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A Retrospective Paired Study: Efficacy and Safety of Nimotuzumab Combined with Radiochemotherapy in Locoregionally Advanced Nasopharyngeal Carcinoma

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Abstract **Objective:** To evaluate the efficacy and safety of nimotuzumab in combination with radiochemotherapy as the primary treatment in patients with locoregionally advanced nasopharyngeal carcinoma (NPC). **Methods:** We retrospectively reviewed patients with locoregionally advanced nasopharyngeal carcinoma from September 2012 to December 2016. 188 newly diagnosed patients with stage III–IV_B nasopharyngeal carcinoma were treated with at least 1-2 cycles of chemotherapy concurrently with planned IMRT. 88 patients received nimotuzumab 200 mg/week. Acute and late radiation-related toxicities were graded according to the Acute and Late Radiation Morbidity Scoring Criteria of Radiation Therapy Oncology Group. **Results:** After 3 months of treatment, the complete response rates of nasopharyngeal tumors in the study group and the control group were 78.4% and 65.5%, respectively (χ^2=4.070, *P*=0.044). The total complete response rates of cervical lymph nodes in the study group and the control group were 80.7% and 67.6% respectively (χ^2=4.022, *P*=0.045).The median cycle for nimotuzumab addition was 6.3 weeks. With a median follow-up of 36.3 months (range, 12–72 months), the estimated 3-year progression failure-free survival and overall survival rates for the study group and the control group were 85.24% vs 81.97% and 96.67% vs 90.0%, respectively. The 3-year local recurrence-free survival rates for the study group and the control group were 96.67% vs 83.60%, respectively (*P*=0.047). Grade 3 radiation-induced mucositis accounted for 36.4% of treated patients. No skin rash and infusion reaction were observed, distinctly from what is reported in control patients. **Conclusion:** Nimotuzumab plus chemoradiotherapy in the treatment of locoregionally advanced nasopharyngeal carcinoma showed promising outcomes in terms of locoregional control, without increasing the incidence of radiation-related toxicities for patients.

Keywords: *Nasopharyngeal carcinoma, Radiochemotherapy, Nimotuzumab*

1. Introduction

Nasopharyngeal carcinoma (NPC) is a malignant tumor which has a high incidence in China, accounting for about 80% of the total number in the world and it has obvious regional aggregation [1]. Because of the specificity of the anatomical location of nasopharyngeal carcinoma and the relative sensitivity to radiotherapy, radiation therapy is the first choice for the treatment of nasopharyngeal carcinoma [2]. However, 60%-70% patients with nasopharyngeal carcinoma are locally advanced, and the effect of radiotherapy alone is poor[3,4]. Combined radiotherapy and chemotherapy has been used as a standard treatment[5,6]. A meta-analysis demonstrates that chemotherapy combined

with chemotherapy was the most effective, and the toxic reaction associated to the regimen could be tolerated[7].With the development of radiotherapy technology, the technique of intensity modulated radiation therapy (IMRT) has obvious advantages in improving the local control rate of nasopharyngeal carcinoma and reducing the side effects of radiotherapy[8]. In spite of this, local recurrence rate and distant metastasis rate of locally advanced nasopharyngeal carcinoma are still around 20-30%[9,10]. Therefore, further improvement of local control rate and reduction of distant metastasis become the primary task for the treatment of locally advanced nasopharyngeal carcinoma.

Nimotuzumab is a therapeutic humanized anti EGFR monoclonal antibody, which could specifically block EGFR of the cells, improve the sensitivity of tumor cells to ionizing radiation, so as to improve the effect of radiotherapy of tumor[11,12]. To further clarify the clinical efficacy and side effects of nimotuzumab combined with chemoradiotherapy in the treatment of locally advanced nasopharyngeal carcinoma, we retrospectively analyzed the clinical data of patients with locally advanced nasopharyngeal carcinoma who received concurrent chemoradiotherapy combined with nimotuzumab in the First Hospital Affiliated to Soochow University from September 2012 to December 2016, compared with local advanced nasopharyngeal carcinoma patients with concurrent radiotherapy and chemotherapy at the same time as control. The results are reported as follows:

