ORIGINAL RESEARCH

Palliative chemotherapy with or without anti-EGFR therapy for de novo metastatic nasopharyngeal carcinoma: a propensity score-matching study

Xue-Song Sun[1–3],*
Yu-Jing Liang[1–3],*
Xiao-Yun Li[1–3],*
Sai-Lan Liu[1–3]
Qiu-Yan Chen[1–3]
Lin-Quan Tang[1–3]
Hai-Qiang Mai[1–3]

[1]Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Centre, Guangzhou, People's Republic of China; [2]Department of Nasopharyngeal Carcinoma, State Key Laboratory of Oncology in South China, Guangzhou, People's Republic of China; [3]Department of Nasopharyngeal Carcinoma, Collaborative Innovation Centre for Cancer Medicine, Guangzhou, People's Republic of China

*These authors contributed equally to this work

Objective: We aimed to investigate the efficacy and safety of cetuximab (CTX) or nimotuzumab (NTZ) on the addition of palliative chemotherapy (PCT) in patients with de novo metastatic nasopharyngeal carcinoma (NPC).

Materials and methods: From 2007 to 2016, 451 eligible patients with de novo metastatic NPC were enrolled in the study. With propensity score matching technique, we created a well-balanced cohort by matching patients who received CTX/NTZ plus PCT (62 patients) with those receiving PCT alone (248 patients) in a ratio of 1:4. The primary endpoint was overall survival (OS). All potential prognostic factors were involved in the multivariate analysis with the Cox regression hazards model. Kaplan–Meier curves were used to compare the survival status, and log-rank test to measure the significance.

Results: The median follow-up time was 27.7 months (range, 1–126 months). No significant difference in survival was observed between the CTX/NTZ plus PCT group and PCT group. (3-year OS: 63.0% vs 58.1%; *P*=0.485). The administration of CTX/NTZ was not found to be an independent prognostic factor in multivariate analysis. With regard to toxicity, the development of a G3-4 skin reaction and mucositis was more common in patients receiving CTX plus PCT. Interaction effects analysis did not show any significant interaction effects on OS between the treatment regimen and prognostic factors (*P*>0.05).

Conclusion: The efficacy of CTX/NTZ and PCT is comparable to single PCT treatment in terms of survival outcomes among de novo metastatic NPC patients. Moreover, the application of CTX exacerbated skin reactions and mucositis.

Keywords: targeted drug, chemotherapy, treatment, nasopharyngeal carcinoma and overall survival

Correspondence: Lin-Quan Tang; Hai-Qiang Mai
Department of Nasopharyngeal Carcinoma, Sun Yat-sen University Cancer Center, 651 Dongfeng Road East, Guangzhou 510060, People's Republic of China
Tel +86 208 734 3643
Fax +86 208 734 3392
Email maihq@mail.sysu.edu.cn;
tanglq@sysucc.org.cn

Introduction

Nasopharyngeal cancer (NPC) is a unique subtype in head and neck cancers both anatomically and biologically; it causes an estimated 51,000 deaths annually, which accounted for 0.6% of all cancer-related deaths worldwide in 2012.[1] Due to the hypersensitivity of NPC to radiotherapy, the combination of radiotherapy with chemotherapy has become the cornerstone treatment for locoregional advanced NPC patients, which has been validated by high-level evidence that a satisfactory 5-year survival rate of approximately 75% has been achieved.[2,3] However, advanced NPC patients are prone to develop distant metastasis,[4] and approximately 15% of NPC patients are detected with metastatic lesions at the time of initial diagnosis.[5] The overall survival (OS) of metastatic NPC patients is poor, and the

median OS reported following first-line chemotherapy is reportedly 29.1 months, which presents crucial challenges for the treatment of metastatic NPC.[6]

Epidermal growth factor receptor (EGFR), also known as ErbB1, has been considered as an important therapeutic target for NPC as increasing evidence indicated that EGFR signaling plays a vital role in NPC pathogenesis.[7] EGFR is reportedly overexpressed in 80–89% of NPC patients, which may be responsible for treatment resistance and poor prognosis.[4,8] Cetuximab (CTX), a chimeric (mouse/human) monoclonal antibody is the first EGFR inhibitor studied clinically in NPC, and has shown effectiveness in recurrent or metastatic NPC patients.[7,9] The humanized therapeutic monoclonal antibody nimotuzumab (NTZ) has also been applied in locoregional advanced NPC. Satisfactory efficacy and tolerable side effects in comparison with chemotherapy have been reported.[10–12] Nevertheless, data on initially metastatic NPC patients treated with PCT in combination with or without NTZ/CTX has been poorly documented. The influence of EGFR monoclonal antibody in this group remains largely unknown. Therefore, in the present study, we aimed to identify the effect of CTX or NTZ in de novo metastatic NPC patients, and provide further information for the treatment of metastatic NPC patients.

