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Original Article

Preoperative chemoradiotherapy with oxaliplatin and tegafur-uracil in locally advanced rectal cancer: Pathologic complete response rate and preliminary results of overall and disease-free survival in a single institute in Taiwan

Jeffrey Yung-Chuan Chao [a,b], Hwei-Ming Wang [c], Feng-Fan Chiang [c], Jing-Chin Lin [a,d], Chen-Fa Chang [a], Jia-Fu Lin [a], Hui-Ling Yeh [a,*]

[a] *Department of Radiation Oncology, Taichung Veterans General Hospital, Taichung, Taiwan, ROC*
[b] *Institute of Clinical Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC*
[c] *Section of Colon and Rectal Surgery, Department of Surgery, Taichung Veterans General Hospital, Taichung, Taiwan, ROC*
[d] *Department of Medicine, National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC*

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Abstract

Background: We conducted a Phase II study of biweekly oxaliplatin plus oral tegafur-uracil in the preoperative chemoradiotherapy (CRT) for locally advanced resectable mid-to-lower rectal cancer in our hospital, to evaluate the feasibility of this drug combination in tumor pathologic response, acute toxicity, local control, disease-free survival (DFS), overall survival (OS), and time to distant metastasis in an Asian cohort.
Methods: Twenty patients with histopathologically confirmed rectal cancer (Stage II–III) were enrolled in the study. Radiotherapy of 50 Gy was delivered in 25 fractions of 2 Gy, one fraction/day, five fractions/week, for 5 weeks. Oxaliplatin 55 mg/m^2 was administered intravenously for 60 minutes on Day 1 every 2 weeks, and tegafur-uracil 350 mg/m^2 was given orally everyday during the whole radiotherapy course, including holidays. Surgery was scheduled 6 weeks after completion of the preoperative chemoradiotherapy. The primary endpoint was to determine the pathologic complete response (pCR) rate after this neoadjuvant chemoradiotherapy. The secondary endpoint was to determine the treatment-related toxicity profile, local control, DFS, OS, and time to metastasis.
Results: All patients underwent a complete course of preoperative chemoradiotherapy. There was no local recurrence during the study period. The complete resection rate was 20/20 (100%) and the close resection margin rate was 3/20 (15%). The pCR rate was 8/20 (40%). During chemoradiotherapy, the most frequent toxicity was diarrhea 9/20 (45% of patients, grade 2 in 3/20, 15%). There were no grade 3 or higher hematologic or non-hematologic events or treatment-related deaths. The 3-year OS and DFS rates were 94.1% and 78.6%, respectively.
Conclusion: Preoperative chemoradiotherapy with oxaliplatin and tegafur-uracil was well-tolerated and achieved an excellent pCR in our patients with locally advanced mid-to-lower rectal cancer.

Keywords: chemoradiotherapy; oxaliplatin; preoperative; rectal neoplasm; tegafur-uracil

1. Introduction

Colorectal cancer is a major health problem in Taiwan. The annual incidence of colorectal cancer has increased up to 43.5% in the past 10 years, with >8000 new cases of colon cancer and >2600 new cases of rectal cancer each year. Because of the unique anatomic location of rectal cancer, it

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* Corresponding author. Dr. Hui-Ling Yeh, Department of Radiation Oncology, Taichung Veterans General Hospital, 1650, Section 4, Taiwan Boulevard, Taichung 407, Taiwan, ROC.
E-mail address: hlyeh@vghtc.gov.tw (H.-L. Yeh).

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tends to recur locally after surgical treatment alone. Total mesorectal excision (TME) can reduce the local recurrence rate to < 10%. Abdominoperineal resection is the standard treatment for distal rectal cancer. However, it has significant disadvantages of anal sphincter sacrifice with permanent colostomy and a high incidence of sexual and urinary dysfunction.

