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ORIGINAL ARTICLE

Phase II study of docetaxel, cisplatin, and 5-FU induction chemotherapy followed by chemoradiotherapy in locoregionally advanced nasopharyngeal cancer

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Abstract
Purpose This study sought to determine the feasibility and safety of induction chemotherapy with docetaxel, cisplatin, and 5-fluorouracil (5-FU) triple combination chemotherapy (TPF) followed by concurrent chemoradiotherapy (CCRT) for locoregionally advanced nasopharyngeal cancer (NPC).
Methods Patients with advanced NPC were treated with three cycles of induction chemotherapy. Docetaxel (70 mg/m^2) and cisplatin (75 mg/m^2) were given on day 1, followed by 5-FU (1,000 mg/m^2) as a continuous infusion for 4 days. After induction chemotherapy, cisplatin was given at a dose of 100 mg/m^2 every 3 weeks with radiotherapy.
Results Thirty-three patients were enrolled; all patients were stage III ($n = 4$, 12.1%) or IV ($n = 29$, 87.9%). Among the patients, 32 patients completed both induction TPF therapy and CCRT, with responses as follows: five patients (15.2%) achieved a complete response (CR), and 27 patients (81.8%) a partial response (PR). At 6 weeks after CCRT, 23 patients (69.7%) had a CR and 9 patients (27.3%) a PR. The 3-year progression-free survival was 75.6% and the 3-year overall survival was 86.1%. Neutropenia (72.7%), febrile neutropenia (9.1%), and nausea (9.1%) were the most severe toxicities (grade 3–4) during induction chemotherapy, and mucositis (39.4%), fatigue (15.2%), and nausea (9.1%) were the most common toxicities (grade 3–4) during CCRT.
Conclusions Although most patients had stage IV NPC, the TPF induction chemotherapy followed by CCRT showed promising activity with manageable toxicity. These results demonstrated the possibility of effective treatment with the aim of not only a palliative, but also a curative, approach to the treatment of advanced NPC.

Keywords Nasopharyngeal carcinoma · Docetaxel · Induction chemotherapy · Chemoradiotherapy

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Introduction

Due to their anatomical location, nasopharyngeal cancers (NPCs) are considered unresectable, and radiation therapy (RT) has been the standard treatment approach. To intensify the effects of radiation, concurrent chemoradiotherapy (CCRT) has been tried. Randomized trials of CCRT for advanced NPC have demonstrated a progression-free survival (PFS) or overall survival (OS) benefit over RT alone [1, 2]. Therefore, the current standard treatment for

advanced NPC is CCRT with or without adjuvant chemotherapy [3, 4], even if the best sequence has not yet been established. Several studies have shown the superiority of CCRT followed by adjuvant chemotherapy over RT alone, especially to control distant metastasis [hazard ratio (HR) = 0.57] [5, 6]. However, patient compliance with adjuvant chemotherapy has been problematic; up to 15% of patients did not receive planned adjuvant chemotherapy, due to toxicity and patient refusal. Thus, ascertaining whether adjuvant therapy has contributed to the reported improvement in OS has been difficult. In this regard, the alternative approach of induction chemotherapy might be expected to provide more tolerable treatment. Recent uncontrolled phase II studies of induction chemotherapy have resulted in favorable outcomes compared to RT alone [7–11].

The taxanes have demonstrated considerable single-agent activity in head and neck cancers [12–14]. For nasopharyngeal cancer, paclitaxel has shown a 22% overall response rate (ORR) as monotherapy [15], and a 59–76.5% ORR in combination with cisplatin or carboplatin [16–18]. Recently, induction chemotherapy has been widely investigated in head and neck cancer, and large-scale randomized trials have shown the benefits of docetaxel, cisplatin, and 5-fluoruracil (5-FU) triple combination chemotherapy (TPF) compared to 5-FU and cisplatin [19, 20]. In contrast to other epidermoid cancers of the head and neck, NPC has a greater tendency to early metastatic spread [21, 22]. The combination of paclitaxel and carboplatin was shown to have a high response rate (75%) in patients with metastatic NPC [18], and has demonstrated encouraging activity and safety profiles as a neoadjuvant treatment of NPC [11].

