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Clinical Research Paper

Induction chemotherapy with docetaxel plus cisplatin (TP regimen) followed by concurrent chemoradiotherapy with TP regimen versus cisplatin in treating locally advanced nasopharyngeal carcinoma

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Key words: nasopharyngeal neoplasm, radiotherapy, induction chemotherapy, docetaxel, cisplatin, efficacy, comparative study

Background and Objective: Clinical trials on docetaxel plus cisplatin (DDP) (TP regimen) in treating nasopharyngeal carcinoma (NPC) are still uncertain due to limited samples. This study was to compare the short-term efficacy and toxicity of induction chemotherapy with TP regimen followed by concurrent chemoradiotherapy with TP regimen versus DDP in treating locally advanced NPC. Methods: Fifty-seven patients with stage T3-4N2-3M0 NPC diagnosed pathologically from December 2005 to December 2006 were randomized into TP group (30 patients) and DDP group (27 patients). Both groups received TP regimen as induction chemotherapy with docetaxel (70 mg/m^2) on Day 1 and DDP (80 mg/m^2) on Day 2, repeating every 21 days for two cycles. For concurrent chemotherapy, TP group were administered docetaxel (60 mg/m^2) on Day 1 and DDP (80 mg/m^2) on Day 2; DDP group were administered DDP (80 mg/m^2) on Day 1. Both schedules were repeated every 21 days for two cycles. Linear accelerator was used as radioactive source. Irradiation field was designed with CT-simulation and conventional fractions. Results: The 57 patients received 111 cycles of induction chemotherapy, and 53 of them received 103 cycles of concurrent chemotherapy; four patients ceased induction chemotherapy and three ceased concurrent chemotherapy. All patients completed radiotherapy. The major toxicity of induction chemotherapy was hematologic toxicity; the main toxicities of concurrent chemoradiotherapy were hematologic toxicity and mucositis. The occurrence rates of Grade 3–4 leucopenia and Grade 3-4 neutropenia were significantly higher in TP group than in DDP groups ($p < 0.05$). In concurrent chemoradiotherapy, the application rate of granulocyte colony stimulating factor (G-CSF) was significantly higher in TP group than in DDP group (100% vs. 72.0%, $p < 0.05$). After concurrent chemoradiotherapy, the complete remission (CR) rates of the nasopharynx and regional lymph nodes were 93.3% and 92.9% in TP group, and were 96.3% and 91.3% in DDP group ($p > 0.05$). Conclusions: The short-term efficacy of induction chemotherapy with TP regimen followed by concurrent chemoradiotherapy with TP regimen on locally advanced NPC is similar to that of TP regimen followed by concurrent chemoradiotherapy with DDP. The toxicity of the former schedule is severer than that of the latter, but it is tolerable with the use of G-CSF. The long-term efficacy of induction chemotherapy with TP regimen followed by concurrent chemoradiotherapy with TP regimen need to be further studied.

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With development of radiation imaging and radiation techniques, and intervention of induction chemotherapy, local control rate of nasopharyngeal carcinoma (NPC) is further improved near to 100%.[1,2] Combined therapy of chemoradiotherapy is designed to treat distant metastasis, but the occurrence rate of distant metastasis is still high. It seems that distant metastasis is beyond local failure and becomes an important cause of therapy failure. Many clinical trials are designed to explore the approaches of induction chemotherapy combined with concurrent chemoradiotherapy[3-6] to reduce distant metastasis and improve survival. The results indicate that both chemotherapy compliance and tumor response were good, however, the sample size was small and follow-up period was short. Due to small sample size of clinical trials, the results of NPC treatment by TP regimen [docetaxel combined with cisplatin (DDP)] are discrepant.[7-11] The efficacy, dosage level and adverse events of TP regimen need further evaluation. In this study, we observed and compared both efficacy and adverse events of concurrent TP regimen versus DDP after induction chemotherapy.

