

Is the Neoadjuvant Docetaxel, Cisplatin and 5-Fluorouracil Regimen Superior to Classic Cisplatin and 5-Fluorouracil for Locoregionally Advanced Nasopharyngeal Carcinoma?

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Abstract: *Objectives:* We retrospectively compared the toxicity and efficacy of two neoadjuvant chemotherapy regimens (docetaxel+cisplatin+5-fluorouracil vs. cisplatin+5-fluorouracil) followed by chemoradiotherapy for locoregionally advanced nasopharyngeal carcinoma.

Patients and Materials: We analysed 135 patients with stage III and IVA-B nasopharyngeal carcinoma. Forty-four patients were treated with docetaxel+cisplatin+5-fluorouracil and chemoradiotherapy (TPF group), and 91 were treated with cisplatin+5-fluorouracil and chemoradiotherapy (PF group). Chemoradiotherapy was administered with weekly cisplatin. Radical radiotherapy with total doses of 70–74Gy was administered using a conventional technique, over 7 weeks in 2.0Gy/fraction; boost doses of 6–10Gy were administered in 55.6% patients (n=75) with locally advanced cancer.

Results: The median follow-up was 46.5 months (range, 9.8–62.8 months), and the follow-up rate was 95%. The TPF group had better 5-year estimated progression-free survival (77.0% vs. 73.5%; $P = 0.510$) and overall survival than the PF group (80.7% vs. 77.9%, $P = 0.446$); however, there was no statistically significant difference between the groups. Toxicities in the two groups were similar; grade 3/4 oral mucositis was more common in the TPF group (27.3%) than in the PF group (15.3%) during chemoradiotherapy.

Conclusions: The neoadjuvant docetaxel+cisplatin+5-fluorouracil chemotherapy led to satisfactory long-term survival and slight improvement in progression-free survival and overall survival as compared with the classic cisplatin+5-fluorouracil regimen; toxicity was tolerable. However, prospective trials are needed to prove whether docetaxel+cisplatin+5-fluorouracil is a substitute for cisplatin+5-fluorouracil.

Keywords: Nasopharyngeal carcinoma, induction-concurrent chemotherapy, docetaxel, cisplatin, 5-fluorouracil.

INTRODUCTION

Locoregionally advanced nasopharyngeal carcinoma (LR-NPC) remains a very common malignant disease with high mortality in endemic regions. Although it has been confirmed that radiotherapy (RT) combined with chemotherapy improves local and distant control, a series of retrospective and prospective studies over the past two decades has determined that the long-term survival benefit, efficacy and outcome for LR-NPC is unsatisfactory [1]. While cisplatin-based concurrent chemoradiotherapy (CCRT) has been widely accepted as standard care for locoregionally advanced patients, the role of neoadjuvant chemotherapy (NC) and adjuvant chemotherapy (AC) is uncertain [2]. Based on the recommendation of the landmark Intergroup 0099 (INT-0099) study, CCRT followed by AC has been adopted as a clinical trial design or treatment guideline

[3]. However, a recent phase III randomised trial conducted by the Cancer Center of Sun Yat-Sen University (CCSYS) did not support the premise that AC could confer survival benefit in endemic areas [4]. In contrast, NC has garnered the attention of clinicians, with the 2013 National Comprehensive Cancer Network guidelines [5] deeming it an effective strategy due to its ability to shrink tumour volumes to provide wider margins for RT, decrease micrometastasis risk and improve locoregional control and because it has better patient compliance than AC [6, 7]. However, the optimal NC regimen and cycles have not been established.

Cisplatin combined with 5-fluorouracil (PF) is a classic NC regimen for squamous cell carcinoma of the head and neck (SCCHN) and for NPC; typically, two or three cycles are administered, and the objective response rate (ORR) is 60%–70% [8, 9]. Studies have concluded that NC could merely improve locoregional and distant control but not long-term survival [8–11]. Docetaxel is a newer cytotoxic agent which can enhance tubulin polymerization and inhibit microtubule

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depolymerization. Following the use of docetaxel for SCCHN in the early 1990s, the addition of docetaxel to PF (TPF) improved the ORR by 10%–20% as compared to the PF regimen; two important phase III trials (TAX323 and TAX324) confirmed that NC with TPF is superior to that with PF for SCCHN, not only in terms of progression-free survival (PFS) but also overall survival (OS) [12, 13]. A series of phase II studies conducted on NC with docetaxel+cisplatin (TP) or TPF for NPC produced very satisfactory preliminary results; the ORR was approximately 80%, and the 3-year OS was 74.1%–94.9% [14–18]. However, data comparing TPF with classic PF for LR-NPC remain limited.

