

# The effectiveness of pancreatic enzyme replacement therapy for malabsorption in advanced pancreatic cancer, a pilot study

Amanda Landers , Helen Brown and Matthew Strother

Palliative Care: Research and Treatment

1–7

DOI: 10.1177/  
1178224218825270

© The Author(s), 2019.  
Article reuse guidelines:  
sagepub.com/journals-  
permissions

**Abstract:** Advanced adenocarcinoma of the pancreas has a globally poor prognosis. One of the characteristic features of pancreatic cancer (PC) is pancreatic exocrine insufficiency (PEI). This leads to a malabsorption syndrome and subsequent digestive symptoms. Given the high prevalence of PEI and malabsorption in PC, empiric use of pancreatic enzyme replacement therapy (PERT) is recommended. The aim of this pilot study was to determine the potential efficacy of PERT in improving symptoms and quality of life in those with metastatic PC. The study recruited patients with advanced PC referred to a specialist palliative care service. Following an initial assessment, patients were commenced on pancrealipase 25,000IU (Creon) and reassessed after 1 week and 3 weeks post-initiation of supplementation. These assessments included demographics, malabsorption symptom checklist, and completion of two validated quality-of-life questionnaires, the European Organisation for Research and Treatment of Cancer QLQ-C30 and QLQ-PAN26. PERT was associated with statistically significant improvement of symptoms in both the general (QLQ-C30) and pancreatic cancer specific tool (PAN26). Within 1 week of PERT initiation, there was a reduction in diarrhoea scores (26 vs. 8,  $p < 0.005$ ), pancreatic and hepatic pain (47 vs. 33 and 24 vs. 11, respectively,  $p < 0.05$ ). After 3 weeks, there were significant improvements in pancreatic pain and bloating/gas symptoms (47 vs. 26 and 46 vs. 26, respectively,  $p < 0.005$ ). PERT appears to have the potential to improve symptoms of malabsorption in patients with metastatic PC.

**Keywords:** malabsorption, palliative care, pancreatic cancer, pancreatic enzyme replacement therapy

Received: 18 November 2018; accepted in revised form: 29 November 2018.

## Introduction

Advanced adenocarcinoma of the pancreas (PC) has a dismal prognosis, with a 5-year survival rate of approximately 5% and a median survival of a few months.<sup>1–3</sup> In New Zealand, the median survival among those with metastatic PC is 92 days, in line with European statistics and slightly less than the United States.<sup>4</sup> In addition to poor survival, PC patients face disease-related symptoms that reduce quality of life.<sup>3</sup> One of the hallmark features affecting these patients is pancreatic exocrine insufficiency (PEI). This leads to malabsorption (MA) and subsequent symptoms of poor digestion.

A healthy pancreas produces 500–1000 ml of digestive enzymes per day. When enzyme production falls below 10% of normal, PEI results, leading to MA.<sup>5,6</sup> This can occur in PC due to loss of pancreatic parenchyma, blockage of the duct, surgical procedures and scarring.<sup>6–8</sup> PEI primarily impacts fat absorption.

In PC, MA is present in 68–92% of patients at diagnosis.<sup>8–10</sup> Prior studies have found that 67–72% of PC patients have symptoms as a result of MA.<sup>11,12</sup> These symptoms may include diarrhoea, excessive flatulence, cramping, steatorrhoea, abdominal bloating and weight loss. A

Correspondence to:  
**Amanda Landers**  
Nurse Maude Hospice  
Palliative Care Service,  
Nurse Maude Association,  
P O Box 36-126,  
Christchurch 8146, New  
Zealand.

