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Anti-epidermal growth factor receptor therapy concurrently with induction chemotherapy in locoregionally advanced nasopharyngeal carcinoma

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Little is known about the efficacy and toxicity of anti-epidermal growth factor receptor therapy concurrently with induction chemotherapy (IC) in locoregionally advanced nasopharyngeal carcinoma (LA-NPC). The present study aimed to address this question. We identified 2848 patients with newly diagnosed LA-NPC receiving IC between January 2012 and May 2015. The propensity score matching (PSM) method was used to balance various factors and to match patients. Survival outcomes and toxicities between different groups were compared. In total, 596 patients were selected at a 1:3 ratio, with 149 in the IC + CTX/NTZ group and 447 in the IC alone group. The 3-year disease-free survival, overall survival, distant metastasis-free survival and locoregional relapse-free survival rates for IC + CTX/NTZ vs IC alone were 84.3% vs 75.2% ($P = .059$), 94.0% vs 87.9% ($P = .053$), 88.0% vs 84.9% ($P = .412$) and 93.3% vs 88.2% ($P = .242$). Multivariate analysis established a treatment group (IC vs IC + CTX/NTZ) as a prognostic predictor for DFS (hazard ratio [HR], 1.497; 95% confidence interval [CI], 1.016-2.206; $P = .041$) and OS (HR, 1.984; 95%, CI, 1.023-3.848; $P = .043$). Grade 3-4 skin reaction (15.4% vs 0.4%, $P < .001$) and mucositis (10.1% vs 2.7%, $P < .001$) were more common in the IC + CTX/NTZ group than that in the IC alone group. Our findings suggested that CTX/NTZ in combination with IC may be a more effective and promising strategy for patients with LA-NPC treated with intensity-modulated radiotherapy.

KEYWORDS
cetuximab, induction chemotherapy, intensity-modulated radiotherapy, nasopharyngeal carcinoma, nimotuzumab

1 | INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a special type of head and neck malignancy because of its unbalanced geographic distribution and

treatment modality. There were 86 700 new cases reported worldwide in 2012, with the highest incidence in South China.[1] Unlike other head and neck cancers, radiotherapy (RT) is the primary and only cure for non-disseminated disease as a result of the anatomic constrain and sensitivity to radiation. Control of early stage disease with RT alone or chemoradiation is usually excellent; however,

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management of locoregionally advanced NPC (LA-NPC) remains unsatisfactory, with a 5-year overall survival (OS) of 67%-77%.[2] Unfortunately, more than 70% of newly cases were locoregionally advanced disease at initial diagnosis.[3] Currently, concurrent chemoradiation (CCRT) is the main standard care for LA-NPC. Although local and regional control has improved greatly, the rate of distant metastasis after treatment remains high and is the main source of treatment failure.[4] Therefore, identification of novel and effective therapeutic strategies is urgent and crucial for clinicians.

Epidermal growth factor receptor (EGFR), a transmembrane protein highly expressed in most human epithelial malignancies,[5] is a promising therapeutic target in oncology for its correlation with aggressive phenotype, treatment resistance and poor prognosis.[6,7] EGFR is also highly expressed in NPC[8] and numerous studies have evaluated the efficacy of anti-EGFR targeted therapy.[9-15] Cetuximab (CTX) or nimotuzumab (NTZ) (anti-EGFR monoclonal antibodies) concurrent with RT could achieve comparable outcomes compared with standard cisplatin-RT.[12,14] When combined with CCRT, different results were produced. You et al[13] and Xia et al[11] revealed that CTX/NTZ additional to CCRT was more effective than CCRT alone, while Li et al[10] did not identify any difference. Regardless of the controversial efficacy, CTX/NTZ significantly increased the incidence of acute mucositis and acneiform rash during RT,[10,12] resulting in poor quality of life or even disruption of RT. It seems that anti-EGFR therapy concurrent with RT may not be the best choice.