In view of these findings, we believe that TPF might substitute PF as the standard NC regimen for LR-NPC. This study aimed to compare NC with TPF followed by CCRT with NC with PF followed by CCRT for LR-NPC in a single institution in an endemic area and during the same period; toxicity, efficacy and long-term survival were assessed.

SUBJECTS AND METHODS

Patients

The study of NC with TPF for LR-NPC was conducted at the First People's Hospital of Foshan Affiliated to Sun Yat-Sen University (FPHFS) between December 1, 2007 and September 30, 2010. The inclusion criteria were pathological diagnosis of World Health Organization (WHO) type XXIII NPC, aged 18–70 years, 6th American Joint Committee on Cancer/International Union Against Cancer (2002) system stage III and IVA-B NPC, adequate pretreatment haematologic reserve (absolute neutrophil count $\geq 1.8 \times 10^9/l$, platelet count $\geq 100 \times 10^9/l$) and organ function (alanine aminotransferase and alkaline phosphatase within normal limits, and creatinine clearance ≥ 40 ml/min). The exclusion criteria were history of anti-cancer treatment, pregnancy or lactation and being unsuitable for RT and chemotherapy due to organ dysfunction.

We retrospectively reviewed the database of NC with PF for cases of stage III and IVA-B NPC between January 1, 2008 and September 30, 2010. All patients had pathologically diagnosed NPC and had undergone NC with PF. We excluded patients diagnosed with recurrent or metastatic disease; those treated with RT alone, CCRT alone or AC; and those who dropped out or did not complete NC or radical RT.

All patients underwent a complete physical examination, fiberoptic nasopharyngoscopy, nasopharyngeal and cervical region magnetic resonance imaging (MRI), chest radiography, abdominal ultrasonography and whole-body bone scan before treatment. If there was lower neck lymph node involvement, chest computed tomography (CT) or whole-body positron-emission tomography/CT was performed to detect distant metastasis. Patients were confirmed as having adequate heart, liver and kidney function and underwent haematological testing before treatment. Nasopharyngeal and cervical region MR and/or cervical ultrasonography were performed after NC and before RT to evaluate efficacy.

All work was conducted in accordance with the Declaration of Helsinki (1964). The ethics committee of the FPHFS approved this study; informed consent was obtained from the patients before the study was carried out.

Chemotherapy

NC

TPF

Patients received NC with TPF (60 mg/m² docetaxel and 80 mg/m² cisplatin on day 1 or 20 mg/m² cisplatin on days 1–4 and a continuous infusion of 800 mg/m²/day 5-fluorouracil on days 1–5); oral dexamethasone (10 mg daily, days 0–2) was administered before (premedication) and during docetaxel infusion. A 5-hydroxytryptamine-3 receptor antagonist such as ondansetron (8 mg) or gelarsichone (4 mg) was administered intravenously as chemotherapy premedication. Patients received vigorous hydration to maintain a urine output > 100–150 ml/h.

PF

Patients received NC with PF (100 mg/m² cisplatin on day 1 or 20 mg/m² cisplatin on days 1–5 and continuous infusion of 1000 mg/m²/day 5-fluorouracil on days 1–5); a 5-hydroxytryptamine-3 receptor antagonist such as ondansetron (8 mg) or gelarsichone (4 mg) was administered intravenously as chemotherapy premedication. Patients received vigorous hydration to maintain a urine output > 100–150 ml/h.

CCRT

Cisplatin (30 mg/m² or 40 mg/m²) was administered weekly *via* intravenous infusion on the first day of RT for 7 weeks. A 5-hydroxytryptamine-3 receptor antagonist such as ondansetron (8 mg) or gelarsichone

(4 mg) was administered intravenously as chemotherapy premedication. Patients received vigorous hydration to maintain a urine output > 100–150 ml/h.

