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ORIGINAL ARTICLE

Research on the efficacy of cisplatin and nimotuzumab combined with concurrent chemoradiotherapy on locally advanced cervical cancer

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Summary

Purpose: *To evaluate the efficacy and safety of cisplatin and nimotuzumab combined with concurrent chemoradiotherapy on locally advanced cervical cancer.*

Methods: *92 patients with cervical cancer in moderate and advanced stages treated in Shanghai Public Health Clinical Center from January 2014 to January 2017 were selected and divided into two groups with 46 cases in each group. They received cisplatin and nimotuzumab combined with concurrent chemoradiotherapy and cisplatin combined with concurrent chemoradiotherapy, respectively. The clinical efficacy, adverse reactions, overall survival (OS) and progression-free survival (PFS) were compared between the two groups.*

Results: *The general clinical characteristics of patients in both groups were comparable. The effective rate was 87.0% and 67.4%, respectively, in nimotuzumab group and cisplatin group, and the local tumor control and short-term efficacy were superior in the nimotuzumab group compared to those in the cisplatin group (p=0.045). There was no statistically significant difference in the incidence of complications after treatment between the two groups (p>0.05), and nimotuzumab did not increase the incidence and severity of adverse reactions. The 3-year OS rate was 87.0% (40/46) and 69.6% (32/46), respectively, in the two groups (log-rank, p=0.070). The 3-year PFS rate in the nimotuzumab group [73.9% (34/46)] was obviously higher than that in the cisplatin group [50.0% (23/46)] (p=0.042).*

Conclusions: *Cisplatin and nimotuzumab combined with concurrent chemoradiotherapy are safe and effective in the treatment of locally advanced cervical cancer, both local tumor control and PFS rate are excellent, and the patient's tolerance is good, so it is worth of clinical popularization.*

Key words: *cervical cancer, concurrent chemoradiotherapy, cisplatin, nimotuzumab*

Introduction

Cervical cancer is one of the most common gynecological malignant tumors. In the past, radiotherapy and surgery dominated in the conventional treatment. According to the staging criteria of FIGO, stage I and IIA cervical cancer is mainly treated with surgery supplemented by postoperative radiotherapy, while above stage IIB is mainly treated with radiotherapy supplemented by chemotherapy. According to statistics, there were more than 500,000 new cases in 2005, most of which were in developing countries [1]. Of the early cases (stage I-IIA) 80-95% can be cured by surgical treatment and chemoradiotherapy, and the cure rate for stage IIb-IVa cases can be up to 60% [2].

Epidermal growth factor receptor (EGFR), one of the four members of the ErbB (HER) family, can form homodimers or heterodimers with ligands, further activating the cellular signal transduction

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pathway, and regulating the cell proliferation, differentiation, activity, invasion and angiogenesis [3-5]. EGFR is overexpressed in a variety of tumors, such as nasopharyngeal cancer, colon cancer, rectal cancer and non-small cell lung cancer. Studies have demonstrated that the EGFR overexpression also exists in cervical squamous carcinoma, which is associated with high stage and poor prognosis [6,7]. Moreover, EGFR overexpression is also associated with tumor resistance to cytotoxic drugs and radiotherapy. It has been found in *in vitro* and *in vivo* studies that blocking EGFR can increase the tumor sensitivity to radiotherapy and improve the efficacy of radiotherapy [8-10]. Therefore, EGFR may be a promising therapeutic target for cervical cancer. Cetuximab is an anti-EGFR monoclonal antibody, and preclinical studies have found that cetuximab can inhibit the growth of about 53% of cervical cancer HeLa cells [11]. Nimotuzumab (Taixinsheng) is a humanized anti-human EGFR monoclonal antibody jointly developed by China and Cuba, which can reduce the phosphorylation of EGFR and displays a good antitumor effect in head-neck tumors and colorectal cancer [12-14]. Due to the high selectivity and long half-life, 200 mg nimotuzumab are reliable during medication for 1 week, and such adverse reactions as acne-like rash and conjunctivitis rarely occur.

