·Original Article·

Neoadjuvant chemotherapy followed by concurrent chemoradiation for locally advanced nasopharyngeal carcinoma

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[**Abstract**] **Background and Objective:** Concurrent chemoradiation therapy (CCRT) is the standard treatment for patients with locally advanced nasopharyngeal carcinoma (NPC). The effect of neoadjuvant chemotherapy followed by CCRT has not been determined. Therefore, we conducted 2 phase II studies to evaluate the efficacy and safety of neoadjuvant chemotherapy with a regimen of docetaxel, cisplatin, and 5-fluorouracil (5-Fu) (TPF) followed by radiotherapy and concurrent cisplatin in patients with stage-III and -IV (A – B) NPC. This article is the preliminary report on treatment-related toxicities and response. **Methods:** Graded according to the 2002 American Joint Committee on Cancer (AJCC) staging criteria, only patients with stage-III or -IV(A - B) poorly differentiated or undifferentiated NPC (World Health Organization type II/III) were included. We planned to recruit 52 patients with stage-III disease and 64 patients with stage-IV(A – B) disease. All patients received neoadjuvant chemotherapy with TPF (docetaxel 75 mg/m^2, day 1; cisplatin 75 mg/m^2, day 1; 5-Fu 500 mg/(m^2·day), continuous intravenous infusion for 120 h), every 3 weeks for 3 cycles, followed by weekly cisplatin (40 mg/m^2) concurrent with radiotherapy. Three-dimensional conformal radiotherapy (3D-CRT) and intensity-modulated radiotherapy (IMRT) were used. Gross disease planning target volume (PTV), high-risk and low-risk subclinical PTV doses were prescribed at 70–76 Gy, 66–70 Gy, and 60–61.25 Gy at 1.75–2.0 Gy per fraction. The lower neck or supraclavicular fields may be treated with conventional AP/PA fields for a total of 54 Gy at 1.8 Gy per fraction. Patients were evaluated for tumor response after the completion of neoadjuvant chemotherapy, and at 3 months after radiation according to the Response Evaluation Criteria In Solid Tumors (RECIST). The latest version of the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE 3.0) was used for grading all adverse events. **Results:** Fifty-nine patients were evaluable for treatment response. Thirty patients had stage-III disease and 29 patients had stage-IV (A–B). All patients completed RT to the prescribed dose and 2 cycles of neoadjuvant chemotherapy, with 51 patients (86.4%) completing 3 cycles. A total of 50 (84.7%) and 39 patients (66.1%) completed 4 weeks and 5 weeks of cisplatin during CCRT, respectively. The overall response rate in the primary site and the neck region were 94.9% [complete response (CR) in 25.4%] and 100% (CR in 19.6%) after completing neoadjuvant chemotherapy. At 3 months after RT, the CR rates increased to 96.6% and 90.2%, respectively. After a median follow-up of 14.3 months, we observed 5 treatment failures and 2 deaths. The 1-year overall survival, distant metastasis-free survival, and locoregional relapse-free survival rates were 100%, 95.7%, and 97.7%, respectively. The rates of grade 3/4 myelosuppression and anorexia/nausea/vomiting during neoadjuvant chemotherapy were 55.9% and 16.9%, respectively. The corresponding rates were 11.9% and 23.7% during CCRT. Grade 3/4 mucositis, skin desquamation, and xerostomia occurred in 6.8%, 44.1%, and 27.1% of patients, respectively. There were no treatment-related deaths. **Conclusions:** Neoadjuvant chemotherapy with TPF followed by CCRT was well tolerated with a manageable toxicity profile. Preliminary results are encouraging and warrant further investigation.

Key words: Nasopharyngeal neoplasm, concurrent/neoadjuvant, chemotherapy, radiotherapy

Nasopharyngeal carcinoma (NPC) is prevalent in Southeast Asia. Radiotherapy can control early stage NPC effectively. However, for patients with locoregionally advanced NPC, which has higher rates of locoregional relapse and distant metastasis, radiotherapy alone can only achieve a 5-year survival rate of about 50%. As a result, to improve the treatment efficacy for

