Paclitaxel poliglumex (XYOTAX; CT-2103): an intracellularly targeted taxane

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Paclitaxel poliglumex (CT-2103; XYOTAX) is an innovative macromolecular taxane designed to increase the therapeutic index of paclitaxel. This large macromolecule conjugate of paclitaxel and poly-L-glutamic acid accumulates in tumor tissues by taking advantage of the enhanced permeability of tumor vasculature and lack of lymphatic drainage. Paclitaxel poliglumex prolongs exposure to active drug and minimizes systemic exposure. Preclinical studies in animal tumor models demonstrate enhanced safety and efficacy relative to paclitaxel when administered as a single agent or in conjunction with radiation. Clinical pilot studies with paclitaxel poliglumex showed improved outcomes compared to standard taxanes and allowed a more convenient administration schedule. Human pharmacokinetic data are consistent with prolonged tumor exposure to active drug and a limited systemic exposure. Based on these results, three ongoing randomized phase III trials were initiated to test the efficacy of paclitaxel poliglumex in patients with advanced non-small cell lung carcinoma. *Anti-Cancer Drugs* 16:243–254 © 2005 Lippincott Williams & Wilkins.

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Introduction

Several important issues limit the efficacy and tolerability of cytotoxic antitumor drugs. First, many of these drugs are relatively hydrophobic and require the use of toxic solubilizing agents, such as Cremophor EL/ethanol, for administration. Second, because of the high volumes of distribution and little selectivity for tumor tissues, only a small proportion of the dose administered actually localizes in tumor tissue. Third, elimination kinetics may necessitate inconvenient dosing schedules to realize optimal efficacy. Lastly, because many cytotoxic drugs are substrates for efflux pumps such as P-glycoprotein, multidrug resistance (MDR) may affect efficacy.

Paclitaxel, one of the most widely used and clinically active cytotoxic agents, is illustrative for all of these issues. Paclitaxel requires Cremophor and ethanol as a vehicle, it is infused over 3–24 h, and it has no preferential tumor localization. Some of the toxicities of paclitaxel are related to the value of its maximum plasma concentration (C_{max}), but its efficacy is related mainly to the value of its area under the plasma concentration–time curve (AUC) [1]. Paclitaxel is also eliminated by cells that express MDR efflux pumps [2].

A number of approaches have been used to increase the therapeutic index of cytotoxic drugs. For example, the liposomal encapsulation of doxorubicin resulted in altered biodistribution [3,4]. Because of difficulty in creating stable liposomes, this approach has been less successful with highly hydrophobic molecules such as taxanes. An alternative method is the covalent linkage of active drugs to macromolecule polymers.

Advantages of polymer–drug conjugates over standard preparations

The characteristics of paclitaxel and the polymer-conjugated form of paclitaxel, paclitaxel poliglumex, are compared in Table 1. This comparison illustrates the potential advantages of polymer–drug conjugates over standard preparations:

(i) Polymer–drug conjugates specifically accumulate in tumor rather than in normal tissue. Because of abnormal cytokine activity and structural differences between the neovasculature in tumors and the mature vasculature in normal organs, tumor vasculature is more permeable to macromolecules than normal vasculature is [5–7]. As a result, polymer–drug conjugates with a high molecular weight preferentially distribute to extravascular tumor tissues. This effect, known as enhanced permeability and retention (EPR) in tumors, can increase the amount of a cytotoxic drug that reaches tumor tissue 10- to 100-fold [5,7]. The EPR effect is molecular weight and size dependent, and is most

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Table 1 Characteristics of paclitaxel and paclitaxel poliglumex

Characteristic	Paclitaxel	Paclitaxel poliglumex
Enhanced uptake in tumor	no	increased through enhanced permeability and retention
Effectiveness in MDR tumors	limited	increased, owing to endocytosis and cleavage at a distal site
High plasma levels of active drug and thus toxicity	yes	no, the conjugated drug is inactive
Poor pharmacokinetic profile	yes, high volume of distribution, short distribution and elimination phases	no, smaller volume of distribution, longer distribution and elimination phases
Poor solubility	yes, requires toxic solubilizing agents and routine premedications	no

effective with agents with molecular weights of 50 000 or greater, which is well above the threshold for renal excretion [5,8]. Therefore, only biodegradable polymers such as poly-amino acids (e.g. poly-L-glutamic acid) or multimeric complexes such as dendrimers that use non-degradable polymers can be used to exploit the EPR effect.

(ii) Polymeric drugs can bypass MDR membrane efflux pumps through active uptake into tumor cells by endocytosis [9]. Optimally designed polymeric conjugates are taken up by tumor cells and are transported to lysosomes where they are metabolized to release free active drug [10]. Therefore, polymer-conjugated drugs are active in tumor cells that would normally be resistant because of high efflux pump activity.

(iii) The slow release of active drug from the polymer carrier results in lower peak plasma concentrations of the active drug [8,11]. Ideally, the polymer conjugate releases the active drug in tumor tissue rather than in the plasma during circulation. As a result, exposure of normal tissues will be limited, which is potentially associated with a more favorable toxicity profile.

(iv) Polymeric conjugation improves the pharmacokinetic profiles of cytotoxic drugs by decreasing the volume of distribution and prolonging the distribution and elimination phases [12,13]. Because of their lipophilicity, many cancer drugs have a large volume of distribution and a short distribution phase. Sustained tumor exposure is therefore dependent on continuous infusion. In contrast, macromolecular drug conjugates allow for the prolonged exposure of tumor cells with intermittent short infusions.

(v) Polymeric conjugation renders hydrophobic agents water-soluble and eliminates the need for toxic solubilizing agents [12].

Paclitaxel poliglumex: rationale and characteristics

Paclitaxel binds to the N-terminal 31 amino acids of the β-tubulin subunit, shifts the equilibrium toward polymerization and prevents depolymerization [14]. In addition to disruption of cytoskeletal microtubules, this activity prevents depolymerization of the mitotic spindle, resulting in aberrant cytokinesis during cell division, triggering mitotic arrest and apoptosis [15]. Both the antitumor efficacy and the systemic toxicity of paclitaxel are related to the length of time that sensitive tissues are exposed to a biologically relevant concentration of the agent. Resistance can be mediated by structural alterations in β-tubulin or greater expression of MDR-associated efflux pumps such as P-glycoprotein [16].

