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ORIGINAL ARTICLE

Prospective Study

Long-term results of paclitaxel plus cisplatin with concurrent radiotherapy for loco-regional esophageal squamous cell carcinoma

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Abstract

AIM

To evaluate the long-term effectiveness and late toxicities of paclitaxel (PTX) plus cisplatin (DDP) with

concurrent radiotherapy for locally advanced esophageal squamous cancer.

METHODS

Between 2008 and 2011, 76 patients were enrolled in a phase Ⅱ study on the treatment of loco-regionally advanced esophageal cancer with radiotherapy (68.4 Gy/44 fractions or 61.2 Gy/34 fractions) combined with 4-cycle chemotherapy consisting of DDP (25 mg/m^2 per day for 3 d) and PTX (175 mg/m^2 for 3 h). The primary endpoints were overall survival and progression-free survival, and the secondary endpoints were toxicity and the treatment failure pattern.

RESULTS

A total of 76 patients were enrolled in this study, of whom 63.2% finished the whole regimen. The 5-year survival rates for the per-protocol population and intent-to-treat population were 25.4% and 26.4%, respectively, and the median survival rates were 23.7 mo and 28.5 mo, respectively. Grade 3 or 4 late toxicity was observed in only one patient (heart failure). In log-rank analysis, the pretreatment stage (stage Ⅱ + Ⅲ: 36.1 mo *vs* stage Ⅳ: 14.9 mo) and the completed cycle (1-3 cycles: 16.1 mo *vs* 4 cycles: 35.5 mo) were significant prognostic factors (P = 0.037 < 0.05 and P = 0.013 < 0.05).

CONCLUSION

Radiotherapy combined with chemotherapy consisting of PTX and DDP is a safe and effective definitive treatment for loco-regionally advanced esophageal squamous cancer.

Key words: Chemoradiotherapy; Long-term result; Loco-regionally advanced esophageal cancer; Phase Ⅱ trial

Core tip: This was a prospective phase Ⅱ trial with 76 patients to evaluate the effect of paclitaxel plus cisplatin combined with concurrent radiotherapy for locally advanced esophageal squamous cancer. Our results showed a good survival rate, which seemed comparable or even better than those of other studies of patients undergoing definitive paclitaxel-based chemoradiotherapy.

Zhu HT, Ai DS, Tang HR, Badakhshi H, Fan JH, Deng JY, Zhang JH, Chen Y, Zhang Z, Xia Y, Guo XM, Jiang GL, Zhao KL. Long-term results of paclitaxel plus cisplatin with concurrent radiotherapy for loco-regional esophageal squamous cell carcinoma. *World J Gastroenterol* 2017; 23(3): 540-546 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i3/540.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i3.540

INTRODUCTION

Concurrent chemoradiotherapy has been recognized as a standard treatment for loco-regionally advanced unresectable esophageal cancers[1,2]. The combination of 5-fluorouracil (5-FU) plus cisplatin (DDP) is most commonly used, with a median survival time of 16 mo. However, the standard regimen remains controversial, as more radiosensitive chemotherapeutic drugs, such as paclitaxel (PTX), have been investigated in esophageal cancer[3-6]. Moreover, with the development of radiation techniques, the appropriate irradiation field and total dosage have not been clarified[7-9].

In 2008, a phase Ⅱ clinical trial commenced to observe the safety and effectiveness of PTX plus DDP combined with concurrent radiotherapy for locally advanced esophageal squamous cancer. The acute toxicity and 3-year survival rates were reported in 2014[10]. Now, the aim of the present study was to update the results to show the long-term survival and late toxicity of the study for loco-regional esophageal squamous cancer. To the best of our knowledge, few long-term prospective studies have been reported to date.

MATERIALS AND METHODS

The study was performed between July 2008 and November 2011 in Fudan University Shanghai Cancer Center. Patients were eligible for this trial if they were histologically confirmed to have loco-regional esophageal squamous cancer with no metastasis [stage Ⅱ-Ⅳa and stage Ⅳb without viscera metastasis, Union for International Cancer Control (UICC) 6th], an age ⩽ 75 years, a Karnofsky performance score ⩾ 80, a neutrophil count of at least 1.5 × 10^9/L, a leukocyte count of at least 3 × 10^9/L, a platelet count of at least 100 × 10^9/L, a serum creatinine level ⩽ 1.2 mg/dL, and a serum urea nitrogen level ⩽ 25 mg/dL. The patients did not receive prior operation/radiotherapy/chemotherapy/targeted therapy, and they had no complete obstruction or tracheoesophageal fistula.