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locoregionally advanced NPC, various phase III clinical trials on treatment modalities combining radiotherapy and chemotherapy have been launched since the 1990s, and concurrent chemoradiation therapy (CCRT) was finally defined as the standard treatment strategy for patients with locoregionally advanced NPC [1-6]. To improve treatment outcomes further, neoadjuvant chemotherapy combined with CCRT gradually became the focus of clinical research. Many phase III clinical trials from western countries have proved that compared with the PF [ciplatin (DDP) + 5-fluorouracil (5-Fu)] chemotherapy regimen, neoadjuvant chemotherapy adding taxanes to the PF regimen (TPF regimen) could significantly improve treatment outcomes [7-9] for patients with head and neck squamous cell carcinoma. However, there have not been any reports on the TPF regimen applied to Chinese patients. Hence in early 2007, investigators at Fudan University Shanghai Cancer Center carried out 2 prospective phase II clinical trials on patients with locoregionally advanced stage-III and -IV(A–B) NPC, to evaluate the efficacy and safety of neoadjuvant chemotherapy of the TPF regimen combined with CCRT. This paper will give a preliminary report on the toxicity and short-term treatment outcomes of this treatment modality.

Materials and Methods

Enrollment Criteria

Patients that met the following criteria were enrolled: (1) age > 18 years and < 70 years; (2) pathology proven to be World Health Organization (WHO) type II/III NPC; (3) stage III/IV(A-B) according to the 2002 American Joint Committee on Cancer (AJCC) staging criteria; (4) no distant metastasis; (5) expected lifespan of at least 6 months; (6) Karnofsky Performance Scale (KPS) score was more than 70; (7) Neutrophil count > 2×10^9/L and platelet count > 100×10^9 /L before treatment; (8) Bilirubin < 1.5 mg/dL, AST/ALT < 2 times the upper limits of normal, serum creatinine < 1.5 mg/dL, creatinine clearance rate > 50 mL/min before treatment; and (9) informed consent was signed before treatment. A total of 52 patients with stage-III NPC and 64 patients with stage-IV(A–B) were planned to be enrolled.

Exclusion criteria included: pathology types that were not WHO II/III NPC; distant metastasis discovered by clinical or imaging examination; previous radiotherapy to the head and neck region; previous surgery in the primary tumor site or neck, except for diagnostic biopsy; history of malignant tumors or simultaneous multiple tumors, except for basal cell carcinoma of the skin; a positive pregnancy test result for women of reproductive age; accompanying disease or status influencing the normal enrollment of patients or safety during the research; active mental disorders or other mental disorders that influenced the patient's signature on the informed consent or comprehensibility; uncontrolled active infections; and participation in other clinical research at the same time.

Treatment

Patients received radiotherapy by three-dimensional conformal (3D-CRT) or intensity modulated radiotherapy (IMRT) techniques. Gross tumor volume (GTV) referred to tumor extent found in clinical and imaging examinations, including primary tumor (GTV-P) and metastatic lymph nodes (GTV-N). To ensure that the pterygomaxillary fossa and areas of lymph node drainage of the upper neck (retropharyngeal lymph nodes and levels II, III, and Va) were included, clinical target volume (CTV) consisted of a certain margin surrounding the GTV, the whole nasopharynx cavity, the anterior one- to two-thirds of the clivus (when invaded, the whole clivus should be covered), the skull base, the pterygoid plates, the parapharyngeal space, the inferior sphenoid sinus (the whole sphenoid sinus should be covered for stages T3 and T4), the posterior one-quarter to one-third of the nasal cavity and the maxillary sinus. Level Ib was at high risk in patients with metastatic lymph nodes in level IIa, and any lymph node drainage pathways containing metastatic lymph nodes were at high risk. Low-risk CTV referred to levels IV and Vb without metastatic cervical lymph nodes.

In 3D-CRT, high-risk GTV-P, GTV-N, and CTV were given a radiation dose of 60 Gy/30 fractions, followed by 10–14 Gy/5–7 fractions to GTV-P and 6–10 Gy/3–5 fractions to GTV-N. Due to the shortage of machine resources, most of the patients receiving IMRT used a simplified IMRT technique to shorten the radiation time in each fraction, with prescription doses of 70 Gy, 66.5/68.25 Gy, and 61.25 Gy (in 35 fractions) for high-risk GTV-P, GTV-N, and CTV, respectively. Part of the patients were given boost irradiation doses of 4–6 Gy/2–3 fractions to the residual focus in the nasopharynx or the neck. CTV at low risk was radiated by 54 Gy/30 fractions in the anterior-posterior fields.