On the basis of previous results with TPF chemotherapy showing its superior efficacy in advanced head and neck cancer, this study was performed to determine the feasibility and safety of induction chemotherapy with TPF followed by CCRT for locoregionally advanced NPC. The primary endpoint was the objective response rate, and the secondary endpoints included PFS and OS.

Patients and methods

Patients

Patients were eligible if they had histologically documented nasopharyngeal carcinoma at a locoregionally advanced stage III to IVB according to AJCC staging system, no previous chemotherapy or radiotherapy, concurrent malignancies, or history of other malignancies. They had to be ≥18 years old with an Eastern Cooperative Oncology Group (ECOG) performance status ≤2 and possess adequate bone marrow and organ function (absolute neutrophil count ≥1,500/μL, platelets ≥100,000/μL, serum bilirubin <2.0 mg/dL, creatinine <2.0 mg/dL, and serum transaminase levels less than twice the upper limit of normal). Pretreatment staging involved examination of the ears, nose, and throat by an otolaryngologist, as well as a computed tomographic (CT) scan or magnetic resonance imaging (MRI) of the primary tumor site and neck. To detect other primary aerodigestive tract malignancies, patients underwent a CT scan of the chest and an esophagogastroduodenoscopy or pharyngoesophagram. Before radiation therapy, all patients received a dental examination to avoid unexpected osteonecrosis or osteomyelitis associated with radiation. Patients gave written informed consent before they entered the study, and the study protocol was approved by the Chonnam National University Hwasun Hospital Institutional Review Board.

Treatment schedule and dose modification

1. Induction chemotherapy: Docetaxel (70 mg/m^2) and cisplatin (75 mg/m^2) were given as a 4-h intravenous infusion on day 1, followed by 5-FU (1,000 mg/m^2) as a 24-h continuous infusion for 4 days. The cycles were repeated every 3 weeks. Thirty minutes prior to the docetaxel infusion, each patient received 20 mg dexamethasone, 50 mg ranitidine, and 5 mg chlorpheniramine maleate intravenously to prevent hypersensitivity reactions. After prehydration with normal saline, the calculated dose of docetaxel diluted in 300 mL of normal saline was infused over 1 h. The calculated dose of cisplatin was then administered over 3 h, followed by posthydration with normal saline. Soon after the cisplatin infusion was completed, 5-FU was infused continuously for 4 days. Ondansetron (8 mg, i.v.) was routinely given. Patients received further cycles of chemotherapy only when the absolute neutrophil count was ≥1,000/mm^3 and the platelets were ≥100,000/mm^3. Toxicity was graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0. Dose modifications were determined based on hematological or non-hematological toxicities. The dose of docetaxel was reduced 75% after any episode of febrile neutropenia or grade 4 neutropenia lasting more than 5 days, or greater than grade 3 fatigue. The cisplatin dose was reduced to 75% in subsequent cycles if one of the following occurred: greater than grade 3 sensory neurotoxicity, grade 2 or greater nephrotoxicity, or persistent grade 4 neutropenia or neutropenic fever after dose reduction of docetaxel. Patients with grade 3 diarrhea that lasted for more than 7 days despite the administration of loperamide, mucositis of grade 3 lasting for more than 5 days, or grade 4 mucositis, had a 25% reduction in

the daily dose of 5-FU. Prophylactic antibiotics (levofloxacin 500 mg) were given orally from days 5 to 10 of each cycle. Prophylactic granulocyte colony-stimulating factor (G-CSF) was used at the physician's discretion.

2. Chemoradiotherapy: After three cycles of induction chemotherapy, intravenous cisplatin at a dose of 100 mg/m^2 every 3 weeks, depending on creatinine clearance, was administered concomitantly with conventional radiotherapy to the primary tumor with a total dose of 68.4 Gy. Radiotherapy was performed using 6 or 10 MV photon beams produced by a linear accelerator. All patients were treated using a standard radiotherapy technique in daily 1.8 or 2 Gy fractions, 5 days per week. Patients with gross disease remaining at a neck node had a boost treatment with a 9 or 12 MeV electron beam. For patients with grade 4 odynophagia, radiation therapy was delayed until recovery to less than grade 2 odynophagia.

