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Nimotuzumab Combined with Chemotherapy is a Promising Treatment for Locally Advanced and Metastatic Esophageal Cancer

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Background: Nimotuzumab is an anti-EGFR monoclonal antibody which has been widely used in cancer treatment. However, the safety and efficacy of nimotuzumab combined with chemotherapy in locally advanced or metastatic esophageal cancer patients remain unclear.

Material/Methods: To address this open question, we collected a total data of 21 patients diagnosed with locally advanced or metastatic esophageal cancer between 2012 and 2016 in a, retrospective study. The patient characteristics, efficacy safety, and toxicity were evaluated in our study.

Results: We observed 1 (4.8%) patient with complete response, 7 (33.3%) patients with partial response, 9 (42.9%) patients with stable response and 4 (19%) patients with progression response. The objective response rate was 38.1% and disease control rate was 81%. The mean progression-free-survival was 7 months and the 18-month overall survival (OS) was 10%. The incidence rate of anemia and leukopenia was 71.4% and 81%, respectively. Two patients showed the serious adverse event of myelosuppression, with nausea, fatigue, and anorexia. No long-term drug-related toxicity was observed during the follow-up.

Conclusions: Nimotuzumab combined with chemotherapy can achieve promising clinical outcomes in locally advanced or metastatic esophageal cancer, without accumulation of toxicity and was well-tolerated.

MeSH Keywords: Antibody Affinity • Antineoplastic Agents • Esophageal Neoplasms

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Background

Esophageal cancer is the most common cause of cancer deaths [1]. In China, 2015 cancer statistics data showed 4.29 million new cancer cases and 2.81 million deaths [2]. The morbidity and mortality of esophageal cancer was higher for these common tumors than for lung cancer and gastric cancer.

Most of the patients with esophageal cancer have middle and advanced stage with distant lymph node metastasis or organ metastasis. So chemotherapy plays an important role in the treatment of their locally advanced or metastatic esophageal cancer. At present, several agents including cisplatin, fluorouracil, irinotecan, docetaxel, and etoposide have also shown single agent activity in patients with locally advanced esophageal cancer [3–8]. Targeted therapies have produced encouraging results in the treatment of patients with advanced esophageal cancer. Trastuzumab plus chemotherapy is included as an option for first-line therapy for patients with Her2-positive advanced or metastatic esophageal cancer [9]. Ramucirumab is recommended as second-line therapy for patients with advanced or metastatic gastric or gastro-oesophageal junction adenocarcinoma [10]. Best supportive care is important for the comprehensive treatment of esophageal cancer. But the efficiency of existing treatment for locally advanced and metastatic esophageal cancer is not high and the effective treatment for esophageal cancer needs to be further explored in the future.

EGFR (epithelial growth factor receptor), also called Her1 or ErbB1, belongs to the family of ErbB receptors [11,12]. EGFR is located in the membrane surface and activated in downstream cellular signal transduction pathways by combining with the corresponding ligand [11,12]. The signal transduction pathways inhibit cell apoptosis, and promote cell division and angiogenesis. Several studies have shown that the EGFR gene is highly expressed among a variety of solid tumors, including colon cancer, non-small cell lung cancer, pancreatic cancer, head and neck cancer, and esophageal cancer [13]. The expression of the EGFR gene is closely related to tumor cell growth, proliferation, invasion, metastasis, and apoptosis [13]. Inhibiting EGFR pathway can inhibit tumor cell proliferation, differentiation, tumor angiogenesis, and promote treatment response of chemotherapy and radiation [13].

The EGFR gene is overly expressed in 80% of esophageal squamous cell carcinoma [13]. However, little is known about the effectiveness of nimotuzumab in esophageal squamous cell carcinoma patients. In this study, we retrospectively evaluated the safety and efficacy of nimotuzumab combined with chemotherapy in locally advanced or metastatic esophageal cancer patients.

