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CLINICAL TRIAL REPORT

# A phase I study of intraperitoneal nanoparticulate paclitaxel (Nanotax®) in patients with peritoneal malignancies

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**Abstract**
*Purpose* This multicenter, open-label, dose-escalating, phase I study evaluated the safety, tolerability, pharmacokinetics and preliminary tumor response of a nanoparticulate formulation of paclitaxel (Nanotax®) administered intraperitoneally for multiple treatment cycles in patients with solid tumors predominantly confined to the peritoneal cavity for whom no other curative systemic therapy treatment options were available.
*Methods* Twenty-one patients with peritoneal malignancies received Nanotax® in a modified dose-escalation approach utilizing an accelerated titration method. All patients enrolled had previously received chemotherapeutics and undergone surgical procedures, including 33 % with optimal debulking. Six doses (50–275 mg/m$^2$) of Cremophor-free Nanotax® were administered intraperitoneally for one to six cycles (every 28 days).
*Results* Intraperitoneal (IP) administration of Nanotax® did not lead to increases in toxicity over that typically associated with intravenous (IV) paclitaxel. No patient reported ≥Grade 2 neutropenia and/or ≥Grade 3 neurologic toxicities. Grade 3 thrombocytopenia unlikely related to study medication occurred in one patient. The peritoneal concentration–time profile of paclitaxel rose during the 2 days after dosing to peritoneal fluid concentrations 450–2900 times greater than peak plasma drug concentrations and remained elevated through the entire dose cycle. Best response assessments were made in 16/21 patients: Four patients were assessed as stable or had no response and twelve patients had increasing disease. Five of 21 patients with advanced cancers survived longer than 400 days after initiation of Nanotax® IP treatment.
*Conclusions* Compared to IV paclitaxel administration, Cremophor-free IP administration of Nanotax® provides higher and prolonged peritoneal paclitaxel levels with minimal systemic exposure and reduced toxicity.

**Keywords** Paclitaxel · Nanotax® · Ovarian cancer · Intraperitoneal · Nanoparticle · Peritoneal malignancy · Pharmacokinetics

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## Introduction

Ovarian cancer is the fifth leading cause of cancer-related death among women in the USA and is the deadliest of gynecologic cancers. Despite advances in chemotherapeutics and surgical procedures, the 5-year survival rate for ovarian cancer was 45 % as of 2010 [1]. An estimated 220,000 new cases are diagnosed worldwide each year with 21,980 cases and 14,270 deaths anticipated in the USA during 2014 [1]. New and novel approaches to address peritoneal malignancies are of high priority. Intravenous (IV) paclitaxel (initially approved as TAXOL®, Bristol-Myers Squibb Co., Princeton, NJ) is an antineoplastic agent approved by FDA in 1992 for ovarian cancer treatment. The taxane family comprises a broad category of compounds that are effective inhibitors of cell growth; however, the hydrophobicity of paclitaxel presents delivery challenges. IV paclitaxel includes the solubilizing agent Cremophor [2] (polyoxyethylated castor oil) which, although generally recognized as safe, has been shown to be responsible for significant side effects necessitating pre-treatment of patients with antiemetics, antihistamines and either oral or IV steroids. IV paclitaxel administration can lead to severe hematological adverse events (AEs), with bone marrow suppression as the major dose limiting toxicity (DLT) [3].

The effect of systemic chemotherapy on peritoneal metastases is somewhat limited, possibly due to the presence of the peritoneum–plasma barrier that prevents effective drug delivery from systemic circulation into the peritoneal cavity [4]. Intraperitoneal (IP) chemotherapy administration bypasses the peritoneum–plasma barrier and maximizes the total amount of drug delivered into peritoneal tumor nodules while minimizing systemic drug exposure [5]. Paclitaxel's high molecular weight (853.9 g/mol), low solubility and continual availability from the Nanotax® depot particles results in low peritoneal clearance and its ability to penetrate more than 80 tumor cell layers after 24-h exposure makes it favorable for IP delivery [6]. Dose-dependent response to IV paclitaxel has been demonstrated in several clinical trials [7–10], with results suggesting that IP delivery of paclitaxel would improve cytotoxic effects due to increased local drug concentration. IP paclitaxel administered in combination with IV (IV/IP) chemotherapy with or without IP platinum has been reported as a viable treatment approach for ovarian and peritoneal carcinomas. IP paclitaxel treatment has been used as a neoadjuvant [11], intra-operatively and hyperthermically [12], as an instillation after primary optimal cytoreductive surgery [13, 14], and after neoadjuvant chemotherapy or primary surgery with optimal debulking [15]. Several of these IP paclitaxel treatment methods resulted in 5-year survival rates >60 % [11, 13, 14]. Additionally, randomized controlled trials have indicated improved progression-free survival (PFS) and/or overall survival (OS) for patients with peritoneal malignancies treated with a combination of IV/IP chemotherapy [13, 16, 17]. The phase III GOG-172 trial randomized patients with Stage III ovarian and peritoneal cancers to either IV paclitaxel (135 mg/m$^2$) over 24 h on day 1 followed by IV cisplatin (75 mg/m$^2$) on day 2, or IV paclitaxel (135 mg/m$^2$) over 24 h on day 1 followed by IP cisplatin (100 mg/m$^2$) day 2 and IP paclitaxel (60 mg/m$^2$) on day 8 every 21 days for six cycles [13]. Improved survival (65.6 months for IV/IP arm vs. 49.7 months for IV only arm) came with increased hematological, gastrointestinal, metabolic and neurologic toxicities as well as decreased quality of life. However, the majority of these toxicities were short-lived with only the increase in reported neurotoxicity remaining after 12 months [18]. These findings led to the publication of a Clinical Announcement by the National Cancer Institute (NCI) recommending that women be counseled about the benefit associated with combined IV and IP chemotherapy [19]. A trial evaluating a modified GOG-172 regimen (mGOG-172), IV paclitaxel (135 mg/m$^2$) over 3 h on day 1, IP cisplatin (75 mg/m$^2$) on day 2 and IP paclitaxel (60 mg/m$^2$) on day 8, given every 21 days for six cycles [14] showed similar levels of improvement in OS (67 months) with the benefits of reduced toxicity and increased number of IV/IP treatment cycles completed.

