Published in final edited form as:
Cancer Chemother Pharmacol. 2013 March ; 71(3): 627–633. doi:10.1007/s00280-012-2048-y.

A phase I study of liposomal-encapsulated docetaxel (LE-DT) in patients with advanced solid tumor malignancies

John F. Deeken,
Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, 3800 Reservoir Road, NW, Washington, DC 20007, USA John.Deeken@gunet.georgetown.edu

Rebecca Slack,
M.D. Anderson Cancer Center, Houston, TX, USA

Glen J. Weiss,
Virginia G. Piper Cancer Center at Scottsdale Healthcare/TGEN, Scottsdale, AZ, USA

Ramesh K. Ramanathan,
Virginia G. Piper Cancer Center at Scottsdale Healthcare/TGEN, Scottsdale, AZ, USA

Michael J. Pishvaian,
Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, 3800 Reservoir Road, NW, Washington, DC 20007, USA

Jimmy Hwang,
Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, 3800 Reservoir Road, NW, Washington, DC 20007, USA

Karen Lewandowski,
Virginia G. Piper Cancer Center at Scottsdale Healthcare/TGEN, Scottsdale, AZ, USA

Deepa Subramaniam,
Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, 3800 Reservoir Road, NW, Washington, DC 20007, USA

Aiwu Ruth He,
Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, 3800 Reservoir Road, NW, Washington, DC 20007, USA

Ion Cotarla,
Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, 3800 Reservoir Road, NW, Washington, DC 20007, USA

Aquilur Rahman, and
NeoPharm, Lake Bluff, IL, USA

John L. Marshall
Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, 3800 Reservoir Road, NW, Washington, DC 20007, USA

Abstract

Correspondence to: John F. Deeken.

Conflict of interest The following author has a financial relationship related to the subject of this article: AR was an employee of NeoPharm, the maker of LE-DT. Research was supported by Neop-harm, Inc.

Background—Docetaxel is a taxane anticancer drug used in a wide variety of solid tumors. Liposomes are versatile drug carriers that may increase drug solubility, serve as sustained release systems, provide protection from drug degradation and toxicities, and help overcome multidrug resistance. This phase I study was conducted to determine the maximum tolerated dose, dose-limiting toxicities (DLTs), pharmacokinetics (PK), and clinical response of liposomal-encapsulated docetaxel (LE-DT) in patients with advanced solid tumor malignancies.

Methods—LE-DT was administered using a standard 3 + 3 dose escalation schema with dose levels of 50, 65, 85, 110, and 132 mg/m^2 IV on a 3-week cycle. Toxicities were assessed using the NCI-CTCAE version 3.0, and response was assessed using RECIST criteria (version 1.0). PK samples were drawn during cycle 1 and analyzed using a non-compartmental analysis.

Results—Twenty-four patients were treated for 1–30 cycles (median = 4). No DLTs were experienced through dose levels of 50, 65, 85, and 110 mg/m^2. Two out of two patients experienced grade 4 neutropenia at the 132 mg/m^2 dose level. When an additional three patients were treated at the expanded 110 mg/m^2 dose level, two experienced grade 4 neutropenia. The 85 mg/m^2 dose level was reassessed with an expanded group of three additional patients, and only one of three patients experienced grade 4 neutropenia. The protocol was amended to allow G-CSF during cycle 1, and an additional three patients were treated at 110 mg/m^2 with no DLTs experienced. No patient experienced significant neuropathy, even patients treated for 19, 20, and 30 cycles. PK followed a two-compartment elimination pattern; there was no correlation between PK and toxicity. Two patients with thyroid and neuroendocrine cancer had partial responses (PR, 8 %), and one patient with non-small-cell lung cancer had an unconfirmed PR. Eight patients (33 %) had stable disease lasting more than 3 months, for a clinical benefit rate of 41 %.

Conclusion—LE-DT was well tolerated with expected toxicities of neutropenia, anemia, and fatigue, but without neuropathy or edema. Clinical benefit (SD + PR) was observed in 41 % of the patients. The recommended phase II dose of LE-DT is 85 mg/m^2 without G-CSF or 110 mg/m^2 with G-CSF.

