Combined chemotherapy and radiotherapy is the standard treatment for advanced nasopharyngeal carcinoma (NPC). Prospective studies have shown that neoadjuvant chemotherapy with PF or PFb regimen for NPC achieves a response rate of more than 75%, but a relatively low complete remission (CR) rate of only about 20%. In recent years, TPF regimen (taxotere, cisplatin (DDP) and 5-fluorouracil (5-FU)) yields a better efficacy than PF regimen in head and neck cancer including NPC, with a CR rate doubled and a total response rate up to 93%. However, hematological toxicities with TPF, especially neutropenia, significantly increased compared with PF and the recommended dose by Western clinical trials may not be suitable for Orientals. So we conducted a phase I study to explore the dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) of TPF in the treatment of advanced nasopharyngeal carcinoma and observe its short-term efficacy.

**Patients and Methods**

**Patients enrollment**

Enrollment criteria were: new histologically confirmed NPC;
stages III–IV according to UICC 2002 staging system; aged 18–65 years; life expectancy > 6 months; ECOG 0–2; peripheral white blood cell (WBC) $\geq 4.0 \times 10^9$/L, neutrophil $\geq 2.0 \times 10^9$/L, platelet $\geq 100 \times 10^9$/L and hemoglobin $\geq 10$ g/L; normal ECG; normal liver and kidney function; and no previous chemotherapy, radiotherapy, surgery and immunotherapy. Informed consent was obtained from all the patients. Before treatment, MRI of nasopharynx and neck was performed routinely for clinical staging, and chest X-ray, abdominal B-ultrasoundography and whole bone scan were carried out to rule out distant metastasis.

**Clinical information**

Between December 2006 and May 2008, a total of 41 patients aged from 29 to 60 years, with a median age of 47 years, were enrolled, among whom 29 patients were male and 12 were female, with a male:female ratio of 2.4:1. There were 2 stage T1, 9 stage T2, 9 stage T3, and 21 stage T4 patients; 1 stage N0, 21 stage N1, 17 stage N2 and 2 stage N3 patients. Among them, there were 22 stage T3–4N0–1M0 and 19 stage T1–4N2–3M0 patients; 18 stage III and 23 stage IV patients. ECOG was 0–1 in 38 patients and 2 in 2 patients.

**Treatment**

**Chemotherapy** At first, neoadjuvant chemotherapy with TPF was given every 3 weeks for 2 cycles. Starting dose for Group 1 was Taxotere 40 mg/m² (day 1), DDP 40 mg/m² (day 1) and 5-FU 400 mg/m² (days 1–5). The daily dose of taxotere and DDP was increased by 5 mg/m² and 5-FU by 50 mg/m². Each dose group enrolled at least 6 patients. Adverse effects were evaluated after the 6 patients all completed 2 courses of chemotherapy. Dose was escalated if DLT did not occur in these patients. If DLT occurred in 3 patients in a group, another 3 patients were enrolled and treated with the same dose. If DLT did not occur in these 3 patients, dose escalation continued; if DLT occurred in 4 patients in a group, the test was terminated. All patients began to take dexamethasone orally in the night before chemotherapy at a dose of 7.5 mg every 12 h for 8 times. G-CSF was used when WBC $< 1.0 \times 10^9$/L or neutrophil $< 0.5 \times 10^9$/L.

**Radiotherapy** Radiotherapy began at the 5th week. Radioactive sources included $^{60}$Co and linear accelerator with 6 MV/8 MV X-ray. Foam pillow and facial mask were used for position fixation and isocenter irradiation was performed. Target volume was set based on simulation film, and low-melting point lead blocks were produced for all fields by computer-controlled cutting machine to perform conformal radiotherapy. Targets in radiation field included primary nasopharyngeal tumor, involved lymph nodes and sub-clinical lesions. Portal verification films were obtained at the first treatment to control the treatment error within 5 mm. Irradiation was given five times a week, each using 2 Gy. At first, bilateral face-neck joint fields were used to include clinical gross tumor, sub-clinical areas and upper cervical lymphatic drainage area with a dose of 36 Gy/18 fractions, and anterior tangent field was used for lower neck and supravacular area with the same dose. Then bilateral pre-auricular fields plus anterior tangent field or spinal cord spared small face-neck joint plus upper neck $\beta$ ray plus lower neck anterior tangent field were used. The dose for the nasopharynx was boosted to 68–72 Gy/34–36 fractions, the prophylactic dose for cervical lymph nodes was 50 Gy/25 fractions, and the dose for cervical positive lymph node was 60–66 Gy/30–33 fractions. Pre-nasal field, parapharyngeal field, skull base field and ethmoid sinus field were designed individually according to the lesion area, and additional 6–8 Gy/3–4 fractions were given by skull base field for patients with skull base destruction. Residual tumor after radiotherapy was observed once a month for 3 months after radiotherapy, and surgical treatment was conducted if residue remained.