[Amanda.Landers@nursemaude.org.nz](mailto:Amanda.Landers@nursemaude.org.nz)

**Amanda Landers**  
Department of Medicine,  
University of Otago,  
Christchurch New Zealand  
Nurse Maude Hospice  
Palliative Care Service,  
Nurse Maude Association,  
Christchurch, New  
Zealand

**Helen Brown**  
Nurse Maude Hospice  
Palliative Care Service,  
Nurse Maude Association,  
Christchurch, New  
Zealand

**Matthew Strother**  
Department of Medicine,  
University of Otago, New  
Zealand  
Department of Oncology,  
Canterbury District Health  
Board, Christchurch, New  
Zealand

recent qualitative study looking at significant unmet psychosocial needs in those with PC identified gut-related symptoms as the major issue.<sup>13</sup> PC patients report that gastrointestinal symptoms and diet have a profound impact on their physical, emotional and social well-being, identifying MA as a clear clinical gap in their management.<sup>13,14</sup>

Pancreatic enzyme replacement therapy (PERT) has been shown to significantly improve fat digestion and symptoms after pancreatic resection and in known pancreatic insufficiency.<sup>15</sup> Among patients with chronic pancreatitis leading to exocrine insufficiency, two randomised controlled trials found PERT improved fat absorption after 3-week trial periods.<sup>16,17</sup> Both studies report few adverse side effects from the medication, despite large doses being utilised. However, there are limited randomized clinical trials of PERT in this population of advanced PC patients, especially with a focus on symptom improvement. Given the high prevalence of exocrine insufficiency and MA in PC, the lack of evidence has led to the empiric use of pancreatic enzyme replacement as recommended by several current guidelines, including the National Comprehensive Cancer Network and the Pancreatic Section of the British Society of Gastroenterology.<sup>12,18–21</sup>

Our research group has recently shown that four out of five patients with advanced PC in New Zealand were not on PERT despite the majority exhibiting symptoms consistent with MA.<sup>11</sup> This current pilot study was designed to explore the efficacy of PERT in improving symptoms of MA in a group of patients with a limited life span, and to measure the impact on quality of life in those diagnosed with metastatic pancreatic cancer.

## Methods

### Study population

The study recruited consecutive patients with a clinical or radiological diagnosis of metastatic pancreatic adenocarcinoma referred to the specialist palliative care team. The patients were referred by local oncology teams, surgeons or general practitioners. Patients were recruited to take part in the study by the palliative care dietitian. Additional inclusion criteria included fluency in English, ability to take oral medications and fill out survey instruments. As these patients have a poor prognosis, those with an Eastern Co-operative Oncology Group (ECOG) or a

Palliative Performance Scale (PPS) of  $\leq 3$  or less than 60% respectively were excluded from the study. Those already taking PERT were also excluded.

### Design

To determine the impact of PERT on quality of life and MA symptoms, we performed a prospective non-randomised cohort study within a specialist palliative care service. The Nurse Maude Hospice Palliative Care team serves the Canterbury region in the South Island of New Zealand. Following written consent, an initial assessment was performed in the home which included the collection of demographics, completion of the MA symptom checklist, and the two quality-of-life questionnaires. Quality of life was measured using the EORTC QLQ-C30 and QLQ-PAN26, both validated tools.<sup>22–24</sup> The patient's functional ability was measured using the ECOG or PPS.<sup>25</sup>

Following completion of this initial assessment, patients were commenced on pancreatic lipase 25,000IU (Creon 25000; Abbotts, Germany). The starting dose was 50,000IU Creon per meal and 25,000IU for a snack as outlined by Domínguez-Muñoz.<sup>26</sup> The average fat content of a standard diet was calculated as approximately 24g of fat for breakfast, 22g of fat for lunch and 24g of fat for dinner. The participants were encouraged not to avoid fat in their diet. The starting dose could be increased on the basis of a 24-h diet recall, with one extra 25,000IU Creon per 16–20g of extra fat per meal or snack.<sup>27</sup>

The patient was reassessed by the dietitian after 1 week and 3 weeks post-initiation of PERT. These timeframes were based on prior published literature researching PERT in other disease processes.<sup>20,21</sup> During reassessment visits, the following data was collected: the EORTC QLQ-C30, QLQ-PAN26, and weight, MA symptoms, ECOG/PPS and a 24-h recall of diet. The dietitian completed the questionnaires with the participants. In patients with on-going MA symptoms or where there was an improvement in appetite and therefore food intake, the Creon dose was increased to meet the higher fat content of the diet.<sup>27</sup>

The primary end point of this study was to evaluate the impact of PERT on symptoms of MA at 1 week and 3 weeks after the initiation of Creon. Secondary end point was intolerance to the medication.