The development of Nanotax® (sterile nanoparticulate paclitaxel powder for suspension, CritiTech, Inc., Lawrence, KS) allows IP delivery of therapeutically relevant concentrations of paclitaxel within the peritoneal fluid without the need for toxic solvents such as Cremophor EL. The Nanotax® production process utilizes supercritical carbon dioxide in combination with organic solvents to reproducibly precipitate paclitaxel as fine particles. This novel employment of supercritical fluid (SCF) technology [20] results in naked, rod-shaped particles that have a narrow size distribution (mean particle size 600–700 nm) with 95 % of all particles measuring smaller than 1 μm [20, 21]. IP administration of Nanotax® particles provide a stable reservoir of paclitaxel which allows for extended drug release, an enhanced rate of solubilization and increased tumor exposure with reduced toxicity. Studies evaluating the relationship between nanoparticle shape and uptake have shown enhanced cellular uptake in cancer cell lines with rod-shaped particles, as well as faster internalization of longer versus shorter rod-shaped silica nanoparticles [22]. In addition to variations in particle size and shape, a variety of paclitaxel encapsulations have been created and evaluated in preclinical studies to improve drug delivery and reduce toxicities [23]. To date, only paclitaxel–albumin bound nanoparticles (Abraxane®) have been shown to be efficacious in clinical studies resulting in FDA approval for treatment of metastatic breast cancer, non-small cell lung cancer and adenocarcinoma of the pancreas via IV administration.

This phase I study was designed to evaluate the safety, dose tolerance and pharmacokinetics (PK) of IP Nanotax® across a range of doses and over multiple cycles of treatment in patients with advanced peritoneal malignancies. A secondary objective was the preliminary evaluation of antitumor activity using the response evaluation criteria in solid tumors (RECIST) criteria [24].

## Materials and methods

This was a multicenter, open-label, dose-escalating, phase I study to evaluate the safety, dose tolerance, PK, and preliminary antitumor effect of Nanotax® administered IP, with the intent of administration for a minimum of six cycles (once every 28 days), in patients with solid tumors whose carcinoma was predominantly confined to the peritoneal cavity.

### Patients

Patients aged 18 years and over were eligible for the trial if they satisfied the following inclusion criteria: (1) Histologic or cytologic diagnosis of carcinoma predominantly confined to the peritoneal cavity; (2) no other curative systemic therapy treatment options available; (3) at least 28 days elapsed since completion of previous chemotherapy; (4) at least 2 weeks elapsed since abdominal surgery and full recovery from effects of surgery; (5) Zubrod performance status [25] of 0–2; (6) granulocyte count $\geq$1500/μL and platelet count $\geq$100,000/μL within 14 days of study registration; (7) adequate renal function; and (8) adequate hepatic function. Patients with stable brain metastases and patients with hepatobiliary stents were eligible, as were patients who had previous treatment with chemotherapeutics (including IV and IP taxanes and platins) or had received radiotherapy.

Exclusion criteria included report of: (1) active inflammatory bowel disease or chronic diarrhea; (2) active infection requiring systemic therapy; (3) known history of uncontrolled hypertension, unstable angina, symptomatic congestive heart failure, myocardial infarction within the previous 6 months prior to study registration or serious uncontrolled cardiac arrhythmia; (4) any sensory neuropathy Grade 2 or higher [NCI Common Terminology Criteria Adverse Events version 3.0 (CTCAE-v3.0)] at time of study registration; (5) planning to receive any concomitant radiation therapy, hormonal therapy or other chemotherapy; (6) concomitant medications demonstrated to inhibit or induce CYP3A4 or CYPC28 drug metabolizing enzymes; (7) preexisting conditions that prohibited the use of IV dexamethasone or any other concomitant medication at the recommended dose; (8) pregnant or nursing women and patients of reproductive age who did not agree to use contraception. All patients gave written informed consent before study entry in compliance with institutional, state and federal regulations. The study was conducted in accordance with good clinical practice (GCP) [26].

### Drug administration and dose escalation

A physical examination (excluding genitourinary examination) with review of body systems and vital signs was performed at pre-study (screening), weeks 5, 9, 13 and continued every 4 weeks throughout treatment. Vital signs were taken pre-infusion, 30 and 60 min after the start of each IP Nanotax® infusion, and prior to discharge. Blood samples for hematology and chemistry were obtained at baseline, following instillation and weekly throughout treatment. If patients had Grade 4 neutropenia, CBC evaluations were to be performed three times a week until neutropenia resolved. Liver profile (AST/ALT, T.Bili., alkaline phosphatase and albumin levels) and tumor markers were obtained at baseline, weeks 5, 9, 13 and every 4 weeks throughout treatment as no anticipation of acute liver toxicity warranted additional testing.

A large bore implantable peritoneal catheter (9.6 French venous port; Port-a-Cath) was placed in the peritoneal cavity for Nanotax® delivery. At the time of catheter placement, and after each IP treatment or at least once a month, the catheter was flushed with heparinized saline. As a pre-treatment antiemetic, patients received IV dexamethasone (20 mg) with additional antiemetics (i.e., ondansetron, granisetron or dolasetron) as needed. To avoid potential infusion-related adverse reactions, all patients received a pre-treatment dose of IV diphenhydramine (50 mg) and an H2 receptor-antagonist [i.e., IV ranitidine (50 mg) or IV famotidine (20 mg)] 30 min prior to IP Nanotax® administration.

Nanotax® was supplied as powder and was suspended prior to use with 25 mL sterile saline for a clinical concentration of 5 mg/mL. Prior to suspension administration, any appreciable ascites was drained from the peritoneal cavity. After an initial infusion of 0.5 L sterile saline, Nanotax® [volume determined by dose and patient body surface area (BSA), no maximum] was delivered as a bolus injection into the administration tubing (paclitaxel tubing with filter removed to prevent trapping of study medication particles) and allowed to flow into the peritoneal cavity by gravity drainage. Following Nanotax® instillation, additional sterile saline up to a total of 2 L was infused over 30–60 min. Patients were placed in multiple positions (15 min each position) in order to distribute the study medication throughout the peritoneal cavity. Mitigation options for abdominal pain or discomfort during saline administration included analgesics, reduction in flow rate and reduction

of instilled fluid volume. The peritoneal cavity was not drained after instillation, and only fluid for PK analysis was removed.