Paclitaxel for injection is supplied in 50% Cremophor EL and 50% dehydrated ethanol. Following dilution to a concentration of approximately 1 mg/ml, it is administered i.v. over a 3- to 24-h period. To prevent hypersensitivity reactions, premedications include two doses of dexamethasone (20 mg), diphenhydramine (50 mg) and cimetidine (300 mg or the equivalent). Even with these premedications, infusion-related and allergic reactions are not uncommon [17]. Furthermore, because Cremophor EL causes phthalate to leach from conventional plastics, only glass or polyolefin containers and nitroglycerin tubing (polyethylene lined) are recommended for the administration of paclitaxel [16].

Paclitaxel has a volume of distribution much greater than that of total human body water and binds extensively to plasma proteins [1]. It has a plasma terminal elimination half-life $t_{1/2\alpha}$ of 0.34 h and $t_{1/2\beta}$ of 5.8 h, with broad tissue distribution [13]. Its elimination is predominantly through hepatic metabolism [18]. In humans, 20% of the dose is eliminated in the bile within 24 h [1]. This pharmacokinetic profile makes it difficult to sustain tumor exposure to paclitaxel over several days without continuous infusion.

Paclitaxel poliglumex was designed to enhance the efficacy and safety of paclitaxel through conjugation to a biodegradable polymer, poly-L-glutamic acid. Poly-L-glutamic acid, a highly charged polyanionic peptide, was chosen as the polymer backbone because it is biodegradable and makes molecular weight optimization based on efficacy possible. Unlike non-degradable polymers, it is not excreted by the kidney because it is broken down to glutamic acid. Poly-L-glutamic acid is highly water soluble, even with a paclitaxel content of up to 40% on a w/w basis. Paclitaxel is conjugated by ester linkage to the γ-carboxylic acid side-chains, resulting in a relatively stable conjugate. Because the conjugation site is through the 2′-hydroxyl of paclitaxel, a site crucial for tubulin binding, the paclitaxel conjugate does not interact with

β-tubulin and thus is not active in this respect until the paclitaxel is released [13,19].

Paclitaxel poliglumex was found to have a volume of distribution approximately equal to that of the total blood volume, with a distribution $t_{1/2}$ of 7–10 h and an elimination $t_{1/2}$ of 10–17 days, depending on the animal species. Preclinical studies in tumor-bearing mice found that its accumulation in tumor tissue was at least 12 times that with the same dose of paclitaxel administered in Cremophor EL [20]. In normal tissues, paclitaxel poliglumex was concentrated in the liver, spleen, and, to a lesser extent, lung and kidney, suggesting active uptake by cells of the reticuloendothelial system (RES) [20]. The proposed mechanism by which paclitaxel poliglumex is metabolized includes endocytosis of the polymer conjugate followed by intracellular release of active paclitaxel by lysosomal enzymes (e.g. cathepsin B). *In vivo* metabolites that have been detected include diglutamyl-paclitaxel and monoglutamyl-paclitaxel. Monoglutamyl-2′-paclitaxel is an unstable compound that can non-enzymatically degrade to release free paclitaxel (Shaffer, manuscript in preparation). As has been previously demonstrated with doxorubicin conjugates, paclitaxel poliglumex had *in vivo* activity in relatively paclitaxel-insensitive human tumors that constitutively express high levels of P-glycoprotein. [21] In preclinical studies, paclitaxel poliglumex was non-immunogenic in guinea pigs and rabbits.

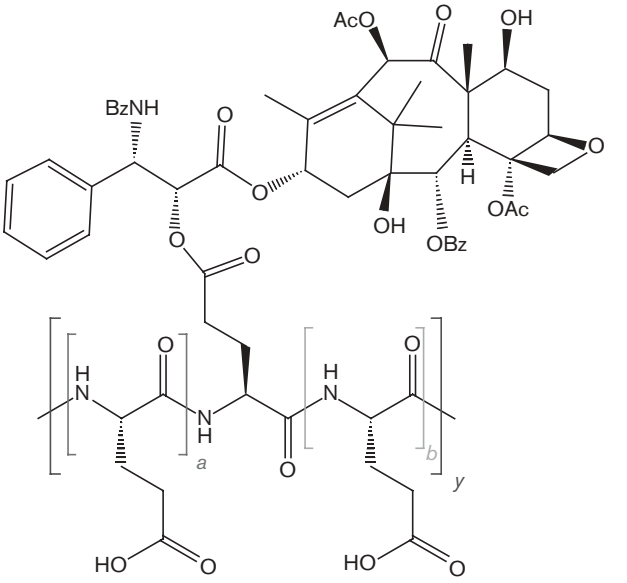
In summary, paclitaxel poliglumex is a macromolecular paclitaxel conjugate that offers the following advantages over conventional paclitaxel:

- Greater efficacy as a result of increasing the effective concentration and the duration of paclitaxel in tumor tissue.
- Greater efficacy in tumors that express MDR efflux pumps [21].
- Elimination of the need for routine premedications because of minimal hypersensitivity reactions.
- An improved safety profile over conventional paclitaxel by decreasing exposure of normal organs to peak concentrations of free paclitaxel.

Chemistry and physicochemical characterization

Paclitaxel poliglumex is formed by an ester linkage between the γ-carboxylic acid moiety of glutamic acid and the paclitaxel 2′-hydroxyl group. The median molecular weight of paclitaxel poliglumex is approximately 48 000 Da, measured by gel-permeation chromatography. Conjugated paclitaxel represents approximately 37%, by weight, of the conjugate, equivalent to about one paclitaxel ester linkage per 11 glutamic acid residues of the polymer [12]. A representative schematic of the chemical structure of paclitaxel poliglumex is depicted in Figure 1.

Fig. 1



Schematic representation of paclitaxel poliglumex. The structure shown is illustrative of a fragment of the molecule, but specific conjugation sites are not implied. On average there are approximately 10.4 non-conjugated monomer glutamic acid units ($a + b$) for every molecule conjugated to a paclitaxel molecule (y). The α-poly-L-glutamic degree of polymerization and the number of conjugation sites with paclitaxel are variable within the drug substance's specifications.

