·Nasopharyngeal Carcinoma Column·

Comparison of the short-term efficacy of two inductive chemotherapy regimens for locally advanced nasopharyngeal caricinoma: docetaxal plus carboplatin versus 5-fluorouracil plus carboplatin

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[Abstract] Background and Objective: The platinum-based chemotherapy combined with 5-fluorouracil (5-FU) is most frequently used for nasopharyngeal carcinoma (NPC), but the efficacy has been maintained at 50%–60%. Docetaxel is an effective drug for head and neck tumors, its administration is simple, and the administration time is short. This study was to compare the short-term efficacy and toxicity between TC regimen (inductive chemotherapy with docetaxol plus carboplatin) and FC regimen (5-FU plus carboplatin) in local advanced NPC so as to provide a new chemotherapeutic regimen for NPC. **Methods:** Fifty-eight local advanced NPC patients without previous treatment in Sun Yat-sen University Cancer Center were randomly assigned to receive either TC or FC regimen inductive chemotherapy, followed by concurrent chemoradiotherapy with two cycles of carboplatin (AUC=6) plus radiotherapy of 60–78 Gy to the nasopharynx and 60–70 Gy to the neck. The short-term efficacy and adverse events were observed. **Results:** More chemotherapy cycles were finished in TC group than in FC group (3.31 vs. 2.83, $P = 0.043$). There was no significant difference in short-term efficacy and 1-year survival rate between the two groups ($P > 0.05$). More grades 3–4 neutropenia appeared in TC group than in FC group (72.4% vs. 37.9%, $P < 0.05$), whereas less thrombocytopenia and emesis occurred in TC than in FC group ($P = 0.013$ and 0.018, respectively). **Conclusions:** The short-term efficacy of TC regimen in local advanced NPC is similar to that of FC regimen with tolerable adverse events. But the long-term outcomes and toxicities need to be further investigated.

Key words: Nasopharyngeal neoplasm, docetaxel, efficacy, adverse events

Nasopharyngeal carcinoma (NPC) is the most common head-and-neck malignancy in southern China. Platinums combined with 5-fluorouracil (5-FU) is the most frequently used chemotherapy for NPC patients[1,2]. However, the response rate has been maintained at 50%–60%. As an effective monotherapy for head-and-neck malignancies[3], docetaxol is characterized by simple and short-term administration. Chan *et al.*[4] reported that the 2-year survival rate and disease-free survival rate were 91.8% and 78.5%, respectivelyin patients with local advanced NPC who were treated by two cycles of inductive chemotherapy with docetaxol plus carboplatin (TC) and subsequent concurrent chemotherapy with cisplatin. In the hope of seeking for new schemes to improve the therapeutic efficacy for localadvanced NPC, we compared TC scheme and 5-FU plus carboplatin (FC) scheme in treating NPC patients in terms of short-term response rate, toxicity and side effects and tolerability.

Materials and Methods

Patient data

Inclusion criteria: patients aged between 18 and 60 years; no contraindications for chemotherapy; pathology confirmed differentiated or undifferentiated non-keratinizing carcinoma (by WHO classification); the disease was clinically rated as stage III, IVa or IVb (by UICC staging system 2002); the patients were initial treated and without chemotherapy-, surgery- or radiotherapy; general condition was good, with a Karnofsky (KPS) score of $\geqslant$ 80. Exclusion criteria: those who had pathologically confirmed type I tumor (based on WHO system) or

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This paper was translated from Chinese into English by Guo-Ping Shen and edited by Wei Liu on 2009-08-07.

The Chinese version of this paper is avaiable at http://www.cjcsysu.cn/cn/article.asp?id=16463.

Received: 2009-08-10; Accepted: 2009-10-20

Grant: Health Department of Guangdong Province (No. B200606s)

adenocarcinoma; those aged > 60 or < 18 years; KPS score < 80; abnormal liver and kidney functions; heart disease or impaired heart function; those who had received surgery for primary or metastatic lesions and those who had received radiotherapy or chemotherapy.

Between November 1st, 2005 and December 1st, 2008, a total of 58 patients with mid- or late-stage NPC were randomly divided into testing group and control group as stratified by clinical staging and genders. The median age was 46 years in testing group and 43 years in control group. Clinical data were generally consistent between the two groups, with statistically insignificant difference ($P > 0.05$) (Table 1).

Table 1 Clinical characteristic of 58 patients in testing group (TC regimen) and control group (TC regimen)

Characteristic	TC regimen (patient No.)	FC regimen (patient No.)	*P*
Gender			0.753
Male	23	22	
Female	6	7	
Stage			0.919
III	16	16	
IVa	8	9	
IVb	5	4	
T stage			0.352
T1	3	0	
T2	3	4	
T3	15	17	
T4	8	8	
N stage			0.854
N0	4	6	
N1	10	11	
N2	10	8	
N3	5	4	

Group assignment and treatment schemes

Testing group (TC regimen) was given two cycles of inductive chemotherapy with docetaxol (70 mg/m^2) combined with carboplatin (AUC = 6), with three weeks in each cycle. After that, two cycles of carboplatin monotherapy (AUC = 6) were conducted as concurrent chemotherapy, with three weeks in each cycle. In control group (FC regimen), docetaxol was replaced by 5-FU; treatment otherwise was the same as in testing group. Within three days before, during and within three days after docetaxol treatment, oral dexamethasone 7.5 mg was administered every 12 h to prevent possible sodium and fluid retention caused by docetaxol. Radiotherapy was given with cobalt-60 (^{60}Co) or 6 MV or 8 MV photon beam by linear accelerator, at the dosage of 2.0 Gy/fraction and 5 fractions/week. Radiation dosage was 60–78 Gy in the nasopharynx and curative dosage of 60–70 Gy in cervical lymph nodes. Radiotherapy was completed within six to nine weeks.