All patients received neoadjuvant chemotherapy before radiotherapy with the TPF regimen [docetaxel 75 mg/m^2, day 1; cisplatin 75 mg/m^2, day 1; 5-Fu 500 mg/ (m^2·day), continuous intravenous infusion (CIV) for 120 h], every 3 weeks for 3 cycles. Dose titration of the neoadjuvant chemotherapy was the following. Complete blood count, liver function, and renal function were tested before each chemotherapy course, and only patients with a qualifying index (see enrollment criteria) could proceed with the next chemotherapy course. Chemotherapy was postponed in patients with hematologic index disqualification. The dosage of docetaxel was decreased by 20% with constant cisplatin and 5-Fu dosages if a grade IV hematology adverse event or febrile neutropenia emerged in the former course. All of the dosages of docetaxel, cisplatin, and 5-Fu were decreased by 20% if more than grade III mucositis or diarrhea happened in the former course. Concurrent chemoradiotherapy would be given after 3 courses of neoadjuvant chemotherapy as planned.

Concurrent chemotherapy consisted of weekly cisplatin (40 mg/m^2) during radiotherapy, with a maximum of 7 courses. Dose adjustments of concurrent chemotherapy went as follows. Complete blood count and serum biochemistry were tested before each course of chemotherapy, and only patients with a qualifying index (see enrollment criteria) could proceed with next course. Chemotherapy at the full dose would be delivered strictly according to the treatment protocol, and no adjustment would be allowed under any situation. The chemotherapy time could be postponed if neutropil < 2×10^9/L or platelets < 100×10^9/L. Chemotherapy could be suspended if the creatinine clearance

rate < 50 mL/min.

Treatment outcome and safety evaluation

Short-term treatment outcomes were evaluated according to physical examinations and magnetic resonance imaging (MRI) of the head and neck after neoadjuvant chemotherapy and 3 months after radiotherapy. According to the Response Evaluation Criteria in Solid Tumors (RECIST), short-term treatment outcomes were divided into complete remission (CR), partial remission (PR), stable disease (SD), and progressive disease (PD). Adverse events were evaluated according to the latest version of the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI CTCAE 3.0).

Statistical analysis

SPSS16.0 was used for statistical analysis. Descriptive statistics were used in summarizing the safety analysis. Survival rates were calculated with the Kaplan-Meier method. Each observation index was calculated from the commencement date of the cancer treatment.

Results

Common conditions

This study analyzed 59 patients who were followed for 3 months. The median follow-up time was 14.3 months (3.1–24.6 months). The median age was 44 years (21–69 years). The study included 46 men (78%) and 13 women (22%). The number of patients with stage-III and stage-IV(A–B) disease were 30 (50.8%) and 29 (49.2%), respectively.

Treatment outcome

The effectiveness of neoadjuvant chemotherapy to the primary tumor and cervical lymph nodes were 94.9% (CR rate was 25.4%) and 100% (CR rate was 19.6%), respectively. Short-term treatment outcomes were evaluated 3 months after treatment, and the efficacy and the CR rate of the primary tumor rose to 100% and 96.6%, respectively, with the CR rate of cervical lymph nodes rising to 90.2% (Table 1). Treatment failure was observed in 5 patients during follow-up, including 1 patient with lymph node relapse alone, 2 patients with distant metastasis alone, 1 patient with primary tumor and cervical lymph node relapse, and 1 patient with cervical lymph node relapse and distant metastasis. Two patients died. The rates of 1-year overall survival (Figure 1), distant metastasis-free survival, and locoregional relapse-free survival were 100%, 95.7%, and 97.7%, respectively.

Adverse events

All patients completed at least 2 courses neoadjuvant chemotherapy, and 51 (86.4%) patients completed 3 courses. Chemotherapy dosage was decreased in 14 (23.7%) patients due to adverse events, including 12 patients in the second course and 2 in the third course. The median course of concurrent chemotherapy was 5 (1–7 courses). The number of patients who finished at least 5 or 4 courses of concurrent chemotherapy totaled 39 (66.1%) and 50 (84.7%), respectively. The incidence of severe bone marrow suppression and gastrointestinal reactions during neoadjuvant chemotherapy was 55.9% and 16.9%, respectively. The incidence of severe bone marrow suppression and gastrointestinal reaction during concurrent chemotherapy was 11.9% and 23.7%, respectively, while the incidence of severe radiation dermatitis, mucositis, and xerostomia were 6.8%, 44.1%, and 27.1%, respectively. No severe liver or renal function damage was observed. No treatment-related deaths occurred. Treatment-related adverse events are detailed in Table 2.