In the present study, the clinical efficacy of cisplatin and nimotuzumab combined with concurrent chemoradiotherapy and cisplatin combined with concurrent chemoradiotherapy was compared in the treatment of locally advanced cervical cancer, the adverse reactions, overall survival (OS) rate and progression-free survival (PFS) rate in the two groups were recorded, and the short-term clinical efficacy and safety were compared between the two therapeutic regimens.

Methods

General data

A total of 92 patients pathologically diagnosed with cervical squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma (FIGO stage IIB-IVA) in Surgery Department from January 2014 to January 2017 were collected. The patient age ranged between 38 and 67 years (median 56). The cardiopulmonary, hepatic-renal function and hemogram were in the normal range, the electrocardiogram had no abnormalities and there were no other serious medical diseases. The Eastern Cooperative Oncology Group (ECOG) performance status score was ≤2 points in all patients. No patient had received radiotherapy, chemotherapy and other antitumor therapies, and had no contraindications for chemoradiotherapy. All patients enrolled were randomly divided into the nimotuzumab group (n=46) and cisplatin group (n=46) using a random number table. No patients had undergone EGFR targeted therapy and chemotherapy, and all of them signed informed consent. This study was approved by the Ethics Committee of Shanghai Public Health Clinical Center. The study followed the Declaration of Helsinki.

Treatment methods

Radiotherapy regimen: The patient drank water and suppressed the urination before positioning. Computed tomography (CT) scan was performed from 2 cm above the umbilicus downward to the inferior margin of the ischial tuberosity. Then, CT images were reconstructed with a slice spacing of 3 mm, and sent to the radiotherapy network center. According to the CT images, the gross target volume (GTV) was delineated, including the uterus, cervix, mass and the upper 1/3 to 1/2 of the vagina. Then the clinical target volume (CTV) was delineated, including the GTV and lymphatic drainage region in the pelvic cavity, namely the left and right common iliac vessels, parametrial, anterior sacral and obturator lymph node region from L4-5 (upper boundary) to the inferior margin of obturator (lower boundary). The CTV was expanded 0.5-1 cm as the planning target volume (PTV), and the rectum, bladder, small intestine, pelvic bone marrow and other organs at risk were delineated at the same time. Under 15 MV X-ray, a total of 6 coplanar radiation fields were set up with the PTV geometric center as the field center using the 23-EX linear accelerator dynamic multi-leaf collimator (Varian, Palo Alto, CA, USA). The dose distribution was calculated. The 90% isodose curve included the target region and was verified using the field imaging system. The prescription dose was 50-55 Gy with a median of 53.5 Gy, and the mean dose of PTV was 54.5 Gy, 1.8-2.2 Gy/time, 4 times a week. The dose volume (TD5/5) of organs at risk was restricted as follows: 50 Gy/100 cm^2 for the small intestine, 60 Gy/100 cm^2 for the rectum, 60 Gy for the whole bladder, and 30 Gy for the bone marrow (local bone marrow). The intracavitary treatment was performed for all patients in both groups after intensity-modulated radiotherapy (IMRT) once a week, the radiotherapy dose was 5 Gy each time, and the total local dose at cervical point A reached 75-80 Gy.

In nimotuzumab group, the chemotherapy regimen (40 mg/m^2 cisplatin + 200 mg nimotuzumab) was given once a week from the first day of radiotherapy for a total of 6 cycles. 200 mg nimotuzumab were dissolved in 250 mL normal saline, and intravenously injected for more than 1 h. Then, cisplatin (40 mg/m^2) was dissolved in 500 mL normal saline and injected intravenously, accompanied by adequate hydration. In cisplatin group, chemotherapy and radiotherapy were performed simultaneously, and cisplatin (40 mg/m^2) was injected intravenously once a week for 6 cycles. During chemotherapy, gastric mucosal protective agents and ondansetron hydrochloride were given for vomiting prevention. The hematological indexes and general conditions of patients were monitored every week, and symptomatic supportive treatment was performed according to the conditions.

