# Phase I Study of Docosahexaenoic Acid-Paclitaxel: a Taxane-Fatty Acid Conjugate with a Unique Pharmacology and Toxicity Profile[1]

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## ABSTRACT

***Purpose:*** **Docosahexaenoic acid (DHA)-paclitaxel, a novel conjugate formed by covalently linking the natural fatty acid DHA to paclitaxel, was designed as a prodrug targeting intratumoral activation. This Phase I trial examined its toxicity and pharmacokinetics (PKs).**

***Experimental Design:*** **Patients with advanced refractory solid tumors received a 2-h i.v. infusion of DHA-paclitaxel every 3 weeks. Plasma and urine samples were obtained to characterize the pharmacological profile of DHA-paclitaxel and paclitaxel.**

***Results:*** **Twenty-four patients received 78 cycles of DHA-paclitaxel over five dose levels (200–1100 mg/m$^2$). Median number of cycles was 2 (range, 1–8). Myelosuppression was the principal toxicity observed (grade 3/4 neutropenia in 21%/53% of courses at 1100 mg/m$^2$); during cycle 1, febrile neutropenia occurred in 1 of 9 patients treated at 1100 mg/m$^2$. Other grade 3 toxicities were infrequent. No patients developed alopecia, peripheral neuropathy > grade 1, or musculoskeletal toxicity > grade 1. At 1100 mg/m$^2$, DHA-paclitaxel had a mean (CV%) volume of distribution of 7.5 (64) liters, β half-life of 112 (56) h, and clearance of 0.11 (30) liters/h. Paclitaxel PK parameters at 1100 mg/m$^2$ were: $C_{max}$, 282 (46) ng/ml; AUC, 10,705 (60) ng/ml × h; and terminal half-life, 85 (101) h. Paclitaxel plasma exposure represented ≤0.06% of DHA-paclitaxel exposure. Paclitaxel AUC was correlated with neutropenia. One partial response was observed.**

***Conclusions:*** **The starting dose recommended for subsequent studies is 1100 mg/m$^2$. DHA-paclitaxel dramatically alters the PK profile of derived paclitaxel compared with values observed after a 3-h infusion of paclitaxel (175 mg/m$^2$). In addition, its favorable toxicity profile offers potential advantages over existing taxanes.**

## INTRODUCTION

Taxanes have become among the most active and commonly used anticancer drugs worldwide (1) after the identification of paclitaxel as the active constituent extract of the Pacific yew *Taxus brevifolia* (2), the characterization of its novel microtubule activity (3) and rapid clinical development (4–6). Consequently, there is considerable interest in developing novel taxane analogues and conjugates that would improve their therapeutic ratio (greater activity with lesser toxicity).

Preclinical perfusion models suggest an increased fatty acid uptake in tumors, presumably for use as biochemical precursors and energy sources (7–9) Chemotherapy drugs conjugated to fatty acids could enhance tumor targeting and deliver prodrugs for intratumoral activation. This concept led to the synthesis of the new chemical entity DHA[3]-paclitaxel (Taxoprexin Injection; Protarga, Inc., King of Prussia, PA; Fig. 1). DHA-paclitaxel is a 2′-*O*-acyl conjugate of the natural fatty acid DHA to paclitaxel via an ester linkage designed to be a prodrug activated in tumor tissue (10). DHA, an ω-3, C22 natural fatty acid with six *cis*-double bonds, is a normal constituent of human milk. It is classified as a nutritional additive by the United States Food and Drug Administration and used in infant formula (10). DHA-paclitaxel is formulated with 80% less CrEL and ethanol on a molar basis than paclitaxel.

DHA-paclitaxel demonstrated significantly enhanced tumor distribution and antitumor activity in various tumor models as compared with paclitaxel after equitoxic or equimolar doses (10). The drug conjugate has no microtubule assembly activity in cell-free solution, and no cytotoxic activity until metabolized to the active molecule paclitaxel. In mice bearing a Madison 109 s.c. lung tumor, administration of equimolar doses of DHA-paclitaxel and paclitaxel resulted in a mean intratumoral AUC

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[3] The abbreviations used are: DHA, docosahexaenoic acid; CrEL, Cremophor-EL; NCI-CTC, National Cancer Institute Common Toxicity Criteria; AUC, area under the curve; PK, pharmacokinetic; DLT, dose-limiting toxicity; MTD, maximum-tolerated dose; ULN, upper limits of normal; ANC, absolute neutrophil count; EOI, end of infusion; BSA, body surface area; HSR, hypersensitivity reaction.

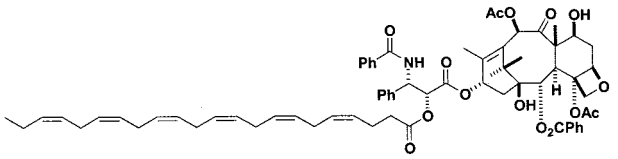


*Fig. 1* Structure of DHA-paclitaxel.

value of paclitaxel derived from DHA-paclitaxel that was 6-fold greater than that seen after treatment with paclitaxel. Only a 2-fold difference in paclitaxel AUC was observed in plasma when DHA-paclitaxel and paclitaxel were administered at equitoxic doses. This suggests enhanced drug delivery to tumor by an apparent higher conversion of DHA-paclitaxel to paclitaxel in tumor than in plasma. In the Madison 109 tumor model, DHA-paclitaxel caused complete regression of tumor at a dose of 120 mg/kg, whereas tumor regression was not observed after administration of paclitaxel at an equitoxic dose of 20 mg/kg. In a HT-29 human colon carcinoma model, DHA-paclitaxel was also more active than paclitaxel, causing two of five complete responses and three of five partial responses compared with zero of five responses for paclitaxel. In addition, DHA-paclitaxel is a 4-fold weaker substrate for P-glycoprotein than paclitaxel and may be active in some drug-resistant tumors that overexpress P-glycoprotein (10).

