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Gimatecan

Rec INN

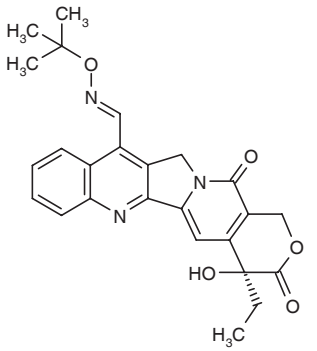
DNA-Intercalating Drug
DNA Topoisomerase I Inhibitor
Oncolytic

CPT-184
LBQ-707
ST-1481

7-(*tert*-Butoxyiminomethyl)camptothecin

(4*S*)-4-Ethyl-4-hydroxy-3,14-dioxo-3,4,12,14-tetrahydro-1*H*-pyrano[3',4':6,7]indolizino[1,2-*b*]quinoline-11-carbaldehyde *O*-(*tert*-butyl)oxime

InChI=1/C25H25N3O5/c1-5-25(31)18-10-20-21-16(12-28(20)22(29)17(18)13-32-23(25)30)15(11-26-33-24(2,3)4)14-8-6-7-9-19(14)27-21/h6-11,31H,5,12-13H2,1-4H3/b26-11+/t25-/m0/s1



$C_{25}H_{25}N_3O_5$
Mol wt: 447.4832

CAS: 292618-32-7
EN: 293886

Abstract

Topoisomerase I is recognized as an important anticancer target and dramatic antitumor activity has been observed with camptothecin, which inhibits the enzyme by stabilizing the topoisomerase I-DNA complex, thereby inducing DNA breakage by preventing DNA religation. Camptothecin was unfortunately unsuccessful in clinical trials due to unpredictable pharmacological activity and severe adverse events. Researchers have focused on modifying camptothecin to synthesize agents with improved pharmacological and toxicological profiles. Gimatecan (ST-1481, LBQ-707) was identified from a series of lipophilic 7-oxyiminomethyl-substituted derivatives and is a particularly promising camptothecin analogue. The lipophilicity of the agent allows for oral administration and increased cellular accumulation, and it exerts potent activity against tumor cell growth in preclinical models. The antitumor efficacy and safety of gimatecan have also been demonstrated clinically in phase I and II trials in patients with advanced cancer.

Synthesis

Gimatecan can be synthesized as follows:

Radical alkylation of camptothecin (I) with hydrogen peroxide and ferrous sulfate in methanolic sulfuric acid provides the 7-hydroxymethyl derivative (II). This compound is also produced, although in lower yields, by heating (I) with MeOH in the presence of hydroxylamine-*O*-sulfonic acid or ammonium persulfate, or by treatment with glycolic acid, ammonium persulfate and silver nitrate. Subsequent heating of alcohol (II) with acetic acid results in the formation of aldehyde (III) along with minor amounts of the acetate ester (IV). A similar oxidation is observed by treatment of (II) with other cationoid reagents, including H_2SO_4, $BF_3{\cdot}Et_2O$, $POCl_3$, $SOCl_2$, TsCl and PPh_3-CCl_4 (1). Finally, condensation of aldehyde (III) with *O*-*tert*-butylhydroxylamine hydrochloride in ethanolic pyridine affords the corresponding oxime (2, 3). The title oxime is similarly prepared by treatment of 7-formylcamptothecin dimethylacetal (V) with *O*-*tert*-butylhydroxylamine in refluxing ethanol (4). Scheme 1.

Background

Extracts from the wood bark of *Camptotheca acuminata*, a tree native to Tibet and China, have been used in traditional Chinese medicine for the treatment of psoriasis, viral infection and cancer, but it was not until 1958 that the 5-ringed molecule camptothecin was finally isolated and identified as the active anticancer agent. Characterization of the mechanism of action of the agent led to the discovery that it inhibits topoisomerase I, resulting in cancer cell death. Topoisomerase I is an enzyme that relaxes DNA by binding to supercoiled DNA via a phosphotyrosine bond and causing single-strand cleav-