Keywords

Phase I; Liposomes; Docetaxel; Clinical trial

Introduction

Docetaxel is a semi-synthetic microtubule disrupting anti-cancer drug indicated for the treatment of breast, prostate, non-small-cell lung, head and neck, and gastric cancers [1–7]. Standard every 3-week dosages range from 60 to 100 mg/m^2, with 75 mg/m^2 being a commonly used dose in these diseases. Dose-limiting toxicities (DLTs) are myelosuppression and neuropathy, among others. For example, at a dose of 100 mg/m^2, docetaxel causes grade 4 neutropenia in 75–86 % of patients [8].

Past clinical trials have shown a dose–response correlation using docetaxel when used in the treatment for prostate and breast cancer [2, 9]. For example, the response rate in patients with metastatic breast cancer was significantly higher in patients receiving 100 mg/m^2 compared to those receiving 60 mg/m^2 although the incidence of significant and severe toxicity was higher in patients treated at the higher dose [9]. Due to poor solubility, docetaxel is administered with Tween 80 in ethanol. Tween 80 has been implicated in causing acute hypersensitivity reactions as well as cumulative fluid retention [10].

Liposomes are versatile drug carriers that may increase drug solubility, serve as sustained release systems, provide protection from drug degradation and drug-related toxici-ties, and help overcome multidrug resistance mediated by P-glycoprotein or similar transporter-

mediated resistance efflux mechanisms [11, 12]. We have found that liposomes can favorably alter the pharmacokinetics and distribution of the encapsulated drug and that liposomes are more readily distributed to tumor tissues compared to normal tissue due to decreased endothelial integrity in tumor vasculature (unpublished data). Already approved encapsulated chemotherapy agents include liposomal doxorubicin (Doxil®) and liposomal daunorubicin (DaunoXome®).

Other approaches to liposome drug delivery have been pursued to further improve drug delivery, to enhance drug formulation, and to increase the stability of the liposome drug product [13–19]. The approach used in the development of liposomal-encapsulated docetaxel (LE-DT) included electrically charged lipids to achieve an electrostatic attraction between the charged lipid and oppositely charged drug to create a stable liposome drug formulation. Negatively charged synthetic phospholipids and cholesterol are used to create small (≤100 nm) and uniformly sized liposomes. It is thought that docetaxel resides in the lipid bilayer of the liposomes in this formulation.

The use of synthetic electrostatic cardiolipin enabled the liposome formulation of a variety of chemotherapeutic agents, including doxorubicin [20], mitoxantrone [21], SN38 [22], and paclitaxel [23]. After favorable preclinical evaluations showing high activity against a wide range of in vitro and in vivo cancer models, a phase I first-in-human, clinical study of LE-DT in patients with refractory solid tumor malignancies was performed to determine the maximum tolerated dose (MTD), DLTs, pharmacokinetics (PK), clinical response, and the recommended phase II dose of LE-DT.

Methods

Patients

Patients with recurrent or refractory solid tumors were enrolled in a two-center, open-label, dose escalation, sequential cohort phase I clinical study of LE-DT. Patients were eligible or the study if they were candidates for docetaxel as appropriate first-line therapy, were no longer candidates for standard therapy, had no standard therapy available, or chose not to pursue standard therapy. Patients could not have received prior therapy with docetaxel. Patients were required to have adequate organ function, an ECOG performance status of 0–2, and sufficient recovery from past therapies.

Trial design and objectives

A 3 + 3 trial design was used to determine the MTD and DLTs of LE-DT. Secondary objectives included evaluating the pharmacokinetics of docetaxel following intravenous administration of LE-DT, as well as to determine the anti-tumor effects in this pretreated population.

Preparation of LE-DT liposomes

Dioleoyl-sn-glycero-3-phosphocholine (DOPC), cholesterol, cardiolipin, and alpha-tocopheryl acid succinate were dissolved in dehydrated alcohol in a compounding vessel. The dehydrated alcohol was evaporated to form lipid film or cake. Sodium chloride and sucrose were dissolved in water for injection in a separate compounding vessel and then added to the dried lipid film or cake. After hydration of the lipid film or cake and adjustment of the final batch weight, the bulk liposome mixture was sized with poly-carbonate filters (0.2 and 0.1 lm). The material was sterile filtered through 0.22-μm filter.

The sterilized material was placed into sterile vials. Lyophilization stoppers were placed into the vials in the lyophilization position. The vials were aseptically loaded into the lyophilizer and then dried at temperatures of -30 °C over 1 day,-22 °C over 3 days, and 25 °C over 8 h.

