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ORIGINAL ARTICLE

A phase II open-label study of DHA-paclitaxel (Taxoprexin) by 2-h intravenous infusion in previously untreated patients with locally advanced or metastatic gastric or oesophageal adenocarcinoma

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Abstract
Purpose Combination chemotherapy regimens can improve survival in patients with advanced gastric and oesophageal adenocarcinoma. Docosahexaenoic acid (DHA)-paclitaxel is a novel conjugate formed by the covalent linkage of the fatty acid DHA to paclitaxel and may result in increased tumour exposure to paclitaxel without increased toxicity.
Patients and methods In this single arm, phase II study of DHA-paclitaxel, eligible patients with previously untreated, inoperable locally advanced or metastatic adenocarcinoma of the oesophagus, oesophago-gastric junction or stomach were treated with DHA-paclitaxel (1,100 mg/m^2) administered by 2-h intravenous infusion every 21 days.
Results Fifty-four patients were recruited of whom 53 were evaluable for toxicity, and 48 for response. There were five confirmed partial responses (9.4%) by the RECIST criteria. The median duration of response was 87 days (range 49–97 days), the median time to progression was 84 days (95% CI 78–124 days), and median overall survival was 262 days (95% CI 205–357 days). Grade $\geq$3 neutropaenia occurred in 93% of patients, and febrile neutropaenia in 17% of patients.
Conclusions DHA-paclitaxel has modest activity in patients with oesophago-gastric cancer and with haematological toxicity that is comparable to paclitaxel and docetaxel.

Keywords Adenocarcinoma · DHA-paclitaxel · Oesophagus · Stomach

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Introduction

Adenocarcinomas of the oesophagus and stomach have a poor prognosis, accounting for approximately 10,000 deaths per year in the UK. Although the incidence of gastric cancer is declining, it remains the second most common cancer world-wide, and the fourth commonest cancer in Europe. Surgical resection is the only potentially curative option. However, within the UK population, 30% of patients will have metastatic disease at presentation. With locally advanced disease, curative surgery is only possible in a minority of patients and disease recurrence occurs in approximately 80% of patients within 5 years of potentially curative surgery. Therefore the prognosis remains poor with an overall survival of around 20% at 5 years [1].

Similarly, approximately 50% of patients with oesophageal adenocarcinoma present with overt metastatic disease, and the majority of patients who present with loco-regional disease will also ultimately develop metastatic disease. Surgery has conventionally been the treatment of choice for operable disease, but has a 5-year survival rate of only 20–25% [2].

Combination chemotherapy results in a significant survival advantage in patients with advanced gastric cancer when compared with best supportive care in randomised clinical trials [3–5]. High response rates may be obtained in these tumours by the use of protracted venous infusional 5FU, epirubicin and cisplatin—the ECF regimen [6]. In a multi-centre randomised study, ECF resulted in a significantly better response rate (45%) and median survival, with significantly less toxicity compared to the FAMtx regimen [7]. Consequently the ECF regimen is considered the treatment regimen of choice for advanced adenocarcinoma of the oesophagus and stomach by most clinicians in the UK. Nevertheless, median survival remains poor in these patients treated with the ECF regimen (8.9 months) [7], and therefore novel agents with activity in oesophago-gastric adenocarcinoma are required. The taxanes, including paclitaxel and docetaxel, are used in the treatment of a wide range of cancers including breast, lung, ovarian and prostate cancer. In gastric cancer, paclitaxel and docetaxel have been associated with objective response rates of 4–23% and 5–29% respectively [8]. In a multivariate analysis, the addition of paclitaxel to cisplatin in the treatment of advanced oesophageal cancer was found to be positively correlated with outcome [9]. Consequently, the development of novel taxane analogues and conjugates that would improve their therapeutic ratio is a promising approach to improve the systemic treatment of advanced oesophago-gastric adenocarcinoma.

