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Title: Phase II trial of neoadjuvant capecitabine plus irinotecan followed by combined modality capecitabine and radiation therapy for patients with locally advanced rectal cancer: a Hoosier Oncology Group study.

Background: The purpose of the study was to determine the pathological response rate of combined capecitabine and irinotecan chemotherapy followed by capecitabine-based radiotherapy for patients with locally advanced rectal cancer. Irinotecan and capecitabine are prodrugs that require activation by carboxylesterase enzymes (CES).

Methods: Patients with endoscopic ultrasound (EUS) staged T3/T4 or \geq N1 rectal cancer were treated with capecitabine 1000 mg/m² twice daily days 1-14 and irinotecan 200 mg/m² iv on day 1 every 21 days for 2 cycles, followed by capecitabine 825 mg/m² twice daily days 1-5 weekly with concurrent radiotherapy 50.4 Gy in 28 1.8-Gy fractions. Surgical resection occurred 4-6 weeks after completion of preoperative therapy. Baseline tumor biopsies were tested for correlative studies of genes expression with clinical endpoints (response and toxicity).

Results: Sixteen patients were enrolled, median age 59 years (range 42-67), male/female 8/8, T3/T4 81%/12% and 81% \geq N1. Thirteen pts completed neoadjuvant chemotherapy and radiotherapy (2 pt discontinued study after 2 cycles of chemotherapy for social reasons, and 1 pt was found to have metastatic disease after 1 cycle of therapy). Full doses of capecitabine, irinotecan and RT were administered in 97% of cycles. Most common toxicity was CTC grade 3 diarrhea in 3 pts (19%). All 13 evaluable pts underwent R0 resection. Tumor downstaging was noted in 12 pts (92%), which was accurately predicted by EUS in 9 pts (75%). Five pts (38%) obtained pathologic complete response (pCR). Eleven pts have complete gene expression profiles. The median values for gene expression were compared in pCR (4 pts) and pathologic non-complete response (pNCR) (7 pts) groups. A significantly higher CES2 expression was observed in the pNCR group ($p=0.0291$) and a trend towards higher expression of CES1, thymidine phosphorylase (TP), and thymidylate synthase (TS) in the pCR group was observed. To date, we have not observed an association of gene expressions with toxicity profiles.

Conclusions: The combination of capecitabine/irinotecan followed by capecitabine-based radiotherapy has significant antitumor activity and tolerable toxicity. The study continues to enroll patients.