Induction chemotherapy (IC), given before RT, has been proven as a promising treatment in LA-NPC for its satisfactory compliance and efficacy in reducing distant metastasis.[16-20] NTZ in combination with IC may further reduce distant metastasis and improve survival outcomes. However, no relative study to date has been carried out. Given this concern, we initiated this retrospective study to evaluate the efficacy and toxicity of CTX/NTZ in combination with IC for LA-NPC.

2 | MATERIALS AND METHODS

2.1 | Study patient

We identified 14 684 patients with newly diagnosed NPC on the big-data, intelligence database platform (YiduCloud Technology, Beijing, China) at Sun Yat-sen University Cancer Center between January 2012 and May 2015. This intelligence platform has been described in detail previously.[21] Inclusion criteria for this study were as follows: (i) stage III-IVB disease; (ii) age $\geq$ 18 years; (iii) karnofsky performance score (KPS) $\geq$ 70; (iv) without prior malignancies; (v) receiving IC followed by CCRT or RT alone; (vi) concurrent chemotherapy, if any, should be single-agent cisplatin; and (vii) receiving intensity-modulated radiotherapy (IMRT).

2.2 | Pre-treatment staging workup

Conventional staging workup in our center included physical examination of head and neck, direct nasopharyngoscopy, chest radiography or computed tomography (CT), MRI of head and neck, abdominal sonography, whole-body bone scan and blood profiling. PET-CT would also be recommended for patients with advanced N (N2-3) category. Magnetic resonance (MR) or CT scans of patients were reviewed separately by 2 radiologists employed at our center with more than 10-years' experience, and any discrepancy was resolved by consensus. Tumor stage was determined according to the 8th edition of the International Union against Cancer/American Joint Committee on Cancer (UICC/AJCC) manual.

2.3 | Treatment

All patients received radical IMRT at our center using the simultaneous integrated boost (SIB) technique as previously described.[18,22] Briefly, the prescribed radiation doses were: 66-70 Gy at 2.12-2.23 Gy/fraction to the planning target volume (PTV) of nasopharyngeal gross tumor volume (GTV), 64-70 Gy to the PTV of GTV of metastatic lymph nodes, 60-63 Gy to the PTV of high-risk clinical target volume, and 50-56 Gy to the PTV of low-risk clinical target volume.

Induction chemotherapy mainly consisted of cisplatin-based regimens including docetaxel with cisplatin (TP), fluorouracil with cisplatin (PF), or docetaxel plus cisplatin with fluorouracil (TPF) every 3 weeks for 2-4 cycles. Concurrent chemotherapy was tri-weekly cisplatin or weekly cisplatin.

Cetuximab was delivered concurrently with IC at a dose of 400 mg/m^2 every 3 weeks, which was diluted in 250 mL saline and intravenously infused over 1 hour. Intravenous NTZ was administered at a dose of 200 mg during IC every 3 weeks. Detailed treatment information is presented in Data S1.

2.4 | Clinical endpoints and statistical analysis

Study endpoints included disease-free survival (DFS, defined as the time from diagnosis to disease progression or death from any cause), OS (time from diagnosis to death from any cause), distant metastasis-free survival (DMFS, time from diagnosis to first distant metastasis) and locoregional relapse-free survival (LRRFS, time from diagnosis to local or regional recurrence or both). Tumor response to IC was evaluated based on Response Evaluation Criteria in Solid Tumors.[23] Acute toxicities during IC were graded according to the Common Terminology Criteria for Adverse Events (version 3.0).

The chi-squared-test was adopted to compare categorical variables and the Mann-Whitney test for continuous variables. Propensity score matching (PSM) was computed by logistic regression for each patient at a 1:3 ratio to balance various factors, including gender, age, lactate dehydrogenase (LDH), IC regimen and cycle, tumor stage and cumulative cisplatin dose (CCD) during RT.[24] The caliper was set at 0.01 to achieve a satisfactory match. Survival outcomes were calculated using the Kaplan-Meier method and compared by log-rank test. The multivariate cox proportional hazards model was

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used to estimate hazard ratios (HR), 95% confidence intervals (CI) and independent prognostic factors.

