

Review Article

Potential applications of fish oils rich in *n*-3 fatty acids in the palliative treatment of advanced pancreatic cancer

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Abstract

The palliative treatment of patients with advanced pancreatic cancer (APC) has undergone little advancement in the last 15 years. Novel therapies that have been investigated to extend survival have shown little benefit over existing chemotherapy regimens. Patients with APC often experience significant weight loss, which is one of the primary factors involved in declining quality of life. Recently, the ability of *n*-3 fatty acid rich oral preparations to attenuate or reverse tumour-related weight loss has been investigated in this patient group with encouraging results. Laboratory investigation has also yielded promising results suggesting a potential direct tumouricidal effect of *n*-3 fatty acids as well as the putative potentiation of existing chemotherapy regimes. The present review aims to examine the potential applications of fish oils rich in *n*-3 fatty acids in patients with APC, present a selection of the studies carried out to date and outline avenues of possible further clinical investigation.

Key words: *n*-3 Fatty acids; Fish oil; EPA; DHA; Pancreatic cancer

Pancreatic cancer is responsible for more than 7700 deaths from cancer each year, making it the fifth most common cause of death from all cancer sites and the third most common from gastrointestinal sources. It is the eleventh most common cancer in the UK, with over 7600 new cases per annum. This represents nine per 100 000 cases in the UK population^(1–3). The male:female ratio is roughly equal, and although the incidence in men has fallen slightly in the last 30 years, the female incidence has remained unchanged. Overall, 1-year survival rates are in the region of 13%, with rates of 25% in the under 50s; 5-year survival is 2–3%. This makes the prognosis one of the worst among all cancers. Only about 10% of patients with pancreatic cancer are suitable for surgical resection, which remains the only possible chance of long-term survival. The remainder will be offered palliative treatments to extend and improve quality of life (QOL). The current standard of care is single-agent gemcitabine chemotherapy; however, this offers only a modest survival advantage with a median benefit of 2–3 months over no treatment. This dismal outlook has prompted the search for alternative therapies, which can be given in conjunction with standard chemotherapy in an effort to further improve survival and QOL. Many different chemotherapeutic combination agents

have been tried, none of which has shown significantly improved activity over single-agent gemcitabine⁽⁴⁾. Novel biological agents have also been extensively examined in phase II trials, in particular those which target specific growth factor receptors such as the epidermal growth factor receptor. Only the epidermal growth factor receptor antagonist erlotinib has shown significantly improved activity in randomised phase III trials in combination with gemcitabine. This improvement was limited to a prolonged overall survival period of 6.24 *v.* 5.91 months ($P=0.038$) and 1-year survival of 23 *v.* 17% ($P=0.024$)⁽⁵⁾. This was at the expense of common and potentially significant cutaneous side effects.

Patients with advanced pancreatic cancer (APC) commonly experience profound weight loss, and therapies that may alleviate this distressing symptom as well as potentially provide enhanced anti-cancer activity are of particular interest.

n-3 Fatty acids are a family of unsaturated fatty acids that have in common a first carbon–carbon double bond as the third carbon–carbon bond from the terminal methyl end of the carbon chain. Important *n*-3 PUFA involved in human nutrition are α -linolenic acid, EPA and DHA. These fatty acids have three, five or six double bonds in a carbon chain of eighteen, twenty or twenty-two carbon atoms, respectively.

Abbreviations: APC, advanced pancreatic cancer; QOL, quality of life.

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The capacity of human metabolism to derive EPA and DHA by the elongation and desaturation of α -linolenic acid is negligible. Furthermore, this synthesis of longer-chain, *n*-3 fatty acids from linolenic acid is competitively slowed by *n*-6 analogues. Therefore, their concentration in tissues is enhanced when they are directly ingested or when competing amounts of *n*-6 fatty acids are relatively small.

Methods

A PubMed/Medline search of 'cell proliferation' OR 'pancreatic cancer' AND 'omega 3' OR '*n*-3 polyunsaturated fatty acids' OR 'EPA' OR 'DHA' was carried out, and relevant articles

were screened manually for inclusion in order to provide a representative selection of the important studies carried out to date. The articles were divided into those that utilised pre-clinical *in vitro* or *in vivo* work to determine the action of *n*-3 fatty acids on cell lines or xenograft models and those that used oral preparations of *n*-3 fatty acids in clinical trials (Tables 1 and 2)

Laboratory studies of *n*-3 fatty acids in pancreatic cancer models

Both DHA and EPA have been shown to have beneficial effects on pancreatic adenocarcinoma cell lines *in vitro*.

