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ORIGINAL ARTICLE

Effect of nimotuzumab and PF induction chemotherapy combined with concurrent chemoradiotherapy in treating locally advanced nasopharyngeal carcinoma

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Summary

Purpose: *To investigate the efficacy and safety of nimotuzumab + cisplatin and 5-fluorouracil (PF) induction chemotherapy combined with concurrent chemoradiotherapy in treating locally advanced nasopharyngeal carcinoma.*

Methods: *The clinical data of 126 patients with stage III-IVa nasopharyngeal carcinoma who were admitted to and treated in our department from September 2013 to May 2016 were collected, and the patients were randomly divided into two groups and treated with nimotuzumab combined with PF induction therapy (NPF group, n=65) and induction therapy of docetaxel, cisplatin and fluorouracil (TPF) regimen (TPF group, n=65). After 2 cycles of induction therapy, all the patients received cisplatin combined with concurrent intensity-modulated radiation therapy (IMRT). Moreover, the clinical efficacy, changes in patients' quality of life and incidence of adverse reactions were observed and compared between the two groups, and the survival of the patients was followed up and recorded.*

Results: *The objective response rate (ORR) and disease control rate (DCR) were remarkably higher in NPF group than those in TPF group [78.5% (51/65) vs. 58.5% (38/65), 93.8% (61/65) vs. 80.0% (52/65)] (p=0.014, p=0.019). During induction therapy, the patients in NPF group had notably ameliorated leukopenia compared with those in TPF group (p=0.018). Only 8 cases of skin rash (grade I) occurred in NPF group (p=0.004), which subsided spontaneously after treatment with nimotuzumab. In the stage of concurrent chemoradiotherapy, NPF group exhibited better tolerance to treatment, but there were no statistically significant differences in adverse reactions between the two groups (p>0.05). Besides, according to the scores of functional assessment of cancer therapy-head and neck (FACT-H&N) scale for measuring the quality of life of patients with head and neck neoplasms in the two groups after treatment, the quality-of-life scores were improved to different extents in both groups. Besides, the functional status score [(19.85±4.74) points vs. (18.14±4.49) points, p=0.037], head and neck additional items score [(23.95±5.20) points vs. (22.21±4.84) points, p=0.040] and total scale score [(108.55±14.65) points vs. (104.65±13.23) points, p=0.023] in NPF group were markedly superior to those in TPF group. It was shown in the results of follow-up that the median overall survival (OS) was (18.9±3.6) months and (16.3±3.8) months in NPF group and TPF group, respectively. Through log-rank test, it was found that the OS was distinctly longer in NPF group than that in TPF group (p=0.017).*

Conclusions: *Compared with TPF induction chemotherapy, nimotuzumab and PF induction chemotherapy combined with concurrent chemoradiotherapy results in better short-term clinical efficacy in treating locally advanced nasopharyngeal carcinoma, higher quality of life and long-term survival rate as well as tolerable adverse reactions.*

Key words: *nasopharyngeal carcinoma, nimotuzumab, induction chemotherapy, concurrent chemoradiotherapy, efficacy*

Introduction

Nasopharyngeal carcinoma is a common head and neck malignancy in China, with a high incidence and occult primary site, and it is difficult to be discovered in the early stage. Most patients have been in the intermediate and advanced stage when definitely diagnosed, and the majority of cancer

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cells manifest infiltrative growth and early metastasis [1,2]. The 3-year progression-free survival (PFS) and 3-year overall survival (OS) of patients undergoing simple intensity-modulated radiation therapy (IMRT) for nasopharyngeal carcinoma are 67% and 83%, respectively [3]. Radiotherapy combined with concurrent chemotherapy can increase local remission rate and disease-free survival (DFS) rate, and reduce distant metastasis and local recurrence rate [4]. Induction chemotherapy is able to decrease tumor burden and subclinical metastasis risk and conducive to enhancing local control. Studies have proposed that cisplatin + 5-fluorouracil (PF) is a commonly used regimen of traditional induction chemotherapy for head and neck neoplasms, and PF induction chemotherapy has survival benefits compared with simple radiotherapy [5, 6]. Taxanes (docetaxel and paclitaxel) also have favorable therapeutic effects on nasopharyngeal carcinoma [7]. In a phase III clinical trial on locally advanced head and neck squamous cell carcinoma, adding docetaxel into induction chemotherapy combined with concurrent chemoradiotherapy can result in survival benefit [8].

