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Optimal induction chemotherapeutic regimen followed by concurrent chemotherapy plus intensity-modulated radiotherapy as first-line therapy for locoregionally advanced nasopharyngeal carcinoma

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Abstract

For patients with locoregionally advanced nasopharyngeal carcinoma (NPC), induction chemotherapy (IC) regimens based on TPF (docetaxel, cisplatin, and 5-fluorouracil), TP (docetaxel and cisplatin), and GP (gemcitabine and cisplatin) have shown excellent survival outcomes as the first-line therapy; however, no trials comparing the efficacy and safety of TPF, TP, and GP have been reported. We report 2 phase II trials comparing the treatment outcomes and side effects of 3 different IC regimens followed by concurrent chemoradiotherapy in locoregionally advanced patients with NPC.

A total of 206 locoregionally advanced patients with NPC treated with a combination treatment from January 2012 to January 2014 were enrolled in the 2 studies. The patients received TPF-, TP-, and GP-based IC regimens every 3 weeks, followed by intensity-modulated radiotherapy and concurrent therapy with cisplatin every 3 weeks.

After a median follow-up duration of 47 months (10–60 months), the 3-year local recurrence-free survival, regional recurrence-free survival, distant metastases-free survival, progression-free survival, and overall survival rates were 96.4%, 100%, 87.7%, 86%, and 94.7% in the TPF arm; 91.7%, 95.9%, 91.9%, 85.2%, and 92% in the TP arm; 98.6%, 100%, 89.0%, 87.6%, and 89.2% in the GP arm. The survival differences among the 3 arms were not statistically significant ($P > .05$). The multivariate analysis demonstrated that the IC regimen was not an independent prognostic factor for any survival outcomes. The patients in the TP arm experienced significantly lower grade 3/4 toxicities than the patients in the other 2 arms.

TP-based IC regimen has similar efficacy compared with TPF- and GP-based IC regimens; however, TP-based IC regimen has a lower toxicity profile.

Abbreviations: AC = adjuvant chemotherapy, AJCC = American Joint Committee on Cancer, CC = concurrent chemotherapy, CCRT = concurrent chemoradiotherapy, CR = complete remission, CTV = clinical target volume, DMFS = distant metastases-free survival, GP = gemcitabine and cisplatin, IC = induction chemotherapy, IMRT = intensity-modulated radiotherapy, LRFS = local recurrence-free survival, MRI = magnetic resonance imaging, NCCN = National Comprehensive Cancer Network, NPC = nasopharyngeal carcinoma, OARs = organs at risk, OS = overall survival, PFS = progression-free survival, PR = partial remission, PTV = planning target volume, RRFS = regional recurrence-free survival, RT = radiotherapy, RTOG = Radiation Therapy Oncology Group, SD = stable disease, TP = docetaxel and cisplatin, TPF = docetaxel, cisplatin, and 5- fluorouracil.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

Nasopharyngeal carcinoma (NPC), a unique cancer located in the head and neck region, is endemic in Singapore, Malaysia, and Southern China, with an incidence of 15 to 50 cases per 100,000 people.[1] Because of the anatomical location of nasopharynx and its high sensitivity to irradiation, radiotherapy (RT) is regarded as a prime treatment strategy for nondisseminated NPC. The survival outcomes of NPC patients were improved significantly owing to the advances in radiological techniques, extensive application of intensity-modulated radiotherapy (IMRT), and the addition of concurrent chemotherapy (CC).[2,3] Distant metastasis became the main treatment failure pattern in patients with NPC, although the 5-year overall survival (OS) rates of 90% to 100% for stage I to II NPC and 60% to 85% for stage III to IVB NPC were reported.[4,5] In addition, >70% of patients are diagnosed with locoregionally advanced NPC.[6] The results of a 0099 trial showed that adjuvant chemotherapy (AC) was not beneficial in improving the survival outcomes of patients with locoregionally advanced NPC owing to the low completion of 3 cycles of AC.[7] In contrast, induction chemotherapy (IC) can improve patients' tolerability, eradicate micrometastases, and protect normal tissues by reducing tumors when compared with the AC. Therefore, IC followed by concurrent chemoradiotherapy (CCRT) seems to become an encouraging option for further improving the survival outcomes in patients with locoregionally advanced NPC and is recommended by the 2014 National Comprehensive Cancer Network (NCCN) guidelines.[8]

The results from previous studies indicated that IC plus RT did not provide any survival benefit when compared with RT alone.[9–12] Effective IC regimens should be further studied and identified. Taxane, a microtubule inhibitor, can interfere with cell division; several randomized phase 3 trials reported that the addition of taxane in the IC regimen with cisplatin and with or without 5-fluorouracil [docetaxel, cisplatin, and 5-fluorouracil (TPF) or docetaxel and cisplatin (TP)] improved the treatment outcomes in patients with locoregionally advanced head and neck squamous cell cancer.[13–15] The studies were performed to confirm that the taxane-containing IC regimens could achieve similar survival benefits in patients with locoregionally advanced NPC. A recent phase III multicenter, randomized trial indicated that the addition of TPF to CCRT significantly improved the OS, failure-free survival, and distant metastases-free survival (DMFS) rates compared with CCRT alone in patients with locoregionally advanced NPC.[16] In a randomized phase II trial reported by Hui et al,[17] 2 cycles of TP IC regimen before CCRT improved the 3-year OS compared with CCRT alone (94.1% vs 67.7%, $P = .012$). In addition, we performed a phase II study to compare the efficacy and toxicities of TPF versus TP IC regimen before CCRT for locoregionally advanced NPC and showed that the TP-based IC regimen is associated with similar efficacy and less toxicity than the TPF regimen.[18]

