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Original Article

Improvement and prognosis analysis of nimotuzumab combined with TP regimen induction chemotherapy and sequential concurrent chemoradiotherapy in patients with locally advanced nasopharyngeal carcinoma

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Abstract: Objective: To explore the effect of nimotuzumab combined with Taxol + Cisplatin (TP) regimen induction chemotherapy and sequential concurrent chemoradiotherapy on the improvement of curative effect and prognosis of patients with locally advanced nasopharyngeal carcinoma. Method: A retrospective analysis was performed on 91 patients with locally advanced nasopharyngeal carcinoma who were admitted to our hospital from February 2017 to February 2019, of which 41 patients received TP induction chemotherapy were assigned to control group (CG), and the remaining 50 patients received nimotuzumab on the basis of control group were assigned to observation group (OG). Both groups of patients received cisplatin chemotherapy concurrently with intensity-modulated radiotherapy (IMRT). Comparisons were made between the two group in terms of clinical efficacy, serum markers squamous cell carcinoma-associated antigen (SCCAg), cytokeratin 19 fragment 21-1 (CYFRA21-1), adverse reactions, and 3-year survival of the patients. Results: Remission rate of cervical lymph nodes in OG was better than that in CG ($P<0.05$). After treatment, SCC-Ag and CYFRA21-1 decreased significantly in both groups, while indexes in OG were markedly lower compared to CG ($P<0.05$). During induction therapy and concurrent chemoradiotherapy, no notable difference was observed in short-term or long-term adverse reactions between the two groups ($P>0.05$). And Cox regression analysis found that clinical stage and treatment were independent factors affecting the prognosis of patients with disease-free survival (PFS). Conclusion: Nimotuzumab combined with TP regimen induction chemotherapy and sequential concurrent chemoradiotherapy can improve the curative effect of patients with locally advanced nasopharyngeal carcinoma.

Keywords: Nimotuzumab, TP regimen, chemoradiotherapy, locally advanced nasopharyngeal carcinoma, efficacy, prognosis

Introduction

Nasopharyngeal carcinoma (NPC) is a malignant tumor originating from the epithelium of the nasopharyngeal mucosa, which is sensitive to radiation and can be clinically cured by early radiotherapy alone [1]. In China, it mostly occurs in southern provinces, with Guangdong accounting for the highest incidence [2]. Studies have reported that the pathogenesis of NPC was related to genetics, EBV infection, environment, diet and other factors [3]. However, the pathogenesis of NPC still remains unclear. Due to the insidious nature of NPC and the lack of typical symptoms in its early stages, 70% of patients are locally advanced at the initial visit [4]. The 5-year survival rate of locally advanced NPC patients after radical treatment is only 50-60%, and the main factors attribute to treatment failure are local recurrence and distant metastasis [5].

At present, radiotherapy-based chemoradiotherapy combined with targeted and immune comprehensive therapy is an important treatment mode for locally advanced NPC, and induction chemotherapy can create better radiotherapy conditions and reduce the risk of me-

tastasis [6]. However, on the basis of platinum-based concurrent chemoradiotherapy, 5-15% of NPC patients still experience local-regional recurrence, and 15-30% of NPC patients undergo distant metastasis [7, 8]. Studies have found that [9] the main targets of intervention in NPC were epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR). In the study of Zhang et al. [10], it was found that EGFR was highly expressed in NPC patients, and there is evidence showing that EGFR overexpression was associated with radiotherapy resistance and poor prognosis of patient. With the continuous development of molecular targeted therapy technology, EGFR inhibitors led by nimotuzumab and cetuximab have entered clinical application in recent years [11]. By competitively binding with EGFR, it can block the downstream signal transduction pathway mediated by EGFR, thereby inhibiting tumor cell proliferation, inducing differentiation, promoting cell apoptosis, and inhibiting tumor angiogenesis [12]. Nimotuzumab is a novel humanized monoclonal antibody that can effectively improve the sensitivity of radiotherapy [13], which has become a hot spot in the treatment of locally advanced NPC in recent years due to its strong specificity and mild side effects [14]. There is, however, no report focused on the combination therapy of nimotuzumab and TP regimen.

To this end, this study aimed to analyze the effect of nimotuzumab combined with TP regimen induction chemotherapy and sequential concurrent chemoradiotherapy on the efficacy in locally advanced NPC patients, and to analyze the impact of this treatment regimen on the prognosis of patients, so as to provide guidance for clinical treatment plans.

Methods and materials

Clinical information

A retrospective analysis was performed on 91 patients with locally advanced nasopharyngeal carcinoma who were admitted to our hospital from February 2017 to February 2019, of which 41 patients received (TP) induction chemotherapy were as assigned to the control group (CG), and the remaining 50 patients received nimotuzumab on the basis of control group were assigned to the observation group (OG). Both groups of patients received cisplatin chemotherapy concurrently with intensity-modulated radiotherapy (IMRT). This study received approval from the medical ethics committee of our hospital, and all patients were informed about the study with informed consent signed. Ethical batch number: LL2020048.