3 | RESULTS

3.1 | Patient baseline characteristics

A flow chart of patient inclusion is presented in Figure 1. In total, 2848 patients were eligible for our study (Table S1). An eventual 596 patients were selected by PSM, with 149 in the IC + CTX/NTZ group and 447 in the IC alone group. Baseline characteristics are summarized in Table 1. The median age for the whole cohort is 43 years, and the male-to-female ratio is 3.8:1. Host and tumor-related factors were well balanced between the IC plus CTX/NTZ and IC alone groups. Moreover, patients in these 2 groups had similar pre-treatment imaging stage workups (Table S2) and chemotherapy intensity (Table S3).

Among the 149 patients receiving anti-EGFR therapy, 56 (37.6%) received CTX and the remaining 93 (62.4%) patients received NTZ. Detailed information on dose and cycle of CTX/NTZ

is shown in Table S4. More patients in the NTZ arm received 2 cycles than those in the CTX arm (P = .001). No dose reduction occurred in the 2 arms.

3.2 | Short-term efficacy after induction chemotherapy

Twenty-five patients with N0 category were not available for regional response evaluation, with 7 (4.7%) in the IC + CTX/NTZ group and 18 (4.0%) in the IC group. After the completion of IC, 17 (11.4%), 121 (81.2%) and 11 (7.4%) in the IC + CXT/NTZ group, and 35 (7.8%), 364 (81.4%) and 48 (10.7%) in the IC alone group achieved complete response (CR), partial response (PR) and stable disease (SD), respectively (P = .233). No patient had progressive disease (PD) in either group. Table S5 provides information on tumor response.

3.3 | Long-term outcome analysis

Up to the last visit (30 September 2017), the median follow-up duration was 40.5 months (range 1.27-64.8). Overall, 26 patients (17.4%) in the IC + CXT/NTZ group and 110 patients (24.6%) in IC alone group experienced treatment failure (P = .071). No treatment-related death occurred. Three-year DFS, OS, DMFS and LRRFS rates for the whole cohort were 77.3%, 89.4%, 85.7% and 89.5%, respectively.

The 3-year DFS, OS, DMFS and LRRFS rates for the IC + CTX/NTZ group vs the IC alone group were 84.3% vs 75.2% (P = .059), 94.0% vs 87.9% (P = .053), 88.0% vs 84.9% (P = .412) and 93.3% vs 88.2% (P = .242, Figure 2). After adjusting for various prognostic factors, the treatment group (IC vs IC + CTX/NTZ) was a significantly prognostic predictor for DFS (HR, 1.497; 95% CI, 1.016-2.206; P = .041) and OS (HR, 1.984; 95% CI, 1.023-3.848; P = .043) but not for DMFS (HR, 1.198; 95% CI, 0.716-2.005; P = .491) and LRRFS (HR, 1.454; 95% CI, 0.773-2.735; P = .246; Table 2).

3.4 | Subgroup analysis

We conducted further exploratory analysis according to tumor stage as the multivariate analysis indicated it was an independent prognostic factor. In patients with stage III disease, 284 patients were selected (Table S6). Univariate analysis found that the IC + CTX/NTZ group achieved better 3-year DFS and OS but the difference was not significant (Figure S1). When entered into the multivariate analysis, no significant survival difference between IC + CTX/NTZ and IC alone groups were observed (Table S7). With regard to the 312 patients selected by PSM (Table S8), similar results were produced for univariate (Figure S2) and multivariate analyses (Table S9).