Patients and Methods

Patients selection. Inclusive criteria were as follow: non-keratinizing or undifferentiated carcinomas (WHO pathologic typing) and stage T3-4N2-3M0 disease (NPC 92' staging);

16–65-years-old without contraindications for chemotherapy; untreated before by chemotherapy, immunotherapy, surgery and radiotherapy; with good general status, KPS ≥ 70; white blood cell (WBC) count ≥ 4.0 × 10^9/L, platelet (PLT) ≥ 100 × 10^9/L and Hb ≥ 10 g/L, normal hepatic and renal functions, and without obvious abnormal electrocardiogram. All enrolled patients signed consent forms. Exclusive criteria were as follow: heart disease with cardiac dysfunction and other internal medical diseases unsuitable for chemotherapy; history of surgery for primary nasopharyngeal lesions and regional lymph nodes; previously treated with radiotherapy or chemotherapy; pregnant and lactating women; expected survival time less than three months; with history of other malignant tumors. Withdraw criteria were as follow: disease progression; unfound distant metastasis at enrollment but distant metastasis found during treatment; intolerable treatment toxicity or reactions; other diseases affecting treatment programs during treatment; patients' request to quit treatment.

Trial grouping. This trial was a prospective randomized clinical trial. Eligible patients were randomized into two groups by a computer: concurrent TP regimen after induction chemotherapy (TP group) and concurrent DDP after induction chemotherapy (DDP group).

Case data. A total of 57 patients, 20–74 years old with a median age of 43, were enrolled from December 2, 2005 to December 11, 2006. Of the 57 patients, 44 were men and 13 were women with a ratio of 3.4: 1. The 30 patients in TP group were 20–64 years old with a median age of 43; the 27 patients in DDP group were 20–63-years-old with a median age of 40. Clinical data of the two groups, including age, gender, T stage, N stage, and KPS, were comparable (Table 1).

Table 1 **Clinical data of the two groups of locally advanced nasopharyngeal carcinoma (NPC) patients**

Item	TP group	DDP group	*P* value
Median age (years)	43	40	0.651
Sex (cases)			
Male	24	20	0.592
Female	6	7	
T stage (92')			
T1	2	1	0.218
T2	6	1	
T3	11	15	
T4	11	10	
N stage (92')			
N0	2	4	0.301
N1	10	12	
N2	16	8	
N3	2	3	
KPS performance	80.3±1.2	81.5±1.3	0.518

Chemotherapy plan and dosage adjustment. **Chemotherapy plan design**. Both groups received two cycles of induction chemotherapy using TP regimen (initial dosage of 70 mg/m^2 docetaxel on Day 1 and 80 mg/m^2 d_2 DDP on Day 2), once every three weeks. Both groups received two cycles of concurrent chemotherapy, once every three weeks: TP regimen (initial dosage of 60 mg/m^2 docetaxel on Day 1 and 80 mg/m^2 DDP on Day 2) was used in TP group while DDP (initial dosage of 80 mg/m^2 on Day 1) was used in DDP group. Time interval between starting time of the first concurrent chemotherapy and that of the last induction chemotherapy was 21 days.

Dosage adjustment. Dosage adjustment of drugs depended on the most serious adverse events occurred during treatment. The adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (NCI CTC3.0). If non-hematological adverse events in a certain patient were recovered within three weeks, delayed chemotherapy was allowed. Two times of 20% reduction of initial administration dosage were allowed for one patient, that is, 70 mg/m^2→55 mg/m^2→45 mg/m^2 for docetaxel and 80 mg/m^2→65 mg/m^2→50 mg/m^2 for DDP in induction chemotherapy while 60 mg/m^2→50 mg/m^2→40 mg/m^2 for docetaxel and 80 mg/m^2→65 mg/m^2→50 mg/m^2 for DDP in concurrent chemotherapy. If severe adverse events still occurred after two times of dosage adjustment, chemotherapy would be terminated. If the dosage of induction chemotherapy after reduction was lower than the initial dosage of concurrent chemotherapy, the dosage of concurrent chemotherapy would refer to the reduced dosage of induction chemotherapy. Termination criteria of chemotherapy were as follow: grade 4 adverse events occurred in initial treatment; more than 21 days of subsequent chemotherapy delay caused by myelosuppression; more than three weeks of delayed recovery of any adverse events except alopecia; grade 3–4 neural toxicity; the indexes of liver function enzyme and renal function were elevated by 5-fold of normal values (the indexes of renal function in DDP group were elevated by 2.5-fold of normal values); the level of total bilirubin was elevated by 2.5-fold of normal value. The indications for 20% dosage reduction were as follow: neutropenia-caused fever; grade 3 neutropenia or leucopenia; subsequent chemotherapy was prolonged for more than 14 days due to leucopenia or thrombocytopenia; grade 3 thrombocytopenia; the indexes of liver function enzyme and renal function were elevated by 2.5–5-fold of normal values. The indications for 40% dosage reduction were as follow: grade 4 neutrophilic granulocytopenia or leucopenia; grade 4 thrombocytopenia; more than five days of infective fever caused by neutropenia; the indexes of renal function were elevated by 1.5-fold of normal values.