Although TME has markedly improved the local control of locally advanced distal rectal cancer, the addition of pelvic radiation concomitant with fluorouracil (5-FU) chemotherapy had provided further improvement in pelvic local control according to the Dutch trial.[1] Many Phase II studies have shown higher rates of complete pathologic responses after chemoradiotherapy compared with radiation alone.[2,3] The German Rectal Cancer Study Group Phase III study further demonstrated the advantages of preoperative chemoradiotherapy over postoperative chemoradiotherapy in acute toxicity, anal sphincter preservation, and local control.[4−6] Studies are now focused on the use of radiosensitizers in combination with 5-FU to determine whether this newly developed preoperative treatment will provide better results than the conventional 5-FU-based chemoradiotherapy. Tegafur-uracil is a composite drug composed of 100 mg tegafur and 224 mg uracil (molar ratio 1:4). It is an attractive oral form of 5-FU and is marketed as tegafur-uracil in Taiwan. Tegafur, a prodrug of 5-FU, is easily absorbed though the gastrointestinal tract and slowly metabolized to 5-FU, mainly in the liver. Tegafur given with radiotherapy for patients with rectal cancer showed significantly less hematologic toxicity without significant treatment outcome difference with 5-FU.[7] Uracil is an inhibitor of dihydropyrimidine dehydrogenase, the rate-limiting enzyme of 5-FU degradation. A stably high concentration of tegafur-uracil is expected to be maintained in the liver and in circulation. It has been approved for treatment of advanced gastric cancer and colorectal cancer, which are usually treated with 5-FU-based chemotherapy in Taiwan.

Oxaliplatin is a platinum derivative which has shown radiosensitizing properties and synergism with 5-FU. Clinical studies have shown high response rates for the combination of oxaliplatin with either 5-FU or radiation therapy. Furthermore, the addition of oxaliplatin to a biweekly regimen with 5-FU proved manageable and beneficial in patients with metastatic colorectal cancer.[8] Recently, several investigators have reported that the combination of oxaliplatin with fluoropyrimidines in preoperative chemoradiotherapy is associated with a pathologic complete response (pCR) of about 15−29% in locally advanced rectal cancer.[9−11]

To achieve downstaging and better resectability in locally advanced or low rectal cancer, preoperative chemoradiotherapy with 5-FU has become the standard of treatment. However, the pCR is still unsatisfactory. We conducted a Phase II study of biweekly oxaliplatin plus oral tegafur-uracil in the preoperative chemoradiotherapy for resectable rectal cancer in a single institute, to evaluate the tumor pathologic response, acute toxicity, local control, disease-free survival (DFS), overall survival (OS), and time to distant metastasis in an Asian cohort.

2. Methods

2.1. Study design and patients

This open-label, single arm, Phase II study was conducted in a single institute and approved by the hospital's institutional review board. Each patient provided written informed consent before participating in the study.

Eligible patients were those aged 18−75 years, with pathologically confirmed rectal adenocarcinoma with an inferior margin no more than 10 cm above the anal verge, including anorectal junction tumor, as assessed by a lower GI scope. The clinical stage was defined according to AJCC 2002 TMN staging by computed tomography (CT) scan or magnetic resonance imaging (MRI) of the pelvis, chest X-ray, whole-body bone scan, or positron emission tomography (PET) scan. Further inclusion criteria were Karnofsky performance scale (KPS) ≥ 70%, and adequate hematological, liver, and renal functions.[12]

Exclusion criteria included metastatic disease when diagnosed, prior chemotherapy or radiotherapy to the pelvic area, other cancers, contraindication for administration of oxaliplatin or tegafur-uracil, pregnancy or nursing, and refusing radical operation after preoperative chemoradiotherapy.

2.2. Treatment plan

After urine voiding, the patients were advised to intake 300 mL of water. Thirty minutes later, the patients underwent CT simulation in the supine position with immobilization with a vacuum cushion. Identical urine voiding and immobilization procedures were taken for each fraction of radiotherapy.

PTV_G was defined as gross tumor volume with 5−10 mm margin, and PTV_C as clinical tumor volume (CTV) with 8−10 mm margin. Gross tumor volume consisted of gross rectal tumor and pelvic lymphadenopathy, and CTV consisted of internal iliac lymph node below the L5-S1 spine level, mesorectum, perirectal fat, and the presacral space. For T4 tumor, an external iliac lymph node was also included in CTV. Radiotherapy consisted of a total of 50−50.4 Gy to planning target volume of gross tumor (PTV_G) and 45 Gy to planning target volume of clinical and subclinical tumor volume (PTV_C) delivered as 10−15 MV photons in 25 fractions, of 2 Gy/fraction, five fractions/week, delivered by a seven-field intensity-modulated technique with five to seven fields. The treatment machine was a VARIAN Clinac 21EX, and planning software was Eclipse Version 10 (Varian Medical Systems Inc., Palo Alto, CA 94304, USA).

During the whole radiotherapy course, concurrent chemotherapy with oxaliplatin 55 mg/m^2 was administered intravenously for 60 minutes on Day 1 every 2 weeks, and tegafur-uracil 350 mg/m^2 was given orally every day, including weekends and holidays.

Radical surgery was performed in all of the patients according to a standardized technique 6−8 weeks after preoperative chemoradiotherapy was completed (Fig. 1). One of the two standard procedures, anterior resection with the TME