2. Materials and methods

2.1 Patients' characteristics

A total of 198 patients with locally advanced nasopharyngeal carcinoma treated in the First Hospital Affiliated to Soochow University, from September 2012 to December 2016, were enrolled. Patients were eligible for this study if they met the following inclusion criteria (1) patients were confirmed by clinical experience and histology. Histopathological classification of nasopharyngeal carcinoma was performed in accordance with the 1991 World Health Organization (WHO) standard. (2) patients with nasopharyngeal carcinoma in Stage Ⅲ-ⅣB according to the staging standard of the 7th edition of UICC/AJCC based on the examination results obtained from imaging methods such as CT, MRI, bone scanning etc.; (3) patients aged 18-70 years; (4) patients with a KPS score ⩾70 points; (5) patients with white blood cell count >3.5×10^9 / L, neutrophil count >2.0×10^9 / L, blood platelet count ⩾100×10^9 / L, a hemoglobin level ⩾100 g / L, liver function indexes 2.5 times of the upper limit of the normal value, creatinine renal clearance rate ⩾60 ml / min, without any severe diseases related to important organs such as heart, lung, liver, kidney etc. (6) patients with an expected survival period >6 months; (7) patients who have neither received EGFR targeted therapy and immunological therapy nor other malignant tumors. The control group comprised 110 patients and the research group comprised 88 patients. The study group had used targeted treatment with nimotuzumab in addition to the chemoradiotherapy received by the control group. Among the 198 patients, there were 150 males and 48 females, aged 26-70 years old, average age was 51.21 years. There were no statistical differences in sex, age, clinical staging, degrees of differentiation etc. between the two groups of patients (P>0.05, Table 1).

2.2 Therapeutic regimen:

(1)Radiotherapy: All patients were in supine position with their heads, necks, and shoulders fixed with thermoplastic masks and subject to CT simulated positional scanning. The upper boundary of scanning was the the top of the head. The lower boundary of scanning was the mediastinum bifurcation. The 6MV X ray, reverse treatment intensity modulated radiotherapy, and boost dosage were applied. Delineation of the target area: Delineation was performed on the enhanced CT image infusion with MRI. The primary focus GTV was the visible tumor focus displayed by the physical examination and imagenological examination. The lymph node GTV was a FDG-PET positive lymph node and highly suspected lymph node with short diameter ⩾1cm or necrosis. CTV refers to GTV and potential tumor lesions and subclinical lesions. CTV1 was the high-risk subclinical target area, including GTV and GTV 5mm, the whole nasopharyngeal cavity, soft palate, slope, pterygopalatine fossa, parapharyngeal space, sphenoid sinus, rear 1/3 maxillary sinus, cavernous sinus, bilateral Ⅱ-Ⅲ areas and Ⅴa area lymph node, also including the posterior ethmoid sinus, nasal cavity, and 1B area lymph node. CTV2 was the low-risk subclinical target area including IV area and ⅤB area lymph

node. PTV was formed after the CTV was extended 3mm. Prescription dose: PGTV: 66-72Gy, PCTV1:60-66Gy, PCTV2: 54Gy, fractionations were 31-33 times. This is necessary which Layer-by-layer evaluation of the dosage distribution in various target areas on the cross section, exposure doses of the organs at risk for delineation of organs at risk and limitation of doses. The dose-volume histogram was used for evaluating and optimizing the therapy regimen. After confirmation of the treatment plan, dosage verification and CBCT accuracy verification, the treatment plan was performed on the accelerator. The CBCT, blood routine examination, biochemical examinations were performed at least once a week during the radiotherapy process. The conditions of the oral mucosa and the skin in the irradiated region were recorded.