Pre-clinical perfusion models suggest an increased fatty acid uptake in tumours, presumably for use as biochemical precursors and energy sources [10–12]. Chemotherapy drugs conjugated to fatty acids could enhance tumour targeting and deliver pro-drugs for intra-tumoural activation. Docosahexaenoic acid (DHA)-paclitaxel (Taxoprexin®) is a novel conjugate designed to be a pro-drug in tumour tissue, and is formed by covalently linking the natural fatty acid DHA to paclitaxel [13]. DHA-paclitaxel demonstrated significantly enhanced tumour distribution and anti-tumour activity in various pre-clinical tumour models as compared with paclitaxel after equitoxic or equimolar doses [13].

In a phase I study of DHA-paclitaxel administered as a 2-h intravenous (IV) infusion to patients with advanced refractory solid tumours, the recommended starting dose for subsequent studies was 1,100 mg/m^2 every 3 weeks [14]. Myelosuppression was the principal toxicity observed, and other grade 3 toxicities were infrequent. No patients developed alopecia, peripheral neuropathy >grade 1 or musculoskeletal toxicity >grade 1. DHA-paclitaxel dramatically alters the pharmacokinetic (PK) profile of derived paclitaxel compared with values observed after a 3-h infusion of paclitaxel (175 mg/m^2). The apparent half-life of paclitaxel was approximately fivefold longer, and the C_{max} was approximately tenfold lower, than that expected after a 3-h infusion of paclitaxel [14], and at a dose of 1,100 mg/m^2, significant plasma levels of paclitaxel were present for an average of 6–7 days [14]. Thus it is possible that, by increasing the duration of exposure to paclitaxel, DHA-paclitaxel may result in superior anti-tumour activity when compared to unconjugated paclitaxel, and it also has a favourable toxicity profile. Consequently, a phase II study was designed to determine the objective response rate of DHA-paclitaxel in patients with advanced gastric or oesophageal adenocarcinoma.

Patients and methods

Study design

This was a non-randomised, multi-centre, two-step Simon design, phase II study of DHA-paclitaxel in patients with advanced gastric or oesophageal adenocarcinoma. The primary objective was the objective tumour response rate of DHA-paclitaxel in this patient population, and secondary objectives included duration of response, time to disease progression, toxicity profile and overall survival.

Eligibility criteria

Eligible patients were those with histologically or cytologically confirmed, locally advanced (inoperable) or metastatic, adenocarcinoma of the lower oesophagus (which was not suitable for a radical combined modality therapy approach), oesophago-gastric junction or stomach. All patients had measurable disease, as defined by the response evaluation criteria in solid tumours criteria (RECIST) [15], ECOG performance status $\leq$1, were at least 18 years of age, and had adequate renal [serum creatinine $\leq 1.5 \times$ institution's upper limit of normal (ULN)], hepatic (bilirubin $\leq 1.5 \times$ ULN; transaminases $\leq 2.5 \times$ ULN), and haematological [absolute neutrophil count (ANC) $\geq$1,500/mm^3; platelet counts $\geq$100,000/mm^3] function. Patients were excluded if they had received any prior chemotherapy for metastatic disease, or if they had received neo-adjuvant or adjuvant chemotherapy for oesophago-gastric cancer. Other exclusion criteria included known clinical evidence of CNS metastases, patients who were pregnant or of child-bearing potential and unwilling to use an acceptable method of birth control, peripheral neuropathy of >grade 1

of any aetiology, known hypersensitivity to cremophor, and any other unstable concurrent medical condition.

This study was approved by the Research Ethics Committees of all participating institutions, and all patients gave written, informed, consent prior to any study related procedure.

Administration of DHA-paclitaxel

Docosahexaenoic acid-paclitaxel was supplied as a concentrate which was reconstituted in Cremophor® within 4 h prior to administration. DHA-paclitaxel was administered at a starting dose of 1,100 mg/m^2 as a 2-h IV infusion on an outpatient basis. Treatment was repeated every 21 days until disease progression, stable disease without symptomatic improvement after two courses, intolerable toxicity, patient refusal or investigator decision to discontinue study therapy. Patients received prophylactic anti-allergy medication with dexamethasone, chlorpheniramine and cimetidine. Chlorpheniramine (10 mg) and cimetidine (300 mg) were both given intravenously 30 min prior to administration of DHA-paclitaxel. Dexamethasone prophylaxis was either 20 or 8 mg given orally both 12 and 6 h prior to DHA-paclitaxel administration, or 10 mg given intravenously 30–60 min prior to administration of the study drug.