Interventions

We designed a phase Ⅱ study of TP regimen (PTX + DDP) combined with concurrent radiotherapy for patients with loco-regional esophageal squamous cancer. The purpose of this study was to evaluate the safety and effectiveness of a four-week regimen of TP plus concurrent radiotherapy (Figure 1).

At the beginning of this study, late-course accelerated radiotherapy (LCAF) was utilized because we had completed some studies of LCAF and obtained higher local control and overall survival[11,12]. The regimen of LCAF was as follows: the first phase of radiation was 41.4 Gy/ 23 fractions over 4.6 wk (1.8 Gy/fraction, 5

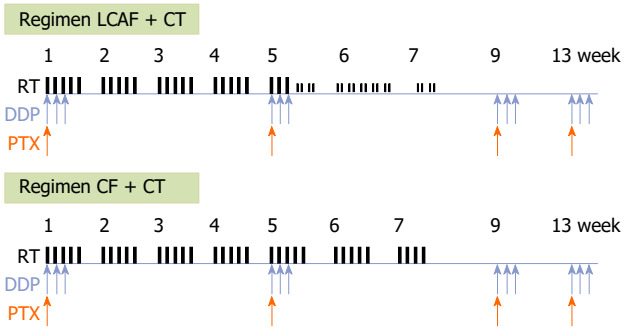

Figure 1 Schedule of the chemoradiotherapy protocol. LCAF radiotherapy consisted of 41.4 Gy (1.8 Gy/fraction, q.d.) using large fields, and 27 Gy (1.5 Gy/fraction, b.i.d.) using reduced fields, with a total dose of 68.4 Gy/41 fractions in 44 d. CF radiotherapy consisted of 61.2 Gy/34 fractions in 48 d (1.8 Gy/fraction, q.d.). The chemotherapy regimen included PTX at 175 mg/m^2, D1 and DDP at 25 mg/m^2, D1-3. RT: Radiotherapy; LCAF: Late-course accelerated radiotherapy; CF: Conventional radiotherapy; CT: Computed tomography; DDP: Cisplatin; PTX: Paclitaxel.

fractions per week). The second phase of irradiation was the accelerated hyperfractionated session of 27 Gy/18 fractions in 1.6 wk (1.5 Gy/fraction, twice daily with a minimum interval of 6 h). The total dose of LCAF was 68.4 Gy/41 fractions in 44 d. After 16 patients had completed LCAF radiotherapy, fractionated radiotherapy (twice a day) was prohibited because of the increased number of patients and the limited number of radiation machines; in particular, it was impossible for patients to receive radiation therapy twice per day. Therefore, conventional radiotherapy (CF) had to be used instead of LCAF. These patients received 61.2 Gy/34 fractions in 48 d, with 1.8 Gy/fraction 5 times per week. The regimen for TP was the same as previously described.

For all patients, the radiotherapeutic technique was the 3-dimensional planning technique or intensity-modulated radiation therapy. The megavoltage photon energy of 6 MV was used. The target volume was localized by computed tomography (CT) planning. The gross tumor volume (GTV) included the primary tumor and nodal metastasis. The clinical target volume (CTV) contained a 2 to 3-cm cephalad and caudad margin beyond the GTV. The planning target volume (PTV) was defined as having a 1-cm margin around the CTV. No prophylactic irradiation was given to any patient.

The study protocol was reviewed and approved by the Ethics Committee of the Cancer Hospital Affiliated to Fudan University (No. 081065). Written informed consent was obtained from all participants.

Follow-up and statistics

Follow-up evaluations were performed every 3 mo during the first year, every 6 mo for the next 2 years, and once a year thereafter. Toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE 3.0).

The treatment completion was defined as the fulfillment of 4 cycles of full-dose PTX + DDP along with a planned total dose of 68.4 Gy or 61.2 Gy radiotherapy.

Survival rates were calculated by the Kaplan-Meier model from the first day of treatment until death, and differences between rates were compared using the log-rank test. Age (65 years or less *vs* more than 65 years), gender (male *vs* female), stage (Ⅱ-Ⅲ *vs* Ⅳ: UICC 6th), number of cycles of chemotherapy (1-3 *vs* 4), pattern of radiotherapy (LCAF *vs* CF) and number of recurrent regions (one region *vs* multiple regions) were included into the log-rank test. A *P* value less than 0.05 was considered significant. All analyses were performed using SPSS22.0.