A treatment cycle consisted of IP therapy on day 1 which was repeated once every 28 days. Patients continued on this treatment schedule until they experienced disease progression, an unacceptable toxicity or until a treatment delay >14 days, a development of an inter-current non-cancer-related illness that prevented continuation of therapy, a request by patient for any reason or initiation of medication that inhibits or induces CYP3A4 or CYP2C8. Treatment was intended to occur for a minimum of six cycles. After cessation of study therapy, patients were followed for survival for up to 2 years.

This study utilized a modification of an accelerated titration design [27] intended to minimize both the number of patients treated at doses below the biologically active level and the time to study completion. Dose escalation, up to a maximum of 275 mg/m$^2$, occurred in two phases: acceleration with single patient cohorts, and standard with cohorts of three to six patients. The acceleration phase was implemented until a Grade 2 or higher non-hematological or Grade 3 or higher hematological toxicity occurred, at which point standard phase was initiated with two additional patients enrolled at the dose level in question. In standard phase, escalation was determined by occurrence of DLT and patients who did not complete cycle 1 were replaced. DLT was defined as any of the following events that occurred during a subject's first treatment cycle and was assessed as study drug-related (possibly, probably or definitely), with toxicities graded according to the CTCAE-v3.0: (1) Grade 4 neutropenia lasting >7 days; (2) Grade 4 thrombocytopenia; (3) ≥Grade 3 non-hematological toxicity, including abdominal pain requiring narcotics (with the exception of alopecia and hypersensitivity); (4) Grade 3 nausea and vomiting which occurred despite antiemetic therapy and required hydration for ≥24 h; (5) Grade 2 or 3 neuropathy persisting on day 28; and (6) treatment delays >2 weeks due to toxicity. If no patients experienced DLT, the next cohort was treated at a higher dose level. If one patient experienced DLT, an additional three patients were enrolled at that dose level. If two or more patients in any cohort experienced DLT, the next cohort was treated at a lower dose level. Dose escalation was determined by the sponsor, the medical monitor, and the principal investigators following assessment of the safety data from patient(s) at the last completed dosing level.

## Safety

Safety was assessed in terms of AEs, serious AEs (SAEs), treatment-emergent AEs (TEAEs), DLTs, clinical laboratory tests, vital sign measurements and physical examination findings. AEs were graded according to the CTCAE-v3.0 and were coded using the Medical Dictionary for Regulatory Activities (MedDRA®), version 16.1. TEAEs, defined as any AE that occurred after the patient received any dose of Nanotax®, were summarized by the number and proportion of patients experiencing at least one occurrence and frequencies were summarized by the MedDRA® preferred term, severity grade (CTCAE-v3.0) and relation to treatment (not related, unlikely related, possibly related, probably related, and definitely related).

## Pharmacokinetics

PK evaluation was determined in patients for whom peritoneal fluid and plasma samples were available following IP Nanotax® administration. Blood samples (5 mL) were collected prior to and at 0.5, 1, 2, 4, 6, 8, 24, 48, 72, 168 and 336 h post-instillation during treatment cycles 1 and 2. Peritoneal fluid sampling (20 mL via peritoneal catheter) was attempted prior to and at 2, 6, 8, 24, 48, 72, 168 and 336 h post-instillation during treatment cycles 1 and 2. The plasma and peritoneal samples were stored at −20 °C until analyzed. Plasma and peritoneal paclitaxel concentrations were analyzed using a validated assay by combined reversed-phase liquid chromatography tandem mass spectrometry according to the method of Mortier [28] [limit of quantification (LOQ) of 4 ng/mL (0.005 μmol/L)]. Non-parametric PK analyses were performed on the resultant plasma concentration–time data using Phoenix WinNonlin®, Version 6.2 (Certara USA, Inc., St. Louis, MO).

## Tumor response

Objective tumor response status was assessed according to the RECIST guidelines [24] at the end of every other treatment cycle. Complete response (CR) was defined as disappearance of all disease with no new lesions and no disease related symptoms, as well as normalization of markers and other abnormal laboratory values. Partial response (PR) was defined as ≥30 % decrease under baseline of the sum of longest diameters of all target measurable lesions in patients with at least one measurable lesion, with no unequivocal progression of non-measurable disease and no new lesions. Stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR or sufficient increase to qualify for progression or symptomatic deterioration.

Progression was defined as one or more of the following: (1) 20 % increase in the sum of the longest diameters of the target measurable lesions over the smallest sum observed (over baseline if no decrease during therapy); (2) unequivocal progression of non-measurable disease; (3) appearance of any new lesion/site; and (4) death due to disease without prior documentation of progression and without

symptomatic deterioration. Symptomatic deterioration was defined as global deterioration of health status requiring discontinuation of treatment without objective evidence of progression.

All measurable lesions up to a maximum of 10 lesions representative of all involved organs were identified as target lesions at baseline, and all disease assessments were made using the same technique as baseline. Additional lesions were identified as non-target lesions and were included as non-measurable disease. CA-125 or CEA serum levels were monitored as indicators of tumor response.

### Statistical analysis

Continuous variables were summarized using descriptive statistics [number of patients with non-missing values, mean, standard deviation (SDEV), median, minimum, and maximum]. Descriptive statistics for PK parameters included the arithmetic mean and SDEV. The denominator for the percentage calculation was based on the total number of patients in the safety population by dose level and overall, unless otherwise specified. All analyses were carried out using SAS 9.2.

## Results

### Patient characteristics

Enrollment began in July 2008, and the study was completed in May 2013. Twenty-two patients were enrolled. One patient was discontinued prior to Nanotax® administration due to fibrin sheath encapsulation of the IP port (Table 1). The median age of patients in the safety population ($N = 21$) was 64 years (range 37–77 years), and the majority were female (81 %) and white (95 %). Thirteen patients (62 %) had ovarian cancers, and one patient each (5 %) had primary cancers of the bladder, brain, endometrium, gastroesophageal junction, pancreas, peritoneum, small bowel or adenocarcinoma of unknown primary site. Cancer stage at initial diagnosis was primarily IIIC (43 %) or IV (38 %) with one patient each presenting at Stage I, II, III or IIIA. All patients had received multiple prior chemotherapy regimens including IV carboplatin and paclitaxel (76 %) and previous IP chemotherapy (10 %). All patients had undergone significant and/or multiple previous surgical procedures with seven patients (33 %) having required tumor debulking.