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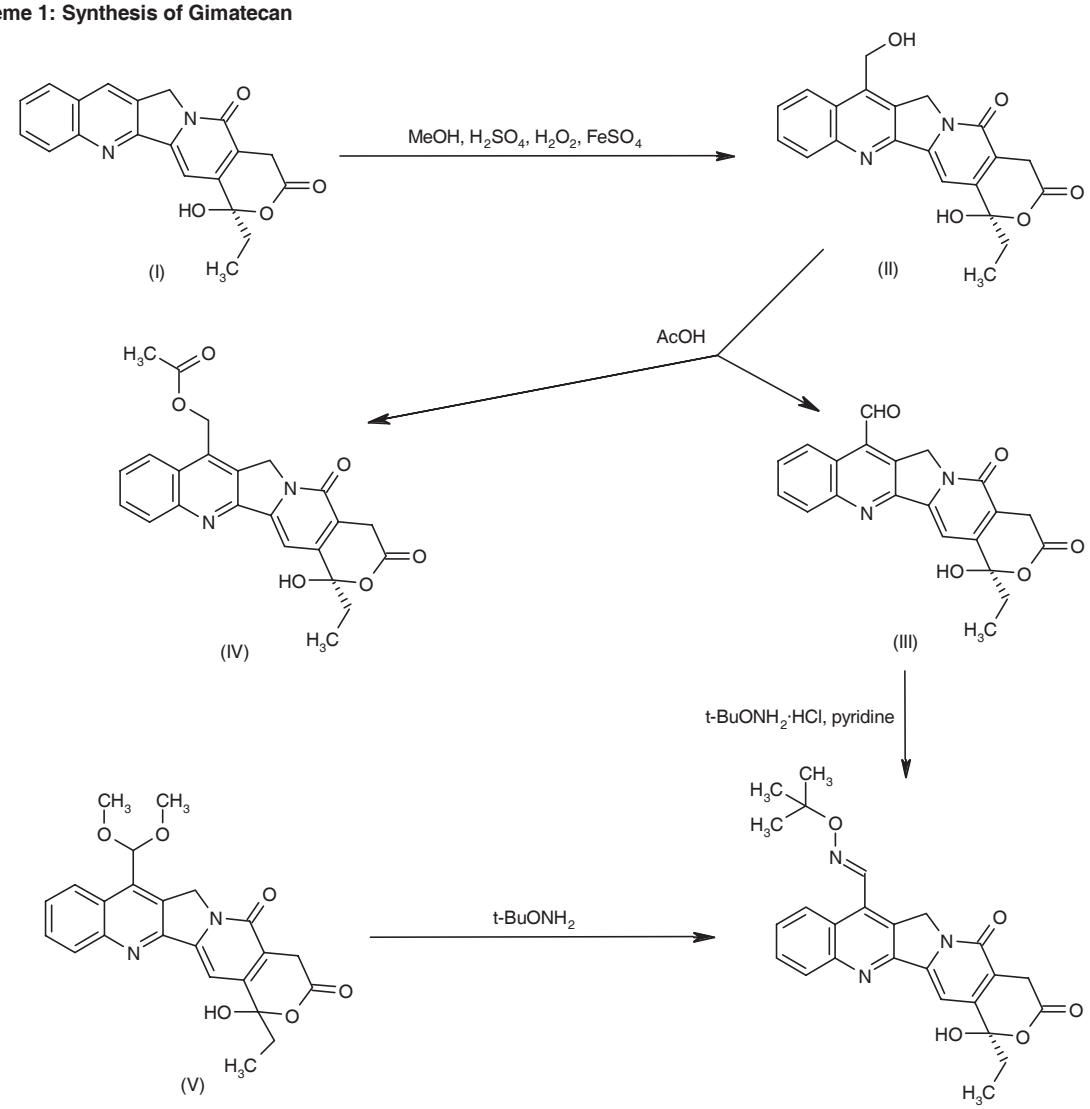
Scheme 1: Synthesis of Gimatecan



age of the duplex in preparation for replication and transcription during the S phase of the cell cycle. Camptothecin inhibits topoisomerase by stabilizing the normally transient covalent linkage between topoisomerase I and the DNA strand, preventing release of the enzyme from the cleavable complex and forming the ternary complex. This induces DNA breakage through the prevention of DNA religation (Fig. 1). This type of lesion is unique to camptothecin and not seen with other anticancer agents (5-10).

Camptothecin acts on both normal and cancer cells. However, studies suggest that topoisomerase I levels are higher in some tumor cells, thus affording camptothecin some degree of specificity. In addition, it appears that DNA damage is more efficiently repaired in normal cells as compared to cancer cells, which lack DNA repair and cell cycle checkpoints. Unfortunately, camptothecin was unsuccessful in clinical trials due to unpredictable pharmacological activity and an association with severe adverse events, such as myelosuppression, diarrhea and hemorrhagic cystitis (11-15).

Due to the validity of topoisomerase I as an anticancer target and the dramatic antitumor activity observed with camptothecin preclinically, researchers have focused on modifying the molecule in an effort to produce semisynthetic and synthetic analogues with improved pharmacological and toxicological profiles. Camptothecin analogues that are currently under active development for the treatment of cancer are shown in Table I. Efforts were made to increase water solubility, which resulted in the synthesis of irinotecan and topotecan, launched in 1994 and 1996, respectively, for the treatment of various cancers. In addition, lipophilic analogues were designed which displayed improved pharmacological profiles, such

