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Original article

Phase II study of preoperative concurrent chemoradiotherapy with oxaliplatin for locally advanced esophageal cancer

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Abstract

Background: We investigated preoperative concurrent chemoradiotherapy (CCRT) with oxaliplatin for locally advanced, potentially operative esophageal cancer in this Phase II study.
Methods: Between October 2009 and October 2011, 35 consecutive patients with newly diagnosed esophageal cancer clinical stage T3-4, N0-1, M0 were enrolled into this study. One dose of chemotherapy with oxaliplatin (35 mg/m^2) on Day 1 and Day 2, leucovorin (200 mg/m^2) on Day 1, and 5-fluorouracil [5-FU; 2400 mg/m^2 intravenously (i.v.) administered continuously for 48 hours] on Day 1 was administered 2 weeks before preoperative CCRT. During preoperative CCRT, radiation dose of 4500 cGy in 25 fractions was administered to the clinical target volume and 5000 cGy to 5040 cGy in 25 fractions was administered to the gross tumor volume; chemotherapy is administered concomitantly with oxaliplatin (45 mg/m^2) on Day 1 of radiation therapy (R/T) every 14 days; 5-FU (400 mg/m^2 i.v. bolus for 1 hour) for 5 days on Weeks 1 and 5 of R/T. Operation was performed 4−6 weeks after preoperative CCRT. Acute toxicity profile, overall survival rate, disease-free survival rate, distant metastasis failure-free survival rate, and local recurrence rate were evaluated.
Results: Four patients withdrew from the study. The total number of patients in this analysis was 31. The resection rate was 64.5%. The pathologic complete response rate was 15%. The overall median survival was 19.3 months. The 5-year overall survival rate was 37.8%. The 5-year disease-free survival rate was 31.1%. The 5-year distant metastasis failure-free survival rate was 40.7% (50.56% for patients with operation; 27.2% for patients without operation, $p = 0.0298$). The acute toxicities were mild, and no Grade 3 or above hematologic toxicity was noted. There was only one patient with Grade 3 esophagus toxicity. Grade 3 lung toxicity occurred in only three patients.
Conclusion: Preoperative chemoradiotherapy with oxaliplatin in the treatment of locally advanced, potentially resectable esophageal cancer is feasible and safe.

Keywords: chemoradiotherapy; esophageal cancer; oxaliplatin; preoperative

1. Introduction

In Asia, the predominant histological type of esophageal cancer is squamous cell carcinoma, accounting for over 90% of all cancers of the esophagus. Most squamous cell carcinomas are located in the midportion of the esophagus, with early local invasion and regional lymph node spreading. Because the early symptoms of esophageal cancer are subtle and nonspecific, patients usually present with obvious

Conflicts of interest: The authors declare that they have no conflicts of interest related to the subject matter or materials discussed in this article.

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difficulty swallowing and body weight loss, which indicate advanced disease. Only a minority of affected patients have a tumor confined to the mucosa, requiring treatment by surgical management alone. Multidisciplinary modalities should be considered to achieve a higher local control and overall survival in the treatment of advanced esophageal cancer. From 1981 to 1999, there were over 46 nonrandomized clinical trials that analyzed over 2700 patients with advanced esophageal cancer who were treated by neoadjuvant chemoradiotherapy. Taken together, the results suggested that the overall survival and local control of advanced esophageal cancer could be improved by neoadjuvant chemoradiotherapy followed by surgery. At least two randomized clinical trials[1,2] and two meta-analyses[3,4] demonstrated the benefits of neoadjuvant chemoradiotherapy in improving the overall survival of patients with advanced esophageal cancer.