### Drug administration and safety

All dose levels of IP Nanotax® were included in the analysis, 50, 82.5, 125, 175, 225 and 275 mg/m$^2$, reflecting an increase of 1.65-, 2.5-, 3.5-, 4.5- and 5.5-fold from the starting dose of 50 mg/m$^2$. Dose escalation was stopped at 275 mg/m$^2$ due to slow patient accrual and a lack of evidence suggesting higher paclitaxel levels would lead to improved clinical benefit. Twenty-one patients received Nanotax®, with a total of 43 treatment cycles administered (Table 2). Depending on dose level and patient BSA, between 19 and 99 mL of Nanotax® were delivered. Dose escalation was switched from the accelerated to standard approach after the second patient (82.5 mg/m$^2$ dose) exhibited a Grade 2 non-hematological toxicity (abdominal pain, pressure and distention during the initial IP infusion of saline). Patients who did not complete cycle 1 were replaced.

All treated patients reported at least one treatment-emergent adverse event (TEAE), and a total of 332 TEAEs were reported for all six dose levels (Table 2). Seventeen

**Table 1** Patient demographics and clinical characteristics

| Variables | *N* | % |
|---|---|---|
| No. of patients | | |
| Eligible | 22 | |
| Assessable for toxicity | 21 | 100 |
| Assessable for response | 21 | 100 |
| Assessable for pharmacokinetics | 21 | 100 |
| Age | | |
| Median years (range) | 64 | (37–77) |
| Sex | | |
| Female | 17 | 81 |
| Disease history | | |
| Ovarian | 13 | 62 |
| Bladder | 1 | 5 |
| Brain | 1 | 5 |
| Endometrium | 1 | 5 |
| Gastroesophageal junction | 1 | 5 |
| Pancreas | 1 | 5 |
| Peritoneum | 1 | 5 |
| Small bowel | 1 | 5 |
| Adenocarcinoma (location not specified) | 1 | 5 |
| Cancer stage at initial diagnosis | | |
| I | 1 | 5 |
| II | 1 | 5 |
| III | 1 | 5 |
| IIIA | 1 | 5 |
| IIIC | 9 | 43 |
| IV | 8 | 38 |
| No. of patients with previous surgical procedures | 21 | 100 |
| Tumor debulking | 7 | 33 |
| No. of patients with previous chemotherapies | 21 | 100 |
| Carboplatin and IV paclitaxel | 16 | 76 |
| IP chemotherapy | 2 | 10 |

patients (81 %) experienced TEAEs that were considered treatment-related by the investigator. The most commonly reported TEAE classification was gastrointestinal disorders (91 %), followed by general disorders and administration site conditions (81 %), metabolism and nutrition disorders (76 %), nervous system disorders (52 %) and infections and infestations (48 %). There was no apparent association between number of TEAEs per patient and dose administered, with the 125 and 275 mg/m$^2$ doses having the fewest TEAEs. Twenty-four treatment-emergent SAEs were reported in 11 subjects during the study and two (delayed wound healing and dyspnea) occurring at the 175 mg/m$^2$ dose were deemed possibly related to Nanotax® treatment.

One patient at the 175 mg/m$^2$ dose experienced a Grade 3 non-hematological toxicity TEAE related to an increase in ascites which was classified as a DLT and thus required a dosage reduction (20 % for cycle 2). The occurrence of ascites was deemed probably related to drug administration and resolved after 14 days. There were no DLTs of Grade 4 neutropenia, neutropenic fever, sepsis or thrombocytopenia, Grade 3 nausea and vomiting, Grade 3 neuropathy or Grade 2 neuropathy persistent on day 28, or treatment delays of >2 weeks due to toxicity. Eight patients experienced Grade 3 TEAEs classified as gastrointestinal disorders: Three had TEAEs of Grade 3 ascites or nausea deemed possibly or probably related to Nanotax® administration, while five had gastrointestinal disorders considered unrelated to Nanotax® administration including abdominal pain, small intestinal obstruction (related to disease progression) and constipation.

Four patients experienced seven laboratory values assessed as ≥Grade 3, one of which was a Grade 3 reduction in platelet count considered unlikely related to Nanotax® administration (225 mg/m$^2$ dose). Grade 2, 3 or 4 neutropenia was not detected in any patient receiving Nanotax®, and three instances of Grade 1 neutropenia were reported in two patients, all of which resolved in subsequent weeks.

Within the safety population, 14 patients discontinued Nanotax® treatment due to documented disease progression, five patients had discontinuation requested by physician for reasons not related to toxicity and two patients discontinued treatment due to non-Nanotax® related toxicities: (1) at the 125 mg/m$^2$ dose, a Grade 3 non-infectious wound complication and (2) at the 275 mg/m$^2$ dose, a Grade 3 SAE associated with a wound infection related to catheter port site. No patient discontinued the study due to a study drug-related AE, and no deaths were associated with study drug administration. One patient was lost to follow-up, and seventeen patients had early study termination due to death. The remaining three patients completed the 2-year follow-up for survival (Table 2).

## Pharmacokinetics

A total of 21 patients were included in the PK analysis. Due to technical difficulties with collection, fewer peritoneal fluid samples were collected than plasma samples. Insufficient peritoneal fluid samples were available to justify conducting a complete PK analysis. The volume of fluid in the peritoneal cavity is highly variable in patients with peritoneal malignancies and is further complicated by the presence or absence of ascites. As such, individual patient PK data are presented in Table 3. Following IP administration of Nanotax®, peritoneal fluid paclitaxel PK demonstrated a concentration–time profile that increased to a high concentration (mean of all doses = 6.7 μmol/L after 2 h) and slowly decreased over the 2-week sampling period (Fig. 1a). The time required to reach peak concentrations ($T_{max}$) was 56 h for the 50–275 mg/m$^2$ IP doses. Importantly, high trough peritoneal fluid concentrations of paclitaxel (mean = 1.0 μmol/L, $N = 6$) were observed prior to the second cycle IP dose at 4 weeks for those patients receiving multiple treatment cycles and for which peritoneal fluid was obtainable (Table 3). Inability to aspirate peritoneal fluid from patients on day 1 of cycle 2 prevented assessment of IP accumulation of paclitaxel. Mean peritoneal fluid paclitaxel levels at 168 h (6.0 μmol/L, $N = 17$) and 336 h (2.6 μmol/L, $N = 17$) demonstrate stable paclitaxel concentrations and reflect low clearance of Nanotax® from the peritoneal cavity due to the continuous release of paclitaxel from the Nanotax® particles.

