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ORIGINAL ARTICLE

Phase II study of capecitabine and cisplatin combination as first-line chemotherapy in Chinese patients with metastatic nasopharyngeal carcinoma

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Abstract
Purpose Cisplatin combined with 5-fluorouracil (5-Fu) is widely used in the management of advanced nasopharyngeal carcinoma (NPC). However, catheters and pumps are necessary for the continuous infusion of 5-Fu, which add to the cost, immobility and inconvenience of treatment. Capecitabine, an oral fluoropyrimidine, is a potentially more active and more convenient substitute to 5-Fu. A phase II study was conducted to evaluate the efficacy and safety of a capecitabine and cisplatin combination in metastatic NPC.
Patients and methods In the multicenter, open-label, single-arm phase II study, patients with metastatic NPC who previously received no palliative chemotherapy were enrolled. Patients received oral capecitabine (1,000 mg/m^2 twice daily from day 1 to 14) and intravenous cisplatin (80 mg/m^2, day1) every 3 weeks.
Results A total of 48 patients were enrolled and included in the intention-to-treat analysis of efficacy and adverse events. There were 3 patients (6.3%) with complete response and 27 patients (56.3%) with partial response, giving an overall response rate of 62.5% (95% CI, 49.1–76.4%). The median duration of response in the 30 responding patients was 7.5 months (range 1.4–22.4 months). With a median follow-up period of 13.3 months (range 2.3–50 months), the median time to progression and median overall survival for all patients were 7.7 months (95% CI, 6.3–9.2 months) and 13.3 months (95% CI, 9.4–17.2 months), respectively. Toxicities were moderate and manageable. Grade 3/4 toxicities included neutropenia (14.6%), anemia (4.2%) and thromocytopenia (2.1%), nausea (8.3%), vomiting (10.4%), diarrhea (8.3%), stomatitis (6.3%) and hand–foot syndrome (HFS) (4.2%).
Conclusions The combination of capecitabine and cisplatin is active and well tolerated as a first-line therapy for patients with metastatic NPC.

Keywords Nasopharyngeal carcinoma · First-line chemotherapy · Cisplatin · Capecitabine

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Introduction

Nasopharyngeal carcinoma (NPC) is endemic in southern China. Eighty cases per 100,000 populations are reported. Non-keratinizing, poorly differentiated and undifferentiated (World Health Organization [WHO] type 2 and 3) NPC are the most common subtypes of NPC and sensitive to

chemotherapy. The prognosis of patients with metastatic disease is reported to be poor, with a median survival time less than 12 months [1].

Platinum-based combination chemotherapy is considered a cornerstone in the management of metastatic or recurrent NPC. Previous clinical studies have shown that the platinum-based combination resulted in higher response rates than other drug combinations, (approximately 50–90% with a complete response rate of 5–30%) [2–8]. Of the platinum-based combination, cisplatin combined with 5-fluorouracil (5-Fu) is widely used as one of the standard regimens [9]. However, catheters and pumps are necessary for continuous infusion of 5-Fu, which add to the cost, immobility and inconvenience of the treatment.

The oral fluoropyrimidine capecitabine (Xeloda, Hoffmann-La Roche) was rationally designed to preferentially generate 5-Fu in tumors and mimic continuous-infusion of 5-Fu without the complications and inconvenience associated with the central venous access. The tumor selectivity is achieved through exploiting the significantly higher activity of thymidine phosphorylase (TP) in many tumor tissues compared with healthy tissues [10]. In a preclinical study, capecitabine resulted in consistently higher tissue-to-plasma concentration ratios of 5-Fu than 5-Fu administered intravenously [11]. In addition, capecitabine showed activity in patients with metastatic colorectal cancer refractory to 5-Fu/leucovorin chemotherapy [12]. This could potentially result in a higher therapeutic index for capecitabine compared with other fluoropyrimidines.

Capecitabine is an active single agent and its safety profile differs from that of cisplatin with little overlap of key toxicities to cisplatin. These good attributes make capecitabine/cisplatin combination an appealing alternative to cisplatin–5-Fu combination. The current multicenter, open-label, single arm phase II study was conducted to evaluate the efficacy and safety of capecitabine/cisplatin combination as a first-line regimen in Chinese patients with metastatic NPC.