The combination of gemcitabine and cisplatin (GP) has been proven to have synergistic cytotoxic effects in vitro.[19] The results from a multicenter, randomized, phase 3 trial established GP regimen as the first-line treatment for patients with recurrent or metastatic NPC because it improved the progression-free survival (PFS) and OS.[20] Zheng et al[21] reported that the GP regimen prolonged the OS and had the tendency to increase the DMFS. Zhao et al[22] recently indicated from a subgroup analysis that the GP regimen significantly increased the OS compared with TP/PF. The results of another single-arm phase II study suggested that the addition of GP-based IC to CCRT had encouraging outcomes with manageable complications.[23]

Based on the above studies, all the 3 IC regimens yet survival benefits in patients with locoregionally advanced NPC. However, comparison of treatment outcomes and toxicities of these 3 IC regimens have never been reported in any previous studies. Here, we report the results of 2 randomized phase II studies and compare the efficacy and safety of 3 different IC regimens before CCRT as the first-line treatment strategy for patients with locoregional advanced NPC.

2. Methods

2.1. Patients and pretreatment

The patients enrolled in this study were hospitalized from January 2012 to January 2014 in the department of radiation oncology, Zhejiang Cancer Hospital. The eligible patients met the following criteria: histologically confirmed NPC; aged 18 to 70 years; stage III/IVA-B NPC at diagnosis [American Joint Committee on Cancer (AJCC) staging system, 7th edition]; adequate bone marrow, liver, and renal function; and without previous anticancer treatment.

The exclusion criteria were that the patients had to be 70 years or older; had received RT, chemotherapy, or surgery for tumors; had distant metastases before treatment; had pregnancy; had a history of other malignancy; or had severe comorbidities.

The prospective randomized study was approved by the medical ethics committee in Zhejiang Cancer Hospital. All the patients signed written informed consent before participating in this research. All treatment protocols in this study were performed in accordance with the NCCN guidelines. All analyses were conducted in compliance with the approved study protocol.

All the patients underwent pretreatment evaluation, including complete medical history, physical examination, hematology and biochemistry profiles, chest radiographs, sonography of the abdomen, bone scan, magnetic response imaging of the nasopharynx, and nasopharyngoscopy. All the patients were staged according to the 2010 AJCC staging system. Tumor histology was classified according to the World Health Organization classification.

3. Treatment schemes

3.1. Radiation therapy

All the patients underwent radical IMRT with simultaneous integrated boost technique using 6 MV photons for 2 to 3 weeks after IC. All the patients were immobilized in the supine position using the head, neck, and shoulder thermoplastic masks. Computed tomography scans with intravenous contrast were performed for treatment planning using 2.5 mm slices from the head to 2 cm below the sternoclavicular joints.

The delineation of target volumes of NPC during the treatment with IMRT was as described previously.[24–27] Briefly, gross

tumor volumes of primary tumor and metastatic lymph nodes were defined as GTVnx and GTVnd, respectively, which were delineated according to pre- and post-IC magnetic resonance imaging (MRI) scans, respectively. The clinical target volume (CTV) of nasopharynx (CTVnx) was defined as GTVnx plus a 7 mm margin that encompassed the nasopharyngeal mucosa plus 5 mm of submucosal volume. The high-risk CTV (CTV1) included the entire nasopharyngeal cavity, anterior one- to two-third of the clivus, skull base, pterygoid plates, parapharyngeal space, inferior sphenoid sinus, posterior one-quarter to one-third of the nasal cavity, and maxillary sinus and any lymph nodes in the drainage pathways containing metastatic lymph nodes. The low-risk CTV (CTV2) included levels IV and Vb without metastatic cervical lymph nodes.

The planning target volume (PTV) was constructed automatically based on each volume with an additional 3 mm margin in 3 dimensions to account for the set-up variability. All the PTVs including PGTVnx, PTVnx, PTV1, and PTV2 were not delineated outside of the skin surface. Critical normal structures, including the brainstem, spinal cord, parotid glands, optic nerves, chiasm, lens, eyeballs, temporal lobes, temporomandibular joints, mandible, and hypophysis, were contoured and set as organs at risk (OARs) during the optimization.

The prescribed radiation dose was 70 or 72 Gy to PGTVnx, 66 to 70 Gy to PGTVnd, 62 to 66 Gy to PTVnx, 60 to 63 Gy to PTV1, and 51 to 54 Gy to PTV2 delivered in 30 or 33 fractions. For IMRT, radiation was delivered once daily, 5 fractions per week, over 6 to 6.5 weeks. The dose to OARs was limited using the Radiation Therapy Oncology Group (RTOG) 0225 protocol.

3.2. Chemotherapy regimens

All the eligible patients were administered 1 to 3 cycles of platinum-based IC at intervals of 3 weeks. The triple IC regimens included the TPF (docetaxel 60 mg/m^2/day on day 1, cisplatin 25 mg/m^2/day on days 1–3, and 5-fluorouracil 500 mg/m^2/day on days 1–3), TP (docetaxel 60 mg/m^2/day on day 1, cisplatin 25 mg/m^2/day on days 1–3), and GP regimens (gemcitabine 1000 mg/m^2/day on days 1 and 8, cisplatin 25 mg/m^2/day on days 1–3).

