The Effect of Supplementary Omegaven® on the Clinical Outcome of Patients With Advanced Esophagogastric Adenocarcinoma Receiving Palliative Epirubicin, Oxaliplatin, and Capecitabine Chemotherapy: A Phase II clinical trial

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Abstract. *Background/Aim:* Previous studies have shown anti-proliferative and anti-apoptotic effects of omega-3 fatty acids (Omegaven®) in vitro and in vivo. Whether this effect can be exploited in patients with advanced esophago-gastric adenocarcinoma is unknown. The present study intended to determine the tumour radiological response and toxicity profile of intravenous omega-3 fish oil infusion when combined with standard palliative chemotherapy, and present the effects of this treatment on plasma cytokine biomarkers. *Materials and Methods:* Participants with advanced esophago-gastric adenocarcinoma were enrolled in a phase II single-arm clinical trial of palliative chemotherapy (epirubicin, oxaliplatin, and capecitabine; EOX) coupled with weekly infusion of Omegaven®. Outcomes were compared to those observed in 37 historical control patients who had received EOX alone. Toxicity was graded using the CTCAE v4.03 and radiological response was assessed using RECIST v1.1. Plasma cytokine levels of IL-1, IL-2, IL-6, TNF- α , and VEGF were evaluated by ELISA. *Results:* Twenty participants were included in the analysis. Radiological responses were as follows: partial response (EOX plus omega-3 group 73% vs. EOX alone 39%, $p=0.03$), stable disease (EOX plus omega-3 21% vs. EOX alone 39%, $p=0.24$), and progressive disease (EOX plus omega-3 7% vs. EOX alone 18%, $p=0.34$). Grade 3 or 4 toxicity was less common (thromboembolism & gastrointestinal) in those who received EOX plus omega-3. This translated into fewer hospital admissions. There were

significant reductions in the concentrations of IL-2 ($p=0.009$), TNF- α ($p<0.0001$) and VEGF ($p=0.002$) following each treatment. *Conclusion:* The treatment with supplementary omega-3 fatty acids reduced chemotherapy-related toxicity and resulted in better radiological responses. The combination treatment resulted in a shift towards a favourable anti-inflammatory cytokine profile. These findings should be evaluated in a randomised clinical trial.

The 2013/2014 United Kingdom National Esophago-gastric Cancer Audit indicated that 37% of patients with esophago-gastric cancer received potentially curative treatment, 48% received palliative treatments, and 15% received best supportive care only. Of those that received palliative treatments, chemotherapy was employed in two-thirds (1, 2). Only half of these patients completed their planned programme because of disease progression or chemotherapy related toxicity (1, 2).

Omega-3 polyunsaturated fatty acids (PUFA), such as EPA and DHA are natural nutritional products derived mainly from fish and fish oil. They have strong anti-inflammatory effects, acting mainly by blocking the release of the pro-inflammatory mediators derived from Arachidonic acid (omega-6 fatty acids) (3). This anti-inflammatory effect acts on and inhibits the inflammatory pathway, which is crucial for cancer development and metastasis (4). A number of studies have reported the favourable effects of EPA and DHA; findings have included improvement in quality of life (5-7), reduced toxicity (8, 9) and improved prognosis (5, 10, 11). There is little information of their application in the palliative setting to patients with advanced esophago-gastric cancer (12).

The cancer microenvironment is a complex setting comprised of tumour cells, fibroblasts and endothelial cells. Cytokines are the key elements controlling communication

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between these cells (13). These inflammatory biomarkers are released in the cancer microenvironment and have been identified in various human cancer cells (12). Tumour angiogenic and pro-inflammatory cytokines include IL-1, IL-6, TNF α and VEGF. These are considered to play a major role in cancer progression, survival and metastasis (4).