Patients and methods

Eligibility of patients

Patients aged 18–75 years with measurable target lesion pathologically confirmed advanced or metastatic NPC diseases were eligible for the study. Prior chemotherapy for advanced disease was not permitted. However, neoadjuvant or concurrent chemotherapy was allowed, provided that the treatment was completed at least 6 months before the start of the current study. Patients were required to have Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, with a life expectancy $\geq$3 months, an adequate bone marrow, liver and kidney function, as indicated by an absolute neutrophil count (ANC) $\geq$1,500/uL, a platelet count $\geq$100,000/uL, serum creatinine $\leq$2.0 mg/dL, serum bilirubin $\leq$1.5 mg/dL, and serum alanine aminotransferase $\leq$2.5 times higher than the upper limit of the normal (except in those cases with liver involvement when a value $\leq$5 times the upper limit of the normal was accepted). All patients were given written informed consents to participate in this study.

Exclusion criteria included unresolved bowel obstruction or malabsorption syndrome, clinical apparent central nervous system metastases, prior malignancies (other than non-melanoma skin cancer or in situ cervical cancer) within the previous 5 years, and uncontrolled infection or severe comorbidity such as myocardial infarction within 6 months or symptomatic heart diseases. Pregnant or lactating women were excluded from the study; women with childbearing potential were required to agree to have adequate contraception.

Treatment

Capecitabine was administered orally at a dose of 1,000 mg/m^2 twice daily (14 days of treatment followed by a 7-day resting period). Cisplatin was administered intravenously on day 1 (before the first dose of capecitabine) at a dose of 80 mg/m^2 with simultaneous hydration and diuresis at first 3 days. A serotonin antagonist and dexamethasone were routinely given before cisplatin administration to prevent emesis. The regimen was repeated every 3 weeks. The planned number of treatment cycles was six. Treatment was continued until the disease progression, unacceptable adverse reactions or patients' voluntary withdrawal.

Evaluation of efficacy

The primary end point was response rate (RR). Duration of the response, time to progression (TTP) and overall survival (OS) were estimated as secondary end points by the Kaplan–Meier method. Tumor response was assessed according to the response evaluation criteria in solid tumor (RECIST) [13]. Evaluation of response was performed every two cycles during the chemotherapy and then every 3 months after the completion of the chemotherapy. Duration of response was calculated for all responders from the onset of complete response (CR) or partial response (PR) until the first evidence of disease progression. If death occurred before a progression was documented, the date of death was to be the date of the disease progression. TTP was calculated from the date of entry into the study until the date of progression and the OS was measured from the date of entry to the date of the last follow-up or death.

Evaluation of safety and dose modification

Adverse events (AEs) were evaluated before each treatment cycle according to the National Cancer Institute Common Toxicity Criteria (NCI–CTC) version 2.0. For hand–foot syndrome (HFS), the following grading system was used: grade I: numbness, dysesthesia, painless swelling or erythema not disrupting normal activities; grade II: painful erythema and/or symptom affecting daily living activities; grade III: ulceration, blistering, moist desquamation, and/or severe pain or symptom making the patient unable to work or perform the daily living activities.

All patients were screened for medical history and underwent a physical examination. Complete blood cell counts (CBCC) were performed every week; blood biochemical tests and electrocardiogram were performed before every cycle. To begin the next treatment cycle, each patient was required to have a platelet count ≥75,000/uL, a neutrophil count ≥1,000/uL, a serum creatinine <1.5 mg/dL and a resolution or improvement of clinically significant non-hematological adverse events (excluding alopecia) to grade 1 or 0. If the treatment was delayed for 3 weeks, patients were excluded from the study.

The dose of capecitabine was adjusted for adverse events of grade 2 or higher intensity, according to the standard scheme, described in detail by Blum et al. [14]. Cisplatin dose reductions were required for serum creatinine >2.0 mg/dL, grade 4 neutropenia or anemia, grade 3 nausea or emesis or grade 4 emesis (in setting of optimal antinausea therapy), or other grade 3 or 4 toxicities by NCI–CTC criteria. Patients on protocol were initially treated with 80 mg/m^2 of cisplatin every 3 weeks; dose level 1 was 60 mg/m^2 and dose level 2 was 45 mg/m^2. If serum creatinine was >2.5 mg/d, the patient was excluded from the study. The use of growth factor was permitted. When doses were reduced for toxicity, re-escalation of dose was not permitted.

