

• Clinical Research •

A phase II trial of docetaxel plus nedaplatin and 5-fluorouracil in treating advanced esophageal carcinoma

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[Abstract] Background and Objective: Accumulating data indicate that docetaxel plus cisplatin and 5-fluorouracil has certain effect on advanced gastric or gastro-oesophageal junction adenocarcinoma. This study was to evaluate the efficacy and toxicity of docetaxel plus nedaplatin and 5-fluorouracil (DNF regimen) in treating advanced esophageal carcinoma. **Methods:** Forty-three patients with pathologically confirmed advanced esophageal carcinoma treated by DNF regimen: intravenous infusion of docetaxel (75 mg/m²) over 1 h, intravenous infusion of nedaplatin (100 mg/m²) over 3 h, intravenous infusion of leucovorin (CF, 200 mg/m²) over 2 h, intravenous injection of 5-fluorouracil (375 mg/m²) over 10 min, followed by a 46-hour infusion of 5-fluorouracil (2.6 g/m²). The cycle was repeated every three weeks. Treatment efficacy was evaluated every two weeks according to the WHO standards. All patients received at least two cycles of chemotherapy. **Results:** Patients received a total of 144 cycles of treatment, and all were evaluable for efficacy and toxicity. Of the 43 patients, 2 (4.65%) achieved complete response (CR), 25 (58.14%) achieved partial response (PR), 9 (20.93%) had stable disease (SD), and 7 (16.28%) had progressive disease (PD). The overall response rate was 62.8%. The median time-to-progression (TTP) was 201 days and the median survival time (MST) was 310 days. Grade III/IV adverse events mainly included neutropenia (20.93%), febrile neutropenia (4.65%), thrombocytopenia (6.98%) and vomiting (9.30%). One patient died of grade IV thrombocytopenia. **Conclusion:** DNF regimen is effective for and well tolerated by patients with advanced esophageal carcinoma.

Key words: Esophageal neoplasm, chemotherapy, nedaplatin, docetaxel, 5-fluorouracil

Esophageal carcinoma is a common malignant gastrointestinal tumor in China, with poor prognosis. Lymph node metastasis and distant metastasis may occur at early stage. In China, most cases of esophageal cancer were diagnosed at advanced stage and can not be treated by radical surgery [1-3]. Nowadays, esophageal carcinomas are mainly treated with multi-disciplinary sequential or simultaneous treatment composed by surgery, radiotherapy and chemotherapy. Certain progression was achieved in treating advanced esophageal carcinoma by chemotherapy in recent years. Accumulating data indicate the response rate of patients with advanced gastric or gastro-esophageal junction adenocarcinoma treated by DCF regimen [docetaxel plus cisplatin (DDP) and 5-fluorouracil (5-FU)]

was up to 54%–86% [4-6]. Forty-three patients with pathologically confirmed advanced esophageal carcinoma were treated with docetaxel plus nedaplatin and 5-FU (DNF regimen) in Hexian Memorial Hospital at Panyu District of Guangzhou between August, 2003 and February, 2009. The results were as follows.

Materials and Methods

General data

All the 43 patients had either distant metastasis or postoperative recurrence, or unresectable lesions, and had at least one measurable lesion which was pathologically confirmed. Of the 43 patients, 29 were men and 14 were women, aged 35 to 72 years old, with a median of 55; 17 had well differentiated squamous cell carcinoma, 12 had poorly differentiated squamous cell carcinoma, 13 had adenocarcinoma, and 1 had adenosquamous carcinoma; 26 had cervical lymph node metastasis, 33 had mediastinal and lung metastasis, 8 had celiac lymph node metastasis, 13 had liver metastasis; 17 had 1 metastatic lesion, 19 had 2 metastatic lesions, 7 had 3 or more metastatic lesions; 9 underwent radical or palliative surgery (7 of them received adjuvant chemotherapy), 4 had recurrence after

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radiotherapy, and 30 were naive patients KPS score of no less than 60, with an estimated survival of more than three months. The functions of patients' heart, lungs, liver and kidneys were normal. No history of other malignancy was recorded.

Treatment

On day 1, the patients received intravenous infusion of docetaxel (75 mg/m^2) over 1 h, intravenous infusion of nedaplatin (100 mg/m^2) over 3 h, intravenous infusion of leucovorin (CF, 200 mg/m^2) over 2 h, intravenous injection of 5-FU (375 mg/m^2) over 10 min, followed by a 46-hour infusion of 5-FU (2.6 g/m^2). The cycle was repeated every three weeks. Treatment efficacy was evaluated every two weeks according to the WHO standards. All patients received at least two cycles of chemotherapy. Tropisetron was routinely adopted before chemotherapy to avoid vomiting. Dexamethasone was routinely used before docetaxel infusion. Chemotherapy would be postponed, no more than 2 weeks, when patient's neutrophil count was less than $1.5 \times 10^9/\text{L}$ or platelet count was less than $75 \times 10^9/\text{L}$. The chemotherapy dose would be reduced by 25% if occurring grade III/IV febrile neutropenia, neurotoxicity or grade IV mucosal response. Treatment would be terminated if grade IV neutropenia appeared twice. Granulocyte colony-stimulating factor (G-CSF) would be used while appearing grade III/IV myelosuppression.