3.5 | Grade 3-4 toxicities

The acute toxicity profile during IC and radiotherapy was evaluated between the 2 groups and is presented in Tables 3 and S10. Generally, patients in the IC + CTX/NTZ group suffered more grade 3-4
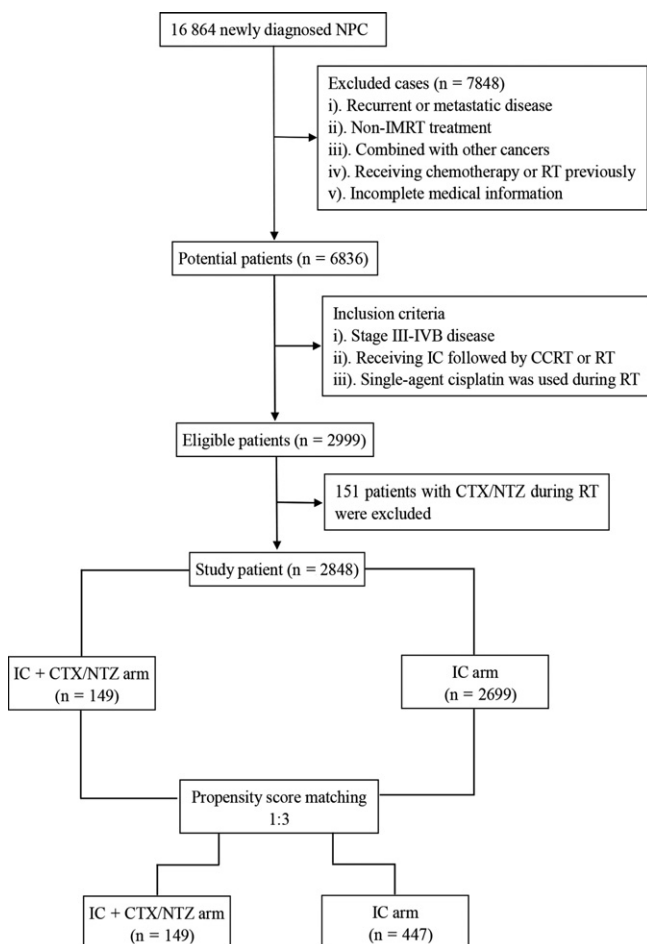
FIGURE 1 Flow chart of patient inclusion. CCRT, concurrent chemoradiotherapy; CTX, cetuximab; IC, induction chemotherapy; IMRT, intensity-modulated radiotherapy; NPC, nasopharyngeal carcinoma; NTZ, nimotuzumab; RT, radiotherapy

TABLE 1 Baseline characteristics of the selected 596 patients with stage III-IVB nasopharyngeal carcinoma receiving IC

Characteristics	IC + CXT/NTZ (N = 149) Number (%)	IC (N = 447) Number (%)	P-value[a]
Gender			
Male	116 (77.9)	355 (79.4)	.684
Female	33 (22.1)	92 (20.6)	
Age (years)			
Median (IQR)	42 (36-51)	44 (36-51)	.422
Smoking			
Yes	57 (38.3)	175 (39.1	.846
No	92 (61.7)	272 (60.9)	
Drinking			
Yes	30 (20.1)	89 (19.9)	.845
No	119 (79.9)	357 (80.1)	
Family history of cancer			
Yes	47 (31.5)	111 (24.8)	.205
No	102 (68.5)	334 (75.2)	
LDH (U/L)			
Median (IQR)	175 (154-216)	185 (160-215)	.155
T category[b]			
T1	6 (4.0)	12 (2.7)	.163
T2	7 (4.7)	47 (10.5)	
T3	81 (54.4)	228 (51.0)	
T4	55 (36.9)	160 (35.8)	
N category[b]			
N0	7 (4.7)	18 (4.0)	.966
N1	49 (32.9)	141 (31.6)	
N2	61 (40.9)	187 (41.8)	
N3	32 (21.5)	101 (22.6)	
Overall stage[b]			
III	71 (47.7)	207 (46.3)	.776
IVA-B	78 (52.3)	240 (53.7)	
IC regimen			
TPF	50 (33.6)	149 (33.3)	.998
PF	45 (30.2)	136 (30.4)	
TP	54 (36.2)	162 (36.3)	
IC cycle			
Two	100 (67.1)	290 (64.9)	.811
Three	43 (28.9)	134 (30.0)	
Four	6 (4.0)	23 (5.1)	
Concurrent chemotherapy			
Yes	137 (91.9)	400 (89.5)	.384
No	12 (8.1)	47 (10.5)	