Moreover, patients with NPC in this study underwent ≥1 cycle of CC with cisplatin (80 mg/m^2) divided over 3 days, and 150 patients received 2 to 3 courses of AC with the PF regimen (cisplatin 25 mg/m^2/day on days 1–3 and 5-fluorouracil 500 mg/m^2/day on days 1–3) for 3 weeks after RT.

3.3. Patient evaluation and follow-ups

The assessment of tumor response was performed thrice after the completion of IC, at the end of IMRT, and 3 months after radiation, which was based on the MRI and nasopharyngeal fiberscope findings according to the Response Evaluation Criteria in Solid Tumors. Systemic chemotherapy adverse effects were graded using the National Cancer Institute Common Toxicity Criteria (NCI CTCAE, version 3.0), whereas RT-induced toxicities were scored according to the Acute and Late Radiation Morbidity Scoring Criteria of the RTOG.

All the subjects underwent weekly examinations for treatment response and toxicities during the radiation therapy. The patients were followed-up every 3 months in the first 2 years, every 6 months from the third to the fifth year, and then annually. Each follow-up included careful examination of the nasopharynx and neck nodes by an experienced doctor; MRI scan of the nasopharynx, nasopharyngeal fiberscope, chest computed tomography, and ultrasound of the abdomen were performed 3 months after the completion of RT and every 6 to 12 months thereafter. Additional examinations were performed when it was indicated to evaluate local relapse or distant metastasis.

3.4. Statistical analysis

The end points of this study included the local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), DMFS, PFS, OS, and acute toxicities from IC and CCRT. The OS was calculated from the date of patient enrollment into the trail to the date of death or the last follow-up. The LRFS, RRFS, DMFS, and PFS were calculated from the date of patient enrollment into the trail to the date of local relapse, regional relapse, distant metastasis occurrence, and the diagnosed evidence of disease progression or the last follow-up, respectively. After relapse or metastasis, patients were administered salvage therapy as determined by their physicians.

The Chi-square test or Fisher exact test was used for comparing the patients' characteristics, treatment adherence, tumor response, and patterns of failure among the 3 arms. The analysis of variance was used for comparing continuous variables. Survival curves were generated using the Kaplan-Meier method, and the curves were compared using the log-rank tests. The multivariate analysis was performed using the Cox regression models for identifying significant prognostic factors. Hazard ratios and 95% confidence intervals were calculated for each prognostic factor. IBM SPSS Statistics version 19.0 was used for all data analysis. A P value of $<.05$ was considered statistically significant.

4. Results

4.1. Patients' characteristics and therapeutic compliance

From January 2012 to January 2014, a total of 206 eligible patients with locoregionally advanced NPC were enrolled. Fifty-seven patients were randomly assigned to the TPF arm, 75 patients to the TP arm, and 74 patients to the GP arm. Basic demographics of the patients and tumor characteristics are summarized in Table 1. The characteristics of the patients and tumor factors were well balanced among the 3 arms.

All the patients completed a full course of radical IMRT protocol and received at least 1 cycle of IC. Among these patients, 175 (85.0%) patients received CC, and 150 patients (72.8%) received AC. Treatment compliance among the 3 arms is listed in Table 2.

4.2. Disease response

Regarding the tumor response of IC, 18 patients (31.6%) had complete remission (CR), 37 patients (64.9%) had partial remission (PR), and 2 patients (3.5%) had stable disease (SD) with the nasopharyngeal tumor confirmed in the TPF arm, whereas CR, PR, and SD in the TP and GP arms were achieved in 23 (30.7%), 49 (65.3%), and 3 (4.0%) patients and 19 (25.6%), 52 (70.3%), and 3 (4.1%) patients, respectively. For cervical metastatic lymph nodes, CR, PR, and SD rates among the 3 arms (TPF, TP, and GP) were 36.8% (21/57), 61.4% (35/57), and 1.8% (1/57); 38.7% (29/75), 58.7% (44/75), and 2.6% (2/75); and 41.1% (30/73), 56.2% (41/73), and 2.7% (2/73), respectively. At the end of IMRT, the CR rates of nasopharyngeal tumor and neck metastatic lymph nodes in the 3 arms (TPF, TP,

Table 1

Basic characteristics of 206 locoregionally advanced nasopharyngeal carcinoma patients in the 3 arms.

Characteristics	TPF regimen N = 57	TP regimen N = 75	GP regimen N = 74	X^2	*P*
Sex				0.029	.986
Male	41	53	53		
Female	16	22	21		
Age, y				0.716	.699
Range	19–63	22–70	18–70		
Median	47	49	55		
<50	39	46	30		
≥50	18	29	44		
WHO pathology				1.847	.764
Type I	3	1	3		
Type II	2	3	2		
Type III	52	71	69		
ECOG performance status				1.628	.443
0	45	60	64		
1	12	15	10		
T stage*				6.197	.045
T1	1	2	1		
T2	10	21	28		
T3	31	32	30		
T4	15	20	15		
N stage*				0.408	.815
N0	0	0	1		
N1	7	11	11		
N2	40	57	55		
N3	10	7	7		
Clinical stage*				1.732	.421
III	35	48	53		
IV	22	27	21		
Comorbidity				4.953	.093
No	48	60	51		
Yes	9	15	23		

ECOG = Eastern Cooperative Oncology Group, GP = gemcitabine and cisplatin, TP = docetaxel and cisplatin, TPF = docetaxel, cisplatin, and 5- fluorouracil, WHO = World Health Organization.
* The American Joint Committee on Cancer staging system, 7th edition.

and GP) were 91.2%, 94.7%, and 97.3% and 92.0%, 93.3%, and 98.6%, respectively. No statistically significant differences in the disease response to the treatments were found among the 3 arms (Table 3).