LE-DT is a sterile lyophilized liposomal powder, containing 30 mg docetaxel per vial. The formulation consists of the lipids DOPC, cholesterol, and tetramyristoyl cardiolipin in a 90:5:5 % molar ratio. Alpha-tocopheryl acid succinate and sucrose were added to the formulation as stabilizers. The total lipid-to-drug molar ratio in the formulation is 33:1. The reconstitution of lyophilized docetaxel liposomes involves the addition of 12.5 mL water to each vial, followed by gentle shaking of the vial to yield 2 mg/mL of docetaxel. After reconstitution, the product is a homogeneous liposome dispersion averaging about 100 nm in mean diameter. The docetaxel liposomes can be further diluted with 5 % dextrose up to eightfold prior to administration.

Treatment

LE-DT was administered by intravenous infusion over 1 h, once every 21 days, until disease progression, unacceptable toxicity, or patient voluntary withdrawal. Planned dose levels were 50, 65, 85, 110, and 132 mg/m^2. Dosage calculations in mg/m^2 of LE-DT were based on the molecular weight of docetaxel in the formulation and did not include the weight of the liposomes. Premedication with dexamethasone was not required, unlike standard docetaxel therapy [8]. In patients who experienced infusion-related reactions, premedication with corticosteroids, antihistamines, and antipyretics was provided in subsequent cycles per physician discretion and a 50 % reduction in the infusion time (to 2 h).

Toxicity and response

Toxicities were recorded using National Cancer Institute Common Toxicity Criteria (NCI-CTCAE, version 3.0). Hematologic dose-limiting toxicities were defined as follows: grade 4 neutropenia lasting for more than 3 days, or ≥grade 3 of any duration with infection and/or fever ≥38.5 °C regardless of prophylactic use of hematopoietic growth factors; grade 3 thrombocytopenia persisting ≥7 days or grade 4 of any duration; and any other grade ≥4 hematologic toxicity. Non-hematologic DLTs were defined as: prolonged QTc interval ≥grade 3; grade ≥2 neurosensory or neuromotor toxicity; hepatic transaminases elevation of grade 3 persisting ≥7 days or grade 4 of any duration; nausea or vomiting grade ≥3 persisting ≥24 h despite administration of recommended doses of antiemetics; and any other grade ≥3 non-hematologic toxicity (except alopecia).

Disease status was assessed radiographically every two cycles. Response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST version 1.0). The protocol and amendments were approved by the respective Institutional Review Boards.

Pharmacokinetic sampling, assay, and analysis

Plasma samples for PK analysis were collected before infusion initiation, immediately before the end of the 60-min infusion, and at 5, 15, and 30 min, and 1, 2, 3, 4, 6, 8, 24, and 48 h after the end of the infusion. Paclitaxel was added to samples as the internal standard. Analytes were extracted from plasma using liquid–liquid extraction, eluted with acetonitrile, evaporated under nitrogen gas, and reconstituted. The plasma was treated with acetonitrile to disrupt all the liposomes. PK values represent total docetaxel levels in plasma at all time points. High-performance liquid chromatography with tandem mass spectrometry was used to quantify the plasma concentration of docetaxel. The lower limit of quantification was 0.25 ng/mL. All samples were diluted into linear range before injection into the LC–MS/MS. The linear range represents working concentration and not the original concentration.

Individual plasma docetaxel concentration–time profiles were analyzed by standard non-compartmental methods using the WinNonlin Professional version 5.2 program (Pharsight, Mountain View, CA, USA). Plasma area under the curve (AUC_{0-t}) values (t being the time of the last plasma concentration measured) were estimated using the linear trapezoidal method. The terminal phase rate constant (Ke) was obtained by linear regression analysis of the terminal phase concentration–time data. $AUC_{t-\alpha}$ was estimated by dividing the last plasma concentration value measured by the terminal plasma rate constant. Plasma clearance (CL), terminal phase half-life ($t_{1/2}$), and volume of distribution (V_d) were estimated based on standard methods. The AUC (0–48 h) was calculated with the default setting of WinNonlin Program that uses the Linear Trapezoidal rule. The AUC (48 h–α) was calculated based on measured concentration at 48 h, and terminal elimination half-life was determined accordingly.