Materials and methods
Patient population

From 2007 to 2016, 451 de novo metastatic NPC patients were enrolled in our retrospective cohort analysis. The inclusion criteria were as follows: (1) pathologically confirmed NPC; (2) received cisplatin-based palliative chemotherapy (PCT) (3) initial Karnofsky performance score (KPS) >70; (4) normal organ functions; (5) no pregnancy, lactation, or second malignant disease. Using propensity scores adjusted for age, gender, T stage, N stage, metastatic sites, PCT cycles, and the use of locoregional radiotherapy (LRRT), a well-balanced cohort was created, wherein each patient receiving CTX/NTZ plus PCT was matched with 4 patients receiving PCT alone. The flow chart was shown in Figure 1. Our study was approved by the clinical research ethics committee of SYSUCC.

Diagnosis and treatment

Before diagnosis, patients underwent a series of evaluations, including physical examination, nasopharyngoscopy and pathology assessment, magnetic resonance imaging (MRI)/computed tomography (CT) with contrast for head and neck and metastatic lesions, chest radiography/CT with contrast, abdominal ultrasound/CT with contrast, and bone scan for whole-body assessment or positron emission tomography–computed tomography (PET/CT) as a substitute.

Platinum-based palliative chemotherapy with or without CTX/NTZ was administered in all patients in this study. The common chemotherapy regimens were as follows—TP: docetaxel (80 mg/m^2 d1) plus cisplatin (75 mg/m^2 d1), PF: cisplatin (20–25 mg/m^2 d1-3) plus 5-fluorouracil (800–1000 mg/m^2, 120 h), TPF: docetaxel (60 mg/m^2 d1) plus cisplatin (60 mg/m^2 d1) plus 5-fluorouracil (500–800 mg/m2, 120 h), and GP: gemcitabine (1000 mg/m^2 d1,8) combined with cisplatin (20–30 mg/m^2 d1-3). Chemotherapy was intravenously administered at 3-week intervals and the median cycle of PCT was five (range: 2–10 cycles). CTX was administered at an initial dose of 400 mg/m^2, followed by a weekly dose of 250 mg/m^2, whereas NTZ was intravenously administered at a median dose of 200 mg weekly. The EGFR-targeted drugs were applied combined with PCT. Forty-nine patients in CTX/NTZ+PCT group received LRRT after PCT and 21 patients received EGFR-targeted drugs during radiotherapy.

Follow-up and outcome

Assessments were performed in patients at 3-month intervals during the first 3 years, and at 6-month intervals thereafter until death. Physical examination, nasopharyngoscopy, MRI/CT with contrast of head and neck metastatic lesions, chest radiography/CT with contrast, and abdominal ultrasound/CT with contrast were routinely performed during follow up. PET/CT and other examinations would be considered when necessary. The primary endpoint in this study was OS, which was defined as the time from the date of diagnosis to the date of death from any cause.