Usage of granulocyte colony stimulating factor. (**G-CSF**). The indications for G-CSF application were as follow: treatment-related decrease of neutrophil count to < 1.5 × 10^9/L; leukocyte count of < 2.5 × 10^9/L; neutropenia-related fever; neutropenia-related infection; more than two weeks of delayed recovery of leukocytes and neutrophils.

Radiotherapy plan. Radiotherapy was conducted using linear accelerator three weeks after the last induction chemotherapy. Foam pillow and mask fixation were applied for body position and isocenter irradiation. Gross tumor volume (GTV), clinical target volume (CTV) and planning target volume (PTV) were set

according to ICRU50 and ICRU62 guidelines. Irradiation target volume included nasopharyngeal primary lesions, involved lymph nodes and sub-clinical lesions. Irradiation field was designed according to CT-Sim. The faciocervical plus cervical anterior tangential fields were irradiated by 36 Gy, then shrank faciocervical field, upper cervical β line plus cervical anterior tangential field or faciocervical split field plus cervical anterior tangential field were irradiated. Auxiliary fields, such as anterior nasal field, parapharyngeal field, skull base field, ethmoidal sinus field, small cervical field, and so on, were irradiated individually according to lesion scope. Irradiation dosages were as follow: 68–72 Gy for primary lesions; 60–70 Gy for involved lymph nodes; ≥ 50 Gy for sub-clinical lesions; 50 Gy for the brain stem and 40 Gy for the spinal cord. Consecutive radiotherapy was performed by 2 Gy/fraction, one fraction/day, five fractions/week.

Examinations before, during and after treatment. Before treatment, the patients received disease history enquiry, physical examination, pathologic biopsy, x-ray chest radiography, routine examinations for blood, urine and stool, blood biochemistry test, serum virology, electrocardiogram, nuclear magnetic resonance detection of the nasopharynx and head-neck, abdominal B-ultrasound, and electric nasopharynomicroscopy. ECT or PET-CT was conducted on stage N2-3 patients to exclude the possibility of distant metastasis. Nuclear magnetic resonance examination of the nasopharynx and head-neck, and electric nasopharynomicroscopy were re-examined three weeks after induction chemotherapy, right after and three months after concurrent chemoradiotherapy to evaluate the responses in nasopharyngeal lesions and cervical lymph nodes.

Evaluation of efficacy and adverse events. WHO response evaluation criteria of solid tumors were used for efficacy evaluation of nasopharyngeal and cervical lesions, which was classified as complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD). NCI CTC3.0 was used to evaluate adverse events.

Follow-up. The patients were re-examined for the statuses of the nasopharynx and lymph nodes as well as metastasis and recurrence monthly in the first-third months after radiotherapy, every three months in the forth-twelve months after radiotherapy, and every six months thereafter. Recurrence, distant metastasis, survival status, initial treatment failure date, salvage measures for treatment failure, and long-term adverse events were recorded.

Statistical analysis. Using software SPSS11.0, intergroup enumeration data were compared with χ^2 test while intergroup measurement data were compared with t test. $p < 0.05$ was considered as significant.

