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

Fangzheng Wang, MD\textsuperscript{a,b,c,d,*}, Jiang Chuner, MD\textsuperscript{a,e}, Wang Lei, MD\textsuperscript{a,b,c,d}, Yan Fengqin, MD\textsuperscript{a,b,c,d}, Ye Zhimin, MD\textsuperscript{a,b,c,d}, Sun Quanquan, MD\textsuperscript{a,b,c,d}, Liu Tongxin, MD\textsuperscript{a,b,c,d}, Fu Zhenfu, MD\textsuperscript{a,b,c,d}, Jiang Yangming, MD\textsuperscript{f,*}

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 ($P > 0.05$). 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.

Editor: Giandomenico Roviello.

This study was supported by grants from the Medical and Health Science and Technology Program of Zhejiang Province (No. 2020KY064, No. 2019KY041, No. 2013KYB033, No. 2009B206, No. 2006A016, No. 2005B012, No. 2004B014) and National Natural Science Foundation of China (No. 81502646, No. 81502647).

The authors declare that they have no competing interests.

Data availability statement: The datasets generated and analyzed during the study are available from the corresponding author upon reasonable request.

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

*Department of Radiation Oncology, Cancer Hospital of University of Chinese Academy of Sciences, 3Department of Radiation Oncology, Zhejiang Cancer Hospital, 2Institute of Cancer Research and Basic Medical Sciences of Chinese Academy of Sciences, 4Zhejiang Key Laboratory of Radiation Oncology, 5Department of Breast Tumor Surgery, Zhejiang Cancer Hospital, Zhejiang Hangzhou, 6Department of Digital Earth, Institute of Remote Sensing and Digital Earth, CAS, Beijing, People’s Republic of China.

Correspondence: Fangzheng Wang, Department of Radiation Oncology, Cancer Hospital of University of Chinese Academy of Sciences (e-mail: wangfz76@126.com).
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 1.5 to 50 cases per 100,000 people. Because of the anatomical location of nasopharynx and its high sensitivity to irradiation, radiotherapy (RT) is regarded as a primary 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). 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. In addition, >70% of patients are diagnosed with locoregionally advanced NPC. 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. In contrast, induction chemotherapy (IC) can improve patients’ tolerability, eradicate micrometastases, and protect normal tissues by reducing tumors when compared with 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.

The results from previous studies indicated that IC plus RT did not provide any survival benefit when compared with RT alone. 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. 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. In a randomized phase II trial reported by Hui et al, 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 TPF-based IC regimen is associated with similar efficacy and less toxicity than the TPF regimen.

The combination of gemcitabine and cisplatin (GP) has been proven to have synergistic cytotoxic effects in vitro. 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. Zheng et al reported that the GP regimen prolonged the OS and had the tendency to increase the DMFS. Zhao et al 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.

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 locoregionally 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. 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/m²/day on day 1, cisplatin 25 mg/m²/day on days 1–3, and 5-fluorouracil 500 mg/m²/day on days 1–3), TP (docetaxel 60 mg/m²/day on day 1, cisplatin 25 mg/m²/day on days 1–3), and GP regimens (gemcitabine 1000 mg/m²/day on days 1 and 8, cisplatin 25 mg/m²/day on days 1–3).

Moreover, patients with NPC in this study underwent ≥1 cycle of CC with cisplatin (80 mg/m²) divided over 3 days, and 150 patients received 2 to 3 courses of CC with the PF regimen (cisplatin 25 mg/m²/day on days 1–3 and 5-fluorouracil 500 mg/m²/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 fibroscope 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 fibroscope, 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 trial 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 trial 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,
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).

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 1

| Characteristics     | TPF regimen N=57 | TP regimen N=75 | GP regimen N=74 | \( X^2 \) | \( P \) |
|---------------------|------------------|-----------------|-----------------|---------|-------|
| Sex                 |                  |                 |                 |         |       |
| Male                | 41               | 53              | 53              | 0.029   | .986  |
| 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.

### Table 2

| Treatment | TPF regimen | TP regimen | GP regimen | \( P \) |
|-----------|-------------|------------|------------|--------|
| Cycle of IC|             |            |            | <.001  |
| 1         | 3           | 3          | 9          |        |
| 2         | 39          | 53         | 58         |        |
| 3         | 15          | 19         | 17         |        |
| 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.
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

| Table 3 |
| Tumor response to the treatment among the 3 arms. |

| Response | Nasopharyngeal tumor | Neck lymph node |
|----------|----------------------|------------------|
|          | 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.
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

![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) distant metastasis-free survival; (D) progression-free survival; and (E) overall survival. IC = induction chemotherapy, TP = docetaxel and cisplatin, TPF = docetaxel, cisplatin, and 5-fluorouracil.

Table 4

| 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            | .600           |
| 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% |
| $P^*$            | .825            | .610            | .351           |
| 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/5-fluorouracil.