Statistical analysis

In this study, continuous variables were converted into categorical variables based on the clinical application or median regular cut-off points. A multivariate logistic regression model was used to calculate the propensity score for each patient, based on the following covariates: gender, age, radiation therapy, tumor stage, lymph node stage, PCT cycles, and metastatic site. Moreover, a 1:4 matching protocol without replacement (greedy matching algorithm) was used, and the caliper width was equal to
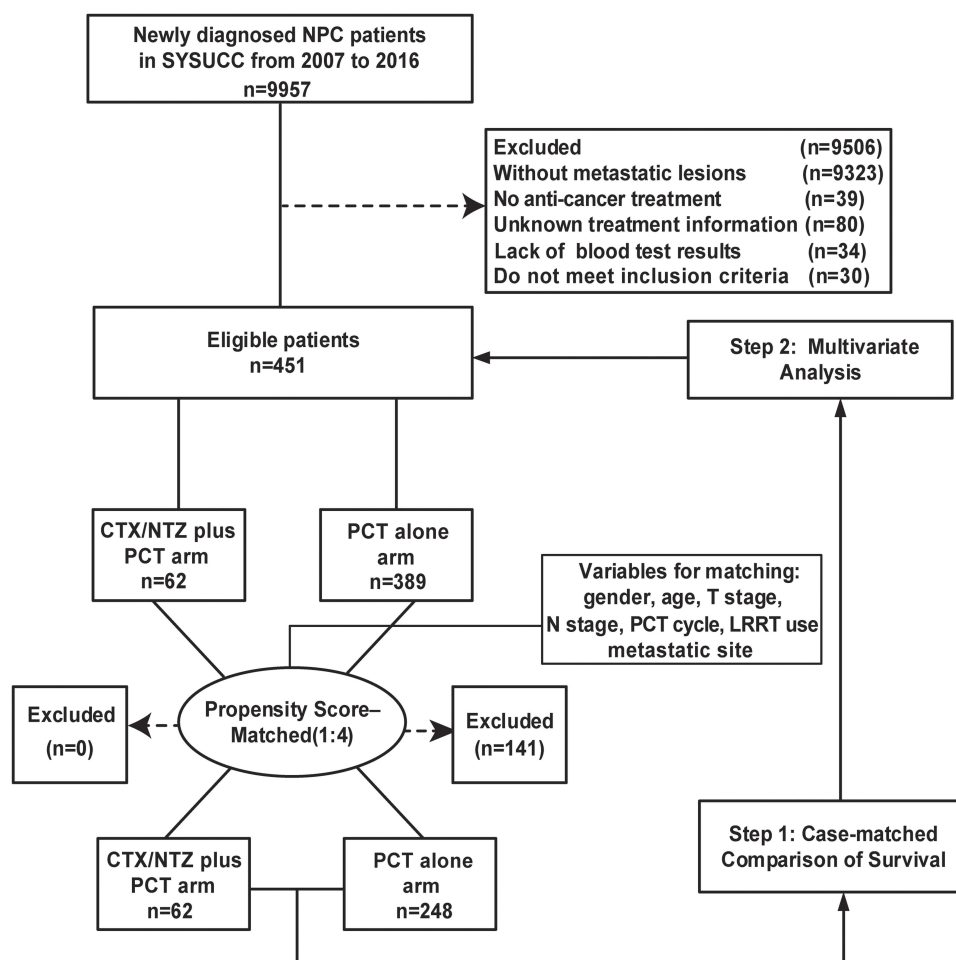
Figure 1 Flow chart of patient inclusion.

0.05 of the logit standard deviation of the propensity score. Kaplan–Meier survival curves were used to compare patient survival with the log-rank test. A Cox proportional hazard model was used to perform multivariate analyses to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the relationship between the characteristics and OS. The Enter method was used for multivariable Cox regression. Statistical analyses were performed using the Statistical Package for Social Sciences 24.0 (IBM Corporation, Armonk, NY, USA) and R (http://www.R-project.org). Statistical tests in this study were two-tailed and *P*<0.05 was considered to indicate statistical significance.

Result
Patient characteristics
From 2007 to 2016, 451 de novo metastatic NPC patients were enrolled in our retrospective study. In order to reduce

the potential confounding, we created a well-balanced cohort using propensity score matching (PSM) with a 1:4 ratio, including 62 patients in the CTX/NTZ plus PCT group and 248 patients in the PCT alone group. Among these patients, the male-to-female ratio was 5.1:1 and the average age of all patients was 46 years. In patients treated with an anti-EGFR drug, NTZ was more frequently used (37/62, 59.7%), in comparison with CTX (25/62, 40.3%). Other patient characteristics are shown in Table 1.