To our knowledge, this is the first phase II clinical trial investigating the clinical, radiological and cytokine effects of intravenous infusion of omega-3 PUFAs in patients with advanced esophago-gastric cancer receiving palliative platinum-based chemotherapy. The aims of the study were to assess toxicity, radiological response rate and survival of patients receiving palliative chemotherapy and omega-3 fish oil (intervention group) compared to a historical control group of patients who received palliative chemotherapy alone.

Materials and Methods

Participants and setting. The study recruited adult patients referred to the University Hospitals of Leicester NHS Trust, UK with confirmed diagnoses of inoperable esophageal, gastroesophageal junctional or gastric adenocarcinoma, eligible for palliative chemotherapy. Treatment intent was determined after discussion at the weekly multi-disciplinary team meeting by the clinical team (14).

Recruitment. Ethical approval was granted by the NRES Committee East Midlands - Nottingham 2 (reference number 11/EM/0412). Eligible participants were offered a participant information sheet at their first Oncology clinic visit. A minimum of 24 h later, potential participants were contacted to enquire about trial participation. Recruitment ran between 05/01/2012 and 07/31/2013. Participants were followed up for a minimum of 12 months. All participants provided written informed consent for trial inclusion (14).

Study design and sample size. This was a prospective, single-arm phase II clinical pilot trial. As this was a pilot/feasibility study, sample size was selected on pragmatic grounds to make an estimate of recruitment, retention, and drug toxicity, while not exposing too many participants to the full range of experimental procedures (14). Intervention. Participants received palliative chemotherapy with IV epirubicin (50 mg/m²) and oxaliplatin (130 mg/m²) every 21 days and oral capecitabine (1,250 mg/m²) daily for 21 days (15). This is standard practice for care of these patients in the UK. As part of the trial, this regimen was coupled with intravenous infusion of omega-3 PUFAs as Omegaven® (Fresenius Kabi, Bad Homburg, Germany). Omegaven® was infused once weekly at a rate of 2 ml/kg body weight for 4 h (*i.e.*, 140 ml for 4 hours in a 70 kg patient). Omegaven® is a 10% fish oil lipid emulsion. Chemical analysis by gas chromatography revealed the contents of the batch used in the current study to be 2.0 g EPA and 2.3 g DHA/100 ml, respectively. Thus, patients received 0.04 and 0.046 g EPA and DHA/kg body weight for each 4-h infusion; in a 70 kg patient this would equate to 2.8 g EPA and 3.2 g DHA during each infusion. Omegaven® was administered through a peripheral venous line immediately after the chemotherapy treatment on day 1 of each cycle and then again on days 8 and 15 of the cycle (14). Blood samples were collected before and after each infusion for plasma cytokine analysis.

EOX alone (Historical control) group. Patients who had received palliative platinum-based chemotherapy for advanced esophago-gastric adenocarcinoma between January 2010 and December 2011 were identified as a control group for comparison of treatment toxicity, radiologic response, and survival. These patients were identified from the Oncology database and case notes reviewed in order to ascertain eligibility for inclusion in the control group. Institutional Clinical Audit Standards and Effectiveness team approval was granted for this. Individual patient consent was not required as patients were not subject to any trial intervention. The two groups were broadly matched for age and sex (Table I).

Radiological assessment. EOX plus fish oil (Intervention) group: Staging computerised tomography (CT) scans were obtained at baseline and after chemotherapy cycles 3, 6 and 8; and 3 months following completion of treatment. Patients in whom chemotherapy was discontinued before completion of the third cycle were not routinely scanned.

EOX alone (Historical control) CT scans were performed as part of routine clinical practice after chemotherapy cycles 3 and 6. After completion of treatment, additional CT scans were performed only if clinically indicated on symptomatic grounds.

Scans were reported according to the RECIST 1.1 criteria (16) by a gastrointestinal oncology interest radiologist.