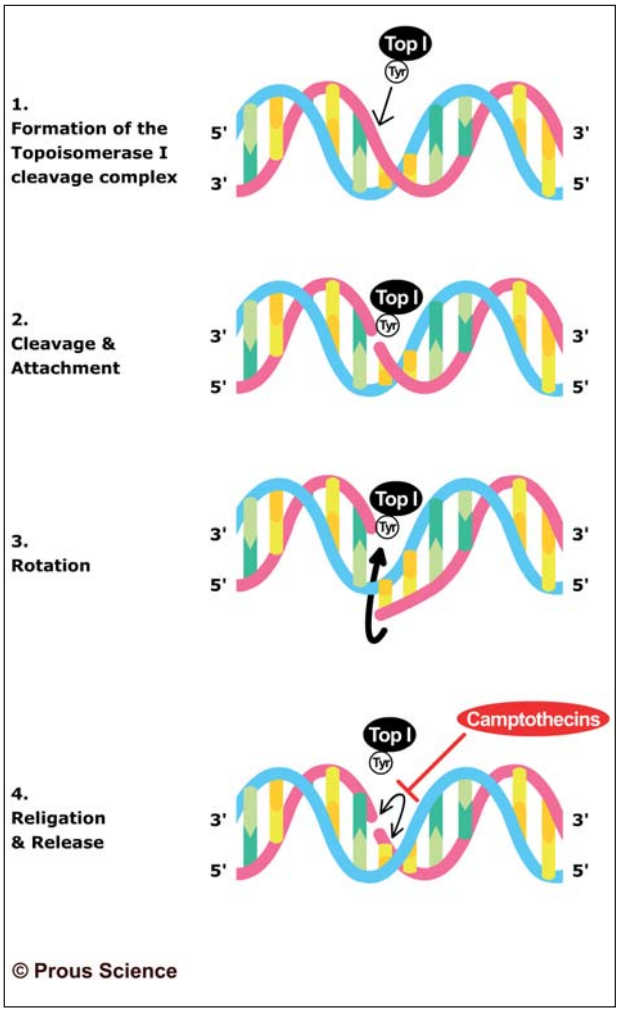


Fig. 1. The type 1 DNA topoisomerase (Top I) reaction for the relief of torsional strain caused by DNA supercoiling. **1.** Top I with a tyrosine (Tyr) at the active site approaches supercoiled DNA. **2.** Top I breaks a phosphodiester bond in a single DNA strand, generating a 3'-terminus (nicking step). Top I covalently binds at this 3'-terminus, thus forming the Top I cleavage. **3.** The torsional strain resulting from supercoiling drives rotation of the 5'-end of the nicked DNA around the intact strand. Top I encircles the rotating nicked DNA and slows its rotation (controlled rotation). **4.** The 5'-end of the nicked DNA realigns with the corresponding 3'-end, thus enabling religation (closing step). The reaction reverses via spontaneous reformation of the phosphodiester bond and regeneration and release of Top I. The Top I-DNA cleavage complex is normally transient because the closing step is faster than the nicking step. Camptothecins prevent religation by blocking release of Top I from the cleavable complex and forming the ternary complex.

as increased stability of the active lactone form, rapid cellular uptake and enhanced drug-target interaction and stabilization of the ternary complex (2, 16-22).

Gimatecan (ST-1481, LBQ-707) is a particularly promising camptothecin analogue that was identified from a series of lipophilic 7-oxyiminomethyl-substituted derivatives. The lipophilicity of the agent allows for oral administration and increased cellular accumulation. In addition, it exhibited a unique subcellular distribution and increased and persistent stabilization of the topoisomerase I-DNA complex. Gimatecan exerted superior activity against tumor cell growth in preclinical models and was selected for further development as an anticancer agent (2, 23).

Preclinical Pharmacology

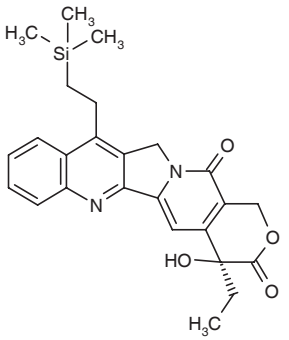
In a cleavable complex assay using purified human topoisomerase I, gimatecan was shown to be a highly potent inhibitor of the enzyme. Experiments performed using human PC-3 prostate carcinoma cells revealed that it induced persistent stabilization of the topoisomerase I-DNA complex, which is consistent with its potent inhibitory effects on the enzyme (2).

The subcellular localization of lipophilic gimatecan was compared to water-soluble topotecan in a study using HT-29 human colon carcinoma cells and the mitoxantrone-resistant subline HT-29/Mit that overexpresses breast cancer resistance protein (BCRP). While topotecan was predominately localized in mitochondria with differences noted between the two cell lines, gimatecan showed similar lysosomal localization in both cell lines, suggesting that lysosomes store the active agent. Gimatecan effectively inhibited the growth of HT-29/Mit cells, which were highly resistant to mitoxantrone and markedly cross-resistant to the camptothecin analogues topotecan and SN-38; the cells displayed limited resistance to doxorubicin. Intracellular accumulation of topotecan was reduced, while gimatecan accumulation was unaffected, suggesting that BCRP is not a substrate for gimatecan. Studies using athymic nude mice bearing s.c.-implanted HT-29 or HT-29/Mit xenografts reported that while topotecan (15 mg/kg p.o. every 4 days x 4) was only moderately effective against HT-29 xenografts (64% inhibition of tumor volume) and ineffective against HT-29/Mit xenografts, gimatecan (2 mg/kg p.o. every 4 days x 4) was significantly more effective in both models, giving tumor volume inhibition rates of 94% and 82%, respectively (23, 24).

