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Clinical Investigation: Gastrointestinal Cancer

Phase 2 Trial of Induction Gemcitabine, Oxaliplatin, and Cetuximab Followed by Selective Capecitabine-Based Chemoradiation in Patients With Borderline Resectable or Unresectable Locally Advanced Pancreatic Cancer

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Summary

This phase 2 study evaluated the safety and efficacy of induction gemcitabine, oxaliplatin, and cetuximab followed by selective capecitabine-based chemoradiation in patients with borderline resectable or unresectable locally advanced pancreatic cancer. This regimen seems relatively effective, allowing complete surgical resections in almost one-third of patients. Survival in resected

Purpose: To evaluate, in a phase 2 study, the safety and efficacy of induction gemcitabine, oxaliplatin, and cetuximab followed by selective capecitabine-based chemoradiation in patients with borderline resectable or unresectable locally advanced pancreatic cancer (BRPC or LAPC, respectively).

Methods and Materials: Patients received gemcitabine and oxaliplatin chemotherapy repeated every 14 days for 6 cycles, combined with weekly cetuximab. Patients were then restaged; "downstaged" patients with resectable disease underwent attempted resection. Remaining patients were treated with chemoradiation consisting of intensity modulated radiation therapy (54 Gy) and concurrent capecitabine; patients with borderline resectable disease or better at restaging underwent attempted resection.

Results: A total of 39 patients were enrolled, of whom 37 were evaluable. Protocol treatment was generally well tolerated. Median follow-up for all patients was 11.9 months. Overall, 29.7% of patients underwent R0 surgical resection (69.2% of patients with BRPC; 8.3% of patients with LAPC). Overall 6-month progression-free survival (PFS) was 62%, and median PFS was 10.4 months. Median overall survival (OS) was 11.8 months. In patients with LAPC, median OS was 9.3 months; in patients with BRPC, median OS was 24.1 months. In the group of patients who underwent R0 resection (all of which were R0 resections), median survival had not yet been reached at the time of analysis.

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Conflicts of interest: none.

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patients was markedly prolonged.

Conclusions: This regimen was well tolerated in patients with BRPC or LAPC, and almost one-third of patients underwent R0 resection. Although OS for the entire cohort was comparable to that in historical controls, PFS and OS in patients with BRPC and/or who underwent R0 resection was markedly improved. © 2014 Elsevier Inc.

Introduction

It is estimated that pancreatic cancer accounted for 43,920 cancer cases and 37,390 cancer deaths in 2010 (1). The overall 5-year survival rate among patients with pancreatic cancer is approximately 5%, and only 10%-20% of patients are candidates for curative surgery (2). Approximately 40% of patients present with borderline resectable or unresectable locally advanced pancreatic cancer (BRPC or LAPC, respectively) secondary to local tumor involvement of the adjacent vasculature (2). These patients are at high risk for an incomplete resection, which is associated with poor outcome (3). Furthermore, recent studies using routine staging laparoscopy in patients with nonmetastatic "locally advanced" pancreatic cancer have reported rates of occult, intra-abdominal metastases ranging from 24% to 37% (4-7).

A potential strategy to treat patients with BRPC or LAPC is to sequence systemic chemotherapy before chemoradiation, to treat systemic disease upfront and optimize selection of candidates for consolidation chemoradiation and/or resection. We designed a phase 2 study to evaluate the safety and efficacy of induction gemcitabine, oxaliplatin, and cetuximab followed by selective capecitabine-based chemoradiation in patients with BRPC or LAPC. The combination of gemcitabine with another, more active chemotherapeutic agent (oxaliplatin) and a second agent targeting other molecular pathways involved in tumorigenesis and metastasis (cetuximab) was selected to optimize treatment of potential, occult metastatic disease at presentation, minimize disease progression, maximize radiologic response rate (and the rate of complete surgical resection), and enhance progression-free and overall survival (PFS and OS, respectively). Chemoradiation was used selectively in patients with persistent vascular involvement after induction chemotherapy to minimize the risk of a positive pathologic margin at the time of attempted resection.