Results

Patients

Between June 2008 and June 2010, a total of 24 patients were treated on study. Patient demographics are listed in Table 1. The median patient age was 58 years (range 43–68), and men comprised two-thirds of the patients. The most common cancer type was gastrointestinal, with additional patients having lung, breast, and other malignancies.

Treatment

The total number of cycles each patient received ranged from 1 to 30 (median = 4). The dose levels and the number of patients treated are listed in Table 2. Dose escalation proceeded without any DLTs through the 110 mg/m^2 dose level. Initially, four patients were enrolled at the 85 mg/m^2 dose level since one of the patients received less than 90 % of the planned dose during the first cycle due to an infusion-related reaction and was replaced but continued to be treated. At the 132 mg/m^2 dose level, two out of two patients experienced grade 4 neutropenia that lasted for more than 3 days. Thus, the 110 mg/m^2 dose level was expanded to six; two of three patients experienced grade 4 neutropenia that lasted for more than 3 days. Therefore, the 85 mg/m^2 dose level was reassessed with three more patients, and only one patient of three experienced prolonged grade 4 neutropenia. The protocol was amended to allow hematopoietic growth factor support and dose re-escalation. An additional three patients were treated at 110 mg/m^2 with granulocyte colony-stimulating factor (G-CSF) (filgrastim or pegylated filgrastim), and none of these patients experienced grade 4 neutropenia. At this dose level, two patients experienced grade 3 fatigue beyond cycle 1. The phase I trial was concluded, and a phase II study was opened with the dose level being 110 mg/m^2 with G-CSF support, with dose reduction to 85 mg/m^2 allowed, to further explore appropriate dosing of LE-DT.

Toxicities

Besides neutropenia, additional toxicities experienced during cycle 1 included fatigue, alopecia, rash, edema, diarrhea, and dyspnea, among others, as shown in Table 3. Most of the non-hematologic toxicities experienced were grade 1. Importantly, in this pretreated population no patient experienced clinically significant neuropathy. No patient experienced grade 3 or 4 neuropathy during cycle 1 or later during treatment, even in three patients treated for 19, 20, and 30 cycles. No patient experienced clinically significant edema, nor did any experience EKG changes during infusion. Five patients experienced symptoms consistent with infusion-related hypersensitivity or pain reactions (four of grade 1 and one of grade 2). Symptoms included chills, rigors, dyspnea, chest discomfort, back pain, or nausea. These occurred during or at the end of the 1-h infusion and not always during the first cycle of LE-DT. For these patients, antihistamines, acetaminophen, meperidine, and/or a decrease

in the infusion rate by 50 % (to 2 h) resolved the symptoms during the index and future infusions.

Response

Two patients (thyroid and neuroendocrine cancer), or 8 % of study participants, had partial responses (PRs), and another patient with non-small-cell lung cancer had an unconfirmed PR. Eight patients (33 %) had prolonged stable disease (SD) lasting more than 3 months. Three patients were on study for 19, 20, and 30 cycles. The patient with thyroid cancer treated for 30 cycles, and who stopped treatment due to patient preference, has remained without radiographic evidence of disease progression off of therapy for more than 2 years.

Pharmacokinetics

Drug pharmacokinetics followed a two-compartment elimination pattern. C_{max} and AUC_{inf} were proportional to dose through the 110 mg/m^2 dose level with a mean clearance of 28.5 L/h/m^2. At the 132 mg/m^2 dose level dose clearance was 45.4 L/h/m^2. Serum half-lives at the differing dose levels ranged from 15.1 to 22.4 h. Specific PK parameters by dose level are listed in Table 4. Of note, there was no correlation between PK measures and toxicity in patients experiencing DLTs.

Discussion

Liposomes as a drug carrier can act to enhance solubility, serve as sustained release systems, provide protection from degradation, and help overcome multidrug resistance to anticancer drugs potentially mediated by P-glycoprotein and similar multi-drug resistance proteins [11]. A major advantage of liposomes is their ability to alter the PKs and distribution of the encapsulated drug. We have found that liposomes are more readily distributed to tumor tissue than to normal tissue, due to the altered endothelial integrity of tumor vasculature (unpublished data). There is some evidence that liposomal-encapsulated chemotherapy agents may cross the blood–brain barrier and be efficacious in treating metastatic brain tumors [24–26]. Thus, liposome encapsulation has been investigated as a method to improve both the delivery and safety profiles of several chemotherapeutic agents, now marketed as liposome drugs.