Preclinical PK studies showed unique disposition characteristics of DHA-paclitaxel in plasma. DHA-paclitaxel had a small volume of distribution of 0.058 liters/kg (74-fold lower than paclitaxel), a low clearance rate of 0.3 ml/min/kg (94-fold lower than paclitaxel), and plasma concentrations were maintained for longer than 300 h posttreatment in rats (10). DHA-paclitaxel appears to be stable in plasma with ≤1.0% conversion of DHA-paclitaxel to paclitaxel. The relative conversion of DHA-paclitaxel to paclitaxel was greater in tumor than in plasma with paclitaxel:DHA-paclitaxel AUC ratio (%) values of 10 and 0.48%, respectively, which indicates a 21-fold higher conversion of DHA-paclitaxel to paclitaxel in tumor relative to plasma. *In vitro*, DHA-paclitaxel was found to be 99.6% bound to human plasma (11). The binding was concentration independent, indicating a nonspecific, nonsaturable process. A relative increase in the fraction unbound paclitaxel of 6.3% was observed with increasing DHA-paclitaxel concentration from 0–1000 μg/ml, suggesting weakly competitive drug displacement from protein binding sites. Despite the small volume of distribution and extensive protein binding, administration of DHA-paclitaxel resulted in greater delivery of paclitaxel to tumor than that after paclitaxel administration (10).

i.v. toxicology studies in female CD2F1 mice (five daily bolus injections via the tail vein) showed that myelotoxicity was the main DLT but required the administration of 4.4-fold higher doses of DHA-paclitaxel than paclitaxel (on a molar basis; Ref. 10). Other toxicities included mucositis, enteropathy, and atrophy of lymphoid organs. Mice treated with paclitaxel developed severe hind-limb paralysis not observed after treatment with doses 6-fold higher of DHA-paclitaxel, both administered in five daily i.v. injections (10). The tissue PK profile of paclitaxel after DHA-paclitaxel administration showed a 2-fold higher paclitaxel AUC in gastrocnemius muscle with a 22-fold lower $C_{max}$ when compared with i.v. paclitaxel.

The unique PK profile, favorable toxicity, and greater activity observed in preclinical studies formed the basis for this Phase I study. Objectives were to characterize the principal toxicities, MTD and recommended Phase II dose, PK behavior, and any preliminary evidence of activity of DHA-paclitaxel administered as a 2-h i.v. infusion every 21 days in patients with advanced solid tumors.

## MATERIALS AND METHODS

**Eligibility.** Patients with advanced solid tumors not candidates for available standard regimens or with refractory disease were eligible for this study. Inclusion criteria included: ages > 18 years; life expectancy ≥ 12 weeks; Eastern Cooperative Oncology Group performance status ≤ 2; no residual adverse effects from prior therapies; no major surgery within 14 days or radiation or chemotherapy within 28 days; adequate organ function defined as total bilirubin ≤ 1.5× the institutional ULN, aspartate aminotransferase/alanine aminotransferase ≤ 2.5× ULN, and serum creatinine ≤ 1.5× ULN, ANC > 1500/μl, and platelet count >100,000/μl; no peripheral neuropathy > grade 1; no unstable or serious concurrent medical/psychiatric conditions; no central nervous system metastasis; and no other concomitant anticancer therapy. All patients gave written informed consent before therapy according to institutional and federal guidelines.

**Dosage and Drug Administration.** DHA-paclitaxel was provided in a two-vial system. One vial was labeled "Taxoprexin Concentrate" and contained 200 mg of DHA-paclitaxel in 2 ml of ethanol. The second vial contained 30 ml of diluent composed of 24 ml of polyoxyethylated castor oil (CrEL) and 6 ml of ethanol and was labeled "Diluent for Taxoprexin Concentrate." The solution for injection was prepared by aseptically transferring the contents of the DHA-paclitaxel vial (two parts) and three parts of the diluent vial (v:v) to an empty sterile vial. The resulting solution was swirled for 5 min. Each milliliter of diluted solution contained 40 mg of DHA-paclitaxel, 48% v/v CrEL, and 48% v/v ethanol. The diluted solution was additionally diluted in 250 ml of Dextrose 5% up to a maximum concentration of 8 mg/ml and administered over 2 h every 21 days via a programmable infusion pump interfaced with nitroglycerin tubing and an in-line 0.22-μm filter.

Initial premedication included dexamethasone (20 mg p.o.) at 12 and 6 h before and diphenhydramine (50 mg) and ranitidine (50 mg i.v.) 30–60 min before each DHA-paclitaxel infusion. If the first two cycles were tolerated well, dexamethasone was reduced to a single 10-mg i.v. dose. The last three patients (nine cycles) had cycle 1 premedication reduced to a single dose of dexamethasone (10 mg), diphenhydramine (25 mg), and ranitidine (50 mg) given i.v. 30 min before the infusion of DHA-paclitaxel. Patients did not receive antiemetic prophylaxis. Dose level 1 of DHA-paclitaxel was 200 mg/m$^2$ (equivalent to 146 mg/m$^2$ of paclitaxel on a molar basis). Toxicity was graded according to the NCI-CTC, version 2.0.

Initially, 1 patient/dose level was to be treated according to a predetermined escalation schedule. Intrapatient dose escalation was allowed during the single-patient cohort phase for

patients with acceptable toxicity if another patient completed a full cycle at a new dose level. The study allowed single-patient cohorts until the first drug-related grade 2 toxicity event (excluding nausea, vomiting, and alopecia), then expanded to 3-patient cohorts. Subsequent dose escalation would then be ≤33% over each preceding dose level until the MTD was determined. Interpatient dose escalation was allowed once 2 of 3 patients completed one cycle at the previous dose level. Intrapatient dose escalation was allowed after receiving three cycles and if no DLT was observed at the new dose level.

