapy, once weekly for 6 consecutive cycles. Afterwards, the same dose was given for consolidation therapy, once every 2 weeks until disease progression or severe intolerable adverse reactions happened, or patients and relatives gave up the treatment, or patients were dead. The efficacy of all patients was evaluated once every 2 cycles.

Observational indexes

The short-term and long-term efficacy and adverse reactions of 2 groups were observed. Overall survival (OS) and progression-free survival time were recorded.

Evaluation criterion

RECIST 1.1 criteria were used for evaluating the efficacy and included complete remission (CR), partial remission (PR), stable disease (SD) and progression disease (PD). The objective response rate (ORR)= (CR+PR)×100% and disease control rate= (CR+PR+SD)×100%.

According to Version 4.0 of National Cancer Institute Common Toxicity Criteria (NCI-CTC 4.0), toxicity was divided into 0~4 grades, and according to this criteria, the corresponding toxic and side effects were given symptomatic treatment.

Statistical data analysis

SAS 9.3 statistical software package was used for data analysis. The rate in groups was compared by χ^2 test. The median OS and PFS were analyzed by Wilcoxon rank sum test. Kaplan-Meier and log-rank test was used for survival analysis. P<0.05 was considered to be statistically significant.

Results

The comparison of short-term efficacy of 2 groups

Of all patients, there were 1 case given other therapeutic method because of increased level of tumor marker and the enlarged tumor. The treatment cycles of the other 33 cases were more than 2, so they were evaluated and complete 158 cycles in total, 2~6 cycles for each case, with the median number of cycles being 4.

The ORR and DCR were 64.71% (11/17) and 82.35% (14/17) in observational group 25.00% (4/16) and 37.50% (6/16) in control group and there were significances in

Table 1. Comparison of Toxic and Side Effects of 2 Groups [n (%)]

Adverse reactions	Groups	Toxicity grading					χ^2	*P* value
		0	1	2	3	4		
Fever	Observational group	16 (94.12)	1 (5.88)	0 (0)	0 (0)	0 (0)	0.3656	0.5454
	Control group	15 (88.24)	2 (11.76)	0 (0)	0 (0)	0 (0)		
Hair loss	Observational group	7 (41.18)	10 (58.82)	0 (0)	0 (0)	0 (0)	0.1193	0.7298
	Control group	8 (47.06)	9 (52.94)	0 (0)	0 (0)	0 (0)		
Rash	Observational group	17 (100)	0 (0)	0 (0)	0 (0)	0 (0)	2.1250	0.3456
	Control group	15 (88.24)	1 (5.88)	1 (5.88)	0 (0)	0 (0)		
Gastrointestinal	Observational group	13 (76.47)	3 (17.65)	1 (5.88)	0 (0)	0 (0)	1.3704	0.5040
reactions	Control group	14 (82.35)	1 (5.88)	2 (11.76)	0 (0)	0 (0)		
Liver damage	Observational group	14 (82.35)	3 (17.65)	0 (0)	0 (0)	0 (0)	0.2345	0.6282
	Control group	15 (88.24)	2 (11.76)	0 (0)	0 (0)	0 (0)		
Reduced	Observational group	0 (0)	5 (29.41)	9 (52.94)	2 (11.76)	1 (5.88)	0.7255	0.8672
leukocyte	Control group	0 (0)	7 (41.18)	8 (47.06)	1 (5.88)	1 (5.88)		
Decreased	Observational group	1 (5.88)	4 (23.53)	11 (64.71)	1 (5.88)	0 (0)	1.2919	0.7311
hemoglobin declined	Control group	1 (5.88)	7 (41.18)	8 (47.06)	1 (5.88)	0 (0)		
Platelet	Observational group	10 (58.82)	3 (17.65)	1 (5.88)	2 (11.76)	1 (5.88)	0.8622	0.9299
	Control group	9 (52.94)	4 (23.53)	2 (11.76)	1 (5.88)	1 (5.88)		

ORR and DCR between 2 groups (χ^2=5.2412, *P*=0.0221; χ^2=6.9453, *P*=0.0084), as shown in Figure 1.