The most popular chemotherapy regimens investigated in previous studies of neoadjuvant chemoradiotherapy contained 5-fluorouracil (5-FU) and cisplatin. One of the severe side effects of cisplatin is renal function impairment. Oxaliplatin, a platinum-based chemotherapeutic agent with a 1,2-diaminocyclohexane carrier ligand, has shown *in vitro* and *in vivo* efficacy against many tumor cell lines, including some that are resistant to cisplatin and carboplatin. Oxaliplatin also lacks ototoxicity and nephrological toxicities that are caused by cisplatin. Preclinical studies have shown that oxaliplatin is a radiation-sensitizing agent and is synergistic with 5-FU.[5] Furthermore, oxaliplatin in combination with capecitabine resulted in a 35% tumor response rate and acceptable toxicities in a Phase II study when used as a first-line therapy for metastatic esophageal cancer.[6] To maximize the treatment effect without compromising the general condition of patients before surgery, we designed this Phase II study to assess the efficacy and safety of one cycle of loading chemotherapy plus preoperative concurrent chemoradiotherapy (CCRT) with oxaliplatin and 5-FU/leucovorin followed by surgery, if possible, in patients with locally advanced esophageal cancer.

2. Methods

2.1. Patient population

Between October 2009 and October 2011, 35 consecutive patients with newly diagnosed esophageal cancer were enrolled into this study. This study was approved by the Institutional Review Board of Taichung Veterans General Hospital and informed consent was obtained from each participant. The imaging studies included positron emission tomography (PET) with 2-deoxy-2-[fluorine-18]fluoro-D-glucose integrated with computed tomography (CT) scan, liver sonography, gastroendoscopy, and bronchoscopy. The histology of the tumors was proved by endoscopic biopsy. The inclusion criteria included Eastern Cooperative Oncology Group performance scores less than 2, age between 20 years and 75 years, American Joint Committee on Cancer stage T3-4 N0-1 M0, and histology of squamous cell carcinoma. Patients who had other histology, previous chemotherapy/radiotherapy, synchronous double cancers, or medical disease likely to require surgery were excluded from this study.

2.2. Loading chemotherapy

One dose of chemotherapy with oxaliplatin [35 mg/m^2 intravenously (i.v.) for 2 hours] on Days 1 and 2, leucovorin (200 mg/m^2 i.v. for 2 hours) on Day 1, and 5-FU (2400 mg/m^2 i.v. continuously for 48 hours) on Day 1 was administered 2 weeks before preoperative CCRT.

2.3. Radiotherapy in preoperative CCRT

Radiotherapy was administered using an intensity-modulated radiation therapy treatment plan. All patients underwent CT simulation in a supine position with their arms above their heads, and a customized vacuum bag was used for immobilization. The CT images were taken at a 5-mm thickness throughout the neck and the entire thorax for the upper and the middle thoracic tumors or the entire thorax and the abdomen for the lower thoracic tumors. The gross tumor volume (GTV), clinical target volume (CTV), planning target volume, and the organs at risk were outlined on the CT images. The GTV included the tumor mass and the enlarged lymph node found from the images of PET scan and CT scan. CTV included the tumor in the esophagus plus 5 cm superiorly and inferiorly, 1 cm radially surrounding the tumor, and possible lymph nodes spreading in the mediastinum, supraclavicular area, and retroperitoneal area, which depended on the position of the tumor in the thoracic esophagus. The total radiation dose of 4500 cGy in 25 fractions was administered to CTV and 5000 cGy to 5040 cGy in 25 fractions was administered to GTV.

2.4. Chemotherapy in preoperative CCRT

Chemotherapy was given concurrently with oxaliplatin (45 mg/m^2 i.v. for 2 hours) on Day 1 of radiation therapy (R/T) every 14 days, and 5-FU (400 mg/m^2 i.v. bolus for 1 hour) for 5 days on Weeks 1 and 5 of R/T.

2.5. Tumor response assessment before the operation

Tumor response assessments were performed 3 weeks after preoperative CCRT was completed by PET scan, and gastroendoscopy. Biopsy of the tumor lesion was performed to assess the clinical tumor response.

2.6. Surgery after preoperative CCRT

Operation was performed 4−6 weeks after preoperative CCRT if the tumor was operable. Esophagectomy was performed by video-assisted thoracoscopy through a three-phase incision with extensive two-field lymph node dissection of the mediastinum and abdomen. The stomach was mobilized to the neck via the retrosternal route, and a cervical esophageal anastomosis was performed.