Material and Methods

Patient selection

From May 2012 to May 2016, 21 patients (2 females and 19 males) with locally advanced or metastatic esophageal cancer, who were treated at the Department of Oncology at the Affiliated Anhui Provincial Hospital of Anhui Medical University, were enrolled in this clinical study. The inclusion criteria were as follows: (1) the histological type of all patients was esophageal squamous cell carcinoma (ESCC); (2) age ranged from 21 to 81 years; (3) the patients were diagnosed as stage III/IV according to the first edition of 2016 NCCN Guidelines; (4) the ECOG performance score of the patients was ≤2; (5) the metastatic site was limited to 4; (6) a life expectancy was ≥6 months; (7) no radiotherapy contraindications; and (8) patients provided written informed consent. The exclusion criteria were: (1) severe myelosuppression; (2) serious heart, liver, and kidney function insufficiency; (3) infectious diseases; (4) other malignant disease; and (5) malignant pleural or pericardial effusion. The baseline characteristics of the patients are listed in Table 1.

Antibody therapy and chemotherapy

The patients with locally advanced or metastatic esophageal cancer were treated by a combination of nimotuzumab and chemotherapy. The patients received a cycle of chemotherapy every 21 days and the dose of nimotuzumab was 200 mg every cycle. All patients received paclitaxel, fluorouracil, or gemcitabine based chemotherapy every three weeks. The chemotherapy regimen included TP (paclitaxel 150 mg/m^2/day on day 1, and nedaplatin 80 mg/m^2/day on day 1), GP (gemcitabine 1,000 mg/m^2/day on day 1 and nedaplatin 80 mg/m^2/day on day 1), GS (gemcitabine 1,000 mg/m^2/day on day 1 and S-1 40 mg/m^2/day on day 1), and PF (nedaplatin 80 mg/m^2/day on day 1 and fluorouracil 800 mg/m^2 IV continuous). The patients were examined by performing routine blood tests and liver and renal function tests. Adverse reactions were assessed by the National Cancer Institute Common Toxicity Criteria version 3.0. If the grade of toxicity was ≥3, the chemotherapy was stopped until the grade of toxicity resolved to 0–1.

Response and toxicity assessment

Therapeutic effect was evaluated every three weeks during chemotherapy. The tumor and lymph nodes were assessed according to imaging examination, including computed tomography (CT). The Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) was used to evaluated the treatment response. Toxicities assessment was evaluated according to the Common Toxicity Criteria 3.0 of the American National Cancer Institute.

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Table 1. Baseline characteristics of the patients with ESCC.

Characteristics	Number of patients (%)
Total	21
Median age (range) – year	60 (42–79)
Sex	
Male	19
Female	2
Age (years) Median (range)	
≤65	15
>65	6
ECOG performance status	
0	16
1	5
Histologic grade	
Weller moderately differentiated	15
Poorly differentiated	6
Other	0
Primary tumor location	
Upper	4
Middle	13
Lower	5
Stage	
III	10
IV	11
Lymph node metastasis	
Absent	3
Present	18
Distance metastasis	
Absent	10
Present	11
Previous therapies	
0	9
1	4
2	5
3	2
≥4	1
Chemotherapy regimen	
TP	15
GP	2
PF	1
GS	3

Table 2. Objective response according to RECIST criteria.

Type of response	Number (%)
Complete response (CR)	1 (4.8%)
Partial response (PR)	7 (33.3%)
Stable disease (SD)	9 (42.9%)
Progerssion disease (PD)	4 (19.0%)
Objective response (CR+PR)	8 (38.1%)
Disease control rate (CR+PR+SD)	17 (81.0%)

Follow up

Patients enrolled in this study were followed up every three months for the first year after the completion of chemotherapy and every six months thereafter. The primary endpoint was progression-free survival (PFS) and overall survival (OS). PFS was defined as the time from the date of randomization until the date of the tumor progression or death. OS was defined as the time from the date of admission to the date of death because of any causes or the last follow-up. Follow-up included a complete history, physical examination, complete blood count (CBC), chemistry profile, and imaging studies. Endoscopy was done if clinically indicated.