Methods and Materials

Eligibility criteria and initial patient evaluation

Patients (aged 18 years or older) with biopsy-proven, measurable (by Response Evaluation Criteria In Solid Tumors [RECIST] criteria) BRPC or LAPC of the pancreatic head, body, or tail with Eastern Cooperative Oncology Group performance status 0-2 were eligible. Chest computed tomography (CT), pancreas-protocol CT or magnetic resonance imaging scan (MRI), and endoscopic ultrasound were performed in all patients. Patients were deemed as having BRPC or LAPC according to CT or MRI findings. Patients with encasement ($\geq$180° or $\geq$50% of the vessel circumference) of the celiac axis, common hepatic artery (CHA), superior mesenteric artery (SMA), and/or extensive encasement/occlusion of the superior mesenteric vein−portal vein (SMV-PV) confluence were categorized as having LAPC. All patients were independently evaluated by a surgical oncologist, a medical oncologist, and a radiation oncologist and deemed medically fit for chemotherapy, chemoradiation, and surgical resection before enrollment. Endobiliary stenting to relieve obstructive jaundice was performed (as needed), but no prior therapy for pancreatic cancer was allowed. Patients were required to have adequate hepatic, renal, and hematopoietic function, and for women of childbearing potential, a negative pregnancy test within 7 days of starting therapy.

Patients were excluded from enrollment in the study if they had active hepatitis, known human immunodeficiency virus infection, an active or uncontrolled infection, a significant history of uncontrolled heart disease, prior anti-endothelial growth factor receptor therapy, prior severe infusion reaction to a monoclonal antibody, a concurrent second malignancy (other than non-melanoma skin cancer), a history of deep venous thrombosis/bleeding diathesis/coagulopathy, recent/current use of anticoagulants, an open biopsy/major surgical procedure within 28 days of initiation of therapy, or any prior radiation therapy or chemotherapy.

All eligible patients signed an informed consent form, and the study was approved and monitored by the institutional review board at our institution. The trial was registered with clinicaltrials.gov.

Study design and treatment plan

All patients were started on induction chemotherapy consisting of gemcitabine (1000 mg/m^2 given intravenously [IV] over 100 minutes on day 1) and oxaliplatin (100 mg/m^2 given IV over 120 minutes on day 2) repeated every 14 days for 6 cycles combined with weekly cetuximab (400 mg/m^2 given IV over 120 minutes on day 1 of week 1, followed by 11 weekly infusions of 250 mg/m^2 given IV over 60 minutes on day 1 of each subsequent week). Patients then restaged at 2 to 4 weeks after completion of induction chemotherapy with a chest CT and pancreas-protocol CT (or MRI) and endoscopic ultrasound, and each case was reviewed/discussed at the gastrointestinal multidisciplinary tumor board. Patients with evidence of radiologic response and resectable disease by CT or MRI criteria (ie, no persistent abutment/encasement of the adjacent celiac axis, CHA, SMA, and/or the SMV-PV confluence) underwent attempted surgical resection. Patients with stable disease went on to chemoradiation, whereas patients with evidence of disease progression were removed from the protocol (but followed) and subsequently treated at their treating physician's discretion.

Chemoradiation consisted of intensity modulated radiation therapy delivered to 45.9 Gy at 1.53 Gy per fraction to the elective nodal regions while simultaneously delivering 54 Gy at 1.8 Gy per fraction (30 fractions) to the gross disease with concurrent weekly capecitabine (800 mg/m^2 orally twice daily on days of radiation therapy). Details of radiation therapy planning and delivery have been reported previously (8). Normal tissue and target planning objectives are listed in Table 1.

Four to 8 weeks after completion of chemoradiation, patients were restaged and reviewed/discussed, as above. Patients with evidence of radiologic response or stable disease (ie, localized or