In this research, therefore, combination therapy regimens were formed by introducing efficacious and low-toxic monoclonal antibodies against epidermal growth factor receptor (EGFR) during induction therapy, and the feasibility and safety of nimotuzumab combined with PF regimen and docetaxel, cisplatin and fluorouracil (TPF) induction therapy in clinical application were compared.

Methods

General data

Naive patients definitely diagnosed with stage III-IVa nasopharyngeal carcinoma in our hospital from September 2013 to May 2016 were selected. The inclusion conditions were set as follows: 1) patients aged >18 years old, 2) those pathologically diagnosed with nasopharyngeal carcinoma via primary tumor biopsy for the first time, 3) those in clinical stage III-IVa, 4) those with lesions that could be measured according to the Response Evaluation Criteria in Solid Tumors (RECIST) [9], 5) those with an KPS score ≥70 points, 6) those who had serum hemoglobin 10 mg/dL, platelet 100,000/μL, absolute neutrophil count 1,500/μL, serum creatinine ≤1.5× the upper limit of normal (ULN) or creatinine clearance rate ≥60 mL/min, serum bilirubin ≤1.5× ULN, and AST (SGOT) and ALT (SGPT) ≤1.5× ULN, and 7) those with a life expectancy ≥3 months. The exclusion criteria involved 1) patients complicated with other malignant tumors, 2) those who previously received radiotherapy, chemotherapy or targeted therapy, 3) those with contraindications to radiotherapy or chemotherapy, 4) those known to be allergic to any therapy in this research, or 5) those complicated with severe diseases of organs such as the heart, lung, liver or kidney. A total of 130 patients meeting the inclusion criteria were enrolled, including 90 males and 40 females aged 31-67 years old, with an average of (44.56±9.37) years old. Next, the patients were randomly assigned into NPF group (nimotuzumab combined with PF induction therapy, n=65) and TPF group (TPF induction therapy, n=65). After 2 cycles of induction therapy, all the patients received cisplatin combined with concurrent IMRT. The baseline clinical data of the patients were comparable between the two groups of pa-

Table 1. Demographics and general clinical data of all studied patients

Parameters	*NPF group (n=65)*	*TPF group (n=65)*	*p value*
Gender (Male/Female)	42/23	48/17	0.342
Age (years)	43.46±9.63	45.05±9.06	0.334
Clinical staging, n (%)			0.437
III	44 (68.3)	49 (68.3)	
IVA	21 (68.3)	16 (77.8)	
T staging, n (%)			0.653
T1	3 (31.7)	2 (22.2)	
T2	12 (55.6)	9 (61.9)	
T3	34 (36.5)	37 (31.7)	
T4	16 (7.9)	17 (6.4)	
N staging, n (%)			0.507
N0	1 (31.7)	2 (22.2)	
N1	13 (55.6)	10 (61.9)	
N2	41 (36.5)	38 (31.7)	
N3	10 (7.9)	15 (6.4)	
Karnofsky Score, n (%)			0.290
80-90	33 (58.7)	39 (65.1)	
70-80	32 (41.2)	26 (34.9)	

NPF: Nimotuzumab + Cisplatin + 5-fluorouracil; TPF: Docetaxel + Cisplatin + 5-fluorouracil.

tients (p>0.05) (Table 1). The *Declaration of Helsinki* was followed, the duty of disclosure was performed, and all the patients enrolled signed the informed consent. This study was approved by the Ethics Committee of Weifang People's Hospital.

Therapeutic methods

The patients in NPF group were treated with nimotuzumab combined with PF induction therapy. Specifically, nimotuzumab (200 mg/time/week) was infused intravenously, cisplatin (75 g/m^2) was infused intravenously on d 1, and fluorouracil [750 mg/(m^2/d)] was pumped persistently on d 1-5. The therapy was repeated every 3 weeks.

In NPF group, TPF induction chemotherapy was adopted, including intravenous infusion of docetaxel (75 g/m^2) and cisplatin (75 g/m^2) on d 1 and persistent pumping of 5-fluorouracil (750 mg m^2/d) on d 1-5. The therapy was repeated every 3 weeks. Following 2 cycles of induction therapy, cisplatin concurrent with IMRT was performed, where cisplatin (80 mg/m^2) was infused intravenously on d 1, which was repeated every 3 weeks for 3 cycles in total. Prophylactic granulocyte colony-stimulating factor (G-CSF) was not administered before the first course of induction therapy or concurrent chemotherapy. For patients with grade 4 neutropenia already, prophylactic leukocyte-increasing therapy was applied in subsequent cycles of treatment. For patients still intolerant of the treatment, the regimens were adjusted based on the dose reduction principles for chemotherapy drugs. Routine antiemetic therapy was adopted during all chemotherapy cycles, and antiemetic regimens in subsequent cycles were adjusted according to gastrointestinal reactions.