Observation indices

According to WHO Efficacy Evaluation Criteria, treatment efficacy was evaluated as complete remission (CR), partial remission (PR), stable disease (SD) and progressive disease (PD). Adverse events were recorded according to NIH Common Toxicity Criteria (CTC3.0). Time-to-progression (TTP) was defined as the time from the beginning of receiving chemotherapy to disease progression. Overall survival (OS) was defined as the time from the beginning of receiving chemotherapy to death or the latest follow-up visit. The patients were followed-up by telephone or questionnaire till June 1st, 2009. No patient was lost to follow. The median follow-up time was 10.3 months. The efficacy was evaluable in all patients.

Statistical analysis

SPSS17.0 software was used for statistical analysis. The Kaplan-Meier method was used to calculate the median survival time (MST), TTP and to draw survival curves.

Results

Efficacy

The 43 patients received 2–8 cycles of chemotherapy (median, 3 cycles) for a total of 144 cycles. Among them, 2 (4.65%) achieved CR, 25 (58.14%) achieved PR, 9 (20.93%) had SD, and 7 (16.28%) had PD. The overall response rate was 62.79%. Among the 7 patients who had previously received chemotherapy, 4 (9.3%) achieved PR, 2 (4.65%) had SD, 1 (2.33%) had PD. The TTP was 201 days and the MST was 310 days.

Adverse events

Grade III/IV adverse events mainly included neutropenia (20.93%, 2 patients had febrile neutropenia), thrombocytopenia (6.98%) and anemia (6.98%). The non-hematologic toxicity was usually mild. No grade III/IV peripheral nerve toxicity occurred. Gastrointestinal reactions mostly manifested as grade I/II nausea and vomiting (65.12%). The mucositis was mild. No patient quitted treatment due to gastrointestinal reaction. The occurrence rate of alopecia was 55.18%, and only 3 (6.98%) patients had grade I/II alopecia. Bilirubin was slightly elevated due to liver and kidney toxicity, only 1 (2.33%) patient had grade III toxicity (Table 1). The treatment for 10 patients was postponed for no more than 1 week due to toxicity of chemotherapy. Two patients had chemotherapy dose reduction due to toxicity. One died of chemotherapy-related events. Among the 7 patients who had previously received chemotherapy mostly had grade I/II adverse events, only 1 (2.33%) had grade III gastrointestinal reaction (nauseating and vomiting), 2 (4.65%) had grade III neutropenia.

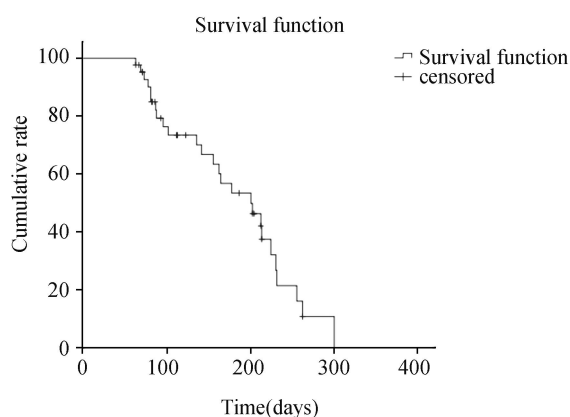


Figure 1 Progression-free survival curve of 43 patients with advanced esophageal carcinoma

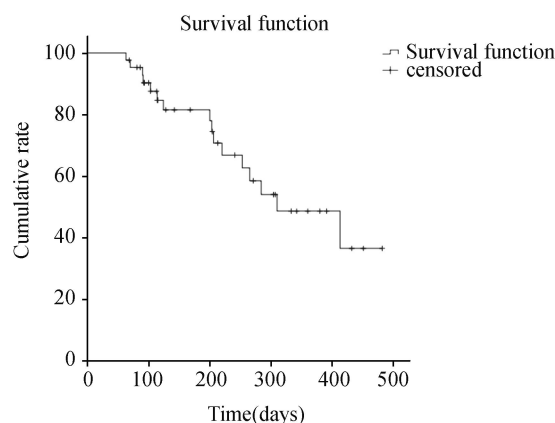


Figure 2 Overall survival curve of 43 patients with advanced esophageal carcinoma

Table 1 Adverse events occurred in 43 advanced esophageal carcinoma patients after treatment of DNF regimen