Treatment toxicities were graded according to the National Cancer Institute Common Toxicity Criteria version 3.0. Granulocyte colony-stimulating factor was administered promptly if white blood cell was $<3.0 \times 10^9/l$ or absolute neutrophil count was $<1.8 \times 10^9/l$.

RT

External beam RT was initiated 1 week after NC, and RT was delivered using a 6-MV linear accelerator (Varian C600, Varian Medical Systems, Palo Alto, CA, USA). Patients were immobilised with a thermoplastic mask and treated in a supine position. The target volume comprised the entire tumour and a >2-cm margin. Two lateral opposed fields were used to irradiate the primary nasopharyngeal tumour volume and the upper neck, and a single anterior field was used to irradiate the lower neck and supraclavicular region with midline blocking to shield the spinal cord. The shrinking field technique was used at least twice to limit toxicity to the vital organs, especially the brain stem and spinal cord. A planned total dose of 70–74Gy, 64–70Gy and 50–54Gy was delivered to the primary tumour, regional metastatic nodes and the uninvolved nodes, respectively. A boost dose of 6–10Gy in 3–5 fractions was administered to patients who had tumours involving the base of the skull and/or intracranial extension.

Follow-Up

Patients were assessed every 2–3 months for the first year, every 3–6 months for the next 2 years and then every 6 months or yearly thereafter. Each follow-up visit included a routine physical examination, head and neck MRI and fiberoptic endoscopy if indicated. Chest radiography, abdominal and pelvic ultrasonography and whole-body bone scanning was performed every 3–6 months or earlier, according to the discretion of the treating physician.

Statistical Analyses

Locoregional failure-free survival (LFS), distant failure-free survival (DFS) PFS and OS were estimated by Kaplan–Meier analysis. Differences between the two groups were compared by the log-rank test. A two-sided P -value ≤ 0.05 was considered indicative of statistical significance. All statistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient Characteristics

We enrolled 135 consecutive stage III and IVA-B NPC patients who underwent NC+CCRT. Among the 135 patients identified from the FPHFS database, 44 underwent the TPF regimen, and 91 underwent the PF regimen. Patients were analysed using follow-up data up to and including April 30, 2013. In total, 95% of patients completed follow-up; only seven patients were lost to follow-up, of which two and five were in the TPF and PF group, respectively. The Karnofsky performance status score of most patients was more than 80 (range, 70–90). All patients completed radical RT with the median dose of 70Gy, 68Gy and 50Gy to the primary tumour, regional metastatic nodes and the uninvolved nodes, respectively. 75 patients (55.6%) received a boost with the median dose of 6Gy. The 135 patients completed 245 cycles of NC in total; the mean number of cycles was 1.81. Seventy-seven percent ($n = 104$) of patients underwent two cycles of NC: 30 and 74 patients in the TPF and PF group, respectively. Stage IVB patients accounted for 10.7%, 26.0% and 33.3% of those who underwent one, two and three cycles of NC, respectively ($P = 0.049$). The characteristics of the 135 patients are listed in Table 1.

Efficacy

In the TPF group, 4 (9.1%), 34 (77.3%) and 6 (13.6%) patients had complete response (CR), partial response (PR) and stable disease (SD), respectively, in the nasopharynx; 15 (34.1%), 23 (52.3%) and 6 (13.6%) patients had CR, PR and SD, respectively, in the cervical nodes. In the PF group, 14 (15.4%), 61 (67.0%) and 16 (17.6%) patients had CR, PR and SD, respectively, in the nasopharynx; 19 (20.9%), 58 (63.7%) and 14 (15.4%) patients had CR, PR and SD, respectively, in the cervical nodes. There was no statistically significant difference between the ORRs of the two groups. The short-term efficacy after CCRT was similar in the two groups ($P = 0.660$); in the TPF and PF groups, 31 (70.5%) and 61 (67%) patients had CR, and 13 (29.5%) and 30 (33.0%) patients had PR, respectively.

The 5-year estimated LFS, DFS, PFS and OS of the entire database were 95.4%, 90.4%, 74.5% and 78.7%, respectively. The TPF group had better PFS and OS than the PF group. The 5-year estimated LFS, DFS, PFS and OS of TPF group patients as compared with those of the PF group patients were 90.1% vs. 89.5% ($P = 0.112$), 87.1% vs. 91.2% ($P = 0.920$), 77.0% vs.