(Continues)

TABLE 1 (Continued)

Characteristics	IC + CXT/NTZ (N = 149) Number (%)	IC (N = 447) Number (%)	P-value[a]
CCD (mg/m^2)			
Median (range)	160 (0-300)	160 (0-300)	.118
≥200	41 (27.5)	90 (20.1)	
<200	108 (72.5)	357 (79.9)	

CCD, cumulative cisplatin dose during radiotherapy; CXT, cetuximab; IC, induction chemotherapy; IQR, interquartile; LDH, lactate dehydrogenase; NZT, nimotuzumab.

[a]P-values were calculated using the chi-squared-test for categorical variables and the Mann-Whitney test for continuous variables.
[b]According to the 8th edition of the International Union against Cancer/American Joint Committee on Cancer (UICC/AJCC) system.

toxic events compared with those in the IC alone group (52.3% vs 42.7%, P = .041) during IC, and a significant difference was mainly observed in anti-EGFR therapy-related skin reaction (15.4% vs 0.4%, P < .001) and mucositis (10.1% vs 2.7%, P < .001). Hematological and gastrointestinal adverse events were similar between the 2 groups (all rates, P > .005). No significant difference with regard to toxicities during radiotherapy was observed between these 2 groups.

4 | DISCUSSION

Advanced disease has always been a difficult issue, not only in relation to NPC management but also in many other cancers because prognosis for this subgroup is poor. Therefore, identification and establishment of a novel and effective treatment is urgent and necessary. As far as we know, our study is the first to evaluate the efficacy and safety of anti-EGFR therapy (CTX or NTZ) in combination with induction chemotherapy in LA-NPC treated by IMRT. We found that additional CTX/NTZ to IC could prolong DFS and OS, but not DMFS and LRRFS. Anti-EGFR therapy-related toxicities of skin and mucositis were also more common in the IC + CTX/NTZ group.

With the wide application of IMRT in NPC, local and regional control has improved greatly and distant metastasis has become the main failure pattern.[4,25] Although CCRT is effective, it may be not powerful enough to reduce distant metastasis for advanced disease.[26] You et al[13] and Li et al[10] enhanced the treatment intensity during concurrent phase by adding CTX/NTZ to standard concomitant cisplatin. However, the efficacy may be unsatisfactory. At the same time, adverse events significantly increased. Possibly, concurrent administration of anti-EGFR therapy with cisplatin is a feasible strategy, but not the best. Additional cycles of chemotherapy like IC or adjuvant chemotherapy (AC) to CCRT may be a better choice. Actually, IC followed by CCRT is a preferable treatment modality for its better compliance and excellent efficacy[16,17,19] compared with CCRT with AC. In our current study, we provide a new insight in improving survival outcomes by enhancing the treatment during induction phase. By adding CTX/NTZ to IC, DFS and OS were significantly improved, indicating this is a promising treatment modality.