Survival analysis
Of the 451 patients, 224 (49.7%) died with a median follow-up of 27.7 months (range, 1–126 months). The 1-, 3-, and 5-year OS rates were 90.4%, 56.3% and 39.9%, respectively. We compared the survival status based on the treatment method in PSM cohort, and found that the 3-year OS was similar in patients who received NTZ/CTX, in comparison with patients who did not (63.0% vs 58.1%;

**Table 1** Clinical characteristic in entire cohort and PSM cohort

Characteristic	The entire cohort CTX/NTZ plus PCT P-value			Propensity score matching cohort CTX/NTZ plus PCT P-value		
	PCT alone	CTX/NTZ plus PCT	P-value	PCT alone	CTX/NTZ plus PCT	P-value
Total	N=389	N=62		N=248	N=62	
Gender						
Male	323 (83.0%)	52 (83.9%)	1.000	207 (83.5%)	52 (83.9%)	1.000
Female	66 (17.0%)	10 (16.1%)		41 (16.5%)	10 (16.1%)	
Age (years)						
≤46	190 (48.8%)	36 (58.1%)	0.218	131 (52.8%)	36 (58.1%)	0.480
>46	199 (51.3%)	26 (41.9%)		117 (47.2%)	26 (41.9%)	
T stage[#]						
T1	17 (4.4%)	1 (1.6%)	0.595	6 (2.4%)	1 (1.6%)	0.695
T2	52 (13.4%)	6 (9.7%)		33 (13.3%)	6 (9.7%)	
T3	191 (49.1%)	33 (53.2%)		112 (45.2%)	33 (53.2%)	
T4	129 (33.2%)	22 (35.5%)		97 (39.1%)	22 (35.5%)	
N stage[#]						
N0	14 (3.6%)	0 (0.0%)	0.332	6 (2.4%)	0 (0.0%)	0.654*
N1	72 (18.5%)	8 (12.9%)		27 (10.9%)	8 (12.9%)	
N2	155 (39.8%)	28 (45.2%)		100 (40.3%)	28 (45.2%)	
N3	148 (38.0%)	26 (41.9%)		115 (46.4%)	26 (41.9%)	
Metastatic sites						
Bone	178 (45.8%)	29 (46.8%)	0.536	128 (51.6%)	29 (46.8%)	0.666
Lung	51 (13.1%)	7 (11.3%)		29 (11.7%)	7 (11.3%)	
Liver	36 (9.3%)	9 (14.5%)		21 (8.5%)	9 (14.5%)	
Distant nodes	28 (7.2%)	6 (9.7%)		20 (8.1%)	6 (9.7%)	
Multiple sites	96 (24.7%)	11 (17.7%)		50 (20.2%)	11 (17.7%)	
LRRT use						
No	130 (33.4%)	13 (21.0%)	0.056	49 (19.8%)	13 (21.0%)	0.860
Yes	259 (66.6%)	49 (79.0%)		199 (80.2%)	49 (79.0%)	
PCT regimen						
TPF	101 (26.0%)	17 (27.4%)	0.095	69 (27.8%)	17 (27.4%)	0.105
TP	82 (21.1%)	20 (32.3%)		52 (21.0%)	20 (32.3%)	
PF	107 (27.5%)	8 (12.9%)		64 (25.8%)	8 (12.9%)	
GP	23 (5.9%)	5 (8.1%)		11 (4.4%)	5 (8.1%)	
Others	76 (19.5%)	12 (19.4%)		52 (21.0%)	12 (19.4%)	
PCT cycle						
≤4	151 (38.8%)	21 (33.9%)	0.485	96 (38.7%)	21 (33.6%)	0.559
>4	238 (61.2%)	41 (66.1%)		152 (61.3%)	41 (66.1%)	

Notes: [#]According to the 8th edition of the UICC/AJCC staging system. *The P-value was calculated with the Pearson χ2 test or Fisher's exact test.
Abbreviations: PSM, Propensity score matching; NTZ, nimotuzumab; CTX, cetuximab; LRRT, locoregional radiotherapy; PCT, palliative chemotherapy; TPF, cisplatin plus docetaxel plus 5-fluorouracil; TP, cisplatin plus docetaxel; PF, cisplatin plus 5-fluorouracil; GP, cisplatin plus gemcitabine.