Observation indexes

At 1 month after treatment, MRI or CT or PET-CT scans and gynecologic examination were performed to evaluate whether to increase the intracavity irradiation; re-evaluation was performed again at 3 months. The condition was reviewed every 3 months within 2 years and every 6 months after 2 years.

The short-term efficacy was evaluated according to RECIST 1.1 [15]: complete remission (CR): All target lesions disappear, and the short diameter of all pathological lymph nodes is reduced to <10 mm. Partial remission (PR): The sum of diameters of target lesions is reduced by at least 30% compared with the baseline level. Progressive disease (PD): With the minimum of the sum of diameters of all measured target lesions as a reference, the sum of diameters is increased by at least 20%, and the absolute value of the sum of diameters is increased by at least 5 mm (or there is one or more new lesions). Stable disease (SD): The target lesions are reduced between PR and PD.

The adverse reactions were evaluated according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0). PFS: the time from the enrollment into the study to the disease progression or death of patients. OS: the time from the enrollment into the study to the death of patients. All patients were followed up until October 2018.

Statistics

SPSS 22.0 software (IBM, Armonk, NY, USA) was used for statistical analyses. Measurement data were expressed as mean ± standard deviation, and t-test was used for the intergroup comparison. Enumeration data were expressed as rates (%), and chi-square test was used for the intergroup comparison. P<0.05 suggested that the difference was statistically significant. Survival curves were plotted using the Kaplan-Meier method, and Log-rank test was used to search for significant survival differences between groups. P<0.05 suggested significant difference.

Results

Preoperative general conditions

A total of 92 patients aged 38-67 years (mean 56.52±10.13) with locally advanced cervical cancer were included in this study. In nimotuzumab group, there were 28 cases (60.9%) of squamous cell carcinoma, 13 cases (28.3%) of adenocarcinoma and 5 cases (10.8%) of adenosquamous carcinoma; in terms of FIGO stage, there were 9 cases (19.6%) in stage IIB, 13 cases (28.3%) in stage IIIA, 11 cases (23.8%) in stage IIIB and 13 cases (28.3%) in stage IVA. In cisplatin group, there were 25 cases (54.3%) of squamous cell carcinoma, 17 cases (37.0%) of adenocarcinoma and 4 cases (8.7%) of adenosquamous carcinoma; in terms of the FIGO stage, there were 11 cases (23.9%) in stage IIB, 11 cases (23.9%) in stage IIIA, 15 cases (32.6%) in stage IIIB and 9 cases (19.6%) in stage IVA (FIGO stage in nimotuzumab group and in cisplatin group, respectively). In terms of ECOG score, there were 29 cases (63.0%) of 0 point, 12 cases (26.1%) of 1 point and 5 cases (10.9%) of 2 points in nimotuzumab group, and 26 cases (56.5%) of 0 point, 16 cases (34.8%) of 1 point and 4 cases (8.7%) of 2 points in cisplatin group. There were no statistically significant differences in the general conditions before treatment between the two groups of patients (p>0.05) (Table 1).

Table 1. Baseline demographic and clinical characteristics of the studied patients

Characteristics	*Nimotuzumab + Cisplatin group (n=46) n (%)*	*Cisplatin group (n=46) n (%)*	*p value*
Age, years, mean±SD	55.43±10.10	57.08±9.91	0.431
Histology			0.814
Squamous cell carcinoma	28 (60.9)	25 (54.3)	
Adenocarcinoma	13 (28.3)	17 (37.0)	
Adenosquamous	5 (10.8)	4 (8.7)	
FIGO stage			0.635
IIB	9 (19.6)	11 (23.9)	
IIIA	13 (28.3)	11 (23.9)	
IIIB	11 (23.8)	15 (32.6)	
IVA	13 (28.3)	9 (19.6)	
ECOG PS score			0.655
0	29 (63.0)	26 (56.5)	
1	12 (26.1)	16 (34.8)	
2	5 (10.9)	4 (8.7)	