Inclusion and exclusion criteria

Inclusion criteria: Patients in line with the 8th edition of AJCC NPC tumor staging criteria [15]; Patients with clinical stage of III-IVa; Patients with an age of 18-70 years; Patients with NPC confirmed by pathological examination with pathological type of undifferentiated non-keratinizing carcinoma, differentiated nonkeratinizing carcinoma, or keratinizing squamous cell carcinoma; Patients who had at least 1 cycle of standard platinum-based induction chemotherapy, with a performance status (PS) score of 0-1 before radiotherapy.

Exclusion criteria: Patients with other tumors; Patients with incommensurable clinical efficacy; Patients with incomplete clinical data; Patients with intolerance to drugs concerned; Patients who had been treated with EGFR receptor inhibitors and similar drugs before concurrent chemoradiotherapy; Pregnant women.

Treatment plan

Chemotherapy regimen: CG patients received TP regimen: docetaxel (Shanghai Chuangnuo Pharmaceutical Co., Ltd., H20113165) 75 mg/m^2 and paclitaxel liposome (Jiangsu Osaikang Pharmaceutical Co., Ltd., H20083848) 135 mg/m^2, intravenous infusion once every 3 weeks; Nedaplatin (Jiangsu Osaikang Pharmaceutical Co., Ltd., H20143132) 80 mg/m^2 and cisplatin 75 mg/m^2, intravenous infusion once every 3 weeks. OG patients were treated with nimotuzumab on the basis of CG: nimotuzumab injection 200 mg, intravenous drip, once a week. The rest of the program was the same as CG. 2-3 times after induction, cisplatin chemotherapy was conducted, with cisplatin 40 mg/m^2 intravenous drip once a week in a total of 6 times, combined with concurrent intensity-modulated radiotherapy (IMRT).

Radiotherapy regimen: All patients in this study received IMRT treatment. Tumor extent was determined by magnetic resonance imaging

(MRI), the target volume was delineated on enhanced CT for the design of treatment plan. Reverse intensity-modulated plan was designed and optimized using 6 MV X-ray intensity-modulated radiotherapy technology. The radiation dose was determined according to the size of the tumor: primary tumor (PGTVnx) 69.96 Gy-71.28 Gy/33 f, cervical lymph node (PGTVnd) 66 Gy/33 f, visible lesions + upper neck lymphatic drainage area (PTV1) 60.06 Gy/33 f, lower cervical lymphatic drainage area (PTV2) 50 Gy-52.8 Gy/33 f. Above therapy was conducted 5 times a week for 6-7 weeks. Organ-at-risk dose-limiting and planning assessments were performed at the request of the Radiotherapy Collaborative Group.

Tumor marker detection

Before and after receiving induction therapy, 5 ml of fasting venous blood was collected and centrifuged at 1500 rpm for 10 min to obtain serum for detection. The level of squamous cell carcinoma-associated antigen (SCC-Ag) was determined by enzyme-linked immunosorbent assay, and that of cytokeratin 19 fragment 21-1 (CYFRA21-1) was by electrochemiluminescence method. SCC-Ag kit was purchased from Shanghai Enzyme Link, ml058616, and CYFRA21-1 kit was from Shanghai Toujing Life Technology Co., Ltd., 18A002.

Adverse reaction statistics

The acute and late adverse reactions of radiotherapy were evaluated according to the RTOG acute and late radiation response scoring criteria. According to the common toxicity standard observation records of the National Cancer Center (NCI-CTC version 3.0), they were divided into grades 0-IV.

Clinical response evaluation criteria

Tumor regression was assessed by imaging (CT or MR) 1 month after the end of treatment. The treatment efficacy was evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST version 1.1) [16]. Specific criteria are as follows: complete response (CR), disappearance of all target lesions, short diameter of all pathological lymph nodes was <10 mm for at least 4 weeks (at the time of overall response assessment, initially elevated tumor markers returned to normal). Partial response (PR), the total diameter of the target lesion decreased by at least 30% for at least 4 weeks; progression of disease (PD), the total diameter of the target lesion increased by at least 20%, or new lesions occurred; stable disease (SD), the reduction of target lesions did not reach the level of PR, and the extent of target lesion did not reach the level of PD but was in between. The total effective rate (RR) = (CR+PR) cases/total cases ×100%.