Follow-up and evaluation

After three cycles of induction chemotherapy, and 6 weeks after completion of CCRT, the patients' clinical response was assessed. The patients underwent examination by an otolaryngologist, as well as CT imaging of the primary tumor and neck. A biopsy of the primary site was recommended if possible. Tumor response was assessed according to response evaluation criteria in solid tumors (RECIST). For all patients with CR on physical examination and CT scan, a [^{18}F] fluorodeoxyglucose positron emission tomography (^{18}F-FDG-PET) scan was performed to confirm CR 1 month after CT confirmation. When the treatment was completed, the patients were followed for evaluation of their disease status monthly by physical examination and monitoring for toxicity; CT scanning was performed every 3 months for 2 years. After that, bimonthly physical examination and CT scanning every 6 months was performed until disease progression.

The dose intensity (DI) was calculated as the ratio of the total dose per square meter of the patient, divided by the total treatment duration (mg/m^2/week). In this calculation, the end of treatment was considered to be 21 days after day 1 of the last cycle of chemotherapy. The relative DI was calculated as the ratio of the DI actually delivered to the DI as planned by the protocol.

Statistical analysis

The primary endpoint was the response rate, and secondary endpoints were the median PFS and OS. The study was conducted using a Simon's two-stage MiniMax design. A sample size of 28 was required to accept the hypothesis that the true response rate was greater than 90% with 85% power, and to reject the hypothesis that the response rate was less than 70% with 5% significance. Initially we planned to enroll 13 patients in the first stage. If 10 or more responses were observed, we planned to continue to the second stage for a total of 28 patients in the analysis. Assuming a dropout rate of 15%, the total number of enrolled patients needed was predicted to be 32. The median OS was measured from the start of chemotherapy until the date of death or the last confirmed date of survival. The PFS was defined as the time from the start of chemotherapy to the first appearance of progressive disease or death from any cause. We compared the Kaplan–Meier curves for OS and PFS using the standard log-rank test. The survival analysis was performed using SPSS software (version 15.0; SPSS Inc., Chicago, IL, USA), and 95% confidence intervals (CIs) were calculated for all relevant estimates using StatXact (version 8; Cytel, Cambridge, MA, USA).

Results

Patients

Thirty-three patients with locoregionally advanced NPC were enrolled in the study between April 2004 and July 2008. 23 men and 10 women were enrolled, with a median age of 50 years. Four patients had stage III carcinoma and 29 patients had stage IV carcinoma, and their characteristics were described in Table 1.

Chemotherapy delivery

Among the 33 patients, a total of 98 cycles of TPF therapy was performed and 32 patients completed the scheduled CCRT. One patient received two cycles of TPF therapy due to reactivation of hepatitis B virus. The median duration from day 1 of cycle 1 to day 1 of cycle 3 of induction chemotherapy was 6.7 weeks (range 3.3–10.1 weeks), and the median duration from day 1 of cycle 3 of chemotherapy to day 1 of RT for CCRT was 30 days (range 19–57 days). The mean DIs relative to target dose of docetaxel, cisplatin, and 5-FU were 95.7% (22.3 ± 2.8 mg/m^2/week), 94.6% (23.6 ± 3.6 mg/m^2/week), and 95.2% (1269.3 ± 47.1 mg/m^2/week), respectively. The most common causes of decreased DI were fatigue and high creatinine level.

Response and survival

After three cycles of induction chemotherapy, 32 patients (97%) achieved an objective response (CR in five patients: 15.2%, 95% confidence interval (CI) 2.9–27.4% and PR in

Table 1 Patients and disease characteristics

Characteristics	Number (%)
Total patients	33
Age (years)	
Median ± SD	50.8 ± 13.7
Sex	
Male	23 (69.7)
Female	10 (30.3)
ECOG performance status	
0	20 (60.6)
1	10 (33.3)
2	3 (9.1)
WHO type	
Keratinizing	3 (9.1)
Non-keratinizing	20 (60.6)
Undifferentiated	10 (30.3)
Tumor (T)	
T1	5 (15.2)
T2	16 (48.5)
T3	4 (12.1)
T4	8 (24.2)
Lymph node (N)	
N0	2 (6.1)
N1	7 (21.2)
N2	21 (63.6)
N3	3 (9.1)
AJCC/UICC staging system	
III	4 (12.1)
IVA	21 (63.6)
IVB	8 (24.2)

27 patients: 81.8%, 95% CI 68.7–95.0%). One patient (3.0%) had disease progression. After sequential CCRT, 32 patients (97%) achieved an objective response (CR in 23 patients: 69.7%, 95% CI 54.0–85.4% and PR in nine patients: 27.3%, 95% CI 12.1–42.5%) (Table 2). One patient who had progressed locoregionally after induction chemotherapy did not finish CCRT because of poor general condition. The median follow-up duration was 36.1 months (range 7–65.3 months). The estimated 3-year PFS and OS rates were 75.6% (95% CI 51.5–99.7%) and 86.1% (95% CI 59.4–106.7%), respectively (Fig. 1).