**Relevant examinations before, during and after treatment**

Pre-treatment evaluation included a complete medical history, physical examination, electronic nasopharyngoscopy and pathological biopsy, blood, urine and stool routine, blood biochemistry, serum antibody and DNA of Epstein-Barr virus, chest X-ray, liver B-ultrasound, electrocardiogram, whole body bone scan and MRI of nasopharynx and neck. Chest CT or whole body PET-CT was examined for stage N3 patients to rule out distant metastasis. During treatment, blood routine, routine biochemistry, physical examination and electronic nasopharyngoscopy were performed weekly to assess adverse effects and record tumor regression. Electronic nasopharyngoscopy and MRI of nasopharynx and neck were performed after two courses of neoadjuvant chemotherapy and at the end of treatment to evaluate the efficacy.

**Adverse effects and efficacy evaluation**

Acute adverse effects were evaluated weekly according to the National Cancer Institute of Canada Common Toxicity Criteria (NCIC CTC) Version 3.0. According to the WHO criteria, clinical efficacy was evaluated at the end of chemotherapy, nasopharyngeal tumor evaluated by electronic nasopharyngoscopy and cervical tumor evaluated by clinical examination; at the end of radiotherapy, efficacy was evaluated by both clinical and radiological examination, nasopharyngeal tumor evaluated by electronic nasopharyngoscopy and MRI, and cervical tumor by MRI. Complete remission (CR): tumor completely disappeared; partial remission (PR): tumor regression by more than 50%; stable disease (SD): tumor regression by less than 50%; progressive disease (PD): tumor progressed. DLT: (1) any grades 3–4 hematological toxicity lasting more than 7 days, or grades 3–4 hematological toxicity lasting more than 3 days accompanied by fever; (2) grade 4 oral mucosal reaction or grade 3 oral mucosa reaction lasting more than 1 week; (3) grade 3 or more diarrhea; and (4) any other adverse effects delaying chemotherapy or radiotherapy for 1 week or more. MTD refers to a higher dose for DLT which developed in more than 4 patients.

**Results**

**Adverse events**

Forty-one patients completed a total of 80 courses of chemotherapy, and the efficacy and adverse events could be evaluated in 40 patients (79 courses). One patient in Group 3 refused and quit the second cycle of chemotherapy due to
abdominal pain. The 4th patient in Group 7 stopped chemotherapy because of grade 4 neutropenia and febrile pneumonia after the first cycle. Adverse events in each group are shown in Tables 1 and 2. No DLT occurred in 24 patients in Groups 1–4, and severe adverse events included four cases of grades 3–4 neutropenia, five grade 3 oral mucosal reaction, five grade 3 weight loss, and the rests were grades 1–2 adverse effects. Three patients in Group 5 had DLT with grades 3–4 neutropenia lasting for more than 1 week, including 2 patients with grade 3 oral mucosal reaction delaying radiotherapy over 1 week. In accordance with the trial design, another 3 patients were enrolled in Group 5, and were given G-CSF routinely as support treatment (Group 6). One patient had transient grade 4 neutropenia within 1 week and grade 3 mucosal reaction, and no DLT occurred. Dose was escalated in Group 7 and all 4 patients suffered from DLT, including three cases of grade 4 neutropenia, one of whom had combined fever and pneumonia; three cases of grade 3 diarrhea, and one grade 3 mucosal reaction lasting 10 days. Thus dose escalation was terminated, but the treatment was continued in 3 patients at dose level 5 (Group 8), resulting in no DLT occurrence. In this regimen, the DLT mainly included neutropenia, diarrhea and oral mucosal reactions. Severe thrombocytopenia was not found, and only 2 patients had grade 1 thrombocytopenia. Hemoglobin decrease was not found, except 1 case of liver metastasis and grade 3 anemia near the end of radiotherapy. There was no severe liver and kidney dysfunction, but ten cases of grades 1–2 liver dysfunction and 12 grades 1–2 renal dysfunction were observed. In addition to four cases of grade 3 vomiting, the rest had grades 1–2 reactions. The weight loss ranged from 1.5 to 10 kg, with an average of 3.6 kg. All patients had grade 2 hair loss. The main adverse events during radiotherapy was sore throat caused by mucosal inflammation. Radiotherapy was delayed for 7–10 days due to grade 3 mucosal reaction in 3 patients, including 2 in Group 5 and 1 in Group 7. Nine of 22 patients in Groups 4–8 required G-CSF support treatment because of leukopenia, but radiotherapy schedule was not affected. Adverse events in each group are shown in Table 1.

Table 1. Hematologic and non-hematologic toxicity

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Efficacy

Primary nasopharyngeal tumor was evaluated in 40 patients, and cervical lymph node was evaluated in 39 patients (1 case with negative lymph node).

