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Original Article

Concurrent chemoradiotherapy via nimotuzumab combined with cisplatin improves clinical efficacy in middle-late staged nasopharyngeal carcinomas

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Abstract: Objective: The aim of this study was to examine clinical efficacy and adverse reactions in middle-late staged nasopharyngeal carcinomas using concurrent chemoradiotherapy of nimotuzumab combined with cisplatin. Methods: A total of 86 patients with locally middle-late staged nasopharyngeal carcinomas were given radiotherapy. A total of 45 patients receiving nimotuzumab and cisplatin, at the same time, were included in the study group, while the other 41 patients receiving only cisplatin were included in the control group. Therapeutic efficacy and adverse reactions of the two groups were compared. Patients were evaluated, before and after therapy, with the Functional Assessment of Cancer Therapy-Head & Neck (FACT-H&N). Moreover, 3-year-survials of the two groups of patients were recorded. Results: The effective rate of the study group was 93.33%, significantly higher than that of the control group (78.05%) (P=0.041). Incidence of adverse reactions in the study group was significantly lower than that of the control group (all P<0.050). FACT-H&N scores, before treatment, were not significantly different between the two groups (P>0.050), while the FACT-H&N score of the study group was significantly higher than that of the control group, after treatment (P<0.001). The 3-year overall survival rate of the study group was 91.11%, significantly higher than that of the control group (67.44%) (P=0.045). Conclusion: Concurrent chemoradiotherapy of nimotuzumab combined with cisplatin will effectively improve clinical efficacy and reduce adverse reactions of patients with middle-late staged nasopharyngeal carcinomas. Thus, this therapy is worthy of extensive clinical promotion.

Keywords: Middle-late staged nasopharyngeal carcinoma, nimotuzumab, cisplatin, clinical efficacy, adverse reactions

Introduction

Nasopharyngeal carcinomas are malignant tumors on the top and lateral walls of the nasopharynx, with an incidence highly diversified from region to region. The population suffering from nasopharyngeal cancer in Asia accounts for approximately 80% of worldwide patients [1]. Incidence of nasopharyngeal carcinoma has increased gradually, year by year, and its pathogenesis is still not clear [2]. Studies have shown that the generation of nasopharyngeal carcinomas is, to some extent, associated with environmental, genetic, and infectious factors [3].

Most nasopharyngeal carcinoma patients experience toxic sensitivity to radiotherapy. Therefore, radiotherapy is primarily preferred in the treatment for nasopharyngeal carcinoma in clinic [4]. Regarding statistics, 5-year survival rates of early nasopharyngeal carcinoma patients, after radiotherapy, are about 60% to 80%. After radio-chemotherapy combinations, it may reach 90% [1]. However, nasopharyngeal carcinoma patients at the early stage display no special clinical symptoms. Thus, the disease, in most cases, develops to the middle-late stage once definitely diagnosed. At this time, the patients will be commonly found with local tumors, distant metastasis, and radiation resistance. The rate of recurrence is extremely high and the prognosis of these patients is quite poor [5, 6].

Therefore, methods to increase sensitivity during radiotherapy and chemotherapy have become a hot topic, as well as how to control recurrence and metastasis of tumors in middle-

late staged nasopharyngeal carcinomas. Nimotuzumab is a functional epidermal growth factor receptor monoclonal antibody for treatment of malignant tumors, with strong specificity to tumor cells. It will achieve the objective of targeted treatment of cancer by reversing the malignant biological behaviors of tumor cells at the molecular level. It is low in toxicity and high in tolerance [7-9]. Until now, nimotuzumab has been proven to be applicable to chemotherapy and radiotherapy for nasopharyngeal carcinomas [10]. However, the clinical efficacy of nimotuzumab in the treatment of nasopharyngeal carcinoma has not been extensively studied at home or abroad. In recent years, concurrent chemoradiotherapy of nimotuzumab combined with cisplatin has been adopted as one of the treatment protocols for nasopharyngeal carcinomas. Therefore, the current study aimed to confirm the significance of nimotuzumab in nasopharyngeal carcinoma treatment, providing reliable reference for future clinical treatments.