The antiproliferative activity of gimatecan was compared to topotecan against a panel of human tumor cell lines, including cisplatin-resistant cells (ovarian carcinoma IGROV-1 and mutant IGROV-1/pt1; osteosarcoma U-2 OS and mutant U-2 OS/Pt; glioblastoma GBM, SW 1783 and U-87 MG; and melanoma LP). Gimatecan was more potent than topotecan in all cell lines tested. With the exception of glioma U-87 MG cells, IC_{50} values for gimatecan ranged from 8 to 30 ng/ml as compared to 80-980 ng/ml for topotecan. The U-87 MG cell line was less sensitive to gimatecan (IC_{50} = 62 ng/ml; IC_{50} topotecan = 560 ng/ml), possibly due to the presence of an efficient S phase checkpoint in this cell line. Moreover, gimatecan (2-3 mg/kg p.o. every 4 days x 4) was markedly effective when administered to athymic nude mice bearing s.c. human tumor xenografts highly resistant to chemotherapy. Dramatic antitumor effects (> 85% inhibition of tumor volume) were observed in 16 of 18 tumor

Table I: Camptothecin analogues under active development for the treatment of cancer (from Prous Science Integrity®).

Drug	Source	Phase
1. BNP-1350	BioNumerik	II
2. Gimatecan	Sigma-Tau/Novartis	II
3. CT-2106*	Cell Therapeutics	II
4. Tocosol camptothecin**	Sonus	I
5. XMT-1001***	Mersana Therapeutics	I
6. ST-1968	Sigma-Tau	Preclinical



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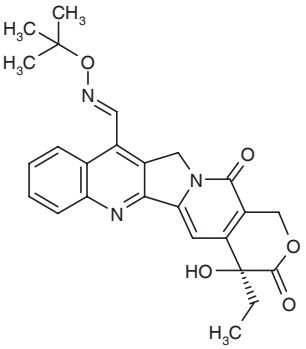

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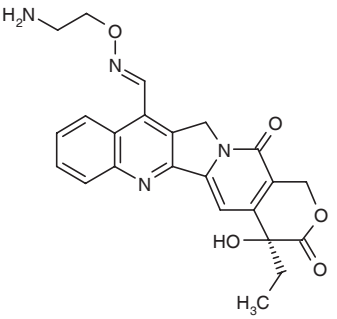

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*Camptothecin polymer conjugate. **Cremophor-free, vitamin E-based camptothecin emulsion. ***Polymer-based camptothecin prodrug.

xenograft models. Of the 16 responsive models, 11 showed complete regression of tumors. Gimatecan was most effect against lung carcinoma, melanoma and osteosarcoma xenografts, producing up to 100% complete responses. Efficacy of the agent was also observed against slow-growing A549 lung carcinoma and HT-29 colon carcinoma xenografts. The antitumor effects of gimatecan were superior to topotecan (15 mg/kg p.o. every 4 days x 4) in 9 of 17 tumor xenograft models (25).

Gimatecan (IC_{50} = 9.0-90 ng/ml) was more potent than topotecan (IC_{50} = 800-900 ng/ml) in inhibiting the proliferation of the slowly proliferating human bladder cancer cell lines HT-1376 and MCR following 1-h exposure. Gimatecan was also shown to arrest cell cycle progression in the S phase, although no evidence of apoptosis was seen. Examination of nuclear protein extracts from treated cells showed that the reduction in topoisomerase I expression and activity was greater, earlier and more persistent in cells treated with topotecan (1 μg/ml for 1 h) as compared to gimatecan (0.01-0.1 μg/ml for 1 h) in both cell lines. Studies using athymic nude mice implanted s.c. with HT-1379 or MCR xenografts indicated that gimatecan (2 mg/kg p.o. every 4 days x 4) was significantly more effective than topotecan (15 mg/kg p.o. every 4 days x 4), which only exhibited moderate activity (26).

A study using the human neuroblastoma cell lines SK-N-DZ, BE(2)M17, LAN-1, RNGA and SK-N-BE(2)c compared the cytotoxic effects of gimatecan with topotecan and SN-38 in a clonogenic survival assay. Although it exhibited relatively less cellular accumulation, gimatecan was 40-fold more cytotoxic than topotecan and 1.4-4 times more potent than SN-38. Further analysis of the effects of gimatecan revealed that it caused a high number of DNA strand breaks, which are most likely responsible for its potent cytotoxic activity (27).

