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Modified irinotecan and infusional 5-fluorouracil (mFOLFIRI) in patients with refractory advanced pancreas cancer (APC): a single-institution experience

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Abstract

Pancreatic adenocarcinoma is the fourth leading cause of cancer death. Recently, MM-398 (nanoliposomal irinotecan) was shown to be associated with significant improvement in outcome measures with acceptable toxicities when combined with 5-fluorouracil (5-FU)/leucovorin (LV) compared to 5-FU/LV alone in patients failing one line of gemcitabine-based therapy. There is a paucity of data evaluating the role of irinotecan in combination with 5FU in advanced pancreas cancer (APC). We performed a retrospective analysis of all patients who received mFOLFIRI (minus bolus 5FU and LV). All patients with metastatic disease who had failed at least one line of gemcitabine-based therapy prior to receiving mFOLFIRI were included in this study. Descriptive statistics were used to assess the continuous variables and adverse events (AEs), and Kaplan–Meier methods were used to calculate the median progression-free survival (PFS) and overall survival (OS). Forty patients were included in this analysis. Patients received 1–5 lines of prior therapy (25 % with more than 3 lines of prior therapy). The mean age at diagnosis was 60, and 98 % had ECOG of 1. The mean CA 19-9 at the start of therapy was 33,169 U/ml. The median PFS was 2.59 months [95 % confidence interval (CI) (1.90, 3.54)], and OS was 4.75 months [95 % CI (3.14, 8.98)]. The most common AEs included fatigue (98 %), neuropathy (83 %), anorexia (68 %), nausea (60 %) and constipation (55 %). Grade 3 toxicities included fatigue (13 %) and rash (3 %). There were no observed grade 4 toxicities. In this single-institution retrospective

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Compliance with ethical standards

Conflict of interest The authors have declared no conflicts of interest.

analysis, mFOLFIRI was found to be both tolerable and relatively effective in a heavily pretreated patient population with APC. Future prospective studies should consider evaluating the role of mFOLFIRI in refractory APC.

Keywords

Pancreatic; Cancer; FOLFIRI; Gemcitabine; Adverse effects; Tolerability

Introduction

Pancreatic adenocarcinoma (PA) will be the third leading cause of cancer-related death by 2030 in the USA with a 5-year overall survival of approximately 6 % [1, 2]. Patients diagnosed with advanced disease have a median survival time less than one year. The only curative option for pancreas cancer patients is surgery; however, only 15–25 % of patients will have resectable disease at diagnosis [3]. For more than a decade, the standard therapy for locally advanced and metastatic pancreas cancer was gemcitabine [4]. More recently, targeted agents have been examined in combination with gemcitabine but did not demonstrate any efficacy with the exception of erlotinib [5], which showed an incremental improvement in overall survival of approximately 2 weeks compared to gemcitabine alone [6]. Based on phase III randomized trials, the current standard of care for metastatic pancreas cancer is a combination of gemcitabine with nab-paclitaxel or fluorouracil [5-FU], leucovorin, irinotecan and oxaliplatin (FOLFIRINOX) [7–9]. These regimens have been shown to improve response rates, correlating with longer progression-free survival and overall survival compared to gemcitabine alone. However, for patients who have failed first-line regimens, there were no standardized second-line therapies until the approval of MM-398 (nanoliposomal irinotecan) in combination with 5-FU [10].

Many treatment options used for patients with refractory, advanced pancreatic cancer are extrapolated from other gastrointestinal malignancies, and oxaliplatin was one of the first drugs to be used for in this setting. CONKO-003 was the first phase III trial to investigate oxaliplatin-containing therapy beyond gemcitabine [11]. In this phase III study, patients were randomized to 5-fluorouracil (5FU), folinic acid and oxaliplatin (OFF) versus best supportive care (BSC). This trial was closed prematurely due to inadequate accrual attributed to BSC as the control arm, but the early results showed benefit to second-line therapy. CONKO-003 was reopened comparing OFF to 5FU and folinic acid alone (FF) [11]. The authors showed a median OS and PFS of 5.9 and 2.9 months, respectively, in patients receiving OFF. These were both statistically greater than for patients receiving FF whose median OS and PFS were 3.3 and 2.0 months, respectively. Conversely, Gill et al. [12] compared mFOLFOX6 to infusional 5-FU/leucovorin in the PANCREOX trial that showed no difference in median PFS (3.1 vs. 2.9 months, respectively) and a greater median OS for infusional 5-FU/leucovorin (9.9 months) then mFOLFOX6 (6.1 months).

