RESEARCH ARTICLE

Clinical Research on Albumin-Bound Paclitaxel-Based Chemotherapy for Advanced Esophageal Cancer

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Abstract

Background: To evaluate the efficacy and safety of albumin-bound paclitaxel-based chemotherapy in treatment for patients with advanced esophageal cancer who failed in first-line chemotherapy. Materials and Methods: We collected29 advanced esophageal cancer patients who received albumin-bound paclitaxel-based chemotherapy fromJune 2009 to September 2013, and the efficacy and safety of the compound were evaluated. These patients were treated with 100-150mg/m² nab-paclitaxel on days 1,8.The cycle was repeated every 3 weeks. Clinical efficacy was evaluated every two cycles. Results: Of the 29 patients, two persons interrupted treatment because of adverse reactions, failed to evaluate efficacy effect. The rest of27 patients who could be evaluated for short-term response, 10 patients (37%) achieved partial response, 2 (7.4%) remained stable disease, and 15 (55.6%) had progressivedisease. The objective response rate was 37%, and the disease control rate was 44.4%.The median time to progression was 6.6 months.The major adverse reactions includedalopecia (62.07%), neutropenia (65.5%), gastrointestinalreaction (10.3%) andsensory neuropathy(6.8%). Conclusions: The albumin-bound paclitaxel-based chemotherapy is efficacy and safety in treatment for patients with advanced esophageal cancer who failed in first-line chemotherapy.

Keywords: Albumin-bound paclitaxel - advanced esophageal cancer - chemotherapy

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Introduction

Esophageal cancer is one of the most common cancers, which ishigh incidence in China.Esophageal squamous cell carcinoma (ESCC) may be associated with a worse prognosis after surgery than esophageal adenocarcinoma. Due to few symptoms at the initial phase and the aggressive nature of esophageal cancer, advanced/metastatic cases with unresectable tumors and recurrent cases after resection are frequently observed. For those patients with unresectable esophageal tumor or metastatic disease, they should receive chemotherapy to and improve the quality of life and prolong the survival (Koshy et al., 2004; Karaosmanoglu et al., 2012). Containing adriamycin, taxane- and platinum-based regimens, as well as fluoropyrimidine-based regimens, have been proven to be reasonable and effective first-line chemotherapy (Cunningham et al., 2008; Kim et al., 2010; Overmanet al., 2010). However, the median survival is only 8-12 months in patients with advanced/metastatic ESCC, regardless of which combined regimen is given. Most ofadvanced ESCCpatients are failureinthe first-line chemotherapy of patients in the short term, and so far, there is no standard and effective treatment.

Thenanoparticle albumin-bound PTX (Nab-PTX) is a novel, solvent-free PTX that uses albumin to deliver PTX. Preclinical models suggest that Nab-PTX may reach tumors more efficiently with enhanced accumulation than solvent-based taxane (Desai et al., 2006). Clinical studies have shown that Nab-PTX is safe with increased objective response rate (ORR) and time to progression in metastatic breast cancer compared with solvent-based PTX and TXT, and great activity has also been shown in various other advanced solid tumors, including non-small-cell lung cancer (NSCLC) and pancreatic cancer (Gradisharet al., 2005; Montanaet al., 2011; Vonet al., 2011). Therefore, Nab-PTX has been an alternative reagent for those cancers that could be treated with PTX or TXT. However, little is known about the safety and efficacy of Nab-PTX in patients who had been received taxane-based therapy in advanced ESCC. The objective of this study was to explore the efficacy and toxicity of Nab-PTXas the second-line and above chemotherapy for patients with metastatic ESCC.

We selected advanced esophageal cancer 29 cases who can evaluate the curative effect of Nab-PTXfor treatment in our hospital. The objective of this study was to analyze the clinical efficacy andtoxicity of Nab-PTXfor patients with metastatic ESCC.