The cytotoxic activity of gimatecan was demonstrated against the human malignant mesothelioma cell line REN. The IC_{50} value obtained for inhibition of cell growth and the concentration inducing 50% cell death after 3 days of exposure to the agent were 0.46 and 225 nM, respectively, and it was found to rapidly induce apoptosis in this cell line. The apoptotic effects of gimatecan were enhanced when it was combined with the protease inhibitor PS-341 (bortezomib). Treatment of nude SCID mice bearing i.p. REN xenografts with gimatecan (0.05 or 0.025 mg/kg/day p.o. every 4 days x 4 weeks) resulted in significant decreases in tumor weight (> 90%) compared to controls and minimal or no ascites or diaphragmatic involvement (28, 29).

The effects of gimatecan were examined and compared to topotecan against the human p53-defective hormone-refractory prostate carcinoma cell lines DU 145 and PC-3. Gimatecan was more potent than topotecan in all *in vitro* and *in vivo* experiments. Treatment of DU 145 cells with gimatecan resulted in cell cycle arrest in the S phase (IC_{50} for inhibition of cell growth = 37 ± 3 nM *vs.* 200 ± 14 nM for topotecan) and early activation of apoptosis. In contrast, gimatecan treatment of PC-3 cells caused persistent lock in the G2 phase (IC_{50} for inhibition of cell growth = 43 ± 8 nM *vs.* 600 ± 70 nM for topotecan) with a cytostatic effect and late apoptosis. Further *in vitro* experiments using these cell lines to compare expression and activation of apoptosis-related factors revealed that both topotecan and gimatecan induced moderate upregulation of the two receptors for tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), TRAIL-R1 and TRAIL-

R2. The relative resistance of PC-3 cells to drug-induced apoptosis was associated with Akt activation, higher levels of cFLIP-L and Bcl-2, and lower levels of Bax. PC-3 tumors implanted s.c. in mice were more responsive to gimatecan (2 mg/kg p.o. every 4 days x 4) than DU 145 xenografts (tumor volume inhibition = 95% for both; complete tumor response = 30% *vs.* 0%) (30, 31).

In an effort to determine the effects of various drug efflux proteins and topoisomerase I mutations on the antiproliferative and antitumor activity of gimatecan, *in vitro* cell survival and growth assays and *in vivo* studies using wild-type and dual P-glycoprotein (Pgp)-negative/Bcrp1-negative mice were performed. Results obtained *in vitro* using parental human ovarian carcinoma cells (IGROV-1) and T8 human ovarian cancer cells overexpressing the ATP-dependent drug transporter ABCG2, and parental and BCRP-overexpressing MDCK II cells indicated that gimatecan is not a substrate for ABCC2 (MRP2) or Pgp and is a weaker substrate for BCRP than topotecan. Experiments using HEK-293 cells expressing wild-type or mutant ABCG2, ABCB1, ABCC1, ABCC2 or ABCC4 demonstrated that gimatecan may be more effective than topotecan and irinotecan in cancers expressing ABCG2, ABCB1 or ABCC2, but not those expressing ABCC4 or those carrying topoisomerase I mutations (32, 33).

Gimatecan (1-4 mg/kg p.o. every 4 days x 4) was especially effective in two human non-small cell lung cancer (NSCLC) xenograft models (NCI-H460, LX-1) in mice and 5 times more effective then topotecan (15 mg/kg p.o. every 4 days x 4). Tumor volume inhibition rates were > 90% for gimatecan, with all mice bearing LX-1 xenografts achieving complete regression. Further studies using the NCI-H460 model showed that gimatecan (0.25 and 0.5 mg/kg p.o. daily 5 days/week x 4 weeks and 5 and 6 mg/kg p.o. every 8-10 days x 10) was also effective in inhibiting tumor volume by > 99% and was associated with good $\log_{10}$ cell kill (LCK) and high complete response rates (2, 34).

The efficacy of gimatecan (0.25-4 mg/kg p.o. daily or intermittently starting 3 days postinoculation) was investigated in several murine tumor xenograft models, including two orthotopic intracranially (i.c.) implanted gliomas (U-87 MG, SW 1783), two i.c. implanted melanomas (LP and LM), i.p. IGROV-1 ovarian carcinoma and s.c. A2780 ovarian and NCI-H460 lung carcinoma metastasis models. The agent was markedly effective in all models. In the intracranial models, all dosing schedules resulted in a significant delay in the time of onset of signs of disease and almost all mice in the metastatic models and i.p. ovarian cancer model were alive and tumor-free at the end of the experimental period. It was concluded that a daily prolonged dosing schedule was the most effective (35).