Observation indicators

Main outcome measures: The changes in serum SCC-Ag and CYFRA21-1 levels before and after treatment were observed. The primary lesions, posterior cervical lymph nodes, and overall treatment efficacy in patients after recent induction therapy were compared, as well as the overall curative effect after the whole course of treatment (the efficacy evaluation is the grade data. The CR, PR, PD and SD patients in each group are regarded as the whole, and the data are analyzed through the rank sum test, that is, the overall effective rate). The Kaplan-Meier (KM) survival curve was used to analyze the overall survival (OS) and disease-free survival (PFS) of the patients, and Cox regression was used to analyze the prognostic factors affecting PFS of patients.

Secondary outcome measures: The clinical data and incidence of adverse reactions of the two groups of patients were compared.

Statistical analysis

In this study, SPSS 20.0 software was used to analyze the collected data. Count data were expressed as n (%) and compared using x^2 test. Rank data were assessed with Mann-Whitney test and expressed as Z. K-M survival curve was used to draw the overall survival of patients, which was analyzed by Log-rank test. Cox regression was used to analyze the independent prognostic factors of the patients. And $p<0.05$ was considered to be statistically different.

Results

Comparison of clinical data

Analysis suggested that there were no notable differences regarding gender, age, T stage, N

Table 1. Clinical data

Factors	Control group (n=41)	Observation group (n=50)	P
Gender			0.412
Male	28	38	
Female	13	12	
Age			0.216
>60 years old	25	24	
≤60 years old	16	26	
T Stage			0.955
T1	5	7	
T2	6	6	
T3	16	18	
T4	14	19	
N Stage			0.185
N1	5	13	
N2	19	23	
N3	17	14	
Clinical Stage			0.442
Stage III	23	24	
Stage IVa	18	26	
Pathological Type			0.810
Nonkeratinizing Squamous Cell Carcinoma	15	17	
Undifferentiated Squamous Cell Carcinoma	1	2	
Poorly Differentiated Squamous Cell Carcinoma	15	15	
Other Differentiated Squamous Cell Carcinoma	10	16	
Induction Therapy Cycle			0.206
2 cycles	11	8	
3 cycles	30	42	

stage, clinical stage, pathological type, induction treatment time between the two groups (P>0.05, **Table 1**).

Changes of tumor markers before and after treatment

Serum levels of SCC-Ag and CYFRA21-1 after treatment were markedly lower than those before treatment in both groups of patients (P<0.05). Further comparison showed that the levels of those in CG after treatment were higher than those in OG (**Figure 1**, P<0.05).

Comparison of clinical efficacy

In this study, we calculated the changes in clinical efficacy of patients after treatment. Analysis showed that there was no difference in the overall curative effect and effective rate in primary lesions after induction chemotherapy between the two group (P>0.05, **Table 2**). Comparison of the lymph node induction chemotherapy effect showed that OG held higher overall efficacy and total effective rate in lymph nodes than those in CG (P<0.05, **Table 3**). Then, the overall curative effect of the two groups of patients after induction chemotherapy was further compared, and it was found that OG held a comparatively higher overall curative effect (P<0.05, **Table 4**), but there was no difference regarding effective rate between the two groups (P>0.05). Finally, we compared the overall effective rate of the two groups after the whole course of treatment and no statistical difference was found in such index (P>0.05, **Table 5**).

Comparison of adverse reaction

The adverse reactions of two groups were statistically analyzed during the induction chemotherapy phase and the concurrent chemoradiotherapy phase (**Table 6**). Analytical comparison suggested no marked difference in such indicators (P>0.05, **Tables 7**, **8**).