In IMRT for all patients, the extent of tumor was determined using magnetic resonance, the target volume was delineated on contrast-enhanced CT, and the plan was designed.

Then, based on the practical situations of each center, prescribed doses were applied to the PTV formed by expanding each target volume by 3-5 mm: GTVnx: 69.69-70.06 Gy, GTVnd: 64.17-70.06 Gy, high-risk region of primary tumor [clinical target volume (CTV) 1]: 66.03 Gy, and low-risk region of primary tumor and cervical lymph node drainage region (CTV2): 50.4-54.25 Gy. The number of divisions was set as 31-33, and the treatment was conducted for 5 times a week. Finally, the dose limitation of organs at risk and plan were evaluated *as per* the requirements of Radiation Therapy Oncology Group (RTOG) 0615 and RTOG 0225.

Observation indexes

The short-term efficacy, including complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD) were assessed according to RECIST. Objective response rate (ORR) and disease control rate (DCR) were calculated using the following formulas: ORR = (CR + PR)/total cases ×100%, DCR = (CR + PR + SD)/total cases ×100%.

Toxic side effects were determined in accordance with the NCI-CTC Version 4.0, and any sign or symptom indicating toxic adverse reactions needed to be evaluated timely. When the toxic and side effects occurred, symptomatic treatments were performed as necessary, and the treatment could be stopped (if necessary) in the case of severe toxic and adverse reactions.

The patients were subjected to appraisal via functional assessment of cancer therapy-head and neck (FACT-H&N) scale before treatment and at 3 months after treatment. The scale contains general module for malignant tumors FACT-G (physiological status, social/family status, emotional status and functional status) and specific modules for tumors. The higher the score of patients is, the better the quality of life will be.

The survival of the patients was followed up. Specifically, the follow-up was carried out once every 3 months in the 1st and 2nd years, and once every 6 months thereafter. OS referred to the period from the start of treatment to the day of death or last follow-up or end of follow-up. For patients lost to follow-up, the survival was calculated until the day of last follow-up. The follow-up ended in March 2020.

Statistics

SPSS 22.0 (IBM, Armonk, NY, USA) was adopted for statistical analysis. The measurement data were expressed by mean ± standard deviation, and two-sample t-test was performed for inter-group comparison. The enumeration data were presented as ratio (%), and x^2 test was conducted for inter-group comparison. P<0.05 suggested that the difference was statistically significant. Kaplan-Meier method was applied to plot the survival curves, log-rank test was utilized to determine whether the difference in the survival rate between the two groups was statistically significant, and p<0.05 suggested statistically significant differences.

Results

Evaluation of short-term clinical efficacy in two groups of patients

Among the 65 patients in NPF group, there were 29 cases of CR, 22 cases of PR, 10 cases of SD and 4 cases of PD, with an ORR of 78.5% (51/65) and a DCR of 93.8% (61/65). TPF group had 21 cases of CR, 17 cases of PR, 14 cases of SD and 13 cases of PD, with an ORR of 58.5% (38/55) and a DCR of 80.0% (52/65). It can be seen that NPF group had remarkably higher ORR and DCR than TPF group, and the differences between the two groups were statistically significant (p=0.014, p=0.019) (Table 2).

Comparison of incidence of adverse reactions between the two groups of patients

During induction therapy, the adverse reactions in both groups were mainly manifested as grade 1-2 leucopenia and gastrointestinal reaction. Compared with that in TPF group, the leukopenia was relieved notably in NPF group, with a sta-

tistically significant difference (p=0.018). Only 8 cases of skin rash (grade I) occurred in NPF group (p=0.004), which subsided spontaneously after treatment with nimotuzumab. The differences in anemia, thrombocytopenia, nausea and vomiting, impairment of hepatic and renal function and oral mucositis were not statistically significant (p>0.05). In the phase of concurrent chemoradiotherapy, NPF group exhibited better tolerance to treatment and alleviated leukopenia, anemia, thrombocytopenia, nausea and vomiting, oral mucositis and impairment of hepatic and renal function compared with TPF group, but there were no statistically significant differences (p>0.05). The incidence rate of radiodermatitis was slightly higher in NPF group than that in TPF group, displaying no statistically significant difference (p=0.658). All the adverse reactions were improved through symptomatic therapies, and no patients in the two groups had the treatment regimens adjusted due to adverse reactions (Table 3).