### Data analysis

The EORTC QLQ-C30 and QLQ-PAN26 questionnaire results were analysed in accordance with the EORTC manual<sup>22</sup>. Missing data were assigned the mean value of the answered items of each domain if more than 50% of the items were completed. There were no clear patterns evident for the missing data except that many did not complete the sex domain questions, and therefore, these have not been summarised. Mean changes for each domain between the baseline and two follow-up periods were analysed using paired *t*-tests. All analyses were undertaken using SPSS v22.0 (SPSS Inc., Armonk, NY, USA). A two-tailed *p*-value <0.05 was taken to indicate statistical significance.

### Ethical considerations

This low-risk research protocol was approved by Nurse Maude Ethics Advisory Group which is an institutional ethics board. The participants were consented and the procedure was approved by the ethics group. The research was retrospectively registered with Australia and New Zealand Clinical Trials registry and has the trial number ACTRN12617000801314.

## Results

### Demographics

Between June 2013 and May 2015, 97 patients with metastatic pancreatic cancer were screened for eligibility to the study. The 53 out of 97 ineligible patients were ineligible due to poor performance status or prior initiation of PERT. There were 53 out of 97 patients deemed ineligible due to poor performance status or prior initiation of PERT. Forty-four participants consented to the study but 15 were unable to complete initial assessment due to progressive disease. Those that did and did not complete assessments were relatively similar, with the group who completed the study having better performance status, higher weight, cancers that originated in the head of the pancreas and local disease (Table 1).

### PERT titration

The majority of subjects did not have their PERT dose escalated as their food diaries did not significantly alter between assessments. However, four (of 29) of the subjects had a dose escalation in

response to increasing appetite and food intake, and one (of 29) had a decrease in the number of capsules prescribed. Dose escalation tended to be one extra Creon with main meals.

### Symptoms of MA

PERT was associated with statistically significant improvement in some symptoms in both the general (QLQ-C30) tool and pancreatic cancer specific tool (PAN26), as shown in Table 2. Within 1 week of PERT initiation, there was reduction in diarrhoea scores (26 v. 8, *p* < 0.005), pancreatic and hepatic pain (47 v. 33 and 24 v. 11, respectively, *p* < 0.05). After 3 weeks of PERT, there were significant improvements in pancreatic pain and bloating/gas symptoms (47 v. 26 and 46 v. 26, respectively, *p* < 0.005). Finally, it is worth highlighting that there was a trend towards improvement in digestive symptoms at the first week (52 v. 39) with borderline statistical significance (*p* = 0.05).

## Discussion

In this study, subjects with advanced pancreatic malignancy were initiated on empiric PERT. Quality of life was assessed by validated instruments (EORTC QLQ-C30 and QLQ-PAN26), and improvement was found in a number of potentially distressing symptoms. Diarrhoea, pancreatic pain, hepatic and bloating/gas all improved significantly. Although diarrhoea improved significantly at Week 1 it had worsened again by Week 3. This may reflect increased appetite and therefore food intake by participants. The diagnosis of advanced pancreatic cancer has a poor prognosis so the focus is to maximise symptom management. PERT shows potential as a simple and effective way of improving quality of life for these patients.

Wakasugi and colleagues was one of the first articles to suggest patients with advanced pancreatic cancer developed MA at rates approaching 80%.<sup>28</sup> This has been confirmed using several different methods by Matsumoto and Traverso<sup>8</sup> in 2006 who found that 68% of pre-operative pancreatic cancer patients had malabsorption. Furthermore, Sikkens and colleagues<sup>10</sup> reported under-treatment of exocrine insufficiency in post-surgical patients, with only 33% having visited a dietitian. In New Zealand, a recent study showed only 21% of those diagnosed with advanced pancreatic cancer were on PERT.<sup>11</sup>

