Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 4, pp. 1367–1375, 2012

0360-3016/$ - see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2011.05.027

CLINICAL INVESTIGATION **Gastrointestinal Cancer**

RADIATION THERAPY ONCOLOGY GROUP 0247: A RANDOMIZED PHASE II STUDY OF NEOADJUVANT CAPECITABINE AND IRINOTECAN OR CAPECITABINE AND OXALIPLATIN WITH CONCURRENT RADIOTHERAPY FOR PATIENTS WITH LOCALLY ADVANCED RECTAL CANCER

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Purpose: To evaluate the rate of pathologic complete response (pCR) and the toxicity of two neoadjuvant chemoradiotherapy (chemoRT) regimens for Stage T3-T4 rectal cancer in a randomized Phase II study.

Methods and Materials: Patients with Stage T3 or T4 rectal cancer of <12 cm from the anal verge were randomized to preoperative RT (50.4 Gy in 1.8-Gy fractions) with concurrent capecitabine (1,200 mg/m^2/d Mondays through Friday) and irinotecan (50 mg/m^2 weekly in four doses) (Arm 1) or concurrent capecitabine (1,650 mg/m^2/d Monday through Friday) and oxaliplatin (50 mg/m^2 weekly in five doses) (Arm 2). Surgery was performed 4–8 weeks after chemoRT, and adjuvant chemotherapy 4–6 weeks after surgery. The primary endpoint was the pCR rate, requiring 48 evaluable patients per arm.

Results: A total of 146 patients were enrolled. The protocol chemotherapy was modified because of excessive gastrointestinal toxicity after treatment of 35 patients; 96 were assessed for the primary endpoint—the final regimen described above. The patient characteristics were similar for both arms. After chemoRT, the rate of tumor downstaging was 52% and 60% and the rate of nodal downstaging (excluding N0 patients) was 46% and 40%, for Arms 1 and 2, respectively. The pCR rate for Arm 1 was 10% and for Arm 2 was 21%. For Arm 1 and 2, the preoperative chemoRT rate of Grade 3-4 hematologic toxicity was 9% and 4% and the rate of Grade 3-4 nonhematologic toxicity was 26% and 27%, respectively.

Conclusions: Preoperative chemoRT with capecitabine plus oxaliplatin for distal rectal cancer has significant clinical activity (10 of 48 pCRs) and acceptable toxicity. This regimen is currently being evaluated in a Phase III randomized trial (National Surgical Adjuvant Breast and Bowel Project R04). © 2012 Elsevier Inc.

Neoadjuvant, Chemotherapy, Radiotherapy, Rectal, Cancer.

INTRODUCTION

Adenocarcinoma of the rectum is a common disease with >40,000 cases diagnosed each year in the United States (1). Despite the potentially high rate of curability with combined modality therapy, some patients experience significant treatment-associated morbidity, and other patients develop locoregional failure or distant metastasis. In addition to achieving cure, sphincter preservation is an important goal of therapy. Improvements in clinical outcome have been realized with wide acceptance of continuous infusion 5-fluorouracil (5-FU)–based neoadjuvant chemoradiotherapy (chemoRT) and the use of total mesorectal excision.

The results of large randomized trials comparing neoadjuvant pelvic radiotherapy (RT) alone versus RT plus concurrent 5-FU have demonstrated improvement in locoregional disease control with the addition of concurrent chemotherapy (2, 3). Attempts to improve on this approach have focused primarily on testing new agents added to the backbone of

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Supported by Radiation Therapy Oncology Group U10 CA21661 and CCOP U10 CA37422 grants from the National Cancer Institute and Roche Laboratories.

Conflict of interest: none.

Received Feb 22, 2011, and in revised form May 2, 2011. Accepted for publication May 12, 2011.

5-FU plus RT to enhance the pathologic complete response (pCR) rate. Drugs with high activity in the metastatic disease setting have been of particular interest to apply to rectal cancer clinical studies. However, the integration of new RT techniques is also pertinent to this clinical research question.

The Radiation Oncology Group (RTOG) 0012 study was a Phase II trial in which patients were randomly assigned to either hyperfractionated pelvic RT plus continuous infusion 5-FU or standard pelvic RT plus continuous infusion 5-FU and irinotecan (4). That study was successful in that both arms achieved very high pCR rates, 26% in each arm. However, both arms were also associated with high rates of acute Grade 3 or greater toxicity (42% and 51%, respectively, for each arm), and therefore, neither regimen was suitable for further development.

The RTOG 0247 trial was designed to evaluate two experimental neoadjuvant chemotherapy regimens, capecitabine plus irinotecan or capecitabine plus oxaliplatin, with concurrent standard fractionated pelvic RT in a multicenter randomized Phase II trial. We sought to examine the efficacy of these two neoadjuvant regimens as determined by the primary endpoint, the pCR rate, and to evaluate the adverse events for these regimens.