The polymeric nature of paclitaxel poliglumex was evaluated by using gel-permeation chromatography, a widely used method for characterizing polymeric moieties [22]. When combined with multiple angle laser-light scattering detection (i.e. GPC-MALLS), the elution profile provides information on the molecular weight and polydispersity. Nuclear magnetic spectroscopy confirmed the conjugation of paclitaxel to the γ and α positions of polyglutamate. Spectral changes were consistent with conjugation through the paclitaxel 2′ position with additional minor amounts of conjugation in the 7 position. The distribution of paclitaxel on the polyglutamate backbone was studied through limited proteolysis of paclitaxel poliglumex with various proteases. The resulting peptide mixtures were analyzed by reverse-phase HPLC and mass spectrometry. The peptide species detected were in good agreement with a distribution of paclitaxel that would be expected if the conjugation occurred in a non-directed fashion [12].

Preclinical studies

Metabolism of paclitaxel poliglumex

The metabolism of conjugated paclitaxel and release of paclitaxel from paclitaxel poliglumex have been

investigated in both *in vitro* and *in vivo* models. Paclitaxel poliglumex releases active paclitaxel by at least two mechanisms: (i) slow non-enzymatic hydrolysis of the ester linkage and (ii) intracellular proteolysis of the polyglutamic acid backbone through the action of lysosomal proteases such as cathepsin B followed by hydrolysis of the paclitaxel γ-carboxylate ester linkage ([12] and Shaffer, manuscript in preparation).

Non-enzymatic hydrolysis

The rate of release of paclitaxel from paclitaxel poliglumex by hydrolysis in buffered saline solution and in mouse or human plasma was evaluated. Incubation of paclitaxel poliglumex in buffered saline or plasma for 24 h at 37°C showed that less than 14% of the bound paclitaxel had been released. This indicates that paclitaxel poliglumex is relatively resistant to plasma esterases and is unlikely to release substantial amounts of paclitaxel in the circulation, even with prolonged clearance times.

Cellular metabolism

Ongoing studies suggest that the intracellular metabolites of paclitaxel poliglumex include monoglutamyl-2′-paclitaxel and diglutamyl-2′-paclitaxel as the major species. This observation is consistent with proteolysis of the polyglutamate backbone through the action of cellular dipeptidases. Subsequent hydrolysis of monoglutamyl-2′-paclitaxel putatively results in the release of paclitaxel. Specific enzyme inhibitors such as CA-074 methyl ester, a cell-permeable irreversible inhibitor of cathepsin B, and EST, a cell-permeable irreversible inhibitor of cysteine proteases, dramatically decreased the formation of monoglutamate paclitaxel and unconjugated paclitaxel in tumor cell lines that had been incubated with paclitaxel poliglumex. The metabolism of paclitaxel poliglumex in non-tumor-bearing cathepsin B homozygous knockout mice is reduced, but not eliminated, indicating that alternative pathways for the proteolysis of paclitaxel poliglumex exist (Shaffer, manuscript in preparation).

Plasma and tissue pharmacokinetics

To determine the pharmacokinetic profile of paclitaxel poliglumex and its tissue distribution, female mice with subcutaneous B16 murine melanomas were given equivalent doses of tritium-labeled paclitaxel 40 mg/kg i.v., either as [^{3}H]paclitaxel in Cremophor EL/ethanol or as [^{3}H]paclitaxel poliglumex in phosphate buffer. Samples were collected from 0 to 144 h after the injection and analyzed by scintillation counting for total taxane concentrations. After ethyl acetate extraction, the concentrations of extractable taxanes, including paclitaxel and its metabolites, were determined both by scintillation counting and by HPLC/radiometric analysis [12].

The total taxane C_{max} and AUC values were markedly higher in animals given [^{3}H]paclitaxel poliglumex than in those given [^{3}H]paclitaxel. The plasma terminal elimination $t_{1/2}$ values for total taxanes were 60.1 h with [^{3}H]paclitaxel poliglumex and 34.6 h with [^{3}H]paclitaxel. The plasma AUC and C_{max} values for total taxanes, extractable taxanes and paclitaxel after the administration of [^{3}H]paclitaxel poliglumex indicated that it had a prolonged circulation in the plasma and negligible release of the active agent, paclitaxel (less than 1% of the total radioactivity). This prolonged circulation allowed for higher concentrations of the drug-conjugate to accumulate in the tumor vasculature (Table 2).

Tumor exposure to total taxanes was greater in animals treated with [^{3}H]paclitaxel poliglumex than in those treated with [^{3}H]paclitaxel, 170% by C_{max} and approximately 1100% by AUC. The distribution of paclitaxel to tumor tissue was more rapid with [^{3}H]paclitaxel, but overall tumor exposure to extractable taxanes was 97% greater with [^{3}H]paclitaxel poliglumex (Table 2 and Fig. 2). The tumor concentration of total taxane and paclitaxel was 32% greater at 144 h after the administration of [^{3}H]paclitaxel poliglumex than it was at 24 h after the administration of [^{3}H]paclitaxel.

In summary, the administration of paclitaxel poliglumex resulted in altered pharmacokinetics, with reduced systemic exposure to free paclitaxel, a prolonged plasma distribution $t_{1/2}$ and greater distribution to tumor tissue.