Comparison of quality of life before and after treatment between the two groups of patients

According to the comparison of score of FACT-H&N scale for measuring the quality of life of patients with head and neck neoplasms in the two groups, there were no statistically significant differences in items such as physiological status, social/family status, emotional status, functional status, head and neck additional items and total

Table 2. Comparison of clinical efficacy of patients in the two groups

Parameters	*NPF group (n=65)*	*TPF group (n=65)*	*p value*
CR	29 (44.6%)	21 (32.3%)	
PR	22 (33.8%)	17 (26.2%)	
SD	10 (15.4%)	14 (21.5%)	
PD	4 (6.2%)	13 (20.0%)	
ORR (%)	51 (78.5)	38 (58.5)	0.014
DCR (%)	61 (93.8)	52 (80.0)	0.019

NPF: Nimotuzumab + Cisplatin + 5-fluorouracil; TPF: Docetaxel + Cisplatin + 5-fluorouracil; CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; ORR: Objective response rate; DCR: Disease Control Rate.

Table 3. Comparison of adverse reactions of patients in the two studied groups

Parameters	*NPF group (n=65)*		*TPF group (n=65)*		*p svalue*
	Grade I-II n (%)	*Grade III-IV n (%)*	*Grade I-II n (%)*	*Grade III-IV n (%)*	
Induction therapy					
Leukopenia	33 (50.8)	2 (3.1)	28 (43.1)	12 (18.5)	0.018
Anemia	10 (15.4)	0 (0)	15 (23.1)	0 (0)	0.266
Thrombocytopenia	6 (9.2)	0 (0)	9 (13.8)	0 (0)	0.410
Nausea and vomiting	46 (70.8)	1 (1.5)	50 (76.9)	4 (6.2)	0.161
Impairment of hepatic function	9 (13.8)	1 (1.5)	16 (24.6)	1 (1.5)	0.296
Impairment of renal function	3 (4.6)	0 (0)	7 (10.8)	0 (0)	0.188
Rash	8 (12.3)	0 (0)	0 (0)	0 (0)	0.004
Oral mucositis	3 (4.6)	0 (0)	8 (12.3)	0 (0)	0.115
Concurrent chemoradiotherapy					
Leukopenia	31 (47.7)	4 (6.2)	38 (58.5)	6 (9.2)	0.260
Anemia	17 (26.2)	0 (0)	25 (38.5)	0 (0)	0.134
Thrombocytopenia	3 (4.6)	0 (0)	5 (7.7)	0 (0)	0.465
Nausea and vomiting	56 (86.2)	2 (3.1)	53 (81.5)	9 (13.8)	0.065
Impairment of hepatic function	14 (21.5)	0 (0)	20 (30.8)	0 (0)	0.231
Impairment of renal function	4 (6.2)	0 (0)	6 (9.2)	0 (0)	0.495
Oral mucositis	48 (73.8)	0 (0)	51 (78.5)	1 (1.5)	0.444
Radiodermatitis	39 (60.0)	6 (9.2)	34 (52.3)	8 (12.3)	0.658

NPF: Nimotuzumab + Cisplatin + 5-fluorouracil; TPF: Docetaxel + Cisplatin + 5-fluorouracil.

Table 4. Comparison of FACT-H&N scores of patients in the two studied groups

Parameters	*NPF group (n=65)*	*TPF group (n=65)*	*p value*
Pretreatment			
Physiological status	21.45±5.36	20.89±4.76	0.530
Social / family status	22.13±4.41	21.04±4.14	0.149
Emotional status	18.18±3.94	19.03±4.48	0.253
Functional status	14.30±3.88	14.86±4.05	0.422
Head and Neck additional items	23.35±5.63	23.92±5.74	0.569
Total scale score	99.41±6.69	99.74±6.46	0.775
Posttreatment			
Physiological status	23.65±4.96	23.02±4.57	0.453
Social and family status	21.62±4.77	21.23±4.36	0.527
Emotional status	19.48±3.97	19.93±4.11	0.427
Functional status	19.85±4.74	18.14±4.49	0.037
Head and Neck additional items	23.95±5.20	22.21±4.84	0.040
Total scale score	108.55±14.65	104.65±13.23	0.023

NPF: Nimotuzumab + Cisplatin + 5-fluorouracil; TPF: Docetaxel + Cisplatin + 5-fluorouracil.

