RESEARCH ARTICLE

A Phase II Study on Continuous Infusional Paclitaxel and 5-Fu as First-line Chemotherapy for Patients with Advanced Esophageal Cancer

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Abstract

Objective: This study was performed to evaluated the efficacy and safety of continuous infusional paclitaxel and 5-Fu as first-line chemotherapy in patients with advanced esophageal squamous cell cancer (ESCC). Methods: A total of 22 patients with advanced esophageal squamous cell cancer with no indications for surgery and radiation therapy, or recurrent patients were enrolled from October 2008 to November 2010. All were treated with PTX 20 mg/m^2 was administered through a 16 hours continuous intravenous infusion on days 1 to 3, 8 and 9. DDP 3.75 mg/m^2 was given on days 1 to 4 and 8 to 11, continuous infusional 5-FU over 24-hours on days 1 to 5 and 8 to 12 at a dose of 375 mg/m^2, and folacin 60 mg orally synchronized with 5-Fu. The treatment was repeated every 21 days for at least two cycles. Results: 22 cases of all enrolled patients could be evaluated for the effect of treatment: 2 cases were CR, 9 cases PR, 5 cases SD and 2 cases PD, giving an overall response rate of 68.2%(15/22). The median time to progression was 7.0 months. The adverse reactions related to chemotherapy were tolerable; the most common toxic effects were marrow depression, alopecia, and fatigue. Conclusion: Low-dose continuous infusional PTX over 16-hours and 5-fu over 24-hours is a promising regimen with good tolerability in treating patients with advanced esophageal squamous cell cancer.

Keywords: Paclitaxel - 5-Fu - continuous intravenous infusion - esophageal squamous cell cancer - chemotherapy

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Introduction

Esophageal squamous cell carcinoma (ESCC) in China is the fourth most common cancer. ESCC is usually diagnosed at advanced stage, and chemotherapy is a main treatment for ESCC. First-line chemotherapy includes cisplatin (DDP), 5 fluorouracil (5-Fu), paclitaxel (PTX) with response rates (RR) ranging from 40%-60%. One- , 3- and 5-year survival rates after diagnosis were about 50%, 20% and 10%, respectively, with a median survival time (OS) about 12 months. Effective and well-tolerated chemotherapy is considered to be a modality to prolong OS and to improve quality of life. Thus, reasonable chemotherapeutic modification includes dose and exposure time adjustment of the conventional regimen administered.

PTX combined with DDP and 5-Fu is commonly used in the chemotherapy for ESCC, because the combination has the synergy effect (Ekman et al., 2008; Al-Batran et al., 2010; Herskovic et al., 2012; Mirinezhad et al., 2012). It is reported that PTX and 5-Fu with continuously intravenous infusion at low dose could expose cancerous tissue to cytotoxic agents at relatively constant concentration, and reduce adverse reactions compared with short-term infusion (Hainsworth et al., 1997; Pasial et al., 1998; Polee et al., 2002; Bucci et al., 2004; West et al., 2005). We conducted a multi-center clinical trial in order to access the efficacy and toxicity of 16-hours continuous infusional PTX and 24-hours 5-Fu at a low dose as first-line chemotherapy in patients with advanced esophageal squamous cancer.

Materials and Methods

Eligibility criteria

Oncology department of three comprehensive hospitals in Jiangsu province participated in this study, and the eligible patients of each center not less than 5 cases. All patients involved in the current study were required to be histologically confirmed with ESCC, aged 18-75 years, to have an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2 and a life expectancy of ≥3 months. Patients were staged III or IV ESCC and not indicated for surgery. The patients

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Table 1. Patient Characteristics (n = 22)

Characteristic	No. of patients	(%)
Sex		
Male	16	72.73
Female	6	27.27
Age (years)		
Median	63	
Range	42-71	
ECOG performance status		
0	3	13.64
1	9	42.77
2	9	42.77
Weight loss (%)		
≥5	18	81.82
Histology		
Squamous cell carcinoma	22	100
Type	14	
Medullary type	9	64.29
Mushroom type	4	28.52
Ulcer type	1	7.14
Tumor focus location		
Cervical segments	2	9.09
Upper thoracic segments	6	27.27
Middle thoracic segments	8	36.36
Under thoracic segments	1	4.55
Histology Differentiation		
High differentiated	2	9.09
Moderate differentiated	17	77.27
Poor differentiated	3	13.64
Prior therapy		
Oesophagectomy	8	36.36
Radiotherapy	0	0
Extent of disease		
Locally advanced/unresectable	0	0
Primary with distant metastases	14	63.64
Metastases after prior resection	8	36.36
Metastatic sites		
Supraclavicular and mediastinal lymph nodes	15	68.18
Pulmonary metastasis	7	31.82
Liver	5	22.73
Other	3	13.64
Multiple metastasis	7	31.82

had no other contraindication. The exclusion criteria included the following: pregnant or nursing women; hemoglobin≤100g/L, leucocyte≤3.6×10^9/L, platelets count≤10×10^{11}/L, and hepatic or renal function abnormal, as well as no clearly evaluating lesions.