PS: performance status

Comparison of short-term efficacy

The efficacy was evaluated at 3 months after radiotherapy. In nimotuzumab group, there were 29 cases (63.0%) of CR, 11 cases (23.9%) of PR, 4 cases (8.7%) of SD and 2 cases (4.4%) of PD, and the effective rate was 87.0%. In cisplatin group, there were 23 cases (50.0%) of CR, 8 cases (17.4%) of PR, 10 (21.7%) cases of SD and 5 cases (10.9%) of PD, and the effective rate was 67.4%. The effective rate had a statistically significant difference between the two groups (p=0.045), and the short-term efficacy in nimotuzumab group was superior to that in cisplatin group (Table 2).

Adverse reactions

The incidence of adverse reactions after treatment between groups had no statistically significant difference (p>0.05; Table 3). The incidence rates of leukopenia, neutropenia and thrombocytopenia were 30.4% (14/46), 37.0% (17/46) and 13.0% (6/46), and 17.4% (8/46), 10.9% (5/46) and 13.0% (6/46), respectively, in the two groups. The conditions returned to normal after treatment with recombinant human granulocyte colony-stimulating factor and recombinant human interleukin-11, then the chemotherapy continued, and no grade 4 blood toxic reaction occurred. Gastrointestinal reactions mainly included nausea, vomiting and diarrhea below grade 2. The incidence rates of adverse reactions in the two groups are as follows: nausea below grade 2: 69.6% (32/46) and 54.3% (25/46), vomiting below grade 2: 19.6% (9/46) and 13.0% (6/46), grade 3 nausea and vomiting: 4.3% (2/46) and 2.2% (1/46), diarrhea below grade 2: 6.5% (3/46) and 6.5% (3/46), radiation dermatitis below grade 2: 21.7% (10/46) and 15.2% (7/46), radiation proctitis below grade 2: 8.7% (4/46) and 13.0% (6/46), urinary symptoms below grade 2: 8.7% (4/46) and 4.3% (2/46), and grade 1 fatigue: 13.0% (6/46) and 21.7% (10/46). All of the above symptoms were relieved and became tolerable after symptomatic supportive treatment, and there were no treatment delays.

Follow-up results of patient survival

All patients were followed up until October 31, 2018, with a median follow-up time of 23 months (range 6-36). In nimotuzumab group, 6 patients died within 3 years at 8, 13, 18, 24, 30 and 35 months after treatment, and OS was 87.0% (40/46). PD occurred in 6 cases at 9, 15, 19, 22, 28 and 30 months after treatment, respectively, with PFS of 73.9% (34/46). In cisplatin group, 14 patients died within 3 years at 6, 9, 11, 19, 20, 26, 29, 31, 32, 33

Table 2. Comparison of tumor response of patients in the two studied groups

Tumor response	*Nimotuzumab + Cisplatin group n (%)*	*Cisplatin group n (%)*	*p value*
Complete response (CR)	29 (63.0)	23 (50.0)	0.293
Partial response (PR)	11 (23.9)	8 (17.4)	0.607
Stable disease (SD)	4 (8.7)	10 (21.7)	0.145
Progressive disease (PD)	2 (4.4)	5 (10.9)	0.435
Tumor response rate (CR + PR)	40 (87.0)	31 (67.4)	0.045

Table 3. Adverse effects of the studied patients in two groups

Adverse effects	*Nimotuzumab + Cisplatin group (n=46) n (%)*	*Cisplatin group (n=46) n (%)*	*p value*
Fever	4 (8.7)	2 (4.3)	0.677
Fatigue	6 (13.0)	10 (21.7)	0. 410
Anemia	17 (37.0)	15 (32.6)	0.827
Leukocytopenia	22 (47.8)	25 (54.3)	0.677
Thrombocytopenia	19 (41.3)	22 (47.8)	0.675
Granulocytopenia	13 (28.3)	16 (34.8)	0. 654
Gastrointestinal reaction	36 (78.3)	31 (67.4)	0.349
Radiodermatitis	10 (21.7)	7 (15.2)	0.592
Radioproctitis	5 (10.9)	8 (17.4)	0.551
Radiocystitis	5 (10.9)	3 (6.5)	0.714