Administration of subsequent courses of DHA-paclitaxel was delayed until the ANC was $\geq$1,500/mm^3, the platelet count was $\geq$100,000/mm^3 and any grade 2 or 3 non-haematological toxicity (other than nausea, vomiting and alopecia) had resolved to baseline or $\leq$grade 1. The study drug was discontinued in the event of grade 4 non-haematological toxicity on the day of scheduled therapy. The dose of DHA-paclitaxel was modified on the second and subsequent cycles of treatment based on haematological and non-haematological toxicities. The dose of DHA-paclitaxel was reduced by one dose level in the event of a previous treatment delay due to inadequate recovery of the ANC or platelet count, if the ANC was <500/mm^3 during the first cycle, if neutropaenia was associated with fever, hospitalization or documented infection or in the event of thrombocytopoenia associated with bleeding. Similarly, the dose of DHA-paclitaxel was reduced after recovery from non-haematological toxicity that resulted in a treatment delay. Up to two dose reductions (to 900 and 700 mg/m^2) were permitted per patient. Patients were withdrawn from the study if there was a treatment delay of greater than 2 weeks or a requirement for more than two dose reductions (for whatever reason).

Palliative and supportive care was permitted during the study, but patients who required radiotherapy during the study were considered to have disease progression and were withdrawn from the study. Patients were not permitted to receive any other anti-cancer therapy during the study (including hormonal agents and immunotherapy). The use of prophylactic granulocyte colony stimulating factor (G-CSF) was not permitted during the first two cycles of drug administration.

Patient assessments

Objective tumour response (i.e. complete and partial response) was determined by CT scan assessments of measurable disease by the RECIST criteria [15]. A pre-treatment CT scan was performed within 28 days prior to administration of the first cycle of treatment, and subsequent scans were performed after every two cycles of therapy.

Physical examination (including vital signs), assessment of performance status, electrocardiogram, urinalysis, pregnancy test (when appropriate), full blood count (including differential and platelets), biochemistry profile (urea, electrolytes, creatinine, liver function tests, glucose) and clotting screen were performed before the first cycle of treatment. Physical examination, vital signs, assessment of toxicities, assessment of performance status, full blood count and biochemistry profile were performed prior to each subsequent administration of the study drug. In addition, biochemistry profile was performed weekly during the first treatment cycle, and full blood count was performed weekly during the entire study. The severity of toxicities was recorded using the NCI Common Toxicity Criteria (CTC), version 2.0.

Statistical analyses

All patients who received study drug were considered to be evaluable for safety and toxicity. Patients who completed two cycles of treatment and had at least one documented post treatment disease assessment were evaluable for objective tumour response. Patients who were withdrawn from the study prior to completion of two cycles of treatment were not considered evaluable for tumour response unless there was clear evidence of disease progression. For a patient experiencing global deterioration of health status that required discontinuation of treatment without objective evidence of disease progression at the time of discontinuation, the best overall response was assessed as 'symptomatic deterioration'.

Duration of response was defined as time in days from the date on which complete response (CR) or partial response (PR) was first documented until disease progression or death. Time to progression was the number of days from the first drug administration until disease progression. Patients who did not progress were censored at their last disease assessment date. Overall survival was measured in days from first drug administration until death. Patients

who were alive at the time of analysis were censored at the last date on which they were known to be alive. Duration of response, time to disease progression and overall survival were estimated using the method of Kaplan and Meier [16].

The sample size was based on Simon's two stage optimal design [17]. With a target activity level of 20%, a lower activity level of 5%, $\alpha = 0.05$ and power = 90% the first stage of patient enrolment was to include 21 evaluable patients. If one or more patients responded in the first stage then an additional 20 evaluable patients were to be enrolled into a second stage. Additional patients were enrolled to allow for patients being declared non-evaluable for the primary outcome measure.