4.3. Survival outcomes

The median follow-up duration was 47 months (range, 10–60 months). The estimated 3-year LRFS, RRFS, DMFS, PFS, and OS rates in all the patients with locoregionally advanced NPC were 95.4%, 96.2%, 85.3%, 86.3%, and 91.7%, respectively (Fig. 1).

There were no statistically significant differences in the LRFS, RRFS, DMFS, PFS, and OS among the TPF, TP, and GP arms (3-year LRFS: 96.4% vs 91.7% vs 98.6%, respectively, $P = .474$, Fig. 2A; 3-year RRFS: 100% vs 95.9% vs 100%, respectively, $P = .179$, Fig. 2B; 3-year DMFS: 87.7% vs 91.9% vs 89.0%, respectively, $P = .541$, Fig. 2C; 3-year PFS: 86.0% vs 85.2% vs 87.6%, respectively, $P = .892$, Fig. 2D; 3-year OS: 94.7% vs 92% vs 89.2%, respectively, $P = .167$, Fig. 2E). And no statistically significant survival differences were observed between any 2 arms (Table 4).

Table 2

Therapeutic compliances among 206 patients with locoregionally advanced nasopharyngeal carcinoma in the 3 arms.

Treatment	TPF regimen	TP regimen	GP regimen	*P*
Cycle of IC				<.001
1	3	3	9	
2	39	53	58	
3	15	19	7	
Cycle of CC				.424
0	8	15	8	
1	26	31	36	
2	23	29	20	
AC				.005
No	7	22	27	
Yes	50	53	47	

AC = adjuvant chemotherapy, CC = concurrent chemotherapy, IC = induction chemotherapy.

4.4. Analysis of treatment failure

Overall, 37 (18.0%) of 206 patients experienced treatment failure, 8 (3.9%) experienced locoregional relapse, 9 (4.4%) experienced locoregional relapse and distant metastasis, and 20 (9.7%) experienced distant metastasis alone. Among these patients, 1 in the TPF arm, 5 in the TP arm, and 2 in the GP arm developed locoregional relapse; 2 in the TPF arm, 4 in the TP arm, and 3 in the GP arm developed locoregional relapse and distant metastases; 6 in the TPF arm, 4 in the TP arm, and 10 in the GP arm developed distant relapse. The patterns of treatment failure in patients with locoregionally advanced NPC are

Table 3

Tumor response to the treatment among the 3 arms.

Response	Nasopharyngeal tumor			*P*	Neck lymph node			*P*
	TPF (n, %)	TP (n, %)	GP (n, %)		TPF (n, %)	TP (n, %)	GP (n, %)	
IC								
CR	18 (31.6)	23 (40.4)	19 (25.6)	.951	21 (36.8)	29 (38.7)	30 (41.1)	.977
PR	37 (64.9)	49 (65.3)	52 (70.3)		35 (61.4)	44 (58.7)	41 (56.2)	
SD	2 (3.5)	3 (4.0)	3 (4.1)		1 (1.8)	2 (2.6)	2 (2.7)	
CCRT								
CR	52 (91.2)	69 (92.0)	72 (97.3)	.458	54 (94.7)	70 (93.3)	72 (98.6)	.502
PR	5 (8.8)	6 (8.0)	3 (2.7)		3 (5.3)	5 (6.7)	2 (1.4)	

IC = induction chemotherapy, CCRT = concurrent chemoradiotherapy, CR = complete remission, GP = gemcitabine/cisplatin, PR = partial remission, SD = stable disease, TP = docetaxel/cisplatin, TPF = docetaxel/cisplatin/fluorouracil.

summarized in Table 5. The median time to failure for the TPF, TP, and GP arms were 19 (range, 8–39 months), 15 (range, 6–55 months), and 18 months (range, 8–45 months), respectively.

4.5. Prognostic factors

The common potential prognostic factors included the patient age (<50 vs ≥50 years), patient sex (male vs female), T category (T1–3 vs T4), N-category (N0–1 vs N2–3), clinical stage (III vs IV), comorbidities (no vs yes), and IC regimen (TPF vs TP vs GP). We identified the factors that influenced the survival outcome and evaluated the prognostic role of these factors using the univariate and multivariate analyses. The univariate analysis showed that the 3-year PFS and OS of patients with stage III NPC were superior than those of patients with stage IVA–B NPC (3-year PFS: 93.4% vs 72.0%, $P < .001$; OS: 97.1% vs 81.4%, $P < .001$), and T1–3 resulted in the longer PFS and OS (Table 6). The multivariate analysis demonstrated that T category was an independent predictor of the DMFS ($P = .018$), PFS ($P = .006$), and OS ($P = .001$). However, the IC regimen was not an