The comparison of long-term efficacy of 2 groups

The patients were followed up until October 2014 and follow-up event was stopped until patients died or the follow up stopped. No patients were lost to follow-up, so follow-up rate was 100%.

PFS time and OS time were 6.50 months and 12.50 months in observational group and 4.50 months and 8.25 months in control group and there were statistical significances in the median PFS and OS between 2 groups (*P*=0.0212; *P*=0.0255). The PFS and OS curves of 2 groups were as shown in Figure 2 and 3.

Safety evaluation

All patients received treatment cycles more than 1 cycle and could be evaluated. The main toxic and side effects of 2 groups were reduced leukocyte and hemoglobin, gastrointestinal reactions (nausea, vomiting and diarrhea) and hair loss and relieved after symptomatic treatment and nutrition support therapy. However, there were no differences in the occurrence of toxic and side effects between 2 groups (Table 1).

Discussion

Gastric cancer is one of common malignant tumors, with the ORR of the first-line chemotherapy less than 60% and the median OS being 6.0~10.0 months (Roy et al., 2012; Tomasello et al., 2014). At present, there were no ideal drugs or combined therapies for the treatment of gastric cancer. And chemotherapy was regarded as the main method for treating late gastric cancer (Wei et al., 2013; Liu et al., 2014). However, it has limitation in clinical application because patients can't tolerate its toxic and side effects. Molecular targeted therapy, a new trend of treating late gastric cancer, can inhibit or kill tumor cells specifically and reduce the damage of normal tissues in human body.

EGFR is closely associated with the occurrence, development, grade of malignancy and prognosis of the tumor and the sensibility of chemoradiotherapy. A large number of literatures were reported that EGFR could be detected in cells of multiple tumors such as nasopharyngeal carcinoma, colorectal cancer, glioma, pancreatic carcinoma and NSCLC (Aichler et al., 2014; Lee et al., 2014; Verdu et al., 2014). There are now multiple drugs targeting EGFR for treating malignancy, with favorable outcomes (Bersanelli et al., 2014).

Nimotuzumab, a kind of humanized monoclonal antibody specifically targeting EGFR, has features of high selectivity and long half-life period. Similar to the combination of rat monoclonal antibody and EGFR, it can inhibit the activity of receptor protein tyrosine kinase through the combination of EGFR and 3A epitope combined closed ligand in extracellular functional domain of EGFR, sequentially effectively blocking EGFR-mediated signal transmission and cellular response and consequently restraining the cell proliferation, inducing the cell apoptosis as well as inhibiting angiogenesis. In addition, it mediates complement dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC). Previous study of nimotuzumab combined with radiotherapy for treating glioblastoma multiforme showed that the median PFS and OS were 10.0 months and 15.9 months, respectively, and patients were well tolerated (Wang et al., 2014). Reddy et al (Reddy et al., 2014) reported in the study of nimotuzumab treating advanced cell carcinoma of the head and neck that nimotuzumab combined with chemotherapy or radiotherapy could reduce the mortality risk to 64% and 24%, respectively, when compared with single chemotherapy and single radiotherapy.

There were many researches showing that nimotuzumab was effective in treating multiple Okamoto et al., 2013; Su et al., 2014, but no researches of effect of nimotuzumab on survival were found. In this study, nimotuzumab combined with chemotherapy for treating late gastric cancer and the results revealed that ORR, OS and PFS significantly increased and patients were well tolerated when compared with single chemotherapy.

In conclusion, targeted therapy for late gastric cancer has become a new trend and nimotuzumab combined with chemotherapy have shown the good curative effects and safety of drug use. In this study, patients profit from use of nimotuzumab combined with chemotherapy in clinic, without unexpected safety events. The adverse reactions are relieved after symptomatic treatment and nutrition support therapy and the patients are well tolerated. However, with the limitation of sample size, enlarged samples is needed for further study to observe the clinical effects of nimotuzumab with chemotherapy for late gastric cancer and obtain more evidence of evidence-based medicine.

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