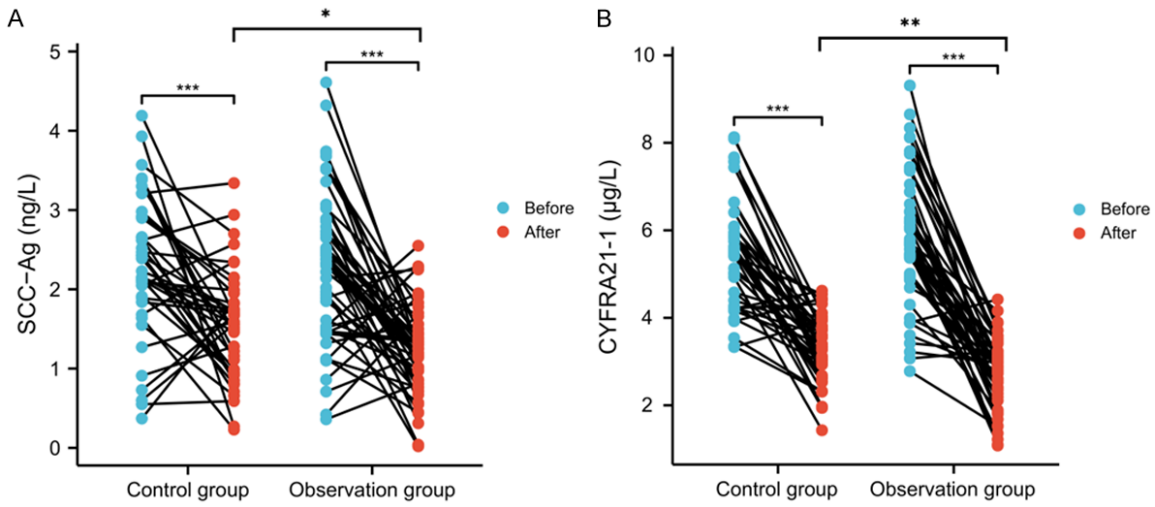

Figure 1. Changes of SCC-Ag and CYFRA21-1 levels in serum of patients before and after treatment. A. Comparison of changes in serum SCC-Ag levels before and after treatment between the two groups of patients. B. Comparison of serum CYFRA21-1 levels before and after treatment between the two groups. Note: * indicates P<0.05, *** indicates P<0.001. SCC-Ag: squamous cell carcinoma-associated antigen; CYFRA21-1: cytokeratin 19 fragment 21-1.

Table 2. Efficacy evaluation of primary lesions in patients after induction chemotherapy

Item	CR	PR	SD	PD	Effective Rate
Control group (n=41)	1	30	8	2	31 (75.60)
Observation group (n=50)	2	40	8	0	42 (84.00%)
x^2/Z		-1.130			0.999
P		0.259			0.317

Note: Complete remission (CR), partial remission (PR), stable disease (SD), progressive disease (PD).

Table 3. Evaluation of lymph node response in patients after induction chemotherapy

Item	CR	PR	SD	PD	Effective Rate
Control group (n=41)	0	28	10	3	28 (68.29)
Observation group (n=50)	1	44	5	0	45 (90.00%)
x^2/Z		-2.752			2.586
P		0.006			0.009

Note: Complete remission (CR), partial remission (PR), stable disease (SD), progressive disease (PD).

Table 4. Overall response evaluation of patients after induction chemotherapy

Item	CR	PR	SD	PD	Effective Rate
Control group (n=41)	0	31	8	2	31 (75.60)
Observation group (n=50)	1	44	5	0	45 (90.00)
x^2/Z		-2.026			3.389
P		0.043			0.065

Note: Complete remission (CR), partial remission (PR), stable disease (SD), progressive disease (PD).

Analysis of prognostic factors

Two groups of patients were followed up for 3 years, and no significant difference was observed in the 3-year survival rate between CG and OG (P=0.950, **Figure 2A**). In terms of disease-free survival time, it was observed to be higher in OG than CG (P=0.008, **Figure 2B**).

Table 5. Evaluation of the overall efficacy of the patients after the full course of treatment

Item	CR	PR	SD	PD	Effective Rate
Control group (n=41)	21	11	6	3	32 (78.04)
Observation group (n=50)	25	20	4	1	45 (90.00)
x^2/Z		-0.464			2.472
P		0.643			0.116

Note: Complete remission (CR), partial remission (PR), stable disease (SD), progressive disease (PD).

Table 6. Adverse reaction statistics

Item	Statistics of toxic and side effects during induction chemotherapy				
	Level 0	Level I	Level II	Level III	Level IV
Control group (n=41)					
Malignant Vomiting	30	9	2	0	0
Decreased White Blood Cells	27	5	5	4	0
Thrombocytopenia	37	2	2	0	0
Rash	39	1	1	0	0
Liver Damage	38	2	1	0	0
Observation Group (n=50)					
Malignant Vomiting	36	10	4	0	0
Decreased White Blood Cells	35	10	3	2	0
Thrombocytopenia	45	3	2	0	0
Rash	48	1	0	1	0
Liver Damage	48	2	0	0	0
Item	Statistics of toxic and side effects during concurrent chemoradiotherapy				
	Level 0	Level I	Level II	Level III	Level IV
Control Group (n=41)					
Malignant Vomiting	23	13	5	0	0
Decreased White Blood Cells	25	12	3	1	0
Thrombocytopenia	38	2	1	0	0
Abnormal Liver Function	39	1	1	0	0
Oral Mucositis	4	33	2	2	0
Radiation Dermatitis	6	25	8	2	0
Dry Mouth	9	30	2	0	0
Hearing Loss	28	10	3	0	0
Restricted Mouth Opening	39	2	0	0	0
Observation Group (n=50)					
Malignant Vomiting	24	16	5	0	0
Decreased White Blood Cells	28	15	4	3	0
Thrombocytopenia	46	2	2	0	0
Abnormal Liver Function	45	5	0	0	0
Oral Mucositis	12	36	2	0	0
Radiation Dermatitis	10	34	6	0	0
Dry Mouth	14	35	1	0	0
Hearing Loss	38	10	2	0	0
Restricted Mouth Opening	47	3	0	0	0

Then through multivariate analysis, it was found that clinical stage was an independent prognostic factor affecting OS, while clinical stage and treatment plan were independent prognostic factors affecting PFS ($P<0.01$, **Tables 9**, **10**).