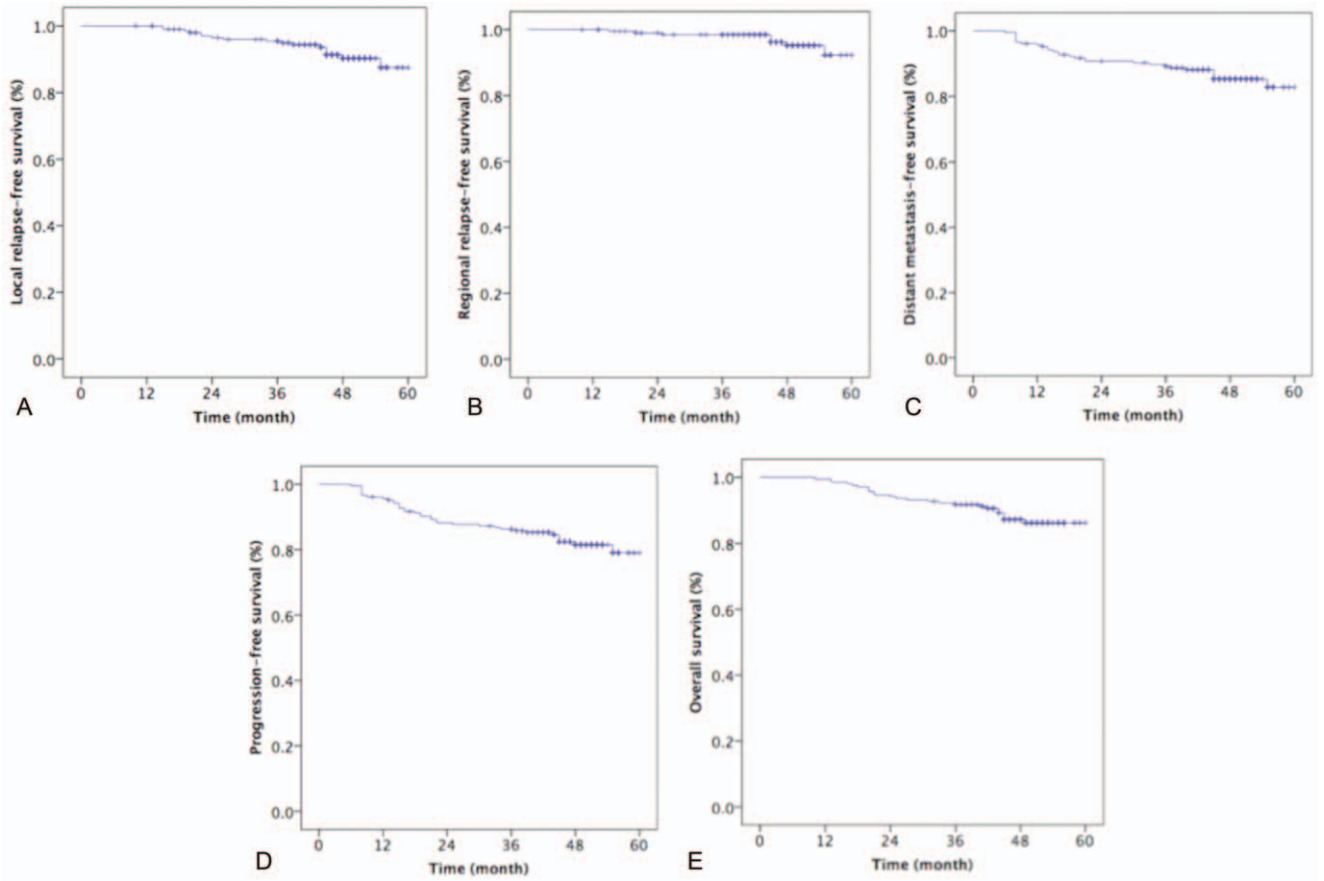

Figure 1. Kaplan-Meier estimates of the survival in 206 patients with nasopharyngeal carcinoma. A, Local relapse-free survival; (B) regional relapse-free survival; (C) distance metastasis-free survival; (D) progression-free survival; and (E) overall survival.