Cytokine analysis. One 7.5 ml serum gel blood bottle was used to collect whole blood samples immediately before (baseline) and after each treatment from all patients who received at least one experimental treatment. The blood was centrifuged at 1,000 $\times$ g for 15 min at 4°C and 500 μ l aliquots of serum were collected and stored at -80°C until analysis was performed. Multi-spot ELISA kit assay (Meso Scale Discovery, Rockville, MD, USA) was conducted in accordance with manufacturer's protocol. The following serum cytokine markers were assessed: interleukin (IL)-1, IL-2, IL-6, tumour necrosis factor (TNF)- α , and vascular endothelial growth factor (VEGF).

All samples were processed in duplicate using 96-well plates. Fifty microliters of diluted sample and calibrator (standard) were added to the 96-well plates; each plate was then sealed with adhesive plate seal and incubated at room temperature for 90 min, while it was agitated. The plate was irrigated three times with a minimum of 150 μ l/well of wash buffer, 25 μ l of detection antibody was added to each well. The plates were sealed and once again incubated at room temperature for 30 min, while being agitated. The plates were irrigated once again with a minimum of 150 μ l/well of wash buffer, 150 μ l of read buffer T was added to each well and the plates were then read using the MSD reading instrument. Cytokine quantification was based upon the principle of electrochemiluminescence (17).

Statistical analysis. Analysis for the clinical study was performed on the intention-to-treat population. Fisher's exact and the chi square tests were used to compare proportions. Survival analysis was estimated using the Kaplan-Meier method, and statistical significance was assumed when $p \leq 0.05\%$.

In order to accurately present the actual changes in serum cytokine concentrations, a statistical model that used a random coefficient model xtmixed was developed in STATA software. This statistical model applied linear regression in which both slope and intercept were allowed to vary between each patient. The logarithms of cytokine concentrations are indicated on the y axis and the week of treatment on the x axis, each slope represents the best fit concentration for each patient.

Table I. Demographic characteristics of the EOX plus fish oil (intervention) and EOX alone (historical control) groups.

	Patient characteristics		
	EOX alone (n=37)	EOX + fish oil (n=21)	p-Value
Gender (male:female)	26:11	16:5	0.63
Median age in years (range)	66 (36-81)	67 (47-80)	
Number of patients aged over 60 years	8	16	<0.001
Performance status (0:1:2)	15:15:7	8:9:4	0.04
Median baseline weight in kg (range)	70.6 (43.1-105.7)	76.5 (49.0-110.6)	0.98
Tumour site			
Oesophagus: GEJ: Stomach	10:11:16	11:5:5	0.14
UICC stage (3:4)	3:34	3:18	0.46
Total number of chemotherapy cycles for all patients (median chemotherapy cycles per patient)	160 (5)	91 (6)	0.83
Number of patients completing 4 cycles (%)	23 (62%)	12 (60%)	0.70
Number of patients completing 6 cycles (%)	16 (43%)	11 (55%)	0.50

EOX, Epirubicin, Oxaliplatin, and capecitabine combination; GEJ, gastroesophageal junction; UICC, Union for International Cancer Control; WHO, World Health Organisation.

In order to explore the relationship between baseline levels of biomarkers and overall survival, the cohort was subdivided into those with high (top 50%) and low (bottom 50%) cytokine expression, based on the median concentration value of each cytokine. Kaplan–Meier curves were applied to determine whether these baseline markers influenced overall survival (OS).

Results

EOX plus fish oil group. Fifty-six patients with advanced esophago-gastric adenocarcinoma were screened for trial inclusion and 21 met the inclusion criteria and agreed to participate. Reasons for exclusion are mentioned in Figure 1. Twenty participants completed at least one cycle of treatment (Table I). One participant experienced a decline in performance status after enrolment and declined further treatment. Recruitment and retention rates were 100% (21 of 21 eligible participants) and 95% (20 of 21 participants), respectively.

EOX alone (Historical control) group. Case notes of 60 patients who had received palliative chemotherapy were reviewed and 37 met the inclusion criteria for the control group (Figure 1).