Table 1. Pre-clinical studies using *n*-3 fatty acids in neoplastic and proliferative cell lines and xenograft models

Study (year)	Model used	Parameters measured and outcome
Falconer <i>et al.</i> (1996) ⁽⁶⁾ Lai <i>et al.</i> (1996) ⁽⁷⁾	PC cell lines + different FA PC cell lines + EPA	Reduction in cell numbers, viability and proliferation with EPA Decrease in cell count and viability mediated by cell cycle arrest and apoptosis with EPA
Ravichandran <i>et al.</i> (2000) ⁽⁸⁾	PC cell lines/mouse xenograft + EPA + GLA	Growth inhibition in cell lines with EPA + GLA but no effect in xenograft model
Merendino <i>et al.</i> (2003, 2005) ^(9,10) Shirotta <i>et al.</i> (2005) ⁽¹¹⁾	PC cell lines + butyric acid, DHA or ALA PC cell lines + EPA	Reduced cell growth and induction of apoptosis, probably by glutathione depletion, with DHA Dose-dependent inhibition of proliferation + induction of apoptosis with EPA
Zhang <i>et al.</i> (2007) ⁽¹²⁾	PC cell lines + EPA or DHA	Growth and proliferation inhibition with induction of apoptosis with EPA or DHA
Hering <i>et al.</i> (2007) ⁽¹³⁾	PC cell lines + <i>n</i> -3 FA/ <i>n</i> -6 FA + - gemcitabine	Inhibition of proliferation in <i>n</i> -3 FA group regardless of gemcitabine. Inhibition of NF- κ B activation and restoration of apoptosis in gemcitabine-resistant cells with <i>n</i> -3 FA
Dekoj <i>et al.</i> (2007) ⁽¹⁴⁾ O'Connor <i>et al.</i> (1989) ⁽¹⁵⁾	PC cell lines + <i>n</i> -3 FA or <i>n</i> -6 FA Rats treated with azaserine to induce pre-neoplastic pancreatic lesions + different <i>n</i> -3: <i>n</i> -6 FA ratios	Cell cycle arrest and induction of apoptosis with <i>n</i> -3 FA Decreased development of pre-neoplastic lesions with increased <i>n</i> -3 FA component
Heukamp <i>et al.</i> (2006) ⁽¹⁶⁾ , Gregor <i>et al.</i> (2006) ⁽¹⁷⁾	Hamsters treated with BOP to induce PC + <i>n</i> -6 FA-rich diet followed by <i>n</i> -3 or <i>n</i> -3, -6 and -9 FA-rich diet	Decreased incidence of liver metastases in <i>n</i> -3 FA group. Decreased incidence of macroscopically visible pancreatic tumours in <i>n</i> -3 FA, although microscopic appearances are not different from other FA groups
Strouch <i>et al.</i> (2009) ⁽¹⁸⁾	EL-Kras mice + <i>n</i> -3 FA-rich diet or standard diet PC cell lines + DHA	Incidence, frequency and proliferation index of pancreatic pre-cancer reduced with <i>n</i> -3 FA-rich diet. Decrease in cell line proliferation and induction of apoptosis with DHA
Funahashi <i>et al.</i> (2008) ⁽¹⁹⁾	PC cell lines + <i>n</i> -3 FA or <i>n</i> -6 FA. Mice injected with PC cells + <i>n</i> -3 or <i>n</i> -6 FA-rich diet.	Decreased cell growth with <i>n</i> -3 FA. Decrease in growth in mouse model with <i>n</i> -3 FA-rich diet
Yang <i>et al.</i> (1998) ⁽²⁰⁾	Bovine endothelial cell lines treated with VEGF + <i>n</i> -3 or <i>n</i> -6 FA	Suppression of VEGF-induced proliferation with EPA
Tsuzuki <i>et al.</i> (2007) ⁽²¹⁾	Human umbilical vein cells treated with VEGF + EPA	Inhibition of VEGF-stimulated migration and tube formation. Reduction in MMP2 and MMP9
Tsuji <i>et al.</i> (2003) ⁽²²⁾	Bovine endothelial cell lines treated with VEGF + EPA or DPA or DHA.	Inhibition of VEGF-stimulated migration and tube formation and VEGF receptor 2 expression strongest with DPA compared with DHA or EPA
Fox & DiCorleto (1988) ⁽²³⁾ Terano <i>et al.</i> (1996) ⁽²⁴⁾	Vascular endothelial cells + EPA Vascular smooth muscle cells + EPA or DHA	Inhibition of PDGF production with EPA Inhibition of vascular smooth muscle proliferation through inhibition of PDGF signal transduction with EPA greater than DHA
Boutard <i>et al.</i> (1994) ⁽²⁵⁾	Macrophages isolated from rats fed <i>n</i> -3 FA-rich or -deficient diets.	NO production in response to lipopolysaccharide reduced by <i>n</i> -3 FA-rich diet
Jeyarajah <i>et al.</i> (1999) ⁽²⁶⁾	Mouse macrophages (treated with IFN- γ or TNF- α) + DHA	DHA inhibitory to NO production at all doses of IFN- γ or TNF- α
Ohata <i>et al.</i> (1997) ⁽²⁷⁾	Mouse macrophage cell line treated with lipopolysaccharide + <i>n</i> -3, <i>n</i> -6, <i>n</i> -9 FA or stearic acid	Inhibition of NO production with <i>n</i> -3 FA in contrast to no inhibition with any other FA regimen
Narayanan <i>et al.</i> (2005) ⁽²⁸⁾	Prostate cancer cell lines + DHA + - celecoxib (COX-2 inhibitor)	Inhibition of growth and induction of apoptosis greatest with low-dose combination of DHA + celecoxib
Reddy <i>et al.</i> (2005) ⁽²⁹⁾	Colon cancer rat model + celecoxib + <i>n</i> -3 FA-rich or -deficient diet	Inhibition of tumour incidence in multiplicity in <i>n</i> -3 FA-rich diet with low-dose celecoxib