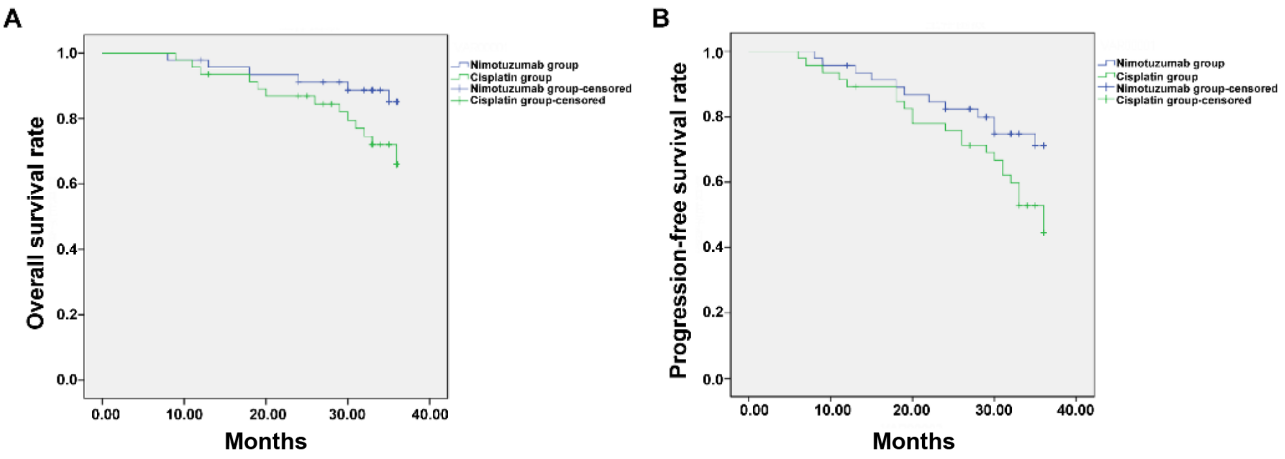

Figure 1. Kaplan-Meier survival curves of patients in Nimotuzumab + Cisplatin group and Cisplatin group. **A:** The difference of overall survival rate of patients in the two group had no statistical significance (p=0.070). **B:** The progression-free survival rate of patients in Nimotuzumab + Cisplatin group was significantly higher than that of Cisplatin group (p=0.042).

and 36 months after treatment, respectively, and OS was 69.6% (32/46). PD occurred in 8 cases at 7, 18, 20, 26, 31, 33 and 36 months after treatment, respectively, and PFS was 50.0% (23/46). The Kaplan-Meier survival curves of patients are shown in Figure 1, and log-rank test showed that OS had no statistically significant difference between the two groups of patients (p=0.070), and the PFS in nimotuzumab group was significantly higher than that in cisplatin group (p=0.042).

Discussion

Although studies have confirmed that platinum-based concurrent chemoradiotherapy can improve the local control rate and the OS of locally advanced and early cervical cancer, the tumor still exists, relapses or metastasizes in 35% of cervical cancer patients after chemoradiotherapy, and the survival is only 4.5-10 months. Local or pelvic recurrence is still one of the main causes of treatment failure. Cytotoxic drugs are combined with radiotherapy in concurrent chemoradiotherapy, and the most commonly used ones are cisplatin and/or other cytotoxic drugs, so the adverse reactions of treatment mainly include significant bone marrow suppression, diarrhea and tenesmus, interrupting or prolonging the treatment. Long-term chronic diarrhea and malnutrition even occur in some patients [16-20]. Therefore, searching for more advanced radiotherapy techniques and effective and less toxic drugs has become the focus of attention at present.