Table 1 Response to neoadjuvant chemotherapy and concurrent chemoradiation therapy

Response	NP			LN		
	CR	PR	CR+PR	CR	PR	CR+PR
After neoadjuvant chemotherapy	25.4%	69.5%	94.9%	19.6%	80.4%	100%
3 months after CCRT	96.6%	3.4%	100%	90.2%	9.8%	100%

CCRT, concurrent chemoradiation therapy.

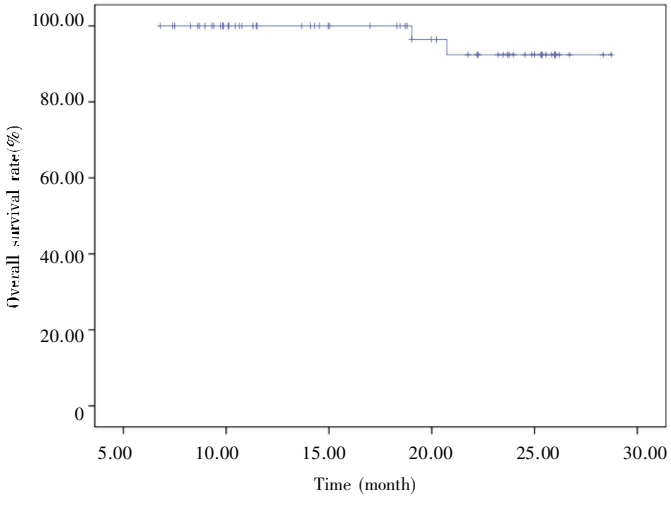

Figure 1 Overall survival rate of patients with NPC

Discussion

Satisfactory treatment outcomes for patients with early stage NPC can be achieved by radiotherapy alone, with the 5-year survival of 90% for patients with stage-I disease, and 70% for patients with stage-II disease. However, treatment results for patients with locoregionally advanced NPC have been

Table 2 Summary of acute adverse events during treatment

Event	During neoadjuvant chemotherapy acute adverse events ratio (%)				During CCRT acute adverse events ratio (%)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Leukopenia	20.3	27.1	30.5	8.5	22.0	54.2	8.5	0
Neutropenia	10.2	22.0	22.0	30.5	37.3	25.4	1.7	0
Neutropenic fever	0	0	18.6	1.7	0	0	0	0
Thrombocytopenia	5.1	0	0	0	11.9	5.1	6.8	0
Anemia	37.3	6.8	1.7	0	42.2	35.6	1.7	0
Nausea/vomiting	33.9	37.3	16.9	0	28.8	42.4	22.0	1.7
Diarrhea	16.9	13.6	1.7	0	0	0	0	0
Liver dysfunction	23.7	3.4	0	0	3.4	0	0	0
Kidney dysfunction	3.4	0	0	0	8.5	0	0	0
Mucositis	5.1	5.1	1.7	0	11.9	44.1	37.3	6.8
Skin reaction	0	0	0	0	44.0	49.2	6.8	0
Xerostomia	0	0	0	0	22.0	49.2	27.1	0

unsatisfactory, with the 5-year survival rate around 35% for patients with stage-IV (A – B) disease (AJCC staging criteria, 1997)[10-12]. NPC cells are sensitive to chemotherapy. As a result, oncologists have tried to combine chemotherapy to improve treatment outcomes for patients with locoregionally advanced NPC. After years of research, CCRT has recently become the standard treatment for patients with locoregionally advanced NPC [1-6].

For NPC patients with advanced N stages, especially those with metastatic lymph nodes in level IV, the risk of distant metastasis after treatment is far higher than locoregional relapse. Neoadjuvant chemotherapy is an effective way to control subclinical metastatic foci, and may be of great help in reducing the rate of distant metastasis, and hence improving overall survival. In patients with local large tumors or tumors close to critical normal tissue such as the brain stem, it is usually hard to deliver radiotherapy directly, and delivering full doses of radiation to tumors is always restricted by surrounding normal tissue. If tumors could shrink after neoadjuvant chemotherapy, it would benefit the design and delivery of radiotherapy.