95% CI: 49.3–76.7% vs 52.6–63.6%). There were no significant differences in the risk of death (HR, 0.86; 95% CI, 0.56–1.31; P=0.485). The Kaplan–Meier curves are shown in Figure 2. Furthermore, we investigated whether the different EGFR drugs influenced the survival of these patients. As shown in Figure S1, there was no significant survival difference between patients treated with CTX and NTZ (P=0.279).
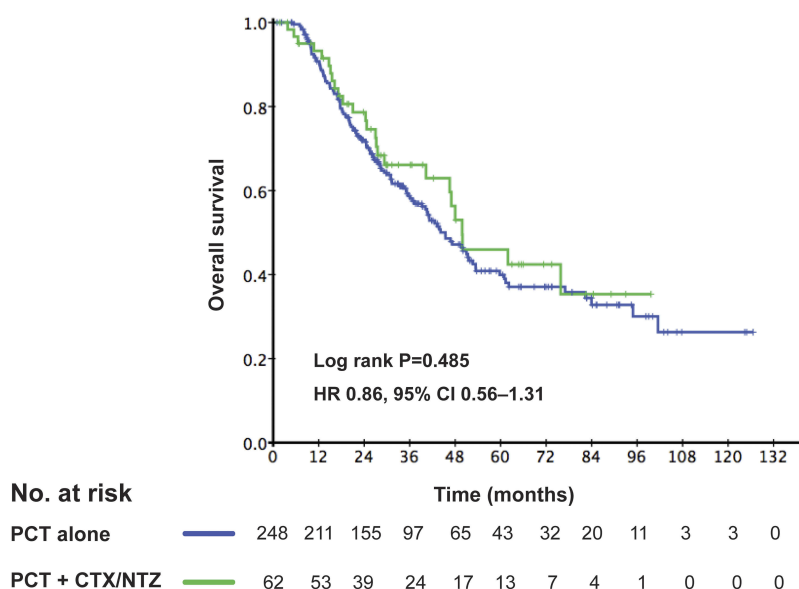
Figure 2 Kaplan–Meier OS curves in the well balanced cohort of patients receiving CTX/NTZ+PCT or PCT alone.

Toxicity

The effect of toxicity in each group in the PSM cohort was shown in Table 2. The rates of serious (G3–G4) hematological toxicities were similar between two groups. The incidence of G3 vomiting was in a low level and comparable between groups. However, a higher frequency of G3 skin reactions (29.0% vs 6.9%, $P<0.001$) and G3–4 mucositis (38.7% vs 10.9%, $P<0.001$) was noted in the CTX/NTZ plus PCT group, relative to the PCT alone group. No significant differences among the treatment groups were observed in terms of hepatotoxicity and nephrotoxicity. In subgroup analysis, patients receiving CTX were significantly more inclined to suffer from G3-4 neutropenia (48% vs 31.4%, $P=0.016$), G3 skin reactions (48.0% vs 16.2%, $P=0.016$) and G3–4 mucositis (64.0% vs 21.6%, $P=0.003$), as compared to those receiving NTZ, which manifested a less safer profile of CTX. Besides, the effect of toxicity in patients receiving different PCT regimens was also compared. As shown in Table S1, intergroup differences in acute toxicities showed no statistical significance.

Multivariate analysis

All 451 eligible patients were included in the multivariate analysis (Table 3). We found that the use of CTX/NTZ was not a significant independent prognostic factor for OS (CTX/NTZ plus PCT vs PCT alone: HR, 0.92; 95% CI, 0.61–1.40; $P=0.695$). Meanwhile, patients with an advanced N stage exhibited a higher risk of death (N2–3 vs N0–1:

HR, 1.66; 95% CI, 1.18–2.35; $P=0.004$). Moreover, patients with multiple metastatic sites were found to exhibit worse OS than patients with bone-only metastasis (HR, 2.73; 95% CI, 1.94–3.85, $P<0.001$). In addition, LRRT use was a protective factor for de novo metastatic patients (HR, 0.56; 95% CI, 0.40–0.77; $P<0.001$).

Interaction effects

Furthermore, we examined the interaction effects between the treatment regimen (CTX/NTZ plus PCT vs PCT) and other prognostic factors (N stage, LRRT, and metastatic sites) after adjusting for age, gender, T stage, N stage, metastatic sites, PCT cycle, LRRT use, and treatment regimen. As shown in Table 4, no significant interaction effects were observed between the treatment regimen (CTX/NTZ plus PCT vs PCT) and N stage (HR, 1.05; 95% CI, 0.29–3.75; $P=0.946$). Similarly, LRRT use and metastatic sites did not exhibit any interaction effect with the treatment regimen ($P>0.05$).