Statistical analysis

Statistical analysis was performed using SPSS 18.0 software. Survival curves were analyzed using the Kaplan-Meier curve.

Results

Patient characteristics

Twenty-one patients with locally advanced or metastatic esophageal cancer were treated with nimotuzumab combined with chemotherapy. The combined chemotherapy regimen included TP, GP, PF, and GS. Among these patients, 15 patients received paclitaxel and nedaplatin. Two patients received gemcitabine and nedaplatin. Three patients received gemcitabine and S-1. One patient received nedaplatin and 5-Fu. The combined chemotherapy regimen was four to six cycles. The deadline for follow-up was September 1, 2016. Characteristics of patients are shown in Table 1. The mean age of these patients was 60 years (range 42–79 years). The number of patients with age ≤65 years was 15 and the number of patients with age >65 years was six.

Efficacy

The response rates were described as follows: one (4.8%) patient had complete response, seven (33.3%) patients had

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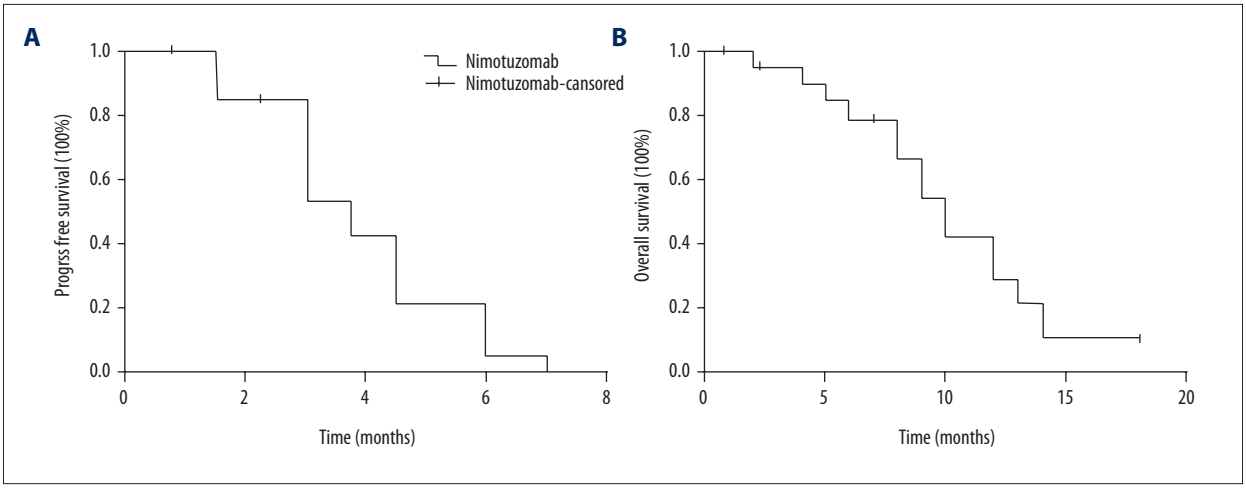

Figure 1. Kaplan-Meier curve of patients with local advanced or metastatic squamuos cell carcinoma. (**A**) Progress-free survival rate. (**B**) Overall survival rate.

partial response, nine (42.9%) patients had stable response and four (19%) patients had progression response. The objective response rate was 38.1% and disease control rate was 81%. Among the total 21 patients, two patients died because of respiratory failure, other than chemotherapy related toxicities. The detailed response rates are listed in Table 2. The mean progression-free-survival was seven months and the 18-month overall survival was 10% (Figure 1).

Safety and Toxicity

The most common adverse events were myelosuppression. The incidence rate of anemia and leukopenia was 71.4% and 81.0%, respectively. We observed two cases with the serious adverse event of myelosuppression. Nausea, fatigue, and anorexia were other common adverse events. No long-term drug-related toxicity was observed during the follow-up. The detailed toxicity of chemotherapy are showed in Table 3.

