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Paclitaxel Poliglumex

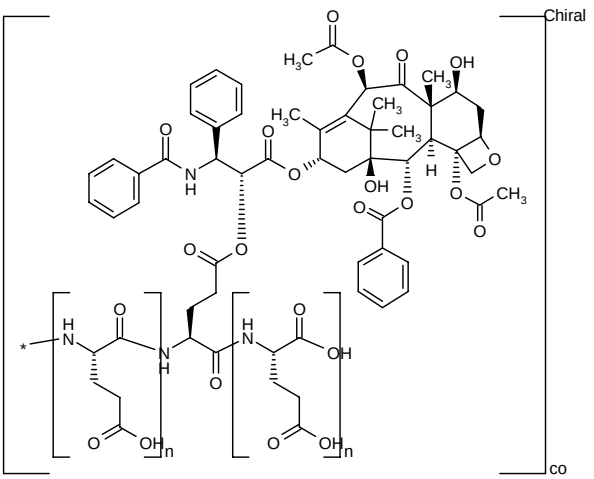
Antimitotic Drug
Oncolytic

Rec INN; USAN

CHC-12103
CT-2103
Polyglutamate paclitaxel
Xyotax™

Poly(L-glutamic acid)paclitaxel

Poly(L-glutamic acid) partly γ-esterified by (2*R*,3*S*)-3-benzamido-1-[4,10β-bis(acetoxy)-2α-(benzyloxy)-1,7β-dihydroxy-9-oxo-5,20-epoxytax-11-en-13α-yloxy]-1-oxo-3-phenyl-2-propyl



$C_{62}H_{71}N_4O_{23}$
Mol wt: 1240.2403

CAS: 263351-82-2

EN: 276960

Abstract

Paclitaxel poliglumex (Xyotax™) is a glutamic acid polymer formulation of paclitaxel in which the active drug is covalently bound with a loading of approximately 38% by weight of the total polymer. Preclinical studies suggested antitumor activity superior to that of equitoxic doses of native paclitaxel, as well as enhanced tumor delivery and retention of the active drug. Subsequent clinical evaluation indicated some activity, but at the expense of neurotoxicity. Clinical evaluation is ongoing, especially in lung cancer, with a specific indication that women with normal or high levels of estrogen may be particularly responsive to this drug.

Synthesis

The original synthesis of paclitaxel bound to a polymer of glutamic acid was described by Li *et al*. in 1998 (1). The starting materials were polyglutamate, with a nominal molecular weight of 36,200, and paclitaxel, in an approximate ratio of 4:1 by weight, in the presence of dicyclohexylcarbodiimide and dimethylaminopyridine. Stopping the reaction by precipitation in chloroform, the sodium salt was formed by subsequent dissolution in $NaHCO_3$. Paclitaxel content (20% w/w) and yield (93%) were confirmed by UV. The structure was confirmed by NMR. Subsequent refinements led to a product with an average paclitaxel content of 38% by weight.

Background

Paclitaxel, together with docetaxel, represents one of the major advances in cancer therapeutics of the last 20 years. The taxanes are a class of drugs with a novel mechanism of action, promoting the assembly of tubulin monomers and inhibiting their disassembly. The resulting inappropriate microtubule structures are associated with blockade of the cell cycle at the G2/M checkpoint, with subsequent apoptosis. While these agents provided an important therapeutic advance, they also presented the acute problem of insolubility and the need for high-molecular-weight components in their formulations. While Tween 80 in the Taxotere® formulation of docetaxel presented relatively few problems, the inclusion of Cremophor EL in the Taxol® formulation of paclitaxel had profound implications for the pharmacology and clinical use of this drug. Firstly, Cremophor may contribute to the hypersensitivity reactions which require pretreatment with a combination of steroids and antihistamines. Secondly, Cremophor forms micelles in the plasma which sequester

Alan V. Boddy. Northern Institute for Cancer Research, Newcastle University, Newcastle upon Tyne NE2 4HH, U.K.

paclitaxel and prevent the drug from accessing tissues or mechanisms of drug elimination. This phenomenon is only apparent at higher doses of Taxol®, leading to the mistaken conclusion that paclitaxel is subject to saturable elimination by either drug metabolism or biliary excretion, or both. Finally, Cremophor is an inhibitor of P-glycoprotein, which appears to be pharmacologically advantageous. However, this characteristic may lead to further complications in the pharmacology of paclitaxel. Thus, there are several reasons why an improved formulation of paclitaxel would be attractive, both therapeutically and commercially. Abraxane® (Abraxis Bioscience), an albumin-bound form of paclitaxel, was recently licensed for the treatment of metastatic breast cancer. In addition to improved pharmaceutical properties, Abraxane® also has a lower incidence of neurotoxicity than Taxol®.