Results

Completion status of treatment. Treatment withdraw. Among the 57 patients, seven quitted chemotherapy. Four patients (two in TP group and two in DDP group) quitted during induction chemotherapy due to grade 4 leucopenia with infection after one cycle of chemotherapy (in three patients) and frequent ventricular premature beats after two cycles of chemotherapy (in one patient). Three patients (two in TP group and one in DDP group) quitted during concurrent chemotherapy due to thromboangiitis in the lower limbs with foot infection after one cycle of concurrent chemotherapy (in one patient in TP group), inferior myocardial ischemia after two cycles of induction chemotherapy which lasted after one cycle of concurrent chemotherapy with 20% dosage reduction (in one patient in TP group), more than three weeks of delayed myelosuppression (in one patient in DDP group). There was no significant difference in treatment withdraw between the two groups.

Completion of radiotherapy. Radiotherapy was completed in all patients. In TP group, the median irradiation dosage was 72 Gy [mean, (73.5 ± 0.6) Gy] for the nasopharynx and 66 Gy [mean, (66.4 ± 0.9) Gy] for cervical lymph nodes; the median irradiation duration was 56 days [mean, (60.6 ± 1.1) days] for the nasopharynx and 53 days [mean, (56.1 ± 1.4) days] for cervical lymph nodes. In DDP group, the median irradiation dosage was 72 Gy [mean, (72.9 ± 0.6) Gy] for the nasopharynx and 64 Gy [mean, (64.5 ± 1.1) Gy] for cervical lymph nodes; the median irradiation duration was 57 days [mean, (57.8 ± 1.0) days] for the nasopharynx and 51 days [mean, (51.2 ± 1.3) days] for cervical lymph nodes. The irradiation duration for cervical lymph nodes was significantly longer in TP group than in DDP group ($p < 0.05$). No significant differences in irradiation dosage, delay and nasopharyngeal irradiation duration were found between the two groups.

Completion of chemotherapy. A total of 114 cycles of induction chemotherapy were expected to be completed in the 57 patients; 111 cycles (97.4%) were completed. Eight patients (14.1%) received eight cycles (0.7%) with 20% dosage reduction; one patient (1.8%) received induction chemotherapy with 40% dosage reduction.

A total of 53 patients received concurrent chemotherapy after induction chemotherapy: 28 in TP group received 54 (96.4%) cycles and 25 in DDP group received 49 (98.0%) cycles. Eight patients (28.6%) in TP group and two (8.0%) in DDP group received concurrent chemotherapy with 20% dosage reduction. Two patients (6.9%) in TP group had concurrent chemotherapy delay for more than one week; three patients (12.0%) in DDP group had delay for more than two weeks. No significant differences in concurrent chemotherapy cycles, chemotherapy delay and dosage reduction were observed between the two groups ($p > 0.05$).

Adverse events. **Adverse events during induction chemotherapy**. As shown in Table 2, adverse events occurred during induction chemotherapy were mainly caused by hematological toxicity: the occurrence rate of grade 4 leucopenia was 7.0% and that of grade 4 neutrophilic granuloaytopenia was 5.3%. Cardiac toxicity occurred in three patients. Ten patients (15.8%) had liver function damage. One patient had grade 1 peripheral neural toxicity, three had grade 1 renal toxicity, two had allergy, and one had water-sodium retention. All patients suffered from grade 1-2 alopecia.

Adverse events during concurrent chemoradiotherapy. Neither grade 5 adverse events nor grade 4 non-hematological toxicity occurred during concurrent chemoradiotherapy. Eight cases (28.6%) of grade 4 leucopenia and eight cases (28.6%) of grade 4 neutrophilic granuloaytopenia occurred in TP group; no grade 4

hematological toxicity occurred in DDP group. Six patients in TP group and two in DDP group had liver function damage. Both TP group and DDP group had one case of grade 1 renal toxicity and one case of cardiac toxicity. The occurrence rates of grades 3-4 leucopenia, grades 3–4 neutrophilic granuloaytopenia and grade 3 skin reaction were significantly higher in TP group than in DDP group ($p < 0.005$) (Table 3).