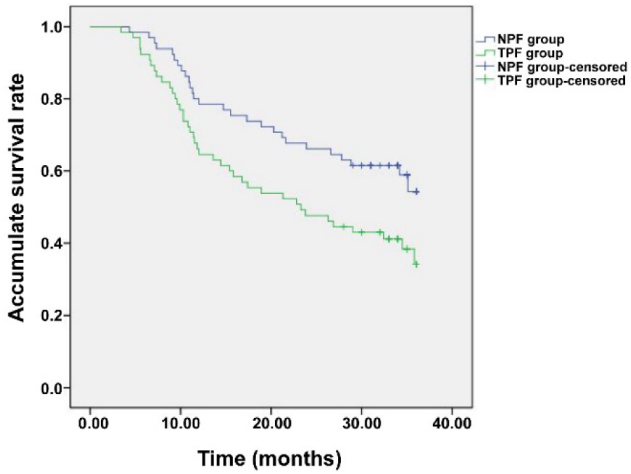

Figure 1. Kaplan-Meier survival curves of the studied patients in the two groups. The overall survival rate of patients in NPF group was significantly higher than that of TPF group (p=0.017).

scale score before treatment (p>0.05). After treatment, the quality of life scores were increased in varying degrees, but the differences in the scores of physiological status, social/family status and emotional status between the two groups were still not statistically significant. However, the functional status score [(19.85±4.74) points *vs.* (18.14±4.49) points, p=0.037], head and neck additional items score [(23.95±5.20) points *vs.* (22.21±4.84) points, p=0.040] and total scale score [(108.55±14.65) points *vs.* (104.65±13.23) points, p=0.023] in NPF group were markedly superior to those in TPF group, with statistically significant differences (Table 4).

Follow-up results of patient survival

All the participants were followed up for 3-36 months. The median OS was 18.9±3.6 months and 16.3±3.8 months, the 1-year OS rate was 78.5% (51/65) and 64.6% (42/65), the 2-year OS rate was 66.2% (43/65) and 47.7% (31/65), and the 3-year OS rate was 58.5% (38/65) and 38.5% (25/65) in NPF group and TPF group, respectively. As shown in the Kaplan-Meier survival curves (Figure 1), NPF group had a distinctly longer OS than TPF group according to log-rank test, and the difference was statistically significant (p=0.017).

Discussion

The 5-year survival rate of patients with early nasopharyngeal carcinoma is relatively high, but approximately 80% of the patients are in the locally advanced stage when diagnosed. Currently, comprehensive treatment modalities, including induction chemotherapy, concurrent chemoradiotherapy, adjuvant chemotherapy, targeted therapy and biological immunotherapy, are developing rapidly [10,11]. The induction chemotherapy can not only decrease tumor volume and improve radiotherapeutic effect on tumor, but also kills subclinical lesions *in vivo* and lower the probability of distant metastasis. Several Chinese and foreign randomized studies and meta-analyses have proven that induction chemotherapy combined with concurrent chemoradiotherapy can evidently improve the survival rate in contrast to radiotherapy alone [12-14]. However, there are no unified standards for

induction chemotherapy regimens, and previous reports indicated that the efficacy and adverse reactions have no statistically significant differences between PT and PF regimens, illustrating that the two-drug regimens have equivalent effectiveness. Hence, many studies attempt to explore three-drug combination chemotherapies. Some new investigations have demonstrated that TPF induction chemotherapy is superior to PF induction chemotherapy [15,16].