Table 7. Statistical analysis of toxic and side effects during induction chemotherapy

Item	Malignant Vomiting	Decreased White Blood Cells	Thrombocytopenia	Rash	Abnormal Liver Function
Control group (n=41)	11	14	4	2	3
Observation group (n=50)	14	15	5	2	2
x^2	0.015	0.178	0.001	0.041	0.477
P	0.900	0.673	0.969	0.838	0.489

Table 8. Statistical analysis of toxic and side effects during concurrent chemoradiotherapy

Item	Malignant Vomiting	Decreased White Blood Cells	Thrombocy-topenia	Abnormal Liver Function	Oral Mucositis	Radiation Dermatitis	Dry Mouth	Hearing Loss	Restricted Mouth Opening
Control group (n=41)	18	16	3	2	37	35	32	13	2
Observation group (n=50)	21	22	4	5	38	40	36	12	3
x^2	0.033	0.229	0.014	0.832	3.154	0.447	0.436	0.672	0.054
P	0.855	0.632	0.903	0.362	0.075	0.503	0.508	0.412	0.815

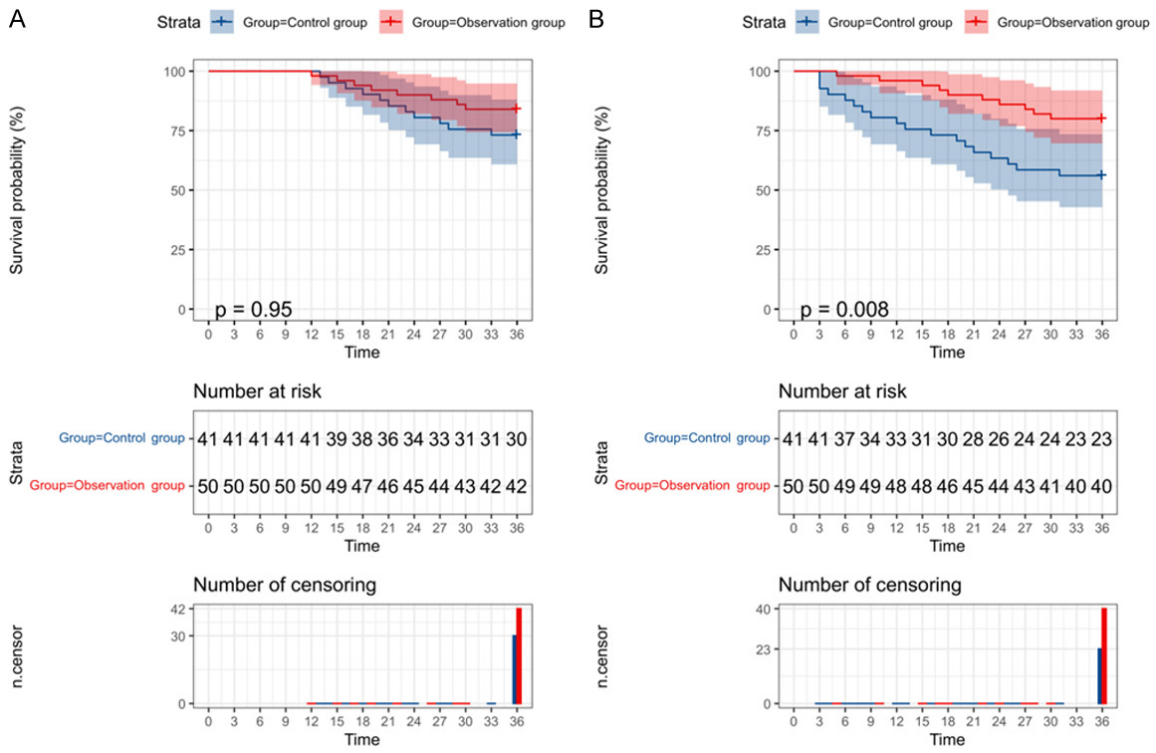

Figure 2. Comparison of OS and PFS in patients. A. Comparison of OS between two groups. B. Comparison of PFS between two groups. OS: overall survival; PFS: disease-free survival.