DLT was defined as the occurrence of the following during cycle 1: grade 4 hematological toxicity (grade 4 neutropenia lasting ≥5 days); grade ≥3 nonhematological toxicity (except nausea/vomiting and alopecia); or grade ≥2 hemorrhage or cerebellar toxicities. Only one dose reduction (to the previous dose level) was allowed for DLT occurring in any cycle. Cohorts were expanded to six patients if DLT was observed in 1 of 3 patients. If there were no additional DLT among 6 patients, dose escalation resumed. If DLT was observed in 2 of 6 patients, dose escalation would cease unless additional escalations were deemed clinically appropriate. The MTD was to be determined as one dose level below where dose escalation should cease. This would be the recommended Phase II dose. A minimum of 6 patients would be treated at the recommended Phase II dose to additionally examine its toxicity profile. Any patient who did not complete cycle 1 for reasons other than toxicity was not evaluable for MTD determination, although still evaluable for toxicity.

Dose reductions occurred for the following: DLT during any cycle; ANC < 1500/μl or platelet count <100,000/μl on day 1 of the next cycle; thrombocytopenia with bleeding during any cycle; and grade 2–3 nonhematological toxicity still present on the day of the next cycle of therapy. Treatment resumed when toxicity resolved to grade 1 or to baseline value. Patients with grade 4 nonhematological toxicity during any cycle discontinued protocol treatment.

**Pretreatment and Follow-Up Studies.** History, physical examination, and routine laboratory tests were performed at baseline and before each treatment. Complete blood counts were obtained twice weekly during cycle 1. Imaging studies were performed at baseline and reassessed every two cycles. Patients remained on study until evidence of disease progression or excessive toxicity. Tumor response definitions were based on WHO criteria (12).

**PK Sampling and Analytical Assay.** Blood samples were collected in lavender top (EDTA) vacutainer tubes from a peripheral site contralateral to the venous access used for drug infusion and immediately placed in an ice water bath. Initially, blood samples were obtained during cycle 1 pretreatment (10 min before the infusion), at the EOI, and after the EOI at 15 and 30 min and at 1, 2, 4, 8, and 24 h. Starting with patient 12, blood was collected pretreatment, 15 min into the infusion, immediately before the EOI, and after the EOI at 0.5, 1, 6, 24, 48, 72 h, on days 8 and 15, and before subsequent courses both pretreatment and before the EOI. Within 30 min of collection, blood samples were centrifuged at 1000 × *g* for 10 min at 4°C. Urine samples were collected during cycle 1 at baseline, then continuously in the time intervals 0–4, 4–8, and 8–12 h after the start of the infusion. Additional collection intervals beginning with patient 18 included 12–24, 24–48, and 48–72 h and one additional 24-h collection on day 8. All samples were frozen immediately on dry ice and then stored at −70°C until the time of analytical assay.

DHA-paclitaxel and paclitaxel concentrations were quantitated in plasma and urine using validated analytical methods according to the document "Guidance for Industry: Bioanalytical Method Validation" (updated February 27, 2003; last accessed April 8, 2003).[4] DHA-paclitaxel and paclitaxel were quantitated in plasma and urine using high-performance liquid chromatography with tandem mass spectrometric detection, as described previously (11). DHA-paclitaxel was quantitated in plasma and urine over the concentration range of 0.4–1100 μg/ml and 5–200 ng/ml, respectively; paclitaxel was quantitated over the concentration range of 10–500 and 5–200 ng/ml, respectively.

**PK and Pharmacodynamic Analyses.** Plasma PK parameters for DHA-paclitaxel and paclitaxel were calculated from individual concentration-time data sets using model independent methods as implemented in the computer software program WinNonLin v3.0 (Pharsight Corporation, Mountain View, CA) and as described previously (13). The AUC from time 0 to 24 h [AUC(24 h)] and from time 0 to the time of the final measurable concentration [AUC(tf)] were calculated for both DHA-paclitaxel and paclitaxel using the linear trapezoidal rule; the AUC was also extrapolated to infinity [AUC(inf)] for paclitaxel. Relative systemic exposure to paclitaxel to that of DHA-paclitaxel was calculated as the AUC(tf) ratio of paclitaxel to DHA-paclitaxel on a molar basis, which was then multiplied by 100 and expressed as a percentage. Individual DHA-paclitaxel PK parameters were also estimated using model-dependent methods as implemented in Adapt II release 4 (Biomedical Simulations Resource, Los Angeles, CA; Ref. 14). Individual plasma concentration-time data were fit with either a linear one- or two-compartment model using weighted least-squares as the estimation procedure and inverse variance of the output error (linear) as the weighting option. Model discrimination was guided by inspection of the weighted sum of squares and the coefficient of variation of the fitted PK parameters and by the Akaike information criterion (15). DHA-paclitaxel AUC(inf) was calculated as dose divided by systemic clearance. Urinary excretion of DHA-paclitaxel and paclitaxel was determined as described previously (13).

Relationships between DHA-paclitaxel dose and drug exposure [$C_{max}$ and AUC(24 h)] were assessed by examination of scatter plots and comparison of mean values at each dose level. Linear least-squares regression was used to assess the relationships between DHA-paclitaxel PK parameters ($Cl_s$ and $V_{ss}$) and BSA. Because tf (time of the final quantifiable sample) varied between the different dose levels, which was principally attributable to extending the PK sampling scheme during the conduct of the trial, statistical assessment of the effect of increasing dose level on DHA-paclitaxel half-life and clearance values was not performed. The *a priori* level of significance was set at 0.05. Statistical analyses were performed using the JMP (version 3.1)

[4] Internet address: http://www.fda.gov/cvm/guidance/published.htm.