Radiological assessment of the tumour response. Fifteen of the 21 patients in the EOX plus fish oil arm were evaluable for radiological response. Among the control group 28 patients were evaluated for radiological response. Six participants in the EOX plus fish oil group and 9 patients in the historical control group did not have radiological tumour response assessment, because of clinical disease progression or discontinuation of chemotherapy before cycle 3. There was a significantly higher overall response and a higher frequency of partial radiological

response in patients treated with chemotherapy plus omega-3 fatty acids compared to EOX alone (73%, 95% CI=51-95 *vs.* 43%, 95% CI=25-61, $p=0.05$ and 73%, 95% CI=51-95 *vs.* 39%, 95% CI=21-57, $p=0.03$, respectively). There were no significant differences between the EOX plus fish oil and the EOX alone group in the frequency of stable disease and progressive disease (21% *vs.* 39%, $p=0.24$ and 7% *vs.* 18%, $p=0.34$, respectively) (Table II).

Survival analysis. Eleven of the 15 evaluable patients in the EOX plus fish oil group achieved at least six months progression-free survival (PFS), satisfying the original trial criteria for progression to the second stage of recruitment. This interim report did not identify any statistically significant difference in either OS ($p=0.37$) or PFS ($p=0.16$).

Adverse events according to CTCAE v 4.03. Grade 3 or 4 haematological and non-haematological toxicities are reported in Table III. There was a significant reduction in nausea/vomiting (0% *vs.* 19%, 260, $p=0.04$) and in the frequency of thromboembolic events (0% *vs.* 19%, $p=0.04$) among the EOX plus fish oil group. The number of patients with grade 3 or 4 neutropenia and leukocytopenia was higher in the EOX plus fish oil group compared to the EOX alone (85% *vs.* 40%, $p=0.002$ and 60% *vs.* 16%, $p<0.001$, respectively), although the participants of the first group had a higher frequency of blood sampling than those in the latter group.

Eleven patients (11/20, 55%) of the EOX plus fish oil group required a total of 14 hospitalization episodes compared to a total of 39 hospitalization episodes for 29 patients in the EOX-alone group (29/37, 78%), $p=0.06$.

Figure 1. Consort chart showing patient disposition.

Regarding adverse events of specific interest to omega-3 infusion, no patient suffered fat overload syndrome or grade 3 or 4 hypertriglyceridemia. Mean baseline and 7 day post-treatment triglyceride levels were 1.7 mmol/l (95% CI=1.6 to 1.79) and 1.66 mmol/l (95% CI=1.56 to 1.75) respectively. The highest recorded triglyceride level was 4.84 mmol/l. Only one patient required statin therapy to counteract hypertriglyceridemia, probably related to the Omegaven® infusion.

Dose reductions due to chemotherapy toxicity were required for 11 patients in the EOX plus fish oil group (55%)

and for 23 patients in the EOX alone group (62%), $p=0.5$. Two patients from each group required cisplatin instead of oxaliplatin chemotherapy because of oxaliplatin-related peripheral neuropathy. There were no dosage modifications to the Omegaven® (omega-3 fish oil) and the treatment delays to the administration of Omegaven® related entirely to those associated with chemotherapy-related toxicity.

Effect of chemotherapy and omega-3 PUFAs on cytokine expression. Immediately after infusion of omega-3 PUFAs, there was a significant reduction in the concentrations of

Table II. Radiological tumour response at six months according to treatment received.

Response	EOX (n=28)	EOX plus fish oil (n=15)	p-Value
CR	1 (4%)	0 (0%)	0.47
PR	11 (39%)	11 (73%)	0.03*
SD	11 (39%)	3 (21%)	0.24
PD	5 (18%)	1 (7%)	0.34
Overall response			
CR + PR	12 (43%)	11 (73%)	0.05*
Disease control			
CR + PR + SD	23 (82%)	14 (93%)	0.31

EOX, Epirubicin, oxaliplatin, and capecitabine combination; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease. *Statistically significant differences.