Table 1: Patient Characteristics

Characteristics	Total (%)	TPF group (%)	PF group (%)	P-value
Sex				0.657
Male	97(71.8%)	30(68.2%)	67(72.2%)	
Female	38(28.2%)	14(32.8%)	24(26.4%)	
Age(year)				0.510
Mean	46	48	46	
Range	20-73	20-69	22-73	
Personal status				0.417
0	34(25.2%)	14(31.8%)	20(22.0%)	
1	96(71.1%)	29(65.9%)	67(73.6%)	
2	5(3.7%)	1(2.3%)	4(4.4%)	
T Stage				0.932
T1	7(3.3%)	3(6.8%)	4(4.4%)	
T2	33(26.7%)	11(25.0%)	22(24.2%)	
T3	65(30.0%)	21(47.7%)	44(48.4%)	
T4	30(40.0%)	9(20.5%)	21(23.1%)	
N Stage				0.762
N0	4(3.0%)	2(4.5%)	2(2.2%)	
N1	13(9.6%)	5(11.4%)	8(8.8%)	
N2	87(64.4%)	26(59.1%)	61(67%)	
N3	31(23.0%)	11(25.0%)	20(22%)	
TNM				0.748
III	81(60.0%)	27(61.4%)	54(59.3%)	
IVa	23(17.0%)	6(13.6%)	17(18.7%)	
IVb	31(23.0%)	11(25.0%)	20(22.0%)	
N cycle				0.166
1	28(20.7%)	12(27.3%)	16(17.6%)	
2	104(77.0%)	30(68.2%)	74(81.3%)	
3	3(2.2%)	2(4.5%)	1(1.1%)	
Cycles of CCRT				0.353
≥5	56(41.5%)	21(47.7%)	35(38.5%)	
< 5	79(58.5%)	23(52.3%)	56(61.5%)	

TPF, docetaxel+cisplatin+5-fluorouracil; PF, cisplatin+5-fluorouracil; CCRT, concurrent chemoradiotherapy.

73.5% ($P = 0.510$) and 80.7% vs. 77.9% ($P = 0.446$), respectively. The survival curves are presented in Figure 1.

Failure Pattern

At the median follow-up of 46.5 months (range, 9.8–62.8 months), 4.4% of patients ($n = 6$) developed recurrence; there were four and two instances of local and regional recurrence, respectively, and recurrence in the two groups was not significantly different ($P =$

0.391). There was distant metastasis in 8.9% of patients ($n = 13$), and bone ($n = 11$) was the most frequent metastatic site. The incidence of distant metastasis in the two groups was not significantly different ($P = 0.223$).

Toxicity

The toxicity profile was similar in the two groups. During NC, neutropenia and vomiting were common, and one TPF group patient had neutropenic fever.