The principles that guided the successful development of Abraxane® are essentially identical to those that were applied to the development of paclitaxel poliglumex. The potential advantages of a polymeric formulation of paclitaxel are perceived to be: 1) increased solubility; 2) avoidance of Cremophor-containing formulations; 3) improved pharmacokinetic profile relative to the active species alone; 4) tumor selectivity due to the phenomenon of enhanced permeability and retention (EPR); 5) tumor-selective release of the active form (if possible); and 6) circumvention of tumor resistance pathways.

Polyglutamate was chosen as the macromolecular carrier as the carboxy groups are amenable to conjugation of active drug and polyglutamate can be readily degraded by lysosomal enzymes. There was also some consideration that glutamic acid might ameliorate some of the neurotoxicity seen with paclitaxel. Whether or not paclitaxel poliglumex benefits from all these potential advantages has been the subject of intensive investigation throughout the preclinical and clinical development of this agent.

Preclinical Pharmacology

For agents where the active species is bound to a macromolecular structure, such as albumin, liposomes or polymers, *in vitro* investigations have only a limited role in preclinical evaluation. In fact, paclitaxel poliglumex has no taxane-like activity *in vitro*, failing to promote the assembly of tubulin to form microtubules and failing to "rescue" the growth of a paclitaxel-dependent cell line (1).

Preclinical *in vivo* investigations have concentrated either on the biodistribution of paclitaxel poliglumex and tumor selectivity or on the comparative antitumor efficacy relative to equitoxic doses of Taxol®. Initial experiments showed good localization of the polymer to syngeneic tumors in mice, with some evidence for local release of the active species. Precise quantitation of the active form of paclitaxel in tumors was estimated from that fraction of the radiolabeled species that could be extracted into organic solvents. In the plasma, paclitaxel poliglumex had a much longer half-life (317 min) compared to paclitaxel from Taxol® (29 min). In contrast to subsequent clinical data, < 0.1% of the radiolabeled drug in plasma was present as unconjugated paclitaxel (1). In a second study on biodistribution, plasma AUC values for paclitaxel were over 100-fold greater after paclitaxel poliglumex compared to Taxol®. Tumor concentrations were 5-fold higher, and importantly, tumor-muscle concentration ratios were 1.7- to 4-fold higher. There was no increase in the ratio of unconjugated to conjugated paclitaxel in any tissue except in the tumor, where there was an increase from 4% to 17% from 5 h to 144 h. Biliary excretion, with recovery of radioactivity in feces, was the primary route of elimination for paclitaxel administered as paclitaxel poliglumex, but at a much slower rate than after administration of Taxol®. Autoradiography indicated that initial penetration into tumor tissue was limited to the tumor periphery, but subsequent observations over 5 days showed more diffuse uptake of active drug into tumor tissue, with a tumor-muscle ratio of 56 (2).

The experiments in the first paper by Li *et al*. used [^{3}H]-paclitaxel as a marker of paclitaxel poliglumex biodistribution and release of active drug. In a second paper, the same group used [^{3}H]-polyglutamate conjugated with unlabeled paclitaxel, where the radioactivity detected reflects the distribution of the macromolecule with or without the active drug.

In preclinical efficacy studies, paclitaxel poliglumex showed promising activity against syngeneic mouse tumors (1, 3), as well as some activity against human tumor xenografts (3, 4). In a HEY human ovarian cancer model, the antitumor effect of paclitaxel poliglumex (180 mg/kg either as a single dose or every 7 days x 3) was superior to that of equitoxic doses of paclitaxel (as Taxol® 10 mg/kg every 7 days x 3), although it should be noted that much of the xenograft work was performed with i.p. tumor implantation and i.p. administration of drug (4). In syngeneic models, paclitaxel poliglumex was also demonstrated to act as a radiosensitizing agent (5). Interestingly, in the same study, radiotherapy appeared to increase the uptake of paclitaxel poliglumex into tumors (5).