*Table 1* Patient characteristics

| | No. of patients |
|---|---|
| No. of patients | 24 |
| Gender: male/female | 13/11 |
| Age (yr) | |
| Median | 60 |
| Range | 29–80 |
| Eastern Cooperative Oncology Group | |
| 0 | 5 |
| 1 | 16 |
| 2 | 3 |
| Previous therapy | |
| Chemotherapy | 24 |
| Median (range) | 3 (1–8) |
| ≥4 prior regimens | 9 |
| Radiotherapy | 13 |
| Immunotherapy | 3 |
| Treatment on study | |
| Median no. of cycles of DHA-paclitaxel | 2 |
| Mean no. of cycles of DHA-paclitaxel | 3.3 |
| Range | 1–8 |
| Tumor type | |
| Colorectal | 8 |
| Breast | 3 |
| Prostate | 3 |
| Prostate | 2 |
| Sarcoma | 2 |
| Esophageal | 2 |
| Other (ovary, anal, hepatoma, and non-small cell lung cancer) | 1 each |

statistical software program (SAS Institute, Cary, NC). The relationships between DHA-paclitaxel and paclitaxel exposure and percentage decrease in ANC were explored as described previously (16); values for DHA-paclitaxel AUC(inf), which was calculated from compartmental analysis, and paclitaxel AUC(tf) were used in this analysis.

## RESULTS

**General.** Patient characteristics and treatment duration are described in Table 1. From June 1999 to February 2001, 24 patients received a total of 78 cycles of DHA-paclitaxel over five dose levels (Table 2). Five patients had dose modification (Table 2). Toxicity was assessed in all patients. Nineteen patients stopped therapy for disease progression, 3 for adverse events, and 2 withdrew consent. The median number of cycles administered was 2 (range, 1–8). However, 10 of 24 patients received four or more cycles of DHA-paclitaxel (6 patients treated with doses ≥880 mg/m$^2$), and 5 of these patients received six or more cycles.

One patient was treated at dose level 1 (200 mg/m$^2$). A total of 2 patients were enrolled to dose level 2 (400 mg/m$^2$) after an episode of grade 1 skin flushing (HSR) within minutes of infusion initiation during cycle 1. Dose level 3 (660 mg/m$^2$) was first expanded to 3 patients after one episode of grade 3 neutropenia during cycle 1 and then subsequently expanded to 6 patients after one episode of DLT (ANC <500 for ≥5 days) during cycle 1. Three patients were treated at dose level 4 (880 mg/m$^2$) with no incidence of DLT. Dose level 5 (1100 mg/m$^2$) initially accrued 3 patients with no DLT but was expanded to 6 patients to additionally characterize the observed myelosuppression (grade 3 neutropenia during one cycle and grade 4 neutropenia during six cycles among 3 patients). One episode of febrile neutropenia during cycle 1 (DLT) was observed among these 6 patients (patient no. 6). At this time, dose level 4 (880 mg/m$^2$) was then expanded to enroll 3 additional patients (total of 6) to obtain more safety data; febrile neutropenia during cycle 1 (DLT) also occurred in 1 of these 6 patients. At this point, dose level 5 was additionally expanded from 6 to 9 patients to obtain additional safety data at this dose level. Available PK data suggested a disproportionate increase in paclitaxel exposure with increasing doses of DHA-paclitaxel from 660 to 880 and from 880 to 1100 mg/m$^2$ (Table 6), and further dose escalation > 1100 mg/m$^2$ was anticipated to produce an unacceptable rate of DLT. Despite not fulfilling the classic predetermined definition of MTD (one dose level below where two DLT episodes were observed), 1100 mg/m$^2$ was selected as the dose recommended for subsequent studies based on available toxicity and PK data.

**Hematological Toxicity.** Neutropenia was the DLT after administration of DHA-paclitaxel every 21 days (Table 3). The neutrophil nadir typically occurred during the second week, with hematological recovery to levels adequate for re-treatment before day 21. Neutropenia was dose-related (Table 3), but did not appear to be cumulative over subsequent cycles of treatment. Grade 3 and 4 neutropenia occurred in 83% of patients (56% of cycles), 90% of patients (52% of cycles), and 100% of patients (74% of cycles) at 660, 880, 1100 mg/m$^2$. Despite frequent incidence of grade 4 neutropenia, little neutropenia-related complications occurred, likely because of its short duration and absence of mucositis. This toxicity was not cumulative and no cycles of therapy were delayed because of persistent myelosuppression. Two patients required dose reductions from 1100 to 880 mg/m$^2$ for febrile neutropenia occurring during cycles one and four, respectively.

**Nonhematological Toxicities.** The number of patients experiencing nonhematological toxicity as a function of dose level and NCI-CTC grade of toxicity is summarized in Table 4. Skin rash and fatigue were the most significant nonhematological toxicities, which were often mild with rare grade 3 events. Six patients in dose levels 4 and 5 developed pruritus and/or skin rash, usually grade 1 and involving axillae and other areas of flexure. One patient at 1100 mg/m$^2$ developed a pruritic rash with mild xeroderma in both axillae and inframammary folds beginning with cycle 2. The rash extended to >50% (grade 3) of her body surface after cycle 3 and resolved with dose reduction to 880 mg/m$^2$.

Fatigue was observed at the majority of dose levels, although it often coincided with disease progression. Two patients developed grade 3 fatigue at dose levels 3 (after cycle 2) and 4 (after cycle 5). One patient at 1100 mg/m$^2$ developed grade 3 fatigue during cycle 1, which required a dose reduction to 880 mg/m$^2$/protocol. However, this toxicity was not clearly drug related and was not considered a DLT for defining the MTD.