PC, pancreatic cancer; FA, fatty acids; GLA, γ -linolenic acid; ALA, α -linolenic acid; BOP, *N*-nitrosobis(2-oxopropyl)amine; VEGF, vascular endothelial growth factor; MMP, matrix metalloproteinase; DPA, docosapentaenoic acid; PDGF, platelet-derived growth factor; IFN, interferon; COX, cyclo-oxygenase.

Table 2. Clinical studies in patients with pancreatic cancer treated with n-3 fatty acid rich oral preparations

Study (year)	EPA/DHA (g/d)	Duration of treatment (weeks)	Number of patients in EPA/DHA group and diagnosis	Outcome
Barber <i>et al.</i> (1999) ⁽³²⁾	2.2/0.9	7	20 (PC)	Significant weight gain, PS and appetite at 3 weeks and weight gain at 7 weeks
Barber <i>et al.</i> (1999) ⁽³³⁾	2.0/1.0	3	18 (PC + supplement) + 18 (PC supplement) + 6 (healthy controls)	Weight gain in treatment group with stabilisation of acute-phase protein response
Barber <i>et al.</i> (2000) ⁽³⁴⁾	2.2/0.96	3	16 (PC) + 6 (healthy controls)	Increase in body weight of PC patients and normalisation of metabolic response
Barber & Fearon (2001) ⁽³⁵⁾	Up to 18 EPA only	4	5 (PC)	These doses can be tolerated by PC patients
Burns <i>et al.</i> (1999) ⁽³⁶⁾	Up to 7.9/5.2*	4*	22 (mixed cancers)	High-dose EPA/DHA can be tolerated well orally
Wigmore <i>et al.</i> (1996) ⁽³⁷⁾	2.16/1.44*	12	18 (PC)	Weight gain and reduction in acute-phase protein response
Wigmore <i>et al.</i> (2000) ⁽³⁸⁾	Up to 5.7 EPA only	12	26 (PC)	This dose well tolerated + stabilised weight
Fearon <i>et al.</i> (2003) ⁽³⁹⁾	1.54 EPA only*	8	95 (PC + supplement) 105 (PC + control)	Weight gain + improved QOL if taken at intended dose (2.2 g/d)
Bruera <i>et al.</i> (2003) ⁽⁴⁰⁾	1.8/1.2*	2	Mixed cancer: 30 (treatment) + 30 (placebo)	No significant difference in any parameter
Kenler <i>et al.</i> (1996) ⁽⁴¹⁾	3.27/1.48*	1	17 (treatment) + 18 (control) in post-surgical patients	Reduction in infections and complications in fish oil group
Moses <i>et al.</i> (2004) ⁽⁴²⁾	2.09 EPA only*	8	9 (PC + treatment) + 15 (PC + control)	Increase in physical activity in treatment group, which may be related to QOL

PC, pancreatic cancer; PS, performance status; QOL, quality of life.