Pharmacokinetics and Metabolism

The plasma pharmacokinetics of paclitaxel poliglumex and unconjugated paclitaxel were investigated in a phase I dose-escalating study, with paclitaxel poliglumex administered as a short infusion (10-30 min) at doses of 11-266 mg/m^2 every 2 or 3 weeks. Polymer-conjugated paclitaxel was distinguished from native paclitaxel by a specific liquid chromatography/mass spectrometry (LC/MS) method following digestion of the polymer. Plasma AUC of conjugated taxanes (reflecting paclitaxel poliglumex concentration) increased with increasing dose, and there was some evidence of nonlinearity of pharmacokinetics, with lower clearances at higher doses (6). However, clearance was very low (< 10 ml/min) and volume of distribution was also small, indicating that paclitaxel poliglumex was largely confined to the plasma compartment. Some distribution outside plasma was suggested by a higher V_z, and this was borne out by the high yield of

unconjugated paclitaxel from paclitaxel poliglumex. Comparison with comparable paclitaxel pharmacokinetic data following administration of Taxol® (7) indicated almost complete bioavailability of the unconjugated drug (6). The half-life of the polymer, measured as conjugated taxanes, was over 100 h at clinically relevant doses, and polymer could be detected in pretreatment samples on both the 2- and 3-weekly schedules.

In preclinical studies, the metabolic pathways of poliglumex have been explored and the mechanism of release of unconjugated paclitaxel elucidated. The initial breakdown of paclitaxel poliglumex depends at least in part on the proteolytic activity of the lysosomal enzyme cathepsin B. Intermediate metabolites of mono- or diglutamate conjugates are formed initially, following subsequent breakdown to release unconjugated paclitaxel. The dependence on lysosomal cleavage indicates that paclitaxel poliglumex may be taken up into cells and offers some potential for tumor selecitivity (8).

Safety

Preclinical investigations suggested that paclitaxel poliglumex could be safely administered at doses higher than the corresponding paclitaxel equivalent as Taxol® (3, 4). Two phase I studies of paclitaxel poliglumex indicated a safety profile similar to Taxol®, with dose-limiting toxicity (DLT) of neutropenia on the 3-weekly schedule (6, 9) and neuropathy on the 2-weekly schedule (6). The corresponding maximum tolerated doses (MTDs) were 233 and 177 mg/m^2. Both phase I studies reported a higher than expected incidence of neuropathy (6, 9), which was a particular problem on later courses of treatment. In a phase II study, neuropathy was also identified as a problem in 30% of patients at 175 mg/m^2 every 3 weeks (10). At the same equivalent dose of paclitaxel as Taxol®, the incidence of neuropathy is reported to be 21% (11). Other toxicities reported include hypersensitivity reactions, nausea and vomiting (6, 9, 10).

Clinical Studies

In the dose-escalating phase I study of single-agent paclitaxel poliglumex, partial responses were seen in 1 patient with mesothelioma (175 mg/m^2 every 3 weeks) and 1 patient with gastric carcinoma (175 mg/m^2 every 2 weeks). In a subsequent phase I study investigating doses of 235 or 270 mg/m^2 every 3 weeks, no responses were obtained in 7 patients who received a total of 16 cycles of treatment (9). In a phase II study in patients with recurrent epithelial ovarian, fallopian tube or primary peritoneal carcinoma, 99 patients were treated with a median of 3 cycles at a dose of 175 mg/m^2 every 3 weeks. The overall response rate was only 10%, with a median time to progression of 2 months. Response rates were slightly higher in patients with platinum-sensitive tumors or in patients with only one or two prior therapies (up to 28% response rate). The incidence of neuropathy was higher than expected from the phase I studies (10).

