Original Study

FOLFIRINOX for Locally Advanced or Metastatic Pancreatic Ductal Adenocarcinoma: The Royal Marsden Experience

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Abstract

The study aims were to determine the efficacy and toxicity of FOLFIRINOX (5-fluorouracil, irinotecan, and oxaliplatin) in patients with advanced pancreatic adenocarcinoma treated at the Royal Marsden. Data from 49 patients treated with FOLFIRINOX between 2010 and 2013 were retrospectively reviewed. Efficacy and tolerability were similar to that reported in clinical trials.

Background: Pancreatic ductal adenocarcinoma (PDA) has a very poor prognosis. Treatment with FOLFIRINOX has been shown to improve outcomes, but can be associated with significant toxicity. **Materials and Methods:** A retrospective review was performed of all patients with locally advanced or metastatic PDA treated with FOLFIRINOX at the Royal Marsden between November 2010 and November 2013. Efficacy, tolerability, and potential prognostic factors were evaluated. **Results:** Twenty-seven patients with metastatic PDA and 22 patients with locally advanced PDA were treated with FOLFIRINOX. Patients received a median of 9 cycles (range, 1-26) of FOLFIRINOX. The overall response rate was 41% (20 patients), and a further 17 patients (35%) had stable disease. Thirty-five patients (71%) received FOLFIRINOX in the first-line setting, with a median progression-free survival and overall survival, respectively, of 12.9 months and 18.4 months for patients with locally advanced disease; and 8.4 months and 12.2 months for patients with metastatic disease. The most frequently occurring Grade 3/4 toxicities were neutropenia (29%), fatigue (18%), febrile neutropenia (14%), thromboembolism (12%), and thrombocytopenia (10%). In a univariate analysis, reduction in CA 19-9 of >50% ($P < .001$), normalization of CA19-9 ($P < .001$), surgery after FOLFIRINOX ($P = .004$), and use of prophylactic pegfilgrastim ($P = .005$) were prognostic for overall survival. **Conclusion:** The efficacy and tolerability of FOLFIRINOX for PDA at our institution is similar to that reported in clinical trials. Careful selection of patients and monitoring of response (according to CA19-9) and toxicities can help maximize advantage in this patient population.

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Introduction

Pancreatic cancer has a very poor prognosis, with a 5-year survival of approximately 6%, and only 10% to 20% of patients present with resectable disease.[1] Gemcitabine became the standard of care after a small randomised trial, which demonstrated an improvement in median overall survival (OS) compared with bolus 5-fluorouracil (5.6 vs. 4.4 months; $P = .002$).[2] Gemcitabine has been evaluated in combination with a variety of cytotoxic and targeted agents. For example, the addition of erlotinib was associated with a median improvement in OS of 2 weeks,[3] and a meta-analysis demonstrated a survival benefit from the addition of capecitabine.[4]

Over the past few years, additional treatment options have become available for patients with pancreatic cancer. In 2011, Conroy et al published the results of the landmark phase II/III Partenariat de Recherche en Oncologie Digestive (PRODIGE) 4/Actions Concertées dans les Cancers Colo-Rectaux et Digestifs (ACCORD) 11 trial, which randomized 342 patients to first-line treatment with either gemcitabine or a regimen comprised of 5-fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX).[5] This

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trial demonstrated that FOLFIRINOX was associated with significant improvements in response rate (RR) and progression-free survival (PFS) and a clinically meaningful improvement in OS from 6.8 to 11.1 months ($P < .001$). However, although patients' quality of life improved compared with treatment with gemcitabine, FOLFIRINOX was also associated with significant toxicities, including neutropenia, diarrhea, and peripheral neuropathy. The trial enrolled relatively younger patients with good performance status and therefore there were concerns as to whether the results could be applied to the general patient population outside of the context of clinical trials. More recently, the MPACT (Metastatic Pancreatic Adenocarcinoma Clinical Trial) trial has also shown a significant OS benefit for the combination of nab-paclitaxel with gemcitabine (8.5 months vs. 6.7 months; $P < .001$)[6] and this is now another treatment option for many patients. The toxicity profile of gemcitabine/nab-paclitaxel is different to that of FOLFIRINOX and there is ongoing debate on how to select the optimal treatment strategy for an individual patient.

At the Royal Marsden (RM), we have been treating patients with pancreatic cancer with FOLFIRINOX since 2010. We conducted a retrospective review of our experience with FOLFIRINOX in patients with locally advanced (LAPC) and metastatic (MPC) pancreatic cancer. The study objectives were to assess the efficacy and safety of FOLFIRINOX outside of a clinical trial, to assess potential prognostic variables, and to evaluate whether initial treatment with FOLFIRINOX affects response to subsequent lines of chemotherapy.