Materials and Methods

Patients

The 29 patients, including 27 cases were men and others were women, with metastatic ESCC were enrolled

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in this study who were required to be pathologically/cytologically diagnosed with esophageal squamous cell carcinomas and received Nab-PTX based chemotherapy in Jiangsu Cancer Hospital & Research Institute from June 2013 to September 2014. Eligibility criteria were as follows: 1. histologically confirmed ESCC and classified as unresectable esophageal cancer with metastatic lesions or recurrent and metastatic ESCC after surgery; 2. failed in first-line and (or) second-line chemotherapy, 2. to have a score of karnofsky performance status (KPS) ≥60;3. to be 43 to 72 years of age (average 54 years old) and a life expectancy of >8 weeks; 4.at least one measurable lesion for assessment by computed tomography (CT) or magnetic resonance imaging (MRI), and no prior radiotherapy or other local treatment for parameter lesions, including primary and metastatic lesions; 5.failed in first-line and (or) second-line chemotherapy, including PTX or TXT, 5-FU and DDP or OXA; 6. adequate hematological (absolute neutrophil count ≥1.5×109/L, platelets ≥ 100×109/L, and hemoglobin ≥9g/dL), hepatic (total bilirubin , 1.5-fold of the upper limit of normal value, aspartate aminotransferase and alanine aminotransferase, 1.5-fold of the upper limit of normal value), and renal (blood urea nitrogen and serum creatinine, the upper normal level) functions; 7.no other active malignancies.

Protocol treatment

Nab-PTX was administered intravenously over 30 minutes at 100-150mg/m^2 on day 1 and day 8, combined with capecitabineor oxaliplatin, every 21-28days. In general, treatment continued until disease progression, unacceptable toxicity, two cycles after maximal response, or a maximum of six cycles, at the discretion of the treating physician.

Efficacy and toxicity evaluation

Baseline tumor measurements were taken before treatment. The objective of this study was to determine the response rate as well as safety of Nab-PTX in patients with metastatic ESCC whatever received taxane-based therapy or not. Evaluation of tumor response was performed with the same imaging technique that was used at baseline every two cycles of therapy according to Response Evaluation Criteria in Solid Tumors (RECIST) (Therasseet al., 2000), and every 12 weeks within the follow-up period until disease progression. The safety measures, including adverse events, physical examinations, and clinical laboratory tests (hematology, blood chemistry, hepatic functions, and renal functions) were completed beforeeach cycle. Toxicities were graded using version 3.0 of the National Cancer Institute Common Toxicity Criteria.

Follow-up analysis

Thepatients with follow-up deadline is August 1, 2014. Progress in disease Free Survival (PFS)was defined as the duration from the initial treatment day of the protocol until the day of disease progression, or until the last follow-up day, or until death.

Statistical analysis

Descriptive statistics were used for patient characteristics, treatments, and safety evaluation. PFS was estimated using χ^2 text and the Kaplan-Meier method and their medians, along with two-sided 95% CIs, were calculated. All analyses were performed using the SPSS 15.0 software package.

Results

Patient characteristics

A total of 29 patients with metastatic ESCC were enrolled in this study. In these patients, 17 patients had received taxane-based agent before entering this study, while 12 patients had not. Chemotherapy for within and second line was 21 cases and more than three lines was 8 cases.

Efficacy and survival in metastatic ESCC patients who treat in Nab-PTX

Of the 29 patients, two persons interrupted treatmentbecause of adverse reactions, failed to evaluate curative effect. The rest of patients were received ranging from two to six cycleschemotherapy per patient.Of lower, the median PFS was 6.3 and 7 months (Figures1B).

Toxicityin metastatic ESCC patients who treat inNab-PTX

In the 29 patients, two people has been excluded this study. One was because of atrial flutter, and another was because of vein thrombosis. The hematologic and non-hematologic toxicities associated with the combined chemotherapy are summarized in Table1. In general, the regimen of Nab-PTX was well tolerated and most adverse events were mild. No unexpected toxicities or treatment-related deaths were observed during this study. The