Usage of G-CSF and alteration in body weight. During induction chemotherapy, 39 patients (68.4%) used G-CSF. The rate of G-CSF usage was significantly higher in TP group than in DDP group (100% vs. 72.0%, $p < 0.005$). There was no significant difference in the occurrence rate of body weight change between TP group and DDP group (35.7% vs. 28.0%).

Short-term efficacy. Among the 57 patients, two in TP group and four in DDP group had stage N0 disease. Therefore, the responses of regional lymph nodes were evaluable in 51 patients. After induction chemotherapy, the response rate of nasopharyngeal lesions was 63.2% and the CR rate was 1.8%; The response rate of cervical lymph nodes was 70.6% and the CR rate was 9.8%. Tumor responses after concurrent chemotherapy were shown in Table 4. No significant differences were found between the two groups.

Patients' survival. Follow-up expired on 31 March 2008 and no patient was missed. The patients were followed for 4.3–16.6 months with a median of 10.1 months. The patients in TP group were followed for 4.3–16.6 months with a median of 11.1 months; those in DDP group were followed for 4.4–16.3 months with a median of 9.3 months. In TP group, one patient developed liver metastasis, one developed lung metastasis and died 13 months later; one developed liver, lung and lumbar metastasis and died 15 months later. In DDP group, one patient had nasopharyngeal recurrence confirmed by pathology.

Table 2 **The occurrence of grade 3-4 adverse events in the 57 patients during induction chemotherapy with TP regimen**

Adverse event	Cases(%)	Cycles(%)
Leukopenia	20(35.1)	22(19.8)
Neutropenia	10(17.5)	11 (9.9)
Thrombocytopenia	2 (3.5)	2 (1.8)
Febrile neutropenia	10(17.5)	11 (9.9)
Nausea	2 (3.5)	4 (3.6)
Emesia	5 (8.8)	9 (8.1)
Diarrhea	3 (5.3)	4 (3.6)
Fatigue	3 (5.3)	6 (5.4)

Table 3 **The occurrence of Grade 3-4 adverse events in the two groups during concurrent chemoradiotherapy**

Adverse event	TP group [cases(%)]	DDP group [cases(%)]	*P* value
Leukopenia	17(60.7)	3(12.0)	<0.001
Neutropenia	15(53.6)	2(11.8)	<0.001
Thrombocytopenia	2(7.1)	0(0.0)	0.522
Febrile neutropenia	8(28.6)	2(8.0)	0.119
Nausea	7(25.0)	4(16.0)	0.420
Emesia	5(17.9)	8(32.0)	0.232
Diarrhea	2(7.1)	1(4.0)	1.000
Mucous reaction	22(78.6)	19(76.0)	0.823
Cutaneous reaction	7(25.0)	0(0.0)	0.023
Hypoacusia	1(1.9)	0(0.0)	1.000

Twenty-eight patients in TP groups and 25 patients in DDP group received concurrent chemotherapy.

Table 4 **Tumor responses at different sites after chemoradiotherapy in the two groups**

Group	Complete remission [cases (%)]		Partial remission [cases (%)]	
	NPC	Lymph nodes	NPC	Lymph nodes
TP	28(93.3)	26(92.9)	2(6.7)	2(7.1)
DDP	26(96.3)	21(91.3)	1(3.7)	2(8.7)