Sufficient plasma samples allowed a PK analysis that demonstrated a concentration–time profile that resembled the peritoneal fluid profile, with an increase after IP dosing of Nanotax® followed by a subsequent stable elevation over the 2-week sampling period (Fig. 1b). Mean plasma paclitaxel concentration of 0.005 μmol/L was observed 2 h after the first treatment cycle of study drug (for all dose levels combined, $N = 21$). The AUC values for the plasma data from each patient are provided in Table 3; however, a larger PK study with more patient data at each dose is needed to draw final conclusions. The maximum mean plasma concentration ($C_{max\_plasma}$) of 0.016 μmol/L ($N = 20$) was reached at a $T_{max}$ of 63 h. $C_{max\_plasma}$ concentrations by dose level over cycles 1 and 2 were comparable, suggesting a rate-limited clearance of paclitaxel from the peritoneal cavity. $C_{max\_IP}$ were 41–7607 times greater than $C_{max\_plasma}$ (Table 3), with a mean per dose $C_{max\_IP}/C_{max\_plasma}$ range of approximately 450–2900.

## Efficacy and tumor response

At baseline, 86 % of patients had a Zubrod performance status of 0 or 1 (nine patients each), one patient reported a value of 2 at baseline, and two patients had no values

**Table 2** Study summary and treatment-emergent adverse events (TEAEs)

| Dose level (mg/m$^2$) (N) | 50 (1) | 82.5 (4) | 125 (3) | 175 (6) | 225 (4) | 275 (3) |
|---|---|---|---|---|---|---|
| Administration schedule | | | | | | |
| No. of patients who received one cycle | 0 | 1 | 2 | 1 | 1 | 1 |
| No. of patients who received two cycles | 1 | 3 | 1 | 3 | 3 | 2 |
| No. of patients who received five cycles | 0 | 0 | 0 | 1 | 0 | 0 |
| No. of patients who received six cycles | 0 | 0 | 0 | 1 | 0 | 0 |
| TEAEs[a] by Grade[b] (patients with at least one event) | | | | | | |
| Grade 1 | 28 (1) | 43 (4) | 5 (2) | 76 (5) | 24 (3) | 3 (2) |
| Grade 2 | | 12 (3) | 7 (3) | 39 (6) | 22 (4) | 16 (3) |
| Grade 3 | | 7 (2) | 6 (3) | 18 (6) | 6 (2) | 14 (3) |
| Grade 4 | | | | 1 (1) | | 2 (1) |
| Grade 5 | | 1 (1) | | | 2 (2) | |
| No. of patients with TEAEs deemed possibly, probably or definitely related to study drug administration per adverse event[a] | | | | | | |
| Hemolysis | | | | | 1 | |
| Abdominal distention | | 3 | | 3 | 1 | |
| Abdominal pain | 1 | 3 | | 4 | 1 | |
| Ascites | | | | 3 | | |
| Constipation | 1 | 2 | | 1 | | 1 |
| Diarrhea | | | | 2 | 1 | |
| Dry mouth | 1 | | | | | |
| Dyspepsia | 1 | | | 2 | | |
| Ileus | | | | | | 1 |
| Nausea | | 1 | 1 | 3 | 1 | |
| Vomiting | | | | 2 | 1 | |
| Early satiety | | | | 1 | | |
| Fatigue | | 4 | | 3 | 2 | |
| Implant site effusion | | | | 2 | | |
| Wound infection | | | | 1 | | |
| Anastomotic leak | | | | | | 1 |
| Wound complication | | | | 1 | | |
| Blood creatinine increased | | 1 | | | | |
| Decreased appetite | 1 | 2 | | 2 | 1 | |
| Dehydration | | | | 1 | 2 | |
| Hypokalemia | | | | | 1 | |
| Muscular weakness | | | | 1 | | |
| Myalgia | | 1 | | | | |
| Dizziness | 1 | | | | | |
| Insomnia | | 1 | | | | |
| Pelvic pain | | 2 | | | | |
| Dyspnea | | | | 3 | | |
| Alopecia | | 1 | | | | |
| Acne | | | | 1 | | |
| Flushing | | | | 2 | | |
| Off study summary | | | | | | |
| Patients lost to follow-up | 0 | 0 | 0 | 1 | 0 | 0 |
| Death not related to study drug administration | 0 | 4 | 3 | 3 | 4 | 3 |

[a] Adverse events coded with MedDRA Coding Dictionary Version 16.1

[b] TEAEs graded according to the NCI Common Terminology Criteria Adverse Events (CTCAE-v3.0)