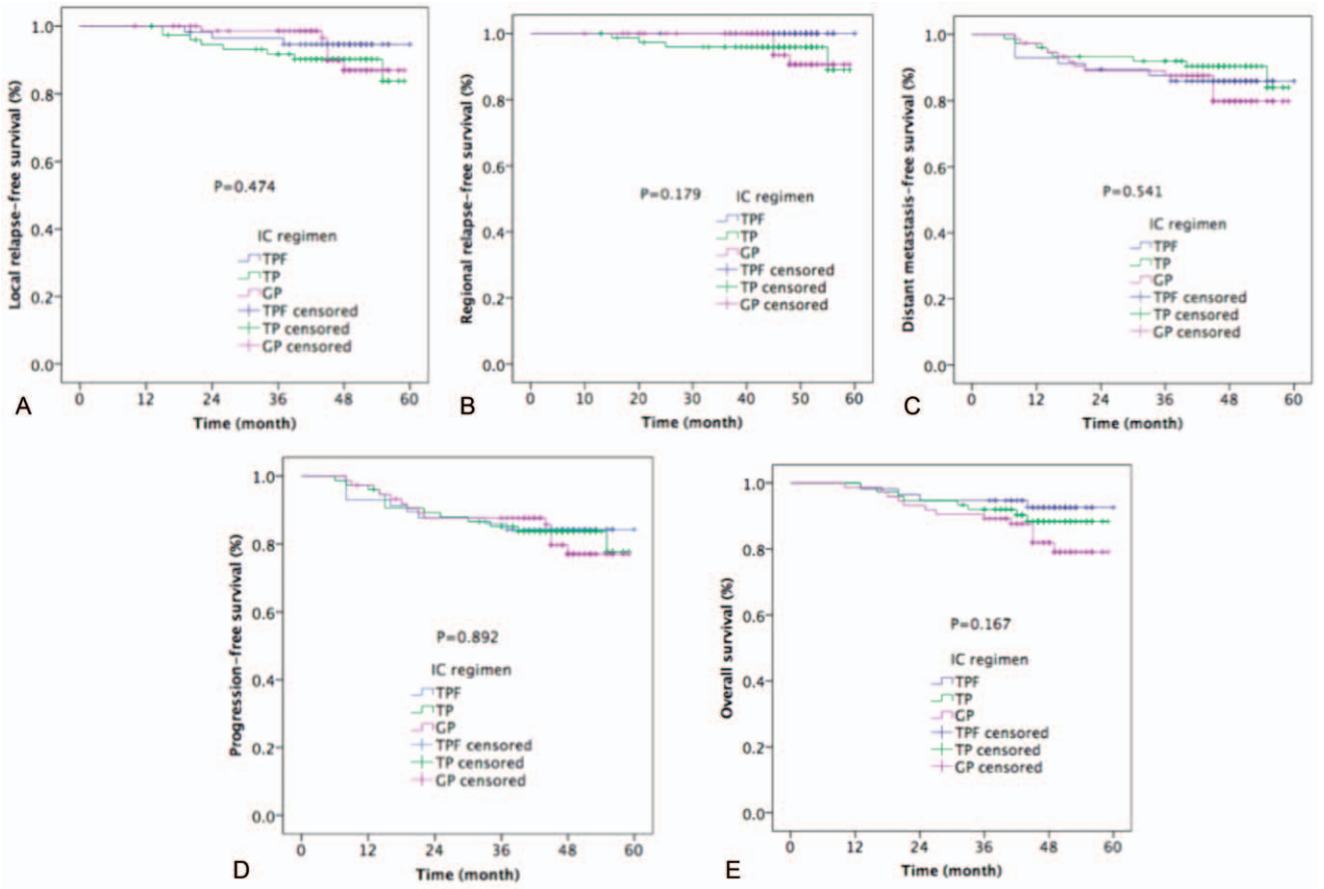

Figure 2. Kaplan-Meier estimates of the survival outcomes in nasopharyngeal carcinoma patients among the 3 arms. A, Local relapse-free survival; (B) regional relapse-free survival; (C) distance metastasis-free survival; (D) progression-free survival; and (E) overall survival. IC = induction chemotherapy, TP = docetaxel and cisplatin, TPF = docetaxel, cisplatin, and 5- fluorouracil.

independent prognostic factor for any survival outcomes (Table 7).

4.6. Safety and toxicity

The hematologic and nonhematologic toxicities were the most observed complications during the treatment. Grade 3/4 toxicities from the IC and CCRT regimen among the 3 arms are listed in Table 8. During the period of IC regimen, 57.8% (33/57) of the patients in the TPF arm, 18.7% (14/75) in the TP arm, and 21.6% (16/74) in the GP arm experienced grade 3/4 leucopenia ($P < .001$). Grade 3/4 neutropenia was reported in 42 (75.7%) patients in the TPF arm, 17 (22.7%) in the TP arm, and 31 (41.9%) in the GP arm ($P < .001$). Thrombocytopenia with

Table 4

Comparison of the survival outcomes between any 2 arms.

Comparison	TPF vs TP N=132	TPF vs GP N=131	TP vs GP N=149
3-Year LRFS	96.4% vs 91.7%	96.4% vs 98.6%	91.7% vs 98.6%
P^*	.286	.431	.560
3-Year RRFS	100% vs 95.9%	100% vs 100%	95.9% vs 100%
P^*	.090	.052	.983
3-Year DMFS	87.7% vs 91.9%	87.7% vs 89.0%	91.9% vs 89.0%
P^*	.554	.585	.273
3-Year PFS	86.0% vs 85.2%	86.0% vs 87.6%	85.2% vs 87.6%
P^*	.835	.610	.851
3-Year OS	94.7% vs 92%	94.7% vs 89.2%	92% vs 89.2%
P^*	.434	.069	.273

DMFS = distant metastases-free survival, IC = induction chemotherapy, GP = gemcitabine/cisplatin, LRFS = local relapse-free survival, OS = overall survival, PFS = progression-free survival, RRFS = regional relapse-free survival, TP = docetaxel/cisplatin, TPF = docetaxel/cisplatin/fluorouracil.

* P values were calculated using the log-rank test.

Table 5

Patterns of treatment failure.

Failure mode	TPF N = 57	TP N = 75	GP N = 74	*P*
Locoregional	1	5	2	.493
Locoregional and distant	2	4	3	
Distant	6	4	10	
Nonfailure	48	62	59	

GP = gemcitabine/cisplatin, TP = docetaxel/cisplatin, TPF = docetaxel/cisplatin/fluorouracil.

grade 3/4 toxicity was observed in one patient (1.8%) in the TPF arm, zero (0%) in the TP arm, and 14 (18.9%) in the GP arm ($P < .001$). The differences in other toxicities among the 3 arms were not statistically significant.