* $P$ values were calculated using the log-rank test.
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] reported that...
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-
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%). Although all the patients in this study received prophylaxis leucocyte therapy using recombinant granulocyte colony-stimulating factor, many patients still experienced grade 3/4 leucocytopenia and neutropenia during IC and could continue with chemotherapy without delay by receiving granulocyte colony-stimulating factor. In conclusion, 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, multicentre phase III clinical trials are needed for assessing the complete efficacy and toxicity of the TP-based IC regimen.

The hematologic and nonhematologic toxicities were most advanced by receiving granulocyte colony-stimulating factor. In 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 conclusion, 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, multicentre 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, LRRS, RRRS, DMFS, DFS, 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.

**Author contributions**

Conceptualization: Zhenfu Fu.
Data curation: Jiang Chuner.
Formal analysis: Jiang Yangming.
Funding acquisition: Fangzheng Wang, Sun Quanquan, Liu Tongxin.
Investigation: Wang Lei, Yan Fengqin, Ye Zhimin, Sun Quanquan, Liu Tongxin.
Project administration: Ye Zhimin, Lei Wang, Fengqin Yan, Zhimin Ye, Quanquan Sun, Liu Tongxin.
Supervision: Fu Zhenfu.
Writing – original draft: Fangzheng Wang, Sun Quanquan, Liu Tongxin.
Writing – review & editing: Jiang Yangming, Fu Zhenfu.

**References**

[1] Tang Li, Chen WQ, Xue WQ, et al. Global trends in incidence and mortality of nasopharyngeal carcinoma. Cancer Lett 2016;374: 22–30.

[2] Zhang B, Mo Z, Du W, et al. Intensity-modulated radiation therapy versus 2D-RT or 3D-RT for the treatment of nasopharyngeal carcinoma: a systematic review and meta-analysis. Oral Oncol 2015;51:1041–6.

[3] Lee N, Harris J, Garden AS, et al. Intensity-modulated radiation therapy with or without chemotherapy for nasopharyngeal carcinoma: Radiation Therapy Oncology Group phase II trial 0225. J Clin Oncol 2009;27:3684–90.

[4] Lee AW, Ng WT, Chan LK, et al. The strength/weakness of the AJCC/UICC staging system (7th edition) for nasopharyngeal carcinoma and suggestions for future improvement. Oral Oncol 2012;48:1007–13.

[5] Chen L, Mao YP, Xie FY, et al. The seventh edition of the UICC/AJCC staging system for nasopharyngeal carcinoma is prognostically useful for patients treated with intensity-modulated radiotherapy from an endemic area in China. Radiother Oncol 2012;104:331–7.

[6] Mao YP, Xie FY, Liu LZ, et al. Re-evaluation of 6th edition of AJCC staging system for nasopharyngeal carcinoma and proposed improvement based on magnetic resonance imaging. Int J Radiat Oncol Biol Phys 2009;73:1326–34.

[7] Chen L, Hu CS, Chen XZ, et al. Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomised controlled trial. Lancet Oncol 2012;13:163–71.

[8] National Comprehensive Cancer Network. NCCN Guidelines. Available at: http://www.nccn.org/professionals/physicians_gls/g_guidelines.asp. Accessed: July 9, 2015.

[9] Cirtkovic F, Eschwege F, Rahal M, et al. International Nasopharynx Cancer Study Group VUMC I trial Preliminary results of a randomized trial comparing neoadjuvant chemotherapy (cisplatin, etoposide, bleomycin) plus radiotherapy vs. radiotherapy alone in stage IV (> or = N2, M0) undifferentiated nasopharyngeal carcinoma: a positive effect on progression-free survival. Int J Radiat Oncol Biol Phys 1996;35:463–9.

[10] Chua DT, Sham JS, Choy D, et al. Preliminary report of the Asian-Oceanian Clinical Oncology Association randomized trial comparing cisplatin and etoposide followed by radiotherapy versus radiotherapy alone in the treatment of patients with locoregionally advanced nasopharyngeal carcinoma. Asian-Oceanian Clinical Oncology Association randomised trial comparing neoadjuvant chemotherapy plus radiotherapy with radiotherapy alone in patients with advanced nasopharyngeal carcinoma. J Clin Oncol 2001;19:1350–7.

[11] Ma J, Mai HQ, Hong MH, et al. Results of a prospective randomized trial comparing neoadjuvant chemotherapy plus radiotherapy with radiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma. J Clin Oncol 2009;27:2421–7.

[12] Harayama M, Sakata K, Shirota H, et al. A prospective, randomized trial comparing neoadjuvant chemotherapy with radiotherapy alone in patients with advanced nasopharyngeal carcinoma. Cancer 2002;94:2217–23.

[13] Vermorken JB, Remenar E, Van Herpen C, et al. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med 2007;357:1695–704.

[14] Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med 2007;357:1705–15.

[15] Pointreau Y, Garaud P, Chaptet S, et al. Randomized trial of induction chemotherapy with cisplatin and 5-fluorouracil with or without docetaxel for larynx preservation. J Natl Cancer Inst 2009;101:498–506.