Results

Patient characteristics

A total of 54 patients with locally advanced inoperable or metastatic, adenocarcinoma of the oesophagus, oesophago-gastric junction or stomach were recruited into the study at six centres (four in the UK, one in The Netherlands, one in Germany) between September 2001 and December 2002. None of these patients had received prior chemotherapy or radiotherapy. Patient characteristics are shown in Table 1.

One patient developed a fatal cerebro-vascular accident 12 days after the initial study visit and did not receive any study medication. The remaining 53 patients were evaluable for toxicity and formed the intention-to-treat study population for all other analyses. Five patients were not evaluable for response of whom four had been removed from the study during course 1 [hypersensitivity reaction ($n = 1$); intercurrent illness ($n = 1$); unacceptable toxicity with neutropaenic fever and stomatitis ($n = 1$); and death ($n = 1$)] and one patient did not comply with the study procedures to return for radiological disease assessment after cycle 2. Thus 48 patients were evaluable for response.

Table 1 Patient characteristics

Characteristic	$N = 54$	N (%)
Gender	Female	11 (20)
	Male	43 (80)
Race	Caucasian	40 (74)
	Unknown	14 (26)
Age (years)	Median (range)	64 (32–81)
ECOG PS	0	17 (31)
	1	36 (66)
	Unknown	1 (2)
Primary site	Gastric	36 (67)
	Oesophagus	12 (22)
	Oesophago-gastric junction	6 (11)
Disease site	Lymph nodes	34 (63)
	Stomach	27 (50)
	Liver	26 (48)
	Oesophagus	12 (22)
	Adrenal gland	9 (17)
	Ascites	9 (17)
	Lung	8 (15)

ECOG PS Eastern Cooperative Oncology Group Performance Status. Disease site distribution is given only for those sites where 10% or more patients had involvement

DHA-paclitaxel administration: dose delays and modifications

A total of 232 cycles of DHA-paclitaxel were administered to 53 patients (median number of cycles = 4; range 1–11). Fifty (94.3%) patients received at least two doses of study drug with a mean time between drug administration of 22.8 (SD = 3.5) days and 20 (37.7%) patients received at least six cycles of study medication.

Dose delays or dose modifications occurred in 34 of 53 patients. The dose of DHA-paclitaxel was reduced from 1,100 mg/m^2 to 900 mg/m^2 for 61 cycles in 27 patients and further reduced to 700 mg/m^2 for four cycles in three of these patients. Dose reductions were due to neutropaenia (17 patients), febrile neutropaenia (3), neutropaenic sepsis (3), other toxicities (3) and clinical deterioration (1). Administration of DHA-paclitaxel was delayed in 20 patients due to neutropaenia (five patients), febrile neutropaenia or neutropaenic sepsis (2), infection without neutropaenia (4) and dysphagia, lethargy, clinical deterioration or peripheral neuropathy (one patient each). In seven other patients the dose was delayed due to administrative reasons (patient holidays or delay of therapy until the results of radiological disease assessment were available).

Efficacy analyses

All efficacy analyses were on an intention to treat basis ($n = 53$). Of the 48 patients (88.9%) who were evaluable for response, there were no CRs and five PRs for an overall objective response rate of 9.4% [95% confidence intervals (CI) 4.1–20.2%], with stable disease observed in 35 (66%; 95% CI 52.6–77.3%) patients and progressive disease in eight patients (15%; 95% CI 7.8–27%) (Table 2). The median duration of response was 87 days (range 49–97 days), and the median time to disease progression for the 53 patients who received study drug was 84 days (95% CI =78–124 days) [Fig. 1]. The median overall survival was 262 days (95% CI 205–357 days) [Fig. 2], with seven patients alive at the time of analysis.