Evaluation criteria for therapeutic efficacy

Short-term efficacy was evaluated by physical examination, nasopharyngofibroscope and MRI at the end of inductive chemotherapy and at three months after radiotherapy. According to the Response Evaluation Criteria in Solid Tumors by WHO in 2003, response was rated as complete remission (CR), partial remission (PR), stable disease (SD) or progressive disease (PD).

Evaluation criteria for adverse events

Adverse events were evaluated based on the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE 3.0).

Statistical methods

Comparisons of short-term efficacy and adverse events after treatment were performed between the two groups using χ^2 test; Kaplan-Meier method was used for analyses on survival. All statistical processing was conducted by SPSS13.0 software. Difference was considered statistically significant when $P < 0.05$.

Results

Treatment compliance in two groups of patients

Each group of patients was supposed to receive 116 cycles of chemotherapy in total, with two cycles of inductive chemotherapy and two cycles of concurrent chemotherapy for each patient. In testing group, a total of 95 cycles of chemotherapy were completed, including 57 cycles of inductive chemotherapy and 38 cycles of concurrent chemotherapy. In this group, 13 patients completed all the chemotherapy as planned. In control group, a total of 86 cycles of chemotherapy were completed, including 57 cycles of inductive chemotherapy and 29 cycles of concurrent chemotherapy. Eight patients completed all the chemotherapy as planned. Due to grade IV myelosuppression, one patient in testing group and one in control group completed just one cycle of inductive chemotherapy. The average number of chemotherapy cycles was 3.31 and 2.83 in testing group and control group, respectively, with statistically significant difference ($P = 0.043$).

Short-term efficacy

Efficacy in primary nasopharyngeal lesion and metastatic lesions in cervical lymph nodes was evaluated for the two groups of patients at the end of inductive chemotherapy and at three months after overall treatment. No significant difference was found in terms of short-term efficacy. At three months after treatment, one patient of testing group and one of control group had incomplete remission of nasopharyngeal lesion; one patient of testing group and two of control group had incomplete remission of regional lymph nodes. However, complete remission was seen for these lesions at six months after the treatment even without further intervention (Table 2).

Survival profile

Survival analyses with Kaplan-Meier showed that the 1-year survival rates were 96.2% and 100% in testing group and control group, respectively, with statistically insignificant difference ($P = 0.317$). During one year of follow-up, three patients of testing group and one patient of control group developed distant

Table 2 Short-term efficacies after inductive chemotherapy and three months after concurrent chemoradiotherapy

Group	Lesion site	After inductive chemotherapy (patiert No.)				Three months after treatment (patient No.)			
		CR	PR	SD	PD	CR	PR	SD	PD
TC regimen	Nasopharynx	0	28	1	0	28	1	0	0
	Lymph node	3	19	3	0	24	1	0	0
FC regimen	Nasopharynx	1	28	0	0	28	1	0	0
	Lymph node	7	15	1	0	21	2	0	0

CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease.

metastasis; among the patients of control group, no local recurrence was seen within one year of follow-up, but one patient in control group had nasopharyngeal recurrence.

Adverse events

Hematological adverse events The occurrence rates of grades III–IV leukopenia were 55.2% and 20.7% in testing group and control group (P = 0.008), and those of grades III–IV neutropenia were 72.4% and 37.9%, respectively (P = 0.005). In testing group, 15 (51.7%) patients had grade IV neutropenia; median time to normal neutrophil level after supportive treatment with colony stimulating factor was 4.5 days (range, 2–9 days). The occurrence rate of thrombocytopenia was lower in testing group than in control group (P = 0.013), but no significant difference was seen for the occurrence rate of anemia between the two groups (P > 0.05). One patient each from testing group and control group gave up the second cycle of inductive chemotherapy due to grade IV myelosuppression and poor efficacy of supportive treatment (Table 3).

Non-hematological adverse events Incidence of grades I–II alopecia in testing group was 100%. In this group, ten patients experienced grades I–II weight gain during treatment and three of them had gained more than 10% of body weight. In all these patients, the body weight restored to pre-treatment level at the end of the treatment. After the inductive chemotherapy, one patient presented swollen lower extremities, which was relieved after diuretic treatment. Another patient presented allergic reactions including mild dyspnea and reddish eruption in upper extremities during inductive chemotherapy and was improved after infusion rate was reduced and anti-anaphylaxis was given. Digestive reactions, mostly grade II nausea and vomiting, were more prominent in control group than in testing group (P = 0.018). After the first cycle of inductive chemotherapy, one female patient experienced grade II diarrhea and two patients had grade II mucositis (Table 3).