Elimination

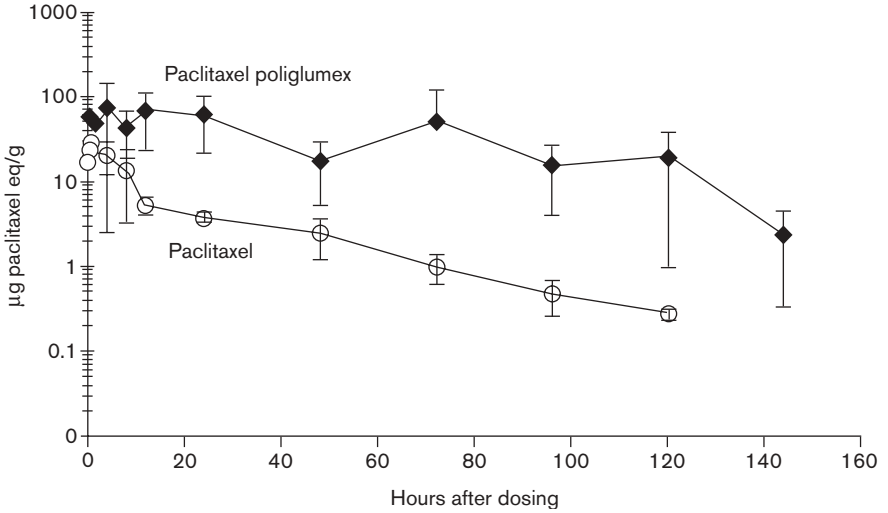
Paclitaxel poliglumex appears to be cleared from the plasma mainly by tissues that comprise the RES. Consistent with this observation, pharmacokinetic analysis of RES tissues, including those of the liver and spleen, found greater exposure to paclitaxel and its metabolites after dosing with [^{3}H]paclitaxel poliglumex than with [^{3}H]paclitaxel in mice. Uptake of [^{3}H]paclitaxel poliglumex in the liver and spleen was followed by the slow release of paclitaxel and its metabolites [12,20].

In rats, the major route of elimination of [^{14}C]paclitaxel poliglumex was by hepatic clearance and biliary excretion;

Table 2 Plasma and tumor pharmacokinetics of paclitaxel poliglumex and paclitaxel in mice [36]

	Plasma		Tumor	
	C_{max} (μg/ml)	AUC_{0-last} (μg/ml·h)	C_{max} (μg/ml)	AUC_{0-last} (μg/g·h)
Paclitaxel poliglumex				
total taxanes	1081	4533	72	4547
extractable taxanes	2.1	18.1	8.3	611
free paclitaxel	1.6	5.4	4.0	345
Paclitaxel				
total taxanes	418	374	27	384
extractable taxanes	424	297	25	310
free paclitaxel	421	271	22	261

Fig. 2



Tumor concentration of [^{3}H]paclitaxel after treatment with [^{3}H]paclitaxel poliglumex and [^{3}H]free paclitaxel in female mice with s.c. B16 melanomas. Animals were administered [^{3}H]paclitaxel 40 mg and the dose equivalent for [^{3}H]paclitaxel poliglumex [12].

urinary excretion was a minor route of elimination (Baker, unpublished observations). The elimination of radioactivity was prolonged in these rats, as was reflected by the relatively long tissue $t_{1/2}$ values of up to 21.9 days in the liver and 25.7 days in the spleen.

Preclinical efficacy studies

The activities of paclitaxel poliglumex and paclitaxel were compared in a variety of syngeneic and xenogeneic tumor models, in both single-dose and multidose studies [21,23]. The maximum tolerated dose (MTD) of paclitaxel poliglumex was approximately 160–200 mg/kg in immunocompetent (e.g. B16 and LL/2) mice and 120–150 mg/kg in immunodeficient (HCT-15, LoVo, COLO320DM, HT-29 and HCT116) animals, depending on their sex and weight [24]. The MTD was defined as the dose at which no more than 10% of the animals died and their weight loss at 15 days after the last dose of the agent did not exceed 20% of their pretreatment weight. At the MTD, single-dose paclitaxel poliglumex was more efficacious than paclitaxel in Cremophor EL/ethanol.

In vivo *studies of paclitaxel poliglumex in combination with other anticancer drugs*

The therapeutic potential of combination therapy with paclitaxel poliglumex was evaluated in a syngeneic tumor model in a two-stage series of experiments. The first set of experiments determined the optimal dose of the standard agent, either gemcitabine, doxorubicin irinotecan or carboplatin, in combination with a fixed dose of paclitaxel poliglumex (20% of MTD, 29.5 mg/kg conjugated paclitaxel). The test drug was given 4 h after the paclitaxel poliglumex. In the second stage, the optimal dose of carboplatin (80 mg/kg) was used to determine the optimal sequence and timing of the administration of paclitaxel poliglumex and carboplatin. Paclitaxel poliglumex, when administered in combination with carboplatin, doxorubicin, gemcitabine or irinotecan, had a synergistic, non-schedule-dependent antitumor effect in these studies. For example, the effect was observed when paclitaxel poliglumex was administered before or after carboplatin (Fig. 3). Similar experiments showed that paclitaxel poliglumex was synergistic when it was administered with gemcitabine, doxorubicin or irinotecan, in a schedule-independent manner (de Vries, unpublished observations).

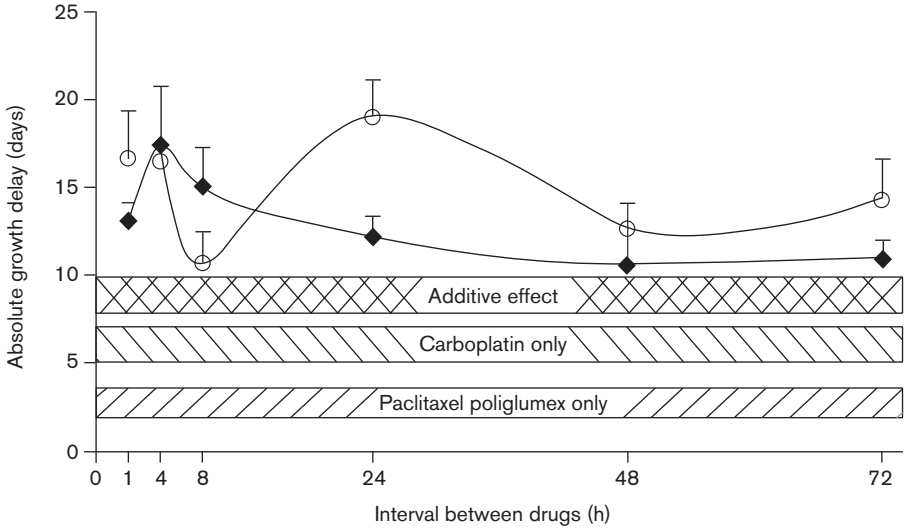
In vivo *studies in combination with irradiation*

Paclitaxel poliglumex also had schedule-independent synergy with therapeutic radiation (both single-dose and fractionated), with an extremely high enhancement factor of approximately 8 (Fig. 4). Unlike paclitaxel or docetaxel, paclitaxel poliglumex did not sensitize normal skin or gut tissue to radiation [25]. These striking findings are currently being explored in phase I–II clinical trials.