* Median values.

They inhibit the growth of human pancreatic adenocarcinoma cell lines in a dose-dependent manner^(6–8). They also induce apoptosis of the same cells in a dose-dependent manner^(7,9–12). They have been shown to inhibit proliferation in gemcitabine-resistant cell lines irrespective of the level of gemcitabine resistance⁽¹³⁾. There are various mechanisms postulated for this action including the induction of apoptosis, cell cycle arrest, intracellular glutathione depletion, down-regulation of cyclin E and inhibition of NF-κB expression^(10,14). In rat models given azaserine to induce neoplastic pancreatic lesions, a diet with a high n-3:n-6 ratio of fatty acids decreased the development of pre-neoplastic atypical acinar cell nodules⁽¹⁵⁾. A different model using N-nitrosobis-2-oxypropylamine to induce ductal pancreatic adenocarcinoma in rats found that a group fed with a diet rich in n-3 fatty acids only had significantly lower incidence of macroscopic tumours and liver metastases compared with the groups fed on a diet rich in n-6 fatty acids alone, or n-3, -6 and -9 fatty acids together^(16,17). More recently, the incidence, frequency and proliferative index of pre-neoplastic pancreatic lesions in an experimental rat model has been shown to be reduced in the cohort fed on a high-n-3 fat diet⁽¹⁸⁾. n-6 Fatty acids have been shown to stimulate the development of pancreatic carcinoma in xenograft models through the increased production of cyclo-oxygenase-2-generated PGE2, whereas in the same model, n-3 fatty acids were shown to reduce the development of pancreatic carcinoma through the reversal of the PGE2:PGE3 ratio⁽¹⁹⁾.

Rapidly growing tumours require new blood vessel formation or angiogenesis in order to initiate and sustain proliferation. Angiogenesis is dependent on many different growth factors, in particular vascular endothelial growth factor and platelet-derived growth factor. n-3 Fatty acids suppress vascular endothelial growth factor-stimulated cell proliferation,

migration and tube formation during angiogenesis^(20–22). n-3 Fatty acids inhibit the production of platelet-derived growth factor-like protein from vascular endothelial cells and inhibit vascular smooth muscle proliferation by interfering with the platelet-derived growth factor signalling pathway^(23,24). In addition, angiogenesis is critically dependent upon the production of NO and the action of cyclo-oxygenase-2. n-3 Fatty acids inhibit NO production and NO synthase *in vitro* as well as in animal models^(25–27). Several recent studies have shown that n-3 fatty acids combined with cyclo-oxygenase-2 inhibitors inhibit growth in experimental cancer cell lines and xenograft models^(28,29).

Furthermore, n-3 fatty acids have been shown to potentiate the effects of gemcitabine chemotherapy on human cancer cell lines. The postulated mechanisms for this action include up-regulation of cytotoxic transporters and initiation of oxidative stress processes.

Human studies into the effects on tumour-related cachexia and quality of life

It has been suggested for 20 years that n-3 fatty acids may be useful in the alleviation of tumour-related cachexia⁽³⁰⁾. In particular, most studies have been performed on patients with pancreatic and upper gastrointestinal tract cancers, although there are some data showing a benefit in patients with other solid cancers⁽³¹⁾. Barber *et al.*^(32–34) showed that patients with pancreatic cancer given approximately 2 g of EPA and 1 g of DHA for 7 weeks showed significant weight gain and improvement in functional status and appetite, in both one single- and two double-armed non-randomised studies comprising seventy-two patients and twelve controls. It was also shown that high doses (up to 18 g) of EPA were well tolerated but with greater side effects such as pain, steatorrhoea and