Similarly, irinotecan (180 mg/m²) in pancreas cancer has been evaluated in small studies and largely based on the extrapolation of treatment in other gastrointestinal malignancies. Review of the literature suggests that the combination of irinotecan and 5FU may have

activity in patients with advanced PC; however, the data are sparse. Thus, we performed a retrospective study evaluating all patients in our institution who received modified FOLFIRI in the refractory setting for tolerability, progression-free survival and overall survival.

Patients and methods

Eligibility criteria

All patients had to be older than 18 years of age with a pathologically confirmed adenocarcinoma of the pancreas, either locally advanced or metastatic, and had received mFOLFIRI. All patients received at least one cycle of therapy with gemcitabine-based therapy prior to mFOLFIRI. In addition, all patients had an Eastern Cooperative Group (ECOG) performance status (PS) of 0 or 1 in this study.

Study design

This is a retrospective analysis of patients who received mFOLFIRI (5-FU 2400 mg/m² continuous intravenous (IV) infusion over 46 h and irinotecan 180 mg/m² IV on day 1 repeated every 2 weeks) at our institution from July 1, 2010, to May 30, 2015. The Ohio State University Institutional Review Board approved this study. All patients were evaluable for toxicity, progression-free survival and overall survival.

Endpoints

The primary endpoints of this study were progression-free survival (PFS) and overall survival (OS) for patients who received mFOLFIRI. Clinical endpoints were determined from treatment initiation with FOLFIRI to disease progression, time of death or last follow-up. The secondary endpoint was to evaluate adverse events with this regimen.

Statistical analysis

Demographics, patient characteristics and toxicities were summarized using descriptive statistics (median/range for continuous outcomes and proportions for categorical outcomes). Progression-free survival (PFS) was defined at the time from the date of clinic visit prior to starting mFOLFIRI to disease progression or death, whichever occurred first. Patients were censored if there was no progression at the time of last follow-up. Overall survival (OS) was defined as the time from the clinic visit prior to starting chemotherapy to death from any cause or last known follow-up if date of death was unattainable. Patients were censored if alive at the time of last known follow-up. Survival curves along with median OS and PFS with 95 % confidence intervals were estimated using the Kaplan–Meier methods. Toxicity incidence is reported for informative purposes only. All statistical analyses were performed using Stata 13 (Statacorp LP, College Station, TX) or SAS 9.3 (SAS Institute Inc., Cary, NC).

Results

Patient characteristics

A total of 40 evaluable patients were included in this analysis. The median age was 60 years (range 39–81), and 97% had ECOG performance status of 1. The median number of doses

was 3 (range 1–12). Patients had received 1–5 lines of prior therapy (27 % with 1 prior and 45 % with more than 3 lines of prior therapy). The median CA 19-9 at the start of therapy was 2445 U/ml. Patient characteristics are summarized in Table 1.

Efficacy analysis

The median PFS was 2.59 months [95 % confidence interval (CI) (1.90, 3.54)], and OS was 4.75 months [95 % CI (3.14, 8.98)] (Fig. 1, Table 2).

Toxicity analysis

All adverse reactions were graded according to the National Cancer Institute Common Toxicity Criteria (version 4.0) [13]. Patients had blood draws and physical examinations prior to every cycle of therapy to assess for toxicities. The majority of the toxicities observed were of grade 1. The most common adverse effects included fatigue (98 %), neuropathy (83 %), anorexia (68 %), nausea (60 %) and constipation (55 %). Grade 3 toxicities were uncommon and included fatigue (13 %) and rash (3 %) (Table 3). No grade 4 toxicities were observed.