Liposomal doxorubicin has been investigated, both as monotherapy and in combination with other agents, for the treatment of several malignancies [27], including breast cancer [28, 29] and platinum-refractory ovarian cancer [30]. Liposomal doxorubicin (Doxil®) is currently used in the treatment for refractory ovarian cancer and AIDS-related Kaposi's sarcoma [31, 32]. Decreased incidence or severity of toxicities compared with free doxorubicin, including relative cardiotoxicity, has been reported in some studies [23, 29, 30], supporting the hypothesis of improved safety provided by liposome encapsulation of the active agent. Another approved liposomal anticancer agent, DaunoXome® (liposomal daunorubicin), is used in the treatment for AIDS-related Kaposi's sarcoma [33].

Taxane agents, including paclitaxel, docetaxel, and ixabepilone, have shown efficacy in a wide range of solid tumors including breast, prostate, head and neck, and ovarian cancers. They are administered as single agents or in combination. While docetaxel dose–response has been observed in the treatment for breast and prostate cancers, dose-limiting myelosuppression typically prohibits dosages above 75 mg/m^2. Further, the incidence of clinically significant polyneuropathy is typically proportional to duration of therapy. For example, in the pivotal prostate cancer trial, patients were limited to receiving a maximum of 10 cycles of docetaxel, in part due to cumulative toxicities including polyneuropathy [2].

In this study of LE-DT, the only DLT observed was neutropenia, which was ameliorated by the co-administration of filgrastim or pegylated filgrastim. This was observed at the 110 and 132 mg/m^2 dose levels. The relatively unpredictable incidence of significant neutropenia was not readily explained by the number of previous therapies or baseline values in our small patient cohort, although both patients who experienced dose-limiting neutropenia at 110 mg/m^2 were heavily pretreated. Past research has highlighted the possible role of pharmacogenetic variation in explaining inter-patient variability in the efficacy and toxicity of docetaxel. Sissung et al. [34] found that docetaxel-induced myelosuppression correlated with genetic diplotype variations in the gene encoding P-glycoprotein (*ABCB1* or *MDR1*). Tran et al. [35] have also found correlations with either PK or toxicity and *ABCB1* variants. Others have found correlations between docetaxel toxicity and variations in the metabolizing enzyme *CYP3A4* [35–37]. DNA was not obtained by patients during this phase I trial, so we could not explore this correlative investigation. This shortcoming highlights the need to include pharmacogenetic testing, including during phase I clinical trials [38].

In conclusion, LE-DT was well tolerated with expected toxicities of neutropenia and fatigue, but without clinically significant water retention (edema). Surprisingly, no patient experienced clinically significant neuropathy. Clinical benefit (SD + PR) was observed in 41 % of the patients treated. Based on the phase I findings, the recommended phase II dose of LE-DT is 85 mg/m^2 without granulocyte colony-stimulating factor (G-CSF) support or 110 mg/m^2 with G-CSF.

Acknowledgments

We thank the patients who participated in this trial and the study coordinators Jon Oneall, BS, nurse practitioners Gayle Jameson, Terri Stone, and Emerson Padiernos, clinical research assistants, and doctors who assisted with the research.