Table 3 Major adverse events after/during chemotherapy

Adverse event	TC regimen (patient No.)	FC regimen (patient No.)	P
Leukopenia			0.008
G0	1	3	
G1 + G2	12	20	
G3 + G4	16	6	
Neutropenia			0.005
G0	1	6	
G1 + G2	7	12	
G3 + G4	21	11	
Hemoglobin			0.729
G0	10	12	
G1	14	11	
G2	5	6	
Thrombocytopenia			0.013
G0	28	21	
G1 + G2	1	6	
G3 + G4	0	2	
ALT elevated			0.591
G0	21	22	
G1 + G2	7	7	
G3 + G4	1	0	
Emesis			0.018
G0	25	15	
G1	1	4	
G2	3	10	

Discussion

Comprehensive strategy including radiotherapy and chemotherapy is currently the golden standard of treatment for patients with locally advanced NPC, whereas platinum-based chemotherapy is the most frequently used scheme for NPC patients[1,2]. The latest meta-analysis showed that radiotherapy combined with chemotherapy could increase the 5-year survival rate by 4%–6% and reduce the risk for death by 18% in patients with locally advanced NPC; it was also found that concurrent chemotherapy provided maximal survival benefit while inductive chemotherapy was slightly better in reducing distant metastasis[5,6]. As an emerging new type of agents in recent years, taxanes (taxol and docetaxol) provide excellent efficacy for various kinds of solid tumors[7]. A phase I/II clinical trial demonstrated that TPF scheme provided a significantly higher 3-year survival rate than PF scheme in treating head-and-neck squamous cell carcinoma[8]. Hui *et al*.[9] reported that patients with locally advanced NPC who were treated by two cycles of inductive chemotherapy with docetaxol plus cisplatin and then concurrent chemotherapy with cisplatin had a significantly higher 3-year progression-free survival rate than those who were only given concurrent chemotherapy

(88.2% vs. 59.5%), and the toxicity and side effects were tolerable. Carboplatin provides radio-sensitization as much as cisplatin, but induces milder gastrointestinal reactions and hematological toxicity than cisplatin[10-14]. Chitapanarux *et al.*[15] reported a phase III clinical trial, which showed that the total survival rate and disease-free survival rate in patients with locally advanced NPC were not significantly different between carboplatin group and cisplatin group, but patients of carboplatin group had significantly less renal toxicity, leukopenia and anemia and better compliance than those of cisplatin group. Chan *et al.*[4] reported that the 2-year survival rate and disease-free survival rate were 91.8% and 78.5% , respectively, in patients with localadvanced NPC who were treated by two cycles of inductive chemotherapy with docetaxol plus carboplatin and subsequent concurrent chemotherapy with cisplatin.

In this study, we observed the short-term efficacy and adverse events with inductive chemotherapy of docetaxol combined with platinums. The results revealed statistically insignificant differences when comparing the response rates in primary nasopharyngeal lesion and regional metastatic lymph nodes of inductive chemotherapy of docetaxol plus carboplatin to those of control group. Therefore, TC scheme could produce similar short-term efficacy as FC scheme. But the follow-up duration was short. Whether or not the tested scheme could provide long-term survival benefit for the patients had to be seen in further follow-ups.

The hematological toxicity in testing group was similar to that shown in previously published reports[16-18]. The main toxicity was neutropenia. During inductive chemotherapy and concurrent chemotherapy, testing group had a higher incidence of grade III neutropenia; statistically significant difference was revealed as compared with control group. But it took just a few days to restore normal neutrophil level after treatment with granulocyte colony stimulating factor, so the chemotherapy would not be delayed or discontinued if supportive treatment was given in a timely manner. However, thrombocytopenia was more common in control group. Since supportive treatment strategies for thrombocytopenia were limited, it had become one of the reasons for treatment delay or discontinuation.

In terms of non-hematological toxicity, we found that, beside prominent alopecia, ten patients with TC scheme experienced weight gain, which was probably due to fluid retention. But the patients did not report significant discomfort, and their body weight returned to the normal level at the end of the treatment. Furthermore, chest X-ray and abdominal B ultrasonic examination revealed no hydrothorax or ascites, and the weight gain had not caused any treatment delay for the patients. Testing group had less other non-hematological toxicity than control group; in particular, gastrointestinal reactions were markedly milder than those in control group.

Patients of testing group had completed more cycles of chemotherapy as scheduled than those in control group, suggesting that patients had better compliance and tolerance with TC regimen than with FC regimen. Moreover, since administration of docetaxol is convenient and takes a minimal amount of time, docetaxol plus carboplatin administration can be completed within just one day, thus reducing the hospitalization stay for the patients. In conclusion, TC scheme provides reliable short-term efficacy and tolerable toxicity and side effects in treating local advanced NPC. It produces better compliance in the patients than FC scheme. But its long-term efficacy should be confirmed by further follow-up studies.

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