nausea^(35,36). Burns *et al.*⁽³⁶⁾ went on to show 66% weight stabilisation and 17% weight gain in the twenty-two patients they enrolled in a single-armed study, with the best QOL scores in the patients with weight gain. Wigmore *et al.*⁽³⁷⁾ showed significant weight gain, with a mean of 0.3 kg/month in pancreatic cancer patients given fish oil for 3 months, as well as stabilisation of resting energy expenditure by indirect calorimetry. They went on to examine an escalating dose of EPA from 1 g/d for 4 weeks to 6 g/d for 12 weeks. This study showed a weight gain of 0.5 kg at 1 month, which remained stable at 12 weeks⁽³⁸⁾. The best-quality and largest study in pancreatic cancer patients to date is from Fearon *et al.*⁽³⁹⁾ who randomised 200 patients to receive 2.2 g EPA/d or placebo. They noted weight and lean tissue gain in the EPA group as well as improved QOL scores. Bruera *et al.*⁽⁴⁰⁾, however, noted no difference in weight, functional status or well-being in their randomised controlled trial comprising sixty patients given either DHA + EPA or olive oil, although it should be noted that this group had tumours of diverse anatomical origin. Kenler *et al.*⁽⁴¹⁾ studied thirty-five patients with surgically operated upper gastrointestinal malignancies and noted a significant reduction in gastrointestinal complications of distension, diarrhoea and nausea, with a significant decrease in the need for total parenteral nutrition and improvement in liver and renal function in the EPA/DHA group. Moses *et al.*⁽⁴²⁾ found a significant increase in total resting energy expenditure and physical activity level in the patients to whom they gave EPA for 8 weeks. In summary, there does seem to be at least some evidence to show a beneficial relationship of fish oils rich in *n*-3 fatty acids in the alleviation of tumour-related cachexia and improving QOL scores. There is limited evidence on the optimal dose: these studies all used oral supplementation, although most showing benefit used a dose >1.5 g/d, with some showing improved results in the 1.5–4.0 g/d range⁽⁴³⁾. In addition, many of these studies reported problems with patient compliance in taking the oral *n*-3 fatty acid preparations, mainly due to the large number of tablets or volume of liquid that was required to achieve the desired dose.

Clinical applications of parenteral fish oils rich in n-3 fatty acids

Many studies have reported beneficial immunomodulatory and nutritional effects of *n*-3 fatty acid containing lipid emulsions as part of total parenteral nutrition^(44,45). So far, few have examined the use of *n*-3 fatty acid emulsions independently in the treatment of inflammatory conditions, and there are no published case series or controlled trials of intravenous *n*-3 fatty acid preparations in the adjuvant treatment of cancers. However, animal models as discussed previously using *n*-3 fatty acid preparations do support the potential utility of *n*-3 fatty acid emulsions in the adjuvant treatment of human pancreatic adenocarcinoma. Notwithstanding the potential direct tumour effect and potential response for patients undergoing chemotherapy for unresectable pancreatic adenocarcinoma, there is a reasonable body of evidence that QOL scores and tumour cachexia may be improved^(30–39).

High-strength oral preparations are available, as mentioned previously, with EPA purity of up to 95% containing up to 18 g of EPA in 100 ml of emulsion⁽⁵⁵⁾. However, data concerning the oral bioavailability of EPA and DHA are limited, and there are no published data comparing oral and intravenous bioavailability⁽⁴⁶⁾. Intravenous preparations containing 10 g of *n*-3 TAG per 500 ml are commercially available.

The safety of high-dose *n*-3 fatty acid parenteral emulsions is well established when it has been used as a component of total parenteral nutrition, but further studies would be required to establish its tolerability and efficacy as a combination therapy in conjunction with gemcitabine chemotherapy for the treatment of APC.

Conclusions

The effective palliative treatment of patients with APC has undergone very little advancement in terms of improving overall survival, since gemcitabine chemotherapy was first introduced 16 years ago⁽⁴⁷⁾. Novel agents that can prolong survival, improve QOL and alleviate cachexia in patients with APC are currently unavailable. Putative adjuvant therapies including parenteral *n*-3 fatty acid emulsions have the potential to address all of these outcome targets and have the additional benefit of proven safety and tolerability albeit in a different study population. The marginal benefits on tumour cachexia and QOL shown in trials using oral *n*-3 fatty acid supplementation may warrant further investigation with parenteral preparations as compliance and maintenance of optimal dosing should be easier to achieve. Clinical trials to investigate *n*-3 fatty acid emulsions in combination with gemcitabine in patients with APC are clearly warranted. Even if there is no demonstrated anti-neoplastic activity, an improvement in cachexia and QOL could result in *n*-3 fatty acid emulsions becoming part of standard care in this challenging patient group.

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