References

1. Nabholtz JM, Falkson C, Campos D, Szanto J, Martin M, Chan S, Pienkowski T, Zaluski J, Pinter T, Krzakowski M, Vorobiof D, Leonard R, Kennedy I, Azli N, Murawsky M, Riva A. TAX 306 Study Group. Docetaxel and doxorubicin compared with doxorubicin and cyclophosphamide as first-line chemotherapy for metastatic breast cancer: results of a randomized, multicenter, phase III trial. J Clin Oncol. 2003; 21(6):968–975. [PubMed: 12637459]
2. Tannock IF, de Wit R, Berry WR, Horti J, Pluzanska A, Chi KN, Oudard S, Théodore C, James ND, Turesson I, Rosenthal MA. TAX 327 investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. N Engl J Med. 2004; 351(15):1502–1512. [PubMed: 15470213]
3. Fossella FV, DeVore R, Kerr RN, Crawford J, Natale RR, Dunphy F, Kalman L, Miller V, Lee JS, Moore M, Gandara D, Karp D, Vokes E, Kris M, Kim Y, Gamza F, Hammershaimb L. Randomized phase III trial of docetaxel versus vinorelbine or ifosfamide in patients with advanced non-small-cell lung cancer previously treated with platinum-containing chemotherapy regimens. The TAX 320 Non-Small Cell Lung Cancer Study Group. J Clin Oncol. 2000; 18(12):2354–2362. [PubMed: 10856094]
4. Fossella F, Pereira JR, von Pawel J, Pluzanska A, Gorbounova V, Kaukel E, Mattson KV, Ramlau R, Szczesna A, Fidias P, Mill-ward M, Belani CP. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. J Clin Oncol. 2003; 21(16):3016–3024. [PubMed: 12837811]
5. Vermorken JB, Remenar E, van Herpen C, Gorlia T, Mesia R, Degardin M, Stewart JS, Jelic S, Betka J, Preiss JH, van den Weyngaert D, Awada A, Cupissol D, Kienzer HR, Rey A, Desaunois I, Bernier J. EORTC 24971/TAX 323 Study Group. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. N Engl J Med. 2007; 357(17):1695–1704. [PubMed: 17960012]

6. Posner MR, Hershock DM, Blajman CR, Mickiewicz E, Winquist E, Gorbounova V, Tjulandin S, Shin DM, Cullen K, Ervin TJ, Murphy BA, Raez LE, Cohen RB, Spaulding M, Tishler RB, Roth B, Viroglio Rdel C, Venkatesan V, Romanov I, Agarwala S, Harter KW, Dugan M, Cmelak A, Markoe AM, Read PW, Steinbrenner L, Colevas AD, Norris CM Jr, Haddad RI, TAX 324 Study Group. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. N Engl J Med. 2007; 357(17):1705–1715. [PubMed: 17960013]
7. Van Cutsem E, Moiseyenko VM, Tjulandin S, Majlis A, Constenla M, Boni C, Rodrigues A, Fodor M, Chao Y, Voznyi E, Risse ML. V325 Study Group. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. J Clin Oncol. 2006; 24(31):4991–4997. [PubMed: 17075117]
8. Taxotere package insert. http://products.sanofi-aventis.us/Taxotere/taxotere.html
9. Harvey V, Mouridsen H, Semiglazov V, Jakobsen E, Voznyi E, Robinson BA, Groult V, Murawsky M, Cold S. Phase III trial comparing three doses of docetaxel for second-line treatment of advanced breast cancer. J Clin Oncol. 2006; 24(31):4963–4970. [PubMed: 17033039]
10. van Zuylen L, Verweij J, Sparreboom A. Role of formulation vehicles in taxane pharmacology. Invest New Drugs. 2001; 19(2):125–141. [PubMed: 11392447]
11. Drummond D, Meyer O, Hong K, Kirpotin DB, Papahadjopoulos D. Optimizing liposomes for delivery of chemotherapeutic agents to solid tumors. Pharm Rev. 1999; 51(4):691–743. [PubMed: 10581328]
12. Rahman A, Husain S, Siddiqui J, Verma M, Agresti M, Center M, Safa AR, Glazer RI. Liposome-mediated modulation of multidrug resistance in human HL-60 leukemia cells. J Natl Cancer Inst. 1992; 84:1909–1915. [PubMed: 1361008]
13. Burke T, Gao X. Stabilization of topotecan in low pH liposomes composed of distearoylphosphatidylcholine. J Pharm Sci. 1994; 83:967–969. [PubMed: 7965676]
14. Daoud S, Fetouh M, Giovanella B. Antitumor effect of liposome-incorporated camptothecin in human malignant xenografts. Anticancer Drugs. 1995; 6:83–93. [PubMed: 7756688]
15. Subramanian D, Muller M. Liposomal encapsulation increases the activity of the topoisomerase I inhibitor topotecan. Oncol Res. 1995; 7:461–469. [PubMed: 8835290]
16. Sadzuka Y, Hirotsu S, Hirota S. Effect of liposomalization on the anti-tumor activity, side effects and tissue distribution of CPT-11. Cancer Lett. 1998; 127:99–106. [PubMed: 9619864]
17. Knight V, Koshkina N, Waldrep J, et al. Anticancer effect of 9-nitrocamptothecin liposome aerosol on human cancer xenografts in nude mice. Cancer Chemother Pharmacol. 1999; 44:177–186. [PubMed: 10453718]
18. Sadzuka Y. Effective prodrug liposome and conversion to active metabolite. Curr Drug Metabol. 2000; 1:31–48.
19. Tardi P, Choice E, Masin D, Redelmeier T, Bally M, Madden TD. Liposomal encapsulation of topotecan enhances anticancer efficacy in murine and human xenograft models. Cancer Res. 2000; 60:3389–3393. [PubMed: 10910044]
20. Vaughn D, Treat J, Drobins P, et al. A phase I study of a new liposome encapsulated doxorubicin (LED) formulation in advanced malignancies. Proc Am Soc Clin Oncol. 1999; 19:231a.
21. Fishman M, Strauss L, LoRusso P, et al. Phase I study of liposome encapsulated mitoxantrone (LEM) in patients with advanced cancers. Ann Oncol. 2002; 13(Suppl 5):23.
22. Fishman MN, LoRusso P, Kraut E, et al. Phase I study of liposome encapsulated SN38 (LE–SN38) in patients with advanced cancer. Proc Am Soc Clin Oncol. 2003; 22:150.
23. Treat J, Huang C, Damjanov N, et al. Phase I trial in advanced malignancies with liposome encapsulated paclitaxel (LEP). Clin Cancer Res. 2000; 6:4492s.
24. Deeken J, Loscher W. The blood–brain barrier and cancer: transporters, treatment, and Trojan horses. Clin Cancer Res. 2007; 13(6):1663–1674. [PubMed: 17363519]
25. Hau P, Fabel K, Baumgart U, Rümmele P, Grauer O, Bock A, Dietmaier C, Dietmaier W, Dietrich J, Dudel C, Hübner F, Jauch T, Drechsel E, Kleiter I, Wismeth C, Zellner A, Brawanski A, Steinbrecher A, Marienhagen J, Bogdahn U. Pegylated liposomal doxorubicin-efficacy in patients with recurrent high-grade glioma. Cancer. 2004; 100(6):1199–1207. [PubMed: 15022287]

