Perioperative versus Preoperative Chemotherapy with Surgery in Patients with Resectable Squamous Cell Carcinoma of Esophagus

A Phase III Randomized Trial

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Background: Perioperative chemotherapy for resectable squamous cell carcinoma of esophagus remains elusive. Thus, we assessed whether a perioperative regimen of paclitaxel, cisplatin, and 5-fluorouracil (PCF) improved outcomes among patients with curable squamous cell carcinoma of esophagus comparing with preoperative chemotherapy alone.

Methods: Overall, 346 patients with resectable squamous cell carcinoma of esophagus were randomly assigned to receive surgery plus perioperative chemotherapy (175, arm A) or preoperative chemotherapy (171, arm B). Both arms received two preoperative cycles of PCF: intravenous paclitaxel (100 mg per square meter of body surface area) and cisplatin (60 mg per square meter of body surface area) on day 1, and a continuous intravenous infusion of 5-fluorouracil (700 mg per square meter of body surface area per day) for 5 days. Arm A received two added postoperative cycles of PCF. The primary end point was relapse-free survival, and the secondary end point was overall survival.

Results: Compared with preoperative chemotherapy group, perioperative chemotherapy group had a greater likelihood of 5-year relapse-free survival (hazard ratio for relapse, 0.62; 95% confidence interval, 0.49–0.73; 31% versus 17%, $p < 0.001$) and of 5-year overall survival (hazard ratio for death, 0.79; 95% confidence interval, 0.59–0.95; 38% versus 22%, $p < 0.001$). A pathologic complete response rate was achieved in 77 of 320 patients (24.1%) who underwent resection after chemotherapy. The increased PCF-related toxic events were not detected with the addition of two postoperative cycles of PCF.

Conclusion: In patients with operable esophageal squamous cell carcinoma, perioperative regimen of PCF can significantly improve 5-year relapse-free and overall survival comparing with preoperative chemotherapy alone. (The trial has been registered at ClinicalTrials.gov, number NCT01225523.)

Key Words: Perioperative chemotherapy, Preoperative chemotherapy, Squamous cell carcinoma of esophagus, Paclitaxel, Phase III.

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With annual new diagnosis of more than 450,000, esophageal cancer is characterized as the eighth most common cancer worldwide, whereas it is a highly lethal disease because of more than 400,000 deaths per year.[1–3] The incidence of esophageal adenocarcinoma is rapidly increasing, whereas that of squamous cell carcinoma of the esophagus remains unchanged.[1–3] In China, esophageal cancer is the second most common cause of cancer-related deaths in males and the fourth in females.[4] Despite improvement in surgical management in the past two decades, the prognosis of patients with esophageal cancer undergoing resection with curable intent was poor with only approximately 20% survival at 5 years.[5] A huge number of patients with resectable esophageal cancer may shortly develop metastatic disease or local recurrence. The factors contribute to this dismal outlook, including the presence of locoregionally advanced disease, undetected micrometastasis at diagnosis, and inadequate preoperative staging. Because of high rates of locoregional and distant failure, there are increasing interests in the combination of treatments with surgery.

As an alternative to resection for locoregional treatment of esophageal cancer, the evidences are growing to favor neoadjuvant chemotherapy with the potential benefits of increasing the likelihood of curative resection by downstaging the tumor, eliminating micrometastasis, and improving survival.[6,7] In parallel, adjuvant chemotherapy has not been shown to yield an absolute survival benefit comparing with surgery alone for esophageal cancer.[8–10] However, the encouraging results

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with perioperative chemotherapy in two randomized phase III clinical trials were shown to significantly improve overall and progression-free survival in patients with the adenocarcinoma of stomach or esophagus,[11–13] despite a divergent outcome from INT 113 USA trial.[14,15] Conversely, a well-conceived and well-executed clinical trial of perioperative chemotherapy in patients with resectable squamous cell carcinoma of esophagus remains blank.

The regimen of cisplatin and 5-fluorouracil achieved the response rates of 40% to 50% for squamous cell carcinoma and 30% to 40% for adenocarcinoma.[16,17] A higher histopathologic response rate has been detected by using more efficient cytotoxic agents, such as paclitaxel in patients with advanced squamous cell carcinoma of esophagus.[18] In the mid-1990s, there were considerable interests in paclitaxel for treatment of esophageal cancer with concerns on hemotologic toxic effects.[18–20] In patients with advanced squamous cell carcinoma of esophagus, although the efficacy between docetaxel and paclitaxel was not significantly different in overall survival, paclitaxel was a more feasible agent with less febrile neutropenia.[21] Accordingly, the combination of paclitaxel, cisplatin, and 5-fluorouracil (PCF) had substantial antitumor activity with an intriguing complete response rate in patients with the advanced squamous cell carcinoma of esophagus.[18] Despite concerns regarding toxicity, this trial established PCF as an active chemotherapy regimen. Given the positive findings of PCF, we sought to investigate whether perioperative PCF could improve the outcomes of resectable squamous cell carcinoma of esophagus comparing with those receiving preoperative PCF.