Clinical development program

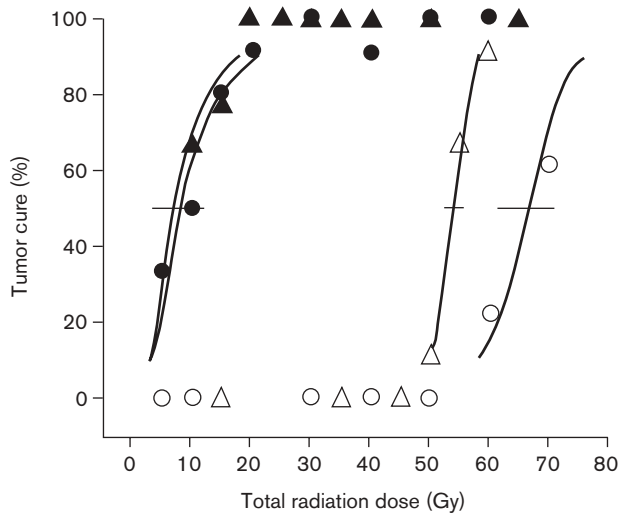
Preliminary data on the efficacy of paclitaxel poliglumex in phase I and II clinical trials are shown in Table 3. Major responses have been observed in a variety of solid tumors, including gastric cancer, mesothelioma, schwannoma, non-small cell lung cancer (NSCLC), ovarian cancer and breast cancer. Clinical activity has also been observed in additional tumor types, including thyroid, colorectal and endometrial cancer.

Fig. 3



Combination treatment with paclitaxel poliglumex is synergistic before or after carboplatin. Four-month-old female C3Hf/KAM mice were inoculated with 5×10^5 viable OCa-I tumor cells s.c. in the right leg. Treatment was initiated when the tumor diameter had reached 8 mm. Mice were treated with 80 mg/kg paclitaxel poliglumex followed by 80 mg/kg carboplatin at the indicated timepoints (circles) or mice were treated with 80 mg/kg carboplatin followed by 80 mg/kg paclitaxel poliglumex at the indicated timepoints (diamonds). Tumor growth delay was defined as the time in days for the tumors to grow from 8 to 12 mm in diameter minus the time in days for the untreated group to reach the same size.

Fig. 4



Effect of paclitaxel poliglumex on radiocurability of OCa-I tumors after single-dose or fractionated radiation [25]. Mice bearing 7-mm hind leg tumors were given 80 mg/kg paclitaxel poliglumex and/or local tumor irradiation with graded doses delivered as single dose or daily fractions for 5 consecutive days. When the two agents were combined, paclitaxel poliglumex was given 24 h before the start of irradiation. Radiation dose–response curves were generated for local tumor control at 120 days after treatment with single-dose irradiation alone. Open triangles = single-dose radiation alone; open circles = daily fractionated radiation alone; solid triangles = paclitaxel poliglumex 24 h before fractionated radiation; solid circles = paclitaxel poliglumex 24 h before single-dose radiation

Safety

More than 400 patients have been treated with paclitaxel poliglumex in phase I and II studies. Most of the reported serious adverse events were disease related. The most frequently reported (more than 20%) drug-related adverse events were fatigue, uncomplicated neutropenia, peripheral neuropathy, nausea and vomiting. Neuropathy appears to be cumulative and dose limiting, particularly in heavily pretreated patients. Prior treatment with a taxane and the number of treatment cycles were associated with a greater risk of neuropathy. Neuropathy was more common in the studies in breast and ovarian cancer than in the other phase I and II studies, and appears to be related to prior exposure to neurotoxic agents [26]. Drug-related events that were reported in 10–20% of patients were thrombocytopenia, diarrhea, leukopenia, myalgia, arthralgia and anemia [27].

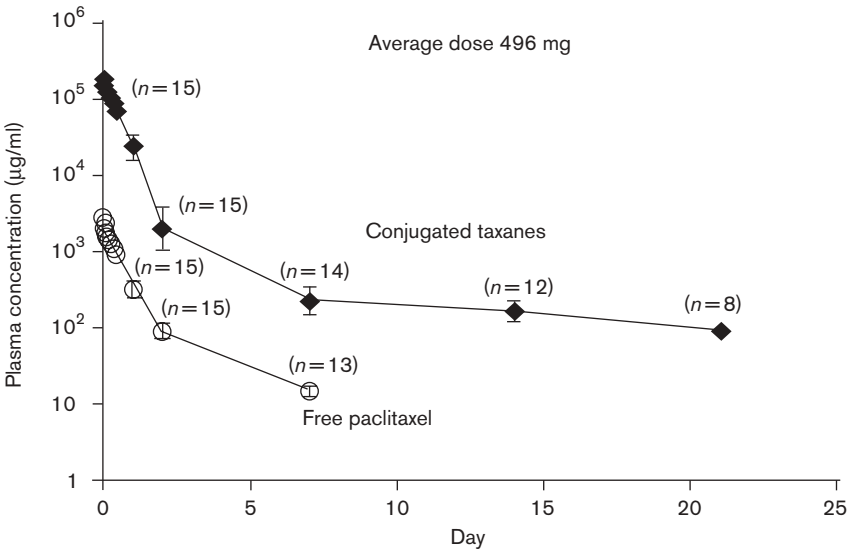
Paclitaxel poliglumex showed some notable advantages over conventional paclitaxel in these studies. First, alopecia was rare and no complete hair loss has been observed. Second, nausea and vomiting were uncommon, and routine premedications were not required. Third, hypersensitivity reactions were rarely observed and were usually mild to moderate; therefore, patients were not given routine prophylactic premedications. The incidence of significant hypersensitivity reactions was less than 1% with no grade 4 hypersensitivity, despite the fact that a high percentage of patients had been treated with

Table 3 Preliminary data on the efficacy of paclitaxel poliglumex in phase I and II studies