26. Caraglia M, Addeo R, Costanzo R, Montella L, Faiola V, Marra M, Abbruzzese A, Palmieri G, Budillon A, Grillone F, Venuta S, Tagliaferri P, Del Prete S. Phase II study of temozolomide plus pegylated liposomal doxorubicin in the treatment of brain metastases from solid tumours. Cancer Chemother Pharmacol. 2006; 57(1):34–39. [PubMed: 16010592]
27. Sharpe M. Polyethylene glycol–liposomal doxorubicin: a review of its use in the management of solid and haematological malignancies and AIDS-related Kaposi's sarcoma. Drugs. 2002; 62:2089–2126. [PubMed: 12269857]
28. Park J. Liposome-based drug delivery in breast cancer treatment. Breast Cancer Res. 2002; 4:95–99. [PubMed: 12052251]
29. Schwonzen M, Kerbacher C, Mallmann P. Liposomal doxorubicin and weekly paclitaxel in the treatment of metastatic breast cancer. Anticancer Drugs. 2000; 11:681–685. [PubMed: 11129728]
30. Johnston S, Gore M. Caelyx: phase II studies in ovarian cancer. Eur J Cancer. 2001; 37(Suppl 9):S8–S14. [PubMed: 11741768]
31. Gordon AN, Fleagle JT, Guthrie D, Parkin DE, Gore ME, Lacave AJ. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. J Clin Oncol. 2001; 19(14):3312–3322. [PubMed: 11454878]
32. Stewart S, Jablonowski H, Goebel FD, Arasteh K, Spittle M, Rios A, Aboulafia D, Galleshaw J, Dezube BJ. Randomized comparative trial of pegylated liposomal doxorubicin versus bleomycin and vincristine in the treatment of AIDS-related Kaposi's sarcoma. International Pegylated Liposomal Doxorubicin Study Group. J Clin Oncol. 1998; 16(2):683–691. [PubMed: 9469358]
33. Gill PS, Wernz J, Scadden DT, Cohen P, Mukwaya GM, von Roenn JH, Jacobs M, Kempin S, Silverberg I, Gonzales G, Rarick MU, Myers AM, Shepherd F, Sawka C, Pike MC, Ross ME. Randomized phase III trial of liposomal daunorubicin versus doxorubicin, bleomycin, and vincristine in AIDS-related Kaposi's sarcoma. J Clin Oncol. 1996; 14(8):2353–2364. [PubMed: 8708728]
34. Sissung TM, Baum CE, Deeken J, Price DK, Aragon-Ching J, Steinberg SM, Dahut W, Sparreboom A, Figg WD. ABCB1 genetic variation influences the toxicity and clinical outcome of patients with androgen-independent prostate cancer treated with docetaxel. Clin Cancer Res. 2008; 14(14):4543–4549. [PubMed: 18628469]
35. Tran A, Jullien V, Alexandre J, Rey E, Rabillon F, Girre V, Dieras V, Pons G, Goldwasser F, Tréluyer JM. Pharmacokinetics and toxicity of docetaxel: role of CYP3A, MDR1, and GST polymorphisms. Clin Pharmacol Ther. 2006; 79(6):570–580. [PubMed: 16765145]
36. Shou M, Martinet M, Korzekwa KR, Krausz KW, Gonzalez FJ, Gelboin HV. Role of human cytochrome P450 3A4 and 3A5 in the metabolism of taxotere and its derivatives: enzyme specificity, interindividual distribution and metabolic contribution in human liver. Pharmacogenetics. 1998; 8:391–401. [PubMed: 9825831]
37. Bosch TM, Huitema AD, Doodeman VD, Jansen R, Witteveen E, Smit WM, et al. Pharmacogenetic screening of CYP3A and ABCB1 in relation to population pharmacokinetics of docetaxel. Clin Cancer Res. 2006; 12:5786–5793. [PubMed: 17020985]
38. Deeken JF. The Affymetrix DMET platform and pharmacogenetics in drug development. Curr Opin Mol Ther. 2009; 11:260–268. [PubMed: 19479659]