**Table 1.** Characteristics of participants who did not complete or completed the study.

Characteristics	Did not complete, <i>n</i> = 15	Completed, <i>n</i> = 29
Age in years, mean $\pm$ SD	70.8 $\pm$ 10.6	69.4 $\pm$ 8.9
Sex (male), <i>n</i> (%)	3 (20)	12 (41.4)
ECOG, <i>n</i> (%)		
1	5 (33.3)	13 (44.8)
2	6 (40)	15 (51.7)
3	1 (6.7)	0
Missing data	3 (20)	1 (3.5)
Initial weight in kg, mean etc	63.4 $\pm$ 13.2	70.6 $\pm$ 12.7
Blood chemistry, mean $\pm$ SD		
Albumin, g/L	39.1 $\pm$ 5.7	39.5 $\pm$ 4.6
Tumour marker, median (range)		
CA19-9 (kIU/ml)	35,433 (1-278,483)	54,289 (1-<999,999)
Location of tumour, <i>n</i> (%)		
Head	6 (40)	20 (69.0)
Tail and body	9 (60)	6 (20.7)
Unknown	0	3 (10.3)
Extent of disease, <i>n</i> (%)		
Locally advanced	8 (53.3)	19 (65.5)
Metastatic	7 (46.7)	10 (35.5)
ECOG, Eastern Co-operative Oncology Group; SD, standard deviation.		

The efficacy of PERT in improving malabsorption symptoms in both chronic pancreatitis and post-pancreatic surgery has been proven in two randomised controlled trials.<sup>16,17</sup> In two non-randomised studies, PERT prevented weight loss for at least a period of time after diagnosis, with weight stabilisation being shown to improve survival and quality of life.<sup>17,29</sup> However, a recent prospective, randomised, placebo-controlled trial undertaken in Korea studied PERT and its effect on weight in patients with unresectable PC. They concluded there was no improvement with PERT. Their results did indicate that 67% of the patients had PEI but only one-third had tumour in the head of the pancreas. This tumour type would be more likely to cause malabsorption. Subanalysis of this group showed different results in the head

of pancreas group to the wider results but was not characterised in detail. They also did not focus primarily on symptoms, forgoing the EORTC QLQ-PAN26 tool designed specifically for indicators of malabsorption.<sup>30</sup>

This pilot study has several potential limitations. However, this study was utilised to help design a possible randomised controlled trial (RCT) and to check recruitment to this type of study was feasible. Malabsorption was defined based on a constellation of clinical symptoms as opposed to an objective measure of poor absorption, such as faecal fat. However, it should be noted that the primary focus of this research was quality of life, and there is poor correlation between laboratory measures of malabsorption and malabsorptive

**Table 2.** EORTC QLQ-C30 and QLQ-PAN26 transformed scores before and after PERT.

Parameters	Pre	Week 1	p-value	Pre	Week 3	p-value
EORTC QLQ-C30 v3						
Global health status/QOL	51	53	0.31	51	52	0.94
Physical Functional Scale	29	32	0.39	29	28	0.89
Role functioning	45	45	0.93	45	47	0.93
Emotional functioning	22	21	0.85	22	24	0.75
Cognitive functioning	28	26	0.53	28	33	0.39
Social functioning	38	35	0.91	38	42	0.44
Fatigue	49	49	1.00	49	48	0.83
Nausea and vomiting	32	29	0.53	32	29	0.67
Pain	41	37	0.47	41	34	0.50
Shortness of breath	30	29	0.83	30	19	0.13
Insomnia	33	30	0.59	33	28	0.16
Appetite loss	56	48	0.23	56	42	0.24
Constipation	32	26	0.09	32	19	0.06
Diarrhoea	26	8	0.004**	26	14	0.29
Financial difficulties	17	11	0.26	17	23	0.13
EORTC QLQ-PAN26						
Pancreatic pain	47	33	0.01*	47	26	0.0018**
Digestive symptoms	52	39	0.05*	52	38	0.09
Altered bowel habit	27	21	0.35	27	22	0.58
Hepatic	24	11	0.02*	24	14	0.10
Bloating/gas	46	35	0.07	46	26	0.0073*
Body image	23	22	0.55	23	20	0.31
Satis with health care	88	92	0.38	88	83	0.71
EORTC, European Organisation for Research and Treatment of Cancer; PERT, pancreatic enzyme replacement therapy. * $p < 0.05$ ; ** $p < 0.005$ .						

symptoms.<sup>5</sup> There was significant attrition of patients between screening and enrolment, and over the course of the 21 days of follow-up. This is not surprising given the rapid clinical progression of many of these patients as reflected in their short survival time. Finally, there was no recording of the subjects' concomitant medications; it is possible that concurrent adjustment in pain

medications or other supportive medications may lead to an overestimation of the effect of PERT. Nonetheless, in this pilot study, there was clear signal that PERT was associated with improved quality of life (QOL) and merits further research.