Materials and methods

General information

A total of 86 patients, diagnosed with locally middle-late staged nasopharyngeal carcinoma, were enrolled as subjects. There were 51 males and 35 females, with an age range of 32-67 years old and an average age of (51.69±8.42) years old. All patients were treated with radiotherapy. The 45 cases receiving chemotherapy with nimotuzumab plus cisplatin were included in the study group, while the other 41 cases receiving chemotherapy with cisplatin were included in the control group. This study was approved by the Ethics Committee of First People's Hospital. All study participants provided written informed consent before participating in the study.

Inclusion and exclusion criteria

Inclusion criteria: Clinical symptoms of patients complied with diagnostic guidelines for nasopharyngeal carcinoma [11]; Patients were definitely diagnosed as nasopharyngeal carcinoma by pathologic biopsy; Patients satisfied the clinical staging criteria of nasopharyngeal carcinoma [12] and all suffered from poorly differentiated squamous cell carcinoma, including 59 cases in stage III and 27 cases in stage IV; Patients were not found with distant metastasis; Patients received follow-up treatment; Patients did not receive any other radiotherapy or chemotherapy within half of a year before admission to the hospital; Patients agreed to cooperate with the arrangement of the medical workers; Patients had complete medical records; Patients were aged 20 to 70 years old.

Exclusion criteria: Patients accompanied with multiple tumors, severe cardiovascular and cerebrovascular diseases, liver and kidney dysfunction, severe inflammation, drug sensitivity, chemotherapy tolerance, dependence in daily life, mental illness, halfway hospital transfers, and pregnancies were all excluded.

Methods

Patients in both groups were given three-dimensional conformal radiotherapy. With reference to the nasopharyngeal MRI and CT examination results, the target areas of radiotherapy were determined from the position of mucosa and submucosal 5 mm. The area of radiotherapy was expanded according to the degree of tumor invasion and, at the same time, the brain stems and parotid glands of the patients were not affected. The nasopharyngeal primary target lesion was a high-risk target area with a radiological dose of 78 Gy/30 F, while surrounding tissues of the focal lesion were the low-risk target area, with a radiological dose of 60 Gy/30 F. During radiotherapy, the two groups of patients were given cisplatin concurrent chemotherapy by intravenous infusions of cisplatin 40 mg/m^2, once/week, for 6 days in total. For the course of chemotherapy in the study group, 200 mg of nimotuzumab was given by intravenous infusions, once/week, for 6 days in total.

Measurement outcomes

Clinical data of the two groups of patients were compared. Therapeutic effects: According to response evaluation criteria in solid tumors (RECIST) [13], the complete response (CR) was evaluated when all lesions disappeared completely and the status kept 4 weeks. Partial response (PR) was evaluated when the size of the lesion reduced by more than 30% and the status was kept 4 weeks. Stable disease (SD) was evaluated when the lesion size was reduced by less than 30% or increased by less than 20%. Progression disease (PD) was evaluated when the lesion size increased by more than 20% or new lesions were found. The effec-

Table 1. Comparison of clinical data [n (%)]

	Research group (n=45)	Control group (n=41)	t or X^2	P
Age	51.24±8.66	51.07±9.12	0.089	0.930
Height (cm)	168.62±10.84	169.72±10.59	0.475	0.636
Body weight (KG)	68.96±7.64	67.57±8.14	0.817	0.416
Course of disease (week)	3.84±1.05	4.08±1.19	0.994	0.323
Red blood cell (× 10^{12})	4.92±0.87	4.76±0.93	0.824	0.412
white blood cell (× 10^9)	16.82±3.24	17.04±4.05	0.279	0.781
Platelet (× 10^9)	329.24±50.77	314.63±52.84	1.307	0.195
Gender			0.019	0.890
Male	27 (60.00)	24 (58.54)		
Female	18 (40.00)	17 (41.46)		
Clinical stage			0.165	0.685
III	30 (66.67)	29 (70.73)		
IV	15 (33.33)	12 (29.27)		
T staging			0.148	0.986
T1	2 (4.44)	2 (4.88)		
T2	6 (13.33)	5 (12.20)		
T3	20 (44.44)	17 (41.46)		
T4	17 (37.78)	17 (41.46)		
N staging			0.566	0.904
N0	2 (4.44)	1 (2.44)		
N1	15 (33.33)	12 (29.27)		
N2	19 (42.22)	20 (48.78)		
N3	9 (20.00)	8 (19.51)		
Smoking			0.191	0.662
Yes	31 (68.89)	30 (73.17)		
No	14 (31.11)	11 (26.83)		
Drinking			0.057	0.812
Yes	35 (77.78)	31 (75.61)		
No	10 (22.22)	10 (24.39)		