Table 1. Basic characteristic of 198 locally advanced nasopharyngeal carcinoma

Characteristic	Study group (n=88)	Control group (n=110)	χ^2/tvalue	*P*value
Gender				
Male	67（76.1）	83（75.5）	0.012	0.911
Female	21（2.9）	27（24.5）		
Age				
Median（years）	50.54±12.12	52.02±10.28		0.365
T stage				
T1	16（18.2）	17（15.5）		
T2	29（32.0）	35（31.8）	0.386	0.943
T3	27（30.7）	36（32.7）		
T4	16（18.2）	22（20.0）		
N stage				
N0	5（5.7）	2（1.8）		
N1	7（8.0）	12（10.9）	4.789	0.188
N2	62（70.5）	86（78.2）		
N3	14（16.0）	10（9.1）		
Histological classification				
Keratinized	34（38.6）	51（16.4）		
Nonkeratinizing	53（60.2）	58（52.7）	1.199	0.549
Unclassified	1（1.1）	1（0.9）		

(2) Chemotherapy: Both groups of patients were first subject to 1-2 cycles of concurrent chemotherapy during the radiotherapy and 0-4 cycles of adjuvant chemotherapy following radiotherapy. The chemotherapy regimens were: TP regimen (docetaxel 75mg/m^2 or taxol 135mg/m^2 combined with cisplatin 75mg/m^2 or nedaplatin 80mg/m^2); PF regimen (fluorouracil 2500mg/m^2 CIV120h) combined with cisplatin 75mg/m^2 or nedaplatin 80mg/m^2). Each treatment cycle was 21 days. Antiallergic, antiemetic, stomach protection, liver protection treatment regimens were administered during the chemotherapy process. Blood routine examinations, biochemical examinations, electrocardiography examinations were conducted before chemotherapy. The patients with significantly abnormal indexes would have chemotherapy delayed or stopped.

(3) Targeted therapy: In addition to the treatment in the control group, nimotuzumab (50 mg/10ml, Baitai Biology Pharmaceutical Co., Ltd.) was used in the study group. The patients in the study group were subject to radiotherapy and intravenous injection of 200 mg of nimotuzumab dissolved in 250ml of 0.9% sodium chloride solution for more than 60 min each week. Allergic reactions, skin reactions, gastrointestinal reactions, and other adverse reactions were recorded during the whole treatment process.

2.3. Follow-up and study endpoint:

Follow-up was conducted by telephone, WeChat, outpatient and inpatient reexamination, with the follow-up period up to December 31, 2017. The follow-up time was 12-72 months, the median follow-up time was 34 months in the study group and 38.5 months in the control group. The follow-up rate was 95.2%.

2.4. Study Endpoints

The primary endpoint of the study was the short-term efficacy at 3 months after treatment. The short-term curative effect according to the curative effect evaluation standard of solid tumor (response evaluation criteria in solid tumor, RECIST) version 1.1 evaluation, divided into complete remission (Complete Response, CR), partial response (Partial Response, PR), stable disease (Stable Disease, SD) and disease progression (Progressive Disease, PD), which is made valid by means of the objective response rate (CR + PR). Secondary outcomes were disease-free survival, overall survival and acute toxicity. Disease-free survival time is defined as the time from initial treatment to local recurrence, distant metastasis, death or follow-up termination. Overall survival time is defined as the length of time from first treatment to death or termination of the follow-up. The toxic and side effects in the concurrent chemoradiotherapy should be assessed according to the international standard of Common Terminology Criteria for Adverse Events (CTCAE) version 3, including also skin and mucous membrane reaction according to the RTOG acute radiation injury classification standard evaluation. The maximum value of the toxicity was recorded and evaluated.

2.5. Statistical analysis:

The data were processed with the SPSS19.0 statistical software. The χ2 test was conducted to compare the enumeration data among groups. The t test was conducted to compare measurement data among groups. The Kaplan-Meier method was used to analyze the survival time of the patients in the two groups. A survival curve was plotted. The Logrank method was used to analyze the survival differences between the two groups of patients. The inspection level was $\alpha=0.05$.