Study description/paclitaxel poliglumex dose (*n*)	No. of patients			
	Partial response	Stable disease	Progressive disease	NA[a]
CTI-1052a: phase I, single agent [37]				
$\leq$ 178 mg/m^2 (6)	1	1	3	1
233 mg/m^2 (7)	0	4	0	3
266 mg/m^2 (6)	0	3	1	2
CTI-1052b: phase I, single agent, ascending dose [37]				
175/177 mg/m^2 (7)	1	0	4	1
210 mg/m^2 (4)	0	2	1	2
CTI-1055: phase I, combination with cisplatin 75 mg/m^2 [23]				
175 mg/m^2 (3)	1	2	0	0
210 mg/m^2 (6)	1	3	2	0
225 mg/m^2 (7)	2	3	2	0
250 mg/m^2 (6)	0	2	4	0
270 mg/m^2 (3)	0	0	3	0
CTI-1072: phase I, combination with carboplatin [AUC, mg/ml·min]				
175 mg/m^2 [AUC=5] (3)	0	3	0	0
210 mg/m^2 [AUC=5] (?)	1	2	0	0
210 mg/m^2 [AUC=6] (7)	0	3	4	0
225 mg/m^2 [AUC=6] (6)	2	2	2	0
250 mg/m^2 [AUC=6] (3)	0	2	1	0
PGT105: phase I, single agent, NSCLC [38]				
235 mg/m^2 (6)	0	0	6	0
270 mg/m^2 (6)	1	2	3	0
CTI-1067: phase II, single agent, resistant colorectal cancer [39]				
210 mg/m^2 (60)	0	17	41	2
CTI-1065: phase II, single agent, breast cancer [40]				
235 mg/m^2 (26)	4	6	4	10

All studies used q^{3}w dosing except for CTI-1052b, which used q^{2}w dosing. All studies are complete except for PGT105, which is ongoing.
[a]Study ongoing, data not yet available or too early to evaluate.

Fig. 5



Plasma pharmacokinetics of paclitaxel poliglumex and free paclitaxel in patients. Data are from four phase I dose-escalation studies with 1-, 2- and 3-week schedules. In all studies, paclitaxel poliglumex was administered as a short (10–20 min) i.v. infusion.

prior paclitaxel therapy. In contrast, between 2 and 4% of prophylactively premedicated patients treated with paclitaxel or docetaxel experience hypersensitivity reactions, which includes grade 4 reactions [28]. Finally, although neutropenia did occur, especially with higher doses, severe neutropenia appeared to be less common than with either standard paclitaxel or docetaxel.

Human pharmacokinetic studies

Paclitaxel poliglumex

In general, the plasma concentrations of paclitaxel poliglumex decline biphasically (Fig. 5). The distribution phase is prolonged and the apparent monoexponential terminal phase that is associated with drug elimination appears approximately 48 h after the administration of the

drug. The decline in the plasma concentration of paclitaxel poliglumex in the terminal phase is slow and, at doses of 200 mg/m^2 or higher, the drug can still be detected in the plasma 3 weeks after its administration [29].

In one study, the dose of paclitaxel poliglumex given once every 3 weeks was escalated from 11 to 266 mg/m^2, and its C_{max} and AUC values increased proportionally with the dose. Systemic clearance ranged from 112 to 310 ml/h/m^2 and was usually lower than the liver plasma flow (about 25 ml/h/m^2). This indicates that the liver has low elimination efficiency for paclitaxel poliglumex, and supports the observation of prolonged drug permanence in the systemic circulation with polymeric backbone degradation and paclitaxel release in peripheral tissue compartments. The volume of distribution at steady state is low, ranging from 1.3 to 5.9 l/m^2, suggesting that the distribution of paclitaxel poliglumex is restricted mainly to the plasma and other extracellular body fluids [29].

Free paclitaxel

Free paclitaxel is progressively released from paclitaxel poliglumex and its plasma concentration declines over time in a biexponential fashion in parallel to the parent drug (paclitaxel poliglumex) concentrations (Fig. 5). This suggests that the disposition of free paclitaxel may be formation rate limited, i.e. its distribution and elimination depend on the release of paclitaxel from the polymer backbone. The pharmacokinetics of free paclitaxel are summarized in Table 4. The AUC of free paclitaxel is approximately 1–2% of the AUC of paclitaxel poliglumex. This observation supports the *in vivo* stability of paclitaxel poliglumex in the plasma and the slow, prolonged release of the active moiety from tissue stores. The concentrations of free paclitaxel are proportional to those of the parent drug.

Repeated-dose administration

After repeated administration of paclitaxel poliglumex once every 3 weeks there was no significant accumulation of paclitaxel poliglumex and free paclitaxel in the plasma. The plasma concentrations of paclitaxel poliglumex in cycles 1 and 2 in patients treated with 235 and 270 mg/m^2 paclitaxel poliglumex are shown in Figure 6. The values were similar in both cycles.

Single-agent and combination phase I studies

The initial phase I clinical study (CTI-1052a), sponsored by the Cancer Research Campaign in the UK (now Cancer Research UK), completed enrollment in August 2001. The primary objectives of this study were to determine the pharmacokinetics, safety and MTD of paclitaxel poliglumex administered every 3 weeks, and to propose a suitable dose for further evaluation in phase II studies. A secondary objective was to determine its antitumor effects in taxane-naive patients [30].