tive rate = (CR + PR)/total × 100%. Adverse reactions: Adverse reactions, including myelosuppression, thrombocytopenia, and ECG abnormalities were evaluated as the toxic side effects of the anti-cancer drug. Quality of life: Quality of life of the patients was evaluated with the FACT-H&N [14], before and after treatment. The total score was 144. Higher scores indicate better the quality of life. Survival after treatment: All patients were followed up for 3 years by telephone, home visits, and hospital reviews. Moreover, 3-year survival curves of the two groups of patients were plotted.

Statistical methods

Data was analyzed and processed with SPSS 24.0 statistical software (Bejing NDTimes Technology Co., Ltd.). Count data, such as treatment efficacy, are expressed by rates. Chi-squared test was applied for comparisons among groups. Measurement data, such as FACT-H&N scores, are expressed with mean ± standard deviation. Student's t-test was used for comparisons between the two groups. The survival rate was calculated with the Kaplan-Meier method and compared with the log-rank test. P<0.050 indicates statistical significance.

Results

Comparison of general information

General information, including age, height, body weight, course of disease, red blood cells, white blood cells, platelet count, gender, clinical stage, T staging, N staging, smoking history, and drinking habits, were not significantly different between the two groups (P >0.050), indicating that the two groups of patients were comparable (**Table 1**).

Comparison of therapeutic efficacy

The effective rate of the study group was 93.33%, significantly higher than that of the control group (78.05%) (P=0.041). In the study group, patients with CR accounted for 57.78% (26 patients). There were no patients with PD. In the control group, patients with CR were only 43.90% (18 cases) and patients with PD were 4.88% (2 cases) (**Table 2**).

Comparison of adverse reactions

In the control group, patients with myelosuppression, digestive tract reactions, radiation dermatitis, red blood cell reduction, thrombocytopenia, abnormal electrocardiogram, oral mucositis, and fevers, as well as other adverse

Table 2. Comparison of treatment effects between the two groups [n (%)]

	Research group (n=45)	Control group (n=41)	X^2	P
CR	26 (57.78)	18 (43.90)		
PR	17 (37.78)	14 (34.15)		
SD	3 (6.67)	7 (17.07)		
PD	0 (0.00)	2 (4.88)		
Effective treatment (%)	93.33	78.05	4.174	0.041

Table 3. Comparison of adverse reactions between the two groups [n (%)]

	Research group (n=45)	Control group (n=41)	X^2	P
Myelosuppression	6 (13.33)	21 (51.22)	14.302	<0.001
Digestive tract reaction	5 (11.11)	15 (36.59)	7.801	0.005
Radioactive dermatitis	4 (8.89)	13 (31.71)	7.043	0.008
Erythrocyte reduction	7 (15.56)	21 (51.22)	12.431	<0.001
Thrombocytopenia	4 (8.89)	14 (34.15)	8.270	0.004
Abnormal electrocardiogram	8 (17.78)	30 (73.17)	26.692	<0.001
Oral mucositis	12 (26.67)	28 (68.29)	14.938	<0.001
Fever	1 (2.22)	14 (34.15)	15.183	
Others	6 (13.33)	17 (41.46)	8.665	0.003

