Pancreatology 16 (2016) 1099–1105

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Original article

Efficacy of pancreatic exocrine replacement therapy for patients with unresectable pancreatic cancer in a randomized trial

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ARTICLE INFO

Article history:
Received 12 May 2016
Received in revised form
30 August 2016
Accepted 2 September 2016
Available online 4 September 2016

Keywords:
Pancreatic cancer
Pancreatic exocrine insufficiency
Early palliative care
Pancreatic exocrine replacement therapy

ABSTRACT

Background: Weight loss in pancreatic cancer is associated with maldigestion due to pancreatic duct obstruction. Pancreatic exocrine replacement therapy (PERT) may significantly improve fat and protein absorption.
Objectives: This prospective, double-blind, randomized, placebo-controlled phase II trial assessed whether PERT could reduce or prevent weight loss in patients with unresectable pancreatic cancer.
Methods: Sixty seven patients with unresectable pancreatic cancer were randomized to receive enteric coated PERT, consisting of 6–9 capsules of pancreatin (457.7 mg/capsule), or placebo. Patients took two capsules each three times daily during main meals and one capsule each up to three times daily when having between-meal snacks. The primary endpoint was the percentage change in body weight at eight weeks.
Results: The mean percentage change in body weight (1.49% [1.12 kg] vs. 2.99% [1.63 kg], $P = 0.381$) and the mean percent change in Patient-Generated Subjective Global Assessment (PG-SGA) score (8.85% vs. 15.69%, $p = 0.18$) did not differ significantly between the PERT and placebo groups. There was no improvement in quality of life and overall survival did not differ significantly between the PERT and placebo groups (5.84 months vs 8.13 months, $p = 0.744$).
Conclusions: PERT did not reduce weight loss in patients with unresectable pancreatic cancer. Larger randomized trials are needed to identify those patients who may benefit from PERT.
Trial registration: ClinicalTrials.gov Number NCT01587534.

Introduction

The prognosis of patients with pancreatic cancer is poor, with a five-year overall survival rate of less than 5%. Pancreatic cancer is the fifth leading cause of cancer deaths in Korea [1]. Most patients have locally unresectable or advanced metastatic disease at the time of diagnosis, and hence are eligible only for palliative treatment options. Almost all patients with pancreatic carcinoma present with weight loss at the time of diagnosis, and this weight loss is progressive [2]. In addition, weight loss prior to chemotherapy was found to have a prognostic effect on survival in patients with several tumor types, including pancreatic cancer [3,4].

Most patients with pancreatic cancer have the impeded flow of pancreatic juice due to mechanical obstruction of the pancreatic duct. This may cause exocrine pancreatic insufficiency with fecal losses of energy through steatorrhea. Pancreatic exocrine replacement therapy (PERT) is standard therapy for fat and protein malabsorption [5]. Despite the high incidence of pancreatic exocrine insufficiency (PEI) in patients with pancreatic cancer, the

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http://dx.doi.org/10.1016/j.pan.2016.09.001
1424-3903/

treatment of these patients is often restricted to the oncological aspect whereas PEI is frequently disregarded. Few studies to date have investigated the incidence of exocrine insufficiency in patients with pancreatic cancer, and those studies have yielded inconsistent results. The incidence of PEI in patients with unresectable pancreatic cancer was shown to be 87% using secretin tests [6] and 68% using stool elastase tests [7]. Among patients with pancreatic cancer undergoing surgery, the incidence of exocrine insufficiency was 92% before surgery [8].

The high rates of exocrine insufficiency in pancreatic cancer patients support the use of PERT in this patient group. Few studies to date have analyzed the effects of PERT in patients with pancreatic cancer and there is no clear guide to identify those patients who benefit from PERT [9–11]. In only one double-blind, randomized control trial, 21 patients with unresectable cancer of the pancreatic head were randomized to PERT or placebo [12]. Patients in the PERT group were given 50,000 units of lipase with meals and 25,000 units of lipase with snacks. Compared with controls, the subjects receiving PERT experienced a 12% increase in fat malabsorption and a 1.2% increase in body weight.

This prospective, randomized, placebo-controlled trial therefore assessed the ability of PERT, combined with dietary counseling, to reduce or prevent weight loss in patients with unresectable pancreatic cancer.