No alopecia was noted. Musculoskeletal symptoms and peripheral neuropathy were infrequent and mild events. Four patients developed grade ≤1 arthralgia/myalgia. Two patients developed grade 1 acute HSR during cycle 1. Five other patients developed minor grade 1 facial flushing beyond cycle 1. Only 1 patient each complained of grades 2 (dose level 2) or 3 nausea

*Table 2* Dose escalation scheme and incidence of DLT

| Dose ($mg/m^2$) | New | Escalated to this dose | Reduced to this dose | Total no. patients | Total no. cycles | New patients with DLT[a]/total no. of new patients |
|---|---|---|---|---|---|---|
| 200 | 1 | 0 | 0 | 1 | 4 | 0/1 |
| 400 | 2 | 1 | 0 | 3 | 10 | 0/2 |
| 660 | 6 | 0 | 0 | 6 | 18 | 1/6 |
| 880 | 6 | 0 | 4 | 10 | 27 | 1/6 |
| 1100 | 9 | 0 | 0 | 9 | 19 | 1/9 |
| Total | 24 | | | | 78 | 3/24 |

[a] First course only.

*Table 3* Hematological toxicity of DHA-paclitaxel (NCI-CTC, version 2.0)

| Dose ($mg/m^2$) | No. of patients/ No. of cycles | Neutrophil nadir | | Total no. of patients with neutropenia (total no. of cycles) | | | | Platelet nadir | | No. of patients with thrombocytopenia | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Median ANC (range)/$mm^3$ | Median day (range) | Grade 3 | Grade 4 | Grade 4 > 5 days | Grade 4 + fever | Median (range) × $10^3/mm^3$ | Median day | Grade 3 | Grade 4 |
| 200 | 1/4 | 3479 (3357–4583) | 15 (10–18) | 0 | 0 | 0 | 0 | 281 (277–283) | 15 | 0 | 0 |
| 400 | 3/10 | 2095 (1120–2724) | 15 (8–23) | 0 | 0 | 0 | 0 | 232 (119–301) | 8 | 0 | 0 |
| 660 | 6/18 | 838 (161–2999) | 15 (8–15) | 3 (4) | 2 (6) | 1 | 0 | 206 (65–334) | 8 | 0 | 0 |
| 880 | 10/27 | 698 (0–4800) | 11.5 (8–15) | 3 (4) | 6 (10) | 0 | 2 (2) | 184 (111–383) | 8 | 0 | 0 |
| 1100 | 9/19 | 403 (23–2850) | 12 (8–15) | 4 (4) | 5 (10) | 0 | 2 (2) | 178 (78–292) | 8 | 0 | 0 |

(dose level 4) after single cycles and did not require subsequent premedication. One heavily pretreated patient (cisplatin, etoposide, vinorelbine, paclitaxel, and five other agents in Phase I evaluation) with non-small cell lung cancer treated at dose level 5 had progressive dyspnea and grade 3 hypoxia during the second week of cycle 1, although no specific correlation with the study drug could be confirmed.

**Antitumor Activity.** Antitumor activity was confirmed in 1 patient at 1100 $mg/m^2$. She was a 65-year-old woman with metastatic breast cancer with initial stage IIb, hormone receptor negative, HER2-negative disease 4 years before enrollment. She had received four cycles of adjuvant doxorubicin and cyclophosphamide. When first diagnosed with pulmonary metastases 3 years later, she received a single cycle of docetaxel (discontinued because of dexamethasone-induced agitation) then cyclophosphamide, methotrexate, and 5-flurouracil with stable disease as best response lasting 6 months. Upon progression, she was offered treatment with DHA-paclitaxel 1100 $mg/m^2$ and had a partial response after two cycles. Additional tumor shrinkage not sufficient to be classified as a complete response was observed after an additional two cycles, despite a one-level dose reduction in cycle 4. She withdrew consent after six cycles when imaging studies documented stable disease, which persisted for an additional 4 more months off any therapy.

**PK and Pharmacodynamic Studies.** Plasma PK studies were performed in 23 patients and evaluable in 22 patients. Data were omitted for 1 patient treated at 400 $mg/m^2$ because of a HSR, which required discontinuation of the infusion. Representative plasma concentration-time profiles for DHA-paclitaxel and paclitaxel are shown in Fig. 2.

**PKs of DHA-Paclitaxel.** Average values for DHA-paclitaxel exposure [$C_{max}$ and AUC(24 h)] increased in near proportion with DHA-paclitaxel dose level (Table 5). At the recommended Phase II dose of 1100 $mg/m^2$, DHA-paclitaxel exhibited a small $V_{ss}$ (8 liters), a long terminal half-life (112 h), and a low systemic clearance (0.11 liters/h). Mean values for DHA-paclitaxel $V_{ss}$ were similar at all dose levels. From inspection of pretreatment and EOI concentrations, no accumulation of DHA-paclitaxel was noted in plasma over multiple courses of treatment (data not shown).

**PKs of Paclitaxel.** At the 1100 $mg/m^2$ dose level, paclitaxel represented 0.06% of DHA-paclitaxel exposure and was characterized by a mean $C_{max}$ of 282 ng/ml, a mean AUC(inf) of 10,705 ng/ml × h, and an apparent half-life of 85 h; paclitaxel concentrations remained measurable and >0.01 μM for an average of 6–7 days. At this dose level, interpatient variation in paclitaxel exposure was twice as variable (~50%) as that for DHA-paclitaxel. In addition, paclitaxel exposure appeared to increase disproportionately with increasing DHA-paclitaxel dose level (Table 6). As the DHA-paclitaxel dose was increased 25% from 880 to 1100 $mg/m^2$, both paclitaxel $C_{max}$ and AUC(24 h) increased 65%.