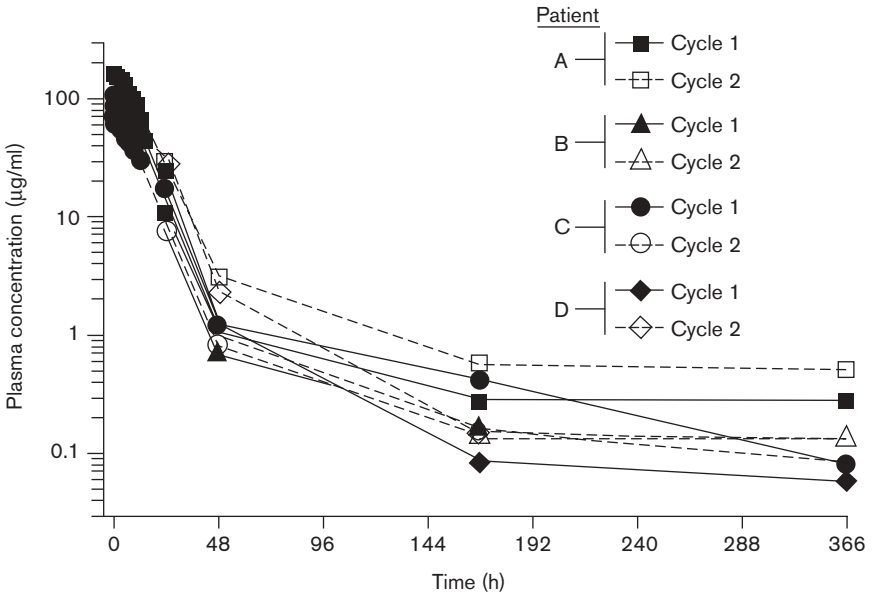
Nineteen patients were treated in study CTI-1052a. The MTD with every-3-weeks dosing in this heavily pretreated population was 233 mg/m^2. The dose-limiting toxicity was grade 4 neutropenia. This dose was generally well tolerated. One patient with a mesothelioma had a partial response (PR) and eight patients had stable disease (SD). A subsequent study (PGT101) in the USA confirmed an MTD of 235 mg/m^2. A follow-on phase I study (CTI-1052b) treated 11 patients with paclitaxel poliglumex once every 2 weeks. The MTD in these heavily pretreated patients was 175 mg/m^2; dose-limiting toxicities were neutropenia and neuropathy. One patient with a gastric cancer had a PR and two patients had SD. Because of the long tissue $t_{1/2}$ in the preclinical studies, the approximately 10-day $t_{1/2}$ in humans and the toxicity of an every-2-weeks regimen, all subsequent efficacy trials used a 3-week schedule.

Studies were then conducted to determine the MTD of paclitaxel poliglumex in combination with cisplatin or carboplatin. Paclitaxel poliglumex was given as a 10-min i.v. infusion and was followed by cisplatin (fixed dose of 75 mg/m^2) (CTI-1055) [31,32] or carboplatin AUC 5 or

Table 4 Pharmacokinetics of paclitaxel poliglumex in human plasma

Study	Dose [mg/m^2 (*n*)]	Mean (SD)		
		C_{max} (μg/ml)	$t_{1/2}$ (h)	AUC (μg/ml·h)
CTI 1052a				
paclitaxel poliglumex	233 (6)	117.7 (21.2)	119.6 (27.7)	1583 (572)
	266 (6)	173.0 (79.2)	119.3 (15.4)	1986 (1078)
free paclitaxel	233 (6)	1.6 (0.8)	42.8 (37.2)	27.8 (14.3)
	266 (6)	1.7 (0.7)	28.8 (22.6)	25.0 (7.5)
PGT101				
paclitaxel poliglumex	235 (3)	115.8 (32.1)	141.9 (68.2)	1827.7 (759.6)
	270 (2)	144.0 (24.0)	108.0 (58.2)	2328.3 (328.4)
free paclitaxel	235 (3)	1.15 (0.36)	9.9 (3.4)	20.1 (6.9)
	270 (2)	1.52 (0.06)	24.5 (18.2)	25.1 (0.7)
PGT105				
paclitaxel poliglumex	235 (6)	131.0 (45.9)	105.5 (79.2)	2101 (1557)
	270 (6)	158.2 (25.6)	112.0 (40.1)	2388 (920)
free paclitaxel	235 (6)	3.1 (2.6)	33.7 (22.4)	30.6 (21.9)
	270 (6)	2.0 (0.8)	32.7 (13.7)	31.5 (1.7)

Fig. 6



Comparison of the temporal profiles of plasma concentrations of paclitaxel poliglumex in four patients receiving 270 mg/m^2 (A) and 235 mg/m^2 (B–D) in cycles 1 and 2 of a q3w regimen.

6 mg/ml·min (CTI-1072) [33,34]. Twenty-five patients were treated in the cisplatin study with doses of paclitaxel poliglumex of 175–270 mg/m^2. No MTD was established, but there was one dose-limiting toxicity at the 270 mg/m^2 dose. A dose of 210 mg/m^2 was chosen for future studies. These studies resulted in PRs in five of the 22 patients with response data available and SD in 10 of them. In study CTI-1072, with carboplatin and paclitaxel poliglumex, 22 patients were treated with doses of paclitaxel poliglumex of up to 250 mg/m^2 and carboplatin AUC 6. The MTD was determined to be 225 mg/m^2. The dose-limiting toxicities were neutropenia and thrombocytopenia. Three patients with recurrent ovarian cancer had PRs that lasted 10+, 25.5+ and 15+ months, and 12 patients had SD for at least three treatment cycles.

Phase II studies

Phase II studies have been completed in patients with relapsed or refractory ovarian cancer, in patients with relapsed or refractory colorectal cancer and in previously untreated high-risk patients with NSCLC.

Study CTI-1071 was an open-label multicenter study to determine the response rate and time to disease progression in a heterogeneous population of patients with advanced epithelial ovarian cancer. Paclitaxel poliglumex was given to 99 patients at a dose of 175 mg/m^2 every 3 weeks. Toxicities were mild in this heavily pretreated population, with no severe alopecia, 10 grade 3 and four grade 4 neutropenias, and 15 grade 3 neuropathies. The evaluation of efficacy (Table 5) in patients who had been treated with one or two prior chemotherapy regimens and who had cisplatin-sensitive disease showed responses in five (28%) of 18 patients and SD in six (33%). Pretreated patients that are platinum resistant are very difficult to treat, yet responses were seen in two (10%) of 21 patients and SD in four (19%) [26].

The multicenter open-label CTI-1069 study evaluated the efficacy and tolerability of paclitaxel poliglumex in patients with NSCLC aged 70 years or older or with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2. Patients were treated with paclitaxel poliglumex 175 mg/m^2 (28 patients) or 235 mg/m^2 (two patients) given as a 10-min i.v. infusion every 3 weeks. Thirty patients have been treated on this protocol, the best response was a PR, in two patients. Sixteen patients had SD that lasted at least 10 weeks. Median survival with paclitaxel poliglumex 175 mg/m^2 was 8.1 months in PS0/1 patients and 5.4 months in PS2 patients. Because of the low toxicity of the 175 mg/m^2 dose, the dose was increased to 235 mg/m^2, the MTD determined in phase I studies. The two PS2 patients who were treated with 235 mg/m^2 died within 30 days after treatment. One patient died of neutropenia and pneumonia, and the other of septic shock and renal failure (Bodkin, unpublished observations).