Discussion

NPC is derived from nasopharyngeal epithelial cells and is a highly aggressive head and neck malignancy [17]. In recent years, induction chemotherapy, concurrent chemoradiotherapy, and targeted therapy are extensively applied in the clinical treatment of locally advanced NPC [18]. Due to the special influence of the anatomical part of the nasopharynx, its operation is comparatively restricted and difficult [19]. And since NPC is sensitive to emission, radiotherapy is often considered as a common treatment [20]. However, the efficacy

Table 9. Risk factors for Os

Factors	Univariate Cox Regression			Multivariate Cox Regression		
	P	HR	95% CI	P	HR	95% CI
Gender	0.341	0.589	0.198-1.753			
Age	0.117	0.434	0.153-1.234			
T Stage	0.951	0.965	0.307-3.030			
N Stage	0.249	1.487	0.757-2.921			
Clinical Stage	0.003	5.833	1.858-18.316	0.005	4.854	1.609-14.643
Pathological Type	0.946	1.015	0.662-1.557			
Scc-Ag	0.407	1.283	0.712-2.314			
Cyfra21-1	0.733	0.934	0.633-1.379			
Treatment Plan	0.328	0.587	0.203-1.704			

Note: Squamous cell carcinoma-associated antigen (SCC-Ag), cytokeratin 19 fragment 21-1 (CYFRA21-1).

Table 10. Risk factors for PFS

Factors	Univariate Cox Regression			Multivariate Cox Regression		
	P	HR	95% CI	P	HR	95% CI
Gender	0.373	0.656	0.259-1.661			
Age	0.488	0.736	0.309-1.751			
T stage	0.356	0.667	0.282-1.577			
N stage	0.129	1.550	0.881-2.728			
Clinical stage	<0.001	5.409	2.209-13.248	<0.001	4.737	1.996-11.241
Pathological type	0.666	1.079	0.764-1.524			
SCC-Ag	0.107	1.491	0.917-2.424			
CYFRA21-1	0.755	1.053	0.761-1.456			
Treatment plan	0.015	0.324	0.131-0.801	0.006	0.345	0.160-0.741

Note: Squamous cell carcinoma-associated antigen (SCC-Ag), cytokeratin 19 fragment 21-1 (CYFRA21-1).

of radiotherapy alone for locally advanced NPC is not satisfactory with a 5-year survival rate of only about 35% [21].

Although locally advanced NPC has better short-term efficacy and higher local control rate with the maturity of IMRT, there are still NPC patients undergoing locoregional recurrence and distant transfer on the basis of platinum-based concurrent chemoradiotherapy treatment. To further reduce the recurrence and metastasis of locally advanced NPC, targeted drugs with mild side effects have become a hot topic in the treatment of locally advanced NPC. EGFR is a glycoprotein belonging to the tyrosine kinase type receptor, originally a receptor for epithelial growth factor cell proliferation and signaling. It mainly binds to cell surface ligand and EGFR to undergo dimerization and autophosphorylation [22]. Studies have shown that EGFR was expressed in a variety of solid tumors, and the expression in NPC was up to 80-90% [23]. Nimotuzumab is an IgG1-type humanized monoclonal antibody drug with a unique safety profile and low skin toxicity compared to cetuximab [24]; however, the efficacy of nimotuzumab combined with TP regimen induction therapy in patients with locally advanced NPC has not yet been confirmed. In this study, no marked difference was observed in the efficacy in primary tumor between the two groups of patients after induction chemotherapy. However, further statistics showed that the effective rate in cervical lymph nodes in OG was higher than CG after induction chemotherapy in terms of both the overall efficacy and the effective rate, suggesting that nimotuzumab combined with TP regimen could significantly improve cervical lymph nodes of patients. Moreover, overall efficacy of OG patients after induction chemotherapy was strikingly and statistically improved than that of CG patients. SCCAg exists in normal squamous epithelium and squamous cell carcinoma cells,

with only a trace amount presented in normal human serum, but it is significantly elevated in the serum of patients with squamous cell carcinoma, and studies have found that changes in SCCAg expression could reflect the severity of squamous cell carcinoma patients [25]. CYFRA21-1 is widely distributed on the surface of normal tissues such as squamous epithelium. When the cells become malignant, the activated protease accelerates the degradation of the cells, so that a large number of cytokeratin fragments are released into the blood. Most of NPCs originate from the lining squamous epithelium of the nasopharynx, their location is hidden, and the diagnosis is often missed. And the detection of serum CYFRA2121 was proven to be helpful for the early diagnosis of NPC [26]. We detected the tumor markers and found that the serum levels of SCC-Ag and CYFRA21-1 in OG were markedly decreased after treatment and were significantly lower compared with CG. This showed from the other side that the combination of nimotuzumab and TP could achieve short-term efficacy in patients. In the follow-up analysis, however, no marked difference presented in the clinical efficacy of two groups of patients after IMRT treatment, indicating that nimotuzumab combined with TP regimen could improve clinical efficacy of locally advanced NPC patients in short term, but the long-term efficacy still remains unclear.