Discussion

Cisplatin is one of the most effective chemotherapy drugs for locally advanced or metastatic esophageal cancer, and the single-agent response rate is about 20%. Cisplatin plus fluorouracil is the most commonly used regimen in esophageal cancer, with the response rates 20–50% [3]. Several other chemotherapy drugs such as paclitaxel, irinotecan, and docetaxel also exhibited excellent antitumor activity [4–7]. Some studies have shown that the efficiency of paclitaxel in advanced esophageal cancer patients was close to or above 50%. Ilson et al. reported that of the 86 patients treated with a single-drug regimen with paclitaxel, 16% of patients with esophageal adenocarcinoma and 31% of patients with esophageal squamous carcinoma had partial response, and the median survival time

Table 3. Toxicity of nimotuzumab plus chemotherapy.

Adverse events	No. of patients (%)	
	All grades	Grade 3 or 4
Any		
Myelosuppresion		
Anemia	15	2
Leukopenia	17	2
Thrombopenia	3	0
Dermatologic		
Rash or pruritus	1	1
Gastrointestinal		
Anorexia	5	0
Consipation	3	0
Diarrhea	1	1
Dry mouth	2	0
Nausea	6	0
Hepatobiliary		
Elevated alanine aminotransferase	2	0
Elevated creatinine	1	0
Insomnia		
Fatigue	7	0
Fever	1	0
Pain	2	0

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was 9.1 months [14]. Such results suggested that paclitaxel can be used as an effective drug as single-agent chemotherapy for patients who cannot tolerate combined chemotherapy [14]. Paclitaxel or docetaxel combined with cisplatin is currently used in patients with locally advanced or metastatic esophageal cancer [15,16]. Cutsem et al. reported that 445 patients were treated with DCF (docetaxel, cisplatin, and fluorouracil) or CF (cisplatin and fluorouracil) regimen in a randomized multinational phase III clinical trial [17]. The median OS for the group treated with DCF was 9.2 months and for the group treated with CF OS was 8.6 months.

Other chemotherapy drugs, including oxaliplatin, carboplatin, mitomycin, and gemcitabine, have also been used in treating esophageal cancer [18–23]. However, some clinical studies suggested that there was no significant improvement with those combination chemotherapy regimens in therapeutic effect [18–23]. The median OS and PFS were not improved in advanced or metastatic esophageal cancer.

Targeted therapy can improve the curative effect of patients with advanced esophageal cancer over traditional chemotherapy. Recently, trastuzumab (Her2 monoclonal antibody) and ramucirumab (EGFR-2 monoclonal antibody) were approved by the Federal Drug Administration (FDA) for the targeted therapy of esophageal cancer. In an open-label multicenter, phase III, randomized clinical trial, patients with advanced gastroesophageal junction tumor with Her2 high expression received trastuzumab plus combined chemotherapy. Compared to 11.1 months OS in the control group, patients in the treatment group had an OS of 13.8 months [24]. In 2014, in another open-label multicenter, phase III, randomized trial, patients with advanced gastroesophageal junction tumor received ramucirumab plus paclitaxel chemotherapy after first-line treatment based on platinum and 5-Fu failure. The OS of the treatment group and the control group were 9.6 months and 7.4 months, respectively [25]. However, gastroesophageal junction tumor represents only a small percentage of esophageal cancers. For the majority of esophageal cancers, there are no effective targeted drugs. Other clinical research of targeted drugs, such as the RILOMET study (rilotumumab, targeted MET/HGFR signal pathway), was stopped because of the imbalance in deaths between the treatment group and the control group [26].

Common EGFR inhibitors, including cetuximab, panitumumab, erlotinib, and gefitinib, have been recently identified. In some clinical studies, these EGFR inhibitors have shown good antitumor activity, and have been approved by the FDA for the treatment of colorectal cancer and non-small cell lung cancer [27–30]. Nimotuzumab was anti-EGFR humanized monoclonal antibody and was first used in the treatment of malignant tumors. At present, nimotuzumab has been approved by the FDA for the treatment of nasopharyngeal carcinoma, head and neck squamous cell carcinomas, malignant glioma, and pancreatic cancer, by combining it with radiotherapy or chemo-radiotherapy [31].