**Table 3** Peritoneal (IP) fluid and plasma paclitaxel PK values for each patient

| Patient no. | Dose ($mg/m^2$) | $C_{max\_IP\ Fluid}$ (μmol/L) | $T_{max\_IP\ fluid}$ (hours, cycle[a]) | $C_{max–plasma}$ (μmol/L[b]) | $T_{max\_plasma}$ (hours, cycle) | $T_{½\_\ plasma}$ (hours) | $C_{max\_IP}$/ $C_{max\_plasma}$ | Trough concentrations of 4 weeks after first cycle treatment[b,c] (μmol/L) | | AUC plasma (μmol/L/$h^{-1}$, cycle) |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | IP fluid | Plasma | |
| 1 | 50 | 4.24 | 168, 1 | 0.008 | 48, 1 | | 549 | | BLQ | 0.442, 1 |
| Mean 50 $mg/m^2$ | | 4.24 | 168 | 0.008 | 48 | | 549 | | BLQ | 0.442 |
| 2 | 82.5 | 1.08 | 6, 1[a] | 0.026 | 48, 1 | 517 | 41 | | 0.008 | 5.730, 1 |
| 3 | 82.5 | 15.32 | 48, 2 | 0.009 | 48, 1 | 561 | 1792 | | BLQ | 1.625, 1 |
| 4 | 82.5 | 0.93 | 2, 1[a] | 0.009 | 8, 1[a] | 269 | 100 | | | 1.700, 1[a] |
| 5 | 82.5 | 3.51 | 48, 2 | 0.008 | 72, 2 | | 435 | | BLQ | 1.892, 2 |
| Mean 82.5 $mg/m^2$ | | 5.21 | 26 | 0.013 | 44 | 449 | 592 | | 0.008 | 2.737 |
| 6 | 125 | 2.05 | 2, 1[a] | 0.007 | 72, 1[a] | 164 | 280 | | | 1.633, 1[a] |
| 7 | 125 | 12.71 | 24, 1 | 0.013 | 24, 2 | 225 | 978 | 0.07 | BLQ | 1.770, 2 |
| 8 | 125 | 1.63 | 2, 1[a] | 0.021 | 24, 1[a] | | 77 | | | 4.184, 1[a] |
| Mean 125 $mg/m^2$ | | 5.46 | 9 | 0.014 | 33 | 195 | 445 | 0.07 | BLQ | 2.529 |
| 9 | 175 | 11.77 | 72, 2 | BLQ | – | | – | | BLQ | – |
| 10 | 175 | 41.49 | 72, 2 | 0.035 | 72, 1 | | 1173 | 1.26 | BLQ | 7.201, 1 |
| 11 | 175 | 8.73 | 48, 2 | 0.028 | 48, 1 | 168 | 307 | 1.25 | BLQ | 5.608, 1 |
| 12 | 175 | 6.67 | 2, 2 | 0.006 | 72, 1 | 164 | 1211 | | BLQ | 1.170, 1 |
| 13 | 175 | 18.43 | 24, 2 | 0.026 | 72, 2 | | 696 | | BLQ | 7.785, 2 |
| 14 | 175 | – | – | 0.041 | 48, 1[a] | 155 | – | | | 7.625, 1[a] |
| Mean 175 $mg/m^2$ | | 17.42 | 44 | 0.027 | 80 | 162 | 847 | 1.25 | BLQ | 5.878 |
| 15 | 225 | 7.04 | 24, 2 | 0.022 | 336, 2 | | 322 | 0.29 | 0.007 | 5.413, 2 |
| 16 | 225 | 11.66 | 48, 2 | 0.032 | 48, 1 | 123 | 362 | | 0.010 | 6.483, 1 |
| 17 | 225 | 1.82 | 2, 1[a] | 0.014 | 72, 1[a] | | 130 | | | 3.532, 1[a] |
| 18 | 225 | 26.73 | 168, 2 | 0.005 | 6, 1 | 233 | 5868 | 4.39 | BLQ | 0.963, 1 |
| Mean 225 $mg/m^2$ | | 11.81 | 61 | 0.018 | 116 | 178 | 1671 | 2.34 | 0.008 | 4.098 |
| 19 | 275 | 6.81 | 24, 2 | 0.029 | 48, 2 | | 232 | | | 3.200, 2 |
| 20 | 275 | 61.47 | 6, 1 | 0.008 | 48, 1 | 103 | 7607 | 0.39 | 0.000 | 1.915, 1 |
| 22 | 275 | 11.15 | 48, 1[a] | 0.013 | 72, 1[a] | | 874 | | | 1.763, 1 |
| Mean 275 $mg/m^2$ | | 26.48 | 26 | 0.017 | 56 | 103 | 2904 | 0.39 | 0.000 | 2.293 |
| Mean all doses | | 11.77 | 56 | 0.016 | 63 | 217 | 1168 | 1.01 | 0.008 | 2.996 |
| SDEV all doses | | 8.80 | 58 | 0.007 | 30 | 134 | 960 | 1.02 | 0.000 | 1.834 |

[a] Cycle 2 samples not collected

[b] Samples below the limit of quantification (LOQ; 0.005 μmol/L) are designated as BLQ

[c] Patients missing from the table either did not have a second treatment cycle administered, or the 0 time point 'trough' concentration for the second cycle were not reported

reported. During the course of the study, patient performance remained stable and no patient reported a Zubrod status of 3 or 4.

No CRs or PRs were recorded over the course of the study; five patients had localized tumor progression, seven patients had regional or nodal progression, and six patients had distant progression. Time to tumor or clinical disease progression was longest in the 175 $mg/m^2$ dose level (median 2.7 months), and time to death was longest in the 82.5 $mg/m^2$ dose level (median 11.1 months). Over the course of the study, objective tumor response was assessed using RECIST guidelines [24]: Five assessments of SD and 15 assessments of progressive disease were recorded. Best response was calculated from the sequence of objective statuses: 12 patients had increasing disease (defined as objective status of progression or symptomatic deterioration within 12 weeks of registration), four patients remained stable or had no response (defined as at least one objective status of stable/no response documented at least 6 weeks after registration and before progression or symptomatic