Cost analysis

Chemotherapy doses were calculated based on a body surface area of 1.86 m², the mean value for USA. The cost for intravenous drugs is 2015 fourth-quarter Medicare average sales price. Administration and clinic fees were based on the Medicare physician fee schedule based on Current Procedure Terminology (CPT). Cost for mFOLFIRI (including drugs, administration and clinic visit) is approximately \$597.59 for a 2-week cycle. These prices were also recently published by Goldstein et al. [14] and were updated for mFOLFIRI in 2015.

Discussion

Until recently, there were no approved treatment options in the refractory setting for patients who progressed on gemcitabine-based therapy for advanced and metastatic pancreatic cancer [15]. Irinotecan is commonly used to treat many gastrointestinal malignancies and was first evaluated as a monotherapy by Yi et al. [16], in patients who have failed gemcitabine-based therapy. Since then, irinotecan has been evaluated in numerous small studies (Table 4), which suggested the efficacy of this therapy in patients with pancreas cancer. Though most of these studies were small, all of them had a similar PFS and OS of approximately 3 and 6 months, respectively.

In our single-institution experience, mFOLFIRI was found to be tolerable and relatively effective in a heavily pretreated patient population with APC, where patients were exposed to up to five lines of prior therapy. Despite having refractory disease and failing several lines of therapies, the majority of observed toxicities were limited to grade 1 or 2, and without any grade 4 toxicities. (Table 3). The reports incidence of neuropathy was higher than expected in our analysis which we attribute is due to prior therapy and not necessarily related to mFOLFIRI. In our analysis, we found the PFS and OS to be 2.59 and 4.75 months, respectively, which are consistent to what has been observed historically (REF).

We acknowledge that our study includes a number of limitations including its retrospective nature, the relatively small number of patients and the potential for a selection bias. We feel the group of patients included, the refractory nature of their disease, and the consistency of our results when historically compared to other reports may control for some of these biases.

Conclusion

We demonstrated that mFOLFIRI could be considered as a reasonable option for patients with refractory pancreas cancer following progression on a gemcitabine-based regimen. Additionally, in an era of value-based care, it is essential to integrate cost in the decision-making process, and mFOLFIRI is a relatively cost acceptable regimen. As such, we recommend that in the absence or lack of access to standardized options in refractory pancreas cancer, mFOLFIRI appears to be a reasonable regimen with minimal toxicities. Future prospective studies validating its efficacy as a treatment option in refractory advanced pancreas cancers are warranted.

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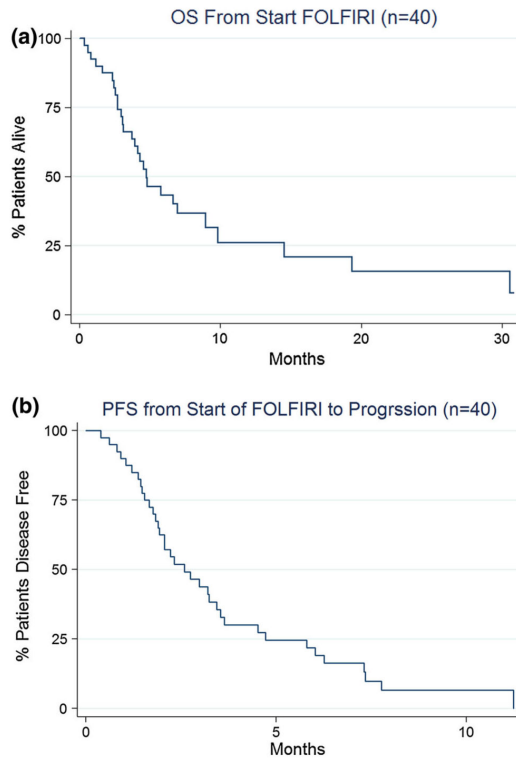