Discussion

Phase II clinical trial results of local advanced NPC treated by induction chemotherapy plus concurrent chemoradiotherapy indicate a high response rate with CR rates near 100%.[3,4-6] Chan et al.[4] used paclitaxel plus carboplatin as induction chemotherapy and mono-drug DDP as concurrent chemoradiotherapy to treat 31 local advanced NPC patients, and reported that the CR and PR rates of nasopharyngeal lesions were 0% and 16%, respectively, while those of regional lymph nodes were 58% and 39%, respectively, after induction chemotherapy; the CR rates of both nasopharyngeal lesions and regional lymph nodes were 100% after concurrent chemoradiotherapy. In our study, the response rates of induction chemotherapy (63.2% for nasopharyngeal lesions, 70.6% for lymph nodes) are consistent with those in head-neck tumors as reported (46–61%);[12,13] the CR rate of nasopharyngeal lesions (1.8%) focuses is similar to that reported by Chan et al.,[4] while the PR rate (61.4%) is higher than that in Chan's report. The CR rates of nasopharyngeal lesions (94.7%) and regional lymph nodes (92.5%) after concurrent chemoradiotherapy are similar to those reported by Chan et al. High CR rate after induction chemotherapy plus concurrent chemoradiocherapy improves local control rate, but whether it can reduce metastasis and improve overall survival still remain uncertain. Oh et al.[3] treated naive local advanced NPC patients with TP regimen as induction chemotherapy plus concurrent chemoradiotherapy, and reported that the 5-year overall survival rate, local control rate, and distant metastasis control rate were 77%, 93% and 92%, respectively. Chan et al.[4] reported a 2-year overall survival rate of 91.8%. In our study, three patients in TP group had distant metastasis and one in DDP group had NPC recurrence during follow-up. Due to

short follow-up duration (median, 10.1 months) and small sample size, long-term efficacy of induction chemotherapy plus concurrent chemoradiotherapy need further observation and validation in randomized clinical trials.

Main dose-limiting toxicity of TP regimen is myelosuppression. Its application in NPC has seldom been reported. McCarthy et al.[7] used TP regimen (dosages of both docetaxel and DDP were 75 mg/m^2) to treat nine NPC patients with metastasis, and terminated their trial due to low response rate of tumors and high occurrence rate of grade 3–5 neutrophilic granulocytopenia. However, they did not report general information of the patients in details. Chua et al.[8] used these two drugs in combination to treat recurrent and metastatic NPC, and found that grade 4 neutrophilic granulocytopenia occurred in 78.9% patients (51.3% chemotherapy cycles) and neutrophil infection occurred in 42% patients (12.5% chemotherapy cycles), two patients died of pyemia; after the dosage was adjusted to 60 mg/m^2, the occurrence rate of grade 4 neutrophilic granulocytopenia was reduced and no neutrophil infection occurred. Therefore, they recommended docetaxel of 60 mg/m^2, however, they did not report the application of G-CSF and their sample size (19 cases) was small.

Johnson et al.[9] reported treatment results of 18 NPC patients at early T stage and advanced N stage when the dosage of docetaxel was 80 mg/m^2: the occurrence rate of grade 4 neutrophilic granulocytopenia is similar to that in Chua's report; while the occurrence rate of neutrophil infection is lower than that in Chua's report. However, Yamouni et al.[10] used TP regimen as induction chemotherapy to treat stage IVA-IVB NPC, and reported that the response rate was high and the occurrence rate of grade 3-5 neutrophilic granulocytopenia was 15.5%. In all trials, the occurrence rates of grade 3–5 non-hematological toxicity were low. TP regimen as concurrent chemotherapy has seldom been used to treat NPC. Lu et al.[11] used DFP regimen [docetaxel (60 mg/m^2) on Day 1, DDP (25 mg/m^2) on Days 2–5, 5-fluorouracil (500 mg/m^2) on Days 2–5] as concurrent chemoradiotherapy to treat NPC, and found that the main adverse events were grade 3–4 oral mucositis (50.0%) and leucopenia (40.0%), which were similar to our results.

In our trial, no grade 5 adverse events had occurred, the main toxicity was granulocyte inhibition, and the occurrence rate of non-hematological toxicity was low. The occurrence rate of grade 3-4 neutrophilic granulocytopenia is similar to that reported by Yamouni et al.,[10] while the occurrence rate of neutrophil infection is consistent with that reported by Johnson et al.[9] During concurrent chemoradiotherapy with TP regimen, grade 3–4 neutrophilic granulocytopenia occurred in 53.6% patients and neurophil infection occurred in 28.6% patients; the status of granulocyte inhibition was similar to those in other reports.[14]