Epidermal growth factor receptor on tumor cells has been established as a factor predicting treatment resistance and poor
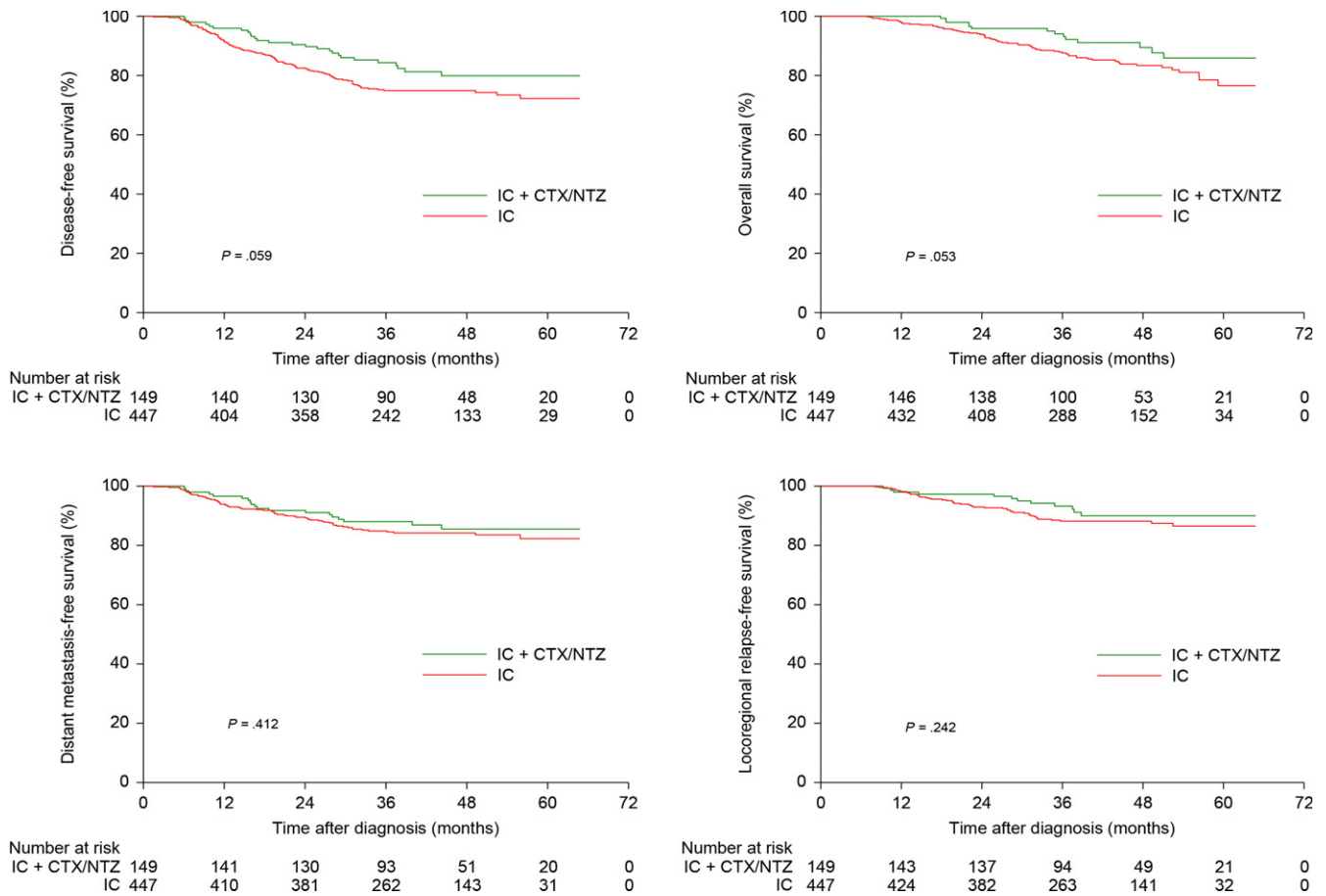
FIGURE 2 Kaplan-Meier survival curves of disease-free survival, overall survival, distant metastasis-free survival and locoregional relapse-free survival for the 596 patients with stage III-IVB nasopharyngeal carcinoma

prognosis,[6,7] making anti-EGFR a potential and promising treatment. Antitumor efficacy of CTX in combination with conventional chemotherapy has been proven in various EGFR-expressing malignancies like colorectal cancer, head and neck cancers and recurrent NPC.[27-29] In recurrent or metastatic head and neck squamous cell carcinoma (HNSCC), CTX combined with fluorouracil-cisplatin chemotherapy achieved significantly better DFS and OS compared with fluorouracil-cisplatin alone when given as the first-line therapy.[30] It seems that CTX adds additional anti-tumor efficacy to previously administered chemotherapy and thereby improved efficacy.[28] Taken this, it's reasonable to speculate that CTX/NTZ adds additional efficacy to induction chemotherapy in NPC. Therefore, CTX/NTZ in combination with IC could achieve better DFS and OS than IC alone in our study.