Fig. 1. Kaplan–Meier curves for PFS and OS for patients treated with mFOLFIRI calculated from start of mFOLFIRI to death (OS) or disease progression or death (PFS)

Table 1

Patient characteristics

| Patient characteristics | All patients (N = 40) |
|---------------------------------------|------------------------------|
| Gender [number (%)] | |
| Female | 13 (32.5) |
| Male | 27 (67.5) |
| Age (years) | |
| Median | 60 |
| Range | 39–81 |
| ECOG PS (baseline) [number (%)] | |
| 0 | 1 (2.5) |
| 1 | 39 (97.5) |
| Metastatic disease sites [number (%)] | |
| Liver | 27 (67.5) |
| Lung | 13 (32.5) |
| Peritoneum | 3 (7.5) |
| Other | 9 (22.5) |

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Table 2

Summary of outcomes

| Outcome | All patients (N = 40) |
|------------------------------------|------------------------------|
| Progression-free survival (months) | |
| Median (95 % CI) | 2.59 (1.90, 3.54) |
| Overall survival (months) | |
| Median (95 % CI) | 4.75 (3.15, 8.98) |
| Best response (N) | |
| Partial response | 0 |
| Stable disease | 8 (20) |
| Progressive disease | 32 (80) |
| Number of cycles (N) | |
| Median (range) | 2 (1–5) |

Table 3

Adverse reactions

| | Grade 1/2 | Grade 3 |
|--------------------------------|------------------|----------------|
| Adverse events—non-hematologic | | |
| Fatigue | 34 (87.5 %) | 5 (12.5 %) |
| Neuropathy | 33 (82.5 %) | 0 |
| Anorexia | 27 (67.5 %) | 0 |
| Nausea | 24 (60 %) | 0 |
| Constipation | 22 (55 %) | 0 |
| Rash | 14 (35 %) | 1 (2.5 %) |
| Adverse events—hematologic | | |
| Neutropenia | 2 (5 %) | 0 |

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Table 4

Clinical trials evaluating irinotecan (mono- or combination therapy) in advanced or metastatic pancreatic cancer

| References [17] | Sample size | Response rate (PR/SD) [%] | PFS (months) | OS (months) | 1-year survival [%] | Type of study | Year |
|--------------------------------|-------------|---------------------------|--------------|-------------|---------------------|--------------------|------|
| Yi et al. [16] | 33 | 9 | 2 | 6.6 | NR | Phase II | 2009 |
| Takahara et al. [18] | 56 | 3.6 | 2.9 | 5.3 | NR | Single institution | 2013 |
| Assaf et al. [19] | 27 | 19 | 5.4 | 8.5 | NR | Retrospective | 2011 |
| Cantore et al. [20] | 30 | 10 | 4.1 | 5.9 | 23 | Phase I | 2004 |
| Oh et al. [21] | 12 | 21 | 1.4 | 4.1 | 7.1 | Prospective | 2010 |
| Yoo et al. [22] | 31 | 0 | 1.9 | 3.9 | NR | Phase II | 2009 |
| Gebbia et al. [23] | 40 | 15 | 3.7 | 6 | 0 | Retrospective | 2010 |
| Zaniboni et al. [24] | 50 | 8 | 3.2 | 5 | NR | Phase II | 2012 |
| Neuzillet et al. [25] | 63 | 7.9 | 3 | 6.6 | NR | Prospective | 2012 |
| Ulrich-Pur et al. [26] | 19 | 16 | 4 | 6.5 | NR | Phase II | 2003 |
| Ko et al. [27] | 14 | 0 | 1.2 | 4.5 | 21 | Phase II | 2008 |
| Wang-Gillam et al. [10] | 117 | 16/6 ^a A | 3.1 | 6.1 | NR | Phase III | 2015 |
| Bupathi et al. (current study) | 40 | 20 | 2.59 | 4.75 | NR | Retrospective | 2016 |

NR Not reported, PR partial response, SD stable disease, PFS progression-free survival, OS overall survival

^a16 % for nanoliposomal irinotecan/5FU/LV and 6 % for liposomal irinotecan monotherapy