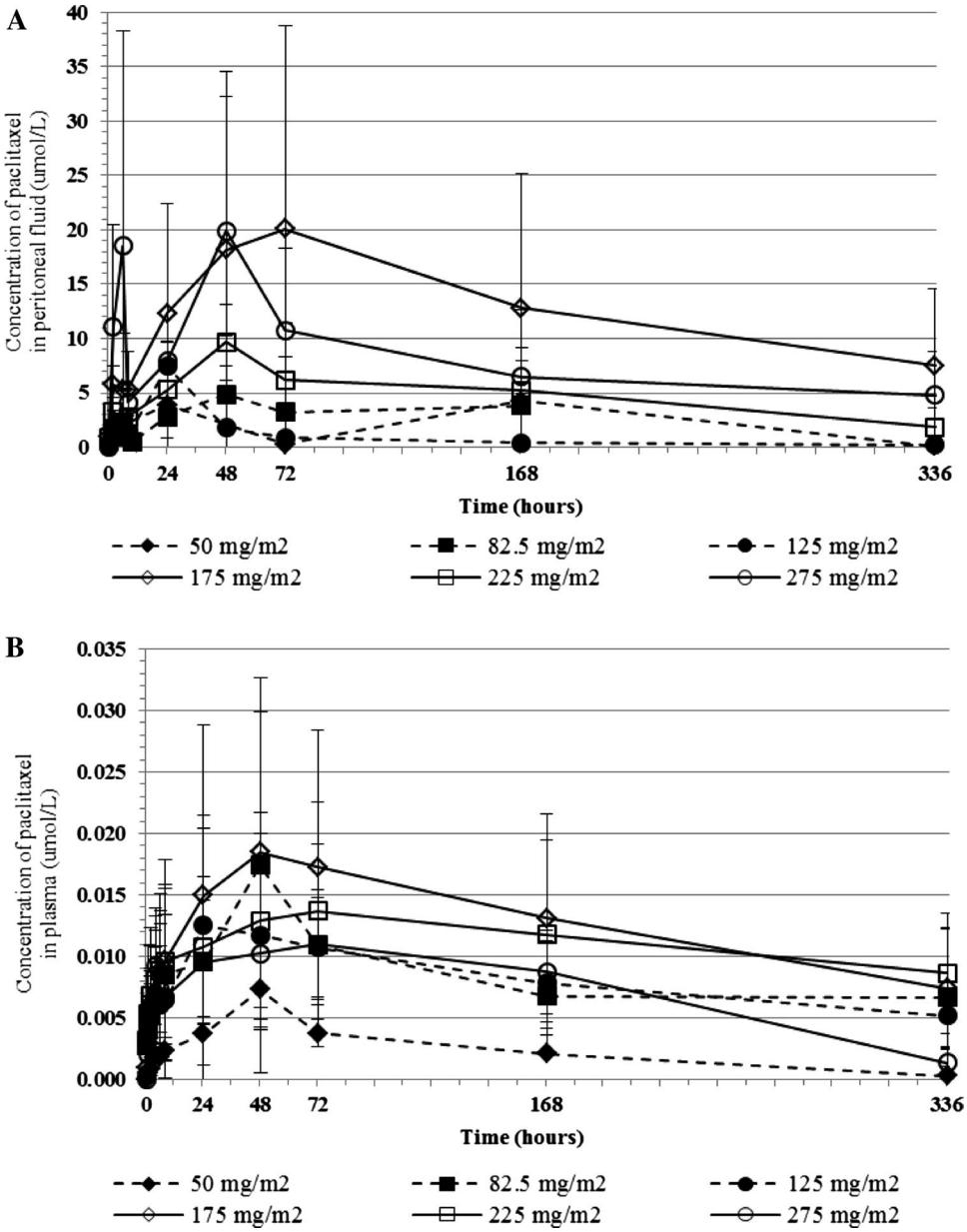


**Fig. 1** Peritoneal fluid (**a**) and plasma (**b**) paclitaxel concentrations averaged over treatment cycles 1 and 2. Mean peritoneal fluid and mean plasma concentrations are presented per Nanotax® dose level. *Error bars* ±1 SDEV

deterioration), and five patients had no best response assessment.

Twelve patients had complete CA-125 assessments. Of these, eight patients had an increase in their levels, three patients had a decrease, and one patient had no change. Patients with decreases or no change in CA-125 levels were in the 175 mg/m$^2$ (three patients) and 225 mg/m$^2$ (one patient) dose levels. One patient who had CEA levels monitored showed an increase.

Seventeen deaths were recorded over the course of the study, primarily due to the patients' advanced cancer. Five of the 21 patients (24 %) treated with IP Nanotax® survived over 400 days after treatment initiation. These data are consistent with the refractory nature and clinical status of these patients at study enrollment (81 % of patients Stage IIIC or IV upon enrollment).

## Discussion

In this phase I study, delivery of nanoparticulate paclitaxel (Nanotax®) directly into the peritoneal cavity was well tolerated in patients with advanced peritoneal carcinomas. There were no Nanotax®-related deaths or Nanotax®-related AEs leading to study discontinuation. Cremophor EL-related adverse treatment reactions commonly noted with IV paclitaxel therapy were avoided. Five of the 21 patients (24 %) with Stage IIIC or IV cancers survived at

**Table 4** Grade 3 and 4 toxicities in IP Nanotax®, mGOG-172 and GOG-172 trials [14]

| Toxicity | IP Nanotax®, all doses ($N = 21$) number (%) | Frequency of Grade 3 or 4 toxicity in modified outpatient IV/IP regimen in mGOG-172, ($N = 102$) number (%) | Frequency of Grade 3 or 4 toxicity in IV/IP therapy group in GOG-172 (%) |
|---|---|---|---|
| Neutropenia | 0 | 12 (12) | 76 |
| Thrombocytopenia | 1 (5) | 0 | 12 |
| Gastrointestinal | 9 (43) | 8 (8) | 46 |
| Renal | 1 (5) | 2 (2) | 7 |
| Metabolic | 3(14) | 5 (5) | 27 |
| Neurologic | 0 | 6 (6) | 19 |
| Infection | 5 (24) | 2 (2) | 16 |
| Febrile neutropenia | 0 | 0 | – |
| Abdominal pain | 4 (19) | 3 (3) | – |
| Fatigue | 4 (19) | 2 (2) | 18 |
| IP port infection | 1 (5) | 2 (2) | 18 |
| IP port blocked | 0 | 1 (1) | 8 |
| Treatment-related death | 0 | 0 | 2 |

least 400 days after initiation of Nanotax® treatment. Based on maintenance of the treatment schedule, tolerability and the expectation that greater anticancer benefit will be derived by patients receiving Nanotax® over multiple treatment cycles, the recommended dose for further study is 175 mg/m$^2$.

Compared to the IV/IP arms of GOG-172 and mGOG-172, which had 76 and 12 %, respectively, of patients presenting with Grade 3 or 4 neutropenia, no patient in this study experienced Grade 2, 3 or 4 neutropenia following IP Nanotax® doses as high as 275 mg/m$^2$ (Table 4). In addition, rates of neutropenia were lower as compared to IV paclitaxel where Grade 4 neutropenia occurs in a dose- and schedule-dependent manner in 14 and 27 % of patients treated with 135 and 175 mg/m$^2$ IV doses, respectively [29].