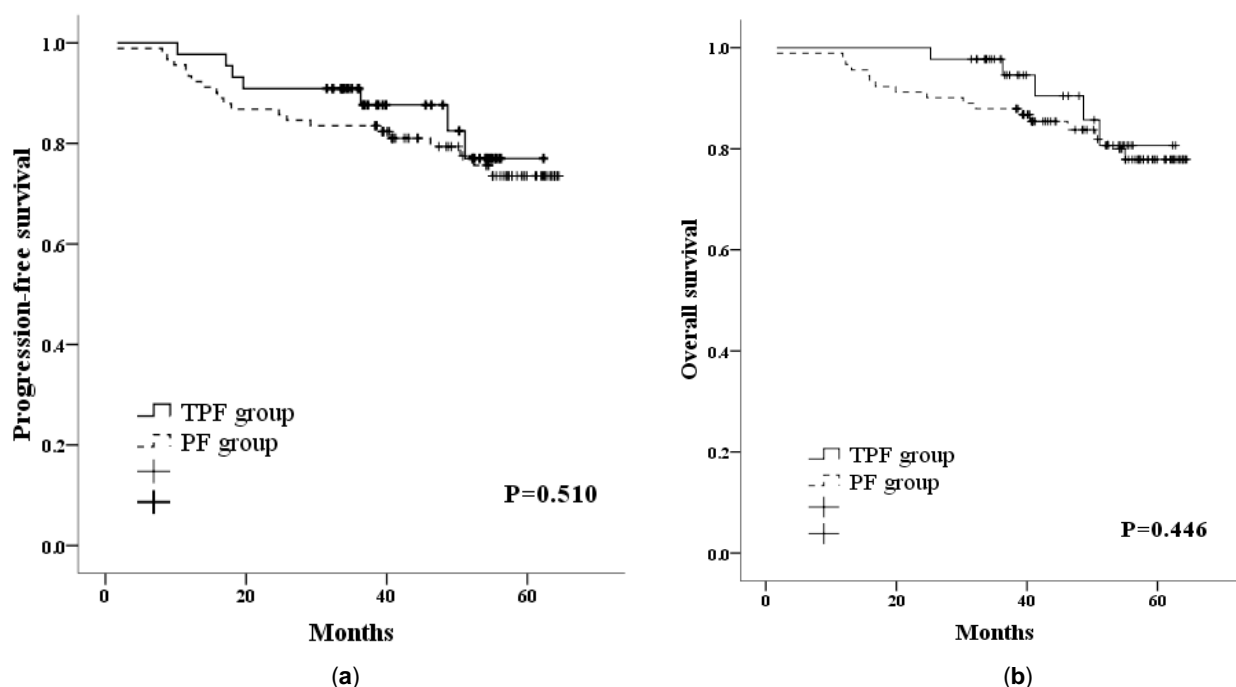


Figure 1: Kaplan–Meier estimates of probability of (a) progression-free survival (PFS) and (b) overall survival (OS) in the docetaxel+cisplatin+5-fluorouracil (TPF) group vs. the cisplatin+5-fluorouracil (PF) group.

Table 2: Toxicity During Treatment

Total	TPF group		PF group		P-value
	3 (%)	4 (%)	3 (%)	4 (%)	
During neoadjuvant chemotherapy					
Hematologic					
Hemoglobin	0(0)	0(0)	0(0)	0(0)	0.209
Neutrophils	7(15.7)	1(2.3)	16(17.6)	10(11.0)	0.368
Platelets	2(4.5)	0(0)	4(4.4)	2(2.2)	0.391
Neutropenic fever	1(2.3)	0(0)	0(0)	0(0)	0.214
WBC	3(6.8)	0(0)	4(4.4)	3(3.3)	0.617
Non-hematologic					
Vomiting	3(6.8)	0(0)	17(18.7)	0(0)	0.323
Hepatic	0(0)	0(0)	0(0)	0(0)	0.652
Creatinine	0(0)	0(0)	1(1.1)	0(0)	0.128
Diarrhea	0(0)	0(0)	1(1.1)	0(0)	0.448
During concurrent chemotherapy					
Hematologic					
Hemoglobin	0(0)	0(0)	7(15.9)	0(0)	0.001
Platelets	2(4.3)	0(0)	6(6.6)	1(1.1)	0.009
WBC	4(9.1)	0(0)	16(17.6)	3(3.3)	0.259
Non-hematologic					
Vomiting	2(4.5)	0(0)	5(5.5)	0(0)	0.916
Hepatic	1(2.3)	0(0)	1(1.1)	0(0)	0.682
Creatinine	0(0)	0(0)	1(1.1)	0(0)	0.645
Oral mucotisis	12(27.3)	0(0)	13(14.3)	1(1)	0.353
Dermatitis	4(9.1)	0(0)	7(7.7)	0(0)	0.689

TPF, docetaxel+cisplatin+5-fluorouracil; PF, cisplatin+5-fluorouracil; WBC, white blood cell.

During CCRT, oral mucotitis occurred more frequently in the TPF group; 27.3% of TPF group patients had grade 3 mucotitis as compared with 14.3% of PF group patients, but the difference between the two groups was not statistically significant ($P = 0.353$). Most of the toxicities were tolerable and manageable; the grade 3 and 4 toxicities are listed in Table 2.

DISCUSSION

In contrast to what we expected, the current findings did not support neoadjuvant TPF as a substitute for the classic PF regimen, though the PFS and OS of the TPF group were improved slightly. The overall 5-year estimated PFS and OS were 77.0% and 80.7% in the TPF group and 73.9% and 77.9% in the PF group, respectively.