Nimotuzumab is an EGFR humanized monoclonal antibody. Some clinical studies have shown that nimotuzumab has a longer half-life, higher area under the curve and rare severe skin toxicity reaction, compared with other EGFR inhibitors. The effect of nimotuzumab on some solid tumors, such as high-level glial cell tumor, esophageal cancer, non-small cell lung cancer, gastric cancer, and colorectal cancer, is currently under investigated in I, II, and III phase clinical studies [32-35]. In a retrospective study, 205 advanced cancer patients with esophageal cancer, head and neck cancer, non-small cell lung cancer, gastric cancer, colorectal cancer, or other cancers were treated with combination therapy of nimotuzumab and chemotherapy. The study indicated that age, sex, and previous treatment might be potential predictive factors for survival in Chinese patients, and patients who received nimotuzumab >six doses and >200 mg/week might benefit more from nimotuzumab therapy [36].

There were quite a few studies on the efficacy of nimotuzumab combined with radiation and chemotherapy in esophageal cancer patients and the majority of these studies have reported encouraging results. For example, Lu et al. conducted a single-center, retrospective, single arm, phase II clinical research and studied the effect of first-line therapy regimen with nimotuzumab plus paclitaxel and cisplatin for advanced esophageal squamous carcinoma patients [37]. The primary endpoint was the objective response rate and secondary endpoint was OS and the disease control time. The overall response rate was 51.8%, the overall disease control rate was 92.9%, and the OS of patients was 14 months. In a phase I clinical trial, patients with advanced esophageal carcinoma received the combined therapy of nimotuzumab with radiation treatment and the drug safety, and tolerability of maximum tolerated dose was studied [38]. The incidence of 3–4 grade esophagitis incidence, leukopenia, and neutropenia was 18%, 18%, and 9%, respectively. Nimotuzumab toxicity related with drug doses did not exist. Of the nine cases of patients who had received and completed the therapy, 78% had 6-months OS and 67% had 1-year OS. The 1 year local PFS rate was 100%.

However, the optimal dose and administration frequency of nimotuzumab that should be used is still unknown. In a retrospective study, the clinical recommended dose of nimotuzumab was >200 mg per week [36]. With the increasing dosage, drug-related adverse reaction did not increase [36]. In our study, the dose of nimotuzumab that patients received was 200 mg/3 weeks and the incidence rate of anemia and leukopenia was 71.4% and 81.0%, respectively. Only two cases with serious adverse event of myelosuppression were observed.

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No long-term drug-related toxicity was observed during the follow-up period. In further studies, the dose of nimotuzumab will be increased and the adverse events will be observed.

Given the small number of patients in this trial, further randomized clinical research is needed for supplemental data. Because of the imbalance in gender assignment, more female patients will be enrolled in our clinical study in the future. In further studies, we will enlarge the sample size and include more chemotherapy regimens. Further analysis will be completed for treatment with the combination of nimotuzumab and chemotherapy for advanced esophageal cancer. In further follow-up studies, the efficacy of chemotherapy, adverse events, and general condition of patients will be observed.

In summary, our study showed that nimotuzumab combined with chemotherapy in the treatment of locally advanced or metastatic esophageal cancer can achieve a better short-term effect without accumulation of toxicity and was well-tolerated.

Conclusions

In our study, nimotuzumab combined with chemotherapy was shown to be a promising novel treatment for locally advanced and metastatic esophageal cancer. The results of the study provide the scientific basis for the application of nimotuzumab in esophageal cancer. In order to further demonstrate the antitumor activity of nimotuzumab, more patients will need to be included and more experiments will be needed to be done in the future.

Declaration of interest

The authors report no conflicts of interest.

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