All patients who received treatment at least once were summarized in the intention to treat (ITT) analysis. The per-protocol (PP) analysis consisted of all treated patients without any protocol violation. The overall survival (OS) and progression-free survival (PFS) rates were analyzed based on ITT and PP populations, respectively. The primary endpoints of this study were OS and PFS, and the secondary endpoints were toxicity and the treatment failure pattern.

Table 1 Patients' characteristics

Characteristic	*n* (%)
Age (yr)	
Median	58 (37-74)
Gender	
Male	63 (82.9)
Female	13 (17.1)
Stage[1]	
Ⅱ	21 (27.6)
Ⅲ	27 (35.5)
Ⅳ	28 (30.3)
Fraction regimen	
LCAF	16 (21.1)
CF	60 (78.9)
Number of chemotherapy cycles	
1	8 (10.5)
2	13 (17.1)
3	7 (9.2)
4	48 (63.2)
Status	
Survival	17 (22.4)
Dead	53 (69.7)
Lost to follow-up	6 (7.9)

[1]UICC 6th. LCAF: Late-course accelerated radiotherapy; CF: Conventional radiotherapy; UICC: Union for International Cancer Control.

RESULTS

Seventy-six patients (median age, 58 years; age range, 37 to 74 years) were enrolled in this phase Ⅱ study from 2008 to 2011 (Table 1). Forty-eight (63.2%) patients completed the whole regimen of chemotherapy without reduction. The median follow-up time was 78.5 mo (range: 67.2-89.8 mo). In July 2016, 6 patients were lost to follow-up because they changed their phone number; 76 (100%) patients were

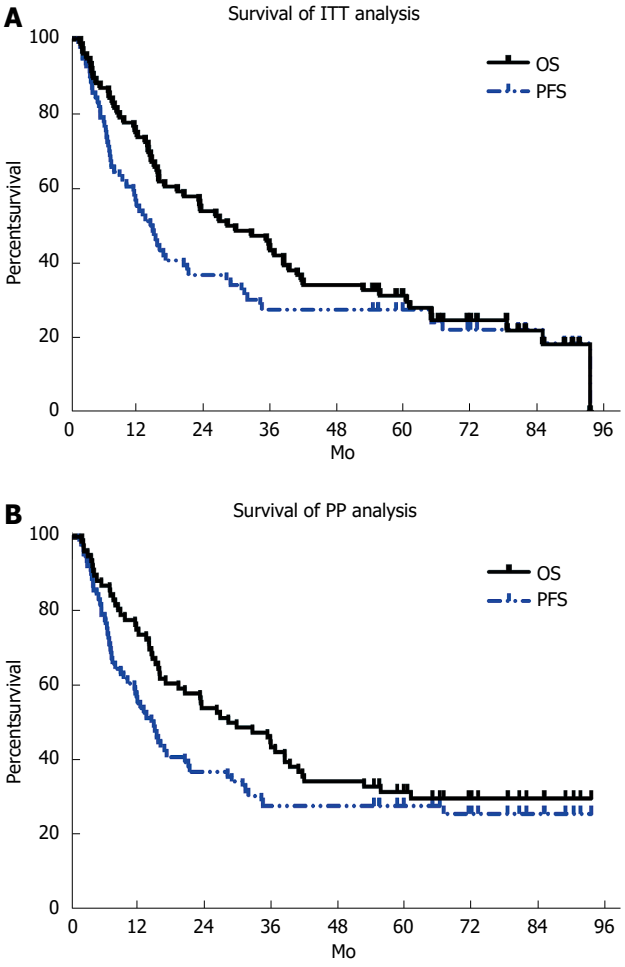

Figure 2 Overall survival and progression-free survival rates in patients with loco-regionally advanced esophageal cancer (Kaplan-Meier method). A: ITT analysis; B: PP analysis. ITT: Intention to treat; PP: Per-protocol; OS: Overall survival; PFS: Progression-free survival.

included in the ITT population and 70 (92.1%) in the PP population. In the PP population, 17 patients were alive, and 16 had no evidence of disease progression. Among the 54 of 70 patients with treatment failure, 17 had only local recurrence, 23 had distant metastasis only, 8 had concurrent local recurrence/distant failure, and 6 had failure due to other reasons, including second primary cancer (2 patients), second primary cancer progression (3 patients), and heart failure (1 patient).