Locoregionally advanced staging denotes the presence of a high risk of recurrence and distant metastasis, and can be considered a systemic disease. Therefore, patients with locoregionally advanced cancer should receive more intensive treatment. The NPC-9901 study by Lee *et al.* [19] involved T1–4/N2–3/M0 patients, and compared with RT, CCRT+AC according to the INT-0099 protocol did not improve their long-term outcome. In subgroup analysis, only stage III patients with lactate dehydrogenase <200 IU/L derived a survival benefit [19]. Recently, a phase III trial conducted by Chen *et al.*, in which stage III and IVA-B patients accounted for 65% and 35% of their database, respectively, proved that AC did not improve survival [4]. By contrast, an increasing amount of data has demonstrated that the NC+CCRT approach is an encouraging strategy for LR-NPC. The 3-year PFS and OS have been reported as 54.3%–88.2% and 74.1%–94.9%, respectively [5–7, 14–18]. Therefore, the clinical significance of NC for NPC should be re-evaluated. Studies that have focused on the NC+RT strategy have reported that the results supported the premise that NC only improved local and distant control, but not OS [8–11]. Other factors, such as the use of regimens other than the classic PF regimen and study designs that compare NC followed by RT with RT alone [8–11], should be taken into account. To date, evidence on the survival benefit of CCRT is adequate, and cisplatin-based CCRT is considered the standard of care. An increasing number of clinicians tend to select the NC+CCRT strategy for patients with advanced T and/or N stage and a high risk of treatment failure. One important reason for this is that NC can reduce tumour bulk and increase an RT boost area to derive better tumour control [7]. In the current study, stage III and

IVA-B patients accounted for 60% and 40% of the cohort, and the overall 5-year estimated LFS, PFS and OS of the database were 95.4%, 74.5% and 78.7%, respectively. An adequate number of cycles were adopted to benefit patients with advanced N stage; our data showed that stage IVB patients comprised 10.7%, 26.0% and 33.3% of those who underwent one, two and three cycles of NC, respectively.

Differing from the pathologic type of SCCHN, WHO type III NPC is most common in endemic areas and is very sensitive to RT and chemotherapy. Docetaxel-based NC led to better tumour control and survival benefit in NPC than in SCCHN. In a phase II study, Hui *et al.* treated LR-NPC with two cycles of neoadjuvant TP (75 mg/m² docetaxel and 75 mg/m² cisplatin on day 1) followed by CCRT with weekly cisplatin (40 mg/m²) as compared with CCRT alone. The neoadjuvant TP improved the 3-year PFS and OS from 59.5% to 88.2% ($P = 0.12$) and from 67.7% to 94.1% ($P = 0.02$), respectively [15]. To date, docetaxel-based NC followed by CCRT has yielded encouraging results in phase II trials [14–18, 20–21] (Table 3), and two phase III trials sponsored by the Radiotherapy Oncology Group for Head and Neck (NCT 00828386) and CCSYS University (NCT 01245959) are in progress to determine whether adding neoadjuvant TPF chemotherapy can improve the survival benefit as compared to that obtained with CCRT alone. Furthermore, data on whether docetaxel-based NC is a substitute for PF is lacking. Johnson *et al.* conducted a trial to investigate NC with docetaxel+carboplatin (TC) for early T and advanced N staging NPC patients; the CR, ORR and 3-year PFS and OS were 11%, 89%, 54.3% and 74.1%, respectively. In their experience, TC was not superior to PF [14]. The only study comparing the efficacy of TP with PF was reported by Xie *et al.* [22]. The CR after treatment with TP (100%) was superior to that after treatment with PF (75%), but lacked statistical significance [22]. PF is a classic regimen, and the substitution of cisplatin with carboplatin or the lack of 5-fluorouracil in an NC regimen might be inadequate. In the current study, we treated LR-NPC with NC with TPF, and the CR and ORR were similar to those of the PF group, but the survival curves (PFS and OS) derived from the TPF regimen were better than those derived from the PF regimen.