Grade 3 thrombocytopenia classified as unlikely related to study medication occurred in one patient treated with Nanotax® versus zero patients in mGOG-172 (Table 5). Upon enrollment, this patient's platelet levels were 103,000/μL and met eligibility requirements for inclusion (platelet count ≥ 100,000/μL within 14 days of study initiation). However, platelets decreased during weeks 0 and 1 of cycle 1 and this patient died soon after due to disease progression deemed not related to study drug administration. With IV paclitaxel administration, 20 % of patients experience a decline in their platelet count below 100,000 cells/μL (Grade 1) at least once while undergoing IV treatment and 7 % have a platelet count <50,000 cells/μL (Grades 3–4) at the time of their worst nadir [29].

No Grade 3 or higher neurologic toxicities were reported (Table 4). In the GOG-172 and mGOG-172 studies, 19 and 6 % of patients, respectively, had Grade 3 or 4 neurologic toxicities (Table 4). The TAXOL® package insert [29] includes a summary of 10 studies in which patients with solid tumors receiving single agent IV TAXOL report peripheral neuropathy rates of 60 %, with 3 % of patients experiencing severe (Grade 3) toxicity.

In this study, peritoneal administration of paclitaxel via IP Nanotax® particles resulted in significantly higher and prolonged paclitaxel peritoneal fluid concentrations with low clearance of study drug from the peritoneal cavity as well as subsequently low systemic paclitaxel levels. Therapeutically relevant paclitaxel levels were reached within the peritoneal cavity, and for those patients receiving multiple doses of Nanotax®, the peritoneal fluid paclitaxel level immediately prior to delivery of the second dose 28 days following the first dose was measurably greater than zero (Table 3). As evidenced by low plasma concentrations, regardless of IP dose, paclitaxel clearance from the intraperitoneal space is rate-limited. Furthermore, PK/PD modeling of IV paclitaxel-induced neutropenia suggests toxicity is related to the duration and extent of systemic exposure to paclitaxel above a threshold plasma concentration of 0.05 μmol/L [30]. IP Nanotax® administration resulted in plasma paclitaxel concentrations well below the threshold for toxicity [$C_{max}$ values of 0.005–0.041 μmol/L (Table 3)] and underscore the low levels of thrombocytopenia, neutropenia and peripheral neuropathy reported.

The mean per patient $C_{max\ ip}/C_{max\ plasma}$ ratio was approximately 1350 and greater than or equivalent to ratios observed in previous instillation or intraoperative hyperthermic intraperitoneal perfusion chemotherapy (HIPEC) trials (Table 5). Notably, the $T_{max}$ for Nanotax® administration was achieved between 1 and 2.5 days after instillation, in contrast to other trials where $T_{max}$ was reached in

**Table 5** Clinical trial pharmacokinetic results of IP paclitaxel instillation therapy

| Study | Year | Paclitaxel delivery method | Dose | $C_{max\_IP}$ (μmol/L)[a] | $T_{max\_IP}$ (hours) | $C_{max\_IP}/C^{a}_{max\_plasma}$ | $AUC_{IP}/AUC^{a}_{plasma}$ |
|---|---|---|---|---|---|---|---|
| Markman [33] | 1992 | Instillation IP chemotherapy | 25–175 mg/m$^2$/3–4 weeks | 175[b] | 0.5–1 | ~1000 | 996[d] |
| Francis [31] | 1995 | Instillation IP chemotherapy | 30–75 mg/m$^2$/week | 50–1273[c] | 0.5–2 | | |
| Hofstra [34] | 2002 | Instillation IP chemotherapy | 75 mg/m$^2$ D1 + 8/4 week | | | | 1350[d] |
| Mohamed [35] | 2003 | Instillation IP chemotherapy | 20 mg/m$^2$/day for 5 days | ~45 | 0.25 | ~800 | |
| deBree [12] | 2008 | HIPEC | 175 mg/m$^2$ for 2 h | 118 | 0.08 | 1178 | 1462 for 2 h (366 total for 5 days period) |
| Nanotax® | 2014 | Instillation IP chemotherapy | 50–275 mg/m$^2$/4 weeks | 1–61[c] | 56 | 1168 | |

[a] Mean values

[b] Mean value for 50–175 mg/m$^2$ range

[c] Range, not mean value

[d] For the duration of IP instillation chemotherapy

2 h or less. This marked increase in peritoneal cavity exposure time to clinically relevant Nanotax® levels represents a unique benefit of nanoparticle technology, in essence, providing a depot for chemotherapeutic delivery beyond that available with current paclitaxel formulations.

IP treatment regimens have been difficult to implement, with previous clinical trials having rates of completion ranging of 61 [31], 42 [13] and 55 % [14]. Although its unprecedented high survival rates triggered an NCI Clinical Announcement regarding IP chemotherapy, GOG-172 still elicited criticisms primarily focused on the inconvenience of an inpatient regimen, the high rate of Grade 3/4 toxicities and the poor tolerance of the regimen [14]. Historically, significant catheter complication rates (34 % of patients in GOG-172 [32]) have also limited the implementation of IP chemotherapy. However, improvements in clinician training and catheter technologies have recently been credited with 79 % (119/150) of patients completing planned IP treatment during the feasibility phase of the ongoing randomized PETROC/OV21 phase II/III trial of peritoneal treatment for ovarian cancer [36]. Future trials investigating IP Nanotax® delivery will benefit from improvements made in catheter technology, improved training in catheter placement and maintenance, and overall improved clinician comfort in administering IP treatment regimens.

In conclusion, treatment of intraperitoneal malignancies, such as ovarian cancer, with IP delivery of Nanotax® has been shown to be safe with minimal related toxicities. The absence of increased neutropenia, thrombocytopenia or peripheral neuropathy make IP Nanotax® treatment well poised to be combined with standard IV chemotherapy regimens, and PK data demonstrate extremely low peritoneal clearance, providing a marked benefit in tumor exposure intensity and duration without accompanying increases in systemic paclitaxel levels.

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