Table 5 Results in phase II study (CTI-1071) of paclitaxel poliglumex 175 mg/m^2 q^{3}w in patients with advanced epithelial ovarian cancer [26]

	No. (%) of patients		
	Partial response	Stable disease	Progressive disease
All patients (N=99)	10 (10)	32 (32)	57 (58)
platinum-sensitive disease (n=42)	6 (14)	17 (40)	19 (45)
platinum-resistant or refractory diseases (n=57)	4 (7)	15 (26)	38 (67)
Patients with one or two previous chemotherapy treatments (n=39)	7 (18)	10 (26)	22 (56)
platinum-sensitive disease (n=18)	5 (28)	6 (33)	7 (39)
platinum-resistant or refractory disease (n=21)	2 (10)	4 (19)	15 (71)

Table 6 Phase III clinical trials of paclitaxel poliglumex in patients with advanced NSCLC

Trial name, patient population	Design	Paclitaxel poliglumex dose (mg/m^2)	Comparator dose (mg/m^2)	Primary end point	No. of patients
STELLAR 2, second line, PS0–PS2	superiority; open label; randomized	210 (PS0, PS1), 175 (PS2) q3w	docetaxel 75 q3w	survival	850
STELLAR 3, first line, PS2	superiority; open label; randomized	210 + carboplatin AUC 6 q3w	paclitaxel 225 + carboplatin AUC 6 q3w	survival	400
STELLAR 4, first line, PS2	superiority; open label; randomized	175 q3w	gemcitabine 1000 days 1, 8, 15 or vinorelbine 30 days 1, 8, 15	survival	477

Phase III program

Three randomized phase III trials (STELLAR 2, 3 and 4) of paclitaxel poliglumex are currently under way in patients with advanced NSCLC (Table 6). Enrollment in these trials is complete and results are due in early to mid 2005. All three trials were designed to detect improved survival with paclitaxel poliglumex as the primary end point, and are expected to show greater tolerability and quality of life as well.

In STELLAR 3, paclitaxel poliglumex 210 mg/m^2 in combination with carboplatin AUC 6 is being evaluated as first-line therapy in PS2 patients; paclitaxel 225 mg/m^2 with carboplatin AUC 6 is the comparator. Randomization will be stratified by disease stage (IV versus other), gender, geographic location (USA versus Western Europe and Canada versus rest of the world) and history of brain metastases (yes versus no). The primary efficacy end point is the duration of overall survival. The secondary efficacy end points are disease control, response rate in patients with measurable disease, time to progression and disease-related symptoms (QOL). This study has completed enrollment with a total of 400 patients—approximately 200 patients in each arm.

In STELLAR 4, paclitaxel poliglumex 175 mg/m^2 monotherapy is being compared to vinorelbine 30 mg/m^2 or gemcitabine 1000 mg/m^2 as first-line therapy in PS2 patients. Randomization will be stratified by disease stage (IV versus other), gender, geographic location (USA versus Western Europe and Canada versus rest of the world) and history of brain metastases (yes versus no). The primary efficacy end point is the duration of overall survival. Secondary efficacy end points are disease control, response rate in patients with measurable disease, time to progression and disease-related symptoms (QOL). This study has completed enrollment with a total of 477 patients.

STELLAR 2 will compare paclitaxel poliglumex 210 mg/m^2 in PS0/1 patients at randomization or 175 mg/m^2 in PS2 patients at randomization to docetaxel 75 mg/m^2 as second-line therapy. Randomization will be stratified by disease stage (IV versus other), PS (0/1 versus 2), start of front-line chemotherapy (< 16 versus 16 weeks), gender and prior taxane therapy (yes versus no). The primary efficacy end point is the duration of overall survival. The secondary efficacy end points are disease control, response rate in patients with measurable disease, percentage of patients who complete at least four cycles, time to progression and disease-related symptoms (QOL). This study has completed enrollment with a total of 850 patients—approximately 425 patients in each arm.

Summary and conclusions

The rationale for developing paclitaxel poliglumex was to improve standard chemotherapy with paclitaxel by overcoming some of its limitations. These limitations include a lack of selective tumor uptake, low effectiveness in MDR tumors, high plasma levels of the active drug associated with toxicity, poor pharmacokinetic profile and low solubility. Preclinical data show that paclitaxel poliglumex indeed surmounts all of these issues. Paclitaxel poliglumex enters the tumor cell presumably by endocytosis, bypassing MDR pumps, and is metabolized to yield active paclitaxel. This unique intracellular mechanism of action results in greater tumor exposure

and less systemic toxicity. The pharmacokinetic profile and tissue distribution seen in animal models was confirmed in human studies. Data from more than 400 patients treated with paclitaxel poliglumex is available, and a strong safety and tolerability profile has been established. Neutropenia (acute) and neuropathy (chronic) are the dose-limiting toxicities, but they appear to be less severe and less frequent than with conventional taxane therapy. Efficacy data have been collected in a variety of solid tumors, including gastric cancer, mesothelioma, schwannoma, NSCLC, ovarian cancer, breast cancer and colorectal cancer. Phase II studies in NSCLC and ovarian cancer have produced encouraging results, even in traditionally difficult populations such as PS2 patients with NSCLC [35] and patients with platinum-resistant ovarian cancer [26]. Three phase III trials in NSCLC, the STELLAR trials, are under way with paclitaxel poliglumex as first-line monotherapy and in combination with carboplatin in PS2 patients, and as second-line monotherapy in PS0, PS1 and PS2 patients. Pending the outcome of these trials, it is too soon to predict the clinical success of paclitaxel poliglumex. However, the convenient administration schedule and good tolerability suggest that paclitaxel poliglumex may become the taxane of choice for treating patients with advanced NSCLC, including the elderly and those with a poor PS.

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