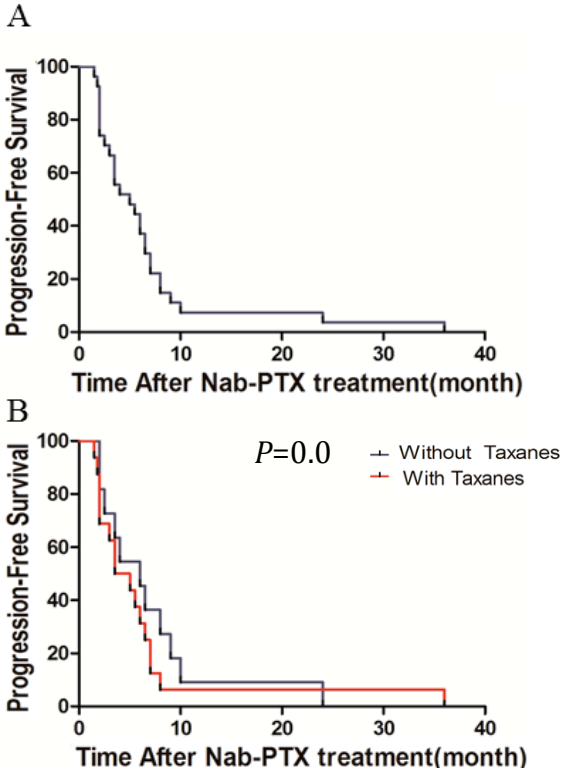

Figure 1. Progress Free Survival (PFS) after Nab-PTX Treatment

Table 1. Toxicity (n=29)

Adverse event	Grade	N (%)
Leucopenia		19 (65.5)
	I	3 (10.3)
	II	9 (31)
	III	7 (24.2)
Alopecia		18 (62.1)
Sensory neuropathy		2 (6.8)
	I	1 (3.4)
	II	1 (3.4)
Gastrointestinal adverse reactions		4 (13.6)
Nausea/vomiting	II	2 (6.8)
	III	1 (3.4)
Diarrhea	I	1 (3.4)
weak	I	1 (3.4)
Muscle soreness	I	1 (3.4)
Arrhythmia		1 (3.4)
Vein thrombosis		1 (3.4)

most common adverse events were leucopenia (65.5%), alopecia (62.07%), and sensory neuropathy (6.8%). The adverse events were taken a turn for the better during the symptomatic treatment (Table 1).

Discussion

Esophageal cancer is a highincidence in our country, accounting for more than half inthe world. Due to few symptoms at the initial phase and the aggressive nature of esophageal cancer, advanced/metastatic cases with unresectable tumors and recurrent cases after resection are frequently observed. For those advanced patients, they should receive chemotherapy to and improve the quality of life and prolong the survival (Koshy et al., 2004; Karaosmanoglu et al., 2012). The taxane-based chemotherapy for advanced esophageal cancer patients has been shown efficacy and survival advantage in clinic (Zhanget al., 2008; Caoet al., 2009; Gonget al., 2009; Takahashiet al., 2010; Yunet al., 2011). The taxane-based chemotherapy become as the first line for the metastatic or locally advanced ESCC. However, many patients progressed in disease after a period of treatment. Nowadays, the specificsecondary and above treatment for ESCC have not been known.

Several studies (Gradisharet al., 2005; Montanaet al., 2011; Vonet al., 2011), have investigated Nab-PTX as a single agent or in combination in breast cancer, NSCLC, and pancreatic cancer and so on. Nab-PTX always showed high efficacy and was well tolerated when people had been received in PTX or TXT in metastasis breast cancer.Also, there were some studies inNab-PTXas first-line therapy in metastatic ESCC patients (Shiet al., 2013). Therefore, whether the Nab-PTXwasbenefit for the patients who had been receivedtaxane-based chemotherapyhad not been known. In the 27 patients treated in this study, the regimen of Nab-PTX showed promising efficacy, with an ORR of 37.0%, a DCR of 44.4%, a median PFS of 6.6months. Patients had received taxane-based chemotherapy can also bebenefit from Nab-PTX, but ORR was lower compared to the patients who had not received taxane-based chemotherapy, the PFS was no significant differences. We need to expand the sample for further study. In this study, one patient had received taxane-based chemotherapy, the PFS was up to 36 months.

The regimen of Nab-PTX was also well tolerated, and toxicity was manageable. The most common toxicity related to hematological toxicity especially myelosuppression, and sensory neuropathy (GRADISHARet al., 2005). In this study, the main common adverse events were leucopenia (65.5%), alopecia (62.07%), gastrointestinal reaction (13.6%), and sensory neuropathy (6.80%). One patient was arrhythmia and Vein thrombosis, respectively. All the adverse events were taken a turn for the better during the symptomatic treatment, theseadverse reactionswere consistent with othertaxane-based chemotherapy previously reported studies (Overmanet al., 2010; Montanaet al., 2011). Among the patients, 17 cases had received taxane-based chemotherapy, but the incidence of sensory neuropathy was low and slight, none of patients experienced grade 3 sensory neuropathy. These patients were all be better after symptomatic treatment.