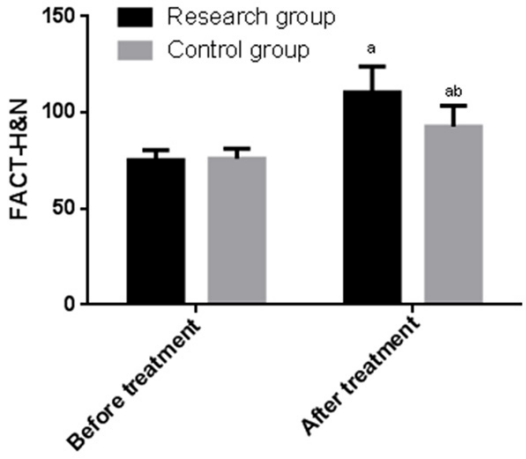

Figure 1. Comparison of FACT-H&N scores, before and after treatment, between the two groups. a represents that compared with the FACT-H&N scores before treatment in the same group, P<0.001; b represents that compared with the FACT-H&N scores after treatment in the study group, P<0.001.

reactions, accounted for 13.33% (6 cases), 11.11% (6 cases), 8.89% (4 cases), 15.56% (7 cases), 8.89% (4 cases), 17.78% (8 cases), 26.67% (12 cases), 2.22% (1 case), and 13.33% (6 cases), respectively. In the study group, patients with myelosuppression, digestive tract reactions, radiation dermatitis, red blood cell reduction, thrombocytopenia, abnormal electrocardiogram, oral mucositis, and fevers, as well as other adverse reactions, accounted for, respectively, 51.22% (21 cases), 36.59% (15 cases), 31.71% (13 cases), 51.22% (21 cases), 34.15% (14 cases), 73.17% (30 cases), 68.29% (28 cases), 34.15% (14 cases), and 41.46% (17 cases). Incidence of adverse reactions in the study group was significantly lower than that in the control group (all P<0.050) (**Table 3**).

Comparison of quality of life

FACT-H&N scores between the two groups were not significantly different before treatment (P>0.050). FACT-H&N scores, after treatment, in the study group were (110.57±13.54), significantly higher than those in the control group (92.73±10.77), P<0.001. FACT-H&N scores, after treatment, were significantly higher than those before treatment (**Figure 1**).

Comparison of prognosis

Of the 86 patients, all were successfully followed up. The follow up success rate was 100%. The 3-year overall survival rate of the study group was 91.11%, significantly higher than that of the control group (67.44%) (P= 0.045) (**Figure 2**).

Discussion

Risk of nasopharyngeal cancer increases day by day. Tumor lesions of nasopharyngeal cancer are difficult to remove by surgery due to the complex structure of the lesion part of the disease [15]. Most nasopharyngeal carcinomas have better sensitivity to radiotherapy. Thus, radiotherapy is the first choice for nasopharyngeal carcinoma treatment [16]. Statistically,

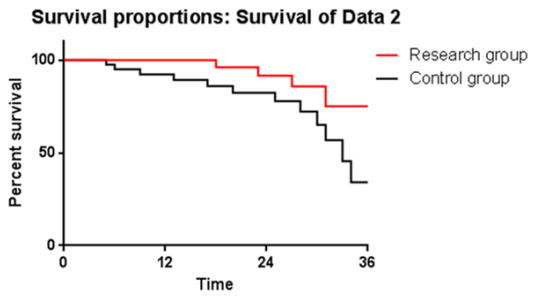

Figure 2. 3-year survival curves of the two groups of patients. The 3-year total survival rate in the group was 91.11%, significantly higher than that in the control group (67.44%) (P=0.045).

nasopharyngeal carcinoma, in approximately 60% of patients, has developed to middle-late stage when it is diagnosed. At this time, radiotherapy alone has failed to treat invasive and metastatic tumor lesions, thus concurrent chemoradiotherapy is necessary to improve therapeutic efficacy in middle-late staged nasopharyngeal carcinomas [17]. However, the side effects of radiotherapy and chemotherapy are great and the cumulative toxicity of concurrent chemoradiotherapy is even greater. Concurrent treatment may be impossible due to intolerance of the side effects. Therefore, discovering methods to improve the efficacy of concurrent chemoradiotherapy is a great challenge.