Pattern of first relapse

Among 23 patients who showed CR after CCRT, two patients showed distant and locoregional recurrence, respectively. One of these two patients developed lung and bone metastases 2 years after diagnosis. The other patient developed local recurrence 21 months after diagnosis. These patients received additional chemotherapy.

Table 2 Response to induction chemotherapy and chemoradiation therapy

Response	Nasopharynx (n = 33)		Lymph node (n = 31)	
	No.	%	No.	%
After induction chemotherapy				
CR	18	54.5	7	21.2
PR	14	42.4	24	72.7
SD	0	0	0	0
PD	1	3	0	0
Combined response (NP + LN, n = 33)				
CR	5	15.2		
ORR (CR + PR)	32	97		
After concomitant chemoradiation				
CR	32	97	22	66.7
PR	0	0	9	27.3
SD	0	0	0	0
PD	1	3	0	0
Combined response				
CR	23	69.7		
ORR (CR + PR)	32	97		

NP nasopharyx, *LN* regional neck lymph nodes, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *ORR* overall response rate

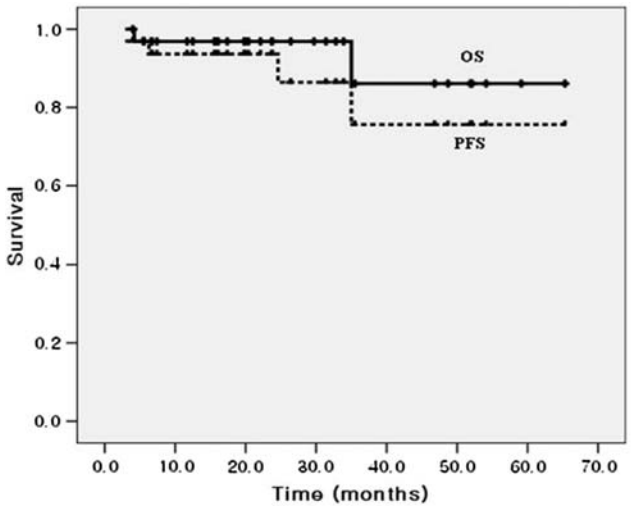

Fig. 1 Kaplan–Meier estimated of progression free survival (PFS) and overall survival (OS) for all patients

Toxicity

The toxicity of TPF chemotherapy was assessed in all 33 patients, and 98 cycles of TPF were analyzed (Table 3). Neutropenia of grade 3 or 4 occurred in 72.7% of the patients. Two patients developed uncomplicated, culture-negative febrile neutropenia during TPF chemotherapy, and

Table 3 Acute hematologic and nonhematologic adverse events during induction chemotherapy and concurrent chemoradiotherapy

	Induction chemotherapy				CCRT			
	Grade 1–2		Grade 3–4		Grade 1–2		Grade 3–4	
	No.	%	No.	%	No.	%	No.	%
Hematologic								
Neutropenia	3	9.1	24	72.7	4	12.1	3	9.1
Neutropenic fever			2	6.1				
Anemia	3	9.1			13	39.4		
Trombocytopenia	1	3.0			1	3.0		
Nonhematologic								
Anorexia/nausea/vomiting	14	42.4	3	9.1	8	24.2	3	9.1
Fatigue/asthenia	13	39.4	3	9.1	13	39.4	5	15.2
Mucositis/odynophagia	10	30.3	2	6.1	5	15.1	13	39.4
Diarrhea	8	24.2			1	3.0		
Neuropathy	1	3.0				1	3.0	
Nephropathy	1	3.0						
Dermatitis						4	12.1	

Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria, version 3.0. The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, see http://www.textcheck.com/certificate/y00TR0

CCRT concurrent chemoradiotherapy

both recovered with G-CSF and antibiotic therapy. G-CSF was used for 26 cycles (26.5%) during induction chemotherapy. The most common non-hematologic toxicities were fatigue, mucositis, and nausea. Fatigue and nausea below grade 2 developed in 39.4 and 42.4% of the patients, respectively. However, fatigue and nausea >grade 3 developed in only 9.1 and 9.1% of the patients, respectively.