The regime of Nab-PTXseems to be a highly effective and well-tolerated first-line regimen for metastatic ESCC. The rate of grade 3-4 toxicities was very low. Further prospective randomized clinical trials with a larger sample size are necessary to obtain more evidence to determine the efficacy and safety of Nab-PTX in metastatic ESCC.

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References

Cao W, Xu C, Lou G, et al (2009). A phase II study of paclitaxel and nedaplatin as first-line chemotherapy in patients with advanced esophageal cancer. *Jpn J Clin Oncol*, **39**, 582-7.

Cunningham D, Starling N, Rao S, et al (2008). Capecitabine and oxaliplatin for advanced esophagogastric cancer. *N Engl J Med*, **358**, 36-46.

Desai N, Trieu V, Yao Z, et al (2006). Increased antitumor activity, intratumor paclitaxel concentrations, and endothelial cell transport of cremophor-free, albumin-bound paclitaxel, ABI-007, compared with cremophor-based paclitaxel. *Clin Cancer Res*, **12**, 1317-24.

Gong Y, Ren L, Zhou L, et al (2009). Phase II evaluation of nedaplatin and paclitaxel in patients with metastatic esophageal carcinoma. *Cancer Chem Pharmacol*, **64**, 327-33.

Gradishar WJ, Tjulandin S, Davidson N, et al (2005). Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oilbased paclitaxel in women with breast cancer. *J Clin Oncol*, **23**, 7794-803.

Gradishar WJ, Tjulandin S, Davidson N, et al (2005). Phase III trial of nanoparticle albumin-bound paclitaxel compared with polyethylated castor oil-based paclitaxel in women with breast cancer III trial. *J ClinOncol*, **23**, 7794-803.

Karaosmanoglu AD, Blake MA (2012). Applications of PET-CT in patients with esophageal cancer. *DiagnInterv Radiol*, **18**, 171-82.

Kim JY, Do YR, Park KU, et al (2010). A multi-center phase II study of docetaxel plus cisplatin as first-line therapy in patients with metastatic squamous cell esophageal cancer. *Cancer Chem Pharmacol*, **66**, 31-36.

Koshy M, Esiashvilli N, Landry JC, et al (2004). Multiple management modalities in esophageal cancer: epidemiology, presentation and progression, work-up, and surgical approaches. *Oncolog*, **9**, 137-46.

Montana M, Ducros C, Verhaeghe *P*, et al (2011). Albumin-bound paclitaxel: the benefit of this new formulation in the treatment of various cancers. *J Chemother*, **23**, 59-66.

National Cancer Institute: Common Terminology Criteria for Adverse Events version 3.0. (CTCAE). http://ctep.cancer.gov/reporting/ctc_v30.html.

Overman MJ, Kazmi SM, Jhamb J, et al (2010). Weekly docetaxel, cisplatin, and 5-fluorouracil as initial therapy for patients with advanced gastric and esophageal cancer. *Cancer*, **116**, 1446-53.

Shi Y, Qin R, Wang ZK, et al (2013). Nanoparticle albumin-bound paclitaxel combined with cisplatin as the first-line treatment for metastatic esophageal squamous cell carcinoma. *Onco Targets Ther*, **27**, 585-91.

Takahashi H, Arimura Y, Yamashita K, et al (2010). Phase I/II study of docetaxel/cisplatin/fluorouracil combination chemotherapy against metastatic esophageal squamous cell carcinoma. *J ThoracOncol*, **5**, 122-8.

Therasse *P*, Arbuck SG, Eisenhauer EA, et al (2000). New guidelines to evalu¬ate the response to treatment in solid tumors. *J Natl Cancer Inst*, **92**, 205-16.

Von Hoff DD, Ramanathan RK, Borad MJ, et al (2011). Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: a phase I/II trial. *J Clin Oncol*, **29**, 4548-54.

Yun T, Han JY, Lee JS, et al (2011). Phase II study of weekly paclitaxel and capecitabine in patients with metastatic or recurrent esophageal squamous cell carcinoma. *BMC Cancer*, **11**, 385.

Zhang X, Shen L, Li J, et al (2008). A phase II trial of paclitaxel and cisplatin in patients with advanced squamous-cell carcinoma of the esophagus. *Am J ClinOncol*, **31**, 29-33.