In recent years, the application of targeted therapy in tumors has been paid increasingly more attention. EGFR mainly mediates the signal of cell division and proliferation, and its overexpression is closely related to cell differentiation, proliferation, metastasis, angiogenesis and apoptosis [21]. After EGFR binds to ligands, a series of downstream signaling pathways can be activated, leading to cell proliferation and apoptosis escape, which is closely related to poor prognosis [22]. Diaz-Miqueli et al [23] argued that EGFR is associated with the sensitivity resistance of tumor cells to radiotherapy. Nimotuzumab is the first highly humanized monoclonal antibody approved in China, which reduces the invasion of tumor cells to normal tissues and their spread to other sites through blocking the abnormal activation of EGFR signal transduction pathway. Diaz-Miqueli et al [23] reported that nimotuzumab combined with radiotherapy and cytotoxic drugs can improve the efficacy and rarely increases side effects. Currently, nimotuzumab combined with radiotherapy has been applied in a variety of solid tumors, such as head-neck cancer, glioma and rectal cancer, and its safety and efficacy have been widely confirmed [24-26].

Villalba et al [27] suggested that EGFR overexpression exists in cervical cancer patients, so EGFR may become an important therapeutic target for cervical cancer. Although the exact biological significance of EGFR overexpression in cervical cancer tissues has not been clarified yet, the effects of EGFR tyrosine kinase receptor inhibitors or anti-EGFR monoclonal antibodies have been evaluated in some clinical studies [28]. Cetina et al [29] conducted induction therapy with nimotuzumab alone for recurrent metastatic cervical cancer for 4 weeks and nimotuzumab combined with concurrent chemotherapy for 18 weeks, and then performed maintenance therapy with nimo-

tuzumab once every 2 weeks until unacceptable adverse events occurred. The results showed that the patient tolerance was good, the SD rate was 35%, and the DFS and OS were 163 and 299 days, respectively. Meira et al [30] found in a basic study that after cetuximab combined with cisplatin and radiotherapy were applied in cervical cancer A431 cells, Caski and C33A cells (high, moderate and low expression of EGFR, respectively), the growth of A431 cells with high expression of EGFR was significantly inhibited, while the growth of the other two cells was weakly inhibited. In a multicenter non-comparative open phase II clinical trial, the researchers applied gefitinib (500 mg/d) in the treatment of 30 patients with cervical squamous cell carcinoma and adenocarcinoma with local recurrence and distant metastasis and found that 20% of patients had SD, the median time of PD was 37 days, the median OS was 107 days, and gefitinib was well tolerated in all cases [31].

In the present study, nimotuzumab was administered in the treatment of locally advanced cervical cancer. It was found that the adverse reactions in the treatment of locally advanced cervical cancer with nimotuzumab and cisplatin combined with concurrent chemoradiotherapy were tolerable, and neither the incidence nor the severity of adverse reactions were increased compared with cisplatin combined with concurrent chemoradiotherapy. The local tumor control rate was better (p=0.045) and the 3-year PFS was significantly improved (p=0.042) in the nimotuzumab group, but the 3-year OS had no statistically significant difference (p=0.070). The possible reason may be related to the small sample size and short follow-up time.

In conclusion, this study proved that nimotuzumab (200 mg) and cisplatin (40 mg/m^2) combined with concurrent chemoradiotherapy for 6 cycles is safe and feasible in the treatment of locally advanced cervical cancer, and its clinical efficacy is better. Whether this regimen can help improve the long-term survival rate of patients and reduce the distant metastasis rate remains to be further studied via large-sample research.

Conclusions

Cisplatin and nimotuzumab combined with concurrent chemoradiotherapy is safe and effective in the treatment of locally advanced cervical cancer, both local tumor control and PFS rate are excellent, and the patient tolerance is good, so it is worth of clinical popularization.

Conflict of interests

The authors declare no conflict of interests.

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