Both antitumor and antiangiogenic effects of gimatecan were observed in the A549 NSCLC and orthotopic melanoma (MeWo implanted intradermally [i.d.]) human tumor xenograft models. Although the agent was only minimally effective in the A549 xenograft model when administered orally at a dose of 2 mg/kg on an intermittent schedule (every 4 days x 4), strong tumor growth inhibition was observed when it was administered at a dose of 0.5 mg/kg daily (5 days/week x 2 weeks) for a prolonged period of time. Moreover, tumors from animals treated on both schedules exhibited a reduction in tumor microvessels, with significantly greater reductions seen in the group receiving daily doses of gimatecan. Similarly, significant decreases in tumor microvessels were observed in mice bearing i.d. MeWo xenografts and treated with 0.06 and 0.12 mg/kg p.o. (daily x 5 days/week x 2 weeks). The antiangiogenic effects of gimatecan were further characterized, with results showing inhibition of endothelial cell migration *in vitro*, inhibition of vascularization in the Matrigel assay and downregulated expression of the proangiogenic basic fibroblast growth factor (bFGF) in A549 tumor cells, which was associated with inhibition of Akt (36).

The human melanoma cell line M14 transfected with a vector containing Bcl-2 (MB6 clone) to induce overexpression of Bcl-2 exhibited reduced sensitivity to gimatecan *in vitro* as compared to empty vector-transfected cells. However, when gimatecan was combined with the anti-Bcl-2 oligonucleotide oblimersen, sensitivity was increased. Similar results were obtained *in vivo* in the two human s.c. melanoma xenograft models 501Mel and Me26414, which express high and low levels of Bcl-2, respectively. The 501Mel cells were about 6 times more resistant to gimatecan then the Me26414 cells (IC_{50} for growth inhibition = 48.3 ± 3 ng/ml *vs.* 7.6 ± 0.7 ng/ml). Treatment of the 501Mel-bearing mice with oblimersen (10 mg/kg i.p daily 5 days/week x 3 weeks) or a suboptimal regimen of gimatecan (0.25 mg/kg daily 5 days/week every other week for two courses) alone was only marginally effective (tumor volume inhibition = 18% and 44% on day 36, respectively). In contrast, when gimatecan in the suboptimal regimen was combined with oblimersen, significantly increased antitumor activity was observed as compared with either agent alone (tumor volume inhibition = 80% on day 36). Gimatecan administered alone on the optimal schedule (0.25 mg/kg daily x 5 days/week x 4 weeks) resulted in antitumor activity (tumor volume inhibition = 96% on day 40) that was not enhanced by the addition of oblimersen. However, combination treatment did provide a more prolonged antitumor effect, so that by day 80 tumor volume inhibition was 98% as compared to 74% in the gimatecan monotherapy group (37).

The antitumor efficacy of gimatecan (0.12, 0.16, 0.24 and 0.32 mg/kg/day p.o. for 5 days/week x 4 weeks) was examined as monotherapy or in combination with the recombinant humanized monoclonal anti-vascular endothelial growth factor (VEGF) antibody bevacizumab, the epidermal growth factor receptor (EGFR) inhibitor erlotinib or the rapamycin analogue/mTOR inhibitor everolimus in human breast cancer, NSCLC and ovarian cancer xenograft models in mice. Gimatecan monotherapy was tolerated in mice bearing breast BC146 tumors, with no deaths or weight loss observed at doses below 0.48 mg/kg. Even low doses of 0.03 mg/kg resulted in complete tumor regression that was prolonged for 90 days after treatment onset; bevacizumab and everolimus,

although ineffective alone in this model, exhibited restored activity when combined with gimatecan. The other breast cancer xenograft models, including one resistant to anthracycline and docetaxel, were also sensitive to gimatecan. The squamous NSCLC IC-1 xenograft model, which is resistant to platinum agents and moderately sensitive to docetaxel, was only marginally sensitive to the highest gimatecan dose. However, the lung adenocarcinoma IC-14 xenograft model, which is resistant to platinum therapy and sensitive to docetaxel, was sensitive to gimatecan 0.12 mg/kg; erlotinib did not enhance the antitumor activity of gimatecan in this model. Both the lung adenocarcinoma IC-8 and the ovarian carcinoma OVA2 models were highly sensitive to gimatecan monotherapy; everolimus and bevacizumab alone were marginally effective in the ovarian cancer model, although both enhanced the antitumor effects of gimatecan (38).

A gimatecan-containing liposome formulation was developed which showed efficacy *in vitro* and *in vivo* against human NSCLC NCI-H460 and murine Lewis lung carcinoma cells/tumors. The new formulation did not alter the pharmacological activity of gimatecan *in vitro* and i.v. administration in murine tumor xenograft models resulted in a slight but significant increase in antitumor activity as compared to orally administered gimatecan (39).

Pharmacokinetics and Metabolism

Oral gimatecan was rapidly absorbed in rats and dogs, showing good bioavailability of 70%. The agent was extensively distributed and was metabolized to yield the polar metabolite ST-1698 (40).

