A pilot study of nimotuzumab combined with cisplatin and 5-FU in patients with advanced esophageal squamous cell carcinoma

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ABSTRACT

Objective: To observe the short-term effect and adverse reaction of Nimotuzumab in combination with chemotherapy on advanced esophageal squamous cell carcinoma (ESCC).

Method: 19 patients were treated with the following protocol: Nimotuzumab 400mg/time/week in the 1st week, 200mg/time/week from the 2nd to 8th week, intravenous drip (IVD); Cisplatin 80 mg/m^2, IVD, 4 weeks a cycle and repeated again; 5-FU 750 mg/m^2, continuous 24-hours pump-in × 5 days, 4 weeks a cycle and repeated again.

Result: 16 of all 19 patients can be evaluated. After treatment, RP is 42.1% (95% CI, 19.9-64.3%) and DCR is 68.4%; the main side effects include arrest of bone marrow, gastrointestinal reactions, asthenia, etc.

Conclusion: Nimotuzumab in combination with cisplatin/5-FU regimens in patients with advanced ESCC is safe and effective, which deserves a further expanded sample research.

KEY WORDS Nimotuzumab; esophageal cancer; squamous cell carcinoma; chemotherapy

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Introduction

Esophageal cancer is a rare disease with a poor prognosis, accounting for approximately 1% of all malignancies, with an estimated 16,640 cases in 2010 and 14,500 deaths (1). The optimal management of esophageal cancer is complicated since institutional preferences vary, patient characteristics often guide management, and there are data to support multiple approaches for locally advanced esophageal cancer. Although surgery is an important component of therapy, alone it results in unacceptably high rates of local relapse and poor long-term survival rates. Well-studied adjuvant approaches include upfront chemoradiation therapy with or without surgery, perioperative chemotherapy, adjuvant radiation or adjuvant chemoradiation (2-4). Advanced esophageal squamous cell carcinoma (ESCC) is one of the most refractory cancers and is associated with poor outcome. Systemic chemotherapy is regarded as one of the most effective treatments for ESCC, and currently forms an important part of the multidisciplinary treatment approach for advanced and metastatic disease. In particular, cisplatin and fluorouracil (CF) combination therapy has become a standard choice. CF regimens result in partial response rates of 25–35%, with a 1-year survival rate ranging from 27.8 to 37.6% (5-7), and median survival time of 9.2 months for responders and 5.3 months for non-responders. To improve the prognosis of patients with advanced ESCC, more effective regimens are urgently needed.

High levels of expression of the epidermal growth factor receptor (EGFR) have been detected in 50%–70% of ESCCs (8-10) and have been correlated with prognosis (9-11). Activated EGFR signals via the RAS, ERK1/2, PI3K/Akt and STAT pathways and may result in chemotherapy resistance, angiogenesis and enhanced tumor proliferation (12-14). In addition, preclinical data showed that cetuximab enhanced the antitumor effect of chemotherapy and, in particular, augmented the activity of cisplatin (15,16). Therefore, it was reasoned that EGFR blockade maybe an effective therapeutic strategy.

Nimotuzumab (also known by the lab code h-R3) is a humanized IgG1 isotype monoclonal antibody. It was obtained

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by transplanting the complementarity determining regions (CDR) of the murine IgG2a monoclonal ior egf/r3, to a human framework assisted by computer modeling (17). The parental murine monoclonal ior egf/r3 was generated by fusing the murine myeloma cells SP2/Ag14 with splenocytes from Balb/c mice immunized with a purified human placenta fraction enriched in EGFR and not with EGFR purified from cultured cells.6 Studies have shown nimotuzumab mediates anti-tumor effects by its capacity to inhibit proliferation, survival and angiogenesis (18). Nimotuzumab has demonstrated a unique clinical profile, where anti-tumor activity was observed in absence of severe skin, renal, gastrointestinal mucosa toxicities commonly associated with EGFR- targeting antibodies, Cetuximab and Panitumumab, even though its clinical benefit was equivalent or superior to other similar anti epidermal growth factor monoclonal antibodies (19,20). Based on these considerations, we conducted a prospective trial to assess the efficacy and safety of the combination of traditional CF regimens with Nimotuzumab in Chinese patients with advanced ESCC.