VEGF ($p=0.002$, 95% CI= -0.0161 to -0.0034), TNF- α ($p<0.0001$, 95% CI= -0.0121 to -0.0046) and IL-2 ($p=0.009$, 95% CI= -0.0283 to -0.0039) (Figure 2). This reduction in VEGF and IL-2 concentration was short-lived, and was no longer evident seven days after treatment, immediately before the subsequent scheduled treatment (VEGF: $p=0.55$, 95% CI= -0.0092 to 0.0172 ; IL-2: $p=0.458$, 95% CI= -0.0051 to 0.1152). The reduction in TNF- α ($p=0.0007$, 95% CI= -0.0075 to -0.002) was longer-lived, with expression falling progressively with each cycle of treatment, suggesting a cumulative effect. As indicated in Figure 2, the immediate effect (difference between baseline and post-treatment levels) of omega-3 PUFAs on the expression of VEGF, IL-2, and TNF- α reduced with time, suggesting reduced sensitivity to the omega-3 PUFAs with time.

There were no significant changes in IL-1 α , IL-1 β or IL-6, at any time point measured (IL-1 α immediately post treatment $p=0.80$, 7 days post treatment $p=0.25$; IL-1 β immediately post-treatment $p=0.85$, 7 days post-treatment $p=0.82$; IL-6 immediately post-treatment $p=0.18$ and 7 days post-treatment $p=0.75$).

Discussion

We have previously reported on the uptake of omega-3 PUFAs in plasma and erythrocyte; this treatment schedule enriched plasma phosphatidyle choline (PC) and Red Blood Cell membranes with Eicosapentaenoic acid (EPA) and plasma non-esterified fatty acids (NEFAs) with EPA and docosahexaenoic acid (DHA) in patients with advanced esophago-gastric cancer receiving palliative chemotherapy (14).

There have been over 50 laboratory studies investigating the effects of EPA and DHA omega-3 PUFAs (fish oil) in gastrointestinal cancers, mainly of colorectal and pancreatic

Figure 2. The graphs demonstrate the serial changes in log 10 cytokine concentration (pg/ml). There were significant reductions in (A) vascular endothelial growth factor (VEGF), $p=0.002$, (B) interleukin-2 (IL-2) concentrations, $p=0.009$ and (C) tumour necrosis factor alpha (TNF- α), $p<0.001$ immediately post omega-3 PUFA infusion with time, although the magnitude of the reductions dropped with successive cycles of treatment. Each slope represents the best fit concentration for each patient. If the slope of the graph is from left to right, this indicates a negative coefficient or a reduction in cytokine concentration. In contrast, if the slope of the graph is upward from left to right, this indicates a positive coefficient or an increase in cytokine concentration.

Table III. Details of all grade 3 or 4 recorded toxicities (CTCAE v4.03) in both groups.

Grade 3 or 4 toxicity	EOX alone n (%)	EOX plus Fish oil n (%)	p-Value*
Clinical manifestations			
Diarrhoea	10/37 (27%)	2/20 (10%)	0.18
Nausea/vomiting	7/37 (19%)	0/20 (0%)	0.045
Peripheral neuropathy	5/37 (14%)	2/20 (10%)	1.00
Fatigue	9/37 (24%)	1/20 (5%)	0.08
Thromboembolism	7/37 (19%)	0/20 (0%)	0.045
Infection or sepsis	1/37 (3%)	4/20 (20%)	0.75
Constipation	1/37 (3%)	0/20 (0%)	1.00
PPE	1/37 (3%)	0/20 (0%)	1.00
Biochemical disturbances			
Anaemia (<8)	3/37 (8%)	5/20 (25%)	0.12
Leucopenia (<2)	6/37 (16%)	12/20 (60%)	<0.001
Neutropenia (<1)	15/37 (40%)	17/20 (85%)	0.002
Thrombocytopenia (<50)	0/37 (0%)	2/20 (10%)	0.12
Thrombocytosis (>800)	3/37 (8%)	1/20 (5%)	0.55
Hypoalbuminaemia (<20)	1/37 (3%)	0/20 (0%)	1.00
AKI (creatinine >360)	0/37 (0%)	2/20 (10%)	0.35
High bilirubin level (>63)	0/37 (0%)	0/20 (0%)	-
High ALK (>650)	2/37 (5%)	2/20 (10%)	0.61
High ALT (>265)	0/37 (0%)	0/20 (0%)	-
Hypercalcaemia (>3.1)	1/37 (3%)	0/20 (0%)	1.00
Hyperglycaemia (>13.9)	0/3 (0%)	1/20 (5%)	1.00
Hypocalcaemia (<1.7)	1/37 (3%)	2/20 (10%)	0.55
Hyponatraemia (<130)	4/37 (11%)	1/20 (5%)	0.64
Hypernatraemia (>155)	0/37 (0%)	0/20 (0%)	-
Hypertriglyceridaemia (>5.7)	0/3(0%)	0/20 (0%)	-
Hypokalaemia (<3)	1/37 (3%)	2/20 (10%)	0.28