The occurrence rates of grade 3–4 neutrophilic granulocytopenia and neutrophil infection were lower in our trial than in some trials stated above,[7-9] which may be related to docetaxel dosage: 75 mg/m^2 in two trials[8,10] and 80 mg/m^2 in another trial,[9] while 70 mg/m^2 for induction chemotherapy and 60 mg/m^2 for concurrent chemotherapy in our trial. Neutropenia and neutropenia-related infection in TP regimen is mainly caused by docetaxel and related to its dosage level. Mouridsen et al.[15] reported that when the dosage of mono-drug docetaxel was adjusted from 100 mg/m^2 to 60 mg/m^2, the occurrence rate of neutrophil infection was reduced from 14% to 5%, and that of drug-related infection was reduced from 74% to 2%, but the overall and disease-free survival showed no significant differences after dosage reduction. In our trial, G-CSF was used in 68.4% patients during induction chemotherapy and in all patients during concurrent chemoradiotherapy. Therefore, low occurrence rate of neutrophilic granulocytopenia during chemotherapy with TP regimen may be benefited from G-CSF. Vogel et al.[16] reported that G-CSF reduced the occurrence of docetaxel-caused neutrophil infection (17%→1%).

In our study, the main toxicities of concurrent chemoradiotherapy in both TP group and DDP group are oral mucositis and granulocyte inhibition, and non-hematological toxicities are mild. The occurrence rate of grade 3–4 neutrophilic granulocytopenia in concurrent chemoradiotherapy was significantly higher in TP group than in DDP group (53.6% vs. 11.8%, $p < 0.005$); the occurrence rate of neutrophil infection was higher in TP group than in DDP group (28.6% vs. 8.0%), but without significant difference which may be the usage of G-CSF (G-CSF was used in all patients in TP group and in 72.0% patients in DDP group).

In our study, the occurrence rate of grade 3 skin reaction was significantly higher in TP group than in DDP group (25.0% vs. 0.0%), which may be due to enhancement effects of both docetaxel and DDP on radiosensitivity of nasopharyngeal cells.[17] Posner et al.[18] reported that the occurrence rate of oral mucositis was higher in NPC patients treated with TP regimen than in those treated with mono-drug docetaxel. Although neither grade 4 skin reaction nor oral mucositis occurred in our trial, the occurrence rates of grade 3 oral mucositis were high in both TP group and DDP group (78.6% vs. 76.0%). The high occurrence rate of oral mucositis in TP group can be explained by above reasons, while whether that in DDP group is related to enhancement effect of docetaxel used in induction chemotherapy on radiosensitivity remains unknown.

Different from above reports on treating NPC with docetaxil and DDP,[7-11] we reported dosage reduction of concurrent chemotherapy, usage of G-CSF, and changes in body weight. The proportions of patients underwent 20% dosage reduction during concurrent chemotherapy were 28.6% in TP group and 8.0% in DDP group, without significant difference; the occurrence rates of body weight loss were 35.7% in TP group and 28.0% in DDP group, without significant difference, suggesting that TP regimen as induction chemotherapy plus concurrent chemoradiotherapy is tolerable.

To sum up, the short-term efficacy of TP regimen as induction chemotherapy and concurrent chemoradiotherapy is good with a high CR rate, and tumor response rate after concurrent chemoradiotherapy in TP group is similar to that in DDP group. Although the occurrence rates of adverse events after concurrent chemoradiotherapy in TP group are higher than those in DDP group, the adverse events in TP group were tolerable when treated with G-CSF. When TP regimen is used as induction chemotherapy, the tumor response rate is high and the occurrence rate of hemato-

logical toxicity is low; 70 mg/m^2 docetaxel and 80 mg/m^2 DDP are recommended for induction chemotherapy with usage of G-CSF. Although the adverse events of concurrent chemoradiotherapy with TP regimen are tolerable, the occurrence rates of grade 3-4 neutrophilic granulocytopenia and neutrophil infection are high, and need to be treated with G-CSF. Hence, the dosage level of TP regimen (60 mg/m^2 docetaxel, 80 mg/m^2 DDP) as concurrent chemoradiotherapy after induction chemotherapy needs further clinical trial validation.

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