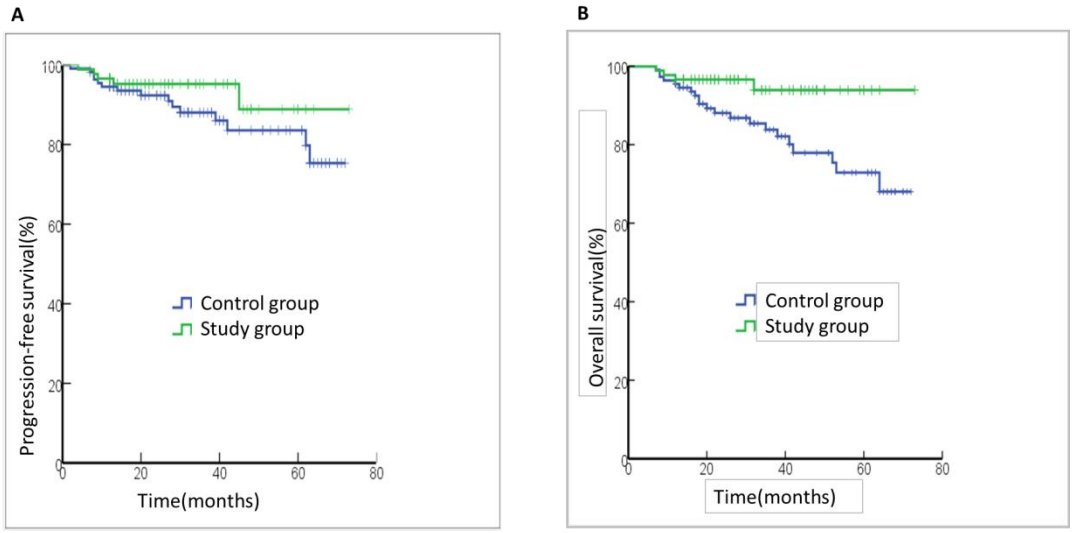

Figure 1. Kaplan-Meier estimates of the survival in patients with locally advanced nasopharyngeal carcinoma. **A**. Progression-free survival and **B**. Overall survival.

Table 2. Comparison of short-term efficacy in nasopharyngeal tumor patients.

Groups	N	CR	PR	SD	PD	Efficacy（%）
Study group	88	69（78.4）	19（21.6）	0（0.0）	0（0.0）	100
Control group	110	72（65.5）	25（22.7）	12（10.9）	1（0.9）	88.2
χ^2value		4.070				16.010
P value		0.044				0.000

Table 3. Comparison of short-term efficacy in cervical positive lymph nodes patients.

Groups	N	CR	PR	SD	PD	Efficacy（%）
Study Group	83	67（80.7）	16（19.3）	0（0.0）	0（0.0）	100
Control Group	108	73（67.6）	29（26.9）	5（4.6）	1（0.9）	94.5
χ^2value		4.228				6.991
P value		0.040				0.008

Table 4. Toxicities of the study group and the control group (n=198)

Toxicities	Study group（n=88）						Control group(n=110)						χ^2value	*P*value
	0	1	2	3	4	3-4 (%)	0	1	2	3	4	3-4 %)		
Mucositis	0	3	53	32	0	36.4	0	1	80	29	0	26.4	4.944	0.176
Skin lesion	0	1	63	23	1	27.3	0	3	83	22	2	21.8	1.707	0.635
Myelosuppression	48	17	18	4	1	5.7	54	26	21	8	1	8.2	1.392	0.846
Nausea/ vomiting	77	10	1	0	0	0	97	7	6	0	0	0	4.349	0.114
Liver function	84	4	0	0	0	0	107	3	0	0	0	0	0.47	0.493

3. Results

3.1. Completion of treatment:

All patients completed their radiotherapy according the scheduled radiotherapy plan. The differences in average radiotherapy dose and radiotherapy time between the two groups of patients were not statistically significant (P>0.05). The 106 (96.4%) patients in the control group had two cycles of concurrent chemotherapy completed. The 84 (95.5%) patients in the research group had 2 cycles of concurrent chemotherapy completed. The remaining patients had 1 cycle of concurrent chemotherapy completed. The average use frequency of nimotuzumab in the patients in the study group was 6.44 weeks. The lowest frequency was 4 weeks and the highest frequency was 9 weeks.

3.2. Local control:

All patients participated in the short-term effects evaluation. The complete remission rates in the study group of nasopharyngeal neoplasm and in the control group were 78.4% and 65.5% respectively. The CR of the patients in the study group was significantly higher than that in the control group. The differences were statistically significant (P<0.05, Table 2). The complete remission rates in the cervical positive lymph node in study group and the control group were 80.7% and 68.2% respectively. The CR of the cervical positive lymph node of the patients in the study group was significantly higher than that in the control group. The difference was statistically significant (P<0.05, Table 3). The objective response rate (CR+PR) of the nasopharyngeal neoplasm and cervical positive lymph node of the patients in the study group was 100%. The objective response rates of nasopharyngeal neoplasm and cervical positive lymph node in the control group were 88.2% and 94.54% respectively. There were statistically significant differences between the two groups (P<0.05, Table 3). In the control group, 12 cases of nasopharyngeal neoplasm were SD and 1 case was PD, 5 cases of cervical positive lymph node were SD and 1 case was PD.