Statistical analysis

The optimal two-stage design described by Simon (1989) for a phase II clinical trial [15] was used to calculate the sample size, based on the following assumptions: alpha error, 0.1; beta error, 0.1; clinically uninteresting true response rate, 40%; and sufficiently promising true response rate, 60%. As a result, this trial was designed to treat an initial cohort of 18 patients, with a termination of the trial if there were seven or fewer responses. If there were more than seven responses, the trial would proceed to the second stage, with the total enrollment of 41 patients.

All enrolled patients were included in the intention-to-treat (ITT) analysis of efficacy and AEs. The primary endpoint was overall response rate as assessed by the investigators. The 95% CI for response risk was calculated. Duration of response, TTP and survival were estimated by Kaplan–Meier analysis. Safety analyses were based on a safety population who received at least one dose of the study medication.

Results

Patient characteristics

Between June 2002 and July 2006, a total of 48 patients from six centers (including State Key Laboratory of Oncology in Southern China, Cancer Center, Sun Yat-Sen University; Tumor Hospital, the First People's Hospital of Foshan; Tongji Hospital of Tongji Medical College of Huazhong University of Science and Technology; Central Hospital of Guangdong Province Agricultural Reclamation; Shantou Central Hospital; Shunde TCM-integrated Hospital) were enrolled. Their baseline characteristics are shown in Table 1.

Table 1 Patients' characteristics

Characteristics	No. of patients (n = 48)	%
Age (years)	Median 49 (range, 32–69)	
Sex		
Female	13	27.1
Male	35	72.9
ECOG performance status		
0	4	8.3
1	40	83.3
2	4	8.3
Tumor involved site		
Nasopharyngeal	5	10.5
Lymph node	19	39.6
Lung	23	47.9
Liver	16	33.3
Bone	7	14.6
Number of involved site		
1	28	58.3
2	15	31.2
≥3	5	10.5
Prior treatment (cases)		
Treatment-naive	10	20.8
Radiation	38	79.2
Operation[a]	5	10.5
Induction or concurrent chemotherapy	5	10.5

ECOG Eastern Cooperative Oncology Group

[a] Operation indicates dissection of residual cervical lymph node

Adverse events

A total of 181 cycles of chemotherapy were given and the patients received a median four cycles (range, 1–8 cycles). AEs frequencies in this population are listed in Table 2. The most common hematological AE was neutropenia which occurred with grade 3/4 in 7 patients (14.6%). Febrile neutropenia was observed in 4 patients (8.3%). Although these cases were successfully treated with antibiotics and granulocyte colony stimulating factor (G-CSF), 3 patients withdrew their consents after febrile neutropenia. Grade 3 anemia was observed in 2 patients (4.2%) and a grade 4 thromocytopenia was observed in 1 patient (2.1%). The most common non-hematological AEs were nausea (91.7%) and vomiting (68.7%). Grade 3 nausea and vomiting were observed in 4 patients (8.3%) and in 5 patients (10.4%), respectively. One patient with grade 3 vomiting withdrew her consent. Hand-foot syndrome (HFS) was observed in 7 patients (14.7%) with grade 3 in 2 patients (4.2%). Other grade 3 non-hematological AEs included diarrhea (8.3%), and stomatitis (6.3%). Hepatic, renal and other toxicities were mild. No treatment-related death occurred during this study.

Efficacy

A total of 42 patients were assessable for response. Two patients were not evaluated because of loss to follow-up after two cycles, and 4 patients withdrew the consents because of toxicities after one cycle. According to ITT analysis of efficacy, 3 patients (6.3%) had CR, 27 patients (56.3%) had PR, 9 patients (18.8%) had SD and 3 patients had PD (6.3%). The confirmed response rate was 62.5% (95% CI, 49.1–76.4%), and the disease control rate (CR + PR + SD) was 81.3% (95% CI, 70.8–92.6%).

The median follow-up period was 13.3 months (range, 2.3–50 months). The median duration of response in the 30 responding patients was 7.5 months (range, 1.4–22.4 months). The median TTP for all patients was 7.7 months (95% CI, 6.3–9.2 months; Fig. 1a). The median OS was 13.5 months (95% CI, 9.4–17.2 months; Fig. 1b), with a 1-year survival rate of 65%.