EOX, Epirubicin, oxaliplatin, and capecitabine combination; PPE, palmar planta erythema; AKI, acute kidney injury; ALK, alkaline phosphate; ALT, alanine transaminase. *p-Value calculated using the Fisher's exact and Chi-square test.

origin. Six studies have indicated that fish oil treatment may enhance the anti-proliferative effects of chemotherapy on treated cancer cell lines (18-23). There have been four clinical trials examining the role of omega-3 PUFAs in the palliative treatment of advanced gastrointestinal cancers in association with chemotherapy, two in colon cancer patients (6, 7), one in pancreatic cancer patients (24), and one in esophago-gastric cancer patients (9).

In the latter study the authors administered an intravenous DHA-paclitaxel infusion every 21 days for up to four cycles (84 days). The authors identified a reduced frequency of haematological toxicity, but in other respects the clinical course was similar to that of patients who received paclitaxel or docetaxel alone. In that study, the PFS and OS were 3 and 9 months respectively (9).

Arshad *et al.* employed short-term infusions of a parenteral omega-3 fatty acids in combination with gemcitabine chemotherapy in patients with advanced pancreatic cancer, and reported a superior response rate and OS compared to historical controls (25, 26). The two studies of patients with colorectal cancer that used EPA-enriched oral nutritional supplements in combination with

chemotherapy reported favourable effects on body weight preservation and quality of life, but no improvement in survival (6, 7).

These findings are broadly similar to the findings reported in studies by the Edinburgh group of single agent oral omega-3 fish oil in advanced pancreatic cancer (5, 10, 11). These studies identified better weight maintenance and improved quality of life.

The current pilot phase II clinical trial has shown that the addition of weekly omega-3 PUFAs infusion (Omegaven®) to combination chemotherapy regimen (EOX) is feasible and safe (27). The most significant findings were a reduced frequency of gastrointestinal toxicity and thromboembolic events, and a greater radiological response rate compared to historical controls who received chemotherapy alone. No survival advantage was demonstrated for those treated with EOX plus fish oil (omega-3 PUFAs), this might be due to the small sample size and lack of randomization. The antithrombotic effects of omega-3 fatty acids may explain the lower frequency of thromboembolic events found in the current study. The reported antithrombotic effects of omega-3 PUFAs include a reduction in blood viscosity

(28), a reduction in platelet count, a reduced sensitivity of platelets to collagen (29), inhibition of platelet aggregation and adhesion (30-32), a reduction in plasma fibrinogen levels and a prolongation of thrombin time, independent of vitamin K (33).

A higher frequency of abnormal haematological tests was observed in patients treated with fish oil, although it should be pointed out that this group underwent a greater level of blood sampling than historical controls. Participants in the EOX plus fish oil group had full blood counts checked three times per chemotherapy cycle, while those in the EOX alone arm had their blood count checked only once per chemotherapy cycle.