3.3. Long-term efficacy:

The 1-year survival rates of the patients in the study group and the control group were 96.36% and 93.64% respectively. The 1-year progression-free survival rates were 97.73% and 94.32% respectively. There were no statistically significant

differences (P=0.0.573, P=0.841). The 3-year survival rates and 3-year progression-free survival rates of the patients in the study group and the control group were 96.67% vs. 90.0% and 85.24%, vs. 81.97%, respectively. There were no statistically significant differences (P=0.303, P=0.073, Figure 1). The 3-year local recurrence-free survival rates in the research group and control group were 96.67% and 83.60%, respectively. There were statistically significant differences (P=0.047).

3.4. Safety and toxicity:

No death arising from toxic adverse reactions occurred in patients. The common side effect of the patients in the two groups included nausea and vomiting, myelosuppression, oral mucositis, and radiodermatitis. However, there were no statistically significant differences between the two groups (P>0.05, Table 4). The incidence rates of severe toxic and side effects of Ⅲ-Ⅳ oral mucosa reactions and skin reactions in the study group were higher than that in the control group, 36.4%, 26.4%vs 27.3, 21.8. However, there were no statistically significant differences (P>0.05, Table 4). The incidence rates of more than 10% of body weight loss in the study group and control group were 37.5% and 30% respectively. The difference was not statistically significant ($\chi 2$=1.234, P=0.267). No rash, allergy, electrocardiogram variation, renal function impairment occurred in patients.

3.5. Causes of treatment failure:

(1) Study group: 1 case had local recurrence in nasopharynx, 5 cases had distant metastasis, and 4 cases died of which 2 died from massive hemorrhage in local nasopharynx and 2 patients died from metastasis. (2) Control group: 9 cases had local recurrence in the nasopharynx, 12 cases had distant metastasis, and 20 cases died of which 3 patients died from massive hemorrhage in the local nasopharynx, 8 patients died from the metastasis,, 3 patients died from concomitant underlying diseases and 6 patients died from treatment.

4. Discussion

With the arrival of the era of molecular targeting, the role of targeted drugs in tumor treatment is becoming more and more important. Targeted drugs have gradually become one of the main means of comprehensive treatment in the management of nasopharyngeal cancer. EGFR is highly expressed in multiple types of tumor tissue. Its expression rate in nasopharyngeal carcinoma is 68-89%[11-13]. Particularly, its expression in the non-keratinizing nasopharyngeal carcinoma is over 90%[14]. High EGFR expression is associated with anti-apoptosis, proliferation, metastasis, and radiation resistance of cells [15,16]. The nimotuzumab can be bound to the EGFR, reducing the phosphorylation level of the receptor and the expression of Ki-67 in tumor cells, blocking the EGFR signal transduction pathway, retarding the cellular cyclic progression, promoting apoptosis, inhibiting angiogenesis, impeding invasion and metastasis of the tumor cells, and strengthening the sensitivity of chemoradiotherapy [17-19].

The results of this study showed that the combination of nimotuzumab with concurrent chemoradiotherapy for treatment of local advanced nasopharyngeal carcinoma had good short-term efficacy. The CR rate of both the nasopharyngeal neoplasm and the cervical positive lymph node was higher than that of the control group observed at 3 months after treatment. The difference was statistically significant (P<0.05). The efficacy of the treatment in the study group was up to 100%, which was significantly better than that in the control group, 88.2% and 94.5%, and the difference was statistically significant (P<0.05). This is consistent with some previous research results [20-22]. Considering that EGFR is highly expressed in nasopharyngeal carcinoma and that nimotuzumab is a monoclonal antibody that can specifically bound to the EGFR on the tumor cells, it can block the downstream signal transduction pathway, improving the radiation sensitivity and improving the local effective rate.