Discussion

Recurrent or metastatic NPC remains a largely incurable disease. Systematic combined chemotherapy has been the mainstay of treatment for this patient population. Although a wide range of cytotoxic chemptherapeutic agents, such as the platinum, 5-fluorouracil, texane, gemcitabine, oxallipatin, and irinotecan, have been used, platinum-based chemotherapy is an indispensable part of the treatment for patients with advanced NPC, whether in the metastatic or curative settings. Cisplatin in combination with continuous infusion of 5-Fu over 120 h as a first-line therapy is widely accepted

Table 2 Adverse events assessment (n = 48)

Adverse event	NCI–CTC grade (% of patients)					Grade 3/4(%)
	1	2	3	4	Any	
Hematological						
Leucopenia	15(31.3)	13(27.1)	4(8.3)	3(6.3)	35(72.9)	14.6
Anemia	7(14.6)	5(10.4)	2(4.2)		14(29.2)	4.2
Thromocytopenia	11(22.9)	1(2.1)		1(2.1)	13(27.1)	2.1
Non-hematological						
Nausea	14(29.2)	26(54.2)	4(8.3)		44(91.7)	8.3
Vomiting	18(37.5)	13(27.1)	5(10.4)		36(75.0)	10.4
Diarrhea	2(4.2)	1(2.1)	4(8.3)		7(14.6)	8.3
Stomatitis	4(8.3)	1(2.1)	3(6.3)		8(16.7)	6.3
Hand-foot syndrome	3(6.3)	2(4.2)	2(4.2)		7(14.7)	4.2
Neutropenia fever	1(2.1)	2(4.2)	1(2.1)		4(8.3)	2.1
Pigmentation	9(18.8)	1(2.1)			10(20.8)	
Fatigue	8(12.7)	1(2.1)			9(18.8)	
Neuropathy	6(12.6)	1(2.1)			7(14.6)	
Hepatic						
AST	3(6.3)	1(2.1)			4(8.3)	
ALT	3(6.3)	1(2.1)			4(8.3)	
Renal						
Serum creatine	1(2.1)	1(2.1)			2(4.2)	