Epidermal growth factor receptor (EGFR) is a type of transmembrane glycoprotein that will derive dimers with ligands to activate a variety of cell proliferation and differentiation pathways. It has been proven that it is closely associated with tumor invasion and metastasis, with expression rates of EGFR in nasopharyngeal carcinomas as high as 85% and above [18, 19]. Nimotuzumab is a clinically popular epidermal-specific factor receptor inhibitor. It will prevent the binding of epidermal growth factor and receptors by rapidly binding to monoclonal antibodies, inhibiting the activity of tyrosine kinase and internalizing epidermis growth factors. This inhibits the growth of tumor blood vessels and enhances the sensitivity of chemoradiotherapy [20, 21]. Therefore, combination application of nimotuzumab and radiotherapy may compete to combine the EGFR targets of specific antigens, blocking the EGFR-mediated transduction pathways and achieving the objective to treating tumors [22]. The study aimed to prove the application significance of nimotuzumab in the treatment of nasopharyngeal carcinomas by comparing the efficacy differences between nimotuzumab combined with concurrent chemoradiotherapy and concurrent chemoradiotherapy alone in patients with nasopharyngeal carcinomas.

Present results show that the therapeutic efficacy of nimotuzumab combined with concurrent radio-chemotherapy was significantly superior to that of concurrent radio-chemotherapy in the control group, suggesting that nimotuzumab will improve the efficacy of concurrent radio-chemotherapy for nasopharyngeal carcinomas. Present results are consistent with the study result of You et al. [23]. The main reason is speculated to be that the nimotuzumab, as a highly specific EGFR monoclonal antibody [24], enhances the sensitivity of tumor cells to ionizing radiation. At the same time, it inhibits the synthesis of EGFR, achieving the sensitization of radiotherapy and chemotherapy and further accelerating the apoptosis of cancer cells. Comparing the adverse reactions between the two groups, it was concluded that incidence of adverse reactions in the study group was significantly lower than that in the control group. Results suggest that nimotuzumab is of high safety when applied during the process of concurrent radio-chemotherapy for treatment of nasopharyngeal carcinomas. It is speculated that the cytotoxicity of cisplatin lies in synthesizing the double-stranded adducts, together with the DNA of tumor cells, to inhibit the synthesis of DNA and tumor angiogenesis, as well as combining with the ionization electrons of DNA molecular induced by radiation to increase the apoptosis of tumor cell [25]. However, in middle-late staged nasopharyngeal carcinomas, metastasis and invasion of lesions requires more extensive radiation areas in the process of radiotherapy and chemotherapy. Especially once the radiation area covers the brain stem, the damage to the bodies of the patients will be more significant. Nimotuzumab is highly humanized. In combining with concurrent chemoradiotherapy, it will effectively inhibit the spread of tumor lesions, concentrate the tumor cells in the target area of the irradiation, and minimize the toxicity of concurrent chemoradiotherapy. Comparing quality of life scores of the two groups of patients, it was found that quality of life scores of the study group were significantly higher than those of the control

group, further proving that nimotuzumab, combined with concurrent radio-chemotherapy, will greatly improve the prognosis of patients. It is worthy of clinical promotion.

At present, treatment of middle late staged nasopharyngeal carcinomas is the emphasis of clinical studies. Results of the current study show that nimotuzumab was of great significance in the treatment of middle-late nasopharyngeal carcinomas with concurrent radio-chemotherapy. However, there were still some shortcomings in the study, due to the limitation of study conditions. For example, the subjects were limited in total and the population was simple. All patients were diagnosed with middle-late staged nasopharyngeal carcinomas. It was possible that the efficacy of nimotuzumab may deviate in patients with nasopharyngeal carcinomas in other stages and other types. The cycle of study was relatively short and only 3-year survival times were recorded.

In summary, nimotuzumab combined with cisplatin concurrent radio-chemotherapy will effectively improve the clinical efficacy of patients with middle-late staged nasopharyngeal carcinomas, reducing adverse reactions. This treatment method is worthy of clinical application and promotion.

Disclosure of conflict of interest

None.

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