The 1-, 2-, 3-, 4-, and 5-year survival rates in the PP population were 72.9%, 50%, 40%, 28.6%, and 25.4%, respectively, while those in the ITT population were 75%, 53.9%, 44.7%, 34.2%, and 26.4%, respectively. The median OS and PFS times were 23.7 mo (95%CI: 13.0-34.4) and 13.3 mo (95%CI: 9.7-16.9) in the PP population, and 28.5 mo (95%CI: 15.2-41.8) and 14.7 mo (95%CI: 10.7-18.7) in the ITT population, respectively (Figure 2).

In log-rank analysis, the difference between the OS rate in the pretreatment stage (P = 0.037; stage Ⅱ + Ⅲ: 36.1 mo, 95%CI: 22.9-49.2 *vs* stage Ⅳ: 14.9 mo, 95%CI: 11.9-17.9) and the completed cycle (P = 0.013; 1-3 cycles: 16.1 mo, 95%CI: 10.2-22.1 *vs* 4 cycles: 35.5 mo, 95%CI: 22.3-48.7) was statistically significant (Table 2).

Table 2 Prognostic factors for overall survival

Factor	No.	Median survival t/mo	Log-rank
Cycle(s)			0.013
1-3	26	16.1	
4	50	35.5	
Stage			0.037
Ⅱ-Ⅲ	48	36.1	
Ⅳ	28	14.9	
Gender			0.093
Male	63	17.3	
Female	13	35.5	
Age			0.708
< 65 yr	58	23.4	
⩾ 65 yr	18	27.0	
Radiation			0.626
CF	60	23.4	
LCAF	16	28.5	

CF: Conventional radiotherapy; LCAF: Late-course accelerated radiotherapy.

As acute toxicities had been reported previously[10], the late toxicities were updated in this article. Only one patient died because of heart failure at 20 mo, although it was not clear whether this was caused by radiotherapy. Other grade 3 or 4 late toxicities were not detected, although grade 1 or 2 focal pulmonary fibrous changes and pericardial effusion were common. Moreover, among the alive patients, only 2 had grade 1 hematological toxicity, which did not need special treatment.

DISCUSSION

Localized esophageal carcinoma is often treated with preoperative chemoradiotherapy; however, when carcinoma is unresectable (Ⅳ stage) or patients do not want to undergo surgery, concurrent chemoradiotherapy would be a suitable treatment[13-15]. Some trials have revealed the effectiveness of chemoradiotherapy in loco-regionally advanced esophageal cancer[1,2,16,17], and 5-FU plus DDP with concurrent radiotherapy was recognized as the initial strategy. As a promising agent, PTX was reported to be effective in concurrent chemoradiotherapy due to its good response rate of 40%[18,19] and its effect as a radio-sensitizer. Various scientists have reported the efficacy of PTX-based chemoradiotherapy, especially TP (PTX plus DDP) and TF (PTX plus 5-FU). However, the details of the regimen remain controversial, including the dosage and the number of cycles.

In this study, we investigated the effectiveness of a 4-wk schedule of PTX plus DDP combined with concurrent radiotherapy. Our results showed good survival rates, with 1-, 2-, 3-, 4-, and 5-year survival

Table 3 Results of TP regimen plus radiotherapy for loco-regionally advanced esophageal cancer in past studies

Ref.	No.	Chemotherapy	Dose and fraction	Grade ⩾ 3 acute hematologic toxicity	Median observation period (mo)	Median survival t/mo	2-yr survival rate
Jingu *et al*[22]	84	PTX 135 mg/m^2 DDP 75 mg/m^2 3-wk based	50.4 Gy/28 fractions	40.00%	NA	14.9	37.00%
Tu *et al*[21]	36	PTX 135 mg/m^2 DDP 75 mg/m^2 3-wk based	52-70 Gy/1.8-2 fractions	13.90%	14	18	42.80%
Song *et al*[20]	82	PTX 135 mg/m^2 DDP 30 mg/m^2 4-wk based	60 Gy/30 fractions	30.50%	20.4	18.2	40.80%

DDP: Cisplatin; PTX: Paclitaxel; RT: Radiotherapy; NA: Not available.

rates of 75%, 53.9%, 44.7%, 34.2%, and 26.4%, respectively, in the ITT model. These results seemed comparable or even better than those with RTOG 0113 and other studies of patients undergoing definitive PTX-based chemoradiotherapy (Table 3).