Although the evidence is conflicting, significant rates of PEI have been shown. The medication

used to treat the symptoms of malabsorption is well tolerated and easy to administer. The most difficult aspect of the treatment is titration and dietary advice/resources. However, use of PERT has the potential to significantly improve aspects of quality of life in this malignancy which has such a poor prognosis, and therefore, it is worth empirically treating all appropriate patients.

### Conclusion

In conclusion, this study shows PERT is a safe therapy for the treatment of malabsorption symptoms in patients diagnosed with advanced pancreatic cancer. It appears to have a positive impact on symptoms and quality of life and this is further support for international guidelines recommending its use empirically.

### Acknowledgements

The authors acknowledge the assistance of Gill Coe and Dr Chris Hendry of the New Zealand Institute of Community Health Care which is part of the Nurse Maude Association. They also wish to thank the participants for their time. HB and AL contributed to the study design. HB collected the data. All authors contributed to the analysis of the data, drafted and reviewed the paper. All authors read and approved the final manuscript before submission.

### Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by the Canterbury Medical Research Foundation, Canterbury, New Zealand.

### Conflict of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

### ORCID iD

Amanda Landers  <https://orcid.org/0000-0002-7385-3739>

### References

- Noone AM, Howlader N, Krapcho M, *et al.* SEER cancer statistics review, 1975–2015. Bethesda, MD: National Cancer Institute, [https://seer.cancer.gov/csr/1975\\_2015/](https://seer.cancer.gov/csr/1975_2015/) (November 2017, accessed April 2018).
- Speer AG, Thursfield VJ, Torn-Broers Y, *et al.* Pancreatic cancer: surgical management and outcomes after 6 years of follow-up. *Med J Aust* 2012; 196: 511–515.
- Carrato A, Falcone A, Ducreux M, *et al.* A systematic review of the burden of pancreatic cancer in Europe: real-world impact on survival, quality of life and costs. *J Gastrointest Cancer* 2015; 46: 201–211.
- Phillips AJR, Lawes CM, Cooper GJ, *et al.* Ethnic disparity of pancreatic cancer in New Zealand. *Int J Gastrointest Cancer* 2002; 31: 137–145.
- DiMagno EP, Vay LW and Summerskil WH. Relations between pancreatic enzyme outputs and malabsorption in severe pancreatic insufficiency. *N Engl J Med* 1973; 288: 813–815.
- Keller J and Layer P. Human pancreatic exocrine response to nutrients in health and disease. *Gut* 2005; 54(Suppl. 6): 1–28.
- Halloran CM, Cox TF, Chauhan S, *et al.* Partial pancreatic resection for pancreatic malignancy is associated with sustained pancreatic exocrine failure and reduced quality of life: a prospective study. *Pancreatology* 2011; 11: 535–545.
- Matsumoto J and Traverso LW. Exocrine function following the whipple operation as assessed by stool elastase. *J Gastrointest Surg* 2006; 10: 1225–1229.
- Ihse I, Arnesjö B, Kugelberg C, *et al.* Intestinal activities of trypsin, lipase, and phospholipase after a test meal: an evaluation of 474 examinations. *Scand J Gastroenterol* 1977; 12: 663–668.
- Sikkens EC, Cahen DL, de Wit J, *et al.* A prospective assessment of the natural course of the exocrine pancreatic function in patients with a pancreatic head tumor. *J Clin Gastroenterol* 2014; 48: e43–e46.
- Landers A, Muircroft W and Brown H. Pancreatic enzyme replacement therapy (PERT) for malabsorption in patients with metastatic pancreatic cancer. *BMJ Support Palliat Care* 2016; 6: 75–79.
- Sikkens EC, Cahen DL, van Eijck C, *et al.* The daily practice of pancreatic enzyme replacement therapy after pancreatic surgery: a northern European survey. *J Gastrointest Surg* 2012; 16: 1487–1492.
- Gooden HM and White KJ. Pancreatic cancer and supportive care: pancreatic exocrine insufficiency negatively impacts on quality of life. *Support Care Cancer* 2013; 21: 1835–1841.