Toxicity assessments

Haematological and non-haematological toxicities (worst grade per patient—all cycles) of ≥grade 3 (NCI-CTC) are listed in Table 3. The most frequent grade 3/4 toxicity was neutropaenia which resulted in neutropaenic fever in 9 (17%) patients. The most frequent non-haematological ≥grade 3 toxicities were lethargy (seven patients; 13%), fatigue ($n = 4$; 8%) and gastro-intestinal (all <10% of patients). There was no ≥grade 3 peripheral neuropathy. Hypersensitivity reactions occurred in five patients. In four of these cases, the patient was able to complete the administration of that dose, but the fifth patient was permanently withdrawn from the study.

There were four deaths during the study period (up to 30 days after the last dose of DHA-paclitaxel), two of which were considered to be directly related to the study drug. Firstly, a 58-year old female died from neutropaenic sepsis resulting in renal failure 9 days after receiving the first dose of the study drug. In the second case, a 79-year old male died 24 days after receiving the third dose of study drug. He developed staphylococcal bacteraemia on day 10 of cycle 3, which had resolved by day 13. However, this patient's condition continued to deteriorate and he developed cardiac failure and a pleural effusion. Post-mortem examination demonstrated diffuse alveolar damage consistent with cytotoxic drug toxicity. This was classified as drug-related pneumonitis. Two other deaths were thought to be unlikely to be related to the study drug. One patient died of cholangitis on day 19 after administration of cycle 4 of the study drug, and one patient died of a pulmonary embolism 30 days after the fifth dose of the study drug. In addition, a 64-year old female developed a cerebro-vascular accident on day 18 of cycle 1. This patient died (on day 45) from this, and again it was considered unlikely that this event was related to the study drug.

Table 2 Objective tumour responses

Response	*N* (%)	95% CI
Complete response	0 (0)	
Partial response	5 (9.4)	4.1–20.2
Stable disease	35 (66)	52.6–77.3
Disease progression	8 (15.1)	7.8–27.0
Total	48 (100)	

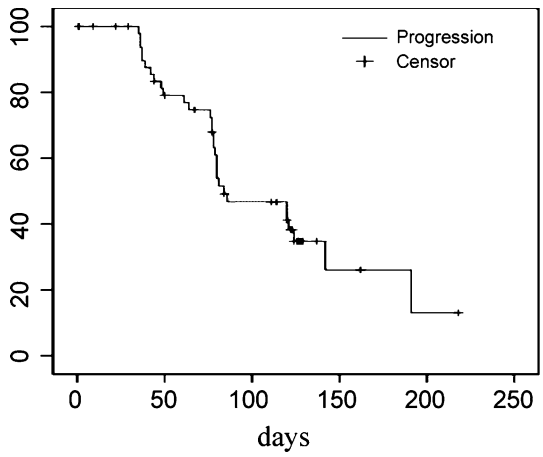

Fig. 1 Kaplan-Meier Curve for Time to Disease Progression (N = 53) Time to disease progression was calculated in days from the first drug administration until disease progression. Patients without disease progression were censored at their last disease assessment. One patient who did not receive any study medication was excluded from the analysis

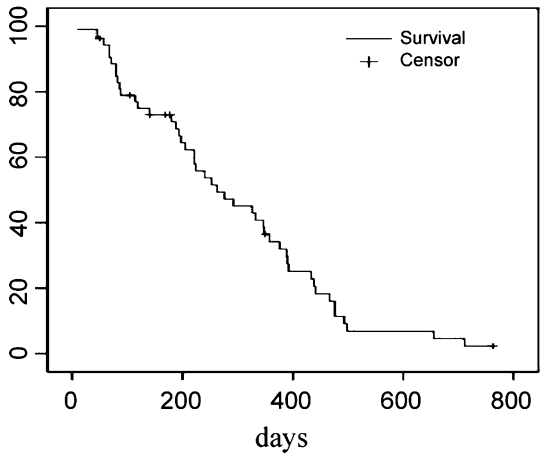

Fig. 2 Kaplan-Meier Curve for Overall Survival (N = 53) Survival duration was calculated from the date of first drug administration to death or the last date at which patients were known to be alive. One patient who did not receive any study medication was excluded from the analysis

Discussion

Randomised clinical trials have demonstrated that combination chemotherapy results in a significant survival advantage compared to best supportive care in patients with oesophago-gastric adenocarcinoma. Nevertheless, the median overall survival remains poor at approximately 9 months with active regimens that are used in this disease, including the combination of epirubicin, cisplatin and continuous infusional 5-fluorouracil [7].