AST Aspartate aminotransferase, *ALT* alanine aminotransferase

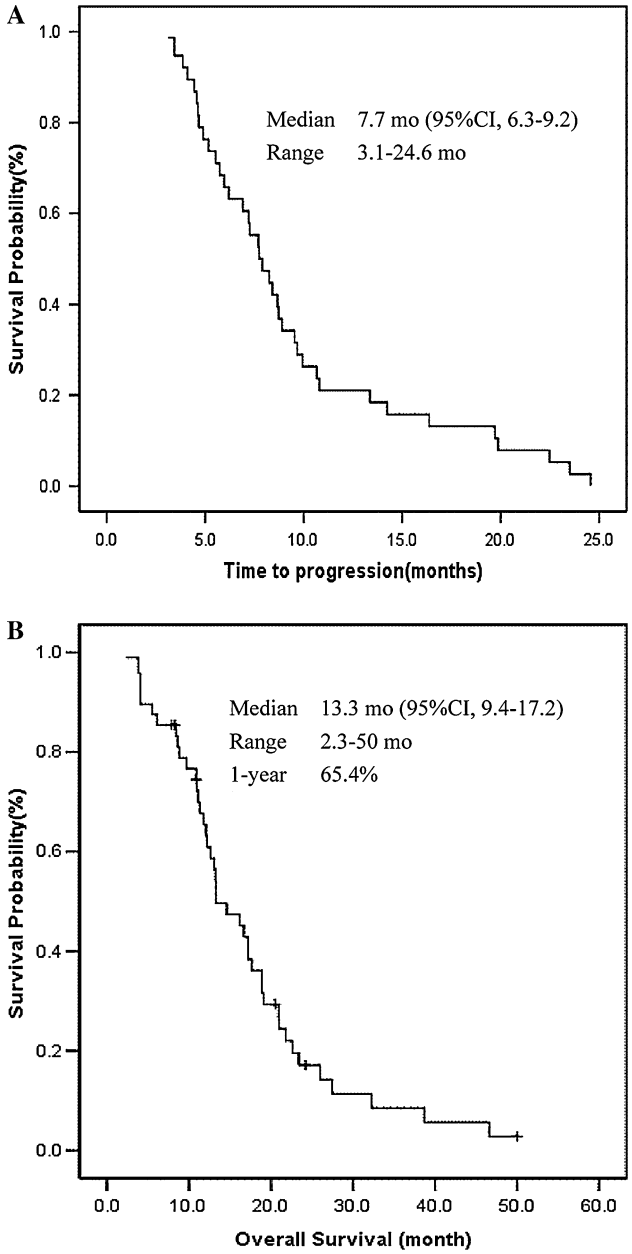

Fig. 1 (**a**) Progression-free survival and (**b**) overall survival

with a RR of 50–65%, a median OS of 11 months and a favorable safety profile [2–4]. Capecitabine, an oral agent that mimics the continuous infusion of 5-Fu without those complications associated with the central venous access, may be a convenient, well-tolerated alternative to the continuous infusion of 5-Fu.

Previous clinical data showed that capecitabine as a single agent was effective to NPC. Chua et al. [16] reported a phase II study in which 17 Chinese patients with platinum-refractory advanced NPC received capecitabine (at a dose of 1,250 mg/m^2 twice daily) in a three-times weekly cycle. The overall RR was 23.5% with a median TTP of 4.9 months and median OS of 7.6 months. Treatment-related AEs were reported to be generally mild except for the HFS, which occurred in 58.8% patients [15]. Additionally capecitabine in combination with cisplatin is reported as an effective and well-tolerated regimen in patients with advanced gastric cancer, advanced biliary cancer, squamous cell carcinoma of the head and neck as well as other solid tumors [17–20]. The efficacy demonstrated in these studies may be is due to the additive or synergetic antitumor activity between the two agents. It seemed very rational and compelling to treat NPC with a combination of 5-Fu and capecitabine. However, to our knowledge, there is no report of this particular combination in the treatment of NPC.

In our current study, the overall RR was 62.5% (81.2% for 42 valuable patients), while the disease control rate was 81.3% with a median TTP of 7.7 months and a median OS of 13.3 months. The result seemed to be similar or somewhat superior to those achieved by platinums in combination with 5-Fu or some other new chemotherapeutic agents (e.g., gemcitabine, taxol or taxotere) as a first-line treatment [6–8]. The combination of docetaxel and cisplatin has been reported to achieve a response rate of 62.5%, a median TTP of 5.6 months and a median OS of 12.4 months. The combination of cisplatin and gemcitabine had a response rate of 73%, a median TTP of 5.3 months and a median OS of 15 months. The combination of carboplatin and paclitaxel was reported to achieve a response rate of 59%, a median TTP of 5.9 months and a median OS of 13.9 months. From our current study results, whether capecitabine in combination with cisplatin is indeed comparable or superior to platinum combined with 5-Fu or other platinum-based regimens in term of efficacy has not yet been fully demonstrated and requires further clinical study. There have been reports of long-term disease-free survivors in metastatic undifferentiated carcinoma of nasopharyngeal type who achieved CR to systemic chemotherapy [21]. It is encouraging to note that in our study, one patient with multiple liver, bone and cervical lymph node metastases, who was treated with the capecitabine/cisplatin regimen and achieved CR, survived more than 50 months and is still alive.

The most common adverse events with the capecitabine/cisplatin combination were nausea and vomiting, which may be attributed to cisplatin, a highly emetogenic agent. Anti-emetic treatment comprising serotonin antagonists and dexamethasone was routinely administered prior to the infusion of cisplatin with good patients' compliance. As a result, Grade 3 nausea and vomiting occurred in 8.3 and 10.4% of patients respectively. The main hematological toxicity was neutropenia, which occurs rarely with single-agent capecitabine [22, 23]. Grade 3/4 neutropenia occurred in 14.6% of patients. Four patients developed febrile neutropenia and were successfully treated with antibiotics and G-CSF. There were no treatment-related deaths.

Among 4 patients who withdrew informed consents voluntarily, one suffered Grade 3 vomiting and the other three suffered febrile neutropenia. HFS was common to capecitabine due to yet unknown mechanism. However, in this study, this AE was mild with the total incidence rate of 14.7% and grade 3 occurred in 4.2% of patients, which maybe attributed to the lower dose and fewer cycles of capecitabine.

In conclusion, the results from our phase II study demonstrated that the combination of capecitabine and cisplatin is active and well tolerated as a first-line therapy for patients with recurrent or metastatic NPC. It provides NPC patients with an effective, safe and convenient chemotherapeutic strategy.

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