A phase I study investigating the combination of paclitaxel poliglumex with carboplatin identified an MTD of 225 mg/m^2 combined with carboplatin AUC6 administered every 3 weeks. This relatively high dose (compared to the phase I single-agent studies) was well tolerated, with myelosuppression being the major toxicity. Three partial responses were obtained in 22 patients treated, all in ovarian cancer patients who had previously failed to respond to paclitaxel therapy (12). Neuropathy, which was a major toxicity in the phase I studies, was only a minor problem in this combination study, although it did limit the therapy in 1 patient who had achieved a partial response.

A potential therapeutic use of paclitaxel poliglumex has been identified in the treatment of patients with non-small cell lung cancer (NSCLC) who have a performance status of 2. These patients have a median survival of only 10 weeks and do not respond to platinum-based chemotherapy, although vinorelbine treatment does provide a survival advantage. More aggressive therapy is often associated with a high incidence of adverse events (13). In fact gemcitabine/cisplatin is the best combination in terms of response rate and time to progression. Combination of carboplatin with paclitaxel was much less toxic than cisplatin-based therapies. Neuropathy was, however, a problem with this combination (paclitaxel 200 mg/m^2, carboplatin AUC6). Other trials have also shown the superiority of this combination over monotherapy. With single-agent paclitaxel poliglumex, the median survival is at least as good as that seen with the combination of paclitaxel and carboplatin, and it was well tolerated in patients with performance status 2 (13).

The ongoing STELLAR 3 phase III study is comparing paclitaxel poliglumex (225 mg/m^2) combined with carboplatin AUC6 against the equivalent dose of paclitaxel combined with the same carboplatin AUC. Another trial, STELLAR 4, is comparing paclitaxel poliglumex as a single agent at 175 mg/m^2 against either gemcitabine or vinorelbine. Results of the STELLAR trials were presented at the EORTC-NCI-AACR meeting in Prague in 2006 (14, 15). These trials showed that paclitaxel poliglumex was at least as active as the control-arm treatments (paclitaxel and carboplatin, docetaxel and gemcitabine or vinorelbine). Intriguingly, women treated with paclitaxel poliglumex responded much better than men receiving the same treatment (15). Preclinical data presented at the same meeting suggest that high levels of estrogen upregulate cathepsin B, the enzyme that is thought to mediate the cleavage of paclitaxel poliglumex to release paclitaxel (16). This led to a women-only trial in patients with performance status 2 NSCLC, with a target recruitment of 600 patients, comparing paclitaxel poliglumex to paclitaxel, both at a dose of 175 mg/m^2. This PIONEER (PGT305) study started in late 2005, but was subsequently terminated in late 2006 due in part to an aberrantly low death rate in the control group (17). Two phase III trials are now planned in women with advanced NSCLC, one monotherapy trial in women with poor performance status (PS2) and normal estrogen levels

(PGT306) and the other comparing combination of paclitaxel poliglumex plus carboplatin *versus* paclitaxel plus carboplatin in female NSCLC patients with performance status of 0, 1 or 2 (PGT307) (18).

In ovarian cancer, phase II data presented at ASCO in 2005 showed unacceptable toxicity at a dose of 175 mg/m^2 combined with carboplatin AUC6. However, this treatment was very effective in producing an initial reduction of tumor growth. A phase III investigation at a dose of 135 mg/m^2 paclitaxel poliglumex as maintenance therapy (*versus* no therapy) has been initiated in collaboration with the Gynecologic Oncology Group of North America. Activity has also been reported in prostate cancer. These results were presented in 2006 in Orlando at The Prostate Cancer Symposium co-sponsored by the American Society of Oncology (ASCO), the American Society for Therapeutic Radiology and Oncology (ASTRO) and the Society of Urologic Oncology (SUO) (19). A response rate of 24% was obtained in patients with androgen-independent disease that was also refractory to prior treatment, including docetaxel. On a 4-weekly regimen, only 1 case of grade 4 toxicity was reported (neutropenia).

Conclusions

The clinical development of paclitaxel poliglumex has identified advantages in terms of toxicity and convenience over paclitaxel formulated as Taxol®. While neuropathy is a potential problem, careful modulation of the dose seems to limit such toxicity. With a more detailed understanding of the mechanism of cellular localization and release of the active drug, more rational use of this drug in specific target patient populations may be advantageous.

Acknowledgements

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Sources

Cell Therapeutics, Inc. (US) (licensed from PG-TXL); developed worldwide in collaboration with Novartis (CH).

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