With regard to the primary analysis, DFS and OS were significantly improved in IC + CTX/NTZ group while DMFS and LRRFS was not. The significantly improved OS and DFS may originate from combined enhancement of DMFS and LRRFS although DMFS alone or LRRFS alone was not significantly improved. When subgroup analysis was conducted according to tumor stage (III or IV), survival outcomes were not significantly difference between IC + CTX/NTZ and IC alone groups in both subgroups. However, survival curves of DFS and OS in the IC + CTX/NTZ groups were always above the

curves in the IC alone group, indicating that IC + CTX/NTZ may still be better than IC alone although the difference was not significant. A main reason responsible for this is the small sample size which was not statistically powerful to detect the difference. Therefore, future study with larger sample is needed to validate these results.

Overall, grade 3-4 toxic events were more common in the IC + CTX/NTZ group than in the IC alone group, and significant differences mainly occurred in anti-EGFR therapy-related toxicities like skin reactions and mucositis. However, the incidence of severe skin and mucositis in our study was significantly less compared with the results in previous studies.[10,12-14] Undoubtedly, CTX/NTZ aggravated radiation-induced skin and oral mucositis. Another reason may be that the total dose used in the induction phase is less than that used in concurrent phase. Notably, personal compliance to CTX and NTZ may produce different survival outcomes or different compliance to concurrent chemotherapy. From these considerations, the appropriate dosage and administration way should be further addressed.

Compared with previous studies focusing on the concurrent phase, our study had 2 advantages. First, patients experienced significantly less anti-EGFR therapy-related severe toxicities during radiotherapy, which could result in better tolerance of chemoradiation. Second, cycles of CTX/NTZ used during the induction phase are

TABLE 2 Multivariate regression analysis for prognostic factors

Variable	HR	95% CI	P-value[a]
Disease-free survival			
IC regimen (PF vs TPF)	1.728	1.118-2.669	.014
IC regimen (TP vs TPF)	1.583	1.022-2.451	.04
N category (N2-3 vs N0-1)	2.139	1.403-3.260	<.001
Overall stage (IV vs III)	2.040	1.415-2.941	<.001
Treatment group (IC vs IC + CTX/NTZ)	1.497	1.016-2.206	.041
Overall survival			
Gender (female vs male)	0.504	0.260-0.977	.043
LDH (>245 vs ≤245 U/L)	1.829	1.059-3.159	.03
N category (N2-3 vs N0-1)	3.073	1.695-5.570	<.001
Overall stage (IV vs III)	2.113	1.318-3.387	.002
Treatment group (IC vs IC + CTX/NTZ)	1.984	1.023-3.848	.043
Distant metastasis-free survival			
N category (N2-3 vs N0-1)	2.939	1.655-5.218	<.001
Overall stage (IV vs III)	2.071	1.306-3.284	.002
Treatment group (IC vs IC + CTX/NTZ)	1.198	0.716-2.005	.491
Locoregional relapse-free survival			
N category (N2-3 vs N0-1)	1.977	1.086-3.597	.026
Overall stage (IV vs III)	1.867	1.092-3.194	.023
Treatment group (IC vs IC + CTX/NTZ)	1.454	0.773-2.735	.246

CI, confidence interval; CTX, cetuximab; HR, hazard ratio; IC, induction chemotherapy; LDH, lactate dehydrogenase; NTZ, nimotuzumab; PF, cisplatin with fluorouracil; TP, docetaxel with cisplatin; TPF, docetaxel plus cisplatin with fluorouracil.