14. Labori KJ, Hjermstad MJ, Wester T, *et al.* Symptom profiles and palliative care in advanced pancreatic cancer: a prospective study. *Support Care Cancer* 2006; 14: 1126–1133.
15. Guarner L, Rodriguez R, Guarner F, *et al.* Fate of oral enzymes in pancreatic insufficiency. *Gut* 1993; 34: 708–712.
16. Seiler CM, Izbicki J, Varga-Szabó L, *et al.* Randomised clinical trial: a 1-week, double-blind, placebo-controlled study of pancreatin 25 000 Ph. Eur. minimicrospheres (Creon 25000 MMS) for pancreatic exocrine insufficiency after pancreatic surgery, with a 1-year open-label extension. *Aliment Pharmacol Ther* 2013; 37: 691–702.
17. Thorat V, Reddy N, Bhatia S, *et al.* Randomised clinical trial: the efficacy and safety of pancreatin enteric-coated minimicrospheres (Creon 40000 MMS) in patients with pancreatic exocrine insufficiency due to chronic pancreatitis - a double-blind, placebo-controlled study. *Aliment Pharmacol Ther* 2012; 36: 426–436.
18. Tempero MA, Arnoletti JP, Behrman SW, *et al.* Pancreatic adenocarcinoma, version 2.2012: featured updates to the NCCN guidelines. *J Natl Compr Canc Netw* 2012; 10: 703–713.
19. Pancreatic Section of the British Society of Gastroenterology, Pancreatic Society of Great Britain and Ireland, Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland, *et al.* Guidelines for the management of patients with pancreatic cancer periampullary and ampullary carcinomas. *Gut* 2005; 54 (Suppl. 5): v1–v16.
20. Bruno MJ, Haverkort EB, Tijssen GP, *et al.* Placebo controlled trial of enteric coated pancreatic microsphere treatment in patients with unresectable cancer of the pancreatic head region. *Gut* 1998; 42: 92–96.
21. Damerla V, Gotlieb V, Larson H, *et al.* Pancreatic enzyme supplementation in pancreatic cancer. *J Support Oncol* 2008; 6: 393–396.
22. Aaronson NK, Ahmedzai S, Bergman B, *et al.* The European Organisation for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993; 85: 365–376.
23. Fayers PM, Aaronson NK, Bjordal K, *et al.* *EORTC QLQ-C30 scoring manual*. 2001.
24. Fitzsimmons D, Kah S, Butturini G, *et al.* Symptoms and quality of life in chronic pancreatitis assessed by structured interview and the EORTC QLQ-C30 and QLQ-PAN26. *Am J Gastroenterol* 2005; 100: 918–926.
25. Oken M, Creech R, Tormey D, *et al.* Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol* 1982; 5: 649–655.
26. Domínguez-Muñoz JE. Pancreatic exocrine insufficiency: diagnosis and treatment. *J Gastroenterol Hepatol* 2011; 26(Suppl. 2): 12–16.
27. Kuhn RJ, Gelrud A, Munck A, *et al.* CREON (Pancrelipase Delayed-Release Capsules) for the treatment of exocrine pancreatic insufficiency. *Adv Ther* 2010; 27: 895–916.
28. Wakasugi H, Hara Y and Abe M. A study of malabsorption in pancreatic cancer. *J Gastroenterol* 1996; 31: 81–85.
29. Davidson W, Ash S, Capra S, *et al.* Weight stabilisation is associated with improved survival duration and quality of life in unresectable pancreatic cancer. *Clin Nutr* 2004; 23: 239–247.
30. Woo SM, Joo J, Kim SY, *et al.* Efficacy of pancreatic exocrine replacement therapy for patients with unresectable pancreatic cancer in a randomized trial. *Pancreatol* 2016; 16: 1099–1105.

Visit SAGE journals online  
[journals.sagepub.com/  
 home/pcr](http://journals.sagepub.com/home/pcr)

 SAGE journals