5. Discussion

Our results indicated that the differences in the LRFS, RRFS, DMFS, PFS, and OS among the 3 arms were not statistically significant. In addition, the incidence of leucopenia, neutropenia, and thrombocytopenia was lower in the TP arm than in the TPF and GP arms. Therefore, TP-based IC had similar efficacy when compared with TPF-based IC and GP-based IC, although TP-based IC had a lower incidence of toxicities.

Among the 3 arms (TPF, TP, and GP), the 3-year LRFS, RRFS, DMFS, PFS, and OS rates were 96.4%, 91.7%, and 98.6%; 100%, 95.9%, and 100%; 87.7%, 91.9%, and 89.0%; 86.0%, 85.2%, and 87.6%; and 94.7%, 92.0%, and 89.2%, respectively, and there were no statistically significant differences. We identified the potential prognostic factors, namely, the patient age, sex, T category, N category, clinical stage, comorbidities, and IC regimen. We found that age was an independent prognostic factor of the LRFS, and T category was an independent predictor of the DMFS, PFS, and OS.

Since TAX 323 and 324 studies had established TPF as the standard for IC to improve the survival outcomes in patients with head and neck cancer,[13,14] several studies have been conducted with taxane-containing IC regimen. Recently, Sun et al[16] reported that 3 cycles of TPF-based IC regimen before CCRT significantly improved the survival outcomes with the 3-year OS of 92%, 3-year failure-free survival of 80%, and 3-year DMFS of 90%. In a study by Kong et al,[28] the TPF-based IC regimen for the treatment of locoregionally advanced NPC showed a 3-year OS, PFS, DMFS, and LRFS of 94.8%, 78.2%, 90.5%, and 93.9%, respectively. Hassan et al. reported that the addition of the TP-based IC regimen to CCRT was a feasible option with good local control and manageable toxicity profile in patients with locoregionally advanced NPC.[29] In a randomized phase II trial by Hui et al,[17] 2 cycles of TP-based IC before CRT improved the 3-year OS rate compared with CRT alone (94.1% vs 67.7%, $P = .0112$).[17] In another phase II trial on the addition of TP to CCRT by Zhong et al,[30] the 3-year OS and PFS rates were 94.1% and 72.7%, respectively. A GP-based regimen conferred survival benefits in patients with recurrent or metastatic NPC.[20] Yau et al[31] retrospectively reported that the GP regimen is a well-tolerated and effective regimen with the overall response rate of >90%, and the 3-year OS and DFS rates of 76% and 63%, respectively. He et al[32]

Table 6

Univariate analysis of the prognostic factors of the survival outcomes of 206 nasopharyngeal carcinoma patients.

Characteristics	N	OS (%)	*P*	PFS (%)	*P*
Age, y			.459		.806
<50	115	92.2		85.0	
≥50	91	91.9		87.8	
Sex			.911		.781
Male	149	90.5		85.6	
Female	57	94.9		87.9	
T category			.002		.008
T1–3	156	94.9		89.7	
T4	50	82.0		75.0	
N category			.279		.427
N0–1	30	96.7		93.3	
N2–3	176	90.9		85.1	
Clinical stage			<.001		<.001
III	136	97.1		93.4	
IVA/B	70	81.4		72	
Comorbidity			.704		.169
No	159	91.2		84.1	
Yes	47	93.6		93.5	
IC regimen			.167		.892
TPF	57	94.7		86.0	
TP	75	92.0		85.2	
GP	74	89.2		87.6	

GP = gemcitabine/cisplatin, IC = induction chemotherapy, OS = overall survival, PFS = progression-free survival, TP = docetaxel/cisplatin, TPF = docetaxel/cisplatin/fluorouracil.

Table 7

Summary of the multivariate analyses of the prognostic factors in 206 nasopharyngeal carcinoma patients.

Endpoint	Factors	HR	95% CI	P
LRFS	Age: <50 vs ≥50 years	0.217	0.065–0.723	.013
	Sex: male vs female	0.707	0.259–1.933	.499
	T category*: T1–3 vs T4	0.434	0.155–1.213	.111
	N category*: N0–1 vs N2–3	1.068	0.332–3.436	.912
	Comorbidity: no vs yes	1.215	0.408–3.613	.726
	IC regimen: TPF vs TP	0.922	0.219–3.876	.912
	IC regimen: TPF vs GP	1.766	0.601–5.187	.301
RRFS	Age: <50 vs ≥50 years	0	0–6.170E+124	.936
	Sex: male vs female	0.632	0.143–2.787	.545
	T category*: T1–3 vs T4	0.730	0.137–3.881	.712
	N category*: N0–1 vsN2–3	0.876	0.158–4.850	.879
	Comorbidity: no vs yes	1.123	0.263–4.792	.876
	IC regimen: TPF vs TP	0	0–1.935E+142	.950
	IC regimen: TPF vs GP	1.537	0.378–6.256	.549
DMFS	Age: <50 vs ≥50 years	1.183	0.533–2.628	.679
	Sex: male vs female	1.142	0.503–2.594	.251
	T category*: T1–3 vs T4	0.397	0.185–0.851	.018
	N category*: N0–1 vs N2–3	0.382	0.089–1.631	.194
	Comorbidity: no vs yes	1.569	0.587–4.191	.369
	IC regimen: TPF vs TP	0.651	0.257–1.653	.367
	IC regimen: TPF vs GP	0.508	0.103–1.273	.149
PFS	Age: <50 vs ≥50 years	0.827	0.406–1.685	.601
	Sex: male vs female	0.987	0.482–2.018	.971
	T category*: T1–3 vs T4	0.383	0.194–8.757	.006
	N category*: N0–1 vs N2–3	0.604	0.210–1.737	.350
	Comorbidity: no vs yes	2.179	0.830–5.721	.114
	IC regimen: TPF vs TP	0.727	0.301–1.757	.479
	IC regimen: TPF vs GP	0.837	0.379–1.845	.659
OS	Age: <50 vs ≥50 years	0.868	0.368–2.046	.746
	Sex: male vs female	1.067	0.442–2.578	.885
	T category*: T1–3 vs T4	0.263	0.119–0.585	.001
	N category*: N0–1 vs N2–3	0.402	0.092–1.759	.226
	Comorbidity: no vs yes	1.439	0.528–3.925	.477
	IC regimen: TPF vs TP	0.318	0.097–1.046	.059
	IC regimen: TPF vs GP	0.533	0.212–1.343	.182