To determine the effect of nimotuzumab combined with TP regimen on the long-term efficacy of patients, we observed the OS and PFS of the two groups of patients. It suggested that the combination of nimotuzumab and TP had no significant effect on the OS of patients. Previous study of Wang et al. [27] revealed that patients receiving nimotuzumab during concurrent chemoradiotherapy experienced no fluctuation in 5-year OS, which was consistent with our study. However, our further analysis indicated that nimotuzumab combined with TP regimen could benefit the PFS of patients. And through Cox regression, it was found that nimotuzumab combined with TP regimen was a protective factor for PFS of patients. These results all suggested that although nimotuzumab combined with TP regimen couldn't improve the OS of patients, it upregulated the PFS of patients with locally advanced NPC. In terms of adverse reactions, previous research [28] found that nimotuzumab combined with induction chemotherapy followed by sequential concurrent chemoradiotherapy was effective and well-tolerated in the treatment of locally advanced NPC. At the end of this study, we calculated the incidence of adverse reactions of patients, and found that the occurrence in OG was not statistically different from that in CG, which also suggested that the addition of nimotuzumab to radiotherapy was superior to platinum-based chemotherapy in reducing hematological toxicity. We speculated that the EGFR receptor may be related to the bivalent binding properties of nimotuzumab.

In this study, we determined through relatively comprehensive analysis that nimotuzumab combined with TP regimen induction chemotherapy and sequential concurrent chemoradiotherapy could improve the PFS of patients without increasing the adverse reactions. However, this study still has certain limitations. First of all, due to the inability to query more survival data of patients, the follow-up time of this study was inadequate. Second, the sample size is relatively small compared to large retrospective analysis sample. Therefore, we hope to carry out randomized controlled trials with long-term follow-up in future study to supplement our conclusions.

In conclusion, nimotuzumab combined with TP regimen induction chemotherapy and sequential concurrent chemoradiotherapy could improve the curative effect of locally advanced NPC patients without increasing the incidence of adverse reactions.

Disclosure of conflict of interest

None.

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References

[1] Lee HM, Okuda KS, González FE and Patel V. Current perspectives on nasopharyngeal carcinoma. Adv Exp Med Biol 2019; 1164: 11-34.

[2] Lam WKJ and Chan JYK. Recent advances in the management of nasopharyngeal carcinoma. F1000Res 2018; 7: F1000 Faculty Rev-1829.