Efficacy after neoadjuvant chemotherapy There were 8 CR (20%), 28 PR (70%) and 4 SD (10%), and the overall response rate (CR + PR) was 90%. There were 13 CR (32.5%), 24 PR (60%) and 3 SD (7.5%) for nasopharyngeal tumor alone. There were 17 CR (43.6%), 19 PR (48.7%) and 3 SD (7.7%) for cervical lymph node alone.

Efficacy after treatment There were 29 CR (72.5%), 10 PR (25%) and 1 SD (2.5%), and the overall response rate (CR + PR) was 97.5%. There were 35 CR (87.5%), 4 PR (10%) and 1 SD (2.5%) for nasopharyngeal tumor alone. There were 32 CR (82.1%) and 7 PR (17.9%) for cervical lymph node alone.

Discussion

The recommended dose of TPF neoadjuvant chemotherapy for advanced head and neck cancer in the foreign literature is taxotere 75 mg/m² (day 1), DDP 75 or 100 mg/m² (day 1), 5-FU 750 mg/m² (days 1–5) or 1000 mg/m² (days 1–4), repeated every 3 weeks. At this dose level, more than 70% of patients have grades 3–4 neutropenia, and 5%–12% of them will develop febrile neutropenia. G-CSF as support treatment and antibiotics are therefore proposed to be used routinely to prevent infection[6,7]. Our study shows that taxotere 60 mg/m² (day 1), DDP 60 mg/m² (day 1), and 5-FU 600 mg/m² (days 1–5), repeated every 3 weeks, is a safe dose for Orientals. In this regimen, the major hematological DLT is neutropenia, but less anemia and thrombocytopenia occur. In the group with recommended dose, neutropenia mostly occurs at the 7th–15th day of chemotherapy, commonly lasting 3–5 days without febrile granulocyte, so G-CSF and antibiotics are not routinely used. In the clinical studies of adverse effects with TPFCL carried out at Dana-Farber Cancer Institute[8], non-hematological DLT was mainly serious oral mucosal reaction, accounting for more than 45%, followed by diarrhea and nausea, each about 11%. The non-hematological DLT in this study was oral mucositis and diarrhea, which needed cleaning mouth, pain drug and antidiarheal treatment, but serious
Neoadjuvant chemotherapy with PF plus radiotherapy increases the local control rate of advanced nasopharyngeal carcinoma and advanced head and neck cancer. In recent years, with the clinical application of taxotere in head and neck cancer, taxotere combined with PF for advanced head and neck cancer achieved a short-term response rate of 75%–85% and CR rate of 25%–35%, while neoadjuvant chemotherapy with TPF for advanced head and neck cancer could get an overall response rate up to 90%–100% and CR rate up to 40%–61% or more[3,4]. In this study, the overall response rate after chemotherapy was 90% and CR rate was 20%. The reasons for low CR rate are: lower doses in Groups 1–4; fewer courses (only two courses) of neoadjuvant chemotherapy; and too early clinical evaluation (it is done immediately after chemotherapy). Efficacy is directly related to chemotherapy dose and course. Three courses of neoadjuvant chemotherapy are recommended for advanced head and neck squamous cell carcinoma abroad. In this study, the short-term overall response rate at the end of treatment was 97.5%, including CR rate of 72.5% and PR rate of 25%. The overall response rate is similar to the report by Hui et al.[3,4], which used two courses of neoadjuvant chemotherapy with TP plus concurrent chemoradiotherapy with DDP weekly, but the CR rate of our patients is lower by nearly 10%, suggesting that neoadjuvant chemotherapy plus concurrent radiochemotherapy can further improve the short-term efficacy.

In terms of long-term efficacy, Posner et al.[4] compared the long-term efficacy of neoadjuvant chemotherapy with TPF or PF plus concurrent chemoradiotherapy with carboplatin for 501 cases of advanced head and neck cancer, and found that the 3-year overall survival rate was 62% with TPF and 48% with PF (P = 0.006). Therefore, neoadjuvant chemotherapy with TPF plus platinum-based concurrent chemoradiotherapy has become the standard treatment for advanced head and neck squamous cell carcinoma.

Concurrent chemoradiotherapy is the standard treatment of advanced NPC, and neoadjuvant chemotherapy plus concurrent chemoradiotherapy is expected to further enhance the efficacy of advanced NPC. This study provides the MTD of TPF regimen as neoadjuvant chemotherapy for advanced NPC, and the recommended dose is taxotere 60 mg/m² (day 1), DDP 60 mg/m² (day 1) and 5-FU 600 mg/m² (days 1–5). We suggest to conduct a randomized controlled clinical study to compare the platinum-based concurrent chemoradiotherapy with or without TPF neoadjuvant chemotherapy for advanced NPC.

References