Adverse event	Grade 0 (Patient No.)	Grade I (Patient No.)	Grade II (Patient No.)	Grade III (Patient No.)	Grade IV (Patient No.)	Grade III/IV occurrence rate (%)	Total occurrence rate (%)
Anemia	26	10	4	3	0	6.98	39.53
Neutropenia	18	7	9	6	3	20.93	58.14
Thrombopenia	31	5	4	2	1	6.98	27.91
Nausea/vomiting	15	17	7	4	0	9.30	65.12
Diarrhea	34	3	6	0	0	0	20.93
Alopecia	19	11	10	1	2	6.98	55.81
Mucositis	35	5	3	0	0	0	18.6
Phlebitis	33	5	2	3	0	6.98	23.26
ALT elevation	36	6	1	0	0	0	16.28
BIL elevation	31	2	9	1	0	2.33	27.91
Cr elevation	41	2	0	0	0	0	4.65
Peripheral nerve toxicity	33	7	3	0	0	0	23.26
Cardiac toxicity	42	1	0	0	0	0	2.33

Discussion

Chemotherapy is one of the main treatments for advanced esophageal carcinoma. Accumulating data indicated the efficacy of platinum-based chemotherapy plus 5-FU on esophageal carcinoma was 20%–50% [7,8]. In recent years, the efficacy of some anti-cancer drugs, such as paclitaxel, vinorelbine, irinotecan, gemcitabine, and so on, used in combination with 5-FU, on esophageal carcinoma was up to 33%–75% [8–12]. The MST of patients received concurrent chemoradiotherapy was 12–35 months [13–15]. However, the adverse events, such as myelosuppression, gastrointestinal reaction, mucositis, were increased, while no significant increase in OS rate was observed [10]. Hence, it is imperative to seek for regimens and drugs with high efficiency and low toxicity.

Docetaxel, a semi-synthetic taxane derivative, has high anti-tumor activity and a broad anti-tumor spectrum with comprehensive cytotoxicity against a variety of solid tumors. The efficacy of docetaxel alone on esophageal carcinoma was about 20% [16,17]. Huang *et al.* [18] reported that the response rate of 65 patients with advanced or refractory and relapsed nasopharyngeal carcinoma after treatment of docetaxel, DDP plus 5-FU was 72.5%, with a CR rate of 9.8%. Wu *et al.* [19] compared the efficacy and toxicity of FOLFOX4 regimen and DP(O)F regimen (docetaxel, oxaliplatin/DDP plus 5-FU) in treating 70 cases of advanced gastric carcinoma, and found no obvious difference in objective response rate, TTP and MST between the two groups, and observed an increase in the occurrence of grade III/IV neutrophils in group DP(O)F as compared with group FOLFOX4.

Nedaplatin, the second-generation platinum anticancer drug, is mainly used in treating head and neck cancer and small cell lung cancer [20–23]. It has a broad anti-cancer spectrum, high efficiency, low renal and gastrointestinal toxicity, good synergetic effect when being combined with other chemotherapeutic drugs, no complete cross-resistance with cisplatin, and can be used easily without hydration. Nedaplatin has synergetic effect with 5-FU and docetaxel [27–30]. Watanabe *et al.* [31] reported that they had cured patients with advanced esophageal carcinoma using

nedaplatin, 5-FU plus concurrent radiotherapy. Kato *et al.* [32] had treated patients with advanced and unresectable esophageal squamous cell carcinoma by nedaplatin, 5-FU plus radiotherapy, and achieved an overall response rate of 77%, the 1- and 2-year survival rates were 30.7% and 10.2%, MST reached to 10.1 months. Recently, Matsutani *et al.* [33] reported that a 69-year-old patient with advanced esophageal cancer who had been treated by DNF plus radiotherapy achieved CR for 20 months, and only had grade II neutropenia and gastrointestinal reaction. Fujita *et al.* [34] had compared the efficacy of DN regimen (docetaxel/nedaplatin) and FP regimen (cisplatin/5-FU) on recurrent esophageal cancer and found that the response rates of the two groups were 36.3% and 10.0%, respectively.

Compared to literature, we appropriately increased the dose of docetaxel and nedaplatin, and achieved an overall response rate of 62.8%, a median TTP of 201 days and a median survival of 310 days. In our study, the hematologic toxicity caused by DNF regimen was mainly grade I/II, the occurrence of grade III/IV toxicity was in balance with those reported in literature, and most cases of grade III/IV toxicity were alleviated after G-CSF and symptomatic treatment. The treatment of 10 patients was postponed due to toxicity of chemotherapy, but no more than 1 week. Two patients had chemotherapy dose reduction because of chemotherapy toxicity. Only 1 patient died of intracranial hemorrhage secondary to chemotherapy-caused grade IV thrombocytopenia. In our study, 13 patients had previously received chemotherapy or radiotherapy, and the symptoms of severe nausea/vomiting, and neutropenia were obvious among these patients.

Our study suggests that DNF regimen is effective and well tolerated as first-line chemotherapy for patients with advanced esophageal carcinoma. Further multi-center study with large sample is needed.

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