[16] Sun Y, Li WF, Chen NY, et al. Induction chemotherapy plus concurrent chemotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial. Lancet Oncol 2016;17:1509–20.

[17] Hui EP, Ma BB, Leung SF, et al. Randomized phase III trial comparing cisplatin-radiation therapy with or without neoadjuvant docetaxel and cisplatin in advanced nasopharyngeal carcinoma. J Clin Oncol 2009;27:429–42.

[18] Wang F, Jiang C, Wang L, et al. Addition of 5-fluorouracil to first-line induction chemotherapy with docetaxel and cisplatin before concurrent chemoradiotherapy does not improve survival in locoregionally advanced nasopharyngeal carcinoma. Oncotarget 2017;8:91130–61.

[19] Bergman AM, Ruiz van Haperen VW, Veerman G, et al. Synergistic interaction between cisplatin and gemcitabine in vitro. Clin Cancer Res 1996;2:521–30.

[20] Zhang L, Huang Y, Hong SD, et al. Gemcitabine plus cisplatin versus fluorouracil plus cisplatin in recurrent or metastatic nasopharyngeal carcinoma: a multicentre, randomised, open-label, phase 3 trial. Lancet 2016;388:1883–92.

[21] Zheng W, Qiu SF, Huang LL, et al. Is gemcitabine and cisplatin induction chemotherapy superior in locoregionally advanced nasopharyngeal carcinoma? Pak J Med Sci 2015;31:781–6.
[22] Zhao LN, Xu M, Jiang W, et al. Induction chemotherapy for the treatment of non-endemic locally advanced nasopharyngeal carcinoma. Oncotarget 2017;8:6763–74.

[23] Wang FZ, Sun QQ, Jiang CE, et al. Gemcitabine/cisplatin induction chemotherapy before concurrent chemotherapy and intensity-modulated radiotherapy improves outcomes for locoregionally advanced nasopharyngeal carcinoma. Oncotarget 2007;8:96798–7808.

[24] Wang FZ, Jiang CE, Wang L, et al. Outcome and long-term efficacy of four facio-cervical fields conformal radiotherapy for nasopharyngeal carcinoma. Oncotarget 2016;8:39756–65.

[25] Wang FZ, Jiang C, Ye ZM, et al. Efficacy and safety of nimotuzumab with neoadjuvant chemotherapy followed by concurrent chemoradiotherapy for locoregionally advanced nasopharyngeal carcinoma. Oncotarget 2017;8:75544–56.

[26] Wang FZ, Jiang CE, Ye ZM, et al. Association of the neoadjuvant chemotherapy cycle with survival outcomes in patients with locoregionally advanced nasopharyngeal carcinoma: a propensity-matched analysis. Oncotarget 2017;8:94127–38.

[27] Wang FZ, Jiang CE, Ye ZM, et al. Long-term use of nimotuzumab in combination with intensity-modulated radiotherapy and chemotherapy in the treatment of locoregionally advanced nasopharyngeal carcinoma: experience of a single institution. Oncol Res 2018;26:277–87.

[28] Kong L, Zhang YW, Hu CS, et al. Effects of induction docetaxel, platinum, and fluorouracil chemotherapy in patients with stage III or IV A/B nasopharyngeal cancer treated with concurrent chemoradiation therapy: final results of 2 parallel phase clinical trial. Cancer 2017;124:2258–67.

[29] Hassan E, Galai K, Esmat E. Neo-adjuvant docetaxel and cisplatin followed by concurrent cisplatin with radiation therapy in treatment of locally advanced nasopharyngeal carcinoma. Gulf J Oncolog 2008;10:46–53.

[30] Zhong YH, Dai J, Wang XY, et al. Phase II trial of neoadjuvant docetaxel and cisplatin followed by intensity-modulated radiotherapy with concurrent cisplatin in locally advanced nasopharyngeal carcinoma. Cancer Chemother Pharmacol 2013;71:1377–83.

[31] Yau TK, Lee AW, Wong DH, et al. Treatment of stage IV(A-B) nasopharyngeal carcinoma by induction-concurrent chemoradiotherapy and accelerated fractionation: impact of chemotherapy schemes. Int J Radiat Oncol Biol Phys 2006;66:1004–10.

[32] He X, Ou D, Ying H, et al. Experience with combination of cisplatin plus gemcitabine chemotherapy and intensity-modulated radiotherapy for locoregionally advanced nasopharyngeal carcinoma. Eur Arch Otorhinolaryngol 2012;269:1027–33.

[33] Jamshed A, Hussain R, Iqbal H. Gemcitabine and Cisplatin followed by chemo-radiation for advanced nasopharyngeal carcinoma. Asian Pac J Cancer Prev 2014;15:899–904.

[34] Bae WK, Hwang JE, Shim HJ, et al. Phase II study of docetaxel, cisplatin, and 5-FU induction chemotherapy followed by chemoradiotherapy in locoregionally advanced nasopharyngeal cancer. Cancer Chemother Pharmacol 2010;65:589–95.