Before treatment, all measurable lesions were documented by chest, upper abdominal computed tomography (CT) scan, bone scanning or other necessary examination. Deadline for follow-up is November 2010. Treatment protocol PTX 20 mg/m^2 was administered through a 16-hours continuously intravenous infusion on days 1 to 3,8 and 9;DDP 3.75 mg/m^2 was given on days 1 to 4 and 8 to 11; continuously infusional 5-Fu was given in 24-hours on days 1 to 5 and 8 to 12 at a dose of 375 mg/m^2; folacin 60mg was administrated orally synchronization with 5-Fu, the treatment was repeated every 21 days and at least two cycles. As prophylactic agents, dexamethasone 10 mg was taked 6h before PTX, methyllprednisolone (iv,40 mg), promethazine (iv, 12.5 mg) and cimetidine (iv, 400 mg) were given 30 min before paclitaxel.

Table 2. Treatment-related Adverse Reactions (number of patient, 22)

adverse reactions*	Grade 1	Grade 2	Grade 3	Grade 4	total incidence (%)
leukopenia	4	3	5	1	59.1
alopecia	12	3	4	1	90.0
nausea and vomiting	6	2	1	0	40.9
fatigue	12	3	0	0	68.2
diarrhea	3	5	0	0	36.4
constipation	2	1	0	0	13.6
Myalgia and arthralgia	5	0	0	0	22.7
Peripheral neuritis	0	0	0	0	0
dysfunction of liver	3	1	1	0	22.7
hand-foot syndrome	7	0	0	0	31.8

All patients received full blood count, hepatic and renal functions and ECG to evaluate the safety and adverse effect before and after each cycle of chemotherapy. After two cycles of treatment, a CT scan and examination of barium meal in digestive tract, when necessary, gastroscopy is performed, to evaluate the response to treatment and the tolerability to chemotherapy.

Treatment assessment

All patients should be followed up till disease progression, which was conformed by imaging technology, and document time to progression. Evaluation of response was carried out according to RECIST criteria, including complete response (CR), partial response (PR), stable (SD) and progress (PD), overall response rate (RR)= CR + PR. Adverse reaction was evaluated according to National Cancer Institute Common Toxicity Criteria version 3.0 (NCI-CTC).

Statistical analysis and Research Experience All statistical analyses were performed with SAS 6.12. To compare the interclass median binary, the rank sum test was adopted. We have enough experience in conducting medical researches, and have published some results elsewhere (Huang et al., 2004; Zhou et al., 2009; Jiang et al., 2010; Yan et al., 2010; Gao et al., 2011; Huang et al., 2011; Li et al., 2011; Li et al., 2011; Li et al., 2011; Li et al., 2011; Xu et al., 2011; Xu et al., 2011; Xu et al., 2011; Yan et al., 2011; Zhang et al., 2011; Gong et al., 2012; Li et al., 2012; Yu et al., 2012).

Results

Patient Characteristics

22 cases were evaluable, with 16 males and 6 females, the median age was 63 years, ranged between 42 and 71 years. ECOG Performance status (PS) was 0–1 in 13 patients and was 2 in 9 patients. 22 patients were proved in stage IV or recurrence patients. Amount to 18 patients lost weight ≥5% nearly two month. 2 cases were high differentiated, 3 cases were poor differentiated, and the rest were moderate differentiated. Among all eligible patients, 15 had supraclavicular and mediastinal lymph nodes metastasis, 7 had pulmonary, 5 liver, 2 celiac, and 1 pleural metastases. Seven patients had multiple metastases. Nine of 14 patients, who had no surgical history, were medullary type,4 were mushroom type, 1 were ulcer type; 2 tumor focuses were located in cervical segments, 6 in upper thoracic segments, 8 in middle thoracic segments, 1 in

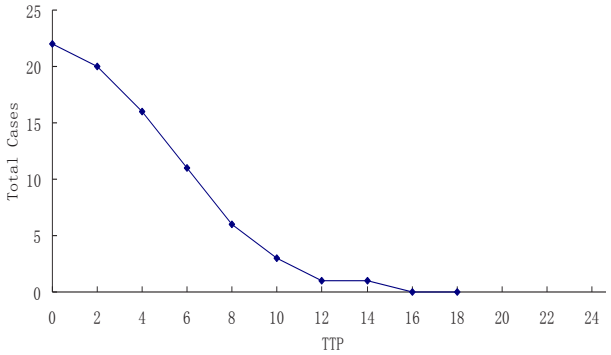

Figure 1. Kaplan-Meier Curve of TTP (by patients, n=22)

under thoracic segments.