However, compared to concurrent chemotherapy, phase III clinical trials have failed to prove that radiotherapy combined with neoadjuvant chemotherapy could improve the survival rate of patients with NPC with locoregionally advanced disease compared with radiotherapy alone[13-15]. However, meta-analyses have shown that combined neoadjuvant chemotherapy could significantly reduce the risks of locoregional relapse (RR, 0.74; 95% CI, 0.60–0.91; P = 0.005) and distant metastasis (RR, 0.67; 95% CI, 0.54–0.83; P = 0.0003)[16]. Recently, Chua *et al.*[17] conducted a pooled analysis for 2 randomized clinical trials that were similarly designed on neoadjuvant chemotherapy for patients with NPC. They collected data of 784 enrolled patients, reconstructed the database, and updated the follow-up results. The results showed that combined neoadjuvant chemotherapy brought down the rates of locoregional relapse (P = 0.037) and distant metastasis (P = 0.088), and significantly improved the rates of 5-year relapse-free survival (50.9% vs. 42.7%, P = 0.014) and disease-associated survival (63.5% vs. 58.1%, P = 0.029). Nevertheless, there was not any improvement in overall survival, with 5-year survival being 61.9% and 58.1%, and 7-year survival being 57.2% and 48%, respectively. Neoadjuvant chemotherapy could reduce the risk of locoregional relapse and distant metastasis, but this could not be converted to the improvement of overall survival. Insufficient intensity and effectiveness of the chemotherapy agents or insufficient intensity of the local treatment might be the cause. As a result, changing to neoadjuvant chemotherapy regimens based on taxanes combined with CCRT might improve treatment outcomes. Various phase III clinical trials on other head and neck squamous cell carcinomas besides NPC have proven that TPF was significantly better than traditional PF regimens[7-9].

In recent years, various phase II clinical trials have been conducted with patients with locoregionally advanced NPC to evaluate treatment efficacy of neoadjuvant chemotherapy combined with CCRT. All of them showed encouraging results, and the 3-year survival rates reached more than 70%[18-23]. The phase II randomized clinical trial reported by Hui *et al.*[23] from Hong Kong was the most representative one. Sixty-five patients with NPC were enrolled on this clinical trial and were randomly assigned to receive CCRT alone (the control group) or neoadjuvant chemotherapy combined with CCRT (the study group). Neoadjuvant chemotherapy with the TPF regimen was as follows: docetaxel 75 mg/m^2, day 1; cisplatin 75 mg/m^2, day 1, every 3 weeks for 2 cycles. The concurrent chemotherapy was as follows: weekly cisplatin 40 mg/m^2 concurrent with radiotherapy. Statistical results indicated that the rate of 3-year survival was significantly higher in the study group compared with the control group (94.1% vs. 67.7%, P = 0.012). Our study adopted TPF as the neoadjuvant chemotherapy regimen combined with CCRT for patients with locoregionally advanced NPC, and also achieved good short-term treatment results. Its long-term outcome still awaits further follow-up to be confirmed.

The most common adverse events during neoadjuvant chemotherapy based on taxanes was neutropenia, and the incidence of severe neutropenia was 37%–97%, whereas the incidence of febrile neutropenia was only 5.2%–12.0%[7-9,23]. Although neoadjuvant chemotherapy with higher treatment intensities were used, it seems that no significantly increased adverse events

were observed during CCRT. In the study by Hui *et al.* [23], incidence of adverse events such as severe neutropenia (15.3% vs. 26.4%, $P = 0.30$) and mucocitis (7.7% vs. 23.5%, $P = 0.11$) in the control and study groups were similar. In the present study, patients showed good tolerance and compliance to the TPF neoadjuvant chemotherapy combined with CCRT. All the patients finished at least 2 courses of neoadjuvant chemotherapy, including 51 (86.4%) patients who completed 3 courses. All patients received radiotherapy as planned, and 66.1% and 84.7% completed at least 5 or 4 courses concurrent chemotherapy, respectively. The incidence of severe neutropenia and febrile neutropenia caused by the TPF regimen was 52.5% and 20.3%, respectively, which was lower than those reported by Vermorken and Posner [8,9]. This might due to the relatively lower dose of 5-Fu in our study. The incidence of severe neutropenia, radiation dermatitis, and mucocitis was 1.7%, 6.8%, and 44.1%, respectively. No treatment related death occurred.

The results of our study indicated that TPF as a neoadjuvant chemotherapy regimen combined with CCRT for patients with locoregionally advanced NPC had tolerable adverse events, good compliance, and satisfying short-term treatment efficacy. Confirming its long-term outcome awaits further follow-up. The taxane-based TPF neoadjuvant chemotherapy regimen combined with CCRT is worth further research in the patients with locoregionally advanced NPC.

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