At the time that this study was planned and initiated, several studies had evaluated the activity of paclitaxel and docetaxel as single-agents in patients with gastric or oesophageal cancer. These studies demonstrated that taxanes had single-agent acitivity in patients with gastric or oesophageal cancer including response rates of 17–34% with paclitaxel as first-line monotherapy [18–20] and 20–33%

Table 3 Haematological and non-haematological toxicities ($N = 53$)

Toxicity	NCI-CTC Grade ≥3 *N* (%)
Haematological	
Neutropaenia	49 (93)
Leucopaenia	32 (60)
Lymphopaenia	12 (23)
Anaemia	3 (6)
Febrile neutropaenia	9 (17)
Gastrointestinal	
Nausea	2 (4)
Vomiting	2 (4)
Diarrhoea	4 (8)
Other	
Lethargy	7 (13)
Fatigue	4 (8)
Weight loss	3 (6)

Toxicities are recorded as the worst grade per patient (all cycles)

when administered with G-CSF to maintain dose intensity [21, 22]. Similarly, response rates of 17–24% had been observed with docetaxel as first-line monotherapy in phase II trials [23, 24]. Furthermore, single-agent paclitaxel had demonstrated responses of 20–22% in patients with advanced gastric cancer that was unresponsive or had progressed after previous chemotherapy [25, 26]. More recently, the combination of docetaxel with cisplatin and 5-fluourouracil has shown a significant improvement in both time to disease progression and overall survival in patients with advanced gastric cancer compared to cisplatin and 5-fluorouracil [27]. However, tolerance of the docetaxel-containing regimen was limited with grade 3/4 treatment-related events occurring in 81% of patients, including neutropaenia, diarrhoea (20% of patients) and stomatitis (21%). Thus the development of a novel taxane, with comparable activity but an improved toxicity profile, would be relevant in this disease.

In this study, an objective response rate of 9.4% was observed with DHA-paclitaxel, and a median time to progression of 84 days (2.8 months), with a median overall survival of 262 days (8.7 months). This response rate is modest compared with the response rates reported in the initial studies with either paclitaxel or docetaxel monotherapy [18–20, 23, 24] and also when compared with the response rates with paclitaxel when used in patients with previously treated gastric cancer [25, 26]. However, subsequent studies have suggested that paclitaxel and docetaxel are associated with objective response rates of 4–23% and 5–29% respectively in gastric cancer [8], which is comparable to that observed in this study.

Dose reduction was necessary in 61 of 232 cycles (26%) in this study as compared to 19% of treatment cycles in the phase II study of docetaxel [24]. Grade ≥3 neutropaenia occurred in 93% of patients in this study which is comparable to that reported with docetaxel (93%) [24] and paclitaxel (86%) [18]. Furthermore, febrile neutropaenia occurred in 17% of patients in this study. There was no grade ≥3 peripheral neuropathy, myalgia, athralgia, alopecia or fluid retention observed in the study reported here, and grade ≥3 gastro-intestinal toxicity occurred in <10% of patients. Nevertheless, grade ≥3 lethargy occurred in 13% of patients, similar to that observed with docetaxel (16%) [24].

In conclusion, DHA-paclitaxel has modest activity as monotherapy in patients with previously untreated, advanced oesophago-gastric adenocarcinoma. Haematological toxicity is comparable with that observed with other taxanes in this patient population, although non-haematological toxicities are observed less frequently. However, DHA-paclitaxel at this dose and schedule is unlikely to be superior to either paclitaxel or docetaxel in this patient population, and further studies of DHA-paclitaxel in combination with other chemotherapy agents are not warranted in patients with advanced gastro-oesophageal adenocarcinoma at this time.

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