All patients completed at least 2 and above cycles chemotherapy, the median cycles of chemotherapy are 4, follow-up time is respectively 8 ~ 16 months and the median time are for nine months.

Efficacy in short-term and long-term

Twenty two cases were evaluable, 2 CR, 9 PR, 5 SD, and 2 PD were documented with an overall response rate of 68.2% (15/22). The median time to progression was 7.0 months. Patient quality of life (QOL) was improved significantly.

Adverse reactions

Adverse reactions related to chemotherapy were tolerable; the most common toxic effects were bone marrow suppression, alopecia, and fatigue. The incidence of leukiopenia was in research/control group was respectively 59.1%, 27.3% of which occurred with grade 3/4 intensity. The mean time when the leucocyte began to decline was the 14 days in chemotherapy cycle, 27 cycles of which lead to postpone the next cycle , the postponed period neither exceeded one week. The incidence of alopecia was respectively 90.9%.The other kinds of adverse reactions related to treatment were mild, such as diarrhea, constipation, myalgia and arthralgia, peripheral neuritis, dysfunction of liver and hand-foot syndrome, no grade 3-4 nausea and vomiting was observed in this study. No allergic reaction and treatment-related deaths were recorded among all the patients.

Discussion

A standard chemotherapy for ESCC has not yet been established, because of the absence of enough clinical evidence from randomized phase III trail. Combination chemotherapy could obtain response rate of 20%-80% when treating patients in this setting. Currently, the most frequently used chemotherapeutic agent for patients with esophageal cancer was paclitaxel, and commonly combined with DDP and/or 5-Fu, due to the synergic effect of the combination (Polee et al., 2002; Bucci et al., 2004 ; Orditura et al., 2010; Mirinezhad et al., 2012). Low-dose, continuous infusional paclitaxel is reported to maximally inhibit cancer through reducing the emergence of drug-resistant tumor cells (Shade et al., 1998-1999; Langer et al., 2007; Bhatt et al., 2010). After an initial report with a response rate of 27% among taxane-resistant patients with breast cancer (Seidman et al., 1996), subsequent trials suggested that the treatment efficacy was improved (Holmes et al., 1998; Markman et al., 1998; Socinski et al., 1998; Socinski et al., 1999; Breathnach et al., 2000). First-line paclitaxel administered as a prolonged infusion (35 mg/m^2/24 h continuously infused over 96 h) in advanced bronchioloalveolar carcinoma (BAC) is active (SWOG 9714). The objective response rate was 14% (all partial responses); 40% of patients demonstrated stable disease. The median progression-free and overall survivals were 5 and 12 months, respectively (West et al., 2005). Twenty four hour continuous infusional paclitaxel combination with oxaliplatin in treating 30 Chinese patients with III-IV stage advanced esophageal squamous cell cancer achieved4 CR, 14 PR, and 4 SD, with RR 60.0% (WANG et al., 2010). Prolonged infusion paclitaxel was reported effective in other studies, eg., ovarian cancer (Markman et al., 1998) and metastatic breast cancer (Seidman et al., 1996; Holmes et al., 1998).

In SWOG 9714 trial, this schedule was associated with considerable toxicity, mostly grade 3/4 hematological toxicity and fatigue/lethargy, each occurring in roughly half of treated patients. In addition, five deaths in SWOG 9714 trial were suspected to be treatment-related (West et al., 2005). In this trial, PTX dose was reduced to 20mg/m^2/ day, and 16 hours continuous intravenous infusion on days 1 to 3, 8 and 9. The most common adverse reaction were bone marrow suppression, alopecia, fatigue, and the occurrence of grade 3-4 leukopenia was about 30%, which could be recovered after G-CSF administration. Other frequent symptoms were mild gastrointestinal adverse reaction, especially in elderly or patients in poor condition. Compared with other regimen containing PTX, adverse reaction in this study was relatively low (Socinski et al., 1998 Polee et al., 2002; West et al., 2005; Mirinezhad et al., 2012).

Some studies suggested that the combination of low dose 5-Fu with cisplatin (low dose FP) might improve therapeutic efficacy and quality of life for patients with advanced and recurrent gastric cancer, advanced colorectal cancer in 1990s (Hainsworth et al., 1997; Pasial et al., 1998). In contrast, ESCC patients presenting with advanced and/or recurrent disease have a median survival measured in months and should be considered accordingly for therapy. Particularly in light of the absence of an optimal standard therapy, clinical trials are an ideal treatment option for these patients.

In conclusion, low-dose continuous infusional PTX in 16-hours and 5-fu in 24-hours is a promising regimen with good tolerability in treating patients with advanced esophageal squamous cell cancer.

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