Materials and Methods

After approval from the institutional review board, we searched the pharmacy section of patients' electronic medical records to identify patients treated with FOLFIRINOX at RM between November 2010 and November 2013. Patients were considered eligible if they received at least 1 cycle of FOLFIRINOX and had histological confirmation of locally advanced or metastatic pancreatic adenocarcinoma.

Standard practice was to start treatment for patients using full-dose FOLFIRINOX, which consisted of oxaliplatin 85 mg/m^2 over 2 hours followed by irinotecan 180 mg/m^2 and leucovorin 400 mg/m^2 given concurrently over 1 hour. This was immediately followed by 5-fluorouracil given as a 400 mg/m^2 bolus and then a continuous infusion of 2400 mg/m^2 over 48 hours. The premedication regimen consisted of intravenous ondansetron and dexamethasone and prophylactic treatment with atropine was given to prevent cholinergic syndrome. Patients received oral dexamethasone and metoclopramide for 3 days and ciprofloxacin 250 mg twice daily for 7 days after chemotherapy. All patients were provided with loperamide and advised to start this at the first sign of diarrhea. The use of prophylactic granulocyte-colony stimulating factor (G-CSF) and dose reductions was at the discretion of the treating physician. Treatment cycles were repeated every 2 weeks until disease progression, unacceptable toxicity, or completion of the planned treatment course.

Clinical information including patient demographic and clinical characteristics, CA19-9, safety/tolerability (measured according to gradable toxicities according to the National Cancer Institute Common Toxicity Criteria version 4.0), hospital admissions, treatment regimes, and patient outcomes were retrospectively collected from patient records. Radiographic response was assessed by S.Y.M. and K.K. according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 and compared with the official radiology reports.

Most of the analysis is descriptive, with frequencies and medians being reported. PFS was calculated from the start of treatment with FOLFIRINOX to the date of progression or death. OS was calculated from the start of treatment with FOLFIRINOX to the date of death. Patients who were still alive were censored at the time of last follow-up. Association of survival outcomes with baseline prognostic factors was determined using Cox regression univariate analysis and hazard ratios (HRs) with 95% confidence intervals (CIs) were presented. Factors included in the univariate analysis were sex, age ($\leq$ 60 vs. $>$ 60 years), T-stage, N-stage, extent of disease (LAPC vs. MPC), performance status, line of treatment, number of cycles ($<$ 6 vs. $\geq$ 6), neutrophil/lymphocyte ratio, baseline CA19-9, normalization of CA19-9 (CA19-9 $\leq$ 37 vs. $>$ 37 U/mL), percentage decrease in CA19-9 ($\leq$ 50% vs. $>$ 50% and $\leq$ 90% vs. $>$ 90%), surgery after FOLFIRINOX treatment, and use of prophylactic G-CSF. A multivariate Cox regression model for OS and PFS was developed using a forward stepwise selection method, which included all significant univariate variables ($P < .05$).

Results

Patient Characteristics

Between November 2010 and November 2013, 49 patients with pancreatic adenocarcinoma were treated with FOLFIRINOX at RM. Baseline demographic and clinical characteristics are shown in Table 1. The median age was 60 (range, 34 -76) years and 26 (53%) of the patients were male. Twenty-two patients had LAPC (9 patients had borderline resectable disease and 13 had unresectable disease) and 27 had MPC at the time of treatment with FOLFIRINOX.

Study Treatment and Adverse Events

Patients received a median of 9 cycles of FOLFIRINOX (range, 1-26), with 12 patients receiving $<$ 4 cycles and 22 patients receiving $\geq$ 12 cycles. The reasons for treatment discontinuation are shown in Table 2. The dose of 1 or more components of FOLFIRINOX was reduced in patients (74%), including omission of bolus 5-fluorouracil in 7 patients (14%). The median number of cycles of oxaliplatin was 9 (range, 1-24). Dose delays of $\geq$ 7 days occurred in 23 patients (47%); with 16 patients (33%) having 1 dose delay, 5 patients (10%) having 2 doses delayed, and 2 patients (4%) having 3 doses delayed. Most dose delays were for 7 days (87%) with 13% of dose delays lasting $\geq$ 14 days.

Treatment-related toxicities are summarized in Table 3. There were no deaths related to chemotherapy toxicities. Fourteen patients (29%) had biliary stents in situ at the time of treatment with FOLFIRINOX (7 metal, 2 plastic, 5 stent type unknown), and there was 1 case of cholangitis. Nineteen patients (39%) had 1 emergency hospital admission during treatment with FOLFIRINOX, with a median duration of 4.5 days (range, 4-5 days) and 2 patients (4%) were admitted twice (median duration of second admission, 11.5 days; range, 2-21 days).

G-CSF (pegfilgrastim or filgrastim) was given as primary prophylaxis from cycle 1 onwards in 29 patients (59%), and these