METHODS AND MATERIALS

Patient characteristics

All patients gave written informed consent in accordance with each center's institutional review board guidelines. The eligible patients were ≥18 years old. They had a Zubrod performance of 0–2; adequate hematologic, renal, cardiac, and hepatic function; potentially resectable adenocarcinoma of the rectum originating at or below 12 cm from the anal verge without evidence of distant metastases; and clinical Stage T3, as determined by endorectal ultrasonography, or clinical Stage T4, as determined by endorectal ultrasonography or physical examination.

The exclusion criteria included pregnancy or lactation, distant metastasis, synchronous colon carcinoma, anal canal extension, previous chemotherapy or RT for malignancy, serious uncontrolled concurrent medical or neurologic conditions, clinically significant cardiac disease, major surgery within 4 weeks of study entry, upper gastrointestinal (GI) disease that might interfere with drug absorption, or uncontrolled coagulopathy.

The prerandomization evaluations included medical history and physical examination, blood counts, serum chemistry and liver function panel, pregnancy testing, chest radiography, computed tomography scan of abdomen and pelvis, and lower endoscopic examination.

Treatment

The planned treatment consisted of 1:1 randomization to one of two arms in which preoperative pelvic RT was administered with concurrent capecitabine (1,200 mg/m^2/d orally Monday through Friday during RT) and irinotecan (50 mg/m^2 intravenously [IV] weekly in four doses) (Arm 1) or concurrent capecitabine (1,650 mg/m^2/d orally Monday through Friday during RT) and oxaliplatin (50 mg/m^2 IV weekly in five doses) (Arm 2; Fig. 1). These chemotherapy doses represent a modification of the initial study design that demonstrated excessive toxicity in the initial 35 patients treated. Pelvic RT was delivered according to the conformational standards established by the RTOG and consisted of 1.8 Gy/fraction, five fractions weekly, with 45 Gy in 25 fractions plus a boost dose of 5.4 Gy in 3 fractions for a total dose of 50.4 Gy within 5.5 weeks. Either two-dimensional or three-dimensional delivery was allowed. Surgery was planned for all patients at 4–8 weeks after RT completion. For both arms, postoperative chemotherapy (folinic acid, fluorouracil, and oxaliplatin) was administered 4–6 weeks after surgery as follows: oxaliplatin 85 mg/m^2 IV within 2 hours (Day 1, every 14 days); leucovorin 400 mg/m^2 IV within 2 hours (Day 1, every 14 days): 5-FU bolus 400 mg/m^2 IV push (Day 1, every 14 days); 5-FU infusion 2,400 mg/m^2 IV continuous infusion within 46 hours (beginning on Day 1 and every 14 days).

Follow-up evaluations

The patients were evaluated weekly during concurrent chemoRT, before surgery, and before each cycle of postoperative chemotherapy. The patients were then followed up every 3 months for the first 2 years after therapy completion, every 6 months for the next 3

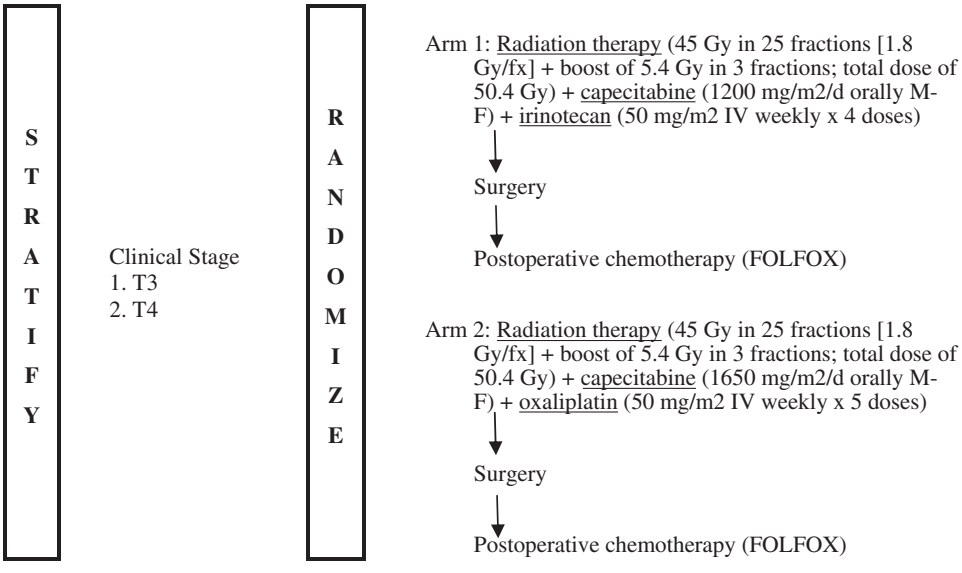

Fig. 1. Schema for Radiation Therapy Oncology Group 0247 Phase II study.