**Urinary Excretion of DHA-Paclitaxel and Paclitaxel.** Complete urine collections were obtained in 19 patients. The mean percentage of DHA-paclitaxel excreted unchanged in urine from time 0 to 12 h after treatment was 0.0013% (range,

*Table 4* Nonhematological toxicity of DHA-paclitaxel (NCI-CTC, version 2.0)

| Dose level | No. of patients/ no. of cycles | No. of patients with toxicity[a] | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Allergy (infusion reaction/flushing) | | Skin (pruritus/rash) | | Constitutional (fatigue/weakness) | | Gastrointestinal (diarrhea) | | Gastrointestinal (nausea/vomiting) | | Neurological (sensory) | | Pain (arthralgia/myalgia) | |
| | | Grade 1 | Grade 2–3 | Grade 1–2 | Grade 3 | Grade 1–2 | Grade 3 | Grade 1–2 | Grade 3 | Grade 1–2 | Grade 3 | Grade 1 | Grade 2–3 | Grade 1 | Grade 2–3 |
| 200 | 1/4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 |
| 400 | 3/10 | 1 | 0 | 0 | 0 | 2 | 0 | 1 | 0 | 1 | 0 | 1 | 0 | 1 | 0 |
| 660 | 6/18 | 1 | 0 | 0 | 0 | 2 | 1 | 0 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| 880 | 10/27 | 1 | 0 | 2 | 0 | 7 | 1 | 3 | 1 | 3 | 1 | 2 | 0 | 1 | 0 |
| 1100 | 9/19 | 4 | 0 | 3 | 1 | 7 | 1 | 3 | 0 | 6 | 0 | 1 | 0 | 1 | 0 |

[a] No grade 4 or 5 toxicities were observed.

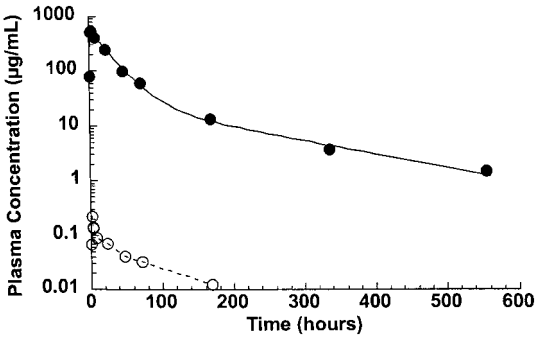


*Fig. 2* Representative DHA-paclitaxel and paclitaxel plasma concentration-time profiles after administration of DHA-paclitaxel (1100 mg/m$^2$). The *closed symbols* represent DHA-paclitaxel, and the *open symbols* represent paclitaxel. The *solid line* is from the fit of a two-compartment model to the DHA-paclitaxel concentration-time data.

0.00031–0.0063%); the average percentage excreted as paclitaxel was 0.021% (range, 0.0076%–0.039%).

**Pharmacodynamics.** Data from 22 patients receiving DHA-paclitaxel 200-1100 mg/m$^2$ were available to characterize drug exposure toxicity relationships. At the three highest dose levels, considerable overlap was observed for neutrophil toxicity; the median (range) percentage decrement in the ANC was 74% (46–96%), 68% (53–92%), and 95% (62–99%) at the 660, 880, and 1100 mg/m$^2$ dose levels, respectively. The variability in toxicity may be explained, in part, by interindividual differences in drug exposure at each dose level. From the fit of the $E_{max}$ model to the data, DHA-paclitaxel and paclitaxel AUC values were equally predictive of percentage decrements in the ANC ($R^2$ = 0.5678 and 0.5286, respectively; Fig. 3); DHA-paclitaxel and paclitaxel $C_{max}$ values appeared to be less predictive ($R^2$ = 0.4429 and 0.4034, respectively). However, because the AUC values of patients with sampling to 24 h might be underestimated compared with patients with plasma sampling to day 22, the drug exposure-toxicity relationship described here should be evaluated in a population of patients with PK studies using a similar plasma sampling scheme.

## DISCUSSION

In a little over 10 years, the taxanes have become among the most clinically useful chemotherapy agents on the basis of their unique mechanism of action and broad clinical use in both the adjuvant and advanced settings. However, the emergence of drug resistance and the occurrence of commonly associated toxicities such as peripheral neuropathy may lessen their full therapeutic benefit. Therefore, there is significant interest to identify novel analogues and delivery systems that can improve on the therapeutic index of existing taxanes by enhancing their antitumor activity, toxicity profile, and pharmacological properties. In the present trial, DHA-paclitaxel administration resulted in a dramatically altered paclitaxel plasma PK profile compared with that observed with clinically relevant paclitaxel administration schedules (*e.g.*, 175 mg/m$^2$ over 3 h). Although paclitaxel AUC values were similar (*e.g.*, 11 μg/ml × h), DHA-paclitaxel administration produced ~10-fold lower paclitaxel $C_{max}$ values and a ~5-fold longer apparent half-life for

*Table 5* DHA-paclitaxel pharmacokinetic parameters[a]

| | No. of patients | tf[b] | Ke ($h^{-1}$) | $V_c$ (liter) | $V_{ss}$ (liter) | $V_{ss}$ (liter/$m^2$) | $t_{1/2,\alpha}$ (h) | $t_{1/2,\beta}$ (h) | Cl (liter/h) | Cl (liter/h/$m^2$) | $C_{max}$ (μg/ml) | (24 h)[c] | (tf)[c] | (inf) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 200 | 1 | 25 | 0.08 | 3.4 | 3.4 | 1.9 | 8.5 | NA | 0.28 | 0.15 | 98 | 1202 | 1202 | 1321 |
| 400 | 1 | 23 | 0.08 | 3.1 | 3.1 | 1.7 | 8.2 | NA | 0.26 | 0.15 | 214 | 2383 | 2383 | 2741 |
| 660 | 6 | 27 | 0.04 | 3.7 | 3.7 | 2.0 | 15 | NA | 0.17 | 0.091 | 333 | 5,338 | 5,338 | 8,278 |
| | | (23–29) | (9.2) | (24) | (24) | (21) | (8.7) | | (29) | (27) | (20) | (20) | (20) | (27) |
| 880 | 2 | 26, 26 | 0.05, 0.03 | 4.3, 5.4 | 4.3, 5.4 | 2.0, 2.7 | 14, 23 | NA | 0.22, 0.16 | 0.10, 0.083 | 416, 310 | 5549, 6252 | 5549, 6252 | 8899, 10,889 |
| 880 | 3 | 279 | 0.03 | 3.7 | 6.6 | 3.3 | 14 | 93 | 0.098 | 0.050 | 543 | 8929 | 18,985 | 19,263 |
| | | (26–506) | (23) | (31) | (48) | (30) | (14) | (47) | (20) | (5.5) | (5.5) | (3.9) | (2.1) | (1.8) |
| 1100 | 9 | 424 | 0.03 | 3.8 | 7.5 | 3.5 | 17 | 112 | 0.11 | 0.055 | 601 | 10,232 | 23,825 | 21,004 |
| | | (75–577) | (13) | (35) | (64) | (49) | (17) | (56) | (30) | (24) | (24) | (24) | (30) | (26) |
| All dose levels | | | | 5.7 | 2.8 | | | | | | | | | |
| | | | | (64) | (49) | | | | | | | | | |