Compared with the PF regimen, the TPF regimen composed of docetaxel, cisplatin and 5-fluorouracil has a higher clinical remission rate, so it belongs to grade I of recommendation in the NCCN clinical practice guidelines for head and neck squamous cell carcinoma. It is applied in the induction therapy for nasopharyngeal carcinoma but remains controversial all the time. Recently, relevant studies have further explored the role of TPF induction chemotherapy in nasopharyngeal carcinoma. A multicenter randomized controlled study conducted by Sun et al [17] revealed that TPF induction chemotherapy combined with concurrent chemoradiotherapy is not statistically significantly different from concurrent chemoradiotherapy in terms of local recurrence-free survival rate as well as overall response rate and CR rate at 4 months after radiotherapy (p>0.05). Nevertheless, TPF induction chemotherapy combined with concurrent chemoradiotherapy is able to efficaciously increase the 3-year OS rate (92% *vs.* 86%, p=0.029), disease-free survival (DFS) rate (80% *vs.* 72%, p=0.034) and distant metastasis free survival rate (90% *vs.* 83%, p=0.031) of patients with locally advanced nasopharyngeal carcinoma (stage III-IVB) in contrast with concurrent chemoradiotherapy. Kong et al [18] also researched and found that TPF induction chemotherapy based on concurrent chemoradiotherapy can enhance the therapeutic effect on locally advanced nasopharyngeal carcinoma, but such a regimen markedly raises the incidence rate of toxic effects and remission rate at the same time. Particularly, the grade 3-4 neutropenia affects the clinical application of TPF regimen.

The expression rate of EGFR is 68-89% in nasopharyngeal carcinoma, far higher than that in other solid tumors, which is closely associated with the prognosis of patients [19,20]. The retrospective matched analysis of Peng et al [21] indicated that induction chemotherapy combined with anti-EGFR therapy may be a more effective strategy for locally advanced nasopharyngeal carcinoma treated by IMRT subsequently. Nimotuzumab, a highly humanized and fairly safe EGFR-specific inhibitor independently researched and developed in China, can competitively inhibit the conjugation between EGF and its receptor, block the phosphorylation of related enzymes and targeted induce immune effector cells to kill cancer cells, thus repressing cell growth and inducing apoptosis of tumor cells. A large number of cytological and *in vivo* experimental studies have demonstrated that nimotuzumab is capable suppressing tumor cell growth and raising the sensitivity of tumor cells to radiation [22]. Kong et al [18] reported an interim analysis of a prospective phase III clinical study on nimotuzumab combined with IMRT and cisplatin combined with IMRT after induction chemotherapy for stage III-IVb nasopharyngeal carcinoma at the 2016 ASCO Annual Meeting. In the analysis, the incidence rates of grade 3-4 gastrointestinal reaction and hematotoxicity at and above grade 2 were remarkably lower after nimotuzumab combined with IMRT than those after cisplatin combined with IMRT (4.2% *vs.* 33.7%, 9.7% *vs.* 49.0%), whereas the 3-year DFS and 3-year OS were similar between the two therapies (93.5% *vs.* 94.8%, 79.8% *vs.* 83.5%). According to the retrospective analysis of Wang et al [23], sequential and concurrent chemoradiotherapy following nimotuzumab combined with induction chemotherapy is effective and well tolerated in treating locally advanced nasopharyngeal carcinoma, the incidence rate of neutropenia in stage 3-4 of induction is 11.4%, and 2.9% patients display mild impairment of hepatic function.

In this research, the patients receiving nimotuzumab and PF regimen combined with concurrent chemoradiotherapy exhibited notably higher ORR and DCR than those undergoing TPF induction therapy (p=0.014, p=0.019). NPF induction therapy also efficiently reduced chemotherapy-related hematotoxicity and gastrointestinal reaction in addition to attenuating chemotherapy intensity, which is consistent with the research results of Wang et al. [23]. Moreover, the advantage of NPF induction therapy in evidently relieving adverse reactions further strengthened the tolerance in subsequent concurrent chemoradiotherapy and increased the treatment compliance of patients. As for the quality of life, NPF group had better functional status, head and neck additional entry and total scale score than TPF group (p=0.037, p=0.040, p=0.023). The follow-up results showed that the OS was prominently longer in NPF group than that in TPF group (p=0.017).

However, there were many limitations in this research. For example, the sample size was small, the evaluation criteria and follow-up content were not comprehensive enough, and the possible mechanism of nimotuzumab treatment was not further explored. In the future, therefore, large-sample

multicenter randomized controlled trials will be conducted to testify the conclusion of this research.

Conclusions

Compared with TPF induction chemotherapy, the NPF induction chemotherapy combined with concurrent chemoradiotherapy in treating locally advanced nasopharyngeal carcinoma results in better short-term clinical efficacy, higher quality of life and long-term survival rate as well as tolerable adverse reactions.

Conflict of interests

The authors declare no conflict of interests.

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