Discussion

To our knowledge, this is the first study exploring the effectiveness of CTX/NTZ on the basis of palliative chemotherapy in metastatic NPC patients in a large cohort of 451 patients. According to data from our matched cased-control cohort, CTX/NTZ combined with PCT yielded a similar treatment efficacy as compared with PCT alone. Moreover, the incidence rates of G3-4 mucositis and G3 skin reactiosn were higher in the CTX/NTZ plus PCT group.

Table 2 Acute toxicities in de novo NPC patients in different treatment groups

	PCT alone	CTX/NTZ plus PCT	P1 value	CTX plus PCT	NTZ plus PCT	P2 value
	N=248	**N=62**		**N=25**	**N=37**	
Leukocytopenia						
G0-1	87(35.1%)	21(33.9%)	0.819	7 (28.0%)	14(37.8%)	0.735‡
G2	94(37.9%)	23(37.1%)		9 (36.0%)	14(37.8%)	
G3	58(23.4%)	14(22.6%)		7(28.0%)	7 (18.9%)	
G4	9 (3.6%)	4 (6.5%)		2 (8.0%)	2 (5.4%)	
Neutropenia						
G0-1	97(39.1%)	19 (30.6%)	0.522	6 (24.0%)	13(35.1%)	0.016
G2	57(23.0%)	19(30.6%)		7(28.0%)	12 (32.4%)	
G3	55(22.2%)	13(21.0%)		3 (12.0%)	10 (27.0%)	
G4	39(15.7%)	11(17.7%)		9 (36.0%)	2 (5.4%)	
Anemia						
G0-1	158 (63.7%)	37 (59.7%)	0.336	13 (52.0%)	24 (64.9%)	0.203‡
G2	54 (21.8%)	16 (25.8%)		9(36.0%)	7 (18.9%)	
G3	21 (8.5%)	8 (12.9%)		2 (8.0%)	6 (16.2%)	
G4	15 (6.0%)	1 (1.6%)		1 (4.0%)	0 (0.0%)	
Thrombocytopenia						
G0-1	184 (74.2%)	54 (87.1%)	0.019 ‡	22 (88.0%)	32 (86.5%)	1.000‡
G2	37 (14.9%)	2 (3.2%)		1 (4.0%)	1 (2.7%)	
G3	18 (7.3%)	2 (3.2%)		1 (4.0%)	1 (2.7%)	
G4	9 (3.6%)	4 (6.5%)		1 (4.0%)	3 (8.1%)	
Vomiting						
G0-1	190 (76.6%)	42 (67.7%)	0.357	18 (72.0%)	24 (64.9%)	0.760‡
G2	47 (19.0%)	16 (25.8%)		6 (24.0%)	10(27.0%)	
G3	11 (4.4%)	4(6.5%)		1 (4.0%)	3 (8.1%)	
Skin reaction						
G0-1	179 (72.2%)	29 (46.8%)	<0.001	7(28.0%)	22 (59.5%)	0.016
G2	52 (21.0%)	15 (24.2%)		6 (24.0%)	9 (24.3%)	
G3	17 (6.9%)	18 (29.0%)		12 (48.0%)	6 (16.2%)	
Mucositis						
G0-1	98 (39.5%)	20 (32.3%)	<0.001	3(12.0%)	17 (45.9%)	0.003‡
G2	123 (49.6%)	18 (29.0%)		6(24.0%)	12(32.4%)	
G3	27 (10.9%)	19(30.6%)		12 (48.0%)	7(18.9%)	
G4	0 (0.0%)	5 (8.1%)		4 (16.0%)	1 (2.7%)	
Hepatotoxicity						
G0-1	220 (88.7%)	51 (82.3%)	0.369	20 (80.0%)	31 (83.8%)	0.391‡
G2	21 (8.5%)	9 (14.5%)		5 (20.0%)	4 (10.8%)	
G3	7 (2.8%)	2 (3.2%)		0 (0.0%)	2(5.4%)	
Nephrotoxicity						
G0-1	238 (96.0%)	60 (96.8%)	1.000	23 (92.0%)	37 (100.0%)	0.159‡
G2	9(3.6%)	2 (3.2%)		2(8.0%)	0 (0.0%)	
G3	1 (0.4%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	

Notes: The P1 value was calculated between the CTX/NTZ plus PCT arm and PCT alone arm; The P2 value was calculated between the CTX plus PCT arm and NTZ plus PCT arm. The *P*-value was calculated with the Pearson $\chi 2$ test or Fisher's exact test (‡).
Abbreviations: NTZ, nimotuzumab; CTX, cetuximab; PCT, palliative chemotherapy.