The majority of previous clinical studies employed oral omega-3 fish oil supplementation. Herein, intravenous supplementation was used in order to achieve better compliance and potentially higher omega-3 fatty acid levels than compare to oral supplementation. Further, it was anticipated that many of these patients with dysphagia would find it an additional challenge, ingesting oral capsules. This might have reduced compliance and masked any potential therapeutic effect.

As we have discussed in previous publication (14), Roodhart *et al.* (34) demonstrated that platinum-induced fatty acid (PIFA; 16:4n-3), could be generated in the presence of platinum-based chemotherapy compounds and this fatty acid could induce resistance to those compounds in some model systems. Recently, Daenen *et al.* (35) reported that PIFA is present at variable concentrations in several fish oil supplements and that its concentration in human blood plasma is increased following consumption of fish oil supplements.

So far, it has not been possible to measure 16:4n-3 in Omegaven® or in the human blood plasma samples generated as part of this study. It is important to note that the analysis of 16:4n-3 and other PIFA is technically challenging; that common techniques for fatty acid analysis, such as gas chromatography used in the current study, lack the sensitivity required to detect the low concentrations of 16:4n-3; and that standards of so-called platinum-induced fatty acids are not yet commercially available. In future studies, it would be important to gather information on the 16:4n-3 content of blood and blood cells to better understand its impact on cancer patients.

To date, no reports have studied the use of intravenous omega-3 PUFAs in patients with advanced esophago-gastric adenocarcinoma receiving palliative chemotherapy. Arshad *et al.* has previously shown an improved OS for patients with low baseline expression of IL-6 and IL-8 cytokines in a cohort of patients with advanced pancreatic cancer who received palliative gemcitabine chemotherapy in combination with omega-3 PUFA's (26). The latter study also demonstrated a significant reduction in platelets derived growth factor and fibroblast growth factor but not VEGF (26).

In esophago-gastric cancer curative settings, Deans *et al.* demonstrated that high expression of IL-1 β was associated with a poorer survival (36). El-Omar *et al.* showed that *H. pylori* gastritis played a major role in inhibition of gastric acid secretion and, as a result, associated with chronic *H. pylori* gastritis with hypochlorhydria and an increase in IL-1 β level (37). The latter was reported to be associated with the development of gastric cancer (37). In the current study, IL-1 β changes were not correlated with survival outcome. Dvorakova *et al.* have previously demonstrated that increased expression of IL-6 in patients with Barrett's esophagus contributed to the development of apoptosis resistance and malignancy (38). Liao *et al.*, noted high expression of IL-6 cytokine to be associated with a poorer survival after gastrectomy for cancer, and that the cytokine carried greater prognostic weight than TNM staging (39).

There are limitations to the current study; the small number of participants, the use of historical patients as a control group and lack of randomization. Nonetheless, 37% of patients screened fulfilled the eligibility criteria, 100% of eligible patients participated in the trial and 95% of enrolled participants completed at least one cycle of chemotherapy and fish oil. Sixty percent of enrolled participants completed at least four cycles of chemotherapy plus fish oil. These findings suggest that a larger-scale randomised clinical study should be possible. The novelty of the current study is the use of repeated short-term infusions of omega-3 PUFAs during palliative chemotherapy (a single infusion of Omegaven® 4 hours per week) over a long period of time (up to 6 months) and assessment of cytokines over the entire treatment period in esophago-gastric cancer patients.

In conclusion, compared to patients treated with chemotherapy alone, those treated with supplementary omega-3 fish oil infusion had reduced chemotherapy-related toxicity and better response to treatment. This benefit in response rate and reduction in chemotherapy-related gastrointestinal adverse events in EOX with or without fish oil should be evaluated at least in a randomised phase II study.

Conflicts of Interest

Amar M Eltweri, Ashley R Dennison and David J Bowrey received Departmental Grant support for this work from Fresenius Kabi. Ashley R Dennison has received speaking honoraria from Fresenius Kabi. David J Bowrey has received Departmental Grant support for unrelated work from Nutricia. The other Authors have no conflicts to declare.

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