[a]Multivariate P-values were calculated using a Cox proportional hazard regression model with backward elimination for the following prognostic factors: gender (female vs male), age (>43 vs ≤43 y), smoking (yes vs no), drinking (yes vs no), family history of cancer (yes vs no), LDH (>245 vs ≤245 U/L), IC regimen (PF vs TPF, TP vs TPF), cumulative cisplatin dose (≥200 vs <200 mg/m^2), T category (T3-4 vs T1-2), N category (N2-3 vs N0-1), overall stage (IV vs III) and treatment group (IC vs IC + CTX/NTZ).

TABLE 3 Acute toxicity profile during induction chemotherapy

Toxicity	IC + CTX/NTZ (N = 149, %)	IC (N = 447, %)	P-value[a]
Any			
G0-2	71 (47.7)	256 (57.3)	.041
G3-4	78 (52.3)	191 (42.7)	
Hematological			
Leucopenia			
G0-2	113 (75.8)	365 (81.7)	.123
G3-4	36 (24.2)	82 (18.3)	
Neutropenia			
G0-2	88 (59.0)	289 (64.7)	.220
G3-4	61 (41.0)	158 (35.3)	
Anemia			
G0-2	147 (98.7)	439 (98.2)	.706
G3-4	2 (1.3)	8 (1.8)	
Thrombocytopenia			
G0-2	144 (96.6)	440 (98.4)	.178
G3-4	5 (3.4)	7 (1.6)	
Non-hematological			
Liver function			
G0-2	146 (98.0)	439 (98.2)	.862
G3-4	3 (2.0)	8 (1.8)	
Renal function			
G0-2	149 (100.0)	447 (100.0)	1
G3-4	0 (0)	0 (0)	
Skin reaction			
G0-2	126 (84.6)	445 (99.6)	<.001
G3-4	23 (15.4)	2 (0.4)	
Mucositis			
G0-2	134 (89.9)	435 (97.3)	<.001
G3-4	15 (10.1)	12 (2.7)	
Nausea			
G0-2	146 (98.0)	439 (98.2)	.861
G3-4	3 (2.0)	8 (1.8)	
Vomiting			
G0-2	141 (94.6)	422 (94.4)	.918
G3-4	8 (5.4)	25 (5.6)	
Diarrhea			
G0-2	146 (98.0)	440 (98.4)	.718
G3-4	3 (2.0)	7 (1.6)	

CTX, cetuximab; IC, induction chemotherapy; NTZ, nimotuzumab.
[a]P-values were calculated by chi-squared-test or Fisher's exact test.

usually less than that in the concurrent phase. Hence, the cost of anti-EGFR therapy is also less.

However, limitations of this study should also be acknowledged. Our study is retrospective and the sample size may be small, meaning that potential bias exists. By employing the PSM method to balance various factors varying from pre-treatment staging workup to chemotherapy intensity, we reduced the potential bias as much as we could.[24] Moreover, the follow-up duration may be insufficient. Therefore, we set DFS as the first endpoint to address this. Notably, the dosage of CTX/NTZ used in our study was less than the standard dosage because we had little published evidence regarding the dosage used concurrently with IC. Undoubtedly, further studies are needed to establish the best regimen and dosage. Furthermore, the cycles of IC were not uniform. In light of previous evidence, we recruited patients receiving at least 2 cycles because 2 cycles were sufficient to achieve therapeutic gain.[22] Importantly, we balanced this factor between the 2 groups.

In summary, CTX/NTZ in combination with IC may be a more effective and promising treatment strategy than IC alone in reducing treatment failure and improving overall survival for patients with LA-NPC in the era of IMRT. Our study provides new insight into the

usage of targeted therapy in NPC, although these findings need to be validated in prospective studies.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.