Patients and methods

Patients Selection

All the selected patients with advanced ESCC meet the following criteria: be indentified as patients with ESCC based on histopathology or cytology; be determined by clinical stage as advanced ESCC patients that can't perform operations; didn't receive other antineoplastic therapy other than operations or combination of operations and postoperative adjuvant therapy; the last chemotherapy of patients who received postoperative adjuvant chemotherapy occurred more than 6 months ago; at the age of 18-75, ECOG result is 0-1, KPS result ≥60, and expected lifetime ≥3 months; have at least one nidus that can be measured by CT or MRI with a depth of ≥10mm; have no other malignant tumor medical history (cured early carcinoma excluded); have no obvious abnormality in routine blood test and liver and kidney function; and have capacity to bear children but willing to take contraception measures. This trial was approved by China State Food and Drug Administration and Hospital Ethics Committees, and all the patients have signed the Informed Consent.

Patient characteristics

There are five oncology centers and 19 (14 males and five females) patients involved in this research between March 1, 2009 and April 30, 2010. The age of patients ranges from 40 to 74, with a median age of 63. They are all at stage IV according to UICC2002. 6 patients are in initial treatment while 13 patients in retreatment. The number of hepatic metastases, mediastinal lymph node metastases, abdominal cavity and retroperitoneal lymph node metastases, and lung metastases are 2, 9, 5, and 2, respectively.

Dosage and Methods

Dosage of Nimotuzumab: 400mg/time/week in the 1st week, 200mg/time/week in the 2nd to 8th week, intravenous drip (IVD); combined chemotherapy: DDP 80 mg/m^2, IVD, 4 weeks a cycle and repeated again; 5-FU 750 mg/m^2, continuous 24-hours pump-in × 5 days, 4 weeks a cycle and repeated again. Before the chemotherapy, generally the 5-HT receptor antagonist is used to prevent gastrointestinal reactions. During the chemotherapy, routine blood test should be carried out every week. And before and after every cycle, liver and kidney function should be rechecked and if white cells and neutrophil leucocytes decrease, generally the granulocyte colony stimulating factor will be used. The first 1-2 cycle(s) is experimental treatment phase. And the short term effects will be evaluated upon the completion of trial therapy stage (the 8th week) and in 4 weeks after that (the 12th week).

Efficacy assessment

The primary endpoint of this study was response rate (RR), and secondary objectives were toxicity. Before entering the study, all patients received physical examination, full blood count, and serum chemistry analyses. Chest radiograph, ECG, upper gastrointestinal endoscopies, abdominal computer tomographic (CT) scans, and other appropriate procedures were also performed as needed. Patients were given a physical examination, a subjective/objective symptom evaluation, and blood tests twice weekly. Comprehensive biochemistry blood examination was performed every 4 weeks. After every two cycles of treatment, response was evaluated using Response Evaluation Criteria in Solid Tumors. Of the lesions observed before treatment, a maximum of five measurable lesions from each metastasized organ up to a total of 10 lesions were selected as target lesions. In cases of partial or complete response (CR), a confirmative CT scan was performed 4 weeks later and this was followed by a CT scan after every two treatment cycles. RR=CR + PR. DCR=CR +PR +SD. Toxicity was graded according to Version 3.0 of the National Cancer Institute-Common Toxicity Criteria. Tumor-related symptoms were assessed at baseline and before each cycle.

Statistical analysis

All enrolled patients were included in the intention-to-treat analysis of efficacy. The duration of response was defined as the interval from the onset of a CR or a partial response until the

Table 1. Tumor response (intention-to-treat analysis).

Response	No (%)
Confirmed response	8 (42.1) [a]
Complete response	-
Partial response	8(42.1)
Stable disease	5(26.3)
Progressive disease	3(15.8)
Not assessable	3(15.8)

[a]95% confidential interval=19.9-64.3%.

Table 2. Correlation between side effects and medicine of 19 patients after treatment.

Side Effects	No.	Correlation with Nimotuzumab
Arrest of Bone Marrow		
Grade 1-2	11	Irrelevant
Grade 3-4	3	Irrelevant
Asthenia		
Grade 1-2	3	Irrelevant
Gastrointestinal Reaction		
Grade 1-2	13	Irrelevant
Impairment of Liver Function		
Grade 1-2	1	Irrelevant
Skin Rash and Canker Sore		
Grade 1-2	1	Relevant
Fever		
Grade 1-2	1	Relevant

evidence of disease progression was found. The statistical data were obtained using an SPSS software package (SPSS 11.5 Inc., Chicago, Illinois, USA).

Results

Efficacy

Among 19 patients, 1 patient can't receive further treatment due to severe adverse reactions, 2 patients was lost to follow up, and the other 16 patients received 40 cycles in total, 2~4 cycles for each one, with a average cycle of 2.5. After treatment, RR is 42.1% (95% CI, 19.9-64.3%) and DCR is 68.4% (Table 1).