[a] Values represent mean (CV%).

[b] tf, time of the final quantifiable sample; NA, not applicable; $K_e$, elimination rate constant; $V_c$, central volume of distribution; $V_{ss}$, volume of distribution at steady state; $t_{1/2,\alpha}$, disposition half-life during the α phase; disposition half-life during the β phase; $Cl_s$, systemic clearance; $C_{max}$, maximum plasma concentration; AUC (24 h), area under the concentration-time curve from time 0 to 24 h; AUC (inf), AUC from time 0 to infinity.

[c] AUC (24 h) and AUC (inf) were calculated using noncompartmental analysis; all other pharmacokinetic parameters and AUC (inf) were determined using compartmental analysis.

paclitaxel (Table 7). At the recommended Phase II dose of DHA-paclitaxel (1100 mg/$m^2$), paclitaxel plasma concentrations remained ≥0.01 μM for an average of 6–7 days, which is substantially greater than that observed with paclitaxel administered as a 3-, 24-, or 96-h infusion every 21 days. Prolonged exposure to low paclitaxel concentrations may produce antitumor activity against disease that progressed during short taxane exposure (17). The schedule-dependent activity of paclitaxel was additionally demonstrated in randomized trials comparing a similar dose of paclitaxel given in a 3- *versus* 24-h infusion schedule (18). Any potential pharmacological benefits derived from continuous exposure to low nanomolar concentrations of paclitaxel may be obtained with a short infusion of DHA-paclitaxel given once every 21 days without neither the inconvenience of a prolonged infusion nor the incidence of severe mucositis observed with continuous infusion paclitaxel.

Neutropenia was the most frequent and DLT after administration of DHA-paclitaxel as a 2-h infusion repeated every 21 days. A relatively high frequency of grade 3–4 neutropenia (21 and 53% of courses, respectively) was observed at dose level 5 (1100 mg/$m^2$), although febrile neutropenia and infectious complications were infrequent. The starting dose recommended for subsequent Phase II studies is 1100 mg/$m^2$, which will require confirmation in ongoing Phase II studies. At this dose, the infused amount of CrEL is similar to the amount infused with 175 mg/$m^2$ paclitaxel. No moderate or severe neurotoxicity was observed during treatment with DHA-paclitaxel. Although peripheral neuropathy is best assessed after data accumulate on large numbers of patients treated with multiple cycles of therapy, the data from this trial are informative as almost half of the patients received four or more cycles and almost a quarter received six or more cycles of therapy. This observation is of particular interest as neurotoxicity is a common DLT seen in weekly paclitaxel schedules and paclitaxel-based regimens in combination with platinum. The low incidence of significant neuropathy will need to be confirmed in subsequent studies. In addition to the lack of any significant peripheral neuropathy, DHA-paclitaxel administration was associated with a low incidence of other nonhematological toxicities.

DHA-paclitaxel represents a taxane with a unique PK profile. At doses ranging from 200 to 1100 mg/$m^2$, DHA-paclitaxel exhibits a linear PK behavior, with proportionate increases in exposure with increasing dose. The half-life of DHA-paclitaxel is ~7-fold longer, the volume of distribution is ~100-fold smaller, and the clearance is ~300-fold lower than that for paclitaxel after administration as the Taxol formulation (Table 7). At each dose level, interpatient variation in DHA-paclitaxel clearance was 2-fold, which was substantially lower than that noted for paclitaxel (~7-fold). The interpatient variability in DHA-paclitaxel exposure ($C_{max}$ and AUC) expressed as the coefficient of variation (CV%) was ~25% at the 1100 mg/$m^2$ dose level. Normalization of clearance to BSA decreased interpatient variability from 29 to 22%, accounting for 24% of the variability in clearance. However, this observation was not a primary objective of the study and is limited by the fact that blood sampling for PK analysis was extended beginning with patient 12 and AUC values from previous patients might thus be underestimated. The small value for $V_{ss}$ (3.8 liters) indicates that DHA-paclitaxel is principally confined to the blood com-

*Table 6* Paclitaxel pharmacokinetic parameters[a]

| Dose ($mg/m^2$) | No. of patients | tf[b] | $t_{1/2}$ (h) | $C_{max}$ (ng/ml) | AUC (ng/ml × h) (24 h) | AUC (ng/ml × h) (tf) | AUC (ng/ml × h) (inf) | Paclitaxel: DHA-paclitaxel AUC ratio (%) |
|---|---|---|---|---|---|---|---|---|
| 200 | 1 | 6.0 | NC | 42 | NA | 112 | NC | 0.013 |
| 400 | 1 | 8.4 | NC | 76 | NA | 183 | NC | 0.011 |
| 660 | 6 | 27 | 52 | 118 | 906 | 906 | 2903 | 0.023 |
| | | (23–29) | (52) | (70) | (25) | (25) | (42) | (20) |
| 880 | 2 | 34, NC | 26, 26 | 110, 134 | 1128, 1404 | 1128, 1404 | 2762, NC | 0.025, 0.035 |
| 880 | 3 | 54 | 50 | 171 | 1639 | 2779 | 5765 | 0.027 |
| | | (26–74) | (51) | (37) | (39) | (58) | (62) | (31) |
| 1100 | 9 | 157 | 85 | 282 | 2702 | 8764 | 10,705 | 0.058 |
| | | (71–314) | (101) | (46) | (53) | (55) | (60) | (80) |

[a] Values represent mean (CV%).
[b] tf, time of the final quantifiable sample; NC, not calculated; NA, not applicable; $t_{1/2}$, apparent half-life; $C_{max}$, maximum plasma concentration; AUC (24 h), area under the concentration-time curve from time 0 to 24 h; AUC (tf), AUC from time 0 to tf; AUC (inf), AUC from time 0 to infinity.