[3] Chen YP, Chan ATC, Le QT, Blanchard P, Sun Y and Ma J. Nasopharyngeal carcinoma. Lancet 2019; 394: 64-80.
[4] Guo R, Mao YP, Tang LL, Chen L, Sun Y and Ma J. The evolution of nasopharyngeal carcinoma staging. Br J Radiol 2019; 92: 20190244.
[5] Mai HQ, Chen QY, Chen D, Hu C, Yang K, Wen J, Li J, Shi YR, Jin F, Xu R, Pan J, Qu S, Li P, Hu C, Liu YC, Jiang Y, He X, Wang HM, Lim WT, Liao W, He X, Chen X, Liu Z, Yuan X, Li Q, Lin X, Jing S, Chen Y, Lu Y, Hsieh CY, Yang MH, Yen CJ, Samol J, Feng H, Yao S, Keegan P and Xu RH. Toripalimab or placebo plus chemotherapy as first-line treatment in advanced nasopharyngeal carcinoma: a multicenter randomized phase 3 trial. Nat Med 2021; 27: 1536-1543.
[6] Huang Y, Feng M, Yang X, Zhou J, Li L, Xu K, Xu G and Lang J. DW-MRI-guided dose escalation improves local control of locally advanced nasopharyngeal carcinoma treated with chemoradiotherapy. Cancer Manag Res 2020; 12: 3107-3116.
[7] Lee AW, Ma BB, Ng WT and Chan AT. Management of nasopharyngeal carcinoma: current practice and future perspective. J Clin Oncol 2015; 33: 3356-3364.
[8] Wu F, Wang R, Lu H, Wei B, Feng G, Li G, Liu M, Yan H, Zhu J, Zhang Y and Hu K. Concurrent chemoradiotherapy in locoregionally advanced nasopharyngeal carcinoma: treatment outcomes of a prospective, multicentric clinical study. Radiother Oncol 2014; 112: 106-111.
[9] Chen X, Liang R and Zhu X. Anti-EGFR therapies in nasopharyngeal carcinoma. Biomed Pharmacother 2020; 131: 110649.
[10] Zhang P, Wu SK, Wang Y, Fan ZX, Li CR, Feng M, Xu P, Wang WD and Lang JY. p53, MDM2, eIF4E and EGFR expression in nasopharyngeal carcinoma and their correlation with clinicopathological characteristics and prognosis: a retrospective study. Oncol Lett 2015; 9: 113-118.
[11] Yuan C, Xu XH, Xu L, Liu Y, Sun M, Ni LH, Wang XL, Chen Z, Zhang K, Wan HL and Zeng G. Cetuximab versus nimotuzumab for the treatment of advanced nasopharyngeal carcinoma: a network meta-analysis. J BUON 2017; 22: 1004-1010.
[12] Liang ZG, Lin GX, Ye JX, Li Y, Li L, Qu S, Liang X and Zhu XD. Cetuximab or nimotuzumab versus cisplatin concurrent with radiotherapy for local-regionally advanced nasopharyngeal carcinoma: a meta-analysis. Asian Pac J Cancer Prev 2018; 19: 1397-1404.
[13] Crombet Ramos T, Mestre Fernandez B, Mazorra Herrera Z and Iznaga Escobar NE. Nimotuzumab for patients with inoperable cancer of the head and neck. Front Oncol 2020; 10: 817.
[14] Liang R, Yang L and Zhu X. Nimotuzumab, an anti-EGFR monoclonal antibody, in the treatment of nasopharyngeal carcinoma. Cancer Control 2021; 28: 1073274821989301.
[15] Huang SH and O'Sullivan B. Overview of the 8th edition TNM classification for head and neck cancer. Curr Treat Options Oncol 2017; 18: 40.
[16] He LN, Chen T, Fu S, Chen C, Jiang Y, Zhang X, Du W, Li H, Wang Y, Ali WAS, Zhou Y, Lin Z, Yang Y, Huang Y, Zhao H, Fang W, Zhang L and Hong S. Reducing number of target lesions for RECIST1.1 to predict survivals in patients with advanced non-small-cell lung cancer undergoing anti-PD1/PD-L1 monotherapy. Lung Cancer 2021; 165: 10-17.
[17] Lee AWM, Ng WT, Chan JYW, Corry J, Makitie A, Mendenhall WM, Rinaldo A, Rodrigo JP, Saba NF, Strojan P, Suarez C, Vermorken JB, Yom SS and Ferlito A. Management of locally recurrent nasopharyngeal carcinoma. Cancer Treat Rev 2019; 79: 101890.
[18] Hui EP, Ma BBY and Chan ATC. The emerging data on choice of optimal therapy for locally advanced nasopharyngeal carcinoma. Curr Opin Oncol 2020; 32: 187-195.
[19] Su L, She L and Shen L. The current role of adjuvant chemotherapy in locally advanced nasopharyngeal carcinoma. Front Oncol 2021; 10: 585046.
[20] Mané M, Benkhaled S, Dragan T, Paesmans M, Beauvois S, Lalami Y, Szturz P, Gaye PM, Vermorken JB and Van Gestel D. Meta-analysis on induction chemotherapy in locally advanced nasopharyngeal carcinoma. Oncologist 2021; 26: e130-e141.
[21] Cai H, Pang X, Dong D, Ma Y, Huang Y, Fan X, Wu P, Chen H, He F, Cheng Y, Liu S, Yu Y, Hong M, Xiao J, Wan X, Lv Y and Zheng J. Molecular decision tree algorithms predict individual recurrence pattern for locally advanced nasopharyngeal carcinoma. J Cancer 2019; 10: 3323-3332.
[22] Chen X, Liang R, Lai L, Chen K and Zhu X. Prognostic role of EGFR/p-EGFR in patients with nasopharyngeal carcinoma: a meta-analysis. Front Oncol 2021; 11: 697369.
[23] Kyrodimos E, Chrysovergis A, Mastronikolis N, Tsiambas E, Ragos V, Roukas D, Fotiades P and Papanikolaou V. Targeting EGFR in nasopharyngeal carcinoma. J BUON 2021; 26: 759-761.
[24] Thai Hoa NT and Quang Huy H. Combined nimotuzumab with chemoradiotherapy for locally advanced head and neck squamous cell carcinoma. Cureus 2020; 12: e8105.
[25] Lee JK, Hsieh JF, Tsai SC, Ho YJ, Sun SS and Kao CH. Comparison of CYFRA 21-1 and squamous cell carcinoma antigen in detecting na-

sopharyngeal carcinoma. Ann Otol Rhinol Laryngol 2001; 110: 775-778.
[26] Chen H, Tian L, Chen J, Sun P, Han R, Wu X and Dai S. Evaluation of 2 commercially systems for detection of serum squamous cell carcinoma antigen in pan squamous cell carcinoma. Cancer Control 2020; 27: 107327482098-3025.
[27] Wang F, Sun Q, Jiang C, Liu T, Rihito A, Masoto S, Wang Y, Fu Z and Chen M. Additional induction chemotherapy to concurrent chemotherapy and intensity-modulated radiotherapy with or without nimotuzumab in first-line treatment for locoregionally advanced nasopharyngeal carcinoma: a propensity score matched analysis. J Cancer 2018; 9: 594-603.
[28] Wang F, Jiang C, Ye Z, Sun Q, Liu T, Xu M, Wu P, Shi K, Long B, Rihito A, Masoto S and Fu Z. Efficacy and safety of nimotuzumab with neoadjuvant chemotherapy followed by concurrent chemoradiotherapy for locoregionally advanced nasopharyngeal carcinoma. Oncotarget 2017; 8: 75544-75556.