During CCRT, the most frequent toxicities were oropharyngeal mucositis and fatigue. Thirteen patients (39.4%) developed a severe mucosal reaction (grade 3–4) with diffuse oral erythema and epithelial ulcers. Seven patients (21.2%) who developed grade 4 odynophagia received further RT when odynophagia was below grade 2 after 1 week of rest and supportive care including analgesics and supplemental feedings. Grade 3–4 neutropenia occurred in 9.1% of the patients during CCRT. However, no deaths due to toxicity occurred during or immediately after treatment.

Discussion

The survival benefit gained from adding adjuvant or neoadjuvant chemotherapy to CCRT presumably results from reduced occurrence of distant metastasis. Accumulating data support the efficacy of neoadjuvant chemotherapy and its ability to increase patients' likelihood of completing the entire course of chemotherapy [11, 23–26]. Hui et al. [16] reported a randomized phase II trial comparing induction chemotherapy with docetaxel and cisplatin followed by CCRT with CCRT alone in patients with advanced NPC. The results were promising with regard to prolongation of survival without impaired quality of life in the patients who received CCRT alone; these results suggested that induction chemotherapy might play a useful role in the treatment of patients with advanced NPC [16].

Induction chemotherapy trials in head and neck cancers have been vigorously investigated. The triple combination of docetaxel, cisplatin, and 5-FU (TPF) was compared with cisplatin and 5-FU (FP) as induction chemotherapy, and TPF was demonstrated to result in superior PFS and OS [19, 20] with manageable toxicity. Although the cancer epidemiology, histology, and natural history of head and neck tumors are different from those of NPC, some similar aspects including radiosensitivity and chemosensitivity exist. Therefore, we chose to investigate the triple combination TPF regimen, and this study was conducted to evaluate the efficacy of TPF induction chemotherapy in patients with advanced NPC. As expected, the results of this study showed both feasibility and promising activity with regard to tumor response and patient survival. The patients enrolled in this study had significantly advanced disease; 29 patients (87.9%) had stage IV disease, and only four patients (13.3%) had stage III disease. The objective response rate was 97% after induction chemotherapy (CR in 15.2% and PR in 81.8%). After CCRT, the objective response rate was 97% (CR in 69.7% and PR in 27%). The 3-year PFS and OS rates in the present study were 75.6 and 86.1%, respectively. These results compare favorably with previous reports on induction chemotherapy. In the study by Ferrari et al. [27], the objective response rate was 79.4%, and the 3-year OS and PFS were 80% and 54%, respectively. In the study by Hui et al. [16], the objective response rate was 76.5%, and the 3-year OS and PFS were 94.1 and 88.2%, respectively. The OS in our study was somewhat lower than that in the study of Hui et al. [16]. This difference might be associated with differences in the

patient characteristics. Most of the patients enrolled in the previous study had stage III disease (61%), compared to only 12.1% in our study.

With regard to toxicity, the TPF induction therapy was well tolerated; all patients completed three cycles of induction chemotherapy. The acute toxicity was mild and reversible in most cases. The increase in acute toxicity during induction chemotherapy was mainly associated with neutropenia, which was uncomplicated and manageable. The hematological toxicity could be treated with growth factor support and prophylactic antibiotics. During CCRT, the RT was interrupted in 12 patients (36%); of these 12 patients, 11 had grade 3 or 4 mucositis and 1 patient had disease progression. However, the CCRT was continued and completed in these patients after 1 week of rest.

In conclusion, this study is the first to report on TPF induction chemotherapy for patients with locoregionally advanced NPC. The results showed that this treatment was very effective with manageable toxicity. In the near future, a large-scale study such as a randomized phase III trial comparing TPF followed by CCRT versus CCRT alone by the Radiotherapy Oncology Group for Head and Neck (GORTEC) might yield more definitive answers about the benefits of this type of therapy compared to more established methods of treatment.

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