In this study, the concurrent chemoradiotherapy combined with nimotuzumab has significant advantages in controlling the short-term efficacy of the nasopharyngeal neoplasm and cervical positive lymph node. However, these advantages did not complete transform into long-term survival advantages. The result showed that the 1-year survival rates of the patients in the study group and the control group were 96.36% and 93.64% respectively, the 1-year

progression-free survival rates were 97.73% and 94.32% respectively, the 3-year survival rates were 85.24% and 81.97% respectively and the 3-year progression-free survival rates were 96.67% and 90.0%. The 1-year or 3-year survival rate and the progression-free survival rate in the study group were higher than that of them in the control group. However, the differences were not statistically significant (P>0.05). We consider that the reason for the above results is that the total survival time of patients with nasopharyngeal cancer were longer, and the 5-year survival rate of patients with local advanced stage was still ranged from 40 to 60%. The research follow-up time was short and the median follow-up period was 34 months in the research group and 38.5 months in the control group. With the extension of follow-up time, the difference between the two groups may increase. Studies have shown that the combination of nimotuzumab and concurrent chemoradiotherapy for treatment of locally advanced nasopharyngeal carcinoma can benefit the long-term survival [23-25].

It should be noted that the 3-year local recurrence-free survival rates for the study group and the control group were 96.67% and 83.60%, respectively. The differences were statistically significant (P=0.047). All patients in the study group had no local recurrence of nasopharyngeal tumor within 3 years. The result suggested that the combination of concurrent chemoradiotherapy and nimotuzumab may have long-term benefits in controlling nasopharyngeal tumors.

The study showed that the adverse reaction were mild and the incidence and severity of adverse reactions were not increased in locally advanced nasopharyngeal carcinoma patients received concurrent chemoradiotherapy plus nimotuzumab. No rash, allergic reactions or death due to toxic adverse reactions occurred in the patients. There were no significant differences of the incidence of nausea and vomiting, myelosuppression, oral mucositis, and radiodermatitis between the two groups. The incidence of severe toxic and side effects of the Ⅲ-Ⅳ oral mucosa reactions and skin reactions in the study group were higher than that in the control group, respectivelywere 36.4%, 26.4% vs 27.3, 21.8. However, the differences are not statistically significant (P>0.05). Nimotuzumab may block the EGFR of the skin and mucosa cells within the radiotherapy region, resulting in the reduction of the cell proliferation and repair ability. However, due to the good compliance of the patients in the study group, most of the patients were hospitalized during the treatment, with proper oral and skin care, and no significant difference compared with the control group. This is consistent with the results of a recent Meta-analysis [26].

In addition, no hierarchical research has been conducted to identify which chemotherapy regimen combined with nimotuzumab can act as the optimal chemotherapy combination regimen in treating the locally advanced nasopharyngeal carcinoma due to the long time span of cases collection, the small number of cases, and different chemotherapy regimens.

This study is a retrospective clinical analysis, and the small sample size and the inclusion of a single center may lead to bias. The research analysis shows that the combination of concurrent chemoradiotherapy and nimotuzumab has significant advantages in controlling the nasopharyngeal neoplasm and the cervical positive lymph node. Longer follow-up time and larger sample size are required to investigate whether these advantages can be converted into long-term survival advantages.

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Conflicts of interest

The authors declare that there are no conflicts of interest.

Ethics approval and consent to participate

Between September 2012 to December 2016, 188 newly diagnosed patients with stage III–IVB nasopharyngeal carcinoma were treated with at least 1-2 cycles of chemotherapy concurrently with planned IMRT at the First Hospital

Affiliated to Suzhou University. 88 patients received nimotuzumab 200 mg/week with complete clinical and follow-up data. This study was performed according to the principles of the Declaration of Helsinki (2013) [27]. At the time the patients gave their consent for synchronous regimens therapy, we did not obtain comprehensive consent including a future research study. Because of retrospective nature of the study, it is difficult to reacquire agreement from the patients or their family. Therefore, we applied for an exemption from requiring ethics approval, which was granted by the Subcommittee on Biomedical Ethics of the First Hospital Affiliated to Soochow University, Soochow University.

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