Methods

Patients

All patients enrolled in this single center, double blind, randomized phase II trial provided written informed consent, and the study protocol was approved by the institutional review board of the National Cancer Center of Korea. Patients were considered eligible for inclusion if they had unresectable pancreatic cancer, proven by cytology or histology; local unresectability, or advanced disease with metastases; were aged over 18 years; had ECOG scale of performance status (0-3); and agreed to record daily food intake. Tumor of pancreas head or body/tail location was not preferred for enrolment. Subjects were excluded if they had a history of major gastrointestinal surgery, chronic gastrointestinal disease (e.g., Crohn's disease), decompensated diabetes, or diabetes mellitus with severe gastroparesis. Gastroparesis was suspected in patients with nausea, vomiting, early satiety, postprandial fullness, abdominal pain, or bloating. A mechanical obstruction was excluded with or upper endoscopy; if pancreatic pseudocysts impeding gastric or duodenal passage were present; if they were being treated with antacids, mucosal protective agents, H 2-receptor antagonists, or proton pump inhibitors that could not be discontinued; if they were taking concomitant medications affecting gastroduodenal motility (e.g. metoclopramide and erythromycin), or interfering with bile secretion (e.g. bile acids); if they had abused alcohol during the three months preceding the study, had a known allergy to pancreatin, had undergone any major surgery within 4 weeks prior to study treatment, or were pregnant or lactating. Patients were randomized to PERT or placebo using unique patient numbers, with treatment started within seven days of date. Randomization was stratified based on extent of disease (locally advanced vs. metastatic).

Treatment

PERT consisted of Norzyme® (Nordmark Arzneimittel GmbH & Co. KG, Germany), a high dose enteric coated pancreatic enzyme preparation. Each tablet contained 25,000 European Pharmacopoeia (Ph. Eur.) units of lipase, 22,500 Ph. Eur. units of amylase, and 1250 Ph. Eur. units of protease. Patients took two capsules each three times daily during main meals and one capsule each up to three times daily during between meal snacks (total, 6–9 capsules/day) for eight weeks. The placebo matched the active drug in appearance, taste, and weight and contained pharmacologically inactive substances.

Using preprinted diaries, patients recorded their daily dietary intake over three consecutive days and randomized one week later. There were no strict rules or prohibitions with respect to dietary intake. After the eight-week double blind trial period, patients were followed for an additional 16 weeks in an open descriptive trial period; during this time, patients were recommended to take PERT. The daily intake of energy and nutrients were calculated using the CAN-pro 3.0 (Korean Nutrition Society, Korea).

Follow-up

Follow up visits were scheduled every four weeks until 12 weeks after the randomization visit. During each visit, body weight, ECOG performance status, and vital signs were measured. At 8 weeks, dietary and nutrition status (Patient-Generated Subjective Global Assessment, PG-SGA) [13] and stool elastase-1 activity were measured. Patients were also evaluated by stool fat-Sudan III staining and on the EORTC QLQ-C30 General Questionnaire, Korean version. PG-SGA score is a continuous measure [14]. Scores of 0–4 were assigned to each component of the PG-SGA score, depending on the impact of that symptom on nutritional status; the total score consists of a sum of the component scores. A higher score is associated with a greater risk for malnutrition.

Pancreatic exocrine function was evaluated clinically. The occurrence and severity of complaints and symptoms associated with abdominal cramp and dyspepsia were assessed using a questionnaire. Patients were also questioned about potential side effects of treatment.

Statistical analysis

The primary goal of the trial was to investigate the percentage change in body weight eight weeks after randomization. The secondary goals were to estimate change in PG-SGA score; daily dietary intake of total calories, fat, protein, and carbohydrates; frequency of abdominal pain daily, frequency of flatulence, change in QOL score, and overall survival.

The sample size calculation was based on the primary endpoint, percentage change in body weight eight weeks after randomization [12]. In the previous study [12], the mean (SD) percentage change in body weight was −3.7 (4.4) % with 95% CI (−4.56%, −2.84%) in a placebo group, and 1.2 (4.3)% with 95% CI (0.36%, 2.04%) in an enzyme group. Thus, the estimated mean difference in percentage change in body weight between two treatment groups was 4.9%. However, considering the small sample size of the study, a conservative estimate of the mean difference in percentage change in body weight was calculated using the difference between the upper 95% CI of the placebo group and lower 95% CI of the enzyme group. This conservative estimate was 3.2% (0.36%, −2.84%), and the current study was powered to detect this difference. Using a two-sided *t*-test with a type I error rate of 5%, sample size of 30 subjects per group can detect this difference with 80% power. Estimating a drop-out rate of 10%, Estimating a drop-out rate of 10%, a 33 and 34 patients were required. It was planned to recruit patients over a 24 month period. The primary statistical analysis was performed for on the intent-to-treat (ITT) population. The frequency and rates of categories were determined for nominal variables and ordered