PATIENTS AND METHODS

Eligibility

The patients were enrolled at the First Affiliated Hospital and the Second Affiliated Hospital of Xi'an Jiaotong University from January 2005 to April 2007, with no evidences of previous chemotherapy or radiotherapy. Patients aged 18 years and older who had a World Health Organization (WHO) performance status 0 or 1 were eligible if they had histopathologically proven squamous cell carcinoma of esophagus that was considered as suitable for curative resection. The disease had to be confined to primary and regional nodes, although celiac nodal involvement (M1a) was permitted for primary tumor localized in the distal esophagus or gastroesophageal junction. Patients had to be operative candidates without excessive clinical risks and had no evidences of distant disease or involvement of tracheobronchial tree or other structures that would preclude a complete resection. Laboratory parameters included adequate bone marrow reserve consisting of a white blood cell count of more than 3500 cells/ml, platelet count of more than 100,000 cells/ml, normal liver function with total bilirubin of less than 1.5 mg/100 ml, and creatinine clearance of more than 60 ml/min. The protocol was approved by ethics committees. The written informed consents were obtained before randomization.

Pretreatment examinations consisted of the followings: esophagogastroscopy; barium esophagram; helical computed tomography scans of the chest, abdomen, and pelvis; and exploratory laparoscopy with biopsy as indicated to confirm nodal disease. All the procedures were performed by experienced gastroenterologists. Patients in this trial were stratified on the basis of clinical characteristics, including age, sex, WHO performance status, body weight loss, site, and maximum diameter of tumor. Pretreatment staging was not reported in the trial, because endocopic ultrasonography (EUS) was not available at the time of trial.

Treatment Plan

Eligible patients with resectable squamous cell carcinoma of esophagus were randomly assigned to receive surgery plus perioperative chemotherapy (175, arm A) or preoperative chemotherapy (171, arm B). Each 3-week cycle consisted of PCF: paclitaxel (100 mg per square meter of body surface area) by a 3-hour intravenous infusion on day 1, cisplatin (60 mg per square meter of body surface area) intravenously with hydration on day 1, and 5-fluorouracil (700 mg per square meter of body surface area) daily through day 1 to 5 by continuous intravenous infusion with a double-lumen Hickman catheter. Both arms received surgery and two preoperative cycles of PCF. Arm A received two added postoperative cycles of PCF. One milligram of warfarin daily was recommended as prophylaxis against thrombosis. All patients were premedicated intravenously 30 minutes before therapy with 8 to 16 mg dexamethasone, 300 mg cimetidine, and 50 mg diphenhydramine hydrochloride as standard antiemetic and antianaphylaxis. The patients were closely monitored for toxic effects of chemotherapy with the use of the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0.[22]

Before each cycle of chemotherapy, a complete blood count, blood urea nitrogen, electrolyte, serum creatinine levels, and liver function were required. Dose modifications of PCF regimen were recommended for patients with myelosuppression and thrombocytopenia, and dose modifications of 5-fluorouracil were recommended for those with stomatitis, hand–foot syndrome, and diarrhea. If there was an increase in the serum creatinine level, the creatinine clearance was determined and cisplatin dose was subsequently modified if appropriate. Cisplatin was discontinued in patients with clinically significant sensory neural damage. The performance status was assessed every 3 weeks before each chemocycle. A 1-week treatment delay was permitted to allow recovery from toxicity. Dose modifications were implemented based on the guidelines established in RTOG 113 (http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0113).

Surgery and Pathologic Examination

Surgery was scheduled within 2 to 4 weeks after completion of the second cycle of preoperative chemotherapy in the two arms. Postoperative chemotherapy was initiated within 5 weeks after surgery in arm A. Tumors of the gastroesophageal junction and the lower third of esophagus were resected through left side of thoracotomy alone, instead of transhiatal resection. In patients with poor respiratory reserve of forced expiratory volume in one second (FEV_1) less than 80%, transhiatal approach was used. The Lewis-Ivor operation in the patients with tumors at the middle third of