Table 1

Demographic information on patients enrolled at two sites for the phase I study of LE-DT

Parameter	Number (%)
Gender	
Male	15 (63)
Female	9 (37)
Age	
Range	43–68
Median	58
Ethnicity	
Caucasian	18 (75)
African-American	6 (25)
Prior systemic therapies	
Range	1–7
Median	2.5
Disease	
GI	14 (58)
Gastric/esophageal	4
Colon	3
Pancreatic	4
Liver	1
Other	2
Breast	2 (8)
NSCLCa	4 (17)
Other	4 (17)

Table 2

Dose level cohorts and number of patients treated at each level

Dose level	LE-DT (mg/m^2)	No. enrolled
1	50	3
2	65	3
3	85	7
4	110	6
5	132	2
4*	110 + G-CSF	3

Table 3

Incidence and grade of toxicities experienced by patients on study during cycle one of treatment with LE-DT

Toxicity	Any grade, *N* (%)	Grade ¾, *N* (%)
Hematologic		
Neutropenia	10 (42 %)	9 (38 %)
Anemia	4 (17)	
Constitutional		
Fatigue	5 (21)	
Pain	6 (25)	1 (4)
Edema	2 (8)	
Gastrointestinal		
Diarrhea	6 (25)	
Nausea	3 (13)	
Constipation	3 (13)	
Neurological		
Neuropathy	1 (4)	
Pulmonary		
Dyspnea	3 (13)	
Rash	3 (13)	
Infusion reaction	6 (25)	
Alopecia	5 (21)	

Table 4

Pharmacokinetics of liposomal-encapsulated docetaxel

LE-DT dose (mg/m^2)	Number of patients (*n*)	$T_{1/2}$(h)	C_{max} (1 × 10^3 μg/mL)	AUC_{inf} (1 × 10^3 μg h/mL)	CL (L/h/kg)	V_{ss} (L/m^2)
50	3	15.1	1.229	1.688	29.6	786.9
65	3	15.9	2.280	2.295	28.3	867.4
85	3	22.4	3.303	2.837	30.0	556.5
110	5	16.0	5.915	4.225	26.0	338.6
132	2	21.5	7.997	2.906	45.4	766.0

$T_{1/2}$ half-life, *C_{max}* maximum serum concentration, *AUC* area under the concentration curve, *CL* clearance, *V_{ss}* volume at steady state