DMFS = distant metastasis-free survival, GP = gemcitabine/cisplatin, HR = hazard ratio, IC = induction chemotherapy, LRFS = local recurrence-free survival, PFS = progression-free survival, OS = overall survival, RRFS = regional recurrence-free survival, TP = docetaxel/cisplatin, TPF = docetaxel/cisplatin/fluorouracil.

*The American Joint Committee on Cancer staging system, 7th edition.

also indicated that the 3-year OS rate in patients with locoregionally advanced NPC was 87.7% after the GP-based IC regimen plus IMRT. A retrospective study performed by Jamshed et al[33] showed that the 5-year OS rate was 71%, and the incidence of acute grade 3 toxicities related to the GP regimen was only 4%.

Based on the above studies, the 3 IC regimens have shown excellent survival outcomes as first-line therapy for locoregion-

Table 8

Grade 3/4 acute toxicities from induction chemotherapy and concurrent chemoradiotherapy regimens among the 3 arms.

	During the period of IC				During the period of CCRT			
Adverse events	TPF	TP	GP	P	TPF	TP	GP	P
Hematologic								
Leucopenia	33	14	16	<.001	4	12	9	.294
Neutropenia	42	17	31	<.001	10	10	6	.265
Anemia	1	2	3	.731	0	0	3	.066
Thrombocytopenia	1	0	14	<.001	3	3	5	.755
Hepatotoxicity	1	0	2	.378	0	0	2	.165
Nephrotoxicity	0	0	0	-	0	0	0	-
Nonhematologic								
Mucositis	2	0	0	.071	3	4	5	.913
Dermatitis	0	0	0	-	1	0	2	.378
Diarrhea	1	0	0	.269	1	0	0	.269
Nausea/vomiting	1	1	0	.551	0	1	0	.416

CCRT = concurrent chemoradiotherapy, GP = gemcitabine/cisplatin, IC = induction chemotherapy, TP = docetaxel/cisplatin, TPF = docetaxel/cisplatin/fluorouracil.

ally advanced NPC; however, no trials comparing the efficacy and safety of TPF, TP, and GP have been reported. Therefore, we conducted a randomized study for comparing the efficacy and tolerability of additional TPF versus TP versus GP to CC and IMRT in patients with locoregional advanced NPC.

The hematologic and nonhematologic toxicities were most observed in patients with NPC during the period of treatment. The incidences of grade ≥3 leucopenia and neutropenia from TP were significantly lower than those from TPF and GP (18.7% vs 57.8% vs 21.6%, $P < .001$ and 22.7% vs 73.7% vs 41.9%, $P < .001$, respectively). The incidences of hematologic toxicities from TPF in our study were similar to those in the previous studies (range, 55%–83%).[13,14,28,34] Although all the patients in this study received prophylaxis leukocyte therapy using recombinant granulocyte colony-stimulating factor, many patients still experienced grade 3/4 leukocytopenia and neutropenia during IC and could continue with chemotherapy without delay by receiving granulocyte colony-stimulating factor. In addition, the incidence of grade 3/4 thrombocytopenia was significantly higher in the GP arm than in the TPF and TP arms (18.9% vs 1.8% vs 0%, $P < .001$). Owing to this reason, compliance of more than 2 cycles of IC was significantly lower in the GP arm than in the other 2 arms ($P < .001$).

Although the survival outcomes in patients with locoregionally advanced NPC were similar for the 3 arms before CCRT, the TP-based IC regimen showed low grade 3/4 hematologic toxicities than the other 2 regimens. The limitation of this study includes the small sample size and short follow-up periods. Therefore, further randomized, controlled, multicenter phase III clinical trials are needed for assessing the complete efficacy and toxicity of the TP-based IC regimen.

In conclusion, this study suggests that the TP-based IC regimen before IMRT plus CC could yield similar disease response, LRFS, RRFS, DMFS, PFS, and OS compared with the TPF- and GP-based IC regimens in patients with locoregionally advanced NPC; however, TP-based IC regimen had a lower toxicity profile. The results of this study need to be confirmed using long-term, large-scale clinical trials.

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