Compared with the study of Song *et al*[20], who used a similar regimen as in our study, the 2-year survival rate in our study was much higher (53.9% *vs* 40.8%), while the acute and late toxicities were comparable even with a higher dose of PTX. These differences may be due to the following reasons: (1) the median age in our study was 54, while the previous authors enrolled much older patients; and (2) the radiation delivery schedule was different. However, a few trials have reported the long-term outcome of regimens involving PTX in unresectable esophageal cancer[20,21]. In our study, the 5-year survival rate (26.4% in ITT model) was comparable to that of RTOG 8501 (26%), which used the combination of DDP + 5-FU[2]. This finding supports the idea that 4-wk PTX plus DDP regimen combined with concurrent radiotherapy is effective in treating locally advanced esophageal cancer, easy to perform and saves time spent in transportation to the treatment center.

The standard radiation regimen is 50.4 Gy/28 fractions in Western countries, and whether a high dosage of radiation can be used in concurrent therapy remains controversial. In the INT 0123 study reported by Minsky *et al*[1], the higher radiation dose (64.8 Gy) did not increase the OS or local control compared with the standard irradiation dose (50.4 Gy), although the higher dosage did not cause greater late toxicity. However, in Asia, 60-70 Gy radiation doses are widely used. In Jingu's study, the median OS was 39 mo, which was excellent after 60 Gy irradiation[22]. In our study, only 1 patient died of heart failure, and whether this outcome had any relationship with late toxicity was unclear. The most common late toxicity was grade 1 or 2 focal pulmonary fibrous changes. Given a good OS, this result suggests that a radiation dose of more than 60 Gy is appropriate for loco-regionally advanced esophageal cancer[22,23]. Differences in radiation doses between Asian and Western countries might be because of the distinct radiation plans applied.

At our hospital, LCAF was investigated for more than 10 years and was confirmed to be safe and show a better local control or 5-year OS rate[11,12]. However, phase Ⅲ trials are still needed to compare this approach with CF. The primary purpose of this study was to assess the effectiveness of TP with concurrent LCAF, but because of the limited number of radiation machines and the large number of patients, it was impossible for one patient to receive radiotherapy twice daily; thus, CF was used instead of LCAF in the other 60 patients. With regard to the final data, there were no significant differences between LCAF and CF, perhaps because of the limited number of patients. Due to economic benefit, CF is recommended for loco-regionally advanced esophageal cancer.

The combination of 4-wk TP chemotherapy with concurrent radiation (61.2 Gy/34 fractions) is a safe and promising definitive treatment for loco-regionally advanced esophageal squamous cancer. A phase Ⅲ randomized clinical trial (NCT 02459457) has since been initiated to compare the efficacy among TP, TF (PTX plus 5-FU) and TC (PTX plus carboplatin) to determine the best PTX-based regimen for concurrent chemoradiotherapy.

COMMENTS

Background

Concurrent chemoradiotherapy has been recognized as a standard treatment for loco-regionally advanced unresectable esophageal cancer. The combination of fluorouracil (5-FU) plus cisplatin (DDP) was mostly used. Paclitaxel (PTX) was investigated to treat esophageal cancer. The current trial was designed to evaluate the safety and effectiveness of PTX plus DDP combined with concurrent radiotherapy for locally advanced esophageal squamous cancer.

Research frontiers

Various scientists have reported the efficacy of PTX-based chemoradiotherapy, especially TP (PTX plus DDP) and TF (PTX plus 5-FU) for locally advanced esophageal squamous cancer, but the details of the regimen remain controversial, including the dosage and the number of cycles. In this study, a 4-cycle TP regimen combined with concurrent radiotherapy showed a good

overall survival rate and low toxicity.

Innovations and breakthroughs

Few long-term prospective studies about locally advanced esophageal squamous cancer have been reported to date.

Applications

Based on our results, a phase Ⅲ randomized clinical trial (NCT 02459457) has since been initiated to compare the efficacy among TP, TF (PTX plus 5-FU) and TC (PTX plus carboplatin) to determine the best PTX-based regimen for concurrent chemoradiotherapy.

Terminology

Paclitaxel was isolated from the bark of the Pacific yew, Taxus brevifolia, used to treat ovarian, breast, lung, pancreatic and other cancers. Cisplatin reacts in the body, binds to DNA and causes the DNA strands to crosslink, which ultimately triggers cells to die in a programmed way.

Peer-review

The authors report the long-term results of a combined chemoradiation regimen for esophageal cancer, which is interesting.

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