Appropriate dose intensity of a triple-drug regimen can maximise its efficacy and minimise toxicity. The optimal dose intensity and cycles of the TPF regimen

Table 3: Docetaxel-Based NC in LR-NPC Treatment

Author	Year	Pts no.	Stage		NC regimen	Response of NC		PFS(y)	OS(y)	Main toxicity of NC (grade3/4)
			III	IV		CR	ORR			
Johnson	2004	18	T1-2N2-3M0		TC×3cycles	11%	89%	54.3%(3)	74.1%(3)	Netropenia 51%
Xie	2007	20	75%	25%	TP×2cycles	0%	90%	-	-	Netropenia 40.5%
						LN				
						35%	90%			
Hui	2009	34	55.9%	44.1%	TP×2cycles	NP		88.2%(3)	94.1%(3)	Netropenia 97%
						23.5%	83.2%			
						LN				
						53.8%	84.6 %			
Bae	2010	33	15.1%	97%	TPF×3cycles	15.2%	97%	75.6%(3)	86.1%(3)	Netropenia 72.7%
Kong	2010	59	50.8%	49.2%	TPF×3cycles	NP		-	100%(1)	Netropenia 52.5%
						25.4%	94.9%			
						LN				
						19.6%	80.4%			
Ekenel	2011	59	63%	22%	TP×2cycles	7%	43%	84.7%(3)	94.9%(3)	-
Bossi	2011	30	43%	57%	TPF×3cycles	-	100%	79%(3)	87%(3)	Netropenia 33%
Du	2013	60	48%	52%	TPF×3cycles	7%	89%	83.9%(3)	91.9(3)	Leucpoania 23%
Current	-	44	61.4%	38.6%	TPF×2cycles	NP		77.0%(5)	80.7%(5)	Netropenia 18%
						9.1%	86.4%			
						LN				
						34.1%	86.4%			

NC, neoadjuvant chemotherapy; CR, complete response; PR, partial response; ORR, objective response rate; PFS, progression-free survival; OS, overall survival; T, docetaxel; P, cisplatin; F, 5-fluorouracil; C, carboplatin; NP, nasopharynx; LN, regional neck lymph nodes; LR-NPC, locoregionally advanced nasopharyngeal carcinoma.

for endemic LR-NPC patients have not been established. One CCSYS study recommended three cycles of 60 mg/m² docetaxel and 60 mg/m² cisplatin on day 1, and 600 mg/m² 5-fluorouracil on days 1-5 [23]. We treated 44 patients using a neoadjuvant TPF regimen with a median of two cycles (60 mg/m² docetaxel and 80 mg/m² cisplatin on day 1 or 20 mg/m² cisplatin on days 1-4 and 800 mg/m² 5-fluorouracil on days 1-5). Thirty patients completed two cycles of NC and toxicity was tolerable; grade 3/4 haematologic toxicity occurred in 18% of the patients. In our experience, it is likely that the incidence of haematologic toxicity was lower because it typically occurs during the third cycle of NC. Since September 2010, we have treated LR-NPC with three cycles of TPF followed by CCRT (weekly cisplatin combined with intensity-modulated RT [IMRT]) at our institution; we found that most patients could not endure >4 cycles of

CCRT due to serious haematologic toxicity. In addition, other studies support the premise that adequate dose intensity of cisplatin during CCRT could lead to good outcomes [19, 24]. Thus, balancing efficacy and toxicity between NC and CCRT and maximising the survival benefit is a direction that LR-NPC treatment should take in the future.

This study has some limitations. As this was a retrospective analysis, we could not derive definitive information on whether the efficacy of NC with TPF was superior to that of NC with PF, though the clinical characteristics of the two groups were balanced and comparable. Second, conventional RT was used, not IMRT. The current precise RT delivery technique might improve patient outcomes and has become the mainstream treatment for NPC. Other limitations included the small size of the TPF group and the lack

of matched-pairs. Future randomised trials for definitive comparison of TPF with PF in NC regimens for LR-NPC are warranted.

CONCLUSIONS

NC+CCRT is an effective treatment strategy for LR-NPC. NC with TPF conferred satisfactory long-term survival and slightly improved PFS and OS as compared with the classic PF regimen, and toxicity was tolerable. However, prospective trials are needed to prove whether TPF is a substitute for PF.

CONFLICT OF INTEREST

None.

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