Side Effects

Main side effects occurred after treatment including arrest of bone marrow (decrease of white cells as the main reflection), gastrointestinal reactions, asthenia, etc. (Table 2). One patient quitted the trial due to severe adverse reactions while others can be alleviated upon heteropathy and nutritional support. Arrest of bone marrow is mainly grade 1-2. In spite of high occurrence of gastrointestinal reactions, the patients can resist them basically. Among the observed side effects, it is considered that the skin rash and canker sore of one patient and moderate fever of another patient during the 3rd cycle are related to the use of Nimotuzumab, and other side effects that are commonly seen in chemotherapy should have nothing to do with Nimotuzumab.

Discussion

50% of the patients with ESCC is at their advanced stage at the time of confirmed diagnosis because generally there are no obvious symptoms at early stage (21), with a natural disease history of 6~8 months and 5-year survival rate of 5~7% (22). For locally advanced ESCC, concurrent chemoradiotherapy was recommended, and then surgical extirpation should be conducted if treatment works or patient's condition has no further development, and palliative chemotherapy should be conducted if patient's condition become serious or distant metastasis occurs (23-25). The most commonly used palliative chemotherapy for advanced ESCC is DDP, followed by 5-FU, PTX, MMC, BLM and NVB. The 5-FU and DDP-based program has wide applications, and the effective rate is 25%-35% when the both of them are used. Though clinical researches have been conducted at home and abroad by combining with other chemotherapy medicines such as anthracyclines, etoposide, taxanes, irinotecan on this basis in treating advanced ESCC, no evidence obviously better than CF program was found (26).

EGFR is the most commonly seen oncogene, occurring over-expression and/or mutation in many tumors of ESCC and having close connection with the incidence, development, infiltration, metastasis and prognosis of tumors (14). Through immunohistochemistry, Boone *et al.* confirmed that EGFR showed expression in 40% of ESCC (27), which provide theoretical basis and experimental basis for EGFR targeted tumor therapy and signal transduction intervention treatment against EGFR. Nimotuzumab is a humanized monoclonal antibody medicines against EGFR, which can competitively inhibit the combination of endogenous ligands and EGFR and further prevent the dimerization of receptor, the phosphorylation of tyrosine kinase, the EGFR-mediated downstream signal conduction path and cytology effect, and finally inhibit the hyperplasia of tumor cells and facilitie their apoptosis (28). In addition, Nimotuzumab can cause the cytolysis of tumor cells and play a anti-tumor role through antibody-mediated and complement-mediated cytotoxic effect (29). These theories above provided theorectical basis for combined chemotherapy.

In addition, EGFR tyrosine kinase inhibitor (TKI) has already

begun its applications in treating ESCC. Janmaat *et al*. in their Phase II clinical trial used Gefinitib as second-line treatment to treat 36 patients with advanced ESCC (30). The patients were administrated gefitinib 500mg/d and response was evaluated every 8 weeks. Result is as follows: 1 achieved CR, 10 had SD, 17 experienced progression on treatment, and 8 were not assessable for response. The progression-free survival time was 59 days, and the median survival time was 164 days. A higher disease control rate was observed in females and in patients with squamous cell carcinoma or high EGFR expression. So EGFR-TKI may have a better curative effect on squamous cell carcinoma. Ferry *et al*. used Gefinitib (500mg/d) to treat 27 patients with advanced ESCC, giving a disease control rate (PR + SD) of 37% (31). It can be seen that the later the stage of diseases, the worse the effects of Gefinitib. Dobelbower *et al*. investigated the safety of combining radiation, 5-fluorouracil (5-FU) and cisplatin with erlotinib (50mg/d, 100mg/d and 150mg/d) in an 11-patient phase I clinical trial and found that it is safe, and the major toxicities were diarrhea (grade 1 and grade 2), skin rash (grade 1), nausea (grade 1, grade 2 and grade) and dehydration (grade 3) (32). It can be concluded preliminary that it is safe to treat ESCC with EGFR and may have a certain curative effect. In this study, we used Nimotuzumab in combination with chemotherapy to treat advanced ESCC, and the result is comparable with the treatments above, so Nimotuzumab has a good curative effect on treating advanced ESCC.

In the current study, the short-term RR of all 19 patients is 42.1%, DCR is 68.4%, which is obviously better than chemotherapy alone. The side effects of combined chemotherapy include arrest of bone marrow, gastrointestinal reaction, asthenia, etc, but they can be alleviated basically through heteropathy and nutritional support, and only two patients can't be alleviated (one skin rash and one moderate fever). It is further manifested that the use of Nimotuzumab in treating ESCC is safe and reliable.

In conclusion, the use of Nimotuzumab in combination with CF regimens in patients with advanced ESCC has a good curative effect, and the side effects can be predictable, controllable and tolerable, which deserves expanded sample research and further observation.

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