A phase I trial in 10 subjects examined the pharmacokinetics of oral gimatecan given daily for 5 days for 1, 2 or 3 consecutive weeks every 28 days (2.65, 4 and 5.6 mg/m^2/cycle). The agent was rapidly absorbed, with plasma C_{max} achieved within 2 h of dosing (median t_{max} = 1.1 h). A prolonged terminal half-life ($t_{1/2}$) of 72 h was obtained, with only negligible amounts of the polar metabolite ST-1698 detected at the highest dose. AUC values were dose-proportional ($AUC_{0\text{-}24h}$ = 1089 ± 481, 2447 ± 598 and 4185 ± 1338 ng.h/ml on day 5, respectively) and plasma levels of the agent were 3-4 times higher on day 5 as compared to day 1; the active closed lactone form accounted for 90% of these plasma levels (40).

Four patients with advanced cancer were administered a single oral dose of 1.5 mg [^{14}C]-gimatecan followed by standard treatment with the agent to assess the pharmacokinetics and metabolism. Rapid absorption (median t_{max} = 1 h) and a long terminal elimination half-life ($t_{1/2}$ = 50-76 h) were seen. Gimatecan was the major circulating compound (47%) in plasma, followed by the active metabolite LCF-775 (*tert*-butyl monohydroxy gimatecan; 2-9%). Radioactivity was mainly excreted in feces (median of 60.1% of dose *vs.* 10.3% in urine); the low levels of unchanged drug detected in feces and urine indicated good absorption (41).

A dose-escalating phase I/II trial conducted in 12 adult patients with recurrent malignant gliomas reported the pharmacokinetics of gimatecan (0.33-1.1 mg/m^2/day p.o. for 5 days every 28 days). The majority of patients achieved peak C_{max} at 2 h postdosing. The $t_{1/2}$ value for patients not receiving concurrent enzyme-inducing antiepileptic drugs (non-EIAED) was 71 ± 28 h and, accordingly, C_{max} and $AUC_{0\text{-}24h}$ values for these patients on day 5 were 112% and 179% greater, respectively, than those seen after the first dose. The $t_{1/2}$ value for the EIAED cohort was 6.3 ± 4.7 h, with minimal accumulation observed; the $AUC_{0\text{-}24h}$ on day 5 in the EIAED group was 81% lower than that observed in the non-EIAED group (74 ± 72 ng.h/ml *vs.* 560 ± 175 ng.h/ml at 0.33 mg/m^2/day). In addition, markedly enhanced clearance of gimatecan was observed in the EIAED group (42).

The pharmacokinetics of gimatecan (starting dose of 1.6 mg/m^2 p.o. once daily for 5 days every 28 days) were examined in another phase I trial conducted in 43 adults with malignant gliomas. Pharmacokinetics were linear, with significant influence of concurrent EIAED administration noted. The $t_{1/2}$ decreased 2-fold (25 ± 12 h *vs.* 53 ± 25 h) and the apparent oral clearance (CL/F) increased almost 5-fold (6.2 ± 4.3 l/h *vs.* 1.3 ± 1.7 l/h) in the EIAED cohort (43).

A phase II trial conducted in patients with pretreated advanced breast cancer further examined the pharmacokinetics of gimatecan (4-5 mg/m^2/cycle given p.o. for 5 days for 2 weeks). Results showed good oral bioavailability, high plasma levels, mostly consisting of the active intact lactone form, and a long $t_{1/2}$. C_{max}, AUC_{72h}, $AUC_{infinity}$ and $t_{1/2}$ values obtained from 9 patients at a dose of 4 mg/m^2 were 64.2 ± 17.7 ng/ml, 2853 ± 915 ng.h/ml, 7554 ± 2671 ng.h/ml and 102 ± 40 h, respectively. The AUC value for the polar metabolite ST-1698 accounted for 5-15% of the AUC value for the parent compound. A linear relationship was observed between the AUC_{72h} for gimatecan and plasma α_1-acid glycoprotein levels (44).

Safety

The safety of single and multiple (5 days and 4 weeks) oral doses of gimatecan was determined in mice, rats and dogs. The toxic dose low (TDL) was concluded to be 0.025 mg/kg/day in dogs after 5 days of dosing and the LD_{10} in male and female rats following single doses was 2.4 and 1.4 mg/kg, respectively. The no observed adverse effect level (NOAEL) in rats (0.05-0.1 mg/kg/day) and dogs (0.0125 mg/kg/day) was the same after 5-day and 4-week dosing. Myelotoxicity and gastrointestinal events were the most common toxicities observed in dogs and these events were related to AUC. Gimatecan was not associated with alterations in the central nervous, cardiovascular, respiratory or renal systems, nor in intestinal transit (45, 46).

Clinical Studies

In the above-mentioned phase I/II trial in 12 patients with recurrent malignant gliomas, gimatecan was well tol-

erated, with no dose-limiting toxicity (DLT) reported. Of the 7 non-EIAED patients, 4 had a radiographic response of disease stabilization after 2 cycles; no responses were observed in the EIAED cohort (42).

In addition to the pharmacokinetics, the phase I trial in 43 adults with malignant gliomas also assessed the efficacy and safety of gimatecan. After 49 cycles of therapy, no DLTs were reported in the EIAED group and dose escalation was stopped at 15 mg/m^2. However, in the non-EIAED group, DLT of grade 3-4 myelosuppression was seen in 1 of 11 patients at 6.1 mg/m^2 and 2 of 3 patients at 8 mg/m^2. The most common adverse events were grade 1-2 gastrointestinal events. After a median of 6 cycles, 2 partial responses and 6 cases of stable disease were obtained in the EIAED cohort, and after a median of 2 cycles, 11 patients had stable disease in the non-EIAED cohort. The maximum tolerated dose (MTD) was not established for the EIAED cohort, while 6.1 mg/m^2 was concluded to be the MTD for the non-EIAED group (43).

The safety and efficacy of gimatecan were further examined in a dose-escalating phase I trial involving 108 patients with advanced solid tumors. The tolerability of gimatecan (0.8-7.2 mg/m^2/cycle given p.o. daily for 5 consecutive days/week for 1, 2 or 3 weeks every 28 days) was schedule-dependent. The predominant toxicity observed was myelosuppression, with DLT of thrombocytopenia. The MTDs for the 1-, 2- and 3-week schedules were determined to be 4.5, 5.6 and 6.4 mg/m^2, respectively. Minor, clinically insignificant diarrhea and asthenia were seen. However, a higher incidence of nausea and vomiting was reported on the 1-week schedule, which required antiemetic prophylaxis. Six partial responses were obtained. Plasma accumulation of gimatecan was seen due to the prolonged half-life ($t_{1/2}$ approximately 77 h) (47).

The tolerability of oral gimatecan (0.26-1.32 mg/m^2) administered once a week for 3 of 4 weeks) was investigated in a dose-escalating phase I trial in 12 patients with advanced solid tumors. This dosing schedule was well tolerated, with no significant drug-related adverse events reported. One patient with melanoma and another with colon adenocarcinoma had stable disease for 4 and 5 cycles of treatment, respectively. The agent was rapidly absorbed and slowly eliminated (mean apparent $t_{1/2}$ = 108 ± 40 h) (48).

Preliminary safety and efficacy data were presented from a phase II trial in 43 patients with anthracycline- and taxane-pretreated advanced breast cancer (ECOG = 0-1) treated with gimatecan (4-5 mg/m^2/cycle given p.o. 5 days/week on weeks 1 and 2 every 4 weeks). A total of 67 cycles had been administered and results were reported from 18 evaluable patients. The starting dose of 5 mg/m^2 was reduced to 4 mg/m^2 due to grade 3 thrombocytopenia (30%) and grade 3-4 neutropenia (40%). Toxicities observed at 4 mg/m^2 included thrombocytopenia (any grade in 36% of the cycles; grade 3 in 9% of the cycles), grade 3 neutropenia (18% of the cycles), diarrhea (1 case), nausea (any grade in 81% of the cycles; grade 3 in 18% of the cycles), grade 1 vomiting (18% of the cycles) and grade 3 asthenia (36% of the cycles). Three confirmed partial responses lasting 5.5, 5.7+ and 9.4+ months and 2 unconfirmed partial responses were observed (49).

Preliminary data on the safety and efficacy of gimatecan were reported from another multicenter phase II trial in 70 women with platinum- and taxane-pretreated advanced epithelial ovarian, fallopian tube or peritoneal cancer (ECOG = 0-1). The predominant toxicities were thrombocytopenia and neutropenia. Of 40 evaluable patients, preliminary response rates of 23.5% based on CA125 and of 10% based on RECIST were obtained (50).

An international phase II trial examined the antitumor activity and safety of gimatecan (0.8 mg/m^2/day p.o. for 5 days every 28 days) in 40 patients with advanced or metastatic soft tissue sarcoma relapsing after anthracycline/ifosfamide-based regimens. The best overall response was stable disease in 37.5% of the patients, 10 patients (25%; 5 leiomyosarcomas and 5 other histologies) having stable disease for at least 4 months. Enrollment was stopped due to lack of efficacy. Three patients with prolonged arrest of progression (up to 8-10 months) remained on treatment at the time of reporting. Gimatecan was well tolerated, the major grade 3-4 toxicity being anemia (15%), thrombocytopenia (20%) and neutropenia (25%) (51).

Gimatecan continues to undergo phase I and/or phase II development for the treatment of advanced solid tumors, malignant gliomas and myelodysplastic syndromes (52-57).

Sources

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