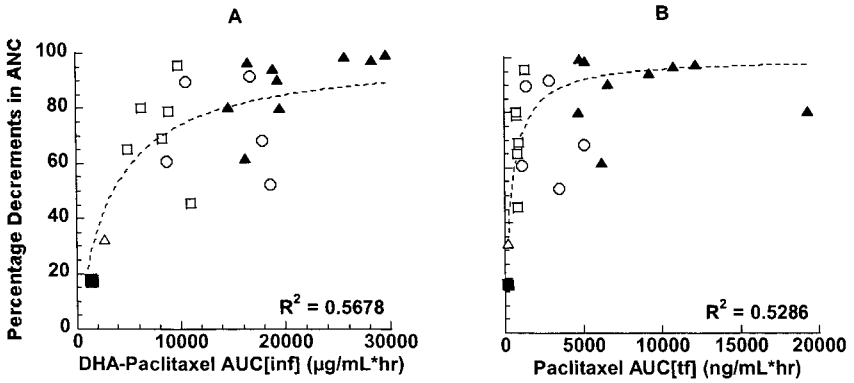


*Fig. 3* Percentage decrements in the ANC as a function of DHA-paclitaxel AUC (*A*) and paclitaxel AUC (*B*). Symbols represent the following doses: (■) 200 $mg/m^2$; (△) 400 $mg/m^2$; (□) 660 $mg/m^2$; (○) 880 $mg/m^2$; (▲) and 1100 $mg/m^2$. The *dashed lines* represent the fits of the $E_{max}$ model to the data.

*Table 7* DHA-paclitaxel and/or paclitaxel pharmacokinetic parameters after administration of different taxane formulations[a]

| Taxane formulation (schedule) | Pharmacokinetic parameter: $C_{max}$[a] (µg/ml) | AUC (µg/ml × h) | $t_{1/2}$ (h) | $V_{ss}$ (liters/$m^2$) | $Cl_s$ (liters/h/$m^2$) |
|---|---|---|---|---|---|
| DHA-paclitaxel (1100 $mg/m^2$/2 h) | | | | | |
| DHA-paclitaxel | 601 | 21,004 | 112 | 1.9 | 0.055 |
| Paclitaxel | 0.28 | 11 | 85 | NA | NA |
| Paclitaxel | | | | | |
| (135/$m^2$/3 h)[c] | 1.6–3.0 | 5.9–11 | 16 | 98 | 16 |
| (175/$m^2$/3 h)[c] | 2.4–5.0 | 11–18 | | | |

[a] Values represent the mean value (or range).
[b] $C_{max}$, maximum plasma concentration; NA, not applicable; AUC, area under the concentration-time curve; $t_{1/2}$, apparent or terminal half-life; $V_{ss}$, volume of distribution at steady state; $Cl_s$, systemic clearance.
[c] Data from Ref. 21.

partment, and small differences in blood volume between patients may contribute, in part, to the low interpatient variability in DHA-paclitaxel exposure. Protein binding studies have shown that DHA-paclitaxel is >99.6% bound to plasma proteins (11). On the basis of the relationship between BSA and DHA-paclitaxel $V_{ss}$ and $Cl_s$, administration of DHA-paclitaxel doses that are normalized to BSA should reduce interpatient variation in DHA-paclitaxel exposure by ~25% at any given dose level. Despite the long half-life, no accumulation of DHA-paclitaxel was noted in plasma when the drug was administered every 21 days. The prolonged circulation of both DHA-paclitaxel ($t_{1/2}$ = 112 h) and paclitaxel ($t_{1/2}$ = 85 h) suggests that more frequent dosing schedules (*e.g.*, weekly) might not be necessary.

In summary, the results of this Phase I trial confirm the preclinical observations and characterize a novel taxane conjugate with a more favorable toxicity and altered PK profile and with preliminary evidence of clinical activity. The PK profile of this 2-h infusion repeated every 21 days appears to mimic that of a protracted exposure to low nanomolar levels of paclitaxel, which are capable of disrupting tubulin dynamics (3). It is

unclear whether more frequent dosing (*e.g.*, weekly) would offer any additional pharmacodynamic advantage. There is significant interest in the development of water-soluble taxane conjugates that are formulated in less CrEL or in CrEL-free vehicles such as polymer- and poly (L-glutamic acid)-bound conjugates. However, the development of some of these compounds may be hampered by the observation of dose-limiting neurotoxicity in the preclinical (19) and clinical (19, 20) settings. The observed favorable toxicity profile of DHA-paclitaxel (*i.e.*, lack of any meaningful alopecia, arthralgia, myalgia, mucositis, and peripheral neuropathy among others) may potentially translate into a greater therapeutic index, although additional clinical experience is needed to examine some of the observed toxicities such as skin rash and fatigue in a less heavily pretreated population. Ongoing single-agent studies in both traditional and nontraditional taxane indications will help further characterize the activity profile of this drug, whereas combination studies may identify potential novel regimens with a more favorable activity and safety profile.

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# Phase I Study of Docosahexaenoic Acid-Paclitaxel: a Taxane-Fatty Acid Conjugate with a Unique Pharmacology and Toxicity Profile

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