Table 3 Multivariate analyses of variables correlated with the treatment regimen status and other prognostic factors in eligible 451 patients

Characteristic	HR	95% CI	P-value
Gender			
Male	Reference		
Female	0.81	0.56–1.17	0.270
Age (years)			
≤46	Reference		
>46	1.14	0.88–1.49	0.325
T stage			
T1-2	Reference		
T3-4	0.96	0.68–1.37	0.833
N stage			
N0-1	Reference		
N2-3	1.66	1.18–2.35	0.004
Metastatic site			
Bone	Reference		
Lung vs Bone	0.75	0.47–1.20	0.226
Liver vs Bone	1.27	0.81–1.99	0.299
Distant nodes vs Bone	0.68	0.34–1.35	0.270
Multiple vs Bone	2.73	1.94–3.85	<0.001
PCT cycle			
≤4	Reference		
>4	0.86	0.62–1.17	0.335
LRRT			
No	Reference		
Yes	0.56	0.40–0.77	<0.001
Treatment regimen			
PCT alone	Reference		
CTX/NTZ plus PCT	0.92	0.61–1.40	0.695

Notes: The data are obtained from all 451 patients included in the study. A Cox proportional hazard model was used to perform multivariate analyses. All variables were transformed into categorical variables.
Abbreviations: HR, hazard ratio; CI, confidence interval; NTZ, nimotuzumab; CTX, cetuximab; LRRT, locoregional radiotherapy; PCT, palliative chemotherapy.

Approximately 15% of NPC patients were diagnosed with de novo metastatic cancer, which usually demonstrated a more aggressive nature, before the initiation of any treatment.[5] The platinum-based PCT was established as the standard treatment for metastatic population with an estimated response rates of >50%.[6,13–15] However, the duration of response and survival time remained limited, while second-line chemotherapy was only effective in patients with good response.[16] Novel anti-cancer drugs were urgently needed to alleviate the plight. EGFR is highly expressed in human epithelial carcinomas and its expression is reportedly correlated with a more aggressive phenotype

accompanied by resistance to treatment and poor prognosis.[8] The use of monoclonal antibodies of EGFR could help block the aberrant signaling in malignant cells. In fact, several studies have reported the presence of EGFR overexpression in NPC, and offered further evidence for the use of anti-EGFR drugs in NPC treatment.[17–22]

The treatment effect of anti-EGFR drugs has been reported in locally advanced NPC patients. Based on the results of a prospective phase II study conducted by Ma et al, patients who received CCRT and CTX achieved a 2-year progression free survival (PFS) rate of 86.5%.[23] Similarly, Liu et al evaluated the efficacy and safety of the combination of CCRT and NTZ. In the cohort of 42 patients, NTZ was well tolerated in locoregionally advanced NPC patients with a 2-year distant metastasis free survival (DMFS) and OS of 93.1% and 96.6% respectively.[24] Moreover, You et al conducted a retrospective study based on a matched case-control study with a larger cohort,[12] and the researchers found that CTX/NTZ plus CCRT could improve the OS, PFS, and DMFS in comparison with CCRT alone, and the toxicity was comparable in these 2 groups. Therefore, we believe that the addition of CTX/NTZ to PCT could further improve the OS in metastatic NPC patients.

Thus far, only a few studies have explored the role of anti-EGFR drugs in metastatic NPC. Xu et al reported a single-arm study assessing the efficacy and toxicity of CTZ in the combined treatment of recurrent and/or metastatic NPC patients.[25] The researchers found that CTX may be effective for the 2-year OS rate reached 53.3% in this cohort. Moreover, the toxicities resulting from the addition of CTX to the chemoradiotherapy were tolerable. Chan et al performed a multicenter, phase II study of CTX in combination with carboplatin in patients with recurrent or metastatic NPC. The median OS time was 233 days in all patients, and 6 of these patients (10%) experienced serious treatment-related adverse events.[9] To our knowledge, no study has compared the survival of metastatic patients with or without anti-EGFR drug treatment.

In the present study, all patients were diagnosed with metastatic NPC prior to receiving any treatment. Using a relatively large cohort and the PSM method, we found that patients treated with CTX/NTZ plus PCT achieved a similar 3-year OS rate as compared to patients with PCT alone (63.0% vs 58.1%; P=0.485). With regard to toxicity, we found that severe mucositis and dermatitis were more common in the CTX subgroup, which was consistent with previous studies.[10,12,23] One possible reason for this

Table 4 Interaction between the treatment regimen status and other significant prognostic factors

Characteristic	Adjusted HR	95% CI	*P*-value
Model 1			
EGFR-targeted regimen			
PCT alone	Reference		
CTX/NTZ plus PCT	0.89	0.27–2.92	0.840
N stage			
N1-0	Reference		
N2-3	1.66	1.16–2.37	0.006
Interaction effect			
CTX/NTZ plus PCT*N2-3	1.05	0.29–3.75	0.946
Model 2			
EGFR-targeted regimen			
PCT alone	Reference		
CTX/NTZ plus PCT	0.89	0.67–3.28	0.330
LRRT use			
No	Reference		
Yes	0.59	0.42–0.82	0.002
Interaction effect			
CTX/NTZ plus PCT*LRRT	0.54	0.21–1.36	0.190
Model 3			
EGFR-targeted regimen			
PCT alone	Reference		
CTX/NTZ plus PCT	1.20	0.69–2.07	0.523
Metastatic site			
Bone	Reference		
Lung vs Bone	0.82	0.50–1.134	0.424
Liver vs Bone	1.48	0.92–2.37	0.103
Distant nodes vs Bone	0.73	0.35–1.52	0.395
Multiple vs Bone	2.80	1.95–4.01	<0.001
Interaction effect			
CTX/NTZ plus PCT*Lung	0.34	0.04–2.73	0.311
CTX/NTZ plus PCT*Liver	0.29	0.06–1.35	0.115
CTX/NTZ plus PCT*Distant nodal	0.62	0.07–5.31	0.661
CTX/NTZ plus PCT*Multiple	0.91	0.33–2.51	0.861

Notes: The data are obtained from all 451 patients included in the study. The multivariable Cox regression model was adjusted for age, gender, T stage, N stage, metastatic site, PCT cycle, LRRT use, and treatment regimen.
Abbreviations: HR, hazard ratio; CI, confidence interval; NTZ, nimotuzumab; CTX, cetuximab; LRRT, locoregional radiotherapy; PCT, palliative chemotherapy.

finding might be that CTX is a chimeric mouse–human IgG1 monoclonal antibody, which displays higher binding affinity to cells expressing high EGFR levels.[26] Given these negative results, we believe that the use of CTX/NTZ in de novo metastatic NPC patients should be carefully considered in the clinical setting. Moreover, novel treatment methods such as the introduction of immune checkpoint inhibitors should be explored. Therefore, we have initiated a worldwide, multicenter, phase III study of cisplatin and gemcitabine with or without PD-1 antibody (toripalimab) in patients with recurrent or metastatic NPC, and the results are awaited (NCT 03581786).

The present study has certain limitations. First, this is a retrospective study, and although some selected biases were

eliminated via propensity scoring, the presence of other confounding factors persisted. Moreover, all the patients involved in this study were enrolled from a single treatment center in a high-prevalence area, and the histological subtype of all patients was World Health Organization type III. Thus, a multicenter prospective study may be needed to better evaluate the role of CTX/NTZ in metastatic NPC patients.

Conclusion

This study demonstrated that de novo metastatic NPC patients may not benefit from the addition of anti-EGFR drugs, whereas the addition of CTX to CCRT might exacerbate the acute mucositis and skin reactions.

Ethics approval and consent to participate

This retrospective study was approved by the Clinical Research Committee of Sun Yat Sen University Cancer Center. Patients were required to provide written informed consent before enrolling in the study.

Author contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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