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Clinical Investigation

A Phase 1/2 and Biomarker Study of Preoperative Short Course Chemoradiation With Proton Beam Therapy and Capecitabine Followed By Early Surgery for Resectable Pancreatic Ductal Adenocarcinoma

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Summary

We report toxicity, efficacy, and tissue and circulating

Purpose: To evaluate the safety, efficacy and biomarkers of short-course proton beam radiation and capecitabine, followed by pancreaticoduodenectomy in a phase 1/2 study in pancreatic ductal adenocarcinoma (PDAC) patients.

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This protocol (NCT00438256) is registered with ClinicalTrials.gov and may be viewed online at http://clinicaltrials.gov/ct2/show/NCT00438256?term=NCT00438256&rank=1.

Drs. Fernandez-del Castillo and Duda are co-senior authors.

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biomarker data from a phase 1/2 study of preoperative short-course chemoradiation with proton beam therapy and capecitabine, followed by early surgery for resectable pancreatic ductal adenocarcinoma. Treatment was well tolerated and was associated with excellent local control. Exploratory studies showed that *KRAS*^{G12D} status and higher tissue levels of CXCR7 expression and circulating plasma hepatocyte growth factor (HGF) were associated with worse survival after neoadjuvant chemoradiation.

Methods and Materials: Patients with radiographically resectable, biopsy-proven PDAC were treated with neoadjuvant short-course (2-week) proton-based radiation with capecitabine, followed by surgery and adjuvant gemcitabine. The primary objective was to demonstrate a rate of toxicity grade $\geq$3 of $<$20%. Exploratory biomarker studies were performed using surgical specimen tissues and peripheral blood.

Results: The phase 2 dose was established at 5 daily doses of 5 GyE. Fifty patients were enrolled, of whom 35 patients were treated in the phase 2 portion. There were no grade 4 or 5 toxicities, and only 2 of 35 patients (4.1%) experienced a grade 3 toxicity event (chest wall pain grade 1, colitis grade 1). Of 48 patients eligible for analysis, 37 underwent pancreaticoduodenectomy. Thirty of 37 (81%) had positive nodes. Locoregional failure occurred in 6 of 37 resected patients (16.2%), and distant recurrence occurred in 35 of 48 patients (72.9%). With median follow-up of 38 months, the median progression-free survival for the entire group was 10 months, and overall survival was 17 months. Biomarker studies showed significant associations between worse survival outcomes and the *KRAS* point mutation change from glycine to aspartic acid at position 12, stromal CXCR7 expression, and circulating biomarkers CEA, CA19-9, and HGF (all, $P<.05$).

Conclusions: This study met the primary endpoint by showing a rate of 4.1% grade 3 toxicity for neoadjuvant short-course proton-based chemoradiation. Treatment was associated with favorable local control. In exploratory analyses, *KRAS*^{G12D} status and high CXCR7 expression and circulating CEA, CA19-9, and HGF levels were associated with poor survival.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a lethal disease that afflicts ~42,000 patients per year in the United States (1). The available treatments for PDAC have limited efficacy. Even at early stages, only surgical resection affords the potential for cure. However, resected PDAC has high rates of local and distant failure, which remains incurable (2-6). Adjuvant cytotoxic therapies have shown only modest impact on cure rates (7-9), and the role of molecularly targeted agents in perioperative setting remains unknown.

Although the high distant metastatic rate renders a survival benefit with radiation that is difficult to demonstrate, controlling local disease with radiation could alleviate morbidity that adversely affects quality of life. Perioperative radiation therapy can delay systemic therapy or surgery, particularly when delivered preoperatively. Given the high metastatic propensity of even localized PDAC, shorter courses of radiation would be highly desirable. In rectal cancer, short-course (1-week) radiation therapy (5 Gy × 5 fractions) followed by early surgery is an effective way of decreasing pelvic recurrence (10-14). More conformal radiation techniques, such as intensity modulated radiation therapy (IMRT) or proton beam therapy, may allow for delivery of efficacious doses in a shortened schedule. In preclinical evaluations, we demonstrated that proton beam therapy was associated with less radiation dose to adjacent organs than IMRT (15). We have previously reported the feasibility of a proton-based 1-week neoadjuvant chemoradiation schedule followed by early surgery in the phase 1 portion of this trial (16). However, safety and tolerability concerns remain with the use of this approach. In addition, improvements in therapy for this extremely aggressive malignancy will likely require identification and targeting of specific molecular pathways that facilitate metastatic progression. Here, we report safety and efficacy data from the phase 1/2 study. We also report the results of exploratory correlative studies in tissue and blood circulation.

Methods and Materials

Patients

Patients with resectable PDAC were prospectively enrolled in a National Cancer Institute-sponsored clinical trial approved by the institutional review board (NCT00438256). Inclusion criteria included biopsy-proven adenocarcinoma of the pancreatic head or neck amenable to surgical resection with a pancreaticoduodenectomy; Eastern Cooperate Oncology Group 0/1 performance status; a pancreatic protocol computed tomography (CT) scan that, in the judgment of the surgeon and the multidisciplinary team, showed a resectable tumor; and no evidence of metastatic disease based on CT of the chest, abdomen, and pelvis and diagnostic laparoscopy (including cytology). Exclusion criteria included ampullary, biliary, or duodenal cancer, as well as distal tumors of the body or tail of the pancreas; prior therapy for PDAC, any invasive cancer in the last 5 years requiring radiation or chemotherapy, prior radiation therapy to the